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TECHNICAL REPORT

The returns from arthritis research

Volume 2: Case Studies

Steven Wooding, Silvia Anton, Jonathan Grant, Stephen Hanney, Stijn Hoorens, Abigail Lierens, Miriam Shergold, Mark Venema

RAND EUROPE

HERG Health Economics Research Group

arc 0870 850 5000 www.arc.org.uk Committed to curing arthritis

The research described in this report was prepared for and funded by the Arthritis Research Campaign (**arc**).

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Preface

This report, prepared for and funded by the Arthritis Research Campaign (**arc**), presents the results of an evaluation of 15 research grants awarded by **arc** in the early 1990s. The main objective was to develop a system for evaluating arthritis research, with a view to allowing **arc** to stimulate and manage the exploitation of research advances so that they translate into outcomes of practical benefit to people with arthritis.

The report is organised into two volumes. This is volume 2 and presents a collection of the case studies, each based on an individual research grant, on which the study is based. These case study reports all follow a similar format based on the conceptual model, providing a rich and detailed narrative on the payback of each research grant.

Volume 1 is an overall analysis of the payback from the 15 case studies. It presents a framework that conceptualises the relationship between research inputs, process, output and outcomes. Using this framework, we catalogue a diverse range of research output and outcomes arising from these 15 grants and make a series of quantitative and qualitative assessments comparing, for example, payback from project grants *versus* programme grants. In conclusion, we make six observations.

1. There is a diversity of research payback.
2. The researcher is the key driver of research translation.
3. Short, focused project grants seem to provide value for money.
4. Intended and unintended flexibility in funding is used advantageously.
5. Referees' contributions to the peer-review process are of variable benefit.
6. The payback framework could be operationalised and embedded by **arc**.

In addition to **arc**'s trustees, senior management, staff, scientists, fundraisers, donors and people with arthritis, this report should be of interest to other research funding agencies and to evaluators who are concerned with measuring the impact of science.

The research was led by RAND Europe in collaboration with the Health Economics Research Group at Brunel University. In addition, we commissioned bibliometric support from the Department of Information Science at City University. RAND Europe is an independent not-for-profit policy research organisation that serves the public interest by improving policymaking and informing public debate. Its clients are European

governments, institutions and firms with a need for rigorous, impartial, multidisciplinary analysis of the hardest problems that they face. This report has been peer-reviewed in accordance with RAND's quality assurance standards (for more information, see http://www.rand.org/about/standards/) and therefore may be represented as a RAND Europe product.

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Contents

Executive summary

The mission of the Arthritis Research Campaign (**arc**) is to improve the lives of people with arthritis. **arc** aims to achieve this mission by raising funds to support medical research into the cause, treatment and cure of arthritic conditions. **arc** is the UK's fourth largest medical research charity, investing £22 million a year in research into arthritis. Currently, clinical and basic scientific research is supported through approximately 400 project grants, programme grants and fellowships in universities and medical schools throughout the UK. **arc** also provides core funding for its two major research institutes, the Kennedy Institute of Rheumatology in west London, and the Epidemiology Research Unit (**arc** ERU) at the University of Manchester.

To mark its 65th anniversary in 2002, **arc** decided to undertake a strategic review that resulted in the publication of a five-year strategic plan, *Research into Practice*. The review was informed by consultations with **arc**'s stakeholders – including trustees, staff, scientists, volunteer fundraisers, donors and people who have arthritis – and concluded that "there seems to be a gap between the aspirations of people affected by arthritis and the ability of science and academia to meet those aspirations". In order to bridge this gap, **arc** decided to "instigate a system of rigorous retrospective evaluation on work which has already been completed, with a view to identifying opportunities for development". To inform this commitment, **arc** commissioned this study to:

- review and document the long-term outcomes of **arc** research grants awarded in the early 1990s;
- identify the factors associated with the successful translation of research;
- illustrate the strengths and weaknesses of different modes of funding; and
- identify "good news stories" that **arc** could use in its public engagement and fundraising activities.

The purpose of this volume is to report on the approach, results, conclusions and recommendations arising from an in-depth evaluation of 15 research grants funded by **arc** in the early 1990s. It supports a first volume, *The returns of arthritis research. Volume 1: Approach, analysis and recommendations*. In this executive summary we set out what we did, reporting our key conclusions and their implications for policy.

Evaluation purpose and approach

This evaluation is intended to improve understanding of how research is translated from "bench to bedside". It examines the historical development of 15 case study research

grants, and assesses the extent to which different types of funding support might prevent or promote the successful translation of research.

To conduct this inquiry, the research team created a framework that breaks down the process by which research translates into practice. The framework had two elements. The first element is the five payback categories (summarised in Box S.1). The second element is the payback model (illustrated in Volume 1, Chapter 2, Figure 2.2 and summarised in Box S.2). The payback categories and model were adapted from the Buxton and Hanney Payback Framework following interviews with a series of key informants.

Knowledge production
Research training and capacity building
Informing policy and product development
Health and health sector benefits
Wider economic benefit

Box S.1: Payback categories

Stage 0:	Topic/issue identification
Interface A:	Project specification and selection (peer review)
Stage 1:	Inputs to research
Stage 2:	Research process
Stage 3:	Primary outputs from research
Interface B:	Dissemination
Stage 4:	Secondary outputs
Stage 5:	Adoption
Stage 6:	Final outcomes

Box S.2: Summary of payback model

Guided by this framework, we conducted case studies of 15 research grants. The case studies were selected from 556 possible grants awarded by **arc** between 1990 and 1994. In order to allow us to compare the effect of the mode of research support, the type of research and the bibliometric impact of the principal investigators (PIs), we constructed a selection matrix. With the help of the Development Committee, we chose six project grants, three programme grants, three fellowships and four institute grants for evaluation. Our collection of grants contained six basic grants, eight clinical grants and two allied health professional (AHP) grants (classified according to the qualifications of the PIs), with nine "high" impact PIs and seven "mid" impact PIs.[1] With 15 case studies we could

[1] As explained in Volume 1, Appendix A, impact was measured using a range of different bibliometric indicators; "high" impact was the top decile of PIs based on those indicators, and "mid" was the 45–55 percentile.

not expect them to be representative of all **arc** grants in a statistical sense; however, by using a selection matrix we aimed to produce a set of case studies that mirrored the diversity of **arc** funding in key dimensions and hence from which could be carefully generalised.

Using the information collected from document and literature reviews, semi-structured key informant interviews and bibliometric analysis, each of the 15 cases was written up as a narrative organised according to the structure provided by the payback framework (Box S.2). Using a common structure facilitates comparative analysis, allowing us, for example, to identify the factors associated with the successful translation of research. We employed two approaches to our cross-case analysis. The first was based on a qualitative assessment of the case studies based on a discussion within the project team of the key observations made by each member of the team. The second involved a novel method of scoring the case studies on the five payback categories.

Conclusions and implications for policy

The study reached six main conclusions, which we discuss below. However, there are several limitations to our approach, the key issues being:

- whether it is reasonable to use a largely linear framework to structure analysis of the scientific process;
- whether the use of, and generalisation from, case studies, is appropriate;
- biases in the process of selecting our case study grants;
- how to determine whether a specific outcome can be attributed to a particular grant or investigator;
- how to pick a suitable time window for the start of study: a compromise between allowing outcomes to come to fruition and ensuring that records are available and investigators' recall are suitably detailed.

Each of these issues is discussed in more detail in Volume 1, Chapter 4 (section 4.2). By discussing them we do not wish to undermine our conclusions, but to illustrate some of the challenges of evaluating research.

There is a diversity of research payback

There is strong evidence from our analysis that there is a considerable range of research paybacks and that these would not have been identified without the structured, case study approach employed in this evaluation. The highlights of these paybacks are listed in Table S.1.

Table S.1: Summary of research paybacks

Payback category	Payback	Example
Knowledge production	• Peer-reviewed publications in the serial literature	• 302 papers receiving a total of 975 citations per year attributable to case studies
Research training and research capacity	• Postgraduate research training • Subsequent career development of PIs and research assistants • The transfer of technical know-how • Informing future research studies	• 28 PhD/MDs from work on the case studies • Development of technological know-how in genetic mapping • Informed >£2 million Medical Research Council (MRC) randomised controlled trial • Use of biologicals as therapeutic targets
Informing policy and product development	• Informing recommendations in clinical guidelines and other policy advice • Informed development of clinical tests	• Recommendation in Royal College of Obstetricians and Gynaecologists (RCOG) guideline on the use of aspirin and heparin for women with antiphospholipid syndrome (APS) • Recommendation in Industrial Injury Advisory Council (IIAC) assessment for hip osteoarthritis (hip OA) in farmers to be a prescribed disease • Clinical test for a rare type of systemic lupus erythematosus (SLE) and chrondrodysplasia type Schmidt
Health and health sector benefits	• Improving the quality of life for people with rheumatoid arthritis (RA) • Reducing the likelihood of recurrent miscarriages for women with APS	• Hundreds of thousands of patients treated with anti-TNF of whom 70% experience a significant improvement in health • Use of aspirin and heparin for women with APS increases live birth rate by 40% compared to the use of aspirin alone and by 60% compared to no treatment at all
Wider economic benefits	• Unquantified economic returns resulting from a reduction in days off work and sales of licensed drugs	

Individuals translate research

There is good evidence from our 15 case studies that when translation of research into developments of practical value to patients occurs it is largely due to the conviction, effort and personal networks of a particular investigator, and is not associated with the type or mode of the funding stream or the bibliometric impact of the investigator. This complements previous studies that have shown that encouraging partnership between researchers, practitioners, policymakers and industrialists promotes successful translation.

Therefore, we propose that **arc** introduces two new types of award. "Translation awards" would be topic-focused and directly linked to the translation of a previous piece of **arc**-funded research. "Partnership awards" would be people-focused and provide resources to **arc**-funded researchers to develop networks with potential users of research. This could include supporting secondments to or from commercial and non-commercial laboratories, and participation in policymaking networks. Criteria for translation and partnership would focus on the potential return or payback from translation, the stated route or plan of translation, relevance to **arc**'s strategic aims and, in the case of translation awards, evidence of existing networks.

Short focused projects grants seem to provide value for money

There is good evidence from our analysis that the payback arising from projects grants is similar to that arising from the other modes of funding. Given that the median value of a project grant is £90,000 (compared to £250,000 for fellowships, £480,000 for programmes and £450,000 for institutes) this indicates that they provide significant value for money. Of all the observations that we have made from our analysis, this was the most unexpected and surprising and illustrates the importance of maintaining a funding mechanism for short-term, focused research of this nature.

Intended or unintended flexibility in funding is used advantageously

There is some evidence from our case studies that investigators successfully exploit flexibility in the scientific and administrative management of grants. In none of the case studies was there any evidence that this flexibility had a negative effect on the scientific outputs and outcomes of the research, and in some cases there were indications that such flexibility was used advantageously. This observation therefore supports the continuation of **arc**'s current policy of flexibility in funding.

Referees' contributions to the peer-review process are of variable benefit

There is some evidence from analysis of successful applications that referees' contributions to review panels do not add significant scientific value to the reviewed proposals. However, it is worth noting that the primary purpose of the review process was to select suitable applications for funding, rather than to improve those successful applications. For nine of the case study proposals, even where the referees' comments were fed back to the PI, they had little or no impact. For four of the case studies, the peer-review process did have an impact on the design of the study. For a further two cases (which had the highest payback), if the referees' comments had been taken at face value and not overruled by the assessing panel, the proposed research would not have been funded.

The payback framework could be operationalised and embedded by **arc**

There is good evidence from this study that the payback framework adapted for **arc** works and, given the appropriate management information, could be operationalised prospectively to stimulate and manage the returns from **arc** research. The payback

framework proved to be effective in capturing the diverse range of research outputs and outcomes, and in identifying cases where research had been translated to benefit people with arthritis. If applied prospectively, the framework could be used to inform the granting of the recommended translation and partnership awards. (In Volume 1, Chapter 4 we describe how **arc** could operationalise and embed the payback framework, and identify a number of issues that would need to be resolved prior to implementation.)

Recommendations

On the basis of these conclusions we make six recommendations, which are intended to help **arc** develop a system to ensure the successful translation of the research that it funds. These are outlined below, along with the aim and context of each recommendation.

Recommendation	Context	Aim
1. **arc** should survey all forms of payback when monitoring and evaluating the returns from arthritis research.	There is strong evidence from our case studies that all types of grant produce a range of research outputs and outcomes, beyond the usually assessed publications in the peer-reviewed literature.	To ensure that the returns from **arc**-funded research are fully recorded and recognised.
2. **arc** should selectively support investigators in translating their research. This might include: • translation awards to promote the successful transfer of knowledge with potential health benefit; • interaction awards to develop productive relationships between researchers and policymakers or industry. These awards could be made in both reactive and directed modes.	There is good evidence from our case studies that when translation occurs, it is largely down to the individuals' conviction, effort and personal networks, although individuals currently have little or no support for these activities.	To recognise the importance of personal networks in the translation of research, and to ensure that translation opportunities are resourced fully and realised.
3. **arc** should continue to support short focused project grants as part of its funding portfolio.	There is good evidence from our case studies that project grants provide value for money when compared to programme grants, fellowships and institutes.	To acknowledge the importance of project grants in funding research.
4. **arc** should maintain its flexible approach to the funding and administration of research grants. In addition we suggest that **arc** considers the costs and benefits of fixed budget funding.	There is some evidence from our case studies that investigators successfully exploit flexibility in the scientific and administrative management of grants.	To confirm that **arc** should maintain its current policy of being flexible in the award and administration of grants.
5. **arc** should review its peer-review processes to maximise their efficiency and effectiveness.	There is some evidence from our case studies that for successful applications referees' contributions to review panels are of variable benefit.	To challenge **arc** into assessing the costs and benefits of its peer-review system, with a view to improving its value to applicants.
6. **arc** should consider developing systems for the ongoing and prospective monitoring and evaluation of its funded research.	There is good evidence from this study that the payback framework developed for **arc** works and, given the appropriate management information, could be operationalised to prospectively monitor the returns of **arc**-funded research.	To develop an approach whereby **arc** will be in a position to "stimulate and manage the exploitation of research … into outcomes of practical benefit to people with arthritis".

Acknowledgements

The Arthritis Research Campaign commissioned this study. Jonathan Grant and Steven Wooding from RAND Europe, in collaboration with Martin Buxton and Stephen Hanney from the Health Economics Research Group at Brunel University, wrote the successful proposal. The subsequent project team involved seven members. Steven Wooding managed the project, with the support and guidance of Jonathan Grant.

Steven Wooding, Steve Hanney, Martin Buxton and Jonathan Grant devised the methodological approach and analysis, as report in this volume. The conclusions that emerged in the final chapter of Volume 1 resulted from a workshop in which all members of the project team participated. Different researchers conducted the case studies reported in this volume, as described in the introductory chapter of Volume 2 of the report. In summary, the case study authors were: Silvia Anton, Jonathan Grant, Stephen Hanney, Stijn Hoorens, Abigail Lierens, Miriam Shergold and Steven Wooding.

As is the nature of a project of this scale and complexity, the project team would like to acknowledge the invaluable support provided by a number of groups and individuals. First, Grant Lewison, Isla Rippon and Kate Wilcox-Jay, all from City University's Department of Information Science, who supplied us with the bibliometric data and analysis that underpin the study. Second, the important role of the Arthritis Research Campaign's Development Committee who acted – in the true meaning of the word – as a steering group and provided excellent guidance during all stages of the study. The Development Committee was made up of the following members: Patrick Sissons, Ann Raven, Fergus Logan, Madeleine Devey, Michael Patnick, Mary Collins, Matthew Brown, Mike Hurley and Tony Woolf. Third, in addition to their participation in the Development Committee, we would also like to acknowledge the role of Arthritis Research Campaign staff, most notably Fergus Logan, Madeleine Devey and Michael Patnick, for initiating the study and for answering our numerous queries. We would also like to thank Charlene Rohr and Dr Cyril Frank for providing very helpful comments and suggestions in reviewing the report, and Lisa Cordaro for copy editing the report.

We would like to reserve our final acknowledgements to all those scientists – 46 in total – who were willing and able to act as our experimental subjects for this study. This involved either being the subject of a case study or being interviewed as a stakeholder of a case study. As is the nature of this type of evaluation it is inappropriate to name these individuals, but without their support and commitment this study would not have been possible.

CHAPTER 1 Introduction

This volume presents a collection of the case studies undertaken as part of the evaluation of the long-term outcomes of research funded by the Arthritis Research Campaign (**arc**). It should be read alongside the main report, *The returns from arthritis research. Volume 1: Approach, analysis and recommendations* (Wooding and others 2004) which sets out the overall evaluation objectives, approach, results and conclusions.

The purpose of this introductory chapter is to provide the reader with a brief study synopsis, explain the payback categories and model, and describe how each of the case studies is presented, including a brief review of the bibliometric indicators used in the case studies.

1.1 Study synopsis

The main source of data employed in the evaluation were 15 case studies selected from a sample of 556 **arc** project, programme, fellowship and institute grants funded between 1990 and 1994 (see Volume 1, Chapter 2, section 2.2 for detail of case study selection).

1.1.1 Data sources

To construct the narrative of **arc**-supported research for each case study, three independent sources were used (data collection is also discussed in Volume 1, Section 2.3):

- **document and literature review** of **arc** archives including, for example, original grant applications, referees' reports, subsequent correspondence between **arc** and the grantholder, and the review of interim and end-of-grant reports. In addition, case study analysts read the peer-reviewed papers and reports considered, by the principal investigator (PI), to have arisen from the **arc** grant and other background literature;
- **semi-structured key informant interviews** with PIs, named and unnamed staff on awards, collaborators and other stakeholders including peers and users of the research. The interviews were based around the Payback Model (discussed below) and explored the origins of the research, primary outputs and any translation of research findings into product development, policy and practice;
- **bibliometric indicators** were derived for each of the peer-reviewed papers attributable to the grant. As discussed in section 1.2.2, the indicators were calculated from the Science Citation Index (SCI) and the Research Outputs Database (ROD) and included measures of volume, collaboration, and impact.

In every case a draft copy of the case study report was sent to the PI for comment, validation and clearance. All the PIs approved the factual accuracy of their case studies, with 15 approving publication.

1.1.2 Payback categories and model

As discussed in Volume 1 (section 2.1), there are two elements to the evaluation framework. The first consists of a multi-dimensional categorisation of benefits from biomedical and health research. The second is a logic model describing the flow, or translation of knowledge, from topic identification to final outcomes, as illustrated in Figure 1.2.

The payback categories provide the evaluation criteria for the outputs and outcomes from **arc** funding, and are summarised briefly below.

Category A: knowledge production – the knowledge produced by research is the first output and is contained in various publications and patent applications. Any types of publications can be considered, but it is generally thought that peer-reviewed articles are the most important, and at least for biomedical research in industrialised countries it is thought reasonable to assume that the overall output of research publications is fairly represented by peer-reviewed papers in international journals. In addition to counting the number of publications, their quality and their impact can be assessed in various ways.

Category B: research targeting and capacity building – the better targeting of future research is frequently a key benefit from research, especially from research that is more basic and/or methodologically oriented. The targeting can be of both the research conducted by others and of the original researcher(s). Research training can be provided both as a result of the employment of staff on research projects and programmes, and through explicit funding for research training and career development. The career development of arthritis researchers goes much wider than specific training and is of considerable importance to **arc**, which aims to ensure that the pool of researchers in this field is a strong as possible.

Category C: informing policy and product development – research can be used to inform policymaking in a wide range of circumstances. Policymaking here is interpreted broadly and covers:

- policies made by managers at many levels within a health service;
- policies agreed at national or local level by groups of health care practitioners in the form of clinical or local guidelines; and
- policies developed by those responsible for training, education or inspection in various forms including training packages, curricula and audit and evaluative criteria.

At a similar level, although involving very different processes, research can be used also to inform product development. Informing policies and product development are conceptually similar in that there generally has to be some subsequent adoption of the policy, or product, before the health and economic benefits can accrue.

- **Category D: health and health sector benefits** – these benefits might be viewed as the "real" payback or outcomes from biomedical and health research. Greater effectiveness resulting from research-informed drugs or procedures will lead to increased health. Various measures of health gain exist, but in most cases for arthritis

the emphasis is likely to be on those that assess reduction in pain or disability, or increased mobility. Cost savings in the provision of health care may result from research-informed changes in the organisation of services or in the particular therapies delivered.

- **Category E: broader economic benefits** – a range of benefits can accrue to the national economy from the commercial exploitation of research. These can take the form of employment and profits resulting from the manufacture and sale of drugs and devices. The national economy could benefit also from exports and/or import substitution.

The second element of the evaluation framework is the logic model, or Payback Model (Figure 1.1), which consists of various stages and interfaces as briefly summarised below.

- **Stage 0: topic/issue identification** – this stage involves the generation of the original ideas for the research and its nature can vary considerably, depending on whether the main driving force is generated internally by the researcher, or generated externally. Most **arc** funding falls into the former category; for many researchers, the topics will be curiosity-driven and based on the researchers' examination of the existing stock or pool of knowledge and opinions about where gaps and/or opportunities exist and further research could advance understanding.
- **Interface A: project specification and selection** – the nature of the activities at Interface A will vary depending on the type of issue identification. Where the issues are generated internally, the interface involves traditional processes where the researcher develops a detailed proposal and submits it for peer review. Where the topics are generated externally, the interface issues become more important as there are potential difficulties in ensuring both that the research community is actively engaged with the priorities that have been identified, and that the project specification meets the needs as identified. In both cases, however, there are issues about how far the proposal was subject to changes as a result of the review process.
- **Stage 1: inputs to research** – in addition to the financial support provided by **arc** in awarding a grant, funding from other research organisations, the experience and knowledge of the research team and the physical infrastructure available to the research team are all considered to be inputs at this stage.
- **Stage 2: research processes** – consideration can be given to how appropriate the proposed methods turned out to be, and whether any difficulties were encountered. In some cases it could be relevant to explore how far potential users were involved at this stage. It is possible that the difficulties identified at this stage could explain later problems with translation or uptake of the research findings.
- **Stage 3: primary outputs from research** – knowledge production as represented by the various types of publications is a major primary output from the research. Most of the primary outputs will feed into the stock of knowledge and become part of the body of knowledge that informs further research or is incorporated into systematic reviews. The research benefits in terms of targeting future research and capacity building can also be seen as featuring here, but they represent either feedbacks to further research conducted by team members or findings that feed into the stock of knowledge and help to target future research.
- **Interface B: dissemination** – usually, dissemination is seen as being somewhat more active than the mere production of academic publications containing the knowledge.

However, there are clear overlaps between some activities, and sometimes it is possible to record not only dissemination activities but also the successful transfer of research findings to potential users in the political, industrial and professional environments and wider society. Presentations to potential academic and user groups, and media activities, are major ways of disseminating findings, as is the production of brief summaries of findings targeted at specific user groups.

- **Stage 4: secondary outputs – policymaking and product development** – a wide range of items can be considered to be secondary outputs. In terms of policies, the key issue is that policymaking involves those in positions of authority making choices that have a special status within the group to which they apply. The results can take many forms, ranging from national health policies made by the government to clinical guidelines determined by professional groups, to guidelines or care pathways, etc which are agreed within local units. Many other items can be included also if they are informed by research findings, for example, "how-to" manuals, criteria adopted by evaluative or inspectorial bodies, training packages and official curricula, legal decisions and media campaigns by health care providers.
- **Stage 5: adoption – by practitioners and public** – for the research findings incorporated into secondary outputs to result in final outcomes there usually has to be some behavioural change by practitioners and/or the public. This may involve take-up of new drugs or procedures as set out in a secondary output such as a guideline from the National Institute for Clinical Excellence (NICE). Sometimes the adoption comes as a direct result of the primary outputs, as when clinicians – who are often at the cutting edge – decide to implement research findings, even prior to the development of clinical guidelines.
- **Stage 6: final outcomes** – these are the health and broader economic benefits identified in the payback categories above. Increasingly, these are seen as being the ultimate goal of health research funding, but their precise estimate in practice often remains difficult. At one level there might be data such as audit figures available from areas where there is known to have been local implementation of the research findings. At an overall level, it is possible that figures would be available for the potential population who could benefit from the new drug or procedure and information about the level of benefit that a patient might receive. If knowledge about adoption levels was then also taken into consideration, it might be possible to indicate levels of benefit.

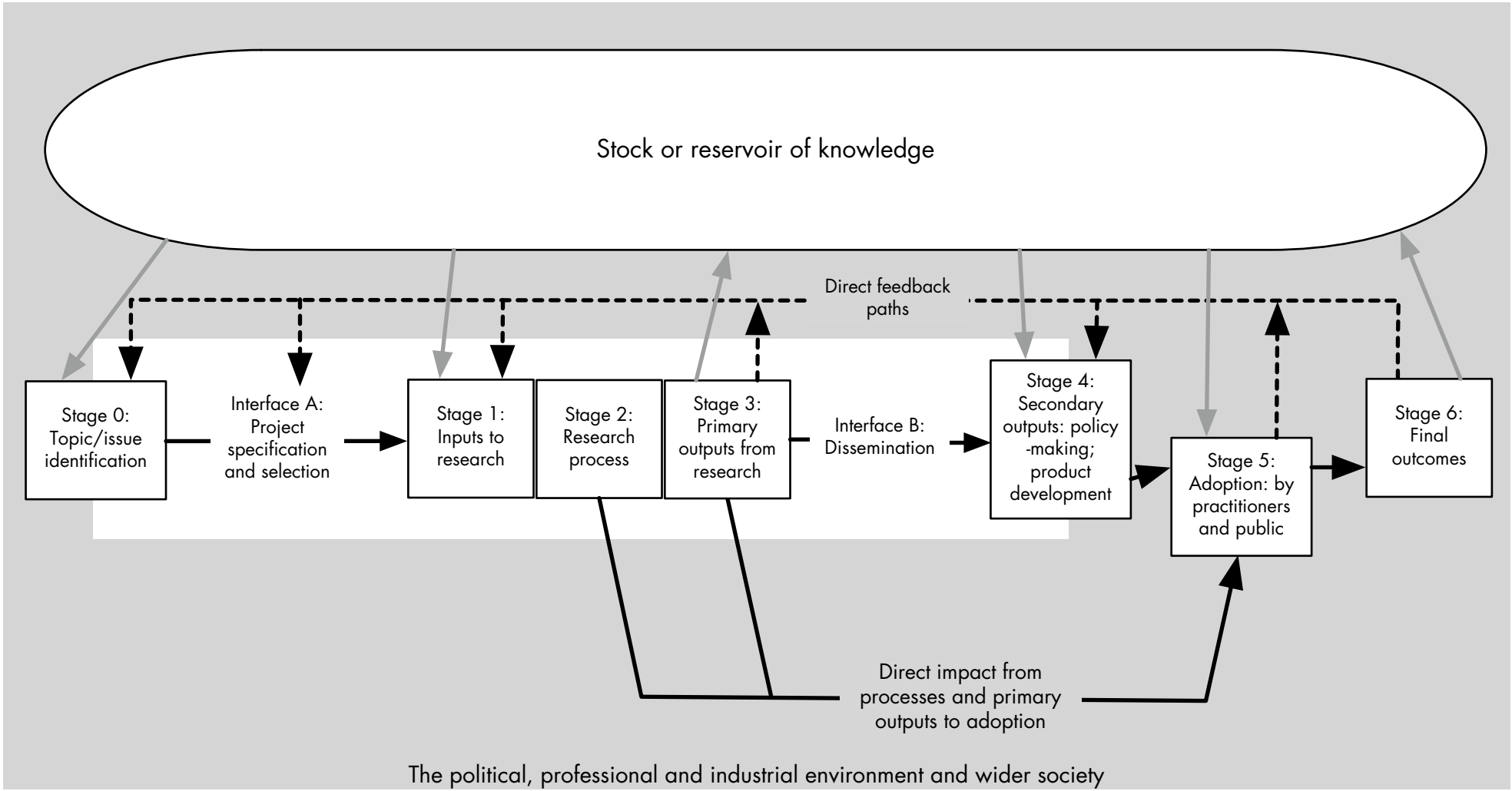


Figure 1.1: Payback model adapted for the arc study

It should be stressed that, although the model is presented in a linear form, the reality is much more complicated: there are numerous feedback loops at all its stages. In addition, while it is not possible to totally tie the categories of benefits to certain stages of the model, it is possible to identify broad correlations. For example, payback categories A and B (knowledge and research benefits, respectively) together are considered to be the primary outputs from research (ie stage 3 in the Payback Model). Similarly, category C (informing policy and product development) relates to the secondary outputs (stage 4), and categories D and E (health and broader economic benefits) are the final outcomes (stage 6).

1.2 Case study presentation

Each of the 15 case studies, where the PI approved publication, are presented as a narrative organised according to a common structure, based on the various stages of the payback categories and model. Each one of the case studies was authored by different members of the case study team, as illustrated in Table 1.1.

Table 1.1: Case study authors

Case study	Author
A	Stephen Hanney
B	Jonathan Grant
C	Steven Wooding
D	Steven Wooding
E	Miriam Shergold
F	Abigail Lierens
G	Silvia Anton
H	Stijn Hoorens
I	Stijn Hoorens
J	Silvia Anton
K	Abigail Lierens
L	Miriam Shergold
M	Silvia Anton
N	Miriam Shergold
O	Mark Venema
P	Mark Venema

In writing up the case studies, a standard template that listed each of the five payback categories at each of the seven stages of the payback model was used. In this way it ensured that that each category was considered at each stage, providing a consistent way to present the information that would aid inter-case comparison in the analysis phase of the study.

1.2.1 Ethics committee

In accordance with the Multi-region Ethics Committee (MREC) approval for this project, we have not named the PIs in the case studies; however, as research translation depends on the context and subject area of the research we have not been able to remove the contextual information about the PIs. Given the nature of scientific and medical research, it is therefore possible that the PIs will be identifiable. Because of this, we have sought permission from all the PIs before publication of their case studies. In the cases where the PI did not consent to publication we have omitted their case studies; this occurred for one case study, case study D.

1.2.2 Bibliometric indicators

In evaluating the knowledge produced from each grant (payback category A), a range of bibliometric methods were used. These are described in Volume 1 (section 2.3.3 and Appendix A), along with an assessment of the strengths and weaknesses of bibliometric analysis. Below, the standard bibliometric indicators used in each of the case studies are defined. They are split into two sets. The first, "Publication Portfolio" indicators, describes the papers arising from the funded **arc** research study. The second, "Knowledge flow" indicators, describes how others use those papers – that is, how often the papers are cited and what are the characteristics of the citing papers.

Publication portfolio indicators

- **Output (number of papers)** – this is the number of peer-reviewed papers published in the serial literature identified by the PI and "attributed" to the case study **arc** research grant.
- **Collaboration (mean number of authors, mean number of addresses, proportion of papers with a non-UK address)** – the average number of authors and addresses on papers attributed to the **arc** research grant, and the percentage of papers with a non-UK address. This indicates the degree of individual (author), institution (address) and international (non-UK address) collaboration.
- **Type (research level distribution, proportion outside "ARTHR" field)** – the distribution of papers attributed to the **arc** research grant by research level. The research level is a journal classification system developed by CHI Inc., which is based on expert opinion and journal-to-journal citations, and has become a standard tool in bibliometric analyses (Narin and others 1976). Journals are allocated into four hierarchical levels in which each level is more likely to cite papers in journals at the same level or the level below it and vice versa. Hence, only 4% of papers in level 1 "clinical observation" journals (eg *British Medical Journal*) will cite papers in level 4 "basic" journals (eg *Nature*), compared to 8% for level 2 "clinical mix" journals (eg *Arthritis and rheumatism*), and 21% for level 3 "clinical investigation" journals (eg *Immunology*).

  The "ARTHR" field is a bibliometric definition of arthritis research, based on key word searches and specialist journals, which aims to identify all arthritis research papers (Lewison and Devey 1999). Attributable papers from **arc** outside the ARTHR field indicate research that will be of general interest to a number of research areas and is more likely to be fundamental or basic in nature.
- **Funding (mean number of funders; proportion acknowledging arc)** – the average number of funding acknowledgments on papers attributed to the **arc** research grant, and the proportion of those papers that explicitly acknowledge **arc**. The funding body acknowledgements are derived from the ROD, which is a database of SCI (and selected Social Science Citation Index) papers with a UK address in the biomedical research field (Dawson and others 1998). This indicates the degree of additional funding of which the investigator is in receipt.

Knowledge flows

- **Strength (mean number of citations per year from start of grant to 2003; the mean number of citations for the five years following publication of the paper)**

– the average number of citations to papers attributed to the **arc** research grant for different timeframes. Both indicators provide a proxy measure of how the research has supported other published research.

- **Knowledge translation (research level of citing papers, relative research level)** – the distribution of research levels for papers citing those papers attributed to the **arc** research grant by research level. This indicator assesses whether, for example, basic research is being cited by clinical research. The relative research level is the research level of the cited paper minus the research level of a citing paper. A positive value is an indicator of forward translation (that is, from basic research into clinical); a negative value is an indicator of backward translation (from clinical research into basic).
- **Knowledge diffusion (proportion of US cites, field distribution of citations)** – the former is the proportion of citations coming from papers with a US address. The US is selected as it is the largest scientific producer (accounting for ~40% of biomedical research papers) and provides an indicator of the diffusion of **arc**-funded research outside the UK. The latter measure shows the proportion of citations coming from papers which do not fall within the bibliometric definition of arthritis research (ie as determined by the "ARTHR" bibliometric filter). This provides an indicator of the diffusion of **arc**-funded research outside the field.

As illustrated in Figure 1.2 below (for case study A), each of these indicators are presented in a standard form for each of the case studies. In addition, all the bibliometric indicators are listed in Annex A of this volume. In Volume 1, the indicators for each case study are put into context by making comparisons with all the 15 case studies, all papers resulting from **arc**-supported researchers between 1991 and 1994 and, where the information is available from secondary sources, arthritis research in the UK and biomedical research in the UK.

1.3 Organisation of volume

The remainder of this volume is organised into one chapter per case study. At the end of each chapter we provide the bibliography for that case study. In Annex A, bibliographic and bibliometric information is provided on all the peer-reviewed papers identified from the SCI.

As noted at the beginning of this chapter, its should be stressed that this volume should be read alongside the main report, *The returns from arthritis research. Volume 1: Approach, analysis and recommendations* (Wooding and others 2004), which sets out the overall evaluation objectives, approach, results and conclusions.

Publication portfolio

Output

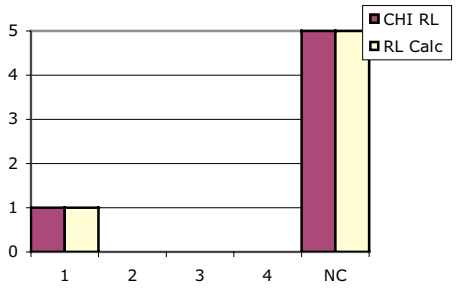
Number of papers	6

Collaboration

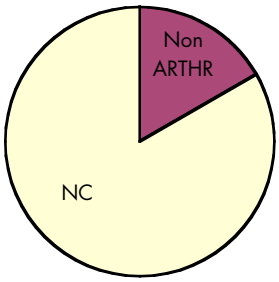
Mean number of authors	4.2
Mean number of addresses	3.0
% with non-UK addresses	0%

Type

Research level distribution



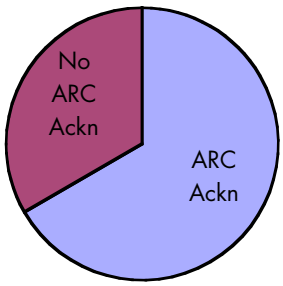
Field distribution



Funding

Mean number of acknowledgements	No data

ARC funding acknowledgements



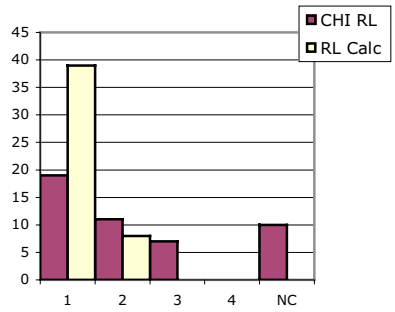
Knowledge flow

Strength

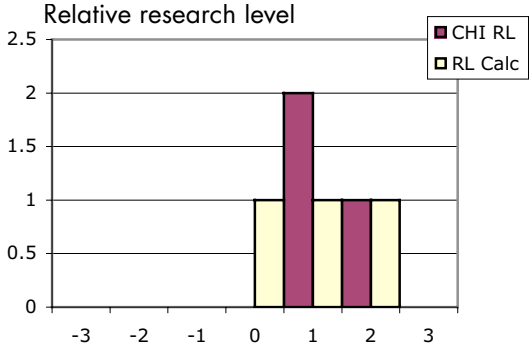
Mean citations per year (all papers)	4.7
Mean C0-4	19.0

Knowledge translation

Research level of citing papers



Relative research level



Knowledge diffusion

% of citations from the US	26%

Field distribution of citations

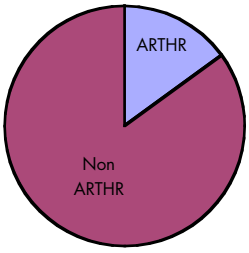


Figure 1.2: Selected bibliometric indicators for case study A

References

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Lewison G, Devey M. 1999. Bibliometric methods for the evaluation of arthritis research. Scientometrics 41:17–27.

Narin F, Pinski G, Gee HH. 1976. Structure of the biomedical literature. Journal of the American Society for Information Science 27:25–45.

Wooding S, Hanney S, Buxton M, Grant J. 2004. The returns from arthritis research. Volume 1: Approach, analysis and recommendations. RAND document MG-251-ARC (available from http://www.rand.org).

CHAPTER 2

Case study A: back pain in primary care – assessment of exercise-based management

2.1 Introduction to the research project

The research project consisted of a randomised controlled trial (RCT). It evaluated the effectiveness, in terms of clinical outcomes and costs, of an exercise programme in a community setting to encourage patients with low back pain to return to normal activities. The study was based at the Centre for Health Economics, York.

By the end of the 1980s the escalating incidence of sickness due to back pain was of great concern, putting a major strain on social welfare systems with socialised medicine (Waddell and Main 1987). Over 2 million individuals in the UK consult their general practitioner (GP) with low back pain, the great majority presenting with "non-specific low back pain". Only 5% have clear-cut signs of a prolapsed intervertebral disc and management of the condition was thought to be unsatisfactory (Roland and Dixon 1989). A survey showed the commonest site of pain reported due to osteoarthritic changes was in the lumbar spine.

Most back pain problems are resolved within six weeks, regardless of treatment; it is the patients whose disability becomes chronic that present the real issue. At the time of the study it was suggested that there was a need to reconsider the traditional model for the management of back pain: medication and advice, often involving bedrest (Roland and Dixon 1989). Therefore, the research project evaluated the usefulness of a new approach to managing back pain in a primary care setting.

The case study based on this research project involved: documentary analysis of the relevant arc files, publications from the project, key citing papers and the principal investigator's (PI) CV; bibliometric analysis; face-to-face or telephone interviews with three members of the research team, two other senior researchers in the field (one of whom plays an important role within arc), and five physiotherapists who organised and/or attended study days based on the project's findings (and who are applying to varying degrees the results of the study in different parts of the country). Details have been made available of the pre-test and post-test assessments conducted by one of the physiotherapists who is running a back reactivation programme, and some of these data (which have already been presented at an international conference) are incorporated into the analysis. Building on

these data, it has been possible to take this case study through the various stages and demonstrate the existence of some long-term outcomes in the form of health gains.

2.2 Stage 0: topic/issue identification

The idea for the project came from the PI and was submitted for funding in open competition. As a result, Stage 0 focuses on topic/issue identification.

The proposal was developed against the general background of an apparently increasing burden of back pain and dissatisfaction with the then current approach that was used most commonly in its management. Prolonged bedrest had been shown to be detrimental to recovery from back pain (Gilbert and others 1985). Following an acute episode of back pain some individuals may respond by becoming overcautious, avoiding all movements or activities that they fear might exacerbate their condition. It was suggested in the application that the development of chronic disability syndromes resulting from back pain depends on various factors, particularly behavioural and cognitive ones.

The PI stressed the importance of her own clinical practice in identifying questions where research could help to improve clinical effectiveness. Increasingly, she viewed psychological processes as being important factors. There was a movement towards more active management of back pain and, in particular, various studies showed an active exercise approach to be of benefit (eg Hazard and others 1989). In the application for the project, it was suggested that research had yet to evaluate the usefulness of a general exercise class for back pain in a primary care setting. The proposal set out how this could be done both in terms of clinical effectiveness and costs.

Of particular importance in the development of the specific intervention to be assessed in the proposed research was a study by Helen Frost in which the PI had played an important role (Frost and others 1995). This was based on a general exercise programme for patients with chronic low back pain and was conducted in a physiotherapy department of an orthopaedic hospital. That exercise programme formed the basis of the one used in the intervention in this study.

The PI's previous arc-funded project (Klaber Moffett and others 1996) had not been in the same field, but she felt that it was of importance in two ways. First, it had provided her with experience of running an RCT (which was itself highly rated for its methodology in the Physiotherapy Evidence Database (PEDro) database, as described later). Second, when (for personal reasons) the PI had to move location, the ability to transfer the final part of the arc project funding was important in enabling her to establish herself at York University, from where this application was made.

2.3 Interface A: project specification and selection

The first application received strong support from one referee, who nevertheless raised some questions, but the three others gave it a rating of "possible support" and also raised issues that needed to be clarified. The application was not accepted, but the comments of

The traditional model of management of back pain in primary care needs to be reconsidered. Sickness absence due to back pain in the UK increased in the last decade by 40% compared with sick-leave due to all other causes, which increased by 5.6%. The aims of the study are to test the hypotheses that: a general exercise programme for sub-acute back patients would reduce the loss of functional ability, compared with standard practice in primary care; and an individual's fear that exercise or activity would be detrimental to his back condition, will lead to a reduction in function.

Phase 1 will ascertain current practice and develop the outcome measures. In Phase 2, 300 patients from general practitioners' lists will be randomly allocated either to an exercise class once weekly for 8 weeks, or to 'standard' primary care management. Patients who take part in the study will be assessed by the research physiotherapist, by means of questionnaires and simple physical tests, before and after the intervention and at 6 months follow-up. Repeated measures of analysis of variance will be used to assess differences between the groups over time. Economic evaluation of the intervention will be carried out by means of a cost-effectiveness analysis.

(SOURCE: arc archive)

Box 2.1: Abstract

three of the reviewers (including the most supportive one) were fed back, along with comments from the award committee discussion, and the PI was specifically invited to re-apply. This application, it was claimed, included as far as possible responses to the points raised. The summary of the assessments of the referees is given in Table 2.1.

Table 2.1: Summary of assessors' report

	High	Medium	Low	None
Originality of project	B, D	A, C		
Potential value to rheumatology	A, B, D	C		
Potential practical value	A, B, D	C		
Appropriateness of overall project design	D	A, B, C		
Suitability of methods	D	A, B, C		
Feasibility within time proposed	B	A, C, D		
Standing of applicant in this field	D	A, B, C		

The three referees who had rated it as "possible support" all stated that the application had been improved. Referee A, therefore, changed his overall rating to one of strong support. Referee B felt there were still some issues that needed clarification, for example, in relation to recruitment of patients, and stated that he remained uncertain until the information requested was supplied. Despite stating that the application had been improved, Referee C still had reservations about the lack of clinician input, for example, and generally shifted his position to give lower scores and an overall assessment of "no support". Referee D, who was strongly supportive the first time around, did not rescore the application but stated that he was even more supportive because his questions had been addressed. His first-round scores are shown on Table 2.2 along with the scores given to the revised application by the other three referees.

2.4 Stage 1: inputs to research

The arc grant was for £143,000, but additions brought the final figure to about £150,000. The original application had sought funds for an economic evaluation to be an integral part of the trial. arc decided not to fund this, but funding for it was provided by a grant of £10,000 from the National Back Pain Association. The Northern and Yorkshire NHS Executive provided £50,000 as an extension to arc funding.

The research, which is sometimes known as the York Back Pain Trial, was conducted from the Centre for Health Economics at York University which, with its vast research experience, was able to offer academic support and liaison in terms of medical statistics, research methodology, project management and computing. Its director was a co-applicant and the Centre provided the health economist for the project. The other co-applicant was director of the Centre for Research in Primary Care at the University of Leeds which provided support for the project in a clinical and advisory capacity.

The research physiotherapists and coordinator recruited for the project did not have previous research experience.

2.5 Stage 2: research process

There were some initial problems, including the illness and eventual resignation of the original research physiotherapist and with patient recruitment. Eventually, however, more GPs were brought into the study and patient recruitment reached satisfactory levels (187) for the analysis to be conducted.

After some of the initial difficulties were addressed the study seemed to run generally smoothly and, as will be seen, has been highly rated in several external studies for the methods that were used. Furthermore, articles describing the methodologies used have attracted quite a bit of interest.

2.6 Stage 3: primary outputs from research

2.6.1 Knowledge (payback category A)

We identified seven peer-reviewed articles that could be described as coming from the project, although only four acknowledged arc funding.

Torgerson and others (1996) focuses on one of the key methodological issues in the project. Drawing on data from the first 97 patients that were enrolled, it concludes that "it is sometimes feasible to randomise patients to their less preferred treatment, thus allowing more robust statistical comparisons between randomised groups", and goes on to daim that this modification "may make RCTs more rigorous and improve their external validity" (p. 194). This has generated quite a bit of interest and been cited on various occasions, even though it was not published in a journal included on the citation indices.

Klaber Moffett and others (1999), published in the *British Medical Journal* (BMJ), is the main account of the research and its key findings: an exercise class is more clinically effective than traditional GP management, regardless of patient preference, and is cost

effective. This has already been cited an above average number of times for an article in the BMJ. One of the citing papers (Herbert and others 2001) consists of an account of a database of RCTs and systematic reviews in physiotherapy (PEDro) in which trials are rated for methodological quality. In addition to a general account of PEDro, Herbert and others describe the findings from a small selection of the several thousand trials and reviews in physiotherapy. The ones that are included are described as "recent systematic reviews or high quality clinical trials with clear conclusions and with potential to improve quality of life" (2001, p. 788), and so the inclusion of Klaber Moffett and others (1999) could be taken as a sign of the quality of that study. Another of the citing articles also serves to demonstrate the wide range of existing research in the field of conservative management of low back pain by including Klaber Moffett and others (1999) as one of 174 references (Frank and De Souza 2001).

Frankel and others (1999) does not acknowledge arc funding, but describes a study that was conducted as an adjunct to the main study. It was based on analysis of patient notes and referral notes of potential subjects for the larger study and was undertaken by the lead author for his Master in Public Health degree. It suggested that the gap between GP practice and recent guidelines appeared to be reducing, but many variations in practice still exist.

Keen and others (1999) does not acknowledge arc funding, but instead a separate research training fellowship from the Northern and Yorkshire region is acknowledged. It funded the higher degree study of the lead author. Twenty-seven informants were chosen from the larger group of participants in the main arc study. A detailed qualitative study showed the importance of identifying, at the earliest possible stage, those patients that avoid physical activity and/or have a fear of pain, then tailoring advice and reassurance appropriately.

Bell-Syer and Klaber Moffett's (2000) article is methodological and, by taking the arc study as a case study, describes the issues involved in recruiting patients to RCTs. arc funding is acknowledged.

Klaber Moffett and Frost (2000) is in *Physiotherapy,* which is not included in the citation indices but is an important source of information for physiotherapists. It does not acknowledge arc funding, and does not really describe the research. Instead, it is a manual of how to conduct the "Back to Fitness" programme that was developed on the basis of the intervention used in the studies described in Frost and others 1995 and Klaber Moffett and others (1999).

Garrett and others (2001), in *Spine*, acknowledges arc funding and describes a comparison of the discriminatory power and responsiveness of three measures of health outcome that were used in the main study. The study concludes that the two specific instruments, the Aberdeen Back Pain Scale and the Roland Disability Questionnaire, are capable of greater levels of discrimination between groups of patients, and are more responsive over time, than the generic EuroQol (an instrument that incorporates descriptions and valuations of health states).

Selected bibliometric indicators for case study A

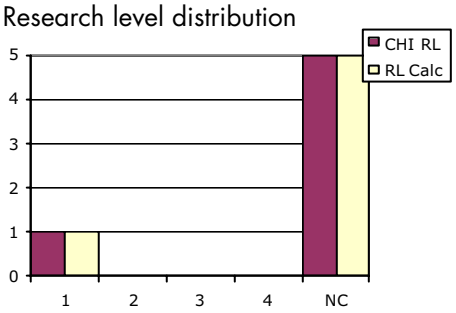
Publication portfolio

Output
- Number of papers 6

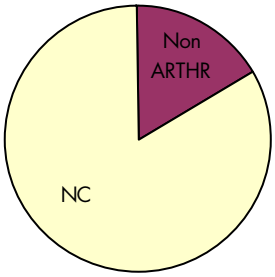
Collaboration
- Mean number of authors 4.2
- Mean number of addresses 3.0
- % with non-UK addresses 0%

Type

Research level distribution

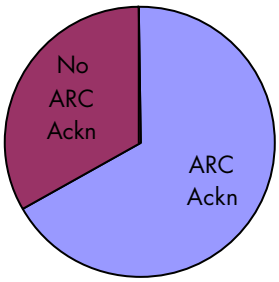


Field distribution



Funding
- Mean number of acknowledgements No data

ARC funding acknowledgements

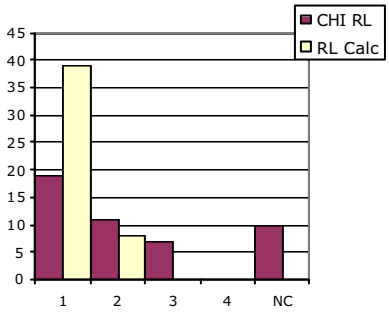


Knowledge flow

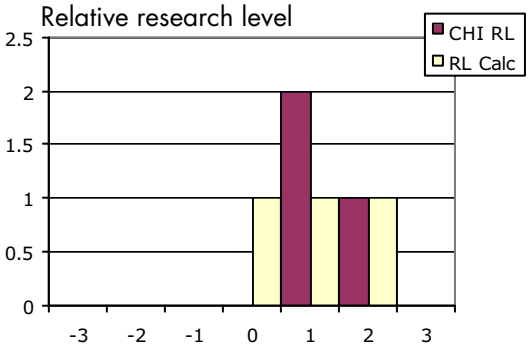
Strength
- Mean citations per year (all papers) 4.7
- Mean C0-4 19.0

Knowledge translation

Research level of citing papers

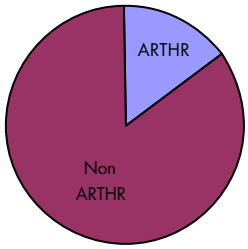


Relative research level



Knowledge diffusion
- % of citations from the US 26%

Field distribution of citations



Further publications will be appearing because an article based on secondary analysis of the data has just been accepted by *Spine*, and an article comparing the experiences of administering the arc trial and another trial in a similar field is in preparation.

2.6.2 Benefits to future research and research use (payback category B)

The project has resulted in considerable payback in terms of helping to target future research (payback category Bi). Further studies by the PI used the intervention and/or philosophy from the arc-funded project to varying degrees. For example, the Hull Exercise Programme for back pain patients is a randomised trial comparing individual physiotherapy with the general community-based exercise programme for patients with back problems. The UK BEAM trial is the major UK trial of treatments for low back pain. The greater than £2 million funding comes from the Medical Research Council (MRC) and the PI is one of the two clinical coordinators. An exercise package is one of the two interventions being tested:

> Building on previous small UK studies [Frost and others 1995; Klaber Moffett and others 1999] members of the MRC working party developed the *Back to Fitness* exercise programme … This trial will help to confirm whether:
>
> 1. This type of exercise programme is effective in the UK NHS, as much of the evidence is from Scandinavia and the US;
>
> 2. An exercise programme is effective among patients recruited from primary care, as most studies have either been in hospital or in the workplace;
>
> The *Back to Fitness* programme is effective when implemented nationally. (UK BEAM Trial 2003)

When the results from this trial are considered, one factor that needs to be taken into account is that the two interventions were compared with a control that consists of active management in general practice, based on a package that itself reflects recommendations from clinical guidelines and *The Back Book* (Roland and others 1996) (see Stage 4: secondary outputs). These recommendations concentrate on encouraging ordinary physical activity and positive attitudes to pain and, therefore, are very much in line with the messages of the "Back to Fitness" programme. They might reduce the scope for the specific intervention to make an additional impact.

Those responsible for running an acupuncture trial for low back pain discussed the details of organising the practicalities of issues such as patient recruitment with the arc trial coordinator. Some of these issues will form the basis of the forthcoming article mentioned above.

It was suggested by one interviewee that in a more general way, this project has had some influence on arc's research agenda. Despite the initial problems with recruitment, etc, the eventual success of the project played a part in encouraging arc to look more favourably at research involving the behavioural approach and involving the allied health professions (AHPs).

As is reflected in the account of the publications, the project provided various contributions to research training and the development of research capacity (payback category Bii). The studies described in Frankel and others (1999) and in Keen and others (1999) were based around the arc study. Furthermore, one of the co-authors of the BMJ article used data from the trial in her PhD at Imperial College, London. The project also provided research training for the two physiotherapists who were recruited to be the research physiotherapists on the project, and it was the first experience in research for the coordinator. As a result of their introduction to research, both physiotherapists took masters' degrees, although not as part of the project. One moved to Hull with the PI and worked with her on many of the subsequent research and dissemination activities. He now focuses on encouraging evidence-based physiotherapy practice. The health economist on the arc project has also worked with the PI on subsequent trials and he (and the trial statistician on the arc project), are part of the UK BEAM Trial.

It is suggested that, as a result of their experiences, some of the research physiotherapists involved in one of the subsequent trials would be more likely to implement the research findings in general.

2.7 Interface B: dissemination

The PI gave many presentations at academic and professional meetings and quite often the findings from this research featured in those meetings. Both academic interviewees thought that they had encountered the work at such meetings, even before reading the main article. At least one of the physiotherapists stated that she had heard of the work at professional meetings.

The article in *Physiotherapy* could be seen not only as a primary output, but also as a major form of dissemination because the journal is widely read in the profession. Previous studies have shown the importance of the role that can sometimes be played in dissemination by articles in journals that are widely read by practitioners (Hanney and others 2003).

In response to the interest generated by the article in *Physiotherapy,* in particular, the PI and one of the research physiotherapists ran a series of study days on the "Back to Fitness" programme. These were held at approximately six locations around the country, at the request of local physiotherapists, and at Hull. Three out of the five physiotherapists included in this study attended a study day at Hull, and the remaining two organised, and attended, a study day in their own location. One of the latter reported that her study day was oversubscribed. All five found the study day to be useful, with one explaining, for example, how helpful it had been to work through the specific exercise programmes. One physiotherapist described how she and her colleagues had read about the programme in the *Physiotherapy* article and heard it described at a meeting. They decided to put it into practice, but she also attended one of the study days to ensure that they were implementing it as intended, which indeed turned out to be broadly the case. The two physiotherapists who organised study days conducted evaluations and, although the fitness instructors who also attended one study day raised questions about elements of the exercise programme, the responses from the attendees were generally most favourable.

2.8 Stage 4: secondary outputs – policymaking; product development

It is difficult to identify examples of where this arc project has clearly had an important impact on guidelines or other policies at a national level. *Effective Health Care Bulletins* generally build on reviews of RCTs conducted by the Cochrane collaboration, summarising evidence rather than making firm recommendations. The bulletin on acute and chronic low back pain (Centre for Reviews and Dissemination 2000) noted that, because of the timing of the main publication, the arc study had not yet been included in the relevant Cochrane review. The bulletin described the main results from the study, but also observed that the patients appeared to be 'a heterogeneous group and the findings should therefore be interpreted with caution' (2000, p. 5).

A recent systematic review of conservative interventions for sub-acute low back pain, conducted by Pengel and others (2002), was unable to pool the evidence from the 13 studies included because they differed with respect to intervention, outcome measures and timing of follow-up measurement. However, it did assess the methodological quality of the studies using two lists of criteria. On both lists the arc-funded study had the highest score out of the 13 studies: 5/9 and 12/19.

At a somewhat different level, as one of the exemplar studies showing the benefits and impact of research, the study was used in a report to a Higher Education Funding Council for England/Department of Health (HEFCE/DoH) task group examining research capacity in nursing and allied health professions (AHPs), (Task Group 3 2001). The task group used that report in making its case for more resources for research in these fields, a position that was partially accepted in the later policy statement from HEFCE and DoH (HEFCE 2002).

The role of *The Back Book* (Roland and others 1996) again highlights the difficulties of identifying the extent to which an individual's overall contribution to policy and practice change comes from one of their specific studies. Of course, this is on top of the problems of identifying the contribution of any one individual when there are many working in the field. *The Back Book* has perhaps a semi-official status in that it was published by the Stationery Office and is linked with the Royal College of General Practitioners (RCGP) clinical guidelines for the management of acute low back pain. The book does not contain any references and predated the completion of the arc study. It was produced by a multidisciplinary team of leading researchers.

The significance of the arc study, in addition to being generally in line with the philosophy of *The Back Book,* is that perhaps it helped to provide the PI with the credibility to be the physiotherapy researcher on that team.

The general policy move towards more active management of back pain was set out not only in the RCGP guidelines, but also in guidelines from the Clinical Standards Advisory Group (CSAG) (1994). Within the overall trends, the arc project seems to have had an influence on local policies. This is nicely captured by one interviewee, who described how the lead clinician in a NHS trust's chronic pain service decided that something should be done to identify people earlier and, where appropriate, treat them in the community. He arranged for a post to be established, the job description for which was to review the evidence and then set up a programme based on the evidence. When the review was

undertaken, the BMJ article describing the arc project was identified as the most relevant publication and a decision was taken to establish back rehabilitation classes, modelled on the "Back to Fitness" approach. Local guidelines for physiotherapy referral to the classes were developed and now local guidelines for the management of back pain are being developed. Another physiotherapist described how the "Back to Fitness" approach influenced the relevant section of the care pathway for back pain for a conurbation covering a number of primary care trusts.

One of the physiotherapists who was interviewed has played a part in introducing the exercises from the "Back to Fitness" approach within the National Back Pain Collaborative, a national project promoted by the Modernisation Agency. The exercises from her back rehabilitation programme, which is a modified version of the "Back to Fitness" approach, will be appearing on the Collaborative's website.

Finally, the work is beginning to appear on reading lists in physiotherapy schools, according to at least one interviewee, and another referred to it as beginning to have an influence on training packages within the fitness/leisure industry.

2.9 Stage 5: adoption – by practitioners and public

The problem of attributing change (in this case in relation to the activities of practitioners) to a specific study is an enormous, and somewhat artificial, task. However, there is some evidence from the interviewees that the "Back to Fitness" programme is being adopted in at least some places. Each of the five interviewees described how they had been involved in establishing and running a programme based on, or influenced by, the "Back to Fitness" programme. On the one hand, this overlaps partially with the previous section, because decisions to establish such programmes could not be taken without some level of agreement and cooperation within the organisation in which the physiotherapists were working, and thus at some level there was a policy decision which counts as a secondary output. On the other hand, each of the physiotherapists interviewed had become actively involved themselves in adopting a programme based on "Back to Fitness"; in this way the classes represent direct applications of the findings. In every case the exact nature of the programme differed somewhat from the "Back to Fitness" programme, while being influenced by it. But this is something that happens often as innovations in health care, and elsewhere, are adopted in practice (Berwick 2003). The classes were run in a variety of settings: health care facilities (including ones in the community); community centres; and leisure centres.

As noted above, several interviewees observed that the PI's work was but one contribution to a field that had been developing for some time, with an increasing interest in the biopsychosocial approach and guidelines from bodies such as the CSAG (1994). Nevertheless, one of the influences that the PI has had is that because she is a physiotherapist, and it is physiotherapists who often carry out the treatments, her work provides a role model and is written in a form that is accessible to working physiotherapists when dealing with patients. Most of the interviewees felt that the approach was being adopted in various parts of the country.

However, the numbers involved are often not very great. Many of the primary care trusts run just one such class a week, and they are not always full. Two main problems have been identified: in some cases, a less than optimal rate of referral by physiotherapists or GPs; and in certain places, especially socially-deprived inner-city areas, a high DNA ("did not attend") rate. Both issues, but especially the first, are being actively addressed.

2.10 Stage 6: final outcomes

Without knowing the extent of application of the findings, it is extremely difficult to make an overall national assessment of the final outcomes in terms of benefits to the health sector, such as health gains and possible cost savings, and benefits to the economy in terms of reduced working days lost. Nevertheless, the arc study did show that there could be some, albeit sometimes rather small, gains in these fields. The exercise class "was more clinically effective than traditional general practitioner management" (Klaber Moffett and others 1999, p. 279). At six weeks after randomisation the intervention group had improved marginally more than the control group on the disability questionnaire and reported less distressing pain. At six months and one year, the intervention group showed considerably greater improvement in the disability questionnaire score. Similarly at one year, the intervention group showed significantly greater improvement in the Aberdeen Back Pain Scale. In addition, the exercise classes were cost-effective and the extra cost of providing them, as compared with ordinary GP management, tended to be outweighed by a combination of the fewer health care resources that were used by the intervention group in the year following the intervention and the fewer working days that were lost by the intervention group. However, the mean difference was not statistically significant. Nevertheless, if the "Back to Fitness" programme is being provided instead of traditional individual physiotherapy, potentially there could be some cost savings in the actual provision of services; one interviewee suggested that, for this reason, her managers were very supportive of the programme.

In terms of broader economic benefits, the figures from the trial show that the intervention group reported only 378 days off work, compared to 607 for the control group (Klaber Moffett and others 1999).

In the article in *Physiotherapy* (Klaber Moffett and Frost 2000), and in the study days, those implementing the "Back to Fitness" programmes were encouraged to conduct audits of the results. Most of the physiotherapists who were interviewed have conducted some type of assessment after the completion of the programme. These generally show satisfaction with the course and a reduced fear of exercising. Naturally, there are no cases of the evaluations being as extensive as in the trial and covering items such as lower use of health care resources and fewer days off work. However, generally these were seen as being likely outcomes.

Quite extensive data about outcomes from the classes in West Wiltshire have been presented at a conference and are reproduced here. Figures are available for 120 participants who were pre- and post-measured on three scales: the Tampa Scale of Kinesiphobia (TSK); Roland Disability Questionnaire; and Functional evaluation test (sit to stand). The results are shown in Table 2.2.

Table 2.2: Results from pre-testing and post-testing of participants in the back reactivation programme

		Mean	Range
TSK (max 68)	Pre	39	(19–63)
	Post	34.6	(18–63)
RDQ (max 24)	Pre	11	(1–24)
	Post	8.7	(0–24)
Sit to stand	Pre	14.2	(4–32)
	Post	24.6	(6–67)

Table 2.3 shows the percentage figures for various assessments, including whether the participants achieved their short- and long-term goals.

Table 2.3: Results by the end of the last session of the back reactivation programme

Improved function	83% (13% missing)
Reduced disability	54% (missing 20%)
Reduced fear of re-injury	55% (missing 20%)
Would do programme again	90%
Fully achieved short-term goal	37%
Achieved 50–100% of short-term goal	65%
Fully achieved long-term goal	21%
Achieved 50–100% of long-term goal	60%

Further results were obtained after one year, and these showed 70% reduction in disability and fear of re-injury.

While detailed figures are available for just one of the five examples reviewed in this case study, it is important to note the similarity with the results from the RCT.

Overall, this case study has been able to move from the original research and its primary outcomes, through the dissemination and adoption stages to identified long-term outcomes.

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CHAPTER 3 Case study B: occupational activity and hip osteoarthritis – a case control study

3.1 Introduction to the research project

The research project assessed occupation activity as a risk factor for osteoarthritis (OA) of the hip (hip OA) using a case control study. The study was a collaboration between researchers at the MRC Environmental Epidemiology Unit, Southampton and the School of Postgraduate Medicine, University of Keele.

Osteoarthritis is the commonest form of joint disease, in which there is damage to the surface of the joint and an abnormal reaction in the underlying bone. The hip is a ball-and-socket joint, linking the pelvis and the leg. The rounded head of the thigh bone (femur) sits in the socket (acetabulum) of the pelvis, both of which are separated by cartilage and synovial fluid in the joint to prevent the bones from rubbing (National Audit Office 2000). Hip OA causes wearing away of the cartilage, making the joint rough and difficult to move. At least 210,000 people in the UK have X-ray evidence of moderate to severe hip OA,[1] with 30,000 people requiring total hip replacements (arthroplasties) each year in England and Wales at a cost to the NHS of some £140m (National Audit Office 2000).

At the time of the study, it was felt that an increased understanding of the risk factors associated with hip OA could lead to preventative public health strategies, in order to reduce its prevalence in the general population.

This case study is based on desk research of arc archival material, review of the research literature feeding into and resulting from the study, further desk and web-based research on other outputs and outcomes and semi-structured, face-to-face interviews with the three co-applicants and one (of two) research nurses.

3.2 Stage 0: topic/issue identification

The idea for the project was initiated by the principal investigators and subsequently submitted for funding in open competition. The proposed project arose from three

[1] See the arc website: http://www.arc.org.uk.

observations in the literature. The first was the higher prevalence of hip OA in farmers than other, sedentary jobs, leading to the hypothesis that different types of occupation activity was a risk factor for hip OA (Croft, Coggan and others 1992). The second was the development of a definition of radiological hip OA, based on "minimal joint space", ie the shortest distance between the femoral head margin and the acetebulum (Croft and others 1990). The third was the research training and methodological development for a similar study assessing the risk factors associated with knee OA, which was supported also by the Arthritis Research Campaign (arc). Each of these points are explored in more detail below.

In the proposal, the applicants cite a 1966 French paper (Louyot and Sarvin 1966) which first showed an association between hip OA and agricultural work. More contemporary studies were cited for Sweden (Vingard and others 1991) and the UK (Croft, Coggon and others 1992; Croft, Cooper and others 1992) confirming that the occupation most closely related to the development of hip OA has been farming. For example, a cross-sectional survey in populations sampled from general practices demonstrated that the prevalence of hip OA was nine times higher in those who had farmed for over 10 years than in control groups (Croft, Coggon and others 1992). However, whether the OA was caused by heavy lifting, body vibration from agricultural machinery or walking on uneven ground remained unclear, as most farmers carried out a range of activities. Thus the authors conclude that "the answer may come more easily from studies of other occupational groups who are exposed to either heavy lifting or whole body vibration, but not both" (Croft, Coggon and others 1992, p. 1271). Moreover, as the authors note, if the risk of hip OA is associated with heavy lifting or body vibration then it will not be confined to farmers, but will occur also for other occupations exposed to similar activity. Three of the co-authors on the British studies were co-applicants for the project, and in our interview with the principal investigator (PI) he confirmed that this "self-citation" was because the research team had published "the main body" of research in this area, as opposed to "grantsmanship".

The second opportunity supporting the proposal was a comparative study to establish the best radiological definition of hip OA for epidemiological studies (Croft and others 1990). As with the farming prevalence study, all but one of the co-authors were co-applicants for the project. The authors compared seven radiologic indices of hip OA and concluded that:

> [M]inimal joint space … is the best radiological criterion of the disease for epidemiological studies [because:] (1) the selected criterion should correlate with symptoms; (2) it should relate to other accepted radiologic features of the disease; (3) its measurement should be repeatable within and between observers; and (4) it should be easy to use. (Croft and others 1990, p. 519)

The final piece in the puzzle was the award, by arc, of a two-year project grant in 1989 to the PI to undertake a case control study on physical activity and knee OA. The project had two supporting consequences. First (and as noted by the PI in the proposal for the hip study): "The project was of major significance in developing my ability to independently administer research funds, and provided a crucial step in my research career." Second, was the development and reliability testing of an interviewer-administered questionnaire inquiring about occupational history, physical activity at work and leisure, cigarette smoking, alcohol consumption, medical and drug history, reproductive variables and functional status. The majority of the questions used in the knee study were also used in the study on hip OA.

These three strands came together in a grant application made to arc in November 1992 (see Box 3.1 for abstract). The stated objectives of the study were:

> To assess the risk of hip OA in occupations which entail repeated lifting on prolonged whole-body vibration and to assess the level of risk in relation to the frequency and severity of these exposures.
>
> To identify other risk factors for hip OA (adiposity – ie, a state of obesity – oestrogen status, trauma, developmental abnormality, cigarette smoking, alcohol consumption) and to study interactions between them.

The application was for a two-year project grant worth £84,747.[2] The majority of costs (£76,686) were for the salaries and employment "on-costs" for two researcher nurses over two years (one per site). An additional £8,720 was requested for stationery, postage, data processing and interview travel.

Osteoarthritis of the hip (hip OA) is a major cause of morbidity and health expenditure in Britain. The aim of the proposed case control study is to test the hypothesis that certain types of occupational activity are risk factors for hip OA. Four hundred cases with hip OA that are consecutively placed on orthopaedic waiting lists for hip surgery in two districts will be compared with 400 community controls matched by age, gender and general practice. Information on exposure to risk factors (occupational and leisure activity, body build, trauma, smoking, alcohol consumption and, in women, reproductive variables) will be obtained using an interviewer-administered questionnaire. Support is requested for the salaries of two research nurses to administer this study and perform the interviews.

(SOURCE: arc archive)

Box 3.1: Abstract

3.3 Interface A: project specification and selection

The research proposal was reviewed by four referees. A summary of their assessments is given in Table 3.1 (note that the letters A–D indicate the different referees' assessments). This information is based on the assessor's report form submitted to arc (see Annex B for a blank copy of this form). Three of the referees (B–D) stated their "strong support" for the proposal; referee A gave his/her "possible support".

Table 3.1: Summary of assessors' report

	High	Medium	Low	None
Originality of project	B	A, C, D		
Potential value to rheumatology	B, C, D	A		
Potential practical value	B, C	D	A	
Appropriateness of overall project design	B, C, D		A	
Suitability of methods	B, C, D		A	
Feasibility within time proposed	A, B, D	C		
Standing of applicant in this field	B, C, D			

[2] The equivalent of £111,333 in current value.

The concerns raised by the dissenting referee (A) were threefold:

- the cases and controls needed to be stratified by age, gender and occupation, in order to avoid oversampling of elderly females;
- there will be differential recall between those with OA and those without; and
- the controls will need X-rays to make certain that their joints are not abnormal.

We explored referee A's comments with the PI in order to assess whether, with the benefit of hindsight, they were legitimate. The PI argued that:

1. stratification was addressed by matching controls for age and gender;
2. differential recall was a concern, but this was examined in a contemporary paper by Campbell and others (1997); and
3. X-raying controls were a "matter of philosophy" – one school of epidemiology, to which the research team subscribe, is that the control group should reflect the heterogeneity of the population. The alternative view is that controls should be absence of the disease which requires passive or invasive interventions, be they X-rays, MRIs or, at the extreme, an operation.

3.4 Stage 1: inputs to research

The arc award was for £79,406 over two years. The small reduction in the value of the grant was associated with the salaries of the two research nurses, although no justification for this is given in the archive material.

In addition to the direct cost of the research, the three co-applicants stated that they would spend a total of 14 hours a week on the project,[3] which is one-third of a full-time equivalent (assuming a 40-hour week). The MRC Environmental Epidemiology Unit, Southampton and arc Epidemiology Research Unit, Manchester provided the research setting within which to perform the studies. The indirect costs borne by these centres is difficult to estimate, but at minimum should be acknowledged as an input into the research.

Finally, it is worth noting that previous funding from (the then called) Wellcome Foundation "enabled the research team to lay the foundations of [their] research into the epidemiology of hip OA".[4] The papers defining OA for epidemiological studies and on hip OA in farmers acknowledged the Wellcome Foundation as the sole funding source.

[3] This must be seen as a lower-bound estimate as one applicant did not fill in this piece of information, the second stated 10 hours and the third, four hours.

[4] In exploring this comment with the PI, it was clarified that it actually referred to a training fellowship of one of the research team which did "provide the foundation" for that person's career.

3.5 Stage 2: research process

There was a delay in recruiting the two research nurses for the study, with the start date for the Southampton arm of the study being delayed by four months (from 1 February 1993 to 1 May 1993) and for the Keele arm by just over eight months (to 25 October 1993), with a subsequent knock-on effect to the end of the grant.

Neither of the co-applicants nor the research nurses we spoke to could recall any problems with the actual research. Response rates for the control arm of the study were high reflecting, in the opinions of one of the interviewees, the engagement of the elderly participants.

Although the grant terminated in 1995, the median publication date of the peer-reviewed output was 1998 (range 1996–2002). The delay in the formal termination of the study and publication of its findings was, according to the PI, normal for epidemiological research. Thus, in effect, the arc study covered the costs of data collection while the indirect costs associated with data-entry, data-cleaning, analysis, writing and managing the peer review process were borne by the MRC through their support for the Environmental Epidemiology Unit.

3.6 Stage 3: primary outputs from research

3.6.1 Knowledge creation

We identified, and agreed with the lead co-application, six peer-reviewed papers resulting from the project grant. Cooper and others (1996) was a review on the relationship between occupational physical activity and the risk of hip OA. This paper was a result of the normal process of reviewing the literature that goes into developing and establishing a research project. The paper concludes that:

> [T]here is clear epidemiological evidence that occupational activity is a contributor to the risk of osteoarthritis of the hip and knee … Studies are consistent in documenting an increase in risk of hip osteoarthritis among agricultural workers, but the precise mechanism for this association remains the subject of study. (Cooper and others 1996, p. 681)

Cooper and others (1998) and Coggon and others (1998) were published consecutively in the same issue of the *American Journal of Epidemiology*. Cooper and others demonstrated that obesity, previous hip injury and polyarticular involvement are independent risk factors for hip OA. This led the authors to conclude that:

> [The] condition arises through an interaction between a generalized predisposition to the disorder and specific mechanical insults to the hip. Obesity and hip injury are important independent risk factors for OA that might be amenable to primary prevention. (Cooper and others 1998, p. 521)

Coggon and others demonstrated that occupational lifting is a cause of hip OA in men. As noted above, this builds on previous work that showed an association between farming and hip OA and leads the authors to conclude that "hip OA [is] an occupational disease in men whose work has entailed frequent heavy lifting over long periods" (Coggon and others 1998, p. 527).

Dennison and others (1998) is interesting inasmuch as the role of hormone replacement therapy (HRT) on hip OA in women was not mentioned in the original project proposal and was not an explicit aim of the study. The reason for this was because it was an ancillary question that emerged during the study. The authors demonstrated that surgical oophorectomy (excision of the ovary) is associated with an increased risk in hip OA and concluded that:

> [O]ur observations add to other epidemiological studies in suggesting that oestrogen deficiency in post-menopausal women is associated with an increased risk of hip OA, and that post-menopausal use of HRT, if continued for > 5 years, might reduce the risk.

Like Dennison and others, Yoshimura and others (2000) was not proposed in the grant application. In one sense this is an example of a payback category *Bii* – benefits to future research and research use: the development of research skills, personnel and overall research capacity (see Volume 1, Chapter 2, Box 2.1) – as the identical method of data collection developed, for the originally proposed project was applied to Japan and the study was influential in the career development of the PI. In contrast to the UK, the results of the study suggested that obesity, previous hip injury and a tendency toward polyarticular involvement are not associated with hip OA in Japan. However, as in the UK, heavy lifting in the workplace was associated with the risk of hip OA.

The final paper, Croft and others (2002) was published some seven years after the termination date of the grant. It describes the results of the questions on health status that were included in the study. The authors found that both physical and social functioning were restricted in patients with hip OA, however such patients' own perception of their health status showed little difference with the controls. That is "mental health, energy and vitality seemed unaffected by the presence of advanced hip OA" (Croft and others 1992, p. 1004). One of the interviewees stressed the important of this finding and how it is opening up a new research field into the psychosocial factors associated with neck pain, back pain and upper limb pain.

3.6.2 **Research targeting, capacity building and absorption**

As noted above, Yoshimura and others (2000) is a good example of category *Bii* payback as it utilised the development of research skills and methods and applied them to another setting – in this case, Japan. In addition, a subsequent arc project grant awarded in 2001 has used the baseline data collected in this study to assess the determinants of incidence and outcome of total hip replacements.

In addition the study was influential on the careers of all the participants to whom we spoke. At the time of the study, one of the three co-applicants had a chair, compared to all three at the time of interview. The PI felt that it built on the work that he had previously undertaken on knee OA, which was his first competitively-won grant. Another co-applicant described the study as "absolutely pivotal" for his career. One of the research nurses who was recruited into the study team subsequently stayed at the research unit and has collaborated with the co-applicants on numerous related studies since that time.

Selected bibliometric indicators for case study B

Publication portfolio

Output

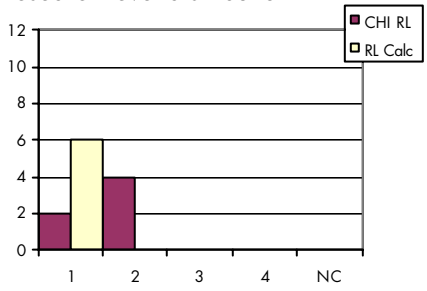
Number of papers	6

Collaboration

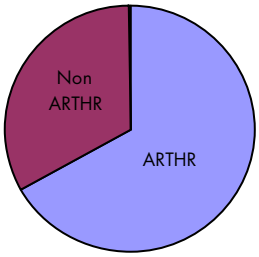
Mean number of authors	6.8
Mean number of addresses	2.7
% with non-UK addresses	16.7%

Type

Research level distribution



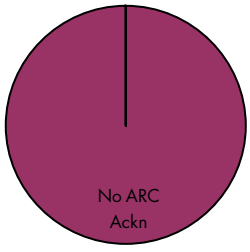
Field distribution



Funding

Mean number of acknowledgements	0.2

ARC funding acknowledgements



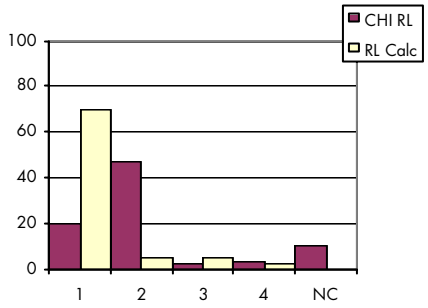
Knowledge flow

Strength

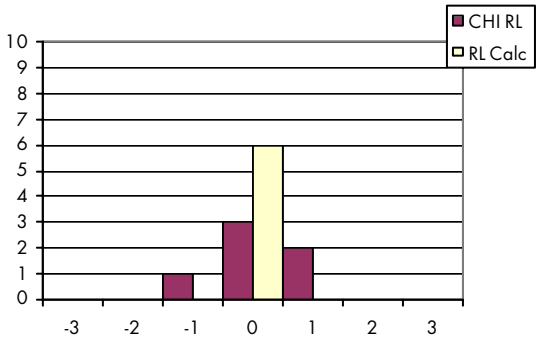
Mean citations per year (all papers)	7.7
Mean C0-4	13.0

Knowledge translation

Research level of citing papers



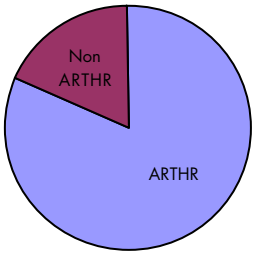
Relative research level



Knowledge diffusion

% of citations from the US	35%

Field distribution of citations



3.7 Interface B: dissemination

The PI claimed that there was a large amount of dissemination activity, ranging from abstracts at various national and international meetings to regular speaking commitments at various academic institutions. This was confirmed by the co-applicants; however (and understandably), a list of such activity was not maintained and therefore it is not possible to assess this independently. Another co-applicant referred to using the material in postgraduate teaching, including to scientific advisers in government and other regulatory bodies.

3.8 Stage 4: secondary outputs – policymaking; product development

3.8.1 Informing policy and product development

Four out of the 76 cited articles were in a series of systematic reviews published by Lievense and others (2001, 2002, 2003), providing an "improved information base on which to take political and executive decisions". Two of the primary output papers – Coggon and others (1998) and Yoshimura and others (2000) – were included in the systematic review on the influence of work on hip OA. Iievense and others (2001) identified a total of 16 studies (including two other papers authored by the research team, Croft, Coggon and others 1992; Croft, Cooper and others 1992) and concluded that "the available evidence in the literature indicates that there is moderate evidence for a positive association between the amount of physical workload and the occurrence of hip OA" (Lievense and others 2001, p. 2526). Interestingly, this paper – and the others by Lievense and colleagues – included a quality assessment of the studies in the review. Quality scores were calculated on the basis of a series of specified criteria. As illustrated in Table 3.2 the arc-sponsored papers were high in terms of quality.

Table 3.2: Quality scores of cited papers in systematic reviews

Review / Cited paper	Number of papers	Quality score %	Median quality score (range)
Lievense and others (2001)	16		62 (23–77)
Coggon and others (1998)		69	
Yoshimura and others (2000)		77	
Lievense and others (2002)	13		60 (15–77)
Cooper and others (1992)		69	
Lievense and others (2003)	9		62 (54–77)
Cooper and others (1992)		69	

The other two reviews on obesity (Lievense and others 2002), and sporting activity (Lievense and others 2003), also conclude that there is "modest evidence" of an association between the risk factor and hip OA.

In addition to being cited in three systematic reviews, Cooper, Inskip and others (1998) was cited in the Dutch Association of Physiotherapists' clinical guideline for hip (and knee) arthritis, and the body of research informed the Industrial Injuries Advisory Council (IIAC) assessment of whether sufficient evidence exists to warrant adding hip OA as a prescribed disease (Department for Work and Pensions 2003). The guideline was developed in 2001 and therefore does not include the articles of Lievense and others. Interestingly, we could not find any citations to the five primary outputs in UK-published clinical guidelines.[5]

The IIAC published advice in November 2003 (Department for Work and Pensions 2003), recommending that "osteoarthritis of the hip in farmers should be added to the list of prescribed diseases for benefit purposes". This advice was reached on the grounds that doubling of the risk[6] for hip OA has been demonstrated in farm workers but not for other occupations. Assuming this advice is accepted by the Secretary of State, this means that anyone who has "engaged in employed[7] work for at least 10 years in aggregate as a farmer, farm worker or farm manager; and has been diagnosed with osteoarthritis of the hip, or has had osteoarthritis of the hip prior to surgery of the hip" (Department for Work and Pensions 2003, p. 6) will be entitled to Industrial Injuries Disability Benefit.

The advice was made on the basis of oral evidence, written evidence and a review of the scientific literature. One of the co-applicants was invited to give an oral presentation to the Council. In addition, of the 18 scientific papers reviewed, one was a direct output of the current study (Coggon and others 1998), and one was a systematic review (Lievense and others 2001) that cited outputs of the study.

3.9 Stage 5: Adoption – by practitioners and public

3.9.1 Health benefits

Assuming that the Secretary of State accepts the advice of the IIAC (at the time of writing there is no reason to believe that he will not), then the health benefits of this new policy will be realised in a number of ways. First, employed farm workers with hip OA will receive Industrial Injuries Disability Benefit which, one assumes, will have in impact on their health status and quality of life. Second, it is likely to raise awareness of other occupational-related musculoskeletal diseases which, arguably, may have an impact on working practices and thus health.

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[5] We used the NHS National Electronic Library for Health Guidelines Finder, searching on the term "hip osteoarthritis", to reach this conclusion. We identified two guidelines, but neither cited the primary outputs given in Annex A.

[6] "Doubling of risk" is the epidemiological interpretation of "on the balance of probabilities", which is that threshold for benefit as set down in the Social Security Administration Act 1972.

[7] Note that this excludes self-employed farmers.

3.9.2 **Broader economic benefits**

The adoption of the IIAC recommendation will cost the Exchequer additional benefit payment. In due course it would be interesting to undertake a cost–benefit analysis of this change in policy.

3.10 **Stage 6: final outcomes**

3.10.1 **Health benefits**

Although the applications of the research have not been fully realised, the PI believes that research will result in an economic benefit from a healthy workforce and a reduction in working days lost, ie, payback category E, *Broader Economic Benefits*.

This is for two reasons. First, the European Union's manual handling regulations should reduce the prevalence of occupational activity-associated hip OA. The second route is via litigation. For example, the PI has been involved as an expert witness in a successful case demonstrating a relationship between occupational activity and knee OA. If other cases are pursued in the area of hip OA, then it is likely that companies will take preventive measures. However, and as one of the co-applicants pointed out, against this background the age-for-age incidence of occupational related hip OA should decline as occupational activity with heavy lifting declines.

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CHAPTER 4

Case study C: a comparison of the tissue inhibitors of metalloproteases TIMPs 1 and 2 by biochemical and biological approaches

4.1 Introduction to the research project

The research project investigated the basic biochemistry of the proteins involved in the destruction of cartilage and other connective tissue in joints. The grant focused on two proteins: the tissue inhibitors of metalloproteases 1 and 2 (TIMPs 1 and 2). These proteins were known to inhibit matrix metalloproteases (MMPs), proteases that play an important role in cartilage destruction. The study was carried out at the Strangeways Research Laboratory in Cambridge.

One of the key processes in arthritis and rheumatism is the destruction of cartilage and connective tissue (Murphy and others 2002). In healthy joints cartilage covers the end of each bone, it acts as a shock absorber and allows the ends of the bones to move smoothly against one another as the joint flexes. In arthritis and rheumatism the cartilage is damaged and roughened, and this often leads to pain and stiffness. MMPs play a key role in the destruction of cartilage by breaking down molecules of the extra cellular matrix (ECM) that make up cartilage. There was evidence that MMPs were overactive in the joints of patients with arthritis and, as such, they are an obvious target for therapeutic intervention (Murphy and others 1990).

It was thought that TIMPs played an important role in inhibiting MMP activity in the body (Docherty and others 1985) so it was hoped that an understanding of TIMPs–MMP interaction would prove useful for the development of therapeutics to block MMP activity and prevent cartilage damage.

At the beginning of the grant five MMPs had been cloned and sequenced along with two TIMPs, although the identification of TIMP-2 was relatively recent (Docherty and Murphy 1990). Cloning of the genes was key as it allowed large quantities of the proteins to be produced that could then be used for biochemical analysis. This grant was one of a portfolio of grants held by the lead principal investigator (PI), including a senior research

fellowship (SRF) from arc – all of these grants looked at other aspects of MMPs and TIMPs.

This case study is based upon: documentary analysis of the relevant arc files, publications from the project and key citing papers; researchers' CVs; bibliometric analysis; face-to-face interviews with three members of the research team; and a long-term industrial collaborator.

4.2 Stage 0: topic/issue identification

The idea for the project grew out of the stream of work that was being pursued already by the PI; it was submitted to arc in open competition (the grant abstract is shown in Box 4.1). At the time of application the PI was already an established researcher working on MMPs, having been awarded an arc project grant in April 1988 and a five-year SRF in October 1989. These earlier grants focused on the biochemistry and biological importance of the MMPs and TIMP-1, a protein which the PI had been involved in identifying in 1985 (Docherty and others 1985).

The new grant was written to take advantage of the discovery of TIMP-2 in 1989 (Stetler-Stevenson and others 1989) and the possibility of comparing the properties, mechanism and distribution of the two inhibitors. The PI's group had been working to identify the second TIMP also at the time, but had been beaten to it by Stetler-Stevenson and colleagues.

Initially, the PI had been attracted to the field of MMPs because of the opportunity to apply her biochemical skills to what she felt was an important but poorly understood family of proteases; although she was initially attracted by an interest in the scientific problem rather than its relevance to arthritis. She also felt that she would benefit from being part of the critical mass of researchers working in similar areas at Strangeways.

In addition to the intellectual reasons for applying for the grant, there were a number of pragmatic reasons:

- to provide assured and continuing support for her team. The PI's arc senior research fellowship only supported her salary and consumables without providing support for additional staff. At the time, her assistant was supported on the PI's previous arc project grant which was due to end in April 1991; the PI's part-time technician was supported on a variety of short-term grants and industrial collaborations;
- to provide support for her assistant to do a PhD, because of his unusual academic route it was unlikely that he would be able to obtain an ordinary PhD studentship;
- to expand her research after she had established a range of techniques and reagents in the first year of her SRF. Adding project grants to her funding portfolio was an effective way to do this.

A comparison of the relative efficacy of the tissue inhibitors of metalloproteinases, TIMP-1 and TIMP-2, in the binding and inhibition of the known connective tissue metalloproteinases is proposed. The mechanism of inhibitor interaction with active metalloproteinases would be analysed, using chemical and recombinant DNA techniques for protein modification, as well as the reason for their different specific binding to proforms of the gelatinises. The expression of TIMP-1 and TIMP-2 by connective tissue cells in culture and in a number of diseased tissues of the cells *ex vivo* in synovial joints would be studied. Both the biochemical and biological information gained would contribute to our understanding of the importance of these inhibitors in degenerative events in connective tissues and the potential for the development of therapeutic agents modelled on their structure and mechanism of action.

(SOURCE: arc archive)

Box 4.1: Abstract

The application was for a three-year project grant worth £153,204. This was the sixth largest project grant awarded in our sampling window, the majority of which was in order to support the salaries of the PI's assistant and technician.

The application was broken down into three main strands of work:

1. preparing natural and recombinant MMPs and TIMPs;
2. using natural and recombinant MMPs and TIMPs to investigate the properties of the proteins and their mechanisms of interaction; and
3. investigating the distribution of the TIMPs in normal and diseased tissues and comparing TIMP distribution with that of other molecules of interest including MMPs and cytokines.[1]

4.3 Interface A: project specification and selection

The research proposal was reviewed by three referees. A summary of their assessments is given in Table 4.1(the letters A–C indicate the different referees' assessments). This information is based on the assessors' report form submitted to arc (a blank copy is provided in Annex B).

Referees A and C "strongly supported" the proposal, referee C considering it an "excellent grant application" and expressing the opinion that the PI would "undoubtedly complete the work in three years". Referee A concurred, suggesting that the work "can honestly be described as being at the cutting edge of modern research". Referee B was less positive, describing the application as "competent and solid". Specifically, referee B wondered whether two people were really needed for the grant and was concerned about possible overlap with other work that was being undertaken at Strangeways, suggesting that it could all be consolidated into one programme grant. Conversely, referee C felt the employment of two supporting researchers was reasonable and again, referee A agreed, noting that "the application is undoubtedly expensive but … well justified".

[1] Messenger molecules that affect the activity of cells.

Pursuing his concern about overlap, Referee B asked for a copy of the abstract for the Wellcome Trust project grant "An Assessment of the Role of Two Newly Discovered Matrix Metalloproteases: a Specific Inhibitor in Connective Tissue Destruction", which was also held in the laboratory. Before consideration of the project grant application by the arc Research Subcommittee, the PI sent this abstract to arc along with a letter explaining why the grants did not overlap. The discussion in the Research Subcommittee seems to have mirrored the assessors' comments, with a feeling that the grant was "A" rated but expensive. In addition, the committee seems to have taken into account that the PI was not a typical senior research fellow as she was also unit head; hence they were more willing to support additional staff.

None of the referees made suggestions for methodological improvements and their comments do not appear to have been sent to the PI. The PI did not recall any referees' comments.

Table 4.1: Summary of assessors' report

	High	Medium	Low	None
Originality of project	A, C	B		
Potential value to rheumatology	A, C*	B		
Potential practical value	A, C*	B		
Appropriateness of overall project design	A, C	B		
Suitability of methods	A, C	B		
Feasibility within time proposed†	A, B			
Standing of applicant in this field	A, C	B		

*C put "?" in High

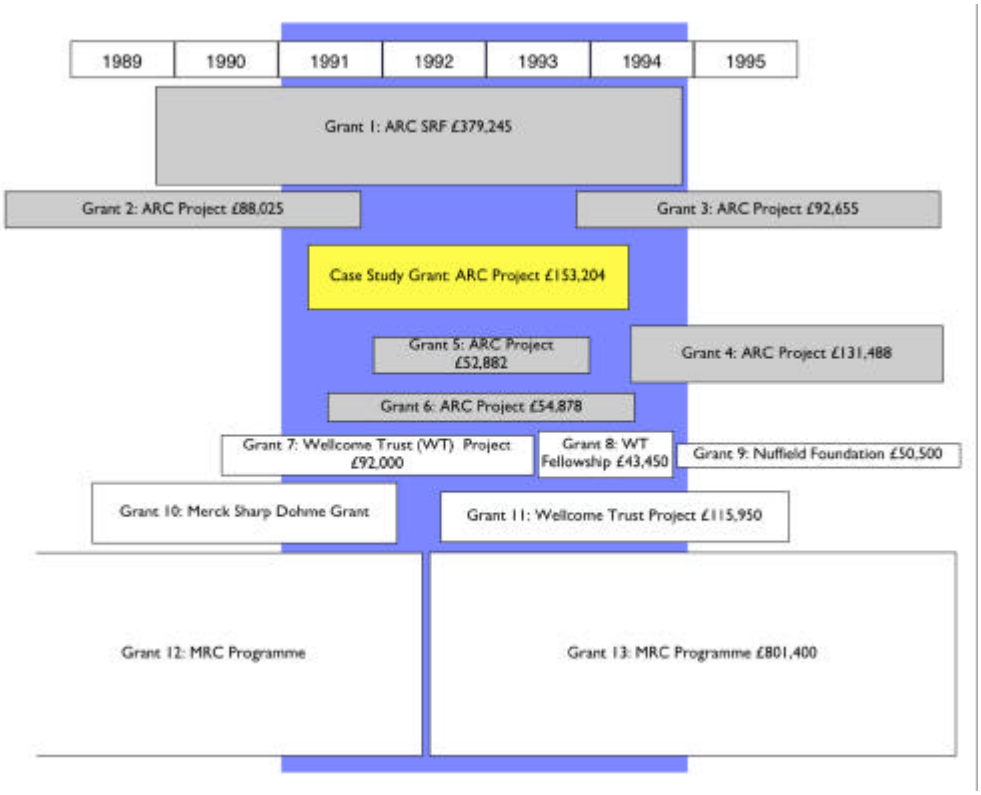
†No comment was given by C

4.4 Stage 1: inputs to research

4.4.1 Funding

arc awarded the full grant, worth £153,204.[2] Approximately half of this money was for the salaries of the assistant and part-time technician (£74,151) in addition to their "on costs" (£16,817). Consumables and reagents, etc made up £36,700 and £6,386 was requested for equipment purchase costs, mainly for molecular biology. In addition to this was a 15% "establishment cost" of £19,150 (an overhead cost that had been agreed between Strangeways Research Laboratory and arc). Strangeways is an independent charity rather than part of a university, so all of its overhead costs have to be found from the research grants that its researchers receive. This means that the overheads of this grant were probably funded from a variety of sources (including a similar establishment cost levied on the PI's senior fellowship) and from the other grants and industrial collaborations which the group held. An indication of the complexity of the issue can be seen in Figure 4.1, which shows the portfolio of grants held by the PI in the period surrounding this project grant. This figure underestimates the number of grants held, as no single comprehensive source was available and the record has been reconstructed from information on various

[2] The equivalent of £208,000 in current value.



Grant 1: "Molecular studies of connective tissue metalloproteases and matrix turnover"
Grant 2: "Metalloprotease activation and matrix degradation"
Grant 3: "Development of antibodies to mouse MMPs to analyse their roles in joint physiology and pathology"
Grant 4: "Structure and function relationships of the MMPs"
Grant 5: "Analysis of novel modes of MMP activation and binding to extra cellular matrix"
Grant 6: "The raising of monoclonal antibodies and the development of ELISA-based assays to measure TIMP-2 in the tissue culture media and body fluids"
Grant 7: "Two new MMPs and TIMPs an assessment"
Grant 8: Title unknown
Grant 9: Title unknown
Grant 10: "Cytoplasmic regulation of MMP expression" (exact amount unknown)
Grant 11: "Determination of structure and function of TIMPs"
Grant 12: Title unknown, held by JJ Reynolds but also supported the work of the PI
Grant 13: "Cellular control of tissue destruction"
(NB: only grants within the blue shaded time window are included)

Figure 4.1: Grants held by the PI around the time of the case study grant

later applications. The figure certainly underestimates the importance of industrial collaborations. In later years the agreement between arc and the Strangeways Laboratory about establishments costs broke down, and the establishment costs were struck out of the PI's senior research fellowship renewal in 1994.

4.4.2 **Human capital**

The PI's assistant had been working with her already for five years, during which time he had gained a graduateship from the Institute of Biology (first class) and was an expert biochemist. The PI's technician was experienced in cell culture and also proficient in carrying out the biochemical assays required for the project. The skills of both of these individuals were an important input into the grant.

4.4.3 Techniques, reagents and equipment

One of the key inputs to the grant was the availability of reagents and techniques in the PI's laboratory. Many of these reagents had been generated as part of the PI's previous work, and much of the first year of her SRF was dedicated to putting the necessary reagents and techniques in place. These included: purification protocols for the MMPs and TIMPs; enzyme-linked immuno-sorbent assay (ELISA) detection techniques for TIMP-1; polyclonal antibodies to TIMP-1 and TIMP-2; and clones of TIMP-1 and TIMP-2. The ability to produce large quantities of recombinant TIMPs and MMPs was also important for the grant and this was one of the important contributions of the PI's industrial collaboration with a group at Celltech.

4.5 Stage 2: research process

The first two strands of the work proceeded much as laid out in the grant application, with no major changes of direction. The final strand of work, which looked at distribution of MMP and TIMP expression using electron microscopy and immunofluorescence,[3] proved harder than expected and the results of this work were not published within the timeframe of the grant. Another researcher in the PI's laboratory subsequently managed to get these techniques to work and published papers detailing the distribution of MMPs and TIMPs.

One of the key features of the process was a close and ongoing collaboration with researchers at Celltech who were working in the same area. This collaboration was very productive and many of the papers attributed to this grant are jointly written with researchers at Celltech. The key to the success of the collaboration was the fit between the different skills of the collaborators and the personalities involved; in essence, the PI had valuable expertise in cell culture and Celltech could provide molecular biology expertise. Celltech had become interested in working with the PI when she cloned TIMP-1, as this was a natural inhibitor of the MMPs with possible therapeutic potential. The advantages of this collaboration to Celltech were, amongst others:

- the kudos of being associated with pre-eminent researchers in the field – an association which also helped them to build contacts with other researchers and companies through the PI's extensive network of contacts;
- the PI's expertise in culturing cells from tissue samples of human and animal tissue, her biochemistry skills and the opportunity to train their researchers in these skills in the PI's laboratory; and
- the intellectual input provided by the PI and her group into the work of the Celltech group.

For the PI the collaboration also had a number of distinct advantages:

- the opportunity to learn molecular biology techniques that were relatively rare in academia at the time. Much of this occurred during a six-month secondment in Celltech's laboratories at the beginning of the grant;

[3] A technique using antibodies labelled with fluorescence dye to identify proteins or other cellular components.

- access to technology and techniques, including facilities for producing large quantities of recombinant proteins and protein-sequencing facilities; and
- the opportunity to see her work taken forward into clinical development.

The collaboration also provided valuable opportunities for the PI's assistant to present his work and gain positive experience of industry which, in turn, influenced his later career choices.

Just under a year before the grant was due to finish, the PI's assistant accepted a job in industry; this prompted a series of salary transfers. Initially, the remaining salary was transferred to a postdoctoral researcher who had done her PhD in the PI's laboratory; however, this researcher had a change of heart and decided that she wished to spend more time with her family. The remainder of the funds was used to extend the support of the PI's technician to carry her over until the PI's SRF renewal, which included a salary for the technician. The PI said that arc's flexibility in transferring remaining salary was crucial to allowing the research to continue, in this and other cases.

4.6 Stage 3: primary outputs from research

4.6.1 Knowledge creation

Because of the diverse portfolio of grants that were held by the PI during the time of this grant, their similar subject areas, and the fact that the laboratory was run – as the PI commented – with "one pot of money", it is very hard to attribute cleanly the outputs to the grant. In total, during the years of the grant (1991–1994) the PI published 58 papers. The PI suggested (and her assistant agreed) that as the assistant's PhD formed much of the grant, a minimum set of papers attributable to the grant could be found, taking into account only the papers co-authored by the PI and her assistant. A few other papers, chiefly those authored by the assistant but not the PI, have been added to the list at the suggestion of other interviewees.

The papers that were claimed for the grant in its first end of year report are notable because they have submission dates before the start of the grant. Murphy and others (1991) was submitted on 27 March 1991, and covers mainly work on the specificity of different MMPs (an area of work which is not included in the grant application), so we have excluded it from the list of papers attributed to the grant. The other paper, Ward, Hembry and others (1991) was submitted on 21 December 1990, and appears to be mentioned in the grant application as "Ward et al, submitted".[4] This paper details the purification of TIMP-2 from cell culture; as it falls within the work described in the grant application we have included it in the list of papers attributed to the grant. These papers illustrate two issues of attribution. First, that researchers may include papers that do not seem directly related to the grant as grant outputs. Second, it lends credence to the suggestion that on occasion, researchers begin the work that is described in a grant application before the grant commences, possibly to ensure that the initial stages of the grant appear productive.

[4] A full reference is not given in the proposal.

The identification of TIMP-2 had been a close race between the PI's laboratory and her US-based competitors, so during 1991 publication speed was of great importance. This explains why the first paper clearly attributable to the grant was published in *Biochimica and Biophysica Acta* as a "Rapid Report" in August 1991 (Ward, Atkinson and others 1991). This paper examined the relative effectiveness of TIMP-2 and TIMP-1 inhibition, using *in vitro* methods and native proteins. It also suggested that components on the outside of the cell membrane were important in activating MMPs. Three papers in the following year extended this work by reporting on the importance of TIMP-2 in controlling the activation of various MMPs and also the role played by plasmin (another extra-cellular protease) in MMP activation (Atkinson and others 1992; Murphy, Ward and others 1992; Murphy, Atkinson and others 1992). Knight and others 1992 was a very different paper describing the development and synthesis of an new artificial substrate for MMPs. This fluorescent substrate allowed more sensitive assays of MMP activity and could be used at concentrations that mimicked the concentration of natural substrates *in vivo*. The importance of this development is shown by the 314 citations that this article has received since publication.

The final paper of 1992 marks the beginning of the analysis of TIMP–MMP interactions and the mechanisms of MMP activation, looking at the level of individual domains (parts) of the protein rather than at complete proteins (Murphy, Willenbrock and others 1992). This more detailed level of analysis was allowed by the production of recombinant proteins missing various domains. This theme of domain analysis continues through papers in 1994 and 1996 (Fujimoto and others 1996; Hayakawa and others 1994; Ward and others 1994). Analysis of the TIMPs moved to a new level of detail in 1993 with the successful crystallisation of the truncated form of the protein, the first step towards determining the protein structure (Tolley and others 1993). Finally, the initial indications of an important role for external cell membrane proteins in the activation of MMPs are followed up with further work pointing to the importance of a membrane-bound MMP in activation of other MMPs in Atkinson and others (1995).

In addition to the research papers described above both the PI and her assistant contributed to a review of how MMP activity is regulated in 1994 (Murphy and others 1994). As the salary of her assistant was paid from the grant we have included this as an output.

When comparing the publications against the three streams of work mentioned in the grant application, it is notable that the final strand looking at the localisation of the expression of TIMPs appears to be almost absent. Discussions with the PI confirmed that perfecting the necessary techniques to carry out these studies took far longer than anticipated, but that the work was continued and developed in the laboratory after the grant ended, principally by another researcher in the laboratory who was not funded on the grant.

4.6.2 **Research targeting, capacity building and absorption**

Although the PI was established already as an independent researcher, this grant provided a solid foundation for her research group. The PI has gone on subsequently to become a professor of cancer biology, although she is still working on the biochemistry of the same proteins. The PI's principal industrial collaborator, who now holds a senior position with

Selected bibliometric indicators for case study C

Publication portfolio

Output

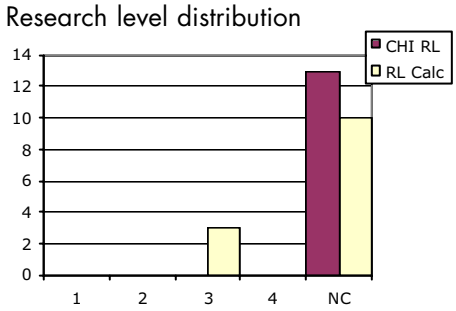
Number of papers	13

Collaboration

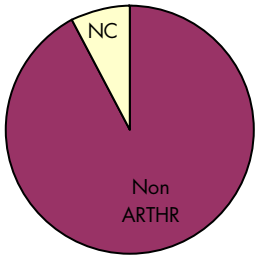
Mean number of authors	5.5
Mean number of addresses	2.2
% with non-UK addresses	23.1%

Type

Research level distribution



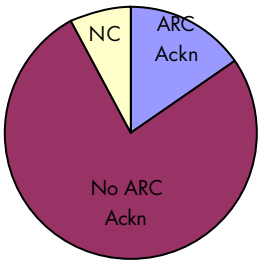
Field distribution



Funding

Mean number of acknowledgements	1.8

ARC funding acknowledgements



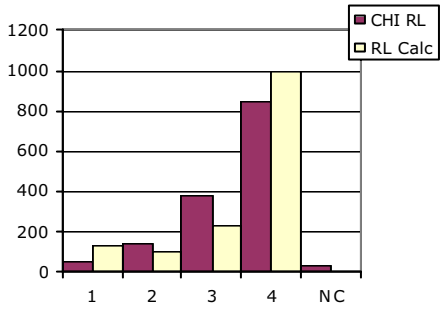
Knowledge flow

Strength

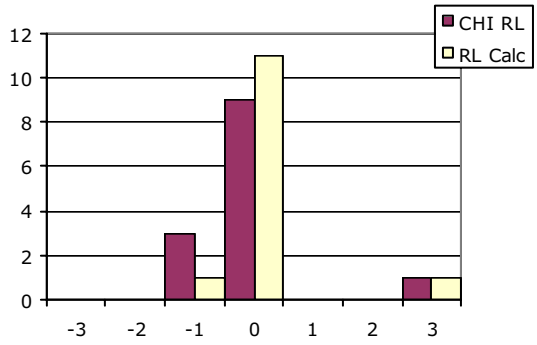
Mean citations per year (all papers)	118.5
Mean C0-4	46.3

Knowledge translation

Research level of citing papers



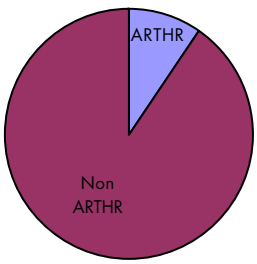
Relative research level



Knowledge diffusion

% of citations from the US	44%

Field distribution of citations



Celltech, also considers that his career benefited from the work done at the time of the grant and the publications attributed to the grant of which he is a co-author.

The grant also provided the foundation for the PI's assistant's career: he had joined Strangeways eight years earlier as a laboratory technician, and during the five years that he worked for the PI he had completed a graduateship of the Institute of Biology (achieving first class) and won the Darbre Prize for highest degree of the year. This qualification was equivalent to a bachelor's degree but often was not recognized as such; hence it would have been very difficult for him to win a standard PhD studentship. His PhD (which this grant supported), along with the PI's close industrial links, provided the foundation for his successful and continuing career in the pharmaceutical industry, which includes over 15 peer-reviewed publications.

The reagents, including the recombinant proteins, expression plasmids,[5] ELISA assays and antibodies produced during this grant, have been used by many other researchers; the PI suggested that they have been sent out to over 100 other researchers and clinicians. Also, new techniques and biochemical assays have been an important output of the grant, with the most highly-cited paper (300 citations) being a description of an enzyme assay for the MMPs (Knight and others 1992).

4.7 Interface B: dissemination

The PI said the research had been presented at many national and international conferences – a suggestion that was confirmed by other interviewees. However (and understandably), no records of these activities are available so it has been impossible to assess accurately the scope of these activities. The most important form of dissemination was probably the industrial collaboration with Celltech, which is discussed in the next section.

4.8 Stage 4: secondary outputs – policymaking; product development

4.8.1 Informing policy and product development

As a result of the PI's close collaboration with Celltech, and the PI's extensive network of contacts, her basic science research was built upon rapidly by industry. Initially, Celltech was interested in the possibility of using recombinant TIMPs as an injectable therapeutic, and the project advanced as far as the production of manufacturing runs of clinical quality TIMP-1. Celltech then decided that an orally active synthetic MMP inhibitor would be more clinically acceptable than recombinant TIMP-1, which had to be injected directly into the arthritic joint. For the programme to develop a synthetic inhibitor, Celltech focused on one MMP: stromelysin. Being a small biotechnology company, they partnered with Merck Sharpe & Dohme during the project for the use of synthetic stromelysin inhibitors in rheumatoid arthritis (RA). The PI's contacts were key in setting up this

[5] A plasmid is a small ring of DNA found outside the chromosome in bacteria. Plasmids are the principal tools for inserting new genetic information into micro-organisms or plants.

partnership and the PI attended the quarterly progress meetings for the project. Unfortunately, although much of the project was successful, when Merck Sharpe & Dohme produced a mouse with the gene for stromelysin knocked out, the mouse continued to suffer from RA and hence the project was abandoned.

While Celltech and Merck Sharpe & Dohme worked to produce synthetic inhibitors of stromelysin for RA, Celltech continued to investigate the use of stromelysin inhibitors in non-RA applications in-house, including their use for cancer and osteoarthritis (OA). At around this time British Biotech was promoting its anti-cancer MMP inhibitor-based drug Marmistat as a "wonderdrug". Celltech were not convinced that Marmistat was as effective as British Biotech were claiming, but felt that they either had to make similar claims for their MMP work or proceed cautiously with additional research work. In order to support this work they partnered the project with Zeneca (now AstraZeneca).

Subsequently, following the failure of Roche's anti-cancer collagenase (MMP) inhibitor Trocade in Phase III trials, AstraZeneca abandoned the anti-cancer use of the stromelysin inhibitor to focus on its use in OA. This project is ongoing and has been widened to look at inhibitors of other newly-discovered MMPs. As this story illustrates, inhibition of MMPs was seen initially as a very promising drug target; however, it has proved to be very hard to take advantage of therapeutically (as reviewed in Docherty and others 2003; Fletcher 2000).

Another important factor affecting the industry view of MMP inhibitors has been the phenomenal success of anti-Tumour Necrosis Factor (TNF) drugs, which have raised the bar for success in the treatment of RA. Anti-TNF drugs also have a number of advantages in the treatment of RA in that they alleviate the symptoms of inflammation (pain and swelling) in addition to slowing joint damage; MMP inhibitors would be expected only to slow joint damage, not to have such impressive effects on symptoms.

4.8.2 **Broader economic benefits**

Although the drug development projects have not produced registered products they have supported researchers and infrastructure in the biotechnology and pharmaceutical sector, contributing to the economy in terms of employment and tax revenue.

4.9 Stage 5: adoption – by practitioners and public

Because none of the drug development programmes that grew, in part, out of this research work have reached the stage of producing registered products, there has been no opportunity for adoption.

4.10 Stage 6: final outcomes

As no registered products have been produced, no final outcomes in terms of health gain can be attributed to this grant.

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CHAPTER 5 Case study E: osteoarthritis of the knee joint – risk factors, process and outcome

5.1 Introduction to the research project

Knee joint osteoarthritis (OA) is the most common condition to cause musculoskeletal pain and disability in the UK. arc estimates that at least 550,000 people in the UK show X-ray evidence of moderate to severe OA of the knee. In 2000, there were 35,351 total knee replacements carried out in the UK (see Guccione and others 1994; March and Bachmeier 1997).[1]

The knee joint is a complex apparatus consisting of the femur (thigh bone), the tibia (shin bone) and the patella (knee cap), which is attached to the thigh muscles and the shin bone by a large tendon. The knee joint is held in place by four ligaments located inside and along each side of the joint. In a joint affected by OA, the cartilage on the end of the femur, tibia or underneath the patella roughens and wears thin. In severe cases, this can lead to the bone ends rubbing directly against each other, leading to swelling, pain and deformity. As the cartilage wears away, the surrounding bone thickens, pushing the bones out of their normal position. This causes the capsule around the joint and the ligaments to contract and the muscles moving the joint to become thin, making the joint unstable. In a common complication, calcium crystal deposits form in the cartilage, irritating the synovium (membrane) surrounding the joint, causing chondrocalcinosis (serious inflammation and swelling).

The risk of developing OA of the knee increases with age, excess weight, physical stress and injury. The disease is twice as common in women than in men and is also more common in Afro-Caribbean and black people.

The research programme funded by arc built directly on previous research carried out by the team, who proposed to investigate (in an integrated manner) 10 specific questions relating to the origins, progression and treatment of the disease. All of these research strands were guided by the central hypothesis that the heterogeneity of outcome in patients with OA of the knee was due to variations in the involvement of different processes and tissues in different individuals. Furthermore, the team proposed that the disease progressed in phases. The programme thus held considerable potential for more

[1] See also http://www.arc.org.uk/about_arth/bigpic.htm#3.

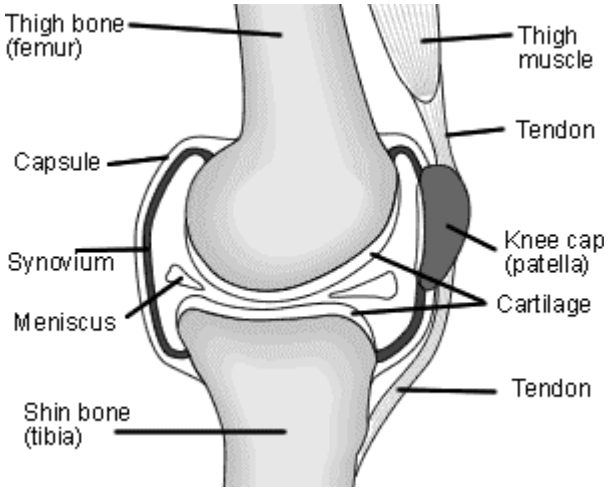


Figure 5.1: Anatomy of a normal knee joint

effective targeting of OA through intervention specific to the site, nature and state of the individual patient's disease.

To obtain relevant data, the team used a wide variety of approaches, including paleopathology, imaging and monitoring of biochemical markers and cytokine[2] activity.

This case study is based on interviews with the PI, the co-applicants and a postdoctoral member of the programme grant team. It also draws on arc archive material and the scientific publications resulting from work undertaken with programme grant support.

5.2 Stage 0: topic/issue identification

The applicants pointed out that even though OA was the most important of rheumatic diseases and caused a great amount of pain, so far it had attracted little interest on the part of research clinicians. The work of the team, by contrast, promised to make an important contribution to the understanding of this condition by providing a clinical background for basic science investigations. The value of this approach had been proven in the course of a previous arc-funded programme grant, which had also enabled the team to build an infrastructure of patient cohorts, equipment and collaborators. The application's choice of OA was motivated by the PI's traditional area of interest. By the time of the application, OA of the knee had emerged as the most painful of arthritic joint conditions in the patient cohort.

The following core areas of investigation had emerged from the team's work over the previous decade. The assessment of bone activity using scintigraphy (bone scans) had proved to be indicative of the future progression of OA and could be correlated with the

[2] Messenger molecules that control the activity of cells.

Our overall objective is to interrelate [the] different aspects of OA at a single joint site. This should lead to a better understanding of the condition, to the development of preventative strategies, predictors of outcome and new therapeutic goals. The objective can be achieved by extension of the current work, combined with a limited number of new patient and laboratory studies.

A central hypothesis is that the different tissues and processes are involved to a varying degree in different patients, explaining the heterogeneity of outcome, and implying that several different approaches to prevention and therapy are possible. For example, different imbalances of synthesis and degradation are potentially detectable in the knee joint; they should result in different states of the joint, and require different treatment. Multiple factors thus interact in a variety of ways to produce different categories of outcome.

The specific objectives of the programme are to:

(1) delineate the major associations or risk factors for OA in a patient population and in the community;

(2) assess the relative contributions of local knee joint dysplasia, and a systemic predisposition to OA of the knee joint;

(3) test a set of clinical hypotheses on the nature and progression of knee OA emerging from our current work;

(4) establish determinants of progression and outcome;

(5) establish a new patient cohort designed to allow us to study knee OA in the pre-clinical phase;

(6) relate local cytokine and enzyme production and levels in synovial fluid to the concentrations of putative biochemical markers of inflammation, degradation and repair;

(7) relate these *in vivo* biochemical changes to an *in vitro* test system of synovial fluid degrading activity on cartilage and to effects on OA chondrocytes;

(8) correlate clinical, imaging and biochemical changes with the pathology of the OA knee joint, including the gross anatomy of the bones;

(9) relate *in vivo* and *in vitro* biochemical findings to X-ray changes and health status, in a prospective framework; and

(10) test a variety of therapeutic strategies.

(SOURCE: arc archive)

Box 5.1: Abstract

localisation of technicium diaphosphonate in the affected joints. This called for further study of markers of progression and the underlying biochemical processes. In the area of basic science, it had been shown that cytokines, particularly IL-1 and TNF, not only played an important role in the pathology of rheumatoid arthritis (RA), but that there was an increased number of IL-1 secreting cells in the synovium of OA patients. In addition, it was found that animal cartilage, which had been used in previous research, reacted differently to cytokines than human cartilage. These findings called for a more detailed investigation of the activity of cytokines and its effect on different joint tissues.

The choice of research areas was influenced further by the availability of new technologies: biochemical markers and MRI (Magnetic Resonance Imaging) scans.

To carry out the proposed programme, the applicants requested a sum of £556,315.75[3] for five years. This was to cover salaries for five full-time and one part-time staff (£403,696.05), equipment (microscope, refrigerator centrifuge, enzyme-linked immunosorbent assay (ELISA) plate, microcomputer, £41,370) and running costs (£111,250, including £22,500 for MRI scans).

5.3 Interface A: project specification and selection

The merit of the proposed programme of research was assessed on the basis of a letter of intent, a written research proposal and a site visit during which the team presented its work to a group of experts.

5.3.1 Assessment of the letter of intent

In the letter of intent, the applicants proposed to examine process and outcome in both RA and OA. However, members of the arc committee scrutinising the submission assessed the scope of this proposal as too wide.

The demand for a better-defined focus led the team to redefine their research aims in the written programme application. Rather than examining OA in conjunction with RA, the applicants would study OA only and would focus on the knee joint as a specific site. Several reasons were given for this choice. During previous research, OA of the knee had emerged as both the most common and the most painful of arthritic conditions; the disease was heterogeneous; synovial fluid and tissue samples were easy to obtain; and the knee was a common site of chondrocalcinosis. No patients or policymakers were involved in this choice of area.

Along with the redefined research programme, the applicants proposed a revised budget of £556,315, which exceeded the sum requested in the letter of intent by £100,000.

When interviewed, the PI considered the restriction to a more closely defined area of research as justified and helpful. However, the team did continue its work on RA, supported by other grants.

5.3.2 Assessment of the written research proposal

The application was reviewed by four referees. All of the referees were UK-based and had a clinical background, although two of them were engaged in basic science research. A summary of their assessments is given in Table 5.1 (the letters A–D indicate the different referees' assessments). This information is based on the assessor's report form submitted to arc (a blank copy is available in Annex B). All of the referees gave an overall assessment of "strong support".

[3] £806,000 in current figures.

Table 5.1: Summary of assessors' report

	High	Medium	Low	None
Originality of project	A, C	B, D		
Potential value to rheumatology	A, D	B		
Potential practical value	A	D		
Appropriateness of overall project design	A, B, C	D		
Suitability of methods	A, B, C, D			
Feasibility within time proposed	A, B, C, D			
Standing of applicant in this field	A, B, C, D			

There was consensus among the four referees that that the team were at the forefront of research in their area and that the programme proposal was highly promising. However, there was some unease regarding the amount of funding requested (£556,316 for five years). While generally very supportive, referees A and B felt that the budget could be sanctioned only after the site visit, especially after inspection of the staff whose salaries would make up the bulk of the requested funding. Referee B recommended a non-rheumatological expert review of the epidemiological aspects of the proposed research. Referee D was the most reserved, although his ratings did not go lower than three "mediums" (originality, practical value, project design). He questioned the team's "absolute need" for equipment items 2 and 3 (refrigerated centrifuge and microcomputer).

During the interview, the PI pointed out that the requested equipment had been necessary, as data collection had been vital to the proposed research.

5.3.3 Assessment based on site visit

The visiting team was composed of three UK-based scientists and one international referee, all of whom had a clinical background, although their research areas covered basic science and epidemiology as well as clinical studies. All the members of the team were impressed with the applicants' track record, novel and well-planned proposals, enthusiasm and the PI's leadership. However, in their comments the referees made it clear that in their opinion, the team's clinical studies held greater promise than the scientific programme, which "would not be in the front line of innovations in its field". During the interview, this assessment was challenged by the PI, who argued that the referees failed to understand the novelty and potential of the work of the basic scientists on the team, which has since received international recognition.

Overall, the referees were satisfied with the team and research plans and recommended the award of the requested sum without further amendments.

5.4 Stage 1: inputs to research

5.4.1 Financial inputs

The programme grant

arc granted £556,315.75 for the programme over five years, as requested by the team. In addition to this, the team was awarded a travel allowance of £2,000. According to a later application for an extension or follow-up grant, the programme grant amounted

retrospectively to £571,315, an increase that was probably due to funding supplements during the programme, as outlined below.

Programme grant add-ons

In November 1990, the team's request for an additional £15,254 over five years was granted, in order to be able to recruit a postdoctoral researcher (rather than the more junior researcher that had been originally envisaged) in order to raise antibodies. The group argued that this would enhance the group's self-sufficiency, as recommended by the site visitors.

In accordance with its standard policy, arc also granted a three-month salary extension of £7,056 to cover the employment of one of the postdoctoral researchers between the end of their employment under the programme grant and news about the outcome of a separate project grant application.

Overheads

The research setting for the programme was provided by the local university and hospital. The overheads were paid for by the university, which received a sum equivalent to 25% of the researchers' salaries towards staff management. Through an informal agreement with the head of the Department of Medicine, the PI's teaching commitments were reduced in order to enable him to devote more time to his research.

Other funding

Over the five years of the programme, the group received funding from several other sources, including a variety of other arc grants, as shown in Figure 5.2 below.

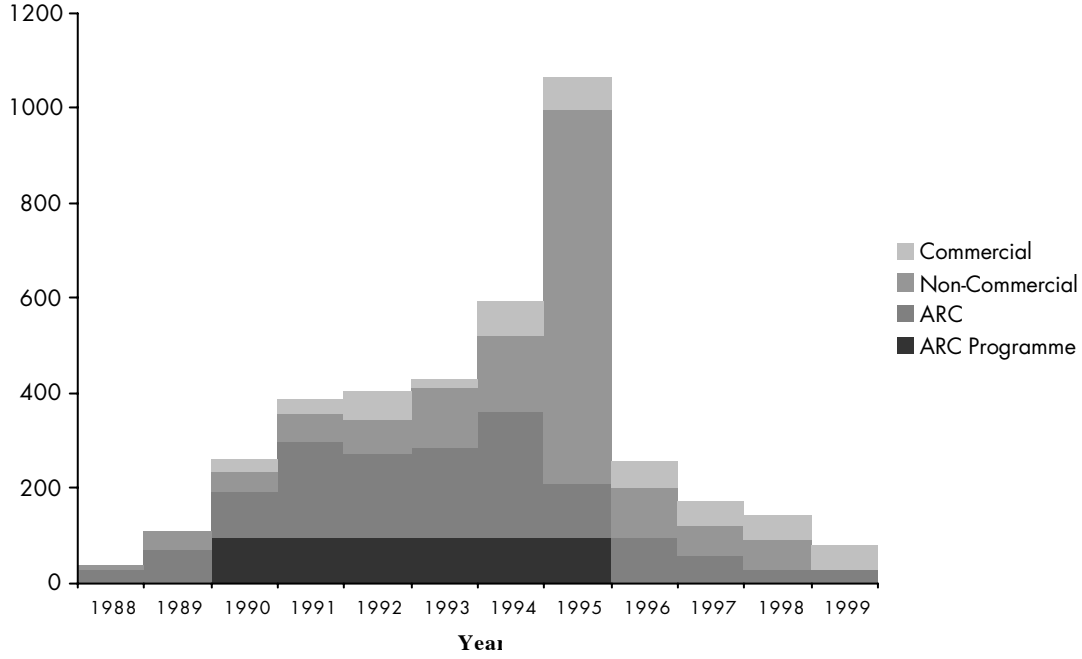
Unspecified other funding

The general practitioner (GP) part-time research fellow working with the team on early OA was in receipt of unidentified "funding from charitable sources".

5.4.2 Human capital

At the time of the application, research into OA at the host institution had been supported by arc and other funding bodies for many years, and its researchers had built a reputation as leaders in the field. The expertise of the co-applicants in measurements, RA and basic science enabled the team to take an unusually global approach to the exploration of OA, combining clinical science with epidemiology, pathology, radiology and fundamental laboratory investigations. The close and longstanding collaboration of the applicants was of considerable value, as this helped to overcome the communication problems that often are perceived to divide clinicians and basic scientists.

The team members working on early OA recruited the help of two GP colleagues who worked part-time at the host institution. Through general practice, these collaborators recruited early knee OA patients, who were essential to the group's research but scarce in surveys of hospital outpatients. In addition, several PhD students, as well as junior clinicians not funded by arc, made an important contribution to the research programme.



NB: Three large grants from NHS R&D, the NIRC and Department of Health are responsible for spike in 1995

Figure 5.2: Amount of grant funding (shown as stacked bars) in relation to other funding received by the team, as detailed in the extension application of 1995 (additional industrial and charity/research council funding won before 1988 and after 1995 is not included)

5.4.3 **Techniques, reagents and equipment**

In the course of previous work, team members had developed specific systems and techniques. For example, the basic scientists had developed an *in vitro* system for assaying the degradative effect of human synovial fluid on human cartilage and the physiotherapist had extensive knowledge about the management and analysis of the patient cohort that had been established five years earlier. The team also benefited from a well-developed, customised infrastructure, as the programme research built on a tradition of OA research at the host institution. This infrastructure included an already established patient cohort, frozen serum and synovial fluid samples from previously studied OA patients as well as several cytokine assays. Under a previous arc project grant, the team had carried out a postal survey of 2,300 people which included a validated enquiry about knee pain. The team was able to set up a special rig for long leg radiographs in the host institution's Department of Radiodiagnosis and received vital scanning and imaging help from the staff there. Within the first two years of the programme, the team had two hours' use per week of a new MRI scanner at the host institution; this use was funded with industrial support.

Furthermore, the group received immortalised chondrocyte cell lines and non-arthritic cartilage from American research institutions. Various sources, mostly from North America, supplied antibodies and antigens for the study of biochemical markers.

5.4.4 Conclusion

All the interviewees agreed that while there were alternative sources of funding for the research undertaken by the team, the long-term support provided by arc through individual and successive programme grants had been central to the realisation of long-term studies, establishment of a sound infrastructure and employment of important specialist staff such as a biostatistician. The grants enabled the researchers to concentrate on their work rather than spend time fundraising and accounting for themselves at short intervals. The value of the human capital of the project, especially the collaborations within the team and with other researchers, was rated extremely highly.

5.5 Stage 2: research process

5.5.1 Mid-term site visit and review

Half-way through the research programme, the team submitted a detailed report which was peer reviewed, and requested a site visit in order to present findings and discuss new research avenues. Mid-term visits of this kind were not compulsory, but were recommended by arc.

5.5.2 International referees' comments

All of the three international referees, two clinicians and one basic scientist, gave very positive assessments of the team's abilities and the PI's leadership. Referee A had nothing but praise for the work produced by the team, in particular work on the definition of different OA patient subsets, the efficacy of various predictive factors for diagnosing and monitoring the progression of the disease, and the use of scintigraphy to predict progress and the correlation of crystal deposits with other biochemical parameters. The other two referees had criticism as well as praise, but differed in their assessment. For example, referee B considered the team's studies of impact loading as very interesting, whereas referee C pointed to another laboratory specialising in this field which was using more sophisticated methods. Opinions about the potential of the study of biochemical markers also differed considerably.

5.5.3 Site visitors' comments

The comments of the team of three site visitors, all of them clinicians, were preserved in the form of the individual's comments and a collective report. The individual referee was concerned mainly with the question of how to channel best the energies of the team. He also highlighted the benefit of establishing a new cohort of early OA cases, which would commit the team "to the primary care arena where the greatest potential lies for their ideas about intervention". He added that "pragmatic" non-steroidal anti-inflammatory drug (NSAID) studies in the primary care population would help to assess their overall cost–benefit effect on OA, an important area which had been overlooked by US researchers so far. The experiments with patellar taping, quadriceps strengthening and shock absorbing insoles seemed to him to be "really attractive bets".

Similarly, the collective report discussed the wide scope of the team's interests. While the visitors were extremely pleased with the progress of the clinical studies, the basic science work, especially the study on cytokines and biochemical markers, was considered to lack

"competitive critical mass". It was advised that the two postdoctoral researchers working in this area should concentrate on one specific hypothesis and consider collaboration with local biomechanics groups.

A referee assessing a subsequent grant application recalled that during the visit, referees had to encourage the group to publish in "internationally ranked journals", such as *Arthritis and Rheumatism*.

5.5.4 Responses by the team

The interviewees agreed that the site visit was helpful, as it made the team take stock of its work through the first half of the programme. While not all of the visitors' recommendations were followed, they did encourage the team to move towards the examination of milder OA and to limit the study of biochemical markers to the three or four most promising ones.

The PI disagreed with the referees' pronounced preference for the team's clinical, particularly biomechanical, work. In his opinion, the lack of appreciation for the achievements of the basic scientists at the time was due to the innovative nature of this work and the basic scientists' lack of self-promotion. The basic science postdoctoral researcher added that there was widespread prejudice against basic science undertaken in a clinical context. Reactions to the criticism regarding the choice of journals for publications varied. One of the co-applicants defended this decision by pointing out that the choice of journals was appropriate, as the papers were based on data collection. In contrast, the PI agreed that the team members should have sought more international platforms to publicise their findings.

5.5.5 Staff fluctuation

A highly-valued postdoctoral member of the basic science team was forced to take well over a year off for health reasons, which had an adverse effect on work progress and publication output.

The experienced full-time physiotherapist who occupied a full-time post from the initiation of programme left after the first three years. To fill the vacancy created by her departure, the group employed a less senior part-time physiotherapist and a nurse specialising in medical trails, for 18 and 13 months respectively.

5.5.6 Project-related difficulties

Supply and material problems

Due to the typically advanced age of knee OA patients, the OA500 patient cohort recruited in the early 1980s diminished over the period of the programme. Furthermore, the collection of specimens was hindered by irregular patient attendance and the already poor state of joints even in "early" OA cases. Group members assessing post-operative knees experienced supply delays due to operation waiting lists. The study of biochemical markers and cartilage degradation was affected by difficulties in obtaining non-arthritic synovial fluid and cartilage. The PI's contacts with pharmaceutical companies eventually enabled the team to establish a small collection of normal synovial fluid samples. Stricter regulations and some uncertainties regarding the storage of body parts also hampered the work of the team.

Persistent difficulties

The programme had established the clinical importance of the distinction between tibiofemoral and patellofemoral departments of the knee joint. However, assessment of the patellofemoral joint proved problematic.

5.5.7 Abandoned approaches, modified methods and new interests

Only half of the hypotheses proposed in the original application were followed up during the programme. The reasons for this were manifold.

On the one hand, the technology required for the planned work never developed, or potential sources of patient or collaborators melted away. For example, the team was interested in tibial osteotomy[4] as a comparative process, but this operation was superseded by knee replacement. The group's planned work on NSAIDs was abandoned due to relevant work being published by scientists in the US. In addition, some aspects of the work proved unexpectedly difficult, absorbing time that otherwise would have been spent on additional, less important work.

On the other hand, new, challenging questions took the place of older plans. For example, one of the postdoctoral researchers developed an assay and showed that the blood test used in the hospital to measure c-reactive protein (CRP) levels was not very sensitive. This redefined the range of "normal" CRP levels and demonstrated the importance of CRP in OA as well as in RA. The evidence of a time-lag between raised CRP levels and disease progression led to further investigation of the phasic nature of OA.

The realisation that knee OA is not a single entity, but that there is patellofemoral and tibiofemoral OA and perhaps further differentiations, was of considerable relevance to all the other work of the group. Imaging had to be adjusted to pick up the difference between the two diseases, and work on synovial fluids, biochemical markers and crystals, cartilage and chondrocyte responses had to refer to the site of disease.

The skeletal material examined revealed deep grooves and ridges in the subchondral bone of knees affected by OA. Consequently, the team decided to investigate this phenomenon further as well as the role of subchondral bone activity in the progression of OA.

According to the PI, the programme thus evolved to encompass three major strands of research:

1. the clinically significant subsets of OA;
2. the importance of subchondral bone activity in OA; and
3. the interaction between the cartilage and bone at cellular level.

5.5.8 Involvement of potential users

The collaboration of patients in the cohort was of major relevance to the programme, as there was a clear gap between X-ray evidence of OA and pain symptoms. Also, the group's biomechnical trials with shock-absorbing soles and taping techniques was based on changes

[4] In osteotomy a wedge is taken from, or inserted into, the femur to straighten the joint.

in patients' pain perception. However, there was little patient involvement beyond data collection.

5.5.9 Research targeting, capacity building and absorption (payback category B)

The group found that animal cartilage, which is normally used in the study of OA, was not a suitable replacement for human cartilage as it reacted differently from human tissues.

The programme also supported the work of one of the UK's only specialists in medical paleopathology (the only scientists in the world to collect and analyse data on arthritis in a large number of skeletons).

5.5.10 Informing policy and product development (payback category C)

The high-profile research carried out by the research team led to a second arc support grant and the opening of a fully integrated specialist rheumatology ward at the host institution in 1994.

5.6 Stage 3: primary outputs from research

5.6.1 Publications (knowledge production, payback category A)

When reviewing the group's application for an extension of the programme grant, one referee remarked that "the major criticism is that no blinding insights had come out of the programme". It was felt that imaging and marker studies had been performed in only relatively small numbers of patients and that the cytokine studies were not outstanding. There was consensus that the clinical, especially the biomechanical, research had been the most valuable.

However, the team made a range of novel contributions to the knowledge of OA. Although the team published some 50 papers over the five years of the programme, there was a considerable time-lag in the publication of some of the results of the research, especially in the basic science areas. According to the interviewees, this was due to delays experienced during the research process and the need to await the end of the collection of cohort patient data over a five-year period. This section describes the publications that were rated most important by the interviewees.

The team's investigation of risk factors, process and outcome of knee OA during the programme (and subsequent research building on the programme) threw light on the complex nature of OA by developing a method of predicting disease progression through bone scans, revealing the involvement of different joint tissues and substances and finding evidence to support the hypothesis of the phasic progression of the disease, as summarised in Kirwan and Elson (2000). These findings contributed to the insight that both the time and method of treatment must be targeted to the state and the location of the disease, suggesting, for example, that treatment with NSAIDs is only beneficial in specific cases and at specific time points.

The study of risk factors in OA led to the differentiation of patellofemoral and tibiofemoral OA as two distinct forms of the disease (Cooper and others 1994; McAlindon and others 1992). At the same time, paleopathological studies suggested that medial compartment tibiofemoral OA is a relatively modern disease and could be linked to

period-specific risk factors such as obesity and hard surfaces (Rogers and Dieppe 1994). Furthermore, the novel differentiation between the causes of the genesis and progression of OA suggested the need for different approaches to the prevention and the treatment of OA (Cooper and others 2000; Kirwan and Elson 2000; Sharif and others 2004).

Findings on the measuring of joint space in patients affected by OA were presented in Dieppe and others (1993), McCarthy and others (1994) and Sharif, George and Dieppe (1995). The method described in these papers was the first means of predicting OA progression and, importantly, extended research attention from the traditional area of the cartilage to the role of the bone in the disease.

The team's realisation that the subchondral bone played a role in OA was investigated through the *in vitro* culturing of normal subchondral bone cells and subchondral bone cells from non-weight-bearing and weight-bearing areas in OA joints. It was observed that, unlike the other two groups of cells, the majority of cells from weight-bearing OA areas stimulated chondrocytes to break down cartilage, supporting the hypothesis that a certain kind of activity in the subchondral bone stimulates chondrocytes to degrade cartilage matrix (Webb and others 1997; Westacott and others 1997).

Further, work on cytokines and chondrocytes revealed that the cytokine Tumor Necrosis Factor (TNF) alpha which, up to that point, had been associated with inflammation in RA only, was also present in the synovial fluid of OA patients. Increased receptor expression of the cytokine TNF and Interleukin 1 (IL-1) on chondrocytes in OA joints was identified as a likely pathway to cartilage damage. The observation that some cartilage samples are susceptible to IL-1 and others to TNF led to the hypothesis that different cytokines evolve in different patients, supporting the idea of OA as a heterogenous disease with a final common pathway (Elson and others 1998; Webb and others 1997; Westacott and others 1994).

The study of biochemical markers in different joint tissues led to the hypothesis that knee OA is a disease of the joint organ, as not only the cartilage but all major tissues (cartilage, bone and synovium) were found to be affected (Sharif and others 1997). In addition, papers on biochemical markers demonstrated that measurements of biochemical markers, especially of hyalronic acid and cartilage oligomeric matrix protein (COMP) in serum, could be related to disease progression (Creamer and others 1994, Sharif, George and Dieppe 1995; Sharif, George, Shepstone and others 1995; Sharif, Saxne and others 1995). A forthcoming paper on COMP, building on this work, suggests that the progression of OA may be cyclic (Sharif and others 2004). Research on markers has included genetic markers which, it is hoped, will allow prediction of OA.

The development of biomechanical measures to alleviate OA was the team's most direct contribution to clinical management (Cushnaghan and others 1994).

In addition to publications in peer-reviewed journals, the PI considered his contribution to two monographs to be part of the output of the grant, a rheumatology textbook (Rogers and others 1992) and a radiographic atlas for osteoarthritis of the hand, hip and knee (Spector and others 1995).

Selected bibliometric indicators for case study E

Publication portfolio

Output

Number of papers 44

Collaboration

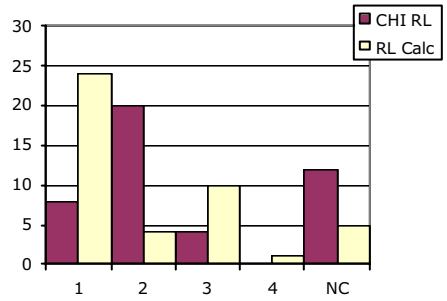
Mean number of authors 4.2

Mean number of addresses 3.0

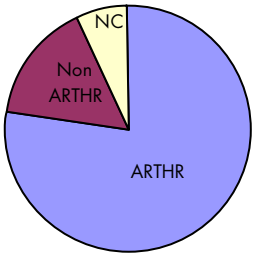
% with non-UK addresses 81.8%

Type

Research level distribution



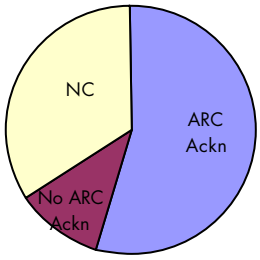
Field distribution



Funding

Mean number of acknowledgements 1.9

ARC funding acknowledgements



Knowledge flow

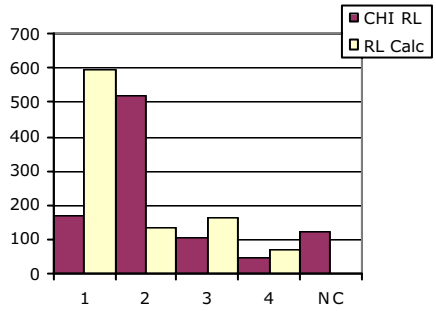
Strength

Mean citations per year (all papers) 73.0

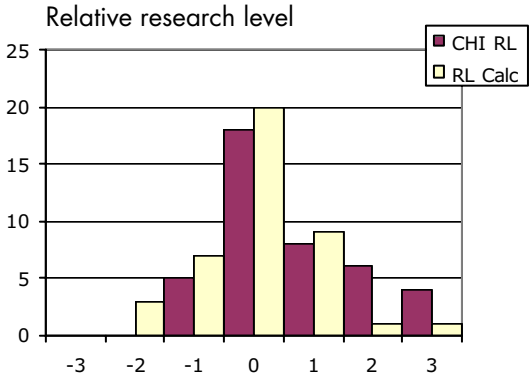
Mean C0-4 13.7

Knowledge translation

Research level of citing papers



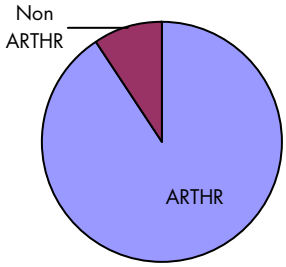
Relative research level



Knowledge diffusion

% of citations from the US 34%

Field distribution of citations



5.6.2 **Research targeting, capacity building and absorption (payback category B)**

In their progress report, the team pointed out that the biostatistician employed through the programme had tutored members of the unit in the use of statistical techniques.

Work on the programme enabled both postdoctoral researchers to establish themselves as researchers. Both won funding that allowed them to remain at the host institution, one of them in a permanent position. Most of the junior clinicians in training during the programme have gone on to become experts in OA in the UK and abroad; in the opinion of the PI, this was the single most significant output of the programme.Over the duration of the programme grant, the PI became involved with various important health fora, an experience which is likely to have contributed to his decision to dedicate himself to health services research. During the programme grant, the PI was appointed to a global advisory board on OA. Within five years of the end of the programme, he took on a leading role in a high profile initiative in health services research.

5.7 Interface B: dissemination

A referee of the programme's follow-up application praised the PI's ability to "introduce effectively his audience to his concepts and acquaint them with his broad knowledge of joint physiology and pathology".

Among other conference contributions, the PI gave the keynote presentation at an international osteoarthritis workshop in 1991. In 1994, he organised a satellite meeting at the World Health Organization on assessment methods in osteoarthritis. As an effective way of drawing attention to the mechanical nature of OA, the PI wore trainers at conferences. In 1996, the team hosted an international symposium on osteoarthritis.

According to the interviewees, several team members were active conference attendants. However, the team experienced difficulties in communicating their findings, such as their work on risk factors, to others working in the field. The interviewees believed that this may have been because their work did not tie up with that of the relatively small number of other groups working on their subject area. Most of these groups resided in the US, where interviewees felt that studies comparable to the arc programme were not possible due to a lack of clinical focus and long-term investment and where, in addition, there was a prevailing focus on epidemiology.

Dissemination of the findings in basic science was hindered by the leading basic scientist's many other commitments, which included managing a large research group, writing papers and teaching.

The PI believed that the mid-term site visitors' criticism regarding the team's lack of international publications was legitimate, as a stronger international profile may have increased the take-up of the scintigraphy work in particular.

The dialogue with policymakers in the UK was more successful: one of the basic science postdoctoral researchers received a five-year NHS career scientist award because the team made a convincing case for the potential of his work for the treatment of patients.

Without direct involvement of the team, the patellar taping technique, first published in the *British Medical Journal* (Cushnaghan and others 1994), was also disseminated via the "tertiary", Oxford-based Internet journal *Bandolier*, the premier source of evidence-based information for GPs in England ("Osteoarthritis of the Knee – Keeping it Taped!" 1994). However, the PI's efforts to interest a major manufacturer of medical tape in the new technique proved fruitless.

There was little contact with stakeholders, although the PI presented his work at arthritis care meetings.

5.8 Stage 4: secondary outputs – policymaking; product development

5.8.1 Knowledge production – reviews and systematic reviews (payback category A)

According to the interviewees, there are no systematic reviews covering the team's work during the programme grant (see Scott and others 2003).

5.8.2 Policy and product development (payback category C)

Clinical guidelines

The medial taping technique was included in the guidelines of the European League Against Rheumatism (EULAR), which were co-written by the PI (Pendleton and others 2000).

As the research into the targeting of treatment with the help of biochemical markers is still in the early stages, it has not yet fed through to any guidelines or frontline treatment.

Product development

The team's novel attention to the role of bone tissue in OA prompted major pharmaceutical industries to undertake trials of bone agents in OA, an interest that would have been unthinkable 10 years ago, according to the PI. Procter & Gamble presented on the subject at this year's meeting of the American College of Rheumatology.

In the period following the end of arc programme support, the team received funding from Roche, which was interested in the patient data collection because the company was developing an anti-OA drug. However, the development of this drug was not successful.

A pharmaceutical company specialising in the discovery of performance-enhanced medicines is presently funding a PhD student at the programme's host institution to validate the phasic hypothesis through mathematical modelling.

5.9 Stage 5: adoption – by practitioners and public

5.9.1 Policy and product development (payback category C)

Although the team's work with the patient cohorts and GPs had some effect in the direct environment in which the research took place, the interviewees believed that there had been very little change in OA treatment, even in the region around the host institution.

However, there had been some take-up of the biomechanical work, which the PI estimated may be promoted further by the recent publication of a PhD thesis on the topic.

Although this was an important finding in the research, prognosis through scintigraphy has not been used much in clinical practice because the radiation dose is relatively high and at present there is little that can be done to stem the diagnosed progression.

Even though the PI was not able to interest two major footwear manufacturers in his research into the benefits of shock absorbing soles, the development of new sports and leisure footwear has since been taken up by the industry.

5.10 Stage 6: final outcomes

5.10.1 Health benefits (payback category D)

When interviewed, the PI concluded that sadly, although the diagnosis and understanding of OA was improved, so far nothing that had happened in OA research had made much difference to the patient.

Nevertheless, there is potential for future health benefits arising from the investigations of the research programme. Currently, team members' research into patient screening with the help of genetic and biochemical markers is being funded by the NHS and a private company, because of its potential to make OA treatment better targeted and therefore effective. It is hoped that the screening will make it possible to select patients whose OA will progress and determine by what means their disease is progressing. This would allow the targeted use of specific drugs, such as TNF inhibitors, and reduce the use and side-effects of the widely-prescribed NSAIDs.

5.10.2 Broader economic benefits (payback category E)

Better targeting of OA treatment through identification of the strand, location and phase of the disease is expected to reduce the cost of treatment. Lower levels of pain and disability can be expected to lead to a decreased demand for knee replacements, and thus a greater degree of mobility and productivity in OA sufferers.

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CHAPTER 6

Case study F: the molecular and cell biology of collagen X and its relation to human disease

6.1 Introduction to the research project

During endochondral ossification (long bone growth), cartilage is replaced by bone. This process is crucial in the development of the normal skeleton. In the mature skeleton this process reoccurs after bone fracture, when cartilage is replaced by bone during repair. It also seems that this whole process is restarted in the osteoarthritic joint, where the cartilage to bone conversion process is reactivated.

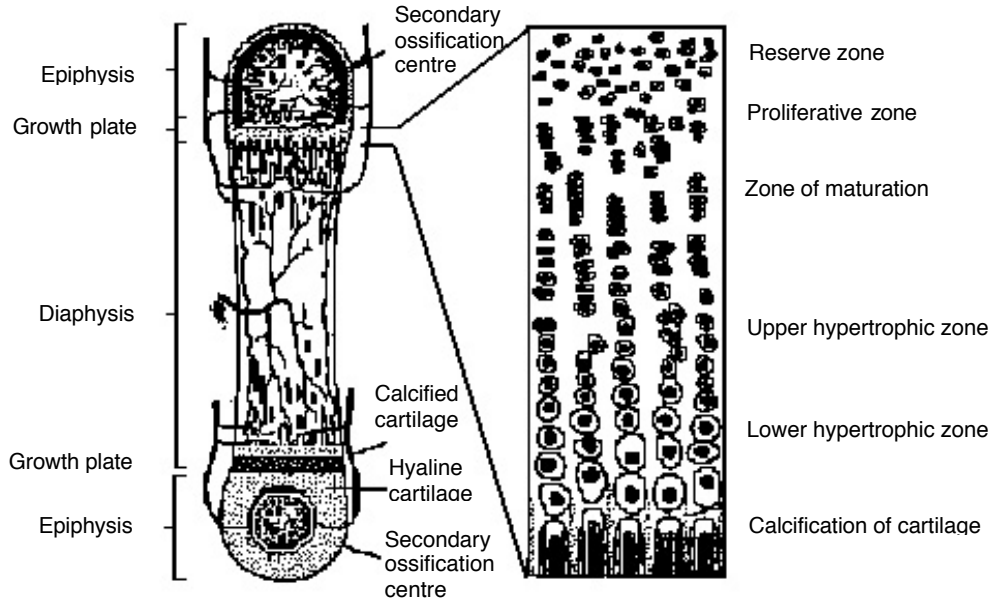
Figure 6.1 shows a long bone in the latter stages of embryonic development. On the right, the growth plate is expanded to show the organisation and differentiation of the chondrocytes.[1] The transition from cartilage to bone takes place at the growth plate, where chondrocytes differentiate through a series of well-defined stages.

Collagen X was discovered in the early 1980s. Its precise function is not known; what is known is that it can only be found at the growth plate during endochondral ossification.[2] Collagen X is the only molecule known to be synthesised exclusively during endochondral ossification. Research in the 1980s suggested that collagen X expression during endochondral ossification is essential for normal bone development. It was hypothesised that mutations in collagen X would cause dysplasia disorders.

Under normal conditions, collagen X ceases to be synthesised once long bone growth is complete. However, collagen X is re-expressed early in the development of osteoarthritis, when the chondrocytes that make the articular cartilage change their characteristics and begin to resemble the chondrocytes that are responsible for making our skeletons during normal development. This leaves chondrocytes unable to maintain the articular cartilage, which subsequently becomes more and more damaged, leading to the joint destruction that characterises osteoarthritis. In the late 1980s, the PI's laboratory had succeeded in cloning the human collagen X gene. For the programme grant, they then went on to characterise the gene and its promoter. At the same time, DNA samples from people with

[1] Cartilage cell: a cell that occupies a lacuna within the cartilage matrix.

[2] The conversion of cartilage into bone.



(SOURCE: Wallis 1993)

Figure 6.1: A long bone in the latter stages of embryonic development

different dysplasias[3] were assembled. The programme identified a number of mutations in the collagen X gene. Two of these were found to caused a specific disorder: chondrodysplasia type Schmid.[4] Currently, a total of 21 different mutations causing chondrodysplasia type Schmid have been identified. Chondrodysplasia type Schmid is a very rare skeletal dysplasia with a prevalence of about 1 per 10 million people.

Based on the research that was done on the programme, a diagnostic has been developed that tests for chondrodysplasia type Schmid. This diagnostic service is now part of the services that are run by the European Skeletal Dysplasia Network along with other diagnostics. Collagen X was identified also as a marker of endochondral ossification, indicating the earliest identifiable stage of osteoarthritis.

6.2 Stage 0: topic/issue identification

The research proposed in the programme application evolved from the work that was done by the PI in the previous years. The PI conducted research in the 1980s on the collagenous components of cartilage and bone, which provided a greater insight into the complexities of the extracellular matrix of these connective tissues. In the early 1980s, three laboratories,

[3] Abnormal tissue development.

[4] Chondrodysplasia is a disturbance in the development of part of the cartilage of the long bones, resulting in arrested growth of the long bones and dwarfism.

including the PI's, discovered collagen X at sites of endochondral ossification. The laboratory subsequently pursued the protein chemistry of collagen X.

Most of the studies on collagen X in the 1980s were conducted with chick tissues. Mammals exhibit very narrow growth plates in comparison with the chick system and consequently it is difficult to isolate sufficient quantities of mammalian collagen X for biochemical analyses. In addition, studies at the mRNA and gene levels in mammalian species had not been possible because the chick cDNAs encoding collagen X do not cross-hybridise with their mammalian mRNA counterparts (Thomas and others 1991).

The small amount of intact collagen X extractable from bovine epiphyseal growth plate made it possible to isolate and biosynthetically label the protein and run it on a protein gel. This analysis showed that significant differences exist in the properties of bovine collagen X compared with chick collagen X. The laboratory also obtained the complete nucleotide sequence of the bovine collagen X. A restriction fragment from this cDNA was used to isolate the human collagen X gene. No other laboratory had managed to clone human collagen X at that time.

At this time, the applicants decided to apply for longer-term funding. There were two main reasons to apply for programme funding instead of project funding. First, the then recent cloning of the collagen X gene gave the laboratory a competitive advantage over other research laboratories. They felt that the way to sustain this advantage was to go forward with the research as quickly as possible. A programme grant could provide the stability and timeframe that was necessary to do this. Second, a lot of time was spent writing grant applications for project funding: one year into a project, attention for a follow-on project is already necessary. This gives a very limited timespan in which to achieve results. A five-year programme usually would allow the lab to think strategically about the research that it wanted to do.

To carry out the proposed programme, the applicants requested a sum of £777,717 for five years. This was to cover salaries for four full-time and two part-time staff (£566,733), equipment (£22,484) and consumables (£188,500).

This research programme seeks long-term funding to address fundamental aspects of the molecular and cell biology of type X collagen and its potential involvement in pathological conditions affecting cartilage, such as osteoarthritis and the chondrodysplasias. The specific aims of the programme are: to characterise the human collagen X gene and the factors that control the expression of this gene such as the protein is only found, under non-pathological states, in the cartilage growth plate associated with endochondral ossification process; to conduct a detailed genetic analysis to determine whether the collagen X gene locus is linked with heritable disorders affecting cartilage such as some forms of osteoarthritis and the chondrodysplasias, and to characterise the nature of such mutations at the DNA level; to examine, at the protein level, the consequences of specific site-directed mutations in collagen X with the longer-term objective of producing cell culture models and animal models of diseases of cartilage caused by collagen X defects; to assess the role of extracellular matrix components in influencing chondrocyte differentiation and the synthesis of collagen X; and to assess the role of DNA methylation in the control of collagen X expression.

(SOURCE: arc archive)

Box 6.1: Abstract

6.3 Interface A: project specification and selection

The application process began when the applicants sent a letter of intent to arc. The type of longer-term programme funding for which they were applying had been awarded throughout the 1980s. However, at the time there was no separate programme grant committee and the process was handled by the research subcommittee along with project grants. arc took six months to respond to the letter of intent, after which they invited the applicant to apply for programme grant support. This long time to respond caused issues for the applicant, as support for his staff was running out and he needed the prospect of new funding to retain them. arc provided funding for his staff pending the decision regarding the programme grant. Although there is a lot of correspondence on this aspect of the application in the file, the applicant did not recall the difficulties with the letter of intent.

There were two steps in reviewing the research proposal. First, three referees reviewed the research proposal (the comments of the third referee were not preserved in the arc archives). A summary of their assessments is given in Table 6.1 (the letters A–B indicate the different referees' assessments).[5] This information is based on the assessors' report form submitted to arc (a blank copy is available in Annex B). Second, a site visit to the research laboratory was organised. During this visit, several scientific presentations concerning the research field were made.

Table 6.1: Summary of assessors' report

	High	Medium	Low	None
Originality of project	A, B			
Potential value to rheumatology	A	B		
Potential practical value	A, B			
Appropriateness of overall project design	A, B			
Suitability of methods	A, B			
Feasibility within time proposed		A, B		
Standing of applicant in this field	A, B			

The referees agreed that the proposed science was excellent and that the group was pre-eminent in the collagen field in the UK. All three commented that the stated objectives seemed very ambitious; it was seen as very likely that the objectives could not be reached in five years. The requested amount was perceived as too high to be funded in full. One of the referees questioned the relevance of the research to arc. He mentioned that the role of collagen X in osteoarthritis had not yet been characterised.

The site visit team were unanimous that the scientific content of the programme grant application and the applicants' track record were first class. They then addressed the four main objectives outlined in this proposal (see Box 6.1 for the abstract describing these objectives). There was unanimity that it was not necessary at the present time to provide funding for aim (3). This required a much greater level of knowledge about collagen X than was presently available. The site visit team felt that, should the other aspects of the

[5] Referee C did not provide a summary of his assessment.

proposal be successful, the applicants should be encouraged to return to arc in the future if they still wished to continue with aim (3). (Although the two applicants on the grant supplemented each other and considered themselves equally important, arc considers the lead applicant to be the PI. As the two applicants on this programme grant had complementary skills, either one of them could not respond to all comments of the site visit team.)

The site visit team recommended the following funding:

- two senior (named) postdoctoral research workers for five years each;
- two junior research scientists (one named) for five years each; and
- consumables of £20,000 per annum and the equipment as requested.

This would lead to a budget of salaries totalling £342,604, with consumables at £100,000 and equipment at £22,484, making a total of £465,088.[6]

arc followed the recommendations of the referees and site visit team and funded aims (1), (2) and (4), making a total of £465,088 for five years.

The research team has only a vague recollection of a part of the proposal being cut. The PI acknowledges that it was the first round of programme grants and at the time of the proposal, arc had not yet decided on the budget size that they wished to fund.

One of the referees queried the relevance of the proposed research with arc. During the interviews, the research team provided two arguments why the research was relevant to arc.

1. There are quite a lot of diseases that arise from abnormal bone growth (eg certain forms of dwarfism). While osteoarthritis is not the primary genetic defect of these diseases, they are characterised by secondary arthritis. Osteoarthritis itself is known to have a strong genetic component.
2. Collagen X is a marker for bone growth. This is relevant to arc as the process of bone growth begins again in osteoarthritis. The discovery of collagen X was an important advance in the understanding of osteoarthritis.

6.4 Stage 1: inputs to research

6.4.1 Funding

Programme grant and extensions

The arc award was for £465,088 over five years. This can be broken down into £342,604 for salaries, £100,000 for consumables and £22,484 for equipment. One year into the study, extra funding of £75,000 was awarded to supplement the reduced level of funding that initially had been made available for the cost of consumables. The total sum awarded was still less than the £777,717 for which the PI applied. There were two main reasons stated in the review process to explain this lower awarded amount. First, it was felt that the

[6] Budget is given in 1990 prices (in 2003 this would give a total budget of £669,238).

study was too ambitious and that one of its aims (see Box 6.1) could not be achieved in timeframe mentioned. Second, the total amount requested was above the amount of funding that arc was willing to award.

According to the PI, it is very unusual to apply for extra funding. As this was their first experience with molecular biology, they had underestimated the costs of consumables. Furthermore, the amount for consumables was cut, as one of the four aims was not awarded funding. However, the aim that was cut was the cheapest in terms of consumables. The PI commented that arc was very flexible in awarding the extra funding, one year into the study. Most funding agencies would not have awarded extra funding.

6.4.2 **Overheads**

The university paid for the overheads. In addition the university had the laboratories refurbished for recombinant DNA procedures (£15,000), and a university-funded technician was assigned to the programme (approximately £15,000).

6.4.3 **Other funding**

The grant represented on average 20% of the total funding that the PI received over the five years of the programme. The largest share of the total funding during that period (including arc programme grant under review) came from the Wellcome Trust (53%) and arc (38%). Most grants were two to three-year project grants.

6.4.4 **Human capital**

A total of six people began working on the programme. The PI stated that he would work five to eight hours a week, while the co-applicant would be working 15–20 hours a week in the programme. Additionally, two postdoctoral research workers and two junior research scientists were appointed full-time for the five-year period. Throughout the period of the programme, at least one to two students were working in the laboratory on subjects related to the programme (these students were not funded by the programme). The members of the research team had different backgrounds (eg biochemistry, molecular biology and genetics) which led to a diversely skilled research team including experts in the all the required research areas.

6.4.5 **Techniques, reagents and equipment**

Equipment

The research group felt that it needed special equipment, and equipment that was solely used for the programme. This included, amongst others, a low temperature freezer including CO_2 backup, CO_2 incubator, 3000V power supply and DNA sequencing apparatus. Most of the equipment necessary to conduct the work was already available at the university.

6.5 Stage 2: research process

The programme began at the point where the human collagen X gene had been isolated. The research team had yet to characterise fully the gene and the promoter. At the same time, the team began to assemble material that could be screened for mutations in collagen

X in order to be able to identify the disorders that are caused by such mutations. This was easier to do in the early 1990s than that it would be today, as currently there would be a much more vigorous ethical approval process.

After fully characterising the sequence of the human gene, the team debated as to whether to publish this sequence directly or to wait until a disease caused by mutations in the gene was found. Because of the recent development of polymerase chain reaction (PCR), publishing the primer sequences would allow others to find such a disease and publish the results before the team could do so. It was decided to publish a paper in which they reported that some diseases were not caused by mutations in collagen X. A group in the US subsequently performed an analysis on a large Mormon family and discovered that mutations in collagen X were responsible for development of chondrodysplasia type Schmid, before the Manchester research group could publish the results of a similar study in the UK.

Three to four years into the grant, the team had fulfilled the objectives of the grant application. They had characterised the human gene, begun to characterise the promoter and identified mutations in the gene that caused chondrodysplasia type Schmid. Also, they had managed to exclude some diseases from the causal link with mutation in the collagen X gene. In the final year they began to look at other aspects of the endochondral ossification process beyond collagen X. By using differential screening techniques, they tried to discover other genes that were involved in endochondral ossification. In addition, they began to look into identifying the ways in which to analyse the gene (collagen X) successfully. During this last year of the programme, the team was working towards a second programme grant (for which they applied and received in 1995).

Staff turnover was very low (because of the researchers' personal circumstances) during the period of the programme grant, and this was seen as one of its success factors. In 1993, the research assistant left. In 1994, a new postdoctoral researcher joined the team as one of the postdoctorals who was working on the programme had been offered a very good position in the US. Although the new postdoctoral researcher only joined the team when the grant was nearing completion, it felt as if the programme was just beginning, as they had already met the objectives of the programme by the end of the third year and were beginning to work towards a second programme grant. During the second programme grant, there was a higher turnover of staff, and there was a problem recruiting good postdoctoral researchers.

This grant was seen as successful also in terms of outcomes. Another success factor was the quality and experience of the postdoctoral researchers. One of the researchers was home-grown and already working in the laboratory. The other researcher came to England because of personal circumstances; they had already completed a postdoctoral position and could direct technicians and PhD students (a task in general done by grantholders and not by the postdoctoral researchers).

The interviewees acknowledged the importance of a programme grant in providing security to researchers. An additional benefit of a programme grant is that it gives stability to recruit PhD students. A programme grant makes it possible to offer five-year funding to a postdoctoral researcher. However, the career development of very good postdoctoral researchers requires that they either become a member of staff or move to another scientific centre within the timeframe of a programme grant.

6.6 Stage 3: primary outputs from research

6.6.1 Knowledge

The research team published 23 major papers on the research done within the five years of the programme. The first article related to the programme was published in 1991, while the latest was published in 2003. The first few articles describe the characterisation of the bovine and human collagen X gene, while later articles describe the mutations in collagen X that were found. The most recent articles go into the role of collagen X in osteoarthritis. (The peer-reviewed journal articles attributed by the PI to this grant are detailed in Annex A of this report.) The PI also attributed one book chapter in which he was involved in writing about collagen family of proteins to this grant (Kielty and others 1993).

6.6.2 Research staff

During the whole timeframe of the grant, there were in total two grantholders, three postdoctoral researchers, two research assistants and a technician working directly on the project. Furthermore, one to two students who were working in the laboratory during the time of the grant could work there because of the grant, even if they were not directly funded it. Two of the postdoctoral researchers were offered permanent jobs due to the programme grant. Both of them acknowledge that the programme grant was key in establishing and furthering their research careers. One of the researchers noted that working on the programme helped to raise her profile within the university and provided independent recognition. The third postdoc received a job offer from a prestigious research group in the US and left during the programme. Both research assistants obtained their PhDs because of the programme.

6.6.3 Knowledge creation

The important output of the programme was that the research team characterised the bovine and human collagen X gene. They developed a strategy for detecting mutations in collagen X genes and subsequently this strategy led to the characterisation of mutations that cause chondrodysplasia type Schmid by the Manchester laboratory and other laboratories.

6.7 Interface B: dissemination

The lead co-applicant claimed that there was a large amount of dissemination activity, ranging from abstracts at various national and international meetings to regular speaking commitments at various academic institutions: the International Symposium Cell Biology of Cartilage and Bone in Oxford; Federation of European Connective Tissue Societies in Poland in 1990; and the Fourth International Conference on the Molecular Biology and Pathology of Matrix (held in Philadelphia in 1992). Twenty-nine conference contributions between 1990 and 1997 can be attributed to the programme grant.

Selected bibliometric indicators for case study F

Publication portfolio

Output

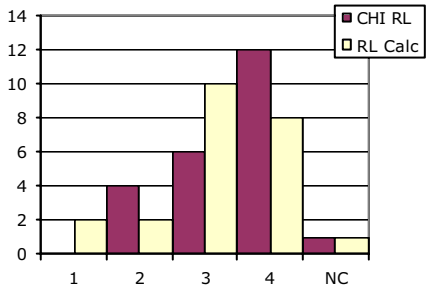
Number of papers	23

Collaboration

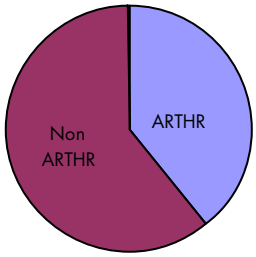
Mean number of authors	6.5
Mean number of addresses	3.3
% with non-UK addresses	95.7%

Type

Research level distribution



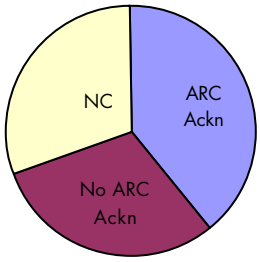
Field distribution



Funding

Mean number of acknowledgements	2.3

ARC funding acknowledgements



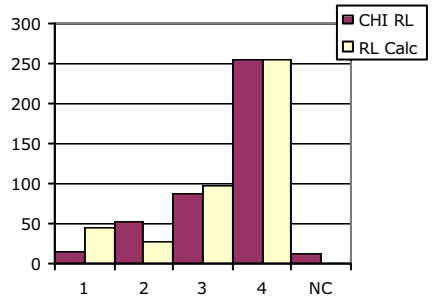
Knowledge flow

Strength

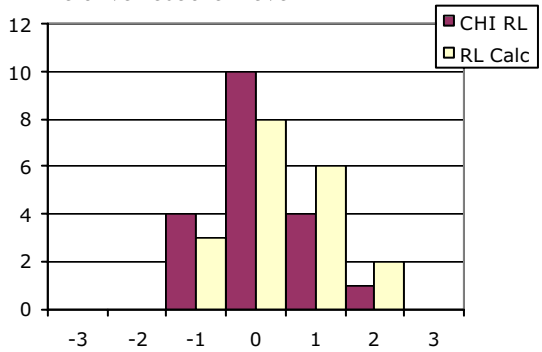
Mean citations per year (all papers)	32.1
Mean C0-4	13.7

Knowledge translation

Research level of citing papers



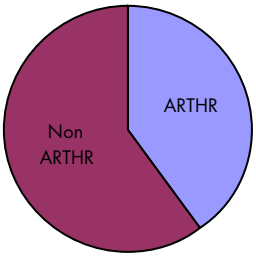
Relative research level



Knowledge diffusion

% of citations from the US	36%

Field distribution of citations



6.8 Stage 4: secondary outputs – policymaking; product development

6.8.1 Knowledge creation

The research team itself has published some reviews on the topic of collagen X and endochondral ossification.

6.8.2 Informing policy and product development

A diagnostic to test for chondrodysplasia type Schmid was developed. A centre that developed diagnostic tests picked up the research results from the literature and used the team's findings to develop a test. They consulted the research team on how to develop such a test. Currently, testing on collagen X mutations is run as a clinical service and is included in the tests of the European Skeletal Dysplasia Network. Testing on collagen X is done in a German laboratory.

6.9 Stage 5: adoption – by practitioners and public

The chondrodysplasia type Schmid diagnostic test is in use, but the patient has to ask for a test. The use of the diagnostic is not included in clinical guidelines. The disease is extremely rare, so it is likely that not all physicians are familiar with it.

6.9.1 Health benefits

A confirmation of chondrodysplasia type Schmid – as is given by the diagnostic – influences the management of care. Medical care has improved because of this diagnostic; people with chondrodysplasia type Schmid are no longer operated on because it is recognised that this will increase problems (eg people with chondrodysplasia type Schmid have bowed limbs, and if this is corrected there will be an increase in joint instability, causing further problems).

6.10 Stage 6: final outcomes

As yet, any outputs of this research grant to have fed through into a final outcome could not be identified.

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Thomas JT, Boot-Handford RP, Marriott A, Kwan APL, Ayad S, Grant ME. 1991. Isolation of cDNAs encoding bovine type X collagen. Annals of the New York Academy of Sciences 580:477–9.

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CHAPTER 7

Case study G: interaction between Complement, immune complexes and the mononuclear phagocytic system

7.1 Introduction to the research project

This research explored fundamental questions related to the underlying disease mechanisms in systemic lupus erythematosus (SLE), one of a number of poorly understood rheumatic diseases. The principal investigator (PI) was one of the first clinical researchers in his domain to develop models in humans as well as animals to test his hypotheses that SLE is associated with abnormal immune processing mechanisms. This case study is unusual because it addressed fundamental research questions by means of human as well as laboratory experiments. This work continues to be developed in mouse models in the same research laboratory. The project funded by this senior research fellowship was supported mainly by arc, and carried out at the Royal Postgraduate Medical School at the Hammersmith Hospital in London.

SLE is a chronic inflammatory disorder resulting from an abnormality of the immune system (American College of Rheumatology 2004). In SLE, the immune system is overactive and produces too many abnormal antibodies that react with the patient's own tissues (American College of Rheumatology 2004). The disease is characterized by certain autoantibodies.[1]

This disease causes a variety of problems. It may cause skin rashes, arthritis, anaemia, seizures or psychiatric illness, and often affects internal organs including the kidneys, lungs and heart. Once a disease with high mortality, SLE is now considered a chronic disease. In 1954, survival after four years was 50%; today it is more than 97% (American College of Rheumatology 2004). It is the second most common autoimmune disorder (after thyroid disease) in women of childbearing age (Imperial College 2003).

Prevalence figures are not easy to measure, because SLE is often difficult to diagnose and has overlapping symptoms and clinical markers that are common with other diseases.

[1] Autoantibodies are cells that are produced by, and attack, one's own body, which subsequently leads to the manifestation of the disease in the blood.

Therefore it is sometimes referred to as a syndrome.[2] Diagnosis is made on the basis of clinical findings, together with blood tests. Some forms of SLE are very rare, for example, the C1q deficiency, which leads to serious health consequences. Prevalence of SLE is estimated at around 40 to 50 per 100,000 (American College of Rheumatology 2004).

There is as yet little understanding of the initial causes of the disease and some treatment consists of pain relief and steroids to reduce inflammation. The PI had studied the role of different immunological components implicated in SLE a number of years previous to the senior research fellowship. arc also supported those studies, in which he was able to lay the foundations for this research. The PI had developed a number of hypotheses to explore the relationships of immunological components in the hope of explaining the underlying disease mechanisms, as well as devising more effective treatments for SLE. Notable is the PI's longstanding relationship with leading scientists at Hammersmith Hospital, who had supported the development of research models upon which the PI's work built. Colleagues in other departments, for example, the Departments of Medicine and Radiology (also based at Hammersmith Hospital) made important contributions to the work that formed the foundations of the PI's work.

More specifically, the focus of this research was the potential link between three immune factors:

- Complement – ie proteins that remove inflammatory substances from the blood;
- immune complexes (ICs) – antigen–antibody complexes which Complement helps to discharge; and
- mononuclear phagocytic system – an important component of the immune system that plays a vital role in activating phagocytes (literally, "cell eaters").

The PI's basic hypothesis was that a lack of Complement predisposes to SLE because of its impact on the normal physiological mechanisms by which ICs are removed and processed by the mononuclear phagocytic system.

The general aim of this research was to gain better insights into the associated autoimmune disease mechanisms, with the possibility to discover new and effective therapies.

7.2 Stage 0: topic/issue identification

Much of the PI's idea development stemmed from work carried out at the Hammersmith research laboratories, where leading scientists had already researched "human models" for the study of IC mechanisms. Previous to the senior research fellowship, the PI had developed his clinical and research career at the Royal Postgraduate Medical School, where there already existed a coherent programme of research in this area.

[2] A set of signs or a series of events occurring together that often point to a single disease or condition as the cause, see: http://www.medic8.com/MedicalDictionary.htm.

The PI explained in his proposal that his hypothesis was based on observations during research experiments in animals carried out by Biozzi (1953), which showed that abnormalities of IC clearance (ie the immune response that aims to rid ICs from the bloodstream) may predispose to IC-mediated disease, including SLE. When the PI actively engaged in this research topic in the late 1980s, the involvement of Complement and ICs, together with certain Complement receptors in SLE, had been established. Previous scientific studies also examined different mechanisms that were involved in processing ICs in the laboratory; however, the PI was the first to look at the fate of ICs formed in the human body.

The actual foundation of the project was laid down by the PI in 1988, when he developed research models to explore the mechanisms of IC clearance in humans. Supported by a two-year junior training fellowship and an additional 18-month project grant by arc, the PI spent three-and-a-half years with the support of facilities and experts at the Hammersmith research laboratory, building on his experimental analysis into IC processing in humans, and interactions between immune system factors, including the interactions between ICs, Complement erythrocytes (red blood cells) and macrophages (cell eaters). In addition, the support for the development of his models came from a longstanding collaboration between the Department of Medicine and the Nuclear Medicine Unit in the Radiology Department.

These studies were decisive for this project, as he characterised for the first time the mechanisms involved in the processing of ICs in man, demonstrating their clearance in the liver, their binding to a cell receptor (referred to as CR1), and the loss of the receptor following the processing of IC complexes. Following these findings, he continued to perform the first imaging studies of ICs in humans with support from the Department of Radiology and studies of white blood cells (leucocytes) function in a patient with a lack in Complement receptors (referred to as Complement receptors 3 and 4). This last study helped to form the specific research ideas for the senior research fellowship application. However, most important was the PI's discovery, in the year previous to the SRF grant, establishing that there was no evidence of IC "trapping" outside the liver and spleen, which went against the perceived wisdom of the time. This was to give added impetus and confidence at the time that he applied for the grant.

These different streams of work supported the research aim stated in the arc senior research fellowship grant in 1992 (see Box 7.1 for abstract).

The application was for a five-year senior research fellowship grant worth £401,702.80.[3] The majority of costs were for the salaries and the rest was spent on equipment and consumables.

[3] £545,000 in current value.

(i) The aim of this programme of research is to explore the hypothesis that genetic or acquired deficiency of classical Complement components may impair the ability of the mononuclear phagocytic system to remove immune complexes (IC) from the circulation and from tissues, which may initiate and perpetuate disease. *In vivo* immune complex processing in humans will be studied using radiolabelled 123I-hepatitis B surface antigen/anti_HbsAg complexes and gamma-camera imaging, addressing specifically the influence of size on IC clearance;

(ii) the relative importance of hypocomplementaemia[4] and low CR1 numbers in complex processing, the question of whether an intrinsic defect in mononuclear phagocytic system function contributes to abnormal processing in systemic lupus erythematosus;

(iii) and the explanation for the observed differences between the patterns of organ clearance of soluble IC and opsonised erythrocytes.[5]

Parallel *in vitro* experiments will be performed, in which monocytes, monocyte-derived macrophages and Kupffer cells[6] will be immobilised on beads. The interactions between IC, erythrocytes and these cells will be studied at a cellular level.

(SOURCE: arc archive)

Box 7.1: Abstract

7.3 Interface A: project specification and selection

The PI was shortlisted and interviewed in competition with seven other applicants. The research proposal was reviewed by five external referees (A, B, C, D and E) and two personal referees (F and G). Below is a qualitative assessment of the referees' comments, because the assessment matrix used for project grants is not applicable for senior research fellowship grants.

The PI received overwhelming support for this study and outstanding reviews that commented on his clinical and research expertise in this area. Referee G pointed out the longstanding collaboration with the Departments of Medicine and Radiology, upon which the PI had relied for the successful execution of previous studies in this research area. At the same time, referee G also praised the novel methodological approaches that the PI had developed and his vital contributions in exploring a yet poorly-understood disease mechanism. Referee A pointed out the PI's unique position in carrying out work that had not been previously assessed in humans, and therefore this made him a good candidate to carry out the work.

Referee B appeared to have slight doubt with respect to the therapeutic application of this research, although he acknowledged its importance, especially with regards to the relevance of the proposal to rheumatic disease in general. Equally, referee C was not sure to what extent this research would be applied, again stressing that the work is undoubtedly

[4] Low levels of Complement in the blood.

[5] Erythrocytes treated with opsonin, ie an agent, usually an antibody, that makes a cell more vulnerable to being engulfed by a phagocyte (cell eater).

[6] Specialised cell-eating cells found in the liver.

important. Referee D voiced some scepticism with respect to his early career and whether the PI would be able to function independently. Since the PI was a senior fellow at the time, according to normal arc procedures he would have been subjected to a site visit in the fourth year of his fellowship. However, since he was appointed as a senior lecturer by his institution during the fellowship, this did not occur.

7.4 Stage 1: inputs to research

The inputs such as resource facilities and expertise that supported the PI's research work are not easy to capture, because the facilities offered at the Hammersmith Hospital at the time, in many instances, were freely available and accessible to the PI. It is important to note that the PI relied on a very strong network of reputable scientists that were affiliated with, or directly worked for, the Hammersmith laboratory. For example, the on-site Department of Radiology made a crucial contribution to the human testing of IC processing through the unique development of a radiolabelling technique, which was not accounted for in the project application. In addition, much expert advice and access to patients was granted at any time during the study period, creating a very favourable context in which the PI was able to carry out his work.

7.4.1 Funding

The PI's salaries totalled £244,098 over five years, with one technical research assistant receiving a total salary of £100,011 over five years. This technical research assistant was in charge of several aspects of the experimental work, most notably the maintenance and preparation of white blood cells, processing of samples and purification of specimens.

The research facilities at the laboratories of the rheumatology unit at Hammersmith Hospital were used, as they had been in the prior years, taking advantage of facilities for tissue culture and the handling of radioactive materials. In addition, the radiolabelling was performed in the specialised handling facility, and waste disposal in the Department of Medical Physics. For running expenses, materials and consumables, the PI was granted £49,750; for equipment purchases the PI requested, and was granted, £7,843.80.

arc awarded the full amount requested in the application totalling £ 401,702.80. In 1995, the PI gained appointment as senior lecturer at the Royal Postgraduate Medical School, which took over payment of his salary. The PI therefore asked arc to transfer his remaining grant to his technical research assistant and one postdoctoral research assistant at no extra cost to arc; however, the grant remained in the PI's name.

As the technical research assistant's position commenced later, the grant transferral was sufficient to cover his work until October 1998. In addition, the postdoctoral research assistant gained further funding through other grants that were able to further his career for another year until 1999 at the Royal Postgraduate Medical School.

7.4.2 Human capital

The PI's assistant was employed on the basis that there was no dedicated technical support in the unit. This research assistant had worked as a technician with the PI before and therefore had brought a range of skills and insight into this research area.

As discussed above, in 1995, the PI asked that the remaining grant of two years be transferred to his research assistant, although he remained the official PI. He asked for the greater part of the funds committed to his salary to pay for a senior research officer, and this was granted at no extra cost to arc. The senior research officer was employed on a three-year contract, with external funding provided throughout 1999. The transferral request followed the PI's appointment as a senior lecturer. The remaining grant amount was sufficient to fund his research assistant until 1998, who also based his PhD research on the proposed work.

7.4.3 Techniques, reagents and equipment

The direct consumables totalled £49,750, which was based on studying 30 patients per annum for the period of the programme of the research. The polyclonal anti-Hepatitis B surface antigen imported from Switzerland was donated to the team, and the additional significant expense was the collagenase required for preparation of human Kupffer cells.

7.5 Stage 2: research process

During the research processes there were no major changes to the suggested course of action that were specified in the proposal. As mentioned above, three years into the research the PI was promoted and transferred his funds to allow his technical research assistant to complete his PhD, and for another postdoctoral research assistant to help explore the PI's hypotheses in mouse models. The research assistant was employed on a three-year contract, with two years covered by the arc grant, and one year covered by other means (the source of this extra funding was not specified).

Two other issues are of interest in the research process. First, the PI's work attracted a number of international researchers who wanted to learn more about the advances in this research area. Many of them would have received substantial training in the context of a thriving research community at the Hammersmith Hospital; equally they were able to give their technical support to the project.

Second, another study was carried out by the PI outside the remit of the senior research fellowship. The study examined the fate of ICs and processing mechanisms in pigs. Although this study made an important contribution to answering fundamental questions about processing mechanisms in humans, other mammals and primates, it had little relevance for xenotransplantation[7] (personal communication with PI; Lechler 2004).

7.6 Stage 3: primary outputs from research

The primary outputs of this research are a widened knowledge base that will inform fundamental questions relating to SLE disease processes. The results did not lead to any therapeutic applications, partly because any further development and tests in humans were not feasible, and the PI's intent lay in exploring mechanisms in humans.

[7] Transplantation between animals of different species.

At the end of this work, the PI felt that he had successfully explored both in humans and in other *in vitro* models the clearance mechanism of ICs to the extent that he felt that there was little left to research further in this particular area of IC studies. Subsequently, his work was developed further by scientists who were more specialised in mouse models, examining another aspect of IC formation and processing; an area that fell outside the remit of this PI's expertise.

In the long term, this programme of experimental work extended the knowledge base of the activity of the mononuclear phagocytic system and Complement in the defence against IC disease. In addition, the PI contributed to a detailed understanding of the different contributions of the liver and spleen to clearance mechanisms of foreign substances from the circulation, which may also provide new information concerning protective mechanisms against infectious disease.

7.6.1 Knowledge creation

The main outcomes of the research can be related to a series of 32 papers that are listed in Annex A of this volume. The findings discussed in this section relate to the following two broad categories: the PI's hypotheses and offshoot studies.

7.6.2 The PI's hypotheses

First, the PI set out to delineate the basic mechanisms involved in IC processing by the mononuclear phagocytic system. This would help to explain which processing factors might be responsible in the pathogenesis[8] of SLE. Second, he wanted to establish the relative importance of low levels of Complement with specific reference to receptor CR1 and explore the defects of the phagocytic system contributing to SLE. Finally, he set out to study clearance patterns of specific ICs and opsonised erythrocytes.

In 1993 (Davies and others 1993), the PI published the findings of his studies in humans, showing that Complement plays an important role in processing ICs in the spleen; at the same time, he observed that the Complement deficiencies in SLE patients may be related to the abnormal processing of ICs.

7.6.3 The importance of CR1

The paper (Beynon and others 1994) showed the results of a successful exploration of IC processing factors that were specific to the PI's hypotheses. The investigator established the importance of receptor CR1 in the prevention of blood vessel inflammation by showing that IC binding with receptor CR1 prevents the interaction of neutrophils[9] and ICs, which would enlarge blood vessels and facilitate the deposition of ICs with subsequent damaging effects.

In 1995, the paper co-authored by the PI (Seelen and others 1995) further described the role of CR1 receptors and associated clearance mechanisms, especially in patients with infections. For example, certain antibodies (E5 in particular) would facilitate the removal of bacteria by macrophages in the liver and spleen. The study showed that binding to CR1

[8] The development of a disease.

[9] A type of white blood cell.

Selected bibliometric indicators for case study G

Publication portfolio

Output

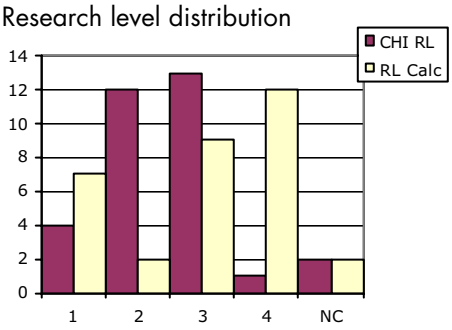
Number of papers	32

Collaboration

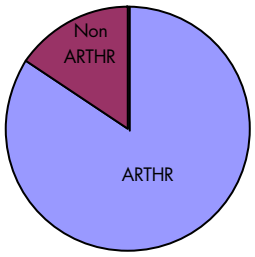
Mean number of authors	5.5
Mean number of addresses	3.2
% with non-UK addresses	90.6%

Type

Research level distribution



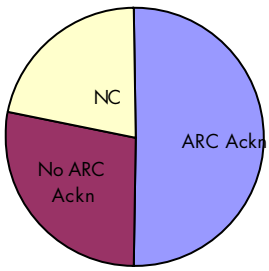
Field distribution



Funding

Mean number of acknowledgements	1.5

ARC funding acknowledgements



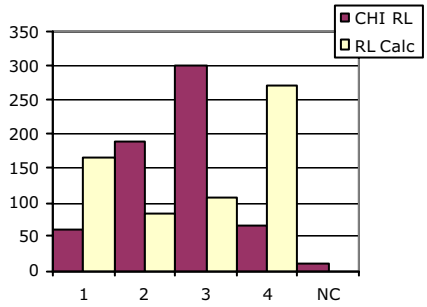
Knowledge flow

Strength

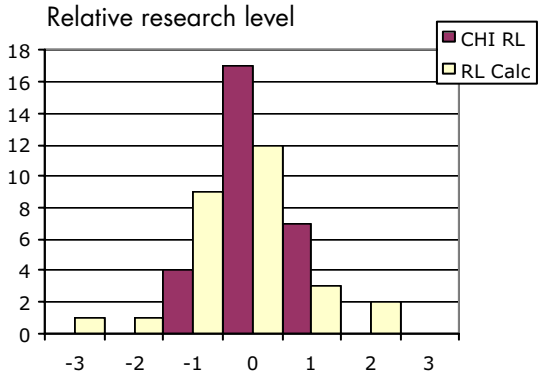
Mean citations per year (all papers)	55.9
Mean C0-4	15.4

Knowledge translation

Research level of citing papers



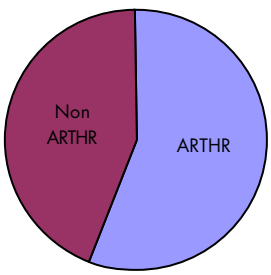
Relative research level



Knowledge diffusion

% of citations from the US	41%

Field distribution of citations



constituted one mechanism by which E5 could contribute to the clearance in patients that were suffering from infection. Because infection is a major risk factor for death in SLE patients, this study demonstrating protective factors of infection in SLE disease is another important contribution to the stock of fundamental knowledge.

7.6.4 The importance of C1q

In a second study published in 1994 (Bowness and others 1994), the PI explored the importance of one hereditary type of Complement protein C1q. This paper stressed the association between C1q deficiencies and severe forms of SLE by reviewing 29 published cases and two patients. Both patients also showed the characteristic signs of autoantibodies in SLE. The PI found that C1q deficiency was the most powerful disease susceptibility gene that had been characterised in humans predisposing to severe SLE (Bowness and others 1994). The C1q factor continues to be explored in mice to date in laboratory studies (Nash et al 2001), and has proven since to be one of the most powerful indicators of SLE.

One of the main collaborators in the latter part of the study, and a colleague of the PI in the same laboratory, continued this research on mice and developed models to test the hypothesis that C1q causes autoimmunity by an impaired clearance of apoptotic (dead) cells. While this appeared to be a shift from the PI's research, apoptotic (dead) cells are an integral part of the mechanisms that the PI explored. Moreover, when binding with antibodies, apoptopic cells are a new formation of ICs and are thought to be a major source of the autoantigens of SLE. This research is continuing to explore whether the impairment of IC removal by Complement may explain the link between hereditary Complement deficiency and SLE.

7.6.5 Diagnostic test development

In 1996, another paper co-authored by the PI (Hogarth and others 1996) describes the importance of anti-C1q antibodies in patients with SLE, and the development of a test to measure them. For example, these autoantibodies are important markers that correlate with low levels of Complement in the blood. The hypothesis to date shows that these autoantibodies may play an important role in the pathogenesis of SLE.

As a result of such studies establishing the importance of anti-C1q antibodies in SLE, this diagnostic test is still being utilised today to measure autoantibodies indicative of the disease.

7.6.6 The importance of Fc receptors

In 1996, a paper co-authored by the PI (Botto and others 1996) described the importance of defects in receptor functions, such as Fc receptors in the processing and clearance of ICs. The studies carried out showed that there was no association between certain Fc receptors, but the hypothesis remained a strong one. The data produced by this study shows that in patients with SLE, there is impaired ability of hepatic Fc receptors to bind and process effectively with ICs.

In a very recent paper (Davies and others 2002), study results indicated that Fc-mediated clearance of ICs is defective in patients with SLE and suggest that binding of ICs by Fc receptors is critical for their efficient binding and retention by the macrophage system in the liver.

7.6.7 Offshoot studies

In 1995 (Davies and others 1995), the PI also began to explore IC processing mechanisms in pigs, which showed interesting comparisons between humans and pigs, and processing mechanisms previously described in primates. For example, he showed that macrophages are Complement-dependent, and that the pigs' lungs appeared to be an important site of IC processing, whereas in humans processing mostly occurred in the spleen and liver. These comparative studies make important contributions to answering fundamental questions about processing mechanisms in humans, other mammals and primates.

As a result of this offshoot study, the PI was able to contribute to the general knowledge pool that ICs in pigs are processed in the lungs, as opposed to the spleen and liver in humans.

7.6.8 Research targeting, capacity building and absorption

This grant helped to build the career of the PI's three researchers. Two of them were supported by the arc grant and one who was not supported by the arc grant but worked at the Hammersmith laboratory at the same time. All of the researchers continue their work in the area of rheumatology: two at Hammersmith Hospital, and one at the Cambridge Medical Research Centre. This research project therefore facilitated the development of research careers in three important ways, which directly relate to the scientists involved at the time:

- the PI was able to establish a successful career as a basic scientist and continue to develop his reputation as a clinical rheumatologist (the PI is now in the process of setting up his own medical school, in his role as foundation chair of medicine);
- the technical research assistant was able to develop as a scientist and technician and gain his doctorate through the senior research fellowship; the postdoctoral research assistant was able to continue his research career in a similar field and now works as a senior research fellow supported by the MRC;
- one of the leading scientists in this field was able to work collaboratively during the grant period, in order to take one strand of the PI's research and develop it further. To date, she continues to build her reputation as one of the leading scientists in this field with the aim to develop a therapeutic application.

7.7 Interface B: dissemination

The preliminary findings of this research were presented at the Annual Meeting of the British Society for Rheumatology in 1994. In addition, the PI won the Michel Mason Prize in 1995, which is awarded by the British Society for Rheumatology on the basis of "excellence in clinical or scientific rheumatological research". This involved a presentation to the members of the British Society for Rheumatology, gaining much publicity in the field.

7.8 Stage 4: secondary outputs – policymaking; product development

7.8.1 Informing policy and product development

The PI's technical research assistant was able to develop a test enabling the measuring of antibodies to C1q in SLE patients, which is still in use today at the Royal Postgraduate Medical School. Therefore, the most notable secondary output of the grant was a diagnostic test method, which helps to establish the nature and severity of SLE disease.

7.9 Stage 5: adoption – by practitioners and public

7.9.1 Informing policy and product development

As a result of the PI's research, infection in SLE patients was identified as a major risk factor that had led to death in a number of cases. As a result, certain SLE patients (ie those with persistently low Complement levels) were put on penicillin treatment routinely. Anti-infective prophylactic treatment for SLE patients with certain characteristic clinical features became unit policy at the Royal Postgraduate Medical School.

7.9.2 Health benefits

Prophylactic treatment prevents infection, yet there are very few patients with this disease profile, and therefore the effects of this policy measure cannot be studied extensively.

7.10 Stage 6: final outcomes

The interest to date in this research area focuses on both the Complement system and Fc receptors in influencing IC clearance in systemic lupus. At the same time, the interaction between autoantibodies to C1q, other Complement proteins, ICs and Fc receptors remain the outcomes of further studies carried out at the Hammersmith Hospital in mouse models today.

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CHAPTER 8

Case study H: lymphocyte differentiation and function in rheumatoid arthritis

8.1 Introduction to the research project

Rheumatoid arthritis (RA) is one of the most common forms of arthritis and is a systemic disease that can affect any part of the body. It is characterized by the inflammation of the membrane lining the joint, which causes pain, stiffness, warmth, redness and swelling. Cells from the inflamed joint lining, the synovium, can invade and damage bone and cartilage. Inflammatory cells release enzymes that may digest bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain and loss of movement (Arthritis Foundation 2003).

Most people suffer from transient events of synovitis or even RA at some time in their lives, episodes that are usually associated with infection. Almost invariably, these resolve themselves spontaneously. In rheumatic arthritis, the inflammation becomes chronic and persistent. However, this is a feature of many chronic inflammatory disorders. arc provided a research grant to the principal investigator (PI) to address the hypothesis that the apparent down-regulation of immune responses in RA may be a perfectly normal response to chronic inflammation in a specific environment. The role of T cells – types of white blood cell which are normally very effective at defending the body against disease – in this process is crucial but still unclear, since in some cases they begin to attack the body's own tissue, as in RA (ARC 2003). Hence, it is necessary to understand the regulation of T cell differentiation, memory and homeostasis[1] in normal individuals. This research project intended to illuminate normal and peripheral T cell differentiation and thus throw some light on the role of T cells in rheumatic joints.

Under this senior research fellowship (SRF), researchers found that primed T cells differentiate progressively in a pattern that can be followed by their inversely-related expression of two CD45 isoforms: CD45RB and CD45RO. All cells have exactly the same amount of CD45 in total, however, since CD45RB is inversely proportional to CD45RO, cells are marked with only one of the isoforms. The researchers originally showed that T cell memory involves the rescue of individual cells from a process of programmed cell death (apoptosis). Virgin T cells are stable, but following activation in response to infection they are maintained in continuous cycle by periodic re-stimulation. Crucially, cells progressively become more unstable with each cycle of activation

[1] The tendency to stability in the normal body states (internal environment) of the organism, which is achieved by a system of control mechanisms activated by negative feedback (Medical Dictionary Search Engine 2004).

and rest, and less likely to survive further re-stimulation. This process appears to define a limit to T cell memory maintained by continuously cycling primed cells, an important mechanism contributing to the maintenance of T cell homeostasis *in vivo* (arc archives).

8.2 Stage 0: topic/issue identification

The Department of Rheumatology, where the PI was based, was founded in 1981 following a £0.5 million endowment from arc, and has had a strong connection with the Arthritis Research Campaign since that time. Before applying for the senior fellowship grant the PI and his group had studied the state of differentiation, and function of cells from patients with established active disease, and patients with acute reactive arthritis. These studies were partly funded by arc grants, including:

- half the cost of a Coulter elite flow cytometer, 1990–1993, equipment grant, co-applicant (£65,000);
- "Lymphokine production by subsets of memory T cells", 1991, PhD studentship, applicant (£35,000); and
- "Just how naive are virgin T cells anyway?", 1991–1994, project grant, applicant (£65,000).

In addition, research conducted by the PI at the time of application was funded by various other sources, including grants from the Nuffield Foundation ("A search for specialised lymphokine production amongst human helper T cells", 1989–1991, £37,080) and the MRC ("The role of apoptosis in selection of memory T cells", 1992–1995, £125,000).

Before applying for an SRF, the PI had demonstrated commitment to research and had an established reputation in basic immunology and its application to the study of rheumatic diseases (arc archives). During the early 1990s the PI began to develop some fairly simple, but controversial, research questions with regard to the function of T cells in RA. The established research community was questioning why the inflammation that was observed in arthritis did not get better in the same way that normal inflammation did. The PI considered the process using a simple equation describing the cells in the inflamed joint: input – output + division – death = 0. This caused him to focus on areas that other researchers had neglected, including the issue of what prevented cells from leaving the site of inflammation and the other T cell development processes in inflamed joints. In addition to preventing T cells from leaving the inflamed joint the T cells also seemed to be surviving longer than would have been expected. This led the PI to investigate whether the T cells in the joint were somehow avoiding programmed cell death (apoptosis). Apoptosis was not a new phenomenon at the time of the SRF application, but the issue of rescue from apoptosis was a novel idea that was still controversial. These two insights into arthritic inflammation – the importance of factors retaining T cells in the joint and the existence of factors preventing their apoptosis – was a new perspective on inflammatory processes and has led to a number of important insights and new understanding.

Three years before this application, the PI submitted a proposal for SRF funding from arc (the proposed start was 1990, for five years, at a cost of £211,987). In it he proposed to "define the nature of the signals which influence lymphokine gene transcription, in order to understand the mechanism of coordinated lymphokine production" (arc archives). In the PI's perception, this

application was "much better than the proposal for the SRF". The referee reports were generally positive and the overall assessment indicated high estimates for the originality of the project, its potential practical value, suitability of the methods and standing of the applicant in this field (arc archives). A referee from an American pharmaceutical corporation indicated that the PI had the appropriate experience in the molecular techniques that was needed to perform the experiments outlined. Furthermore, he considered the PI to be a "skilled scientist who has made a commitment to research into the immunological basis of rheumatoid disease and deserves the support of the ARC in this application for a Senior Research Fellowship" (arc archives). Another referee, a professor of anatomy in the UK, thought that the PI had shown a "very careful and rigorous approach" in his work to the difficult problem of understanding the regulation of the immune response in RA. He also emphasised that this application merited serious consideration: "[the PI] is hardworking and has a good grasp of the field and is well aware of what is required" (arc archives). Despite these positive referee reports, some of which suggested that the SRF should be awarded, the application was rejected.[2] According to the feedback report, the proposed project was "very ambitious" and there were concerns about "how different external signals were to be examined" (arc archives). Also, it was felt that the PI's record to date was "perhaps not an outstanding one for this highly competitive area of research" (arc archives). However, these qualifications could not be traced back within the referee reports. These observations suggest that this application was not discarded due to insufficient quality of the proposal, but for other reasons. Because this was a fellowship application, a panel interview was also part of the selection process and there are suggestions from arc records that the PI's interview did not go well. The PI suggested, first, that at the age of 31, he might have been seen as rather young to be awarded an SRF; and second (although there is no evidence of this in the referees' reports), he felt that the SRF might have been rejected because the ideas behind the proposed study were seen as too controversial.

For these reasons, in his second attempt to apply for an SRF, the PI did not want to submit a proposal that would be regarded as highly controversial. Although his ideas remained radical, in order to secure funding for the research, he wrote and submitted a fairly general and less controversial proposal. He emphasised that it would be worth conducting the research, and he reverted mainly to the field in which he had a solid reputation.

The PI indicated that his relatively new perspective on inflammatory processes lacked responsiveness from his colleagues in the field of rheumatology. He felt that he was not regarded as part of the mainstream, since neither did his fairly unconventional ideas follow a well-defined path, nor did they have a strong theoretical background. Despite these sceptical views in the rheumatology field, the PI still believed that his ideas could induce a fundamental change in RA research. Hence, he decided to submit an application for a senior fellowship grant regardless. Since the PI had a strong connection with arc, he applied for funding there. An abstract of the proposed research is provided in Box 8.1.

[2] The arc archive material does not indicate conclusively whether these reports were written by external or personal referees.

Lymphocyte differentiation and function in rheumatoid arthritis (1993–1998)

T cells are a prominent feature of chronic rheumatoid synovitis, but their precise role is unclear. We have concentrated on CD45 as the principal marker of differentiation in CD4 T cells. A large range of isoforms exists; we have correlated the expression of CD45RA, RB and RC to CD45RO, and shown a spectrum of differentiation among primed cells. Cytokines[3] production also shows a progressive change with the state of differentiation. We have shown a selective accumulation of $CD45Rb^{dull}$ cells within the inflamed synovium which function poorly in terms of cytokine production and activation.

The aims of this proposal are to elucidate the state of differentiation and the function of T cells in early and established rheumatoid arthritis. The cytokine production of cells defined by CD45 isoform expression will be examined at the time of isolation, over progressive rounds of activation, and in relation to various culture conditions intended to reconstitute the *in vivo* microenvironment. The functional interactions of different populations will be studied in co-cultures. The precise role of different isoforms in immunological memory, and the question of whether this is an irreversible differentiation pathway, will be addressed. The role of apoptosis in the selection of memory T cells will also be examined. These studies will both derive from, and directly enhance, an understanding of clinical disease.

(SOURCE: arc archive)

Box 8.1: Abstract

As described in the application (arc archive), the long-term aim of this study was to achieve an integration of the areas of differentiation and the function of T cells in early and established RA. This integration was to lead to a clear model of immunoregulation in RA. The specific and medium term objectives of this proposal were as follows:

1. a detailed characterisation of the relationship of CD45 isoform expression to lymphokine production and synergistic interactions of helper T cells;
2. an analysis of memory in $CD4^+CD45RA^+$ T cells;
3. the role of apoptosis and protection in the selection of memory T cells; and
4. the relationship of lymphocyte differentiation to immunoregulatory function in the rheumatoid synovium.

8.3 Interface A: project specification and selection

The application appeared to be reviewed by four referees, and the candidate was interviewed also in competition with seven other candidates. One of the referee reports in the archives was unattributed, and therefore could have been part of one of the other reports. A qualitative assessment of the referees' comments is given, because the assessment matrix used for project grants is not applicable for SRF grants. Each of the referees was asked to deliver a written review assessment of the SRF application. This summary is based on these three reviews (arc archives).

[3] Chemical messengers that control the activity of cells, particularly of the immune system.

In general, the referees considered the proposal to be "schematic, somewhat superficial and underdeveloped", especially when comparing it to the top basic research grants in the US (referee A). The application was essentially a "descriptive study with some potential for future studies, which may elucidate the origin and regulation of memory T cells in rheumatoid arthritis" (referee A) and it did not have well-defined testable hypotheses. Moreover, according to referee A, this referee would have probably been inclined to fund this application if it were a US application. Referee B also had a slight reservation about its theoretical basis (see Aim 1). Referee C added that "the work is of a detailed descriptive character; no strikingly new thinking or methodology is involved", nor is it "intellectually stimulating".

Nevertheless, the three referees acknowledged that the area of proposed research was clearly important and on the cutting edge of clinical research for RA. They felt that the questions were interesting and would certainly throw some light on normal T cell differentiation and, perhaps, rheumatoid joint pathology. Hence, they felt it could be of groundbreaking significance for the understanding of the processes causing RA. The referees were impressed with the reputation and the experience of the applicant; he was regarded as "a highly competent individual" (referee C) and has "made the area [of T lymphocyte differentiation and its role in RA] his own. The applicant also has strengths in his methods and key collaborators". The PI's department has had a "long and successful interest in the role of T cells in the pathogenesis of RA" (referee B) and its "research environment clearly meets the requirement for a multidisciplinary setting with a strong clinical impute" (referee A). Therefore, the referees were confident that the applicant was capable of carrying out the proposed research.

In some instances the referees referred to specific research aims in the application. The key comments for these four research objectives are discussed below.

8.3.1 Aim 1: elucidate the relationship between CD45 isoform expression and cytokine production in $CD4^+$ T cells

Referee A believed that the applicant "has the assays and flow cytometry methods in hand to carry out his aim" and in the perception of Referee B "the review of the background and presentation of data is excellent". However, he believed that the only serious flaw in the application was related to this first aim. He mentioned much work recently suggests that the TM1 and TM2 phenotype may depend on environmental influences at the time of T cell stimulation. He suggested that the existence of this relationship "could have a crucial bearing on the experiments proposed, since CD45 isoforms may reflect differentiation, ease of induction of apoptosis, etc, rather than cytokine production". The applicant's assumption, that the very low grade of functional activity in $CD45RB^{dull}$ state cells will result in minimal acceleration of damage to joints, was considered premature by referee B. He believed that these cells could be involved just as easily in joint destruction by the release of as yet undefined cytokines. Furthermore, referee A included the critique that this first objective was "essentially a descriptive study and is not hypothesis driven".

8.3.2 Aim 2: analyse memory responses of $CD4^+CD45RA^+$ T cells

This aim is particularly worthwhile, according to referee A:

> The applicant alludes to [the] possibility that different antigen presenting cell sources vary in their ability to activate RA^+ versus RO^+ $CD4^+$ cells. However, he does [not] really propose any detailed experiments other than [that] he wants to continue working in this interesting area.

8.3.3 Aim 3: investigate the role of apoptosis versus the selection of memory T cells

Referee A thought that the third aim was clearly one of the stronger ones of the application: "[It] is a very important area to continue to support and may be quite relevant to the potential dysfunction in RA." He also acknowledged that the PI had made "important contributions to this area and has the assays for monitoring and preventing apoptosis".

8.3.4 Aim 4: focus on CD4+ T cells in rheumatoid synovium

The final aim was clearly appropriate and worthwhile, according to referee A Despite the hypothesis that $CD45Rb^{dull}$ cells and synovial fluid are different, "it is possible that unclear results will be obtained or that the populations are similar". It was not clear to referee A what the appropriate control population would be: "this is not discussed sufficiently in the application".

8.4 Stage 1: inputs to research

8.4.1 Funding

The PI applied for a research grant of £288,074 for a period of five years covering £213,811 in salaries and £72,200 in consumables. However, arc indicated that his salary was already covered for two-and-a-half years by a programme grant held by the head of his department. Consequently, for the first two-and-a-half years, his salary (£65,709) would continue to be paid from this programme grant but was formally transferred to the SRF. According to the grantholder, this did not impose any restrictions on the work conducted during his fellowship, since he already gained a substantial amount of independence under the programme grant. In effect, he continued those activities and did not consider it to be unreasonable that arc would not fund this work twice. This reduction would have left £222,365 on the SRF, however, it was reduced further for other reasons, including the decision that the five years of technical assistance that the PI had requested would not be fully awarded by arc, which in the end funded only three years. The arc award remaining was for £170,310 over five years (arc archives).

The PI's SRF was funded by a single general bequest from a former supporter of arc who died in 1992. His executors and solicitors particularly requested that the legacy should be used for a specific research fellowship and arc agreed that this fellowship would be named after the particular individual supporter of arc (arc archives). The PI was nominated to become the recipient of this fellowship. The letter describing the nomination gives the reasons that the PI was regarded as an up-and-coming research scientist, his research was fairly central to the objectives of arc and that the Department of Rheumatology to which he was attached was regarded as a good unit (arc archives).

In January 1995, the university where the PI was based requested additional funding for the PI's salary due to an administrative oversight by the university's financial department. According to an arc internal memo from the chairman of the arc Fellowships Committee, arc was surprised by the size of the discrepancy; however, this memo also noted that, had the application been originally submitted with the intended salary costs, "it was most likely that this would have been awarded in full" (arc archives). Therefore, the requested additional amount of £13,432 was

awarded in May 1995, which brought the awarded amount to a total of £249,451.[4] Overhead costs for the senior fellowship grant were provided by the university.

In addition to the SRF, the PI and his team had various other sources of funding at the time, including grants from the Biotechnology and Biological Sciences Research Council, Nuffield Foundation, an arc clinical fellowship, an arc PhD studentship "Lymphokine production by subsets of primed helper T cells" (1991–1994) and several arc project grants, including "Why are Rheumatoid synovial T cells resistant to apoptosis?" (1994–1996) and "Why are Rheumatoid Arthtitis T cells resistant to apoptosis?" (1996–1998).

8.4.2 Human capital

The grant covered the full salary of the PI and a technical post, which was fulfilled by a technical assistant. Additionally, various other scientists and PhD students were involved in the activities conducted under the SRF grant.

8.4.3 Techniques, reagents and equipment

The research involved various techniques (eg cellular immunology, flow cytometry, polymerase chain reaction and mRNA analysis) and equipment (eg Elonex 486 computer with basic software, Techne PHC3 dri-block, Gilson pipettes (six), MSE microcentrifuge and minigel apparatus and powerback). These are fairly standard methods and instruments and therefore not specific to this research. However, the PI's experience with flow cytometry was central to the grant application.

8.5 Stage 2: research process

This senior fellowship enabled the PI to build an effective research team and pursue a range of topics centred on the relationship between T cell differentiation, apoptosis, homeostasis and cytokine regulation. These studies involved research on basic immunity and clinical diseases, particularly RA.

8.5.1 Research targeting, capacity building and absorption

The original SRF grant covered three years' salary for a technical post. However, it rapidly became clear that the technical assistant was highly competent and overqualified for the salary grade that he was receiving on the grant. Therefore, the PI asked permission to promote the technical assistant from Technician grade C to Research Associate 1b. arc agreed to this suggestion, provided that it would be cost-neutral for arc. Because the promotion increased the technical assistant's salary, arc would only fund him for a shorter period than initially planned. This could have been a problem for the PI, however, after working on the SRF, the PI successfully applied for additional grant for an extra period, which enabled the technical assistant to conduct PhD research at the PI's department.

[4] £328,000 in current value. This amount includes the salary (£65,709) which was transferred from the programme grant to this SRF.

8.6 Stage 3: primary outputs from research

8.6.1 Knowledge creation

Working model for T cell differentiation

The PI has benefited by closely integrating these basic and clinical studies to devise a working model for T cell differentiation which has generated considerable interest in the field. He and his team retested the concept of progressive differentiation that underpins much of the work by measuring telomere lengths in cells sorted from blood by CD45 phenotype into recently recruited and highly differentiated populations. He found that highly differentiated primed cells ($CD45RB^{dull}$) have much shorter telomeres than those ($CD45RB^{bright}$) cells recently recruited from the $CD45RA^{+}$ pool. This evidence strongly supports his model of post-thymic T cell differentiation. He also showed that although the overwhelming fate of T cells recruited to, and expanded in, the primed population is death by apoptosis, a small number revert to the stable state and are hard to distinguish from naive cells; this is an important mechanism to avoid depletion of antigen responsiveness over time. To perform these experiments the PI devised a novel limiting dilution analysis method for T cells which optimises co-stimulation and is therefore highly accurate. This method has been adopted internationally by many laboratories in the field.

The research conducted under the SRF contributed considerably to the understanding of inflammatory processes. The PI and his team discovered that the first few months that the synovium is inflamed, the resistance to controlled cell death (fibrosis) is regulated by macrophages. In this stage the disease is maintained by a different mechanism than in the longer term, and since this stage is reversible, the PI and his team anticipated that this should be the period in which to provide medication targeting the process. Rescue of T cells from apoptosis was caused by integrins,[5] expressed on structural cells (stromal cells). As mentioned before, the rheumatoid process appears not to be grossly abnormal, however, its consequences are; it is this interaction between T cells and stromal cells that causes the problem.

RGD-blockers

One offshoot of the this project, which has been developed to treat cancer and deep vein thrombosis (DVT), was some work that the PI did to unravel the side-effects of drugs termed RGD peptides. Cancer cells become malignant when they develop the ability to move to other parts of the body, spreading the cancer. DVT is caused by blood platelets clumping together and forming a blood clot in a vein. Both of these conditions are examples of inappropriate cell to cell interactions. These interactions often occur via integrin proteins. In 1986 Erkki Ruoslahti identified a class of short peptides, containing an Arg-Gly-Asp motif, that could block integrin interactions – because of the single letter abbreviations for the three amino acids, these were termed RGD peptides (Ruoslahti and Pierschbacher 1986). By the early 1990s RGD peptides were being prescribed to treat DVT and were in phase 3 clinical trials for preventing metastasis.[6]

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[5] Adhesion molecules, which are key to cell to cell interactions important in genesis of the cellular phase of the inflammatory response (Kansas University Medical Center 2004).

[6] Spread of the disease to other body parts.

Selected bibliometric indicators for case study H

Publication portfolio

Output

Number of papers 20

Collaboration

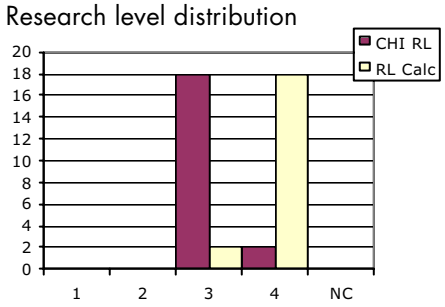
Mean number of authors 7.8

Mean number of addresses 4.1

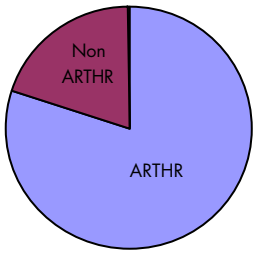
% with non-UK addresses 100.0%

Type

Research level distribution



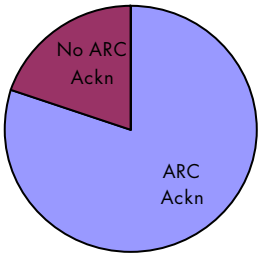
Field distribution



Funding

Mean number of acknowledgements 3.8

ARC funding acknowledgements



Knowledge flow

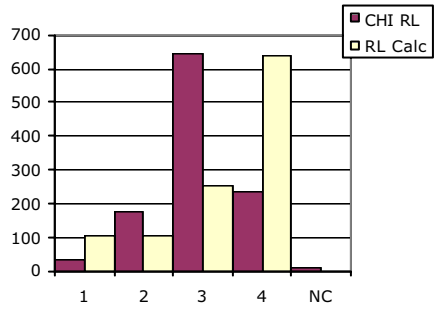
Strength

Mean citations per year (all papers) 107.9

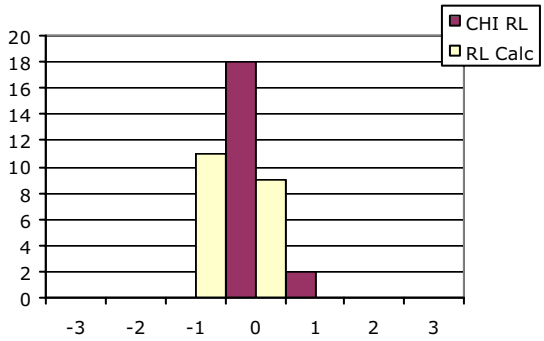
Mean C0-4 48.5

Knowledge translation

Research level of citing papers



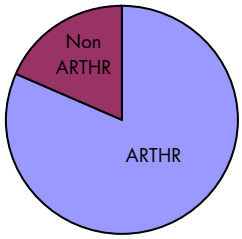
Relative research level



Knowledge diffusion

% of citations from the US 34%

Field distribution of citations



The peptides also appeared to lessen inflammation in arthritic joints, and this was thought to be due to their blocking of the integrins interactions necessary for T cell migration into the joint. The PI investigated this effect but was unable to identify the integrin on the T cells which the RGD peptides were blocking. It also became clear that the peptides had effects at far lower concentrations than would be necessary to block integrin interactions.

It eventually transpired that the RGD peptides were crossing the cell membrane of the T cells and triggering an apoptosis signalling pathway causing cell death. The T cells were not being prevented from migrating into the joint – they were being triggered to commit suicide. This observation was published in *Nature* (Buckley and others 1999). Prior to the PI's work it had been noticed that patients treated with RGD peptides for DVT had a slightly higher likelihood of heart attack and a cardiologist, Desmond Fitzgerald (Adderley and Fitzgerald 2000), then demonstrated that this was due to the signalling pathway identified by the PI.

Publications

The PI and his team contributed to a large amount of scientific papers, which were directly attributable to the SRF. The overview of papers published during and after the grant is restricted to the 1993–2000 timeframe (see Appendix A for a list of the peer-reviewed papers published by the PI and his collaborators which the PI indicated were directly attributed to the SRF). The PI's department also makes use of bibliometric analysis to assess the impact of its research. This department and its scientists have analysed which factors are crucial for a research institution to be successful and adjust their strategy to these factors. This may explain why the department has successfully established a reputable name in the field.

8.6.2 Research targeting, capacity building and absorption

This SRF has been crucial in the development of the careers of both the PI and the students and fellows working with him. Although the PI assumes that possibly other donors would have funded the research as well, he acknowledges that the arc SRF has had decisive positive impact on his career. In the PI's view, without the SRF the department (of which he is now head) would not even have existed. An important outcome in this area has been the establishment of an internationally recognised research team. The team's profile and expertise has enabled it to become a key player in the MRC Centre for Immune Regulation in Birmingham (established in 1999). The team has ensured that inflammatory joint disease is a key focus of the centre's activities. The Centre, in which various departments are represented including rheumatology, immunology, cancer studies and a liver unit, adopts a collaborative approach to study the multiple facets of immune responses in the context of selected diseases, among with RA.

The PI indicated a conflict of interest between the researcher and the university: while it is better financially for the university for its researchers to be funded externally through programme grants or SRFs, the scientist may prefer the long-term security that comes from a university appointment. In this case, the PI requested a long-term contract at the university 18 months before the termination of the SRF grant. However, as the university was in need of external funding, it preferred an extension of the arc grant. As a result, the PI considered leaving the Department of Rheumatology in favour of a position at the Department of Immunology. Finally, as a way to meet the PI's appeal, the Department of Rheumatology offered him a position as

[7] Spread of the disease to other body parts.

reader. Because this appointment was made prior to the end of the grant, the PI did not receive a site visit after four years of the grant as would have been expected. Several years later, the PI was made head of department.

The PI claims that all programme grants and project grants awarded to the Department of Rheumatology after 1997 are either directly or indirectly derived from the SRF. Furthermore, most of the colleagues with whom he collaborated at the time of the SRF are now leading scientists in the field of immunology and rheumatology:

- collaborator A: a fellow of the Royal Society and a researcher at an institute for cancer studies;
- collaborator B: a professor of rheumatology at a university division of cancer studies;
- collaborator C: a professor of hepatology and honorary consultant physician, a director of liver unit research laboratories at a university.

Furthermore, various PhD students contributed to the PI's research. Generally they remained active in the field of rheumatology and their careers have benefited substantially from their participation in the SRF:

- A: PhD (1995) "The progressive differentiation of primed T cells and its relation to immunological memory"; A currently holds a postdoctoral position in Nottingham;
- B: PhD (1996) "The mechanisms of T lymphocyte persistence in rheumatoid synovitis"; B is currently head of the immunology in laboratory at a university;
- C: PhD (1995) "The progressive differentiation of primed T cells and its relation to immunological memory"; after working for three years on the SRF as technical assistant, C applied successfully for additional grant. In this way he was able to conduct a PhD and continue working with the PI. Subsequently, he left for Houston, Texas, where he received a fellowship;
- D: PhD (1996) "T cell activation in rheumatoid arthritis"; D is now a consultant rheumatologist in Coventry;
- E: MmedSci (1997) "T cell cytokines in uveitis"; E currently holds a senior technical position in Leicester; and
- F: MMedSci (1993) "Immune complexes in autoimmunity" and PhD (1998) "T cell differentiation and repertoire use"; F currently holds a postdoctoral position at a university rheumatology department.

8.7 Interface B: dissemination

The SRF was referred to as a named fellowship in recognition of the bequest to arc from the individual supporter. In addition to arc requirements, which included the provision of an annual report, the grantholder was supposed to deliver an annual layperson's report to inform the fellowship's executors on progress and preliminary findings. The PI was convinced of the added value of such a deliverable, since each "research scientist should be able to communicate his work to lay-persons". Therefore, he suggested that a layperson's report should become a standard for

arc grantholders. According to the PI, these reports did not have an effect on the outcomes of the study, but they did help to communicate research to a wider public.

The PI visited various conferences. In 1994, for example, he submitted a successful abstract to the Keystone Symposia conference on lymphocyte activation. This conference involved a poster presentation (arc archives) and publication of the abstract in *Journal of Cellular Biochemistry* (arc archives).

8.8 Stage 4: secondary outputs – policymaking; product development

8.8.1 Informing policy and product development

So far, no specific products or policies have derived from this grant, although there have been some developments. The RGD work described above (see Stage 3: primary outputs from research) led to the development of KGD peptides. In these peptides the Asparagine amino acid is replaced by Lysine, producing a more polar peptide that cannot cross cell membranes and hence cannot activate the apoptosis pathway. These peptides are currently used and being tested in the treatment of DVT and the prevention of metastasis; however, as they do not cross the cell membrane they are not capable of causing T cell death and therefore are not useful as arthritis therapeutics.

The key to using RGD peptides in arthritis therapy will be targeting them to ensure that only the unwanted T cells in the inflamed joint are destroyed. The PI's group have not developed or patented their work in this area because: (1) they did not have the resources to do so; and (2) RGD peptides and their derivatives are covered by wide-ranging patents held by Erkki Ruoslahti, who originally identified the peptide motif (reviewed in Ruoslahti and Pierschbacher 1986). However, there are active programmes in industry pursuing the use of RGD peptides in arthritis with 20 to 30 patents being filed each year since 1995.

The PI has had a number of long-term industrial collaborators including Celltech and SmithKlineBeecham (now GlaxoSmithKline). The PI is happy to work with industry, provided that it does not place restrictions on his ability to publish. Industry will come to him for ideas or for smaller projects that he is better suited to carrying out. In return they may provide money or access to technology – for example, large-scale gene chip expression screening that otherwise the PI would be unable to use. One major barrier preventing collaboration is the reluctance of one industrial collaborator to allow work in partnership with both them and their competitors. The facilitators of collaboration are common interests and likeable personality.

8.9 Stage 5: adoption – by practitioners and public

No payback related to the adoption phase has been identified.

8.10 Stage 6: final outcomes

As yet, any outputs of this research grant to have fed through into a final outcome could not be identified.

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CHAPTER 9 Case study I: the pathophysiology of muscle in osteoarthritis

9.1 Introduction to the research project

Osteoarthritis (OA) is a very common form of joint disease in which there is damage to the surface of the joint and an abnormal reaction in the underlying bone. Sometimes various other words are used to describe this disease, including "osteoarthrosis", "arthrosis" and "degenerative joint disease". They all refer to the same condition, which chiefly affects knees, hips and hands (the most common form), as well as the foot and the neck and back (spondylosis), but does not affect other body tissues. OA causes pain, stiffness and disability, as cartilage wears away in the joint, making it rough and the joint difficult to move. Usually affecting only a few joints, OA causes painful limitation of joint movement with bony swelling and crepitus (creaking) on movement.[1]

While a large proportion of the total population of people who present with cartilage destruction – which is diagnosed in OA by X-ray – do not develop the characteristic symptoms of disability and knee pain, the remaining group of people do suffer from these symptoms. The factors that influence the OA process towards symptomatic OA or asymptomatic OA are ill-understood and it has been argued that muscle strength may be of crucial importance (McAlindon and others 1993). The ARC awarded the principal investigator (PI) a junior clinical research fellowship (JCRF) grant to test the hypothesis that muscle strength and the symptoms of OA are related. The objectives of the research were to characterise the pattern of muscle weakness (localised or generalised) in patients with knee OA and to determine whether reduced muscle strength correlates with the presence of cartilage damage or primarily with symptomatic OA. Another important objective of a JCRF (for arc) is to provide an opportunity for training in educational research methodology and/or medical education in a project relevant to arthritis.[2]

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[1] arc glossary definitions of rheumatic diseases: http://www.arc.org.uk/about_arth/glossary.htm (accessed 9 February 2004).

[2] arc grant schemes: http://www.arc.org.uk/research/schemes.htm (accessed 8 April 2004). At the present time arc no longer recognises JCRFs. Instead, arc awards educational research fellowships to clinicians (usually at specialist registrar level in rheumatology or general practice) and non-clinicians (including allied health professionals and educationalists).

9.2 Stage 0: topic/issue identification

Before submitting a research proposal for a JCRF to the ARC, the PI was a registrar in geriatrics (the medical specialty treating the diseases and problems of old age). Being interested in rheumatology and clinical research, he met with his supervisor, who had some soft-money[3] funding for research in this field with a focus on OA. Since the PI was a registrar considering a career as a clinical consultant, application for a junior clinical research fellowship did seem to be a clear-cut career move, and yet his supervisor managed to persuade him to be involved with research into rheumatology. The subject of muscle strength and its effect on OA, which had drawn interest from various scholars in the field, was suggested by his supervisor. The Department of Rheumatology at the Bristol Royal Infirmary had done some pioneering work (McAlindon and others 1993) in this emerging field of research. Driven by his interest in rheumatology and the enthusiasm of his supervisor, the PI wrote an application for a JCRF in this field.

9.2.1 Hypothesis initiation

When classifying patients that show the biological characteristics of OA (ie cartilage destruction) by X-ray, one may distinguish between patients with symptomatic OA ("decompensated") who show disability and knee pain, and patients with asymptomatic OA ("compensated"). The latter group, almost 50% of the total population of OA patients, show the radiographic characteristics of OA but do not feel any pain. McAlindon and others hypothesised that muscle strength was a key determinant of the manifestation of symptoms in OA. They suggested that OA patients with weak muscles are more likely to develop symptomatic OA than those with stronger quadriceps. To test this hypothesis, McAlindon and others conducted a study on the relation between muscle strength and OA. McAlindon's work was based on the assessment of so-called "voluntary quadriceps strength", ie the power that the patient is able to exert on a measuring device. According to researchers, this strength is based on physiological factors and is possibly influenced by a process called "inhibition" under the influence of knee OA. Inhibition is a reflex-stopping model contraction when there is a problem with the knee; this reflex prevents muscles from inflicting further damage on the knee. For acute situations this phenomenon is well understood (Hayes and Falconer 1992); however, in the case of chronic conditions such as OA, the process is ill-defined (Hammerman 1989).

The PI understood that voluntary assessment of muscle strength did not measure the maximum power that the quadriceps are able theoretically to exert. The reduction in strength seen in voluntary measurement could be due to psychological factors such as depression; when patients are feeling despondent, they do not try as hard during testing. This means that researchers using only voluntary strength would not be able to assess whether reduced muscle strength was due to physiological or psychological factors. Therefore, the PI suggested assessing both voluntary and maximum muscle strength to assess psychological effects; he proposed stimulating the muscle with electrical stimulus, and reading out how much power the muscle is using. This methodology would enable the researcher to test the hypothesis that patients with weaker quadricep muscles are more

[3] Soft money is money that is not tied to any particular project or programme.

prone to developing symptomised OA. The PI was encouraged by his supervisor to submit an application for a JCRF on this topic.

9.2.2 Failed application

Whereas identification of the research topic was initialised by his supervisor, the proposal was written primarily by the PI. The successful fellowship followed a failed application by the same researchers and on a similar subject several months earlier. The failed application proposed to test the hypothesis that decline in muscle strength is a factor leading to symptomatic OA. The fellowship panel had decided not to award this application because they "were very worried by certain aspects of the proposed project, particularly the muscle biopsy studies" (arc archive).

With regard to this failed application, the comments of only one referee were available in the arc archive. This referee acknowledged that the proposed area of research was important and that it had been investigated relatively little; however, he was left with many unanswered questions. First, he was not convinced that the applicant would be able to measure adequately muscle power and strength in the quadriceps and upper body. According to the referee, the instruments that were suggested for this measurement were renowned for their relative inaccuracy and uncertainty. Second, he suggested that it was well known that knee damage, pain or swelling can lead to muscle inhibition and that the method best able to assess muscle strength – isometric contraction – was not available to the applicants; in the absence of this, any attempt to measure strength or power would be virtually meaningless. In his view, the application lacked explanation of how the sample of OA patients and healthy people would be recruited and measured. Furthermore, the project as a training exercise would require substantial assistance from the supervisor. Finally, the referee felt that the suitability of the candidate was hard to assess – however, due to the excellent reputation of his supervisor this was not expected to be a key concern.

9.2.3 Re-application

According to the PI, the referees' comments were justified; there were areas in the literature of which he was not aware and he acknowledged that the emphasis of the proposal might have been misplaced. However, his supervisor did not consider the comments to be very useful. Whereas nowadays it is not possible to resubmit an application, at the time promising applicants were encouraged to re-apply. This provided the PI with the opportunity to rethink the project and come up with an improved research proposal. Therefore, during the following months the applicant had "taken the opportunity of taking wider advice from several experts in this field [osteoarthritis] and of further considering and modifying the details of the project, particularly in relation to the points raised by the reviewer" (arc archive). Experts included a muscle physiologist at University College London, department of medicine and a professor at the University of Bristol, department of social medicine, under whom the supervisor used to work on a clinical research fellowship (an abstract of the resulting application is given in Box 9.1). Before the JCRF was awarded, the PI and his supervisor had already begun the research project using soft money from his supervisor.

The hypothesis that muscle strength and the decompensation of osteoarthritis (OA) are related will be tested in subjects with symptomatic ("decompensated") OA knees and normal controls. Assessment will involve clinical features, customary physical activity, isometric muscle strength and muscle power. Using the method of twitch superimposition the role of reflex inhibition will be explored. Both lower limb and upper limb muscle will be studied in order to permit assessment as [to] whether this is a local or generalised phenomenon. This work will help to clarify the interrelationship between muscle changes and the OA process.

(SOURCE: arc archive)

Box 9.1: Abstract

9.3 Interface A: project specification and selection

9.3.1 Referees' assessment

The application was reviewed by two referees. The peer review process did not involve a quantitative assessment. Referees were asked individually to deliver a confidential written review assessment on the JCRF application and to focus on three areas:

1. the scientific quality of the proposed project;
2. its suitability as a training exercise; and
3. the suitability of the candidate for academic rheumatology.

A summary of the comments from the referees, which were retrieved from the arc archive, is given below.

9.3.2 Scientific quality of the proposed project

The referees' comments on the scientific quality of the proposal concentrated primarily on three issues; these are similar to the referee's comments on the failed application. These three issues are discussed in turn:

1. the soundness of the research question and the testability of the main hypothesis;
2. the recruitment of patients; and
3. the applicability of the methodology for the assessment of muscle strength.

9.3.3 Research question

Referee B did not consider the central research question to be a crucial one. To him, it seemed clear that a relationship between the symptoms and muscle strength would be established. However, once it had been found, the relevance of such a correlation would be unclear, since he acknowledged the certainty that all patients tested would show reflex inhibition, whether symptomatic or asymptomatic. When confronted with this statement the PI considered this comment to be proven wrong by his work and that of subsequent researchers (as will be shown in Stage 4: secondary outputs).

Referee A was concerned about a notable omission in the approach to test the hypothesis that there was a correlation between muscle strength and decompensation of OA: investigation of muscle size. In his view, muscle atrophy and muscle weakness could not be separated, and although causes and effects are very different, both were likely to be present

in OA. To help the interpretation of the results, the referee recommended separating these phenomena by adding measurements of muscle size to the proposed protocols, even at the cost of omitting some other measurements.

9.3.4 Recruitment of patients

Referee B had reservations about how to recruit the correct sample of patients. Although the title of the grant suggested that the study would focus on pathophysiology of muscles in general in OA, the application refined the scope by excluding patients with hip OA. The referee mentioned that the proposal did not explain how the researchers would ensure that hip OA was not present.

9.3.5 Assessment of muscle strength

Finally, Referee B detected more unsatisfactory elements in the proposal with regard to the use of the leg extensor power rig to assess muscle strength. According to the proposal, other groups had not encountered any difficulties in employing this method in patients with mild arthritis. However, his concern stemmed from personal communication without a particular reference mentioned. Furthermore, it was not clear to the referee how the patients were to be differentiated, since "the symptoms due to knee OA vary enormously both with time and from patient to patient so that some patients could quite conceivably move from group one to group two". According to him, this led to the question of whether "it is really justified to lump together all patients with any kind of symptoms due to osteoarthritis of the knee".

9.3.6 Suitability as a training exercise

Both referees accepted the suitability of the project as a training exercise. Referee A thought that the trainee would certainly gain experience of a good range of techniques from the proposed study, while noting that it was an ambitious project for two years. He argued that the real scientific training would come with the attempt to draw conclusions from the data gathered. For this analysis, the referee suggested support from experienced scientists, such as the proposed supervisor of this study. He pointed out that the proposal did not indicate to what extent this scientific support was available.

9.3.7 Suitability of candidate for academic rheumatology

Both referees were happy with the quality of the applicant. Although referee A claimed that he was not able to make any comments on this, since he was not familiar with career patterns in the field of academic rheumatology, referee B had no doubt about the capabilities of the trainee. Since he knew his supervisor fairly well, he assumed that the trainee "will be given a very good grounding in rheumatology and could well have much to offer the sub-speciality".

9.3.8 Overall assessment

The referees appeared to agree that the proposed study could well be suited as a training exercise in academic rheumatology; however, they were less convinced of the soundness of the scientific programme. Although referee A was generally supportive of the application with only some reservations about the science, referee B remained dubious about funding the fellowship. He argued that the present proposal was indeed an improvement on the application that had recently failed. However, in consultation with the head of the research physiotherapy group in the division of biomedical sciences, referee B thought that:

> [W]hile there is nothing obviously wrong or terribly inappropriate about it, it just seems very unlikely that the study will come up with findings of any real importance. The scientific rating of this application therefore cannot be considered to be very high.

The PI was interviewed in competition with 10 other candidates and the award panel decided to award a two-year fellowship on two conditions: namely, that the trainee should attend a specific statistics course; and that he would take detailed epidemiological advice about the project. Therefore, the panel recommended contacting an expert at the arc Epidemiology Research Unit (arc ERU) in Manchester. Selected referee comments were passed onto the supervisor (arc archive).

9.3.9 Epidemiological advice

As a consequence, an expert from the arc ERU was asked to provide detailed epidemiological advice about the project. However, in his reaction (arc archive) he claimed that it was not clear to him exactly what the arc assessors had in mind when requesting his advice. He did not feel able to offer much feedback, as it seemed to be a sound application to him. He remarked that although he had not been able to check the power calculations in the application, the numbers seemed to be intuitively sound. The PI felt that the peer review panel lacked epidemiological expertise and therefore wanted to ensure that this area would be covered. The supervisor suggested also that the panel requested additional advice in areas in which it felt insecure. Neither the PI nor the supervisor had further inquiries to arc related to this epidemiological advice comprehended since, as he stated, "there was not much of a dialogue back then".

Despite suggesting that he did not understand the reason for consultation, the epidemiologist commented that he had similar reservations to the referees with regard to the recruitment of patients. He suggested recruiting "asymptomatic OA patients from either X-ray screening of normal individuals, or from individuals who were both asymptomatic as far as knees were concerned but yet referred for X-ray". The PI thought this remark was sound and justified, however, he lacked the resources to attempt this.

9.4 Stage 1: inputs to research

9.4.1 Funding

The applicants (the trainee and his supervisor) applied for a total grant of £47,330,[4] covering only the salary costs for the trainee, who received "registrar" as the grade of honorary clinical contract (arc archive). Expenses for materials and consumables were met by the Rheumatology Unit Research Fund, of which the PI's supervisor was in charge (arc archive). During the course of the grant the ARC decided that junior clinical research fellows should be entitled to an additional sum of 20% on salary in lieu of loss of income from "on-call" work. Therefore, the university where the PI was based requested a corresponding increase in salary allowance. The increase over the two years including on-costs was £9,466, which was approved by arc. The total amount of the grant over two years was then endorsed at £56,796.[5]

[4] £65,000 in current values.

[5] £78,000 in current values.

The university charged 40% overheads on top of the salary costs for expenses, such as library availability. The supervisor has been able to attract a considerable amount of alternative grants from various sources, mainly the pharmaceutical industry. Through this additional funding the department managed to achieve 15% of the total of 40%, which provided an opportunity to spend this on such elements as additional employment and computer costs. The supervisor indicated that in the last four years (1999–2003) his department had "received more than £2.5 million worth of funding from industrial partners", among which was GlaxoSmithKline. These funds are "no-strings-attached", implying that the department is eligible to spend it according to their needs. This has been very useful for the JCRF, because the fact that arc fellowship applications tend to extend for a period up to six months caused a funding problem for the PI and his supervisor. Therefore, during the process of application and re-application period the PI had already commenced the research on soft money from so-called "discovery grants" funded by industrial collaborators. Nearing the end of his JCRF, the PI applied unsuccessfully for an extension of his fellowship grant (the reasons for the rejection of this application are discussed in Stage 2: research process). Since the research had not been finished when the fellowship grant was determinated, the PI used another six months to finish his work funded by soft money from his supervisor. The department had also received various arc project grants, a few other fellowships and an Integrated Clinical Arthritis Centre (ICAC) grant all the way through to the present time. ICAC grants provide the necessary infrastructure to promote the development of clinical research programmes in departments of academic rheumatology.[6]

9.4.2 Human capital

Prior to the beginning of the fellowship the PI was a registrar in geriatrics, while his supervisor was a professor in rheumatology. The department has a good track record, according to the supervisor, although it has not had any clinical researchers who ended up with a clinical PhD. Under the supervisor all the researchers received an MD (Doctor of Medicine), which he considered as equally valuable as a PhD.

9.4.3 Techniques, reagents and equipment

Clinical findings in the knee would be scored using a refined scheme that was being validated at the time of application: the Nottingham Knee Score (Doherty and others 1988). OA changes in the knees and hands would be scored blind and body mass index was to be recorded from height, demispan[7] and weight.

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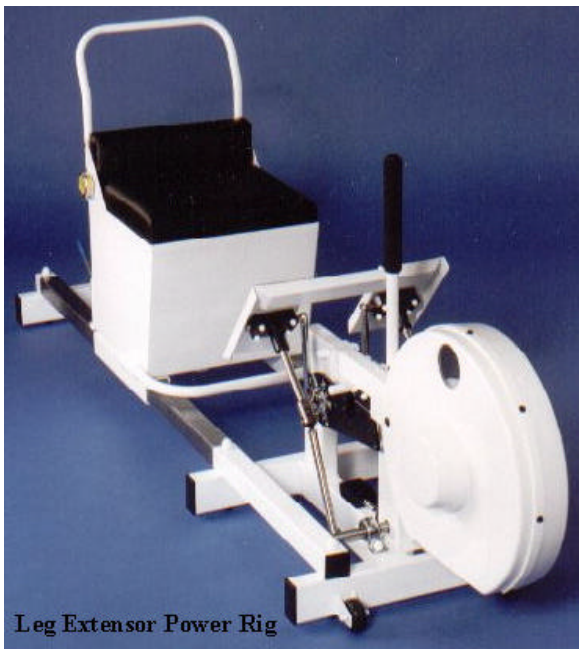
[6] arc integrated clinical arthritis centre grant: http://www.arc.org.uk/research/forms/icac.htm (accessed 6 April 2004).

[7] The distance between the sternal notch (the most superior part of the breast bone) and tip of the middle finger of the outstretched arm.

Initially, there was no consensus as to the most appropriate method to employ in the assessment of muscle strength. A leg extensor power rig (see Figure 9.1) was built locally by developers at the university, who were involved in the application for this study (Bassey and Short 1990). This method had the disadvantage that it tested more than one muscle group and was not amenable to testing for reflex muscle inhibition using "twitch superimposition" (Rutherford and others 1986).[8] Moreover, although other research groups using the leg extensor power rig had not found difficulties when applying this method to patients with mild OA, its acceptability in patients with more severe arthritis had not been tested. Therefore, for this project the measurements were complemented by an isometric method for measuring quadriceps, biceps brachii and abductor pollicis brevis.[9] The severity and pattern of any weakness would be determined and any correlation with intrinsic neuromuscular change or reflex inhibition (arc archives) could be examined. Isometric quadriceps muscle strength was measured with a modified Tornvall chair (Tornvall 1963).



(SOURCE: Nottingham University website: http://www.nottingham.ac.uk)

Figure 9.1: Leg extensor power rig

[8] Twitch superimposition provides a method of assessing absolute muscle strength to compensate for psychological factors.

[9] The biceps brachii is the arm biceps. The pollicis brevis is the muscle for flexion and adduction of the thumb.

Three groups of patients were to be recruited, requiring 40 individuals per group. The groups were matched for age, gender and ethnic origin and hip patients were excluded. The three groups comprised:

- symptomatic knee OA patients;
- asymptomatic knee OA patients; and
- normal matched controls.

Using these techniques, the study intended to determine the mechanism by which muscle weakness was caused. A number of methods and instruments were used (or planned to be used) to achieve this objective:

1. a semi-automated method of EMG analysis was employed to determine the presence of any abnormal conditions of muscle tissue (myopathy);[10]
2. a needle muscle biopsy study in a limited number of individuals using well-recognised techniques (eg Bancroft and Stevens 1990; Blomstrand and Ekblom 1982) was planned. The Department of Histopathology at the university could provide the pathology facilities to freeze, orientate, store and process muscle biopsy specimens. All the specimen preparation, histological staining and interpretation was performed by the PI under the supervision of an expert of the Department of Histopathology, who had wide experience in interpreting needle muscle biopsies. Many of the methods were quantitative and semi-automated but help was required with histological interpretation of haematoxylin and Eosin-stained[11] material.
3. raised intra-articular pressure is a mechanism by which both acute reflex inhibition of muscle and more chronic changes may occur (Jayson and Dixon 1970). Little is known concerning intra-articular pressure in OA but techniques by which pressure can be measured are becoming more available (Blake and others 1989) and if time permitted, the researchers intended to utilise these (arc archive).

9.5 Stage 2: research process

9.5.1 Staff development

An important objective of a JCRF is to provide training in research skills and techniques in order to prepare the trainee for a career in rheumatology. Therefore the supervisor has an important role in providing the necessary research support and training. In the case of this JCRF the training involved a statistics course, which was paid for by the Department of Rheumatology headed by the supervisor. The PI valued this course as very useful, although it did not apply to the work for the JCRF very much. Nevertheless, since the successful completion of this course the PI has been involved in providing statistical advice for

[10] An EMG is a graphic representation of the electric currents associated with muscular action. It can be used to evaluate nerve and muscle function. See: http://www.sprojects.mmip.mcgill.ca/neuropath/glossary/glossbot.htm.

[11] Chemicals for staining tissue for microscopy.

various studies. The intensity and level of supervision and training was scant, hence it was necessary for the PI to have a high level of autonomy. Although the PI would have wished for a more structured and well-defined training path, he considered his autonomy as an incentive to develop self-reliance and noted that it forced him to develop critical research skills. In this way he had gained research experience and learned methods that he would not have done otherwise. However, this also caused him to spend a considerable amount of time on peripheral issues, which he was not able to delegate. Consequently, the PI thought that there was a lack of time to stand back and retain an overview. Additionally, the infrastructure at his department, with a secretary and two research fellows, was not well developed to provide research support such as patient recruitment, etc. Therefore, the PI had to conduct basically every subtask of the research himself: patient recruitment, statistics, patient assessments, etc.

9.5.2 Project-related difficulties – institutional problems

The supervisor supposed that it was a problem for the PI to be in a relatively small unit. The professional infrastructure was fairly narrow and there were few academics with whom the PI would have been able to discuss matters.

9.5.3 Supply and material problems

The construction of the device to assess isometric quadriceps muscle strength, the Tornvall chair, imposed a critical time delay in the research process. The Department of Medical Physics at the university had responsibility for the construction. Whereas the leg extensor power rig had not caused any problems, getting the right equipment for the Tornvall chair took the university 13 months. Since this device was crucial to the assessment of muscle strength, the construction problems delayed the project by approximately one year. This was possibly beyond the PI's control; however, he felt that he might been able to expend more effort in holding the university to its deadlines. These problems caused a delay in the JCRF study, but the PI's supervisor thought that the PI had spent this time profitably on different studies.

The leg extensor power rig was developed and functioning in time. Patients were asked to sit on this chair, which did not provide much support, and push down the pedal quickly (see Figure 9.1). Since this involved a complex movement, it appeared that users learned relatively easily how to get the best results. This learning effect may have influenced the measurement of voluntary muscle strength.

9.5.4 Persistent difficulties

As the referees had already identified in the peer review process, the recruitment of patients was a weak spot in the research set-up. The PI recognised such difficulties with the approach for the recruitment of patients: OA patients were recruited from radiographic assessment in a clinical environment and the spouses and other people who accompanied patients were used for the control group. According to the PI, a target of 40 patients in each group was overambitious and the approach that had been followed was not ideal. The study was slightly flawed in this area and in retrospect he would have used a completely different set-up. However, the supervisor thought that for the available resources, especially with regard to funding, the method of patient recruitment used was appropriate. The ideal approach would have involved at least 1,000 patients diagnosed with OA and a control group of at least 1,000 people who were healthy. This approach would not have been

feasible with regard to costs and study conduct. A subsequent arc JCRF, which was held by one of the PI's colleagues, built on the experience and results of the PI's JCRF and did use an improved approach to patient recruitment, by recruiting volunteers from all three groups in the community.

Due to various problems, in particular those associated with the development of the Tornvall chair, the PI had difficulties producing any results within the timeframe. In all, the study had not delivered what it promised to deliver and therefore arc decided not to award an extension to the fellowship.

9.6 Stage 3: primary outputs from research

9.6.1 Knowledge

This fellowship was concerned with examining more closely the association of muscle weakness and outcome in OA. Evaluation of clinical assessment has demonstrated that, provided that single observers are employed, clinical assessment of physical signs is reasonably reproducible. The elements of the history and examination that previously comprised a single "inflammation" index for knee OA were included in the study. Previously, radiographic assessments of OA were particularly poor for the assessment of patellofemoral OA,[12] the JCRF produced a grading system that is both reproducible and sensitive for patellofemoral osteoarthritis. The system has been applied to 200 radiographs of hospital-referred patients with knee OA in order to determine more precisely patterns and associations of structural change in knee OA. It has also been applied to patients undergoing evaluation of disability and muscle strength.

Patients with high degrees of self-reported disability demonstrated reduced quadriceps strength compared to those without disability. However, in contrast to previous reports a significant number of patients with knee OA demonstrated inhibition. This inhibition was not relieved by aspiration of synovial fluid[13] and it did not seem to be reduced by injection of intra-articular steroid. Analysis showed that the best correlate of inhibition is self-reported anxiety and depression; this raised concerns regarding the current methods that are used in assessing disability and the influence of psychological factors. On a more positive note, it suggested several strategies whereby self-reported disability, ie the patient's perception of their his or her health status, could be improved (arc archive).

After the end of the research grant, the PI extended his study, supported by soft money from his supervisor, despite the rejection of a fellowship extension.

When the Tornvall chair was finally finished, the expertise was in-house to build such a device. The PI was involved in advising several other researchers on how to build and use it for research purposes. However, the study also revealed that twitch superimposition is not a required technique when a study aims at therapeutic intervention in OA. A fairly simple chair is sufficient to assess muscle strength without the need to stimulate the muscle

[12] The patellofemoral joint is one of the knee joints. This is a matter of concern, since patellofemoral disease might be expected to be a significant cause of quadriceps dysfunction, and hence disability (ARC Scientific Reports 1992, published by arc).

[13] Aspiration is a medical intervention to remove synovial fluid from the joint space.

electrically. Although commercial physiotherapy devices such as CYBEX (cardiovascular and fitness/strength training) machines are expensive, they are available for such tasks. At the time of research these instruments were available, however, the PI and his colleagues did not have the contacts in physiotherapy or the financial resources to use them. Alternative and affordable methods to assess muscle strength, such as the leg extensor power rig, proved to be reasonable for their purposes despite their disadvantages.

During the course of the fellowship it became apparent that the recruitment process was not ideal, there were problems both with approaching patients in a clinical setting and using spouses as a control group. This control group can be biased for various reasons, including the fact that spouses may not be normal. Additionally, there are ethical issues relating to possible perceived coercion. Finally, possible sample biases include the possibility of a skewed gender mix and a different age distribution from the patient sample. In collaboration with various experts in the field, whom the PI met informally or at meetings of the International Research Society of Osteoarthritis, a more suitable approach towards recruitment of patients was developed, which was used in subsequent work on an arc project grant held by researchers from the same rheumatology department. In this study a postal survey was sent to 9,296 patients aged 45 and over who were registered at two general practices in Nottingham (Thomas and others 2002).

As an integrated component of the work conducted under the JCRF, the PI had had to analyse radiographs in order to identify OA patients. However, considerable divergence existed with regard to the methods to assess these X-rays; the academic literature was ambiguous as to how to X-ray OA and the symptoms that clinicians should look for when assessing these radiographs. Often, radiographic OA is not detected on standard anteroposterior (AP or PA) radiographs, which only image the tibiofemoral[14] joint. To detect OA in the other joint in the knee, the patellofemoral joint (which connects the kneecap and the end of the femur), skyline or lateral views are needed (Chaisson and others 2000). Therefore, a grading system has been developed, comprising assessment of osteophytosis,[15] joint space narrowing, sclerosis, cysts and attrition, which could be applied to the skyline patellofemoral view (Jones and others 1993; Ledingham and others 1993). The minimum joint space in each compartment was measured using a ruler. Two views of a single normal subject were measured to determine the effect of knee flexion. The measurement using a ruler was relatively easy to perform. The PI evaluated the system and readily achieved radiographic grading of the skyline patellofemoral view. The results of this system are more reproducible than assessment of the lateral view and allow more precise localisation of change. Although, initially, it was not one of the intended key outputs, it has been a very successful outcome of the JCRF, and has contributed to the international debate on X-ray grading.

9.6.2 Research targeting, capacity building and absorption

At the end of the JCRF, arc had decided not to extend the fellowship. Because of the lack of external funding, his supervisor provided the PI with a soft-money extension for about another year in order to finish the work that he had begun on the fellowship. In August

[14] The tibiofemoral joint consists of the end of the femur (thigh bone) and the end of the tibia (shin bone).

[15] The outgrowth of immature bony processes (psteophytes) from a bone.

1993 he accepted a combined position as senior registrar at both Leicester and Nottingham, which was a usual career step at the time. Finally, in October 1994 he finished his MD thesis which was based on, but not confined to, the work on muscle and OA that he had conducted under the JCRF. Later he became a consultant in rheumatology and general medicine in the hospital where he had conducted his JCRF research.

Despite the fact that the PI encountered various difficulties and frustrations (for example, with respect to the development of the Tornvall chair and the non-extension of the JCRF) during his fellowship, he considered the JCRF as "fabulously valuable". He found this period to be "one of the few times in his career that he had really time to sit down and think". He attributed a large part of this success to his supervisor, who introduced him to a range of experts in the field, would allow him to take the initiative and would never take credit for something that he did not do. The PI claims that he is now a better clinician as a result of the experience that he had during the fellowship; the training was not rigorous, but it gave him the incentive to take the initiative and develop research skills.

As a result of the PI's pioneering work, the Department of Rheumatology had gained significant expertise in the role of muscles in OA. Moreover, it had learned from the difficulties and mistakes made during the JCRF; the testing techniques, such as the Tornvall chair, were already in place and the researchers knew that patients should be recruited from the community instead of the hospital population. Based on this JCRF, the department was able to apply successfully for a project grant to show that intervention in muscle strength would improve outcome. This subsequent study was essentially an extension of the JCRF, since it tested a similar hypothesis. A junior fellow and the PI's supervisor, who conducted this randomised control trial, included 200 community-dwelling adults with knee OA for a period of six months. The study compared groups that had a period of aerobic walking with programmes of resistance exercise and health education, for their effects on self-reported disability, physical performance, aerobic capacity, strength, radiographic signs and pain, with a control group. As the PI had hypothesised several years before, the study found evidence that inactivity produces and progresses the signs and symptoms associated with arthritis, namely muscle weakness and atrophy, decreased flexibility and cardiovascular fitness, osteoporosis, depression and lowered pain threshold (O'Reilly and others 1999). Furthermore, it showed that people with knee OA can tolerate weight-bearing exercise such as walking. An important conclusion was that a simple programme of home quadriceps exercises can significantly improve self-reported knee pain and function. In fact, according to a review at the University of Missouri (King and Minor 2003), the study shows great benefits in exercise for people with OA.

As was discussed above, the JCRF fed into a project grant held by the Department of Rheumatology. This project grant validated the hypothesis that inactivity produces and progresses symptomatic arthritis, which was already laid down in the JCRF, in a sound and consistent manner. These results led to an extensive subsequent study with 800 patients funded on a grant from the Department of Health and the British Occupational Health Research Foundation. This study extended to a two-year timescale and showed that exercise in OA helps to relieve disability and pain (Thomas and others 2002). This project

Selected bibliometric indicators for case study I

Publication portfolio

Output

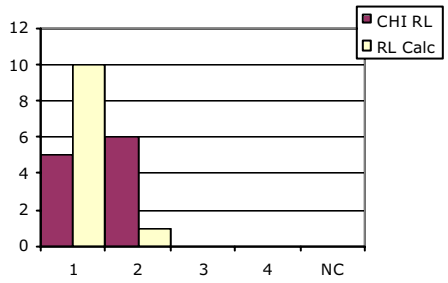
Number of papers	11

Collaboration

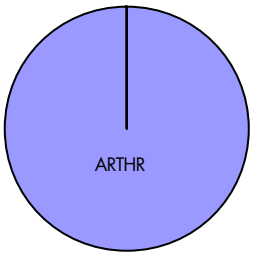
Mean number of authors	5.1
Mean number of addresses	2.2
% with non-UK addresses	18.2%

Type

Research level distribution



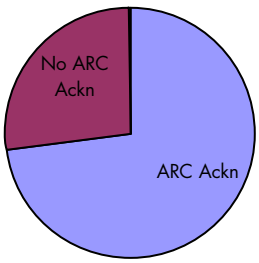
Field distribution



Funding

Mean number of acknowledgements	1.2

ARC funding acknowledgements



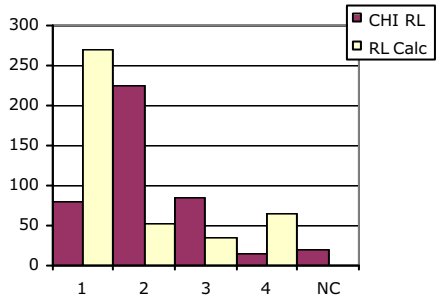
Knowledge flow

Strength

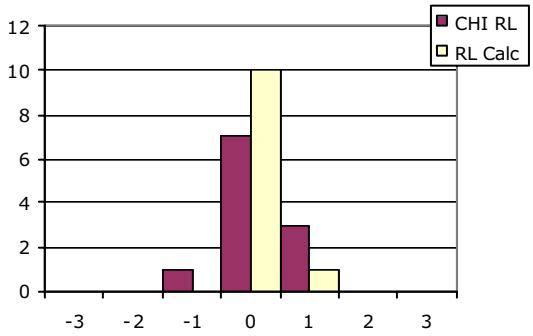
Mean citations per year (all papers)	32.4
Mean C0-4	17.7

Knowledge translation

Research level of citing papers



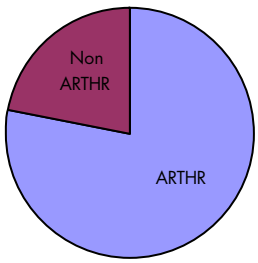
Relative research level



Knowledge diffusion

% of citations from the US	28%

Field distribution of citations



produced results that were complementary to the preceding project grant. According to the PI, it has also influenced the awarding of an arc grant for a community-based, long-term (two-year) clinical trial in knee pain and OA, examining the efficacy of lifestyle modification (exercise, weight loss if obese) and simple pharmacological interventions, determining clinical predictors of response. Aside from the pioneering research work that was completed during his JCRF, the PI has been involved in the planning phases of these studies.

9.7 Interface B: dissemination

During the course of the JCRF the PI had pursued some activities in disseminating his research results. Aside from contributing to journal papers and occasional conferences on the topic, he did not pursue potential users or industrial collaborators to take up his work. However, he was closely involved in an informal network of experts who were interested in issues around OA. As a result of these informal meetings, the PI was able also to disseminate his work in an academic setting. Furthermore, the PI disseminated his work during meetings and discussion at the Osteoarthritis Research Society, which was established in the period of the JCRF.

Although the development and construction of the Tornvall chair had not been without difficulties, once the university had finally delivered the chair, the expertise was in-house to build such a device. This expertise was then used to disseminate information among the community of researchers in OA. For example, a research team from the US has visited the hospital to learn about the construction of the chair for a large-scale clinical trial.

9.8 Stage 4: secondary outputs – policymaking; product development

9.8.1 Knowledge creation

While the JCRF did not contribute to extensive primary knowledge creation, it has led to a series of subsequent studies which contributed to the body of evidence that muscle strength is an important factor in OA.

One of the primary results of the JCRF was the development of a grading system which enabled clinicians to assess radiographic OA. Since the PI had learned to validate such assessment systems during the JCRF, he was also involved (albeit slightly peripherally to his JRCF) in the design and validation of a simple screening test, known as GALS: Gait, Arm and hands, Legs and feet, Spine (Doherty and others 1992). The GALS system is a simple two-minute screening test for rheumatological problems in general medical patients. This system was published under the arc education sub-committee in the form of guidelines to teach undergraduate students how to assess the locomotor system. The education sub-committee supports the education of undergraduate and postgraduate healthcare professionals working with people affected by arthritis. Its inclusion in the undergraduate guidelines for diagnosing patients could improve junior doctors' awareness and recognition of rheumatic disease and general disability. Also, it could provide a valuable screening test for use in general practice (Doherty and others 1992). The PI thinks that this grading system has made junior doctors more comfortable with assessing patients with possible locomotor problems. Furthermore, a paper (Fox and others 2000)

notes that students who had formal instruction in the GALS screening system were as proficient in examining the locomotor system as they were regarding other organ systems. The screen has been incorporated in several other textbooks for medical students.

9.8.2 Informing policy and product development

The conclusions of the subsequent project grant have been incorporated in both European and American guidelines for OA. This included a health economics evaluation (the results of which were not available to this study).

9.8.3 Broader economic benefits

The study for the Department of Health delivered a relatively cheap method of intervention to treat OA patients (approximately £40 per patient).

9.9 Stage 5: adoption – by practitioners and public

The GALS system has been incorporated in various education programmes for the training of students to examine OA. It is unclear to what extent this system has yet been adopted in the clinical field; there is no information available to assess this.[16] The grading system's ease of use and its successful results are promising indications for its adoption.

Studies subsequent to the PI's JCRF have built on the PI's notion that inactivity produces and progresses symptomatic OA. These studies, including the JCRF, have contributed to the body of knowledge on OA. Based on this evidence, it has now become common for clinicians and foundations for OA patients to recommend physical training of the muscles. The Virtual Health Care Team at the University of Missouri (King and Minor 2003), for example, refers to the subsequent project grant work when providing the following advice:

> Exercise may be the most effective treatment for OA available. Exercise is proven to improve general health and mood, reduce disability and fatigue and to favorably modify risk factors in disease progression. It is important to understand the different types of exercise and the difference between exercising for health and exercising for fitness. An appropriate exercise program should be as healthy, effective and comfortable as possible … All patients with arthritis should see their doctor for a careful history and physical examination before beginning an exercise program.

Although there is no evidence available as to the extent of adoption of intervention in OA in clinical practice, the number of (online) references to the work conducted in the PI's department seems to be promising.

9.10 Stage 6: final outcomes

Although the secondary results seem promising, as yet no payback related to the final outcomes phase has been identified.

[16] The supervisor mentioned that GALS has been adopted in a wide range of medical schools in both the UK and continental Europe.

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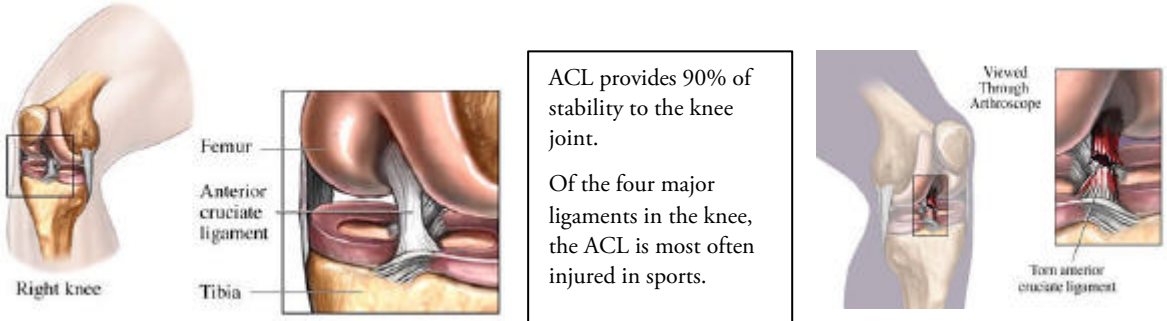
CHAPTER 10

Case study J: proprioceptive rehabilitation of the anterior cruciate ligament deficient patient

10.1 Introduction to the research project

This research examined the anterior cruciate ligament (ACL) as contributing an important proprioceptive role in the provision of stability to the knee joint. Proprioception literally translates as having, in the PI's words "an awareness of oneself", and in this project this refers to the ability to sense the position, location, orientation and movement of the knee in patients with anterior cruciate ligament deficiency (ACLD).



(SOURCE: RAND Europe)

Figure 10.1: Anatomy of the knee

The focus of this research was on learning about the control centre for the reflex that would help to stabilise the knee and prevent any degenerative changes. The principal investigator (PI) set out to understand how proprioception works in the knee and how this control centre is affected when the ligament is torn,"deficient" or surgically reconstructed. The hypothesis stated that if the ACL is gone, then the articular receptors controlling the stability of the knee are also gone.

The conventional belief about the function of the ACL was that it solely played an important biomechanical role in providing stability to the knee. While traditional therapeutic management of patients with ACLD focused on building up muscle strength around the knee, this research presented a challenge to this approach. The PI proposed

that the ACL also plays a vital proprioceptive role that may be overlooked in physiotherapy exercises for patients with ACLD and anterior cruciate ligament reconstruction (ACLR).

The research was divided into two parts. The first was to assess whether ACLD patients needed proprioceptive exercise and established a measure for proprioception. The second involved a research controlled trial (RCT) to assess whether exercise regimes were equally effective at home and in the hospital, in which case substantial savings could be made for the hospital, or alternatively physiotherapists' time could be spent on other cases with other patients (evaluating rehabilitation following ACL reconstruction in an attempt to achieve effective and standardised treatment).[1]

There is a significant amount of dscomfort, pain and swelling with the condition of ACLD and in particular, athletes' lives are severely disrupted by this sports injury. The length of recovery varies and at present is determined by many factors, which may lie with patients' compliance with physiotherapy regimes or their previous fitness status. It is clear that not all factors that lead to full recovery are known, however, at the outset of this research, proprioception was considered to be an important component of rehabilitation.

ACLD is a common cause of disability in young people who are recreationally active. Any athletic or non-athletic related activity in which the knee is extended too far and/or forced into internal rotation may result in an ACL tear (Your Medical Source, 2004). ACL ruptures occur at a rate of 60 per 100,000 people per year in the US (Your Medical Source, 2004). However, the incidence of ACLD is set to rise with society's increasing interest in physical fitness.

Little research had been carried out surrounding the role of proprioception in the knee at the time when the PI first eveloped an interest in this area. At the time of this research the most effective treatment for ACLD was still in question. Conservative physiotherapy approaches in ACLD management had limited success. Moreover, little interest about research into proprioception (particularly among physiotherapists) existed at the time when the PI began to develop his ideas further. Therefore, this research was critical in the evaluation of traditional physiotherapy management techniques of ACL. The PI had a strong clinical background in physiotherapy practice. Traditionally, there had been little development in in research-based practice in this field. Therefore, arc funded a highly-innovative project, both in the nature and content of the research and as far as the challenge to the researcher himself was concerned, who was able to build a scientific career from a clinical foundation.

10.2 Stage 0: topic/issue identification

ACL rupture is becoming more common due to an increasing amount of sporting activities among athletes and non-athletes. Physiotherapy is an important part of patient rehabilitation. Even if surgery is not considered, physiotherapists play an important role in rehabilitating patients. However, research evidence showed that the multifactorial nature of ACLD warranted a series of investigations such as that initiated by the PI.

[1] Treatment has been highly variable in form and content.

Initially, the PI had responded to an advertisement made by a surgeon to do physiotherapy research in proprioception. The surgeon identified a study from the US literature (Ihara and Nakayama 1986) that proprioception was considered to be an important component of rehabilitation. The surgeon, who was stimulated by this paper, wanted to recruit someone with a background in physiotherapy to evaluate this observation. A sum of regional research money from the NHS was set aside for this research position. The PI responded to this advertisement approximately two years prior to the arc grant, in which he developed the technique for measuring proprioception. The intellectual development and mechanical design for the PI's method prior to the project grant provided the key to gaining arc funds.

10.2.1 **Proposed technique**

The PI's method was based on a number of assumptions that describe the underlying complexity of this project.

The challenge was to find an appropriate measure for proprioception. The PI based his research on two assumptions. The first was that proprioception can be measured by looking at ACL receptors that give feedback about how the joint or limb moved under strain. Consequently, the hamstring muscles are activated to pull the strained knee back into position. This feedback mechanism ultimately protects the knee from injury or dislocation, provides stability and strength and, most importantly, prevents degenerative changes that lead to arthritis.

The second assumption was that if the ACL was torn, this feedback reflex loop would be deficient, and there would be "no sense of where you are in space" (PI's words). Consequently, it would take longer for the muscles to react and pull the knee into its normal position, and prevent any knee damage. Therefore, the PI proposed using a technique that would measure the delay or inactivity of the protective reflex contraction effected by the hamstring muscles. This would allow the PI to explore the activity of ACL receptors and role of proprioception in ACLD/ACLR. The scientific aspects of this research would feed then into clinical application for patients with ACLD/ACLR by advocating specific proprioceptive exercises; these would condition alternate neurophysiological pathways and structures in order to compensate for the loss of the signals that were usually discharged from the ACL.

There were two other studies that proved decisive in the PI's idea development, methodological design and testing prior to the arc grant:

1. in the early 1990s, Sinkajaer and Arendt-Nielsen (1990) showed that the ACL has a proprioceptive role, ie the ligament allows for joint protection;
2. one of the PI's assumptions was that nerve endings in the ligament (identified by Haus and Halata 1990) had an important role. The work was developed from the ideas of Solomanow and others (1987) who claimed that there is an important relationship between the ligament and the hamstring muscles, ie a simple reflex loop existed between the ligament and the muscle.

The crucial difference between any previous studies and this approach was that this research was based predominantly in the scientific laboratory, where the PI developed his own method for measuring proprioception. As mentioned in the introduction, the PI had

developed the methods prior to the arc grant. More specifically, the method consisted of an apparatus that could measure how fast the muscle could respond to the force of tibial displacement. The key to this method was that the PI had developed a unique technique that enabled him to measure reflexes, rather than measuring "higher thoughts", ie processes that take place at brain level rather than at joint level. Therefore, this method was unique because it conceptualised proprioception at a different anatomical level.

The total amount awarded to the applicant was £47,828 over two years, although the amount requested was £77,247 over three years.. The reasons for this reduction is not clear, however, one referee was sceptical with respect to the resources requested. The reason that the PI hoped to embark on a three-year project was that it tied in neatly with his intention to complete his PhD within that time period. All other monies were provided for technical equipment, with no additional technical support granted as originally requested.

The most effective treatment for anterior cruciate ligament deficiency (ACLD) is still in doubt. Secondary degenerative joint damage and arthritic changes, resulting from ligament deficiency, are common clinical findings in these patients. Research evaluating physiotherapy programmes for conservatively managed ACLD patients has shown that there is a deficit in proprioception of the injured knee. Surgical reconstruction of the ligaments is now increasingly preferred. This described proprioceptive deficit in the ACLD knee may also exist in the ACL reconstructed knee (ACLR).

This research aims to firstly measure the proprioceptive changes in the surgically repaired cruciate deficient knee and secondly to evaluate the efficacy of two different physiotherapy methods for ACLR in a randomised clinical trial. One group will complete and unsupervised "home programme", the other a twice-weekly hospital-based supervised exercise session. The outcome measures will be functional ability and reflect hamstring contraction latency. Knee joint laxity will also be monitored.

If a similar proprioceptive deficit exists in the reconstructed knee as the deficient knee then proprioceptive enhancement exercises could be recommended in the rehabilitation for ACLR patients. Also if a "home programme" of treatment for reconstructed patients is as effective as hospital-based treatment then valuable physiotherapy resources can be utilised elsewhere without ethical compromise.

(SOURCE: arc archive)

Box 10.1: Abstract

It is significant to reiterate the fact that the PI had little background in research as a whole, and only two years prior to the arc grant did he begin to develop an interest in a research career. The arc grant came at a time when the PI had little scientific knowledge; however, he was able to thrive in the right academic environment surrounded by high calibre scientists and "a lot of goodwill".

10.3 Interface A: project specification and selection

Three referees reviewed the research proposal, and the comments of two of these reviewers were fed back to the PI. A summary of their assessments is given in Table 10.1 (the letters

Table 10.1: Summary of assessors' report

	High	Medium	Low	None
Originality of project	B	A, C		
Potential value to rheumatology		A, B, C		
Potential practical value	B	A, C		
Appropriateness of overall project design	A	B, C		
Suitability of methods		A, B, C		
Feasibility within time proposed		A, (B)* C		
Standing of applicant in this field		A, (B)*		C

*Referee not known

(SOURCE: arc archive)

A–C indicate the different referees' assessments). This information is based on the assessors' report form submitted to arc.

Based upon the referees' comments, a conditional award letter expressed the need to clarify the following points:

- written confirmation of surgical collaboration and a guarantee that the stated number of patients could be provided;
- evidence of ethical approval;
- if the salary requested was to be the PI's alone, to submit the proposal jointly with the head of department.

While the arc archive did not have the PI's response letter, the PI was awarded the arc grant as stated in the conditional letter and, therefore, we can assume that the PI met these conditions. Most notable from referee B's comments is the request for formal surgical collaboration as well as general management responsibility from the head of the department, which was taken into consideration and requested from the PI by arc. In response, the surgeon who was chosen as supervisor also confirmed in his letter to arc the necessity to carry out research in this area from an economic perspective, ie ACL reconstructive surgery being carried out once per week.

One referee mentioned the logistical problems of carrying out this work. The application of this type of research project was questioned also, considering the clinical background of the applicant and the intent to investigate physiotherapy management issues. However, the referees made suggestions on improving the application, and these were addressed satisfactorily by the PI.

It is worth noting that referee B considered the procedural details of the RCT (comprising part two of the research proposals) to be sketchy. The numbers of research subjects were not provided and compliance was not addressed in the original proposal. Referee A noted that the patient numbers were quite small. Interestingly, this was an issue that was justified as far as the process and outcome of the research was concerned. The PI himself admitted that there were some logistical problems in carrying out the work that led to "contamination of trial arms".

10.4 Stage 1: inputs to research

This research relied on the goodwill of many people involved at the research site. It benefited from the input of other departments, in particular the engineering centre, which invested time, know-how and on-site facilities in the PI's research.

As mentioned in Stage 0: topic/issue identification, the final amount awarded to the applicant was £47,828 over two years. The reduction in timescale reflected the fact that the grant was awarded as a two-year pilot. In addition, any technical or other assistance was not granted as had been requested originally; however, the allowance for expenses amounted to £7,350.

In order to carry out the experimental exercise regimes in which proprioception was measured in terms of muscle reflexes, the PI was provided with the following equipment through on-site facilities (some of which were provided in return for a hiring fee, others for free):

- isokinetic dynamometer (Kincom) for measuring between limb latency difference and muscle strength;
- KT 1000 arthrometer for measuring laxity;
- Vicon Interfaced Knee Displacement Equipment (VIKDE) for measuring reflex hamstring contraction latency. The VIKDE equipment required an update and overhaul, with added materials estimated at £675 and labour at £300.

In addition, the on-site facilities at the engineering centre allowed for the use of computer technology, for example, to record the movement of the tibia.

10.5 Stage 2: research process

The PI's prior methodological development allowed him to make a convincing case to be awarded the arc grant, and also allowed him to register for a PhD. There were several process delays involved in this research project. First, in the set-up period, the PI had decided to take time out for personal travel. However, this did not have an impact on the research process to any degree, because the PI had developed most of his methodologies prior to the project grant. Therefore, arc did not object to a slight delay of approximately three months. The research finally began at the beginning of 1993.

Second, a delay was caused in the mid-period when the director of the physiotherapy research took maternity leave. The arc grant was held in abeyance for six months to cover this post during this time period.

Following the six months, the PI was offered a shared position of directorship, and was only able to work on his research project part-time. As a part-time researcher for arc, his grant therefore ran until the end of 1996, over another 26 months. At the same time, a salary upgrade was granted, which meant an increase to the grant of £2,584. This period of delay was not unwelcome as this allowed the PI to recruit more patients for his trials.

The PI finished his research earlier than envisaged in July 1996 when he accepted a senior lectureship in Australia. The remaining monies were returned to arc.

10.5.1 **Recruitment problems**

Recruitment of patients for the RCT of rehabilitation created a number of problems:

- local patients were not freely available for controlled rehabilitation and follow-up after six months, causing a lack of study subjects. This was partly due to financial restrictions at the clinical level, which resulted in a freeze of ACLR operations for that year;[2]
- compliance: patients did not always fill out questionnaires, and not all of them adhered to the prescribed exercise regime;
- there was cross-contamination of the arms of the trial, ie some carried out exercises at home as well as at the clinic.

In sum, these problems diluted the effort in measuring the effectiveness of home-based and clinically-based exercise. The PI stated that he would have liked to have been helped by a clinical assistant, but there was no one available. When he discovered some problems with cross-contamination of research arms, there were no adequate clinical resources to monitor progress more closely. At the time that the PI became a part-time researcher, there was more time to recruit patients for the study.

10.6 **Stage 3: primary outputs from research**

Some preliminary outcomes partly identified during the research process were that:

- the PI became increasingly involved in the scientific aspects of his work and developed his career as a scientist;
- the development of a new stabilometric measure of proprioception was beginning to take shape, and with that the establishment of rational rehabilitation guidelines for ACLR patients;
- the PI received his PhD on the basis of the arc grant.

The PI produced 13 peer-reviewed articles with this research project. These publications show that the PI proved through his experimental work that proprioception plays an important role in ACLD (Beard, Kyberd and others 1994). It is interesting to note that the PI began work on the project before the award was made and hence argues that Beard and others (1993), which was published before the grant began, should be considered as attributable to the grant.

Moreover, the proprioceptive enhancement exercises in the rehabilitation programme showed that they were more effective than traditional muscle strengthening exercises for ACLD patients (Beard, Dodd and others 1994). An important observation in the early stages of the research was that in the surgically reconstructed knee the proprioceptive

[2] The PI stated that these difficulties could not have been foreseen at the time of the proposal and may have affected the overall sample size. To compensate, some patients having a prosthetic ligament replacement in a neighbouring hospital were recruited.

deficits were equally relevant. This research was particularly relevant considering that increasingly, surgery was becoming the preferred treatment for ACLD.

This became the focus of the second year of the project, as the PI assessed any changes in the knee joint proprioception before and after surgical reconstruction of the ACL. Twenty-eight patients who had undergone ACLR were measured for proprioception prior to reconstruction and then twice more over the rehabilitation period (at three and six months post-reconstruction). The results suggested that there was an improvement in proprioception following reconstruction of the ACL. The reasons for pre-operative variation in proprioception and the mechanism whereby proprioception improves following reconstruction remained unclear. The research was then extended to evaluate the rehabilitation following ACL reconstruction in an attempt to achieve effective and standardised treatment. In the third year, the focus continued to be on elucidating the mechanisms for ACL change which, ultimately, did not deliver any clear results. The most important result of the experimental work involved in this research showed that ACLD and ACLR patient management needed to take account of the importance of proprioceptive exercises, and that traditional management techniques in building up muscle strength were wrongly targeted.

The general scientific focus in this research project was on learning about the control centre for the reflex that would help to stabilise the knee and prevent any degenerative changes. Ultimately, the PI did not show how ACLD has an impact on ligament receptors. Instead, the PI found it to be much more likely that the muscles and their receptors were responsible for the underlying mechanisms of ACL change. The PI resorted to putting to rest the idea that ACL receptors were responsible for the reflex loop, in particular because the neurological experts in this field did not encourage him to explore further.

The results also showed that there were other research avenues that could have been explored within this field. The main areas identified for further investigation included the reasons for pre-operative variation in proprioception and the mechanisms whereby proprioception improves following reconstruction. This is viewed particularly in the light that there is little association between pre-operative propioception and history of intensive rehabilitation programme prior to surgery.

On the basis of the PI's prior method development, he made a convincing case to be awarded the arc grant and later, a PhD. According to the PI, the arc funding allowed him to register for PhD, as it would have been unlikely, particularly in the Faculty of Medicine, without the guaranteed funding. Following his PhD, the PI went to Australia as a senior lecturer in physiotherapy and transferred this knowledge base successfully to two MSc students, who carried out similar experiments to test proprioceptive exercises in the shoulder and ankle.

Selected bibliometric indicators for case study J

Publication portfolio

Output

Number of papers 13

Collaboration

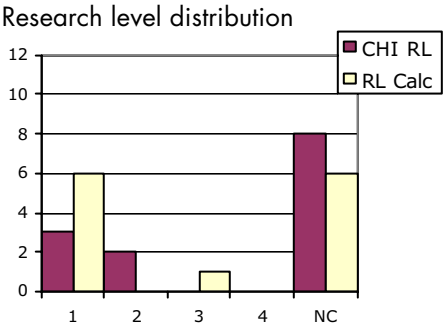
Mean number of authors 2.8

Mean number of addresses 2.8

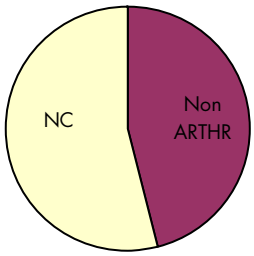
% with non-UK addresses 7.7%

Type

Research level distribution



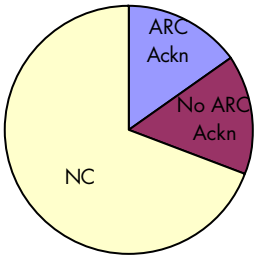
Field distribution



Funding

Mean number of acknowledgements 2.3

ARC funding acknowledgements



Knowledge flow

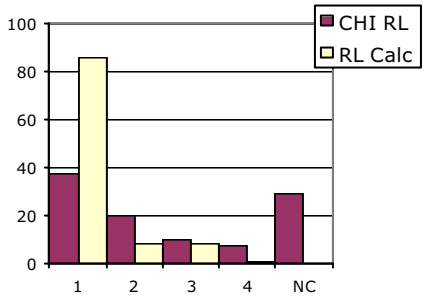
Strength

Mean citations per year (all papers) 9.6

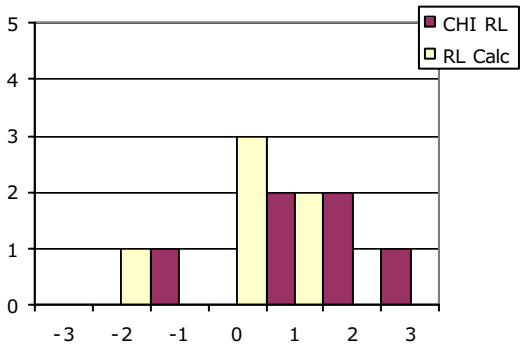
Mean C0-4 5.2

Knowledge translation

Research level of citing papers



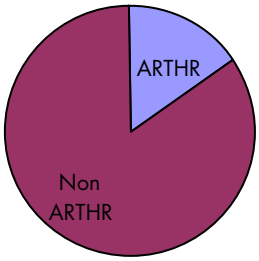
Relative research level



Knowledge diffusion

% of citations from the US 40%

Field distribution of citations



10.7 Interface B: dissemination

The PI was involved in a wide variety of dissemination activities. He attended nine international conferences in countries such as Hungary, Finland and Germany; as well as 11 national conferences. Larger orthopaedic conferences were held in the Netherlands and the US, for which the PI was able to submit papers. Notable is the 1996 abstract submitted for the Orthopaedic Research Society at their 42nd annual meeting in Atlanta, GA (Beard and others 1996). The PI stated that very few British abstracts are accepted for the Orthopaedic Research Society conference in the US.

Further dissemination occurred when the PI took up a senior lectureship in Australia, where he supervised two MSc students who carried out similar work to his own for different joints to measure proprioception.

The PI also disseminated his work through the production of brief summaries for user groups, ie other physiotherapists and scientists who were interested in his work. In addition, he held study days and training at local clinics, but also spoke to commercial companies about his work. While there was no direct commercial interest from these companies, they were keen to learn about developments in this field.

arc also granted travel expenses of over £1,000 for travel and dissemination purposes. The full amount was used to travel to attend the Second World Congress of Biomechanics in the Netherlands, and the Orthopaedic Research Society Conference in Atlanta.

10.8 Stage 4: secondary outputs – policymaking/product development

Developing a measure for proprioception, or a proxy measure, required an examination of where the control aspect of the joint was embodied by the hamstring muscles in the cruciate-deficient patient and how it contracted to put the tibia back into place. Although the mechanisms for proprioception were not elucidated fully, this measure for proprioception was sufficient to test the PI's hypothesis that proprioception played an important role in ACLD and ACLR.

The PI was able to transfer his knowledge to the physiotherapy centre on-site and teach physiotherapists about the importance of proprioceptive exercises, which was incorporated into local physiotherapy guidelines. It is not clear to what extent the PI's research influenced a shift in national guidelines to incorporate proprioceptive exercises; however, from the PI's perspective it was clear that his research was influential in effecting such changes.

Later, active knowledge transfer occurred when he taught two MSc students in Australia to carry out similar exercises in different joints. According to the PI, both were able to develop their research careers around this topic. Lastly, the PI himself was able to further his research skills as a scientist, and apply it to the field of engineering. He is currently

using this knowledge to conduct further research in arthroplasty,[3] more specifically in the engineering of artificial joints.

10.9 Stage 5: adoption – by practitioners and public

The research had important applications in physiotherapy practice. This consisted of a shifting emphasis on proprioceptive exercises rather than a quadriceps exercise.

The research had major impact particularly at at a local level, with adoption of new practice that was directly based on the studies. At a national and international level the research provided scientific basis to practices that were being adopted gradually over the duration of the research project. The PI felt that that his research group was the most active in Europe at the time.

10.10 Stage 6: final outcomes

The PI's research affected a change in physiotherapy ACLD/ACLR management approaches, one which now includes proprioceptive exercises in local clinical guidelines and which contributed to a similar shift nationally. However, the health benefits cannot be elucidated clearly due to other parallel clinical developments, for example, improvement in surgical techniques and possible lifestyle changes that could not be controlled for in the study.

[3] Replacement of a joint.

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CHAPTER 11

Case study K: a prospective randomised therapeutic trial of low-dose aspirin versus aspirin plus low-dose subcutaneous heparin in women with recurrent pregnancy loss

11.1 Introduction to the research project

Recurrent pregnancy loss is defined as the loss of three or more pregnancies. It affects around 1% of women who become pregnant. Only a proportion of women presenting with recurrent miscarriage will have a persistent underlying cause for their pregnancy loss (Royal College of Obstetricians and Gynaecologists (RCOG) 2003). One of the underlying causes is the existence of antiphospholipid antibodies (aPL)[1] (eg lupus anticoagulant)[2] that are present in 15% of women with recurrent miscarriage (Rai, Regan and others 1995). This existence of aPL is a marker for antiphospholipid syndrome (APS), which is a cluster of conditions that includes vascular thrombosis as well as adverse pregnancy outcome (Greco and others 1999) and has a similar pathogenesis to certain rheumatological conditions. It is believed that potentially 2% of the general population harbour aPL in their blood and that it is likely to be heritable (Greco and others 1999). Adverse pregnancy outcomes include:

1. three or more consecutive miscarriages before 10 weeks of gestation;
2. one or more morphologically normal foetal deaths after the 10th week of gestation; and

[1] aPL are antibodies that react with phospholipids, a type of fat molecule that is part of the normal cell membrane; see: http://www.hamline.edu/lupus/articles/Antiphospholipid_Antibodies_and_Systemic_Lupus_Erythematosus.html.

[2] A percentage of patients with Systemic Lupus Erythematosus (SLE – an autoimmune rheumatic disease that often affects the skin, joints and sometimes the internal organs) carry antiphospholipid antibodies, including the lupus anticoagulant or anticardiolipin antibodies. However, some patients have antiphospholipid antibodies without suffering from SLE.

3. one or more pre-term births before the 34th week of gestation due to severe pre-eclampsia,[3] eclampsia or placental insufficiency (Royal College of Obstetricians and Gynaecologists 2003).

In women with recurrent miscarriage associated with aPL, the live birth rate in pregnancies with no pharmacological intervention may be as low as 10% (Rai, Clifford and others 1995).

A meta-analysis of two controlled trials of women with a history of recurrent miscarriage associated with aPL concluded that treatment with low-dose heparin plus low-dose aspirin significantly reduced pregnancy losses by 54%, when compared with aspirin alone (Empson and others 2002). The live birth rate of women with recurrent miscarriage associated with aPL who are treated with low-dose aspirin alone is 40%, and this is significantly improved to 70% when they are treated with low-dose aspirin in combination with low-dose heparin (Rai, Cohen and others 1997). Although aspirin plus heparin treatment substantially improves the live birth rate of women with recurrent miscarriage associated with aPL, these pregnancies remain at high risk of complications during the third trimester, including pre-eclampsia, foetal growth restriction and pre-term birth, necessitating careful antenatal surveillance.

Various other therapies have been advocated for prevention of foetal death in APS. These include prednisone, and intravenous (IV) immunoglobulin (Greco and others 1999). In two randomised controlled trials of a small sample size, no improvements in the live birth rate have been reported when treated with prednisone, as compared to aspirin or aspirin plus heparin (Royal College of Obstetricians and Gynaecologists 2003). Another trial reported that low-dose aspirin and heparin combined were more effective than IV immunoglobulin. Another randomised controlled trial reported a high success rate with aspirin alone, and no significant benefit in the live birth rate with the addition of heparin. However, this study included women with low titres of aPL, some of whom were randomised at up to 12 weeks' gestation, by which time most of the aPL-related pregnancy losses would have already occurred.

11.2 Stage 0: topic/issue identification

In the 1980s, some treatments against miscarriage were based on presumption and anecdotal data, coupled with empirical therapies. At the same time there was a great deal of interest in the immunological causes of miscarriages. The studies that had been done were advocating immune therapy. At that time, the principal investigator (PI) conducted a study on the antibody response in pregnant women who had miscarried and what was demonstrated was that an antibody response could not be seen before or in early pregnancy, while the therapists advocated the use of this antibody response as a possible treatment. At the same time, there was interest from the rheumatology world, as clinicians

[3] Pre-eclampsia is an abnormal state of pregnancy characterised by high blood pressure, fluid retention and the presence of albumin protein in urine.

were finding that women who had autoimmune diseases (eg SLE) were at greater risk of foetal loss if they carried one of the antiphospholipid antibodies.

During the same period, the PI was running a referral service in Cambridge for women who miscarried. In the late 1980s, a couple of case reports were published about the possible use of aspirin, or aspirin and steroids, in women with full-blown lupus who also had foetal loss. One of the patients who came to the referral service was found to have aPL in her blood. She was treated experimentally with aspirin and heparin and had a successful pregnancy. A couple of other women were treated successfully also with aspirin and heparin. It then became important to set up a trial to test whether aspirin and heparin together really gave better results than aspirin alone, before people could begin to adopt the treatment as practice.

Before it was possible to run the trial, the PI had to become established at a new post where, according to the PI, there was little interest in the haematology department or any hospital nearby in performing the test for phospholipid antibodies according to international standards. It took some time to set up the structures that allowed the trial to be run.

The PI applied for arc funding because she thought that arc would have an understanding of the seriousness of the condition, while obstetrics and gynaecology funding agencies were unlikely to consider that phospholipid antibodies were a serious cause of pregnancy loss. Because arc was familiar with autoimmune diseases such as lupus, it could recognise the seriousness of the antibodies in the whole picture. At that time, the PI re-emphasised that this was a different cohort of patients. They were not patients with severe illness, but women presenting with pregnancy loss; women who did not have lupus, but who did have phospholipid antibodies.

Recurrent pregnancy failure is a tragedy which affects one woman in a hundred. In approximately 15% of affected women, pregnancy loss is associated with the presence of antiphospholidid antibodies (lupus anticoagulant and/or anticardiolipin antibodies). In the majority of women with these antibodies, pregnancy loss is associated with placental infarction[4] and thrombosis. Therapeutic intervention in further pregnancies is based largely on anecdotal experience, although there is clinical evidence that anticoagulant therapy may be beneficial. There is an urgent need for controlled prospective studies in this disorder to determine the optimal management of this unfortunate group of women. We propose to conduct a randomised therapeutic trial of low-dose aspirin versus aspirin plus low-dose subcutaneous heparin in women who have antiphospholipid antibodies and a history of three or more first or second trimester miscarriages, with serial assessment of foetal growth and pregnancy outcome, and correlations with the presence of lupus anticoagulant and anticardiolipin antibody levels during pregnancy. This study will enable us to establish whether low-dose heparin therapy, with its potential side effects, can be justified in the management of pregnant patients with a history of recurrent miscarriage and documented circulating antiphospholipid antibodies.

(SOURCE: arc archive)

Box 11.1: Abstract

[4] A rupture of the barrier between maternal and foetal blood in the placenta.

To carry out the proposed trial, the applicants requested a sum of £101,498 for two years. This was to cover salaries for a research registrar and a research technician (£91,836) and recurrent expenses (£9,662).

11.3 Interface A: project specification and selection

Three referees reviewed the research proposal. A summary of their assessments is given in Table 11.1 (the letters A–C indicate the different referees' assessments). This information is based on the assessors' report form submitted to arc (a blank copy is available in Annex B).

Table 11.1: Summary of assessors' report

	High	Medium	Low	None
Originality of project	B, C			
Potential value to rheumatology		B, C	B, C	A
Potential practical value	B, C			
Appropriateness of overall project design	C	B		
Suitability of methods	C	B		
Feasibility within time proposed	C	B		
Standing of applicant in this field				

(SOURCE: arc archive)

The referees viewed the science as good. However, referee A thought that it was too far removed from mainstream rheumatological research to merit funding by arc. Referee B was in favour of funding, but at a substantially reduced level. His reasoning was that care would be given to the women enrolled in the study irrespective of the trial, and that therefore arc should not fund that care. Referee C saw the requested budget as appropriate. Both referees B and C mentioned that although the science proposed was of good quality, it extended beyond the area of rheumatology.

The PI commented that the money she received from arc was insufficient to run the full study. Any project associated with pregnancy has nine months' minimum duration. One of the strengths of the project was that women were recruited (and randomised) before pregnancy, and this extended the duration to 18 months' minimum (if all the women could be recruited at the same time). An obstetrician among the referees would have been likely to argue that the study would take a long time, as well as that it was a fundamentally new treatment (one that was not without morbidity and which required a special treatment of both the patients enrolled in the study and the clinicians who looked after them). These patients were not receiving standard care, as they had to inject themselves on a daily basis as well as travel hundreds of miles for an antenatal appointment.

A rheumatologist on the research team would not have added value to the study, as one of the issues addressed in the study was that the vast majority of foetal loss is due to phospholipid syndrome occurring before 12 weeks, which means that a rheumatologist would not normally see the women. Rheumatologists usually only see pregnant women after their first visit to the antenatal clinic at about 12 weeks.

Based on the referees' assessments, arc granted funding of £46,295 for 2 years.[5] In their justification, they mention that:

> The scientific assessors felt that the research registrar was not needed to coordinate the study and this could be done by a paramedic or research assistant. Therefore, arc is prepared to fund 1 salary for an appropriate person at the research assistant level to a maximum of £18,000 in year 1 and £19,000 in year 2, including all extra salary costs, with running costs as requested.

The PI then commented that a research registrar was necessary to conduct the research for three reasons:

1. the patients entering the trial were a high-risk group for life-threatening complications, such as foetal growth retardation or death, and maternal arterial and/or venous thrombosis; therefore they should be enrolled by a doctor with specialist knowledge to enable adequate counselling;
2. for reasons of comparability, quality assurance and scientific validity, specialised antenatal care and studies (which are not standard) should be performed by the same individual;
3. because of the size of the study (80–90 patients) a dedicated clinical research fellow was required to enrol suitable patients, prescribe treatment and ensure that study protocols were followed correctly.

For these reasons, the PI made a new request of £83,182 for a full-time research registrar and a part-time research assistant.

arc obliged and increased the grant to £55,593 to cover the cost of a part-time research registrar and a part-time research assistant. In their decision, they wrote:

> The scientific assessors of your application felt that it was likely that the clinical care of the patients was likely to continue whatever the outcome of ARC funding and therefore the only necessity was for a laboratory research assistant to enable maximum information to be gleaned from the ongoing patient care.

Although the grant was awarded in May 1992, the work only commenced in December 1992. This led to a need for an eight-month extension, which was granted by arc. Because the amount requested was more than could be given outside the formal application process, the referees were asked to give their comments on the request for extension.

11.4 Stage 1: inputs to research

11.4.1 Funding

Project grant and extensions

In total, arc funded an amount of £75,488. This included the initial grant (£55,593) and the eight-month extension (£19,895).

[5] At 1992 levels of currency (in 2004 this would be £60,819).

Overheads

The hospital paid all other costs that were incurred.

11.5 Stage 2: research process

To identify eligible women for the trial, all the women attending the recurrent miscarriage clinic at St Mary's Hospital (London) were screened for the presence of aPL (lupus anticoagulant and/or anticardiolipin antibodies) using standardised laboratory techniques. Halfway through the study, 500 women with a history of three or more miscarriages had been screened. At that time, it was the largest group of women who have suffered recurrent miscarriages to be screened for the presence of these antibodies (annual reports, arc archive).

In total, 86 women between the ages of 22 and 42 with a history of recurrent miscarriage who had persistently positive tests for aPL were randomised to receive low-dose aspirin or low-dose aspirin plus heparin during pregnancy. All the women took low-dose aspirin from the time of a positive pregnancy test and were randomised once foetal viability was demonstrated via ultrasound. All treatment was stopped at 34 weeks' gestation.

There were no problems with recruitment. The PI states that the main reason for this is that the right person was selected to recruit these women. The research team recruited these women themselves. The recruitment of people to studies in an emotional field such as miscarriage requires a fully-dedicated team. If people believe in the uniqueness and prospects of a study, they will want to participate. Therefore, it is very important to choose very carefully the person who is going to run the trial.

11.6 Stage 3: primary outputs from research

11.6.1 Knowledge

In total, over 40 articles, book chapters, reviews and letters can be attributed directly or indirectly to the grant. In this section, only the articles that came out of the work directly supported by the grant are discussed. The research facilitated by the grant is discussed in the secondary outputs section. The main results of the trial are discussed in Rai, Cohen and others (1997). It describes the recruitment, process and outcomes of the trial. The objective of the trial was:

> To determine whether treatment with low dose aspirin and heparin leads to a higher rate of live births than that achieved with low dose aspirin alone in women with a history of recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies), lupus anticoagulant, and cardiolipin antibodies (or anticardiolipin antibodies).

In the recruitment process for this trial, women had to be screened for the presence of aPL. A total of 500 women (median age 33 years, range 19–45) were screened in order to recruit the right sample size for the trial. The findings of this screening process are described in Rai, Regan and others (1995).

At the same time, a study was done into the foetal loss rate of women with aPL who declined pharmacological treatment in their next pregnancy (Rai, Clifford and others 1995). They compared this group's loss rate to a group of women with recurrent miscarriage in whom no underlying cause for pregnancy loss could be found. This study concluded that the loss rate in the group of women who declined treatment was significantly higher than in the second group.

Because more women made it through the first trimester, it was now possible to assess whether the presence of aPL also led to complications in the later stages of pregnancy. This is discussed in Rai and Regan (1997a, 1998) and Backos, Rai, Chilcott and others (1999). These papers conclude that there is a high risk of complications during all trimesters that makes close antenatal surveillance a necessity. Rai and Regan (1998) find that

> pregnancies that survive the first trimester risk developing pre-eclampsia, intrauterine growth retardation and fetal distress during labour. Pregnancy loss is initially caused by defective embryonic implantation and later by thrombosis of the placental vasculature. In women with aPL, thromboprophylaxis[6] during pregnancy improves the live birth rate.

One of the concerns of long-term heparin therapy is osteopenia.[7] Backos, Rai, Thomas and others (1999) studied the bone mineral changes during pregnancy in 123 women with aPL who were treated with low-dose aspirin and heparin. They found that

> long-term heparin treatment during pregnancy is associated with a small but significant decrease in BMD [bone mineral density] at the lumbar spine and neck of [the] femur. This decrease is similar to that previously reported to occur in untreated pregnancies.

Sebire and others (2003) examines whether there are characteristic histological features in placentas from the ongoing pregnancies of patients with a history of recurrent miscarriage that relate to clinical outcome. The study looked both at patients without aPL and patients with aPL who where receiving aspirin and heparin treatment. The study found that the pregnancy outcome and type of complications in each of the groups was similar.

11.6.2 **Research staff**

The research registrar on the trial received a commendation for his MD thesis, which was based on the trial. In addition, he has received a variety of prizes and specialist training in reproductive medicine, after which he was appointed as a consultant at the hospital. The trial resulted in an international profile for the research team.

11.6.3 **Knowledge creation**

The results of the trial led to a new treatment protocol that was based on a combination of aspirin and heparin. Results from the screening process and observations of complications later in pregnancy led to the generation of new research areas (which are discussed in Stage 4: secondary outputs).

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[6] Therapy designed to reduce blood clotting.

[7] Decreased calcification or density of bone.

Selected bibliometric indicators for case study K

Publication portfolio

Output

Number of papers 7

Collaboration

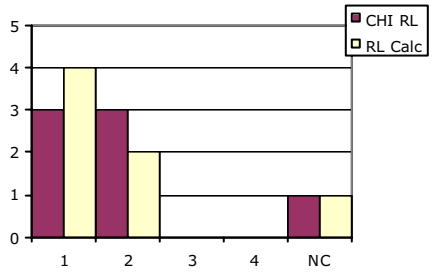
Mean number of authors 4.5

Mean number of addresses 2.3

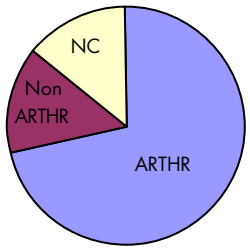
% with non-UK addresses 0.0%

Type

Research level distribution



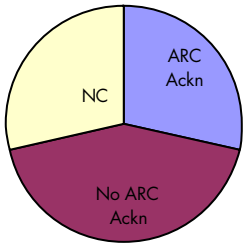
Field distribution



Funding

Mean number of acknowledgements 0.6

ARC funding acknowledgements



Knowledge flow

Strength

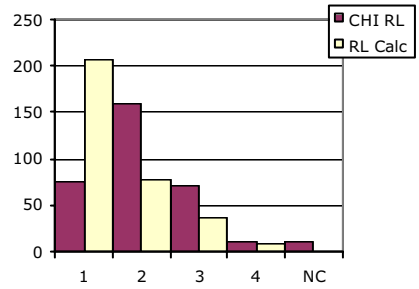
Mean citations per year 29.5

(all papers) 37.7

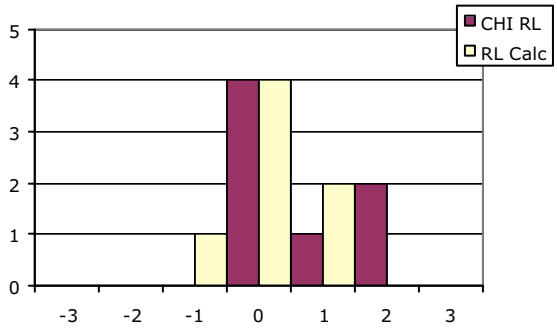
Mean C0-4

Knowledge translation

Research level of citing papers



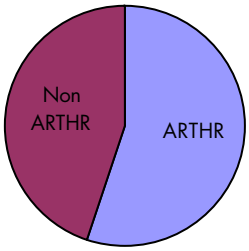
Relative research level



Knowledge diffusion

% of citations from the US 16%

Field distribution of citations



11.7 Interface B: dissemination

Alongside publishing scientific papers and presenting the work at learned societies, the PI also provided layperson information on the results of the trial in both publications and at meetings of patients' groups. Presentations to lay groups and media included those to the Chana infertility network, the KitKat Club (for miscarriage and infertility) as well as presentations for BBC radio. The PI's work was represented also in a Channel 4 documentary on miscarriage.

The PI has published a book on miscarriage for lay people (Regan 1997), which received favourable reviews in the United Kingdom as well as the United States. This book was originally published by Bloomsbury in 1997 and was reprinted in 2001 by Orion (Regan 2001).

11.8 Stage 4: secondary outputs – policymaking; product development

11.8.1 Knowledge creation

The trial facilitated numerous strands of research. Two of them include the effect of aPL on fertility and *in vitro* fertilisation (IVF). Backos and others (2002) and Chilcott and others (2000) are examples of these strands of research. They conclude that, although the prevalence of aPL is higher in women who are referred for IVF, this does not affect the outcome of the treatment. The research team also performed a study into the effect of aspirin as a treatment for women who experienced unexplained, recurrent miscarriages. It concludes that the use of aspirin does not improve the live birth rate (Rai and others 2000). In addition, the PI was requested to write a number of reviews (eg Rai and Regan 1997b, Regan and Rai 2002) as well as book chapters (eg Rai and Regan 1996; Regan 1998).

11.8.2 Informing policy and product development

The UK RCOG guidelines, written by the PI and reviewed by six national and three international experts, relating to recurrent pregnancy loss due to APS are based on the outcomes of the trial (Royal College of Obstetricians and Gynaecologists 2003). They state:

> In women with a history of recurrent miscarriage and aPL, future live birth rate is significantly improved when a combination therapy of aspirin plus heparin is prescribed. Pregnancies associated with aPL treated with aspirin and heparin remain at high risk of complications during all three trimesters.

In the section on APS, the RCOG mentions three treatment options, of which only the combined treatment of aspirin and heparin was judged positively. In this section they refer to three studies: the study by the PI; a second which performed a meta-analysis partly based on the PI's work; and a third which found that the combined treatment did not improve the live birth rate compared to treatment with aspirin alone. However, there were flaws in the research method.

Next to the UK guidelines, guidelines in the US (Aetna 2003), the Netherlands Association for Obstetrics and Gynaecology (Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) 2001), and Australia (Medical Journal Australia 2004) recommend a combination therapy of aspirin plus heparin.[8] They all refer back to the trial carried out by the PI.

11.9 Stage 5: adoption – by practitioners and public

Although guidelines do not have to be followed, they carry significant weight – leading to the assumption that the combined treatment of aspirin and heparin is widely used. In support of this assumption is the fact that, over the years, the PI has received a huge number of enquiries about the treatment and is confident that its use is widespread.

11.10 Stage 6: final outcomes

11.10.1 Health benefits

The trial led to the conclusion that a combined treatment increased the chances of a live birth for women who had tested positive for aPL. A substantial number of these women would not have successfully completed a pregnancy without this treatment.

11.10.2 Economic benefits

The combination treatment of aspirin plus heparin requires daily injections with heparin. These can be self-administered after suitable training. Furthermore, special antenatal care is required. Due to the complications that can arise, intensive guidance is needed. However, as the live birth rate increases, there are fewer costs involved because of a decrease in the repetition of pregnancies. Furthermore, the management of recurrent pregnancy has improved due to the sound evidence base that the trial provided.

[8] This is not necessarily an exhaustive list of countries in which guidelines are (partly) based on the trial carried out by the PI. It is used as an example of the widespread effects of the results of the trial.

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CHAPTER 12 Case study L: the Kennedy Institute core grant

12.1 Introduction to the research project

The selected strand of research supported by the arc core grant to the principal investigator's (PI's) research institute aimed to investigate and, if possible, manipulate the activity of specific cytokines in rheumatoid arthritis (RA). Cytokines are intercellular proteins that act as chemical messengers among immune cells, and between immune cells and the rest of the body. As such, they are involved in the process of damage to cartilage and bone in RA.

RA is a chronic inflammatory disease in which the body's immune system attacks the joints. The disease is chronic, leading to pain, progressive joint damage, disability and increased premature mortality. In addition to causing great suffering to the individuals affected (who are estimated to make up approximately 1% of the UK's population), RA poses a considerable economic burden on society. In 1999–2000 9.4 million working days, representing £833 million in production, were lost in the UK due to the disease. Direct costs, such as treatment and hospitalisation, have been calculated to average £3,231 per year, with indirect cost of lost productivity amounting to an average £3,289 (Cooper 2000). The highest costs are caused by loss of joint function in patients with severe RA (Pipitone and Choy 2003; Yelin and Wanke 1999).

The molecular processes involved in the initiation and progression of RA are extremely complex, and are still far from being understood fully. However, in the period preceding the work to be discussed in this case study, it had become apparent that specific cytokines played an important role in mediating the inflammation and tissue damage that occurs in RA. Careful study of the regulation of the cytokine network, and examination of molecules present in tissues from key joint sites, pointed to a single cytokine as a key driver of RA: Tumor Necrosis Factor alpha (TNFa). A series of experiments using monoclonal antibodies in animal models led to the hypothesis that the disease could be treated by using targeted TNF inhibitors. The experiments that led to the hypothesis were performed mostly at the Kennedy Institute of Rheumatology.

The use of a monoclonal TNF antibody in RA patients proved this hypothesis, bringing about dramatic improvements in the symptoms of the first patients that were treated.

Larger scale, international clinical trials confirmed the broad effectiveness and low risk of the treatment, and demonstrated that as well as reducing inflammation, it counteracted joint destruction. The successful outcome of the trials paved the way for the development of three anti-TNF drugs which, in recent years, have been approved for use in the UK. Thus the development of the team's work, from molecular research through to clinical trials, represented a fortuitous and fruitful symbiosis of basic and clinical science.

This study is based on interviews with the PI and his principal collaborator. It also draws upon arc archive material, institute archive material and annual reports, as well as the scientific publications resulting from the research described. The period chosen, 1992 to 1995, represents the earlier part of the five-year arc core grant that was awarded to the PI's institute in 1992, which forms the backdrop of the research discussed.

12.2 Stage 0: topic/issue identification

The collaboration between the PI and his principal collaborator, which was key to the work discussed here, dated back to the mid-1980s. The PI had been exploring the pathogenesis of RA and allied connective tissue diseases from a clinical perspective. The principal collaborator had longstanding expertise in basic autoimmunity. Both shared an interest in lymphocytes and cytokines. Realising that they possessed complementary spectra of skills and knowledge, they founded a collaboration to embody the research principle "from bench to bedside". Both were interested and experienced in using authentic human disease tissue to study pathogenesis.

The PI and his principal collaborator worked on two parallel areas. The investigation of human immune responses to autoantigens was the major focus initially (from the early 1980s) but in 1984 collaboration began on cytokine expression, which led the collaborator to move to Charing Cross Sunley Research Centre in 1985, close to the Kennedy Institute. As the work on immune responses did not prove to be as productive as anticipated, more effort was put into cytokine analysis to see if any of these inflammatory mediators might be a therapeutic effect target.

From a general interest in investigating the presence of, and ascribing a role to, individual cytokines in RA, the team homed in on TNF in two stages. First, alongside other researchers working in the area, they established that very many cytokines were present in RA tissue. Second, they used novel modifications of cell culture using human tissue to investigate whether any of the cytokines found were worth blocking as therapeutic targets. Positive results led to a focus on TNF, whose blockade was tested subsequently in animal models.

The path to this research had been opened up by breakthroughs in molecular biology in the preceding decade, which had made it possible to relate cytokine activity to proteins, and to clone cytokines, including TNF. As the PI pointed out in 1991, the advent of monoclonal antibodies and "designer" peptides "which might interfere with disease processes and hold promise as therapeutic agents" was the primary motivation to focus the Institute's efforts on "understanding disease mechanisms by intervening in model systems

and in patients with biological tools". To develop a tool for intervention, the PI collaborator's team cloned TNF receptors, molecules which bind TNF.

Moreover, work was driven by an important clinical need and the assumption that the emerging treatment was likely to be safe. However, in the early stages of the research it was hoped only that the neutralising effect would help to underline the importance of TNF, and would provide "proof of principle". The team did not expect to uncover a long-term treatment for a chronic disease. As the PI explained, this outcome is not generally an expectation of an academic group. Moreover, it had never been shown that antibodies could be used long-term.

By 1992, success in blocking TNF with antibodies had been shown in tissue and animal models. The next step was the transfer of the treatment to patients, and systematic examination of its effects in clinical trials, beginning with a proposed first clinical trial with two groups of five patients. As the trial required could not be financed with Institute funding, the team looked for industrial partners with suitable TNF inhibitors and forged a collaboration with an American biotechnology company. A description of the planned work in the Institute's core grant submission in December 1991 is given in Box 12.1.

> […] Studies [with human RA tissues] suggesting that blocking TNF would be beneficial in rheumatoid arthritis have led to experiments to verify this concept in an animal model of arthritis … It has been found that monoclonal (hamster) anti-murine TNFa or rabbit anti murine TNFa has beneficial effects … There was partial reduction in joint swelling, but more importantly a dramatic reduction in joint destruction and fibrosis.[1] Subsequently, it was demonstrated that in rheumatoid arthritis there is augmentation of the endogenous TNF inhibitory system, the soluble TNF receptors. This acts to partially inhibit TNF activity in rheumatoid arthritis … [but] there is still bioactive TNF and so disease activity … In order to investigate whether the beneficial effects observed in mice can also be obtained in patients, the present study, using a chimeric anti-human TNF monoclonal antibody in patients with rheumatoid arthritis, has been proposed.

(SOURCE: Institute archive)

Box 12.1: Extract from core grant application (submitted in December 1991)

12.3 Interface A: project specification and selection

Although the work discussed here led to the development of a highly-effective new drug treatment in a field where few other therapeutic advances had been seen, its eventual importance was far from obvious when the Institute submitted its five-year core grant application in 1991. The clinical results were not yet known and, as mentioned above, the PI and his principal collaborators did not expect to bring to light a long-term treatment, or indeed generate a highly successful commercial product. In this light, it becomes more understandable that the referees' comments regarding the proposed clinical trials with anti-TNF treatment were neither plentiful, nor always enthusiastic. The work was viewed as controversial for two reasons: the principle of a single dominant cytokine (TNF) regulating

[1] Fibrosis: formation of tissue as a reaction or repair process.

others was not accepted; and there was a belief that interleukin-1 (IL-1) was the most important cytokine.

The Institute submitted a research plan in March 1991, which was extended and updated in December 1991 at arc's request. The latter version was sent out to be reviewed. Six referees commented on the the clinical immunology division's core grant submission. Of these, five were UK scientists and one was an international referee; four were based mainly in basic science and two were clinicians. Comments were submitted in letter format. Standard form ratings, as used for other arc grant reviews, were not included but overall assessments are summarised in Table 12.1. Only three referees referred to the proposed anti-TNF trial, which was presented in the form of a trial protocol.

Referee A, a clinician, complained that the submission did not include the document describing the rationale and experimental model behind the proposed anti-TNF trial. However, while giving only lukewarm support to the therapeutic monoclonal area as a whole, he concluded that the anti-TNF trial was "of interest". Referee B, a basic scientist, was more vigorous in backing the proposal, judging the anti-TNF trial a "good bet" to start trials with anti-cytokine therapy. Referee C, a clinician, doubted the success of the proposed therapy. He warned that his own experiences had demonstrated the limitations of monoclonal antibodies in more straightforward cases of cell blocking, and that it was likely that any therapeutic effects that were achieved would be short-lived. However, he conceded that the approach may have merit as "a short-term investigative tool to examine the effect of inhibiting TNF activity", and therefore should be adopted. Regarding the proposed industrial collaboration, he felt that the arrangement outlined would not leave the team enough space for academic questions to justify public or charitable support. Therefore, he supported the work only on the condition that all the funding came from industrial sources.

Table 12.1: Summary of assessors' reports

	High	Medium	Low	None
Overall value of the project	B	A, C		

(SOURCE: arc archives)

During the interview, the PI and his principal collaborator philosophically remarked that there are always comments that a given proposal is either too commercial, or too academic. They pointed out that the trial work proved to be a very important part of dissecting the biology of anti-TNF treatment. The PI pointed out that subsequent events did not support the contention that the proposed work was too industry-focused, as a number of mechanism of action studies were performed in collaboration with the company. Although the proposed initial trial was unlike the smaller, low-risk trials of existing products that were usually funded by arc, the team felt that it was not out of place in the arc funding application, as this funding was used for longer-term research and connected work on animal models and tissue histology and cell biology.

arc funding decisions do not appear to have been negatively affected by the comments, and the division's programme was not required to be reformulated. The overall core funding requested was granted.

12.4 Stage 1: inputs to research

12.4.1 Funding

For several reasons, it is difficult to put funding figures against the team's work on anti-TNF. As is typical for research institutes and groups, arc core funding and much of the funding from other, public, charitable and industrial sources were pooled into one budget. This budget was divided up under the aegis of the Institute's heads of division committee and director, who was also the PI of the project discussed. No written records of the internal division of this "pot" has survived.

Up to the period studied here, arc funding for the Institute had been divided into annual core grants and individual projects and programme grants won in open competition. Following a major review of the arc's funding arrangements for the Institute in 1991–1992, individual arc grants and core funding were rolled into one enlarged core grant. This core grant was fixed at £2.7 million for five years, from October 1992 to September 1997.[2] The amount, which was to be paid out in fixed yearly portions, reflected the total sum that the Institute had received from arc in previous years (eg in 1991–1992, £1,819,000 core grant and £700,000 in individual grants),[3] but it was not calculated to take inflation into account. In 1993, the Institute merged financially with another charity, the research centre at which the PI's principal collaborator had been formerly employed. This merger increased revenues by £80,000 with expenditure rising accordingly. The Institute benefited from the donation of the building inhabited by its merging partner, estimated to be worth £5 million.

The new core grant arrangement barred members of the Institute from applying for other, individual arc grants. While the Institute was successful in attracting other funding, arc remained its single most important sponsor. In the years studied, the arc core grant provided approximately 60–70% of the Institute's total income. This support was a crucial to cover overheads: for example, in 1995, the Institute expected to spend £250,000 of the core grant on occupancy costs and £340,000 for laboratory expenses and consumables. In its annual report for 1993, it explicitly acknowledged that its success in winning external funding was made possible by the Institute's arc core-funded staff and facilities. Between 1992 and 1995, annual income from research grants grew from £854,000 to £1,175,000.

When interviewed, the PI and his principal collaborator did not remember the exact proportion of arc core grant allotted to the anti-TNF work since most of the translational science was performed in collaboration with the industrial partner. However, they pointed out that as the importance of the area became clear, the proportion to support new initiatives on understanding the regulation of TNF production grew gradually larger, from the size of approximately one programme grant to that of several programme grants. For example, one of the developments sparked by the anti-TNF work was the creation of a signalling group in 1996. The signalling group has since emerged as a very important strand of research at the Institute.

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[2] In today's money: 1992–1993: £3,550,000; 1993–1994: £3,460,000; 1994–1995: £3,420,000; 1995–1996: £3,320,000.

[3] In today's money: £2,470,000 and £950,000 (= £3,420,000 total support from arc).

In terms of funding elements that can be attributed, 50% of the PI's salary was funded partly by the arc core grant, and the other 50% by the medical school at which he held a professorship, which also provided the infrastructure required for clinical research. arc also funded the PI's principal collaborator and two further senior scientists working on anti-TNF, as well as several secretarial and support staff.

The infrastructure for the translation of the work from the laboratory to the patient was funded almost entirely by sources other than arc. The registrars taking part were paid from other sources, including the NHS, medical school funds and international sources. The trial nurses were funded by the industrial partner. However, as the PI pointed out, arc's input was vital in providing key elements that allowed the clinical trials unit to be set up and in underpinning the longevity of the research. For example, the senior nurse was funded by arc and was of central importance to the unit, managing the database, recruiting suitable patients and generally acting as mediator between service and research.

Funding provided by the US-based industrial partner supported the entire infrastructure connected with the first trial (20 patients) and the following larger scale multi-centre trial (73 patients), as well as later trials in 1995–1996 and 2000–2002. This included resources for monitoring patients, analysing the data, medical liability insurance and 40% overheads. According to the interviewees, the total investment of the company ran to over £500,000 over two or three years. The overheads were ploughed back into the Institute's budget, for example, to create additional positions for specific research tasks. Initially, the team had approached a number of pharmaceutical companies within the UK, but were frustrated by deep scepticism regarding the verity of their claims. Success with the eventual partner was helped by the fact that its research director was a former PhD student of the PI's principal collaborator, who acted as an internal champion of the project.

The interviewees emphasised that they wished to give arc as much credit as they could for the support given to the anti-TNF work: while arc did not have the resources to be the Institute's sole funding source, without arc's support for infrastructure, the team would have had no basis from which to operate. The five-year support by arc funding made long-term planning possible, which is key to being able to undertake more ambitious projects, such as the work discussed here. It also helped to enhance the scientific credibility of the work, "as anyone can do a trial with a drugs company". The interviewees felt that, thanks to additional arc support, they were able to benefit from the resources of a large company to realise their favourite research idea.

12.4.2 **Human capital**

The mainstays of the research described were the PI and his principal collaborator, whose symbiotic basic clinical teamwork has been described already. However, the work also profited from a number of other skilled scientists. One longstanding team member's success in tissue culture experiments to study the role of TNF in regulating the production of IL-1, which was already known to be important in cartilage turnover, had been crucial in paving the way for further research in the late 1980s. Another member, a technician and part-time PhD student, brought experience in animal models to the group, and could thus mediate the relationship between clinical and animal models used by the group.

Just as the increasingly apparent success of the trial attracted growing shares of the internal resources, the resulting international prestige allowed the PI to recruit additional high-quality staff. This was important, as the focus on anti-TNF required a team that was skilled in a wide range of areas, such as cell biology, histology, arthroscopy,[4] tissue procurement, documentation and classification of patients, animal model studies and disease transfer between animals.

12.4.3 **Techniques, reagents and equipment**

For the team's initial work, the proximity of laboratory and clinical setting, of "bench and bedside", acted as an important facilitator. The interviewees considered it as a rare advantage to have "the whole enterprise under one management".

The animal models previously developed by the PI and collaborators at the Institute were a key part of the infrastructure that was needed for proof of principle.

Importantly, the collaborating pharmaceutical company supplied the antibody needed for anti-TNF treatment trials, which was engineered to resemble to human antibodies in order to avoid rejection. The company also provided the required good manufacturing practice (GMP) conditions for producing antibodies and carrying out the trials. Previously, the company had carried out tests of the therapeutic potential of anti-TNF in treating other conditions, such as septic shock. Several other companies had tried also to block TNF in sepsis.

12.5 **Stage 2: research process**

It is important to be aware that in the period preceding the first trial, the team were not anticipating that anti-TNF therapy would assume the importance that it did later. The initial expectation was that TNF would be identified as an important target, which would lead the team somewhere else, for example, to finding a key small molecule drug, which is an objective to this day. Therefore, they were still vigorously pursuing other research avenues. In particular, a considerable share of the PI's time was spent on researching antibodies and the development of a B-cell project. However, this latter strand eventually had to be wound up due to lack of support from arc.

In order to validate the very positive results of the first clinical trial, the team needed to carry out long-term, multi-centre trials. This approach would provide a robust, representative data set based on different groups of patients, and throw light on anti-inflammatory effects and consequences for long-term damage. In order to achieve the desired trial structure, the PI and his principal collaborator had to spend a lot of time influencing the partner company's trial strategy. Although the PI's connections with international researchers proved to be very helpful in recruiting collaborators for the multi-centre trial, progress was slowed down by several circumstances. As the company was short of funds at the time, the funding needed for a larger scale, longer trial was not immediately available. Moreover, the team was unable to stop the company from being sidetracked into

[4] Arthroscopy: the technique of looking at, diagnosing (and treating) a joint by inserting an arthroscope containing a video camera.

exploring anti-TNF as a treatment for Crohn's disease,[5] in the hope that this drug – which would be used on hospital patients – would be easier to register.

Even though eventually the partner company was able to raise funds from a large pharmaceutical company, the described delays enabled another company to develop a rival drug rapidly. Borrowing the team's trial designs, this company succeeded in having their product licensed before the team's partner did.

12.6 Stage 3: primary outputs from research

12.6.1 Knowledge creation

As already described, the anti-TNF research and trials were funded from a variety of sources. It will be remembered that one of the referees of the Institute's core grant application thought that the trials were too commercially "streamlined" to qualify for funding from arc, which, he believed, should be reserved for work on more wide-ranging, academic questions. Even though the team demonstrably worked on the wider field of cytokine biology surrounding anti-TNF therapy, and acknowledged arc as a major supporter of this research, clear-cut attributions of papers to individual funding sources are difficult to make. The following description of papers identified as key publications by the PI provides an overview of the contribution of the anti-TNF work to scientific knowledge.

TNF as a therapeutic target first emerged from studies on cultures of human rheumatoid synovium, which were initiated and perfected by two postdoctoral researchers, one of whom went on to become a professor at the Institute. This advance provided a test bed to evaluate regulation of cytokines produced by the cells taken from RA joints. It was found that anti-TNF wiped out the production of IL-1, an unexpected observation that had profound impact.

By the time of the publication of the first key paper identified (Chu and others 1991), the team had made several important advances towards the eventual use of TNFa antibodies to halt the disease process – most notably, in 1988, a team member had succeeded in studying TNF in tissues from patients in tissue culture (Brennan and others 1989). Chu and others (1991) achieved a further step by identifying TNFa as a worthwhile therapeutic target. By localising TNFa producer cells in the inflamed tissue of RA patients, the team showed that TNFa is produced locally in the synovium and the pannus (a tissue layer between bone and cartilage that grows as a result of inflammation in RA).

Building on this insight, Deleuran and others (1991) further explored the local actions of TNFa by investigating the expression of TNF receptors on cells in the same sites. The finding of a strong expression of these receptors compared to normal and osteoarthritis (OA) tissue, and expression of the receptors by a variety of cell types in synovial tissue, suggested that "a wide range of cells are potential targets for TNFa in this tissue", underlining the important role of TNFa in the RA disease process.

[5] An inflammatory bowel disease that can affect any part of the digestive tract, leading to pain and diarrhoea.

Williams and others (1992) developed the findings of the previous work in an animal model, which made it possible to study the actions of TNFa in a physiological system. Crucially, the results showed that blocking TNF in an animal model of RA not only reduces inflammation, but also protects joints.

The next, major step was translation of the findings into treatment for RA patients. Elliott and others (1993) describes the first clinical trial, in which a chimeric monoclonal antibody to TNFa was used. This trial, which involved 20 patients treated with 20mg/kg anti-TNFa over eight weeks, demonstrated both the safety and efficacy of the treatment. There were no adverse events and the participants experienced significant improvements, which were borne out in addition by a range of clinical and laboratory assessment methods. The results strengthened the case of TNFa as an important regulator and therapeutic target in RA.

In order to validate the results of the initial trial and achieve registration of the treatment, a large-scale, multi-centre trial under approved GMP conditions was required. The strategy and outcome of this trial, a randomised and double-blind clinical trial which took place at four separate sites, are reported in Elliott and others (1994). The result confirmed the positive findings of the initial trial, with significant improvements in individual disease-activity assessments in over 60% of high-dose patients. One patient developed pneumonia, which was found to be related possibly to the treatment. The size and methodology of the trial presented sound evidence for the beneficial effects and therapeutic potential of targeted cytokine blockage.

12.6.2 Research targeting, capacity building and absorption

The clinical trials were fruitful for the wider field of cytokine research, as they were found to pose a "whole generation of new questions". The PI and his team, who had never been involved before in large-scale clinical trials, became skilled in clinical trial methodology. In turn, they passed this knowledge onto the international collaborators, who hosted some of the multi-centre trials and needed to follow a standardised protocol. Importantly, these collaborations helped to establish a large international network of scientists in the field, which not only spawned further constructive collaborations but also helped the PI's Institute to gain international recognition and contacts.

The work attracted considerable international interest and helped to develop the careers of the researchers involved. About one-third of the core team remained at the Institute for many more years, including junior members who went to become senior scientists there. Other team members moved on to academic research abroad. Two of the team members went into industry, one of whom went to work for the team's partner company in the trials. Two team members gained PhDs in the context of the work described, one of them being a technician working on his degree part-time. A further team member, a visiting researcher from Denmark who joined the Institute for two years, carried out substantial work for his MD.

In the wider field of arthritis research, the work led to a paradigm shift. Given estimates that there are about 250 cell types, 30,000 genes and that each gene has three or four products, there are several hundred thousand molecules that could be relevant to the damage or regeneration process. The importance of the anti-TNF research lay in the

Selected bibliometric indicators for case study L

Publication portfolio

Output

Number of papers 41

Collaboration

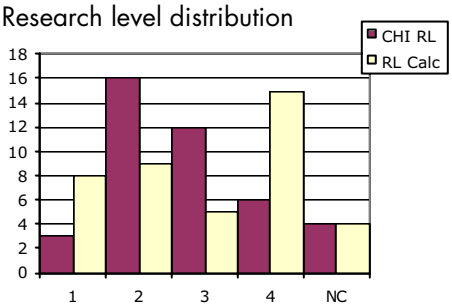
Mean number of authors 5.5

Mean number of addresses 2.2

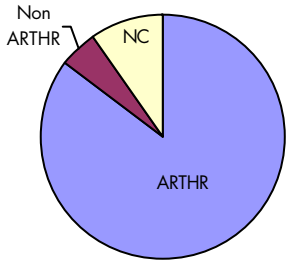
% with non-UK addresses 26.8%

Type

Research level distribution



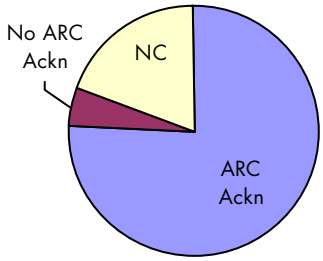
Field distribution



Funding

Mean number of acknowledgements 2.9

ARC funding acknowledgements



Knowledge flow

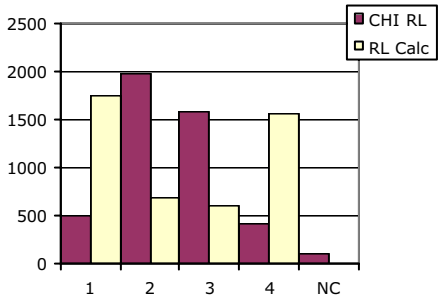
Strength

Mean citations per year (all papers) 329.8

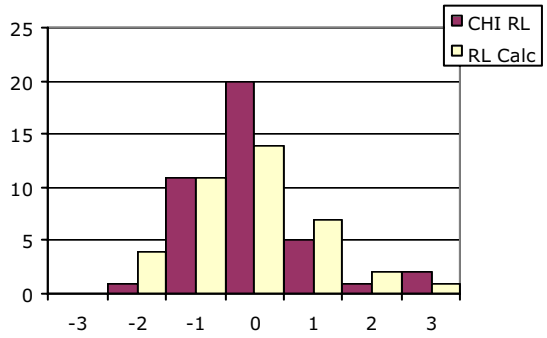
Mean C0-4 56.9

Knowledge translation

Research level of citing papers



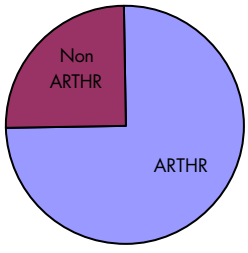
Relative research level



Knowledge diffusion

% of citations from the US 32%

Field distribution of citations



insight that, in a complicated disease involving multi-step processes, one single molecule can have profound effects on pathogenesis and can be targeted in therapy over an extended period of time. The team's discovery of these properties thus led the scientific community to accept biologicals as therapeutic agents. Previously, the idea that antibodies could be useful in treating chronic disease had been viewed with scepticism. It was felt that such treatment would be expensive and inconvenient for patients, and that the improvements experienced in short-term trials would not prove to be robust in the long term: in time, other compensatory molecules, like those occurring in cancer, would emerge and take over the inflammatory cascade. Thus, it came as a surprise that TNF could be inhibited for years, with the effect of reducing joint damage, and possibly permitting repair.

For this body of work, the PI and his principal collaborator received two highly prestigious research awards in 2000 and 2003.

12.6.3 **Health benefits**

In the course of the trials, the large majority of the 73 patients who were treated (including those who had not responded previously to drug therapy) experienced rapid and dramatic improvements of their condition.

12.7 **Interface B: dissemination**

The interviewees spent a considerable amount of time communicating the findings of their research into anti-TNF. This was particularly necessary in the early days of the discovery, when the team had to convince a sceptical audience for whom the dramatic results of the trials were simply "too good to be true". Dissemination took place through publications and conference papers. For example, in 1993 the PI spoke at 13 conferences, workshops and meetings in six countries. In 1994, he made at least 17 appearances as an invited speaker. The PI highlighted that, unlike many other industrial companies, the partner company did not try to suppress these dissemination activities.

The amount of interest generated by the work was helpful in convincing arc that the team were pursuing a worthwhile avenue. The first paper on the trials, delivered at a workshop in Israel in 1992, already had great impact in the community. The first paper on the first clinical trial, presented at the American College of Rheumatology in 1993, generated considerable media attention and was picked up by American newspapers.

More unusually, and therefore memorably, the PI and his principal collaborator stepped into the limelight of public consciousness at a press call in February 1994 to announce the successful evaluation of the treatment in the first clinical trial. The announcement was complemented by a video shot of a formerly disabled patient ascending a flight of stairs, which proved highly media-effective, and was shown on the national evening news. As a result of this coverage, the Institute received 4,000 to 5,000 phone calls, and had to divert four scientists from their normal work to deal with the queries.

12.8 Stage 4: secondary outputs – policymaking; product development

12.8.1 Informing policy and product development

The research of the team lead to the development of three drugs: Infliximab (Remicade – which binds and blocks TNF and was the first drug to enter clinical trials); Etanercept (trade name: Enbrel); and Adalimumab (Humira). Following the licensing of Humira in the UK in September 2003, all three drugs are now available in the UK. Remicade, which is suitable for adults only, is given through regular infusions in combination with Methotrexate;[6] Enbrel is suitable for adults and children and is injected under the skin twice a week; Humira, which is also most effective when taken together with Methotrexate, is injected under the skin once a fortnight.

Summarising ownership of the development of these products, the PI stated that the development of the antibody cA2 (Infliximab/Remicade), had not been a concern of the Institute, as in the early 1990s, the academic community was much less aware of the potential value of patents than is currently the case. However, he and his collaborators' work had made it possible for this development to be applied to RA through arc-funded work between 1988 and 1992, prior to clinical trials.

As mentioned earlier, the collaboration with the biotechnology company began as an academic project without expectation of financial gain. Due to earlier patent disputes and ambiguities in the field of TNF antibody treatment in severe infections, the patent situation surrounding drug development grew extremely complex. A still-unresolved point of dispute between the team and the company is the company's use of an initial data set provided by the team to strengthen the application for the company's original anti-TNF patent. However, as a result of a research and licensing agreement with the partner company in 1992, the PI and his principal collaborator did succeed in patenting Methotrexate co-administration with Remicade, which was later shown to be the most effective method of harnessing the drug and has earned substantial royalties for the Institute and arc.

Anti-TNF treatment has been included in the guidelines of the NHS National Institute for Clinical Excellence (NICE), as well as the national clinical guidelines of various other countries (National Institute for Clinical Excellence 2002). Furthermore, it has been recommended by national international consensus groups with a focus on arthritis (American College of Rheumatology (ACR) Subcommittee on Rheumatoid Arthritis 2002; Emery and others 2001; Furst and others 2000, 2003).

12.9 Stage 5: adoption – by practitioners and public

12.9.1 Health benefits

All subsequent trials have reproduced the team's original positive results; safety has been proven for a longer period of time; and the use of Infliximab and Etanercept has been recommended by the ACR and NICE. Nevertheless, the uptake of anti-TNF treatment

[6] Methotrexate is a drug which is able to block the metabolism of cells.

has been limited due to lack of resources to fund the treatment, at approximately £9,000 per patient per year.

The highest uptake of the treatment can be found in the US, where an estimated 15% of RA patients benefit from it. In Europe, uptake is highest in Scandinavia (6–7%), followed by Spain and the Netherlands. Even though the treatment is a British discovery, uptake in the UK is low (2%). Pressure groups, notably arc and the European League Against Rheumatism (EULAR), are currently campaigning for the treatment to be made more extensively available. Recent studies suggest that the treatment is, in fact, cost-effective (National Institute for Clinical Excellence 2002; Pipitone and Choy 2003).

12.10 Stage 6: final outcomes

12.10.1 Health benefits

Anti-TNF treatment works by achieving a therapeutic "downstream" effect: if the treatment is stopped, the disease returns, although recent trials in the Netherlands suggest that long-term benefits can be induced by treatment at diagnosis. Therefore, the search for an "upstream" treatment – tackling RA at source – continues. In the absence of breakthroughs in this area, the drugs developed on the basis of the team's research have brought about considerable improvements in the lives of arthritis sufferers with access to the treatment. As mentioned in the previous section, uptake has been limited due to the initial cost involved. Nevertheless, it is estimated that over 500,000 patients have benefited worldwide.

In approximately 70% of patients, anti-TNF treatment leads to significant improvement. Recent trial results show that the treatment is able to arrest joint damage in patients with longstanding RA, an unprecedented achievement in rheumatological therapy.

As TNF is involved also in other chronic inflammatory diseases, anti-TNF therapy is being used successfully to treat Crohn's disease, psoriatic arthritis, ankylosing spondylitis,[7] various forms of vasculitis and children with chronic arthritis. Furthermore, early-stage clinical studies have suggested that anti-TNF therapy may be beneficial in a range of other diseases (Thomson Current Drugs Investigational Drugs Database).

The evidence available so far suggests that monoclonal antibodies such as Infliximab (Remicade) can be used in the long term. There is a risk of increased susceptibility to infections such as tuberculosis; however, this can be minimised by appropriate screening.

In a recent study on patient preferences for the treatment of RA, when offering information to 120 patients in the US on the side-effects, effectiveness and cost of four medications (Methotrexate, gold, Leflunomide and Etanercept), 90% of patients preferred an anti-TNF inhibitor, Etanercept (Enbrel) due to lower toxicity (Fraenkel and others 2004).

[7] Ankylosing spondylitis is a form of chronic inflammation of the spine. As a systemic rheumatic disease, it can also affect other parts of the body, such as the eyes and other organs.

12.10.2 Broader economic benefits

Several studies and organisations, notably NICE, have argued the case of the cost-effectiveness of anti-TNF treatment through reduction of premature morbidity and mortality. Traditionally, investigations into this question have been based on modelling, comparing the cost of the treatment to the costs incurred by the absence of the treatment. Such costs include direct costs, for example, surgery, hospital admissions, associated diseases such as heart attacks and strokes, which are estimated to average approximately £3,210 per year, as well as the indirect cost of productivity loss, estimated to average approximately £3,270 per year (Cooper 2000; Pipitone and Choy 2003; Yelin andWanke 1999).

Recently, a new study has advanced the argument on the basis of patient data, comparing outcomes before and during a year of anti-TNF treatment in 160 patients (Kobelt and others 2004). The study concluded that during the first year of treatment, direct costs were reduced by 40%, while indirect costs did not change substantially. Patients' ability and resulting quality of life increased. For the participating group of 160 patients, the estimated costs per quality-adjusted life year (QALY) that was gained amounted to €50,000 (approximately £33,440).[8] However, this study does not take into account possible improvements in cost-effectiveness due to the long-term benefits of the treatment. Drug sales represent a substantial source of income for the industrial producers. Recently, a British company developing a new anti-TNF treatment was bought by a large biopharmaceutical firm at the price of £1.5 billion.

[8] Using benchmarks for cost-effectiveness figures and estimated values for a QALY between €35,000 and 55,000 in Sweden, the UK and the US, Kobelt deduces a willingness to pay for a QALY of €60,000. The NICE guidance on the use of Infliximab and Etanercept, which recommend the treatment, assume an incremental cost-effectiveness ratio of £27,000 to £35,000 (Kobelt 2004, p. 7). Traditionally, the NHS has given only restricted approval for treatments at more than £30,000 per QALY; see Towse and others (2002).

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CHAPTER 13

Case study M: mapping and characterisation of the genes involved in rheumatoid arthritis

13.1 Introduction to the research project

This research presents one of a number of attempts into the identification of heritable factors contributing to common multifactorial diseases. Specifically, this programme grant supported the efforts of a group of researchers to carry out genome-wide screening[1] for genes influencing susceptibility to rheumatoid arthritis (RA). Because adequate analytical techniques for genome-wide screening were still being developed at the time of the programme award, research also relied heavily on the recruitment of families with at least two affected siblings (sibling pair analysis). In addition, because RA is a complex disease syndrome, this programme presented many challenges from the outset.

RA is a disease that affects the entire body and is one of the most common forms of arthritis. It is characterised by the inflammation of the membrane lining the joint, which causes pain, stiffness, warmth, redness and swelling. RA affects up to 1% of the world's population and is a disease with a clear gender bias: women are affected 2.5 times as often as men (Jirholt and others 2001). However, RA is considered a syndrome that is composed of several distinct diseases, and this makes the frequency estimates and disease characteristics variable (Jirholt and others 2001).

13.1.1 Genetic research in RA

A lack of a precise disease definition and specific RA subtypes, and the influence of environment and other possible factors such as gender and lifestyle, makes it difficult to find the most important genes associated with the pathogenic events leading to RA (Jirholt and others 2001). However, the frequency of monozygotic twin pairs in which both twins are affected with RA (12–15%), in comparison with the frequency of affected dizygotic twins (2–4%) provides evidence of a genetic contribution (Seldin and others 1999; Silman 1997; Wiles and others 1999). This project had two components for the researchers: first, to screen the *whole* of the genome for susceptibility genes associated with RA; and second,

[1] Testing a population group to identify a subset of individuals at high risk for having or transmitting a specific genetic disorder (in this case, RA).

to apply their knowledge more widely to other diseases that are related to RA (for example, ankylosing spondylitis (AS)[2] and chondrocalcinosis).[3] Very few genes had been identified with RA at the time this research programme was conceived. While it was recognised that RA was a multifactorial disease,[4] the principal investigator (PI) believed that his investigation could give important insights into the causes and processes of the disease.

13.1.2 Complicating features of RA: disease specific and genetic factors

At the outset, this research was presented with a number of complicating factors:

- RA is not a well-defined disease but rather presents a set of clinical syndromes overlapping with several diseases with wide-ranging causes;
- the differing ages of onset of the disease tend to complicate estimations of sibling risk and causes problems with adequate sampling and testing; therefore, the work relied on samples of gene material that was not readily available. In the ideal scenario, the PI would have obtained a large number of samples from two generations where parents and siblings were affected. However, because the time of disease onset varies, the chances of two-generation samples are reduced;
- genetic research at the time was still in its infancy, and the capacity was not readily available to develop powerful analytical techniques.

Despite these complications, there was a lot of impetus for this work to take place. The PI was able to collaborate with the arc Epidemiology Research Unit (arc ERU) in Manchester (which specialises in the collection of family samples for the purposes of genetic analysis) as well as other researchers who had developed and successfully used techniques for genetic screening already; thus he benefited from their intellectual and moral support as his named co-applicants.

13.1.3 Context of the research

The research programme was set in the context of two important parallel developments. One was the establishment of an important overarching research centre in human genetics/molecular medicine with different research "pillars" representing multifactorial diseases such as type I diabetes mellitus and hypertension. The unit had separate sponsors that provided important facilities to the RA research programme, without which the programme would have had difficulties in carrying out the work. One research leader for the diabetes pillar had returned to the UK from the US with advanced knowledge in this research field. In addition to being one of the named applicants, he provided an important

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[2] AS is a painful, progressive, rheumatic disease. It mainly affects the spine but it can also affect other joints, tendons and ligaments. Other areas, such as the eyes, lungs, bowel and heart can also be involved (see: http://www.nass.co.uk/questions.htm). It is a debilitating condition affecting 175,000 people in the UK.

[3] Chondrocalcinosis is a common cause of arthritis in the elderly, affecting around 10% of those over 60 years of age (arc archive, Application for an ARC Project Grant, 2004; arc archive). Although most cases are asymptomatic, it can cause acute joint swelling and destruction, and chronic low-grade inflammatory arthritis and joint damage.

[4] A disease that may have different causes such as the environment, genes, lifestyle and gender.

impetus to this centre, and helped to develop further the analytical techniques employed for whole genome screening.

The other parallel development had been a longstanding collaboration with the arc ERU, where the family repository centre had collected a sizable proportion of the genetic sample material for analysis already, and was to be in charge of further collection of samples and some analysis for specific genetic markers.

13.1.4 Background to genetic mapping technique

Broadly speaking, gene mapping is the process of determining the position of genes on a chromosome and the distance between them. Whole genome screening is searching for the genes involved in disease development without any *a priori* assumptions about their chromosomal location or function in the pathogenesis of the disease (Jirholt and others 2001). Researchers do this by using genomic segments which exhibit heritable variation (polymorphic markers), dividing the whole genome into different sections and then testing for linkage with disease in families with at least two affected siblings. Given the general rule that siblings share parental forms of genes on a chromosome 50% of the time, a significant distortion towards greater sharing of genes in affected siblings is indicative of genetic linkage with the disease (Ollier and Worthington 1997). Large numbers of affected sibling pair families are required for this technique in order to detect genes; in addition, this technique has been dependent on the development of automated high-throughput genotyping (Ziegle and others 1992). Criticism has mounted against this approach as a "fishing expedition" and subject to a high level of serendipity (Ollier and Worthington 1997). Besides the fact that, as yet, there is no alternative strategy for identifying genes for diseases such as RA, its defendants claim that whole genome screening presents a systematic approach driven by the hypothesis that multiple susceptibility genes exist within the genome for a given disease (Ollier and Worthington 1997).

13.2 Stage 0: topic/issue identification

The PI had become involved in genetic research as a clinician at a time when genetic cloning was in its infancy. The particular research centre where the PI was based prior to the grant was heavily involved, through collaborations and the involvement of major UK research funders including arc, in establishing a national genetic research centre. Prior to the programme grant, the PI had worked closely with one named co-applicant on two separate arc grants, and had made important observations and discoveries about the involvement of genetic components in RA which helped him to build on this research, but also kept his interest in other rheumatic diseases and associated genetic disease factors alive. This is particularly true for AS, which had become a specific focus of his later research during and after the programme grant.

The arc programme grant was vital in developing capacity and furthering the development of any analytical techniques for carrying out this type of research. At the same time, the programme benefited from the establishment of other research programmes based at the same location, amongst others, for type I diabetes and hypertension, as well as the injection of large sums of money for building an overarching on-site centre of genetic research that provided the necessary facilities for the development of this research.

In the earlier years of the PI's research career, he focused on the genetics of specific disorders (ie collagen genetic disorders),[5] then later became interested in genome-wide screening in more common diseases. Importantly, the PI became involved in genetic research at the time when the method for sibling pair analysis was being conceived; a method that now underlies many whole-genome approaches in looking at the genetic components of multifactorial diseases such as RA. The first test of this type of analysis was used in looking at osteoarthritis (OA) in families in order to see whether type II collagen genes might be involved. When this experiment succeeded, the same method was applied to the whole genome in looking at the genetic components of diseases. However, the technology was not available to apply the method readily.

As mentioned in the previous section, prior to this research programme the PI had shifted his interests from rare diseases to more common diseases, and developed a particular interest for RA. According to the PI himself, RA was considered the "jewel in the crown". Important in the PI's development was the working relationship with a renowned researcher for another autoimmune disease, type I diabetes. He had moved to the same research centre as the PI, and began working with him from 1987 onwards. arc also largely sponsored this work. As the PI put it, the money he received through arc was very much a career development grant, which he used to build on his research interests in genetics in RA and other inflammatory diseases in the time running up to the programme grant.

The studies that had built up to the programme grant had shown that there was one major genetic component of RA linked to genes in the gene cluster that controls certain aspects of the immune response, referred to as Major Histocompatibility Complex (MHC). The research that focused on RA concentrated on predisposing genetic sequences within the human leukocyte antigen (HLA) region known as HLA-DR4. Subsequent studies confirmed the position within the specific HLA class II region contribution to RA. However, it was not clear whether the HLA-linked component of RA accounted for the whole of the genetic contribution. The PI and fellow researchers estimated that the non-HLA linked component of RA was between 50 and 75% of the total genetic contribution. This formed the basic justification for the programme grant, that is, a systematic search for non HLA-linked genes in RA, which involved a whole genome screen.

The total amount awarded was £480,302, the majority of which went towards the purchase of equipment and other non-recurrent expenses to support the programme; it also provided for the initial employment of three researchers on the programme (one postdoctoral research assistant and two technicians). Later, after a period when the grant was held in abeyance for family recruitment purposes, two more research assistants were employed on the remaining funds.

[5] Collagen genetic disorders are caused by mutations in genes encoding collagen proteins or enzymes involved in collagen biosynthesis (De Paepe 1998).

Rheumatoid Arthritis (RA) is a multifactorial disease to which there is a significant genetic component, about one-third of which can be accounted for by HLA-linked genes. We shall generate a rough linkage map of genetic effects in RA using a molecular genetic linkage approach based in the segregation of 500 evenly spaced (5-10 cM) microsatellite markers in 130 nuclear families containing affected sibling pairs. Significant linkages will then be refined to the 5cM level by defining new markers and applying them to a larger number of families. YAC [yeast artificial chromosome] contigs[6] will then be generated to achieve physical maps of any regions of interest, which will facilitate the identification of candidate genes. Polymorphisms will be identified either by single-strand conformation polymorphism or sequencing and these will be applied to carefully matched populations with RA and controls to detect linkage disequilibrium. Ultimately these studies should identify genes influencing the development of RA.

(SOURCE: arc archives)

Box 13.1: Abstract

13.3 Interface A: project specification and selection

Four referees reviewed the research proposal and a summary of their assessments is given below. (This information is based on peer-reviewed comments accessed through the arc archives.)

Generally, the referees were enthusiastic and supportive of the proposed programme, but also voiced concern over the critical nature of the clinical and epidemiological information on the families with this type of research. Referee C also requested more detail on the exact contribution of the laboratories involved in the grant application as it seemed that they were only mentioned as a general rather than a specific resource for the programme. Referee D expressed some reservations regarding the power of the study, given the small number of available families and the genetic effect already accounted for by HLA. Despite the general concern over the number of families, referee B suggested that the PI had made all the right kinds of contacts needed to maximise the shortfall in families. Referee C noticed the high number of other projects that were ongoing at the time of the programme grant and wondered whether progress would not be hampered by the investigators having to spread themselves too thinly.

In addition, there was a considerable problem of clinical heterogeneity inherent in the study, particularly for RA. The problem was explained further as one individual suffering from RA and the second one showing any symptoms related to rheumatology; however, that it could not be assumed automatically that they were suffering from the same haematological disease. The referee[7] asked for a detailed clinical review to be carried out before the families were accepted into a DNA panel (which was supposed to solve the question of the susceptibility genes contributing to this disease). Therefore, if the authors

[6] A "contig" is a set of overlapping segments of DNA; DNA segments that are contiguous in the genome.

[7] It was not clear from the archival information whether this referee was a fifth person that was asked for his opinion, or one of the existing four referees.

were invited to submit a programme, they should be advised to ensure stringent clinical control of the cases accepted for study.

In view of the importance of these comments, the applicants were shown a copy of the report and asked specifically to address the criticisms during a site visit. Following the site visit, the programme grant was reduced from five years to three years, to which the PI happily agreed.

The site visit was to convince arc of the feasibility of carrying out the proposed work. The review suggested in particular that the programme should address concerns over insufficient family resources to study the problem adequately. In consequence, two important changes were made:

- a restructuring of the way in which the families were recruited (the PI and co-applicant were to benefit from the collaborators' family repository which already stored a sizable number of samples, and their commitment to provide further samples). The effort between the two research centres should have been divided broadly between data sharing and analysis, which could benefit both centres; and
- a reduction of the programme funding from five to three years.

At the end of the three-year period, the researchers would demonstrate the capacity to map and identify genetic linkages, in which case further funding would be provided; or new approaches to the problem would be assessed.

13.4 Stage 1: inputs to research

This research work built upon a number of projects run over approximately 10 years (many of which were sponsored by arc) that gave researchers confidence and credibility for carrying out this type of work. The core researchers at the centre had gathered experience in the field of monogenic[8] disorders, autoimmune diseases and complex disorders relevant to the study of rheumatic diseases. However, it should be added at this early stage that the programme suffered from a lack of continuity in building research capacity that could ensure its ability to thrive and long-term growth.

With the advent of the new overarching research centre, the PI stated that there were also over 450 members at the local department of medicine (many of whom were involved in the investigation of diseases with a genetic component), who therefore represented a very valuable resource, especially as many of the techniques and results from the other groups would have considerable implications for his programme.

13.4.1 Prior knowledge and expertise

In terms of prior knowledge and expertise, there were three important inputs into this programme. The work built upon the following foundations:

[8] Monogenic: of or regulated by one gene or one of a pair of allelic genes (see http://www.bartleby.com/61/39/M0393900.html).

- core facilities of patient resources including family collections and cell transformation; a mapping core (15 technicians); a genome core (eight staff) using essential technologies including YAC cloning, cytogenetics and DNA sequencing; and an information technology core for computation and statistics run by one co-applicant and others;
- the PI's work on HLA associations with RA, which suggested the influence of non-HLA genes. The PI presented work on HLA associations with RA using data compiled from a number of small studies worldwide;
- one co-applicant's skills in data processing and analysis. This co-applicant outlined the screening approach of linkage to microsatellite markers and discussed the minimum number of markers and families necessary to obtain useful information. He emphasised that information from random mapping and candidate gene screening could be combined, stressing the importance of certain genetic classifications of disease in order to detect linkages.

Most importantly, however, in terms of input the grand vision of the overarching research centre was to be able to provide the facilities and capacity for technology development and general and statistical analysis of the research data.

The largest requirement for the gene mapping was twofold:

- the extension of core facilities already established for the mapping of genes (£230,000 was spent on capital investment);
- the recruitment of a large number of families from locally and abroad through the main collaborator site:
  - 200 sibling pairs;
  - international recruitment from Europe and the North with at least two affected siblings and both parents alive.

13.4.2 Funding

Following a site visit and general review of referees' comments, the total amount awarded was £480,302[9] for three years. This amount was used to pay one postdoctoral research assistant (RS1A Point 4) for three years (first year £21,718, second year £22,577 and third year £23,579), and two technicians (MLS01 Point 3) (first year £13,363, second year 13,897 and third year £14,453). Therefore, the total salary costs amounted to around £150,000, whereas the general expenses in the first, second and third years were £33,000 per annum respectively. Clearly, the majority of monies awarded were spent on capital investment, although salaries also represented a sizable amount.

At the end of the three-year period, the PI suggested using the remaining grant of £69,325.88. While this figure showed around £37,000 for salaries and £19,000 for capital equipment, the PI suggested optimising the use of these funds by shifting more towards salaries in order to complete the work in good time. This would pay for a research

[9] £610,000 in current values.

assistant, who previously had been employed through funding from Zeneca for the programme. In addition, he wanted to guarantee payment for another researcher for two years.

There were some changes to staffing arrangements which affected payments during the course of the research. While there were regular increases to the grant to cover pay awards, arc calculated that £3,799.55 of some £13,750 remained unused when two technicians left the programme at the end of December 1996. Therefore, the budget was adjusted and reduced to £69,325.88 in 1996.

13.4.3 Collaboration

This research built upon the strength of many collaborators, ie one other research centre specialising in epidemiology and international collaborators as well as the newly-conceived genetic research centre that built on a number of research pillars such as diabetes and hypertension.

Full collaboration was envisaged with the Manchester arc ERU at every stage in the process of this research. The PI had envisaged carrying out the initial genome screen in his centre; however, he felt that candidate gene mapping could be done by the collaborators.

The PI relied heavily on the databank from the principal collaborator for his analysis. Without their genetic data, this research would not have been able to take place. At the same time, the overarching research centre was set up to accommodate research efforts examining genetic factors in other multifactorial diseases. For the purposes of this new venture, a major UK charity funder invested in excess of £30 million, including running costs of £1 million per year for five years. The input included the use and maintenance of core technologies, for example, genotypers,[10] logistics and statistical support.

13.4.4 Techniques, reagents and equipment

During the process of setting up the programme, the lead researchers had established that the main collaborators at Manchester could provide £38,000 towards equipment purchase and extra laboratory space. In addition, another major research funder setting up the core facilities of the main research centre was able to provide further DNA samples.

The mapping approach was based on semi-automated technology (two ABI 373A automated sequencers) which was not as sensitive and reliable as subsequent technology, according to the PI. Major investment went into these machines, but it was essential because it minimised the errors that can occur in the manual handling of samples and data. These machines played a vital role in the generation of the large amounts of data sequences that were necessary in the later stages of the programme. In addition there was other equipment, ie fluorescent primers, required for the detection of polymerase chain reaction (PCR) products, that represented a huge resource freely available from the core facility.

[10] A DNA array, or an orderly arrangement of samples that provides the environment for matching known and unknown DNA samples (see http://genearrays.uchsc.edu/basic.html).

13.4.5 Other data

Institutes have supported much of the work around the country in the form of provision of family data. For example, the main collaborator was able to obtain samples from French and Irish sources as well as the UK. The goal was to obtain some 50 first and/or second-division families and a further 75 families with two affected and two non-affected siblings. The existing data made up 170 sibling pairs from the Manchester repository.

13.4.6 Human capital

Initially, one postdoctoral researcher and two research assistants were employed on the programme grant. At the start-up phase of the programme, delays were caused by a period of sick leave and changes to the arrangements with the postdoctoral researcher (who left the programme at quite early stages due to personal circumstances). The researcher was replaced by a clinical researcher who helped to set up the programme for AS. He was funded as a Michael Mason fellow from Australia for one year initially, and then by two years' additional arc funding for a clinical research fellowship. Importantly, he helped to recruit family samples for genome screening in AS. He completed his MD on the genetics of AS (ie HLA genetics).

When the family sampling problems (see Stage 2: research process) from the Manchester family repository became apparent, the AS programme began to assume greater importance. The newly-assigned clinical research had begun with some of the recruitment of family samples, which was continued by another arc fellow who later became an arc senior research fellow.

There were two research assistants that were recruited to carry out work in the laboratory. As the PI mentioned later, these assistants became more heavily involved in the analysis, and therefore he requested an upgrade of their salaries. arc permitted upgrading, and a further sum of £13,750 on the programme grant to cover the additional costs. However, both these research assistants left (one to further her academic career; it is unclear what the other person went on to do).

One researcher was recruited in 1997 to replace one of those that had left. Previously she had been employed on a "small grant" from Zeneca to help with the collection of family samples.

Following a period between 1997 and 1998 where the grant was held in abeyance in order to allow for more time to recruit family samples, the residue of this programme grant was used to employ two further research assistants. The grant was held until such time as 300 families were available through the arc ERU. The two researchers began their work at the beginning of 1998 for the second phase of the study and were then joined by a clinical research fellow at the beginning of May 1998.

13.4.7 Travel expenses

Approximately £500 was set aside from the total budget of £99,000 to cover travel expenses which were necessary for the operation of the programme (ie to travel up to Manchester up to six times a year). Additional funds were awarded for travel support (£1,112.98).

13.5 Stage 2: research process

This programme grant suffered from a number of process issues that were mainly of a political, logistical and intellectual nature. The process issues listed below were paramount to some of the successes and failures of the research programme.

13.5.1 Collaborations: political and technical issues

The decision for collaboration between Oxford and Manchester was a strategic decision taken by arc, who were the main funders of the arc ERU where the personnel and infrastructure were already in place to do the collection of data.[11] Some analysis for specific genetic markers was to be carried out by the collaborator. However, issues of ownership and doubt arose when data did not appear to be shared readily, and the PI recruited an assistant from Zeneca to help with the recruitment of samples. Some confusion may have arisen from the fact that it was not very clear from the outset whether the analysis of data was to be carried out solely or partially at the main site.

The family repository at the arc's research centre seemed an obvious place with which to collaborate; with some of the technological expertise missing to analyse the data, the idea to collaborate was a natural consequence which arc was hoping to enforce. The broad agreement appeared to be that the arc ERU was to coordinate the collection of multi-case families (ie families where more than one person – ideally, at least two siblings – were affected with RA), which would then form the basis for carrying out a systematic approach to genetic studies in RA. As stated above, it was agreed that the PI's group would incorporate the whole genome scan, while the arc ERU would examine candidate genes.

The decision to collaborate was taken because there had been an existing relationship with the UK research centre for a number of years, where the personnel and infrastructure were already in place to do the collection of data. In hindsight, this agreement proved difficult. According to the PI, the research collaboration could have worked better on one geographical site where regular contact could be ensured. The first reason flows into the second reason, as insufficient and irregular contact resulted in a lack of trust.

In the end, the whole genome screen in RA was completed jointly with the main research collaborator, being split equally between the two sites. Towards the end of the grant, it became clear that the centre of gravity for the RA work had shifted to the other collaborator's site. Together with one other research assistant, the PI became more engaged in the pursuit of the genetic basis of AS, which received another arc programme grant in 1998. The PI explained that the AS work was much more rewarding in the sense that there were no split sites, and that recruitment was adequate to carry out the work satisfactorily.

13.5.2 Capacity/recruitment issues and other reasons for project delays

There was a delayed start a period of sick leave for one of the research assistants. At the end of 1996, the programme grant had been held in abeyance since the resignation of one research assistant. Two important staff also decided to leave to join other programmes at the end of 1996. The PI then requested a further delay in reactivating the grant and arc

[11] The PI could not remember precisely who had agreed to this arrangement.

was in agreement with this, so long as the gap between the appointments did not extend beyond the end of 1997.

Another reason for deferment on completing the arc programme was that the PI needed to address recruitment issues of family samples that mounted during that time. The PI expressed that they would have substantially more families to study in the laboratory by the end of that year and that it would be logical to complete the analysis on 350 rather then 230 families. The PI realised at that time that a larger number of families would be necessary to increase the power of the analysis, and that it would be essential if one were to confirm any of these genetic linkages from the first phase. This coincided with the staff changes mentioned above, and a strategic decision was made to wait until at least 300 families were available to compete the analysis. For this reason, over one year in 1996–1997 the residue of this programme grant was held over until such time as 300 families were available through arc ERU and other potential collaborators.

Two research assistants were then employed form the beginning of 1998 to continue with this work and were also joined by a clinical research fellow from the beginning of May 1998.

13.5.3 Upgrading of funds

Interestingly, in the beginning, it was not clear what precisely the research assistants' role would be. The PI had envisaged that they would be employed very much in a technical capacity –essentially loading gels and not doing very much laboratory work that would involve intellectual effort. However, this was far from the case and it became increasingly apparent that the assistants' grading was substantially less than for those doing similar work. Therefore, the PI successfully requested an upgrade of their salaries from the end of 1995, although both left at a later stage.

13.5.4 Virement of funds

In 1997 the PI asked permission for a virement of funds on his arc programme grant from consumables and equipment to salaries in order to be able to offer extended contracts to the two research assistants that he wished to appoint to the grant.

13.5.5 Insufficient technology

The equipment on the programme grant was insufficient for the project. One of the reasons was that the ABI 373As machine was not particularly good at distinguishing the size of genetic markers.

With the delay in recruitment, and other projects gaining importance in the main research centre, DNA samples were recruited simultaneously at both sites. While it was not clear to what extent patients were adhering to the same diagnostic criteria in the collection of material, other issues arose concerning ownership. In sum, there were general difficulties in recruitment, scarce data, a lack of technology and a shift of interest towards AS that hampered the process of this research programme.

13.6 Stage 3: primary outputs from research

The primary outputs of this programme grant consists of around 40 papers (see Annex A).[12] The papers report on the progress of the genome-wide search for genetic regions associated with RA.

The programme was separated broadly into two phases. The first phases successfully identified linkage to genetic markers; but it was clear from the outset that these results should be refined in a second round of the whole genome scanning. Therefore, in the second phase, another genome screen was initiated in order to validate the findings of the first phase. As above-mentioned in Stage 2: research process, 50% of this work was then carried out largely at the collaborators' site at the arc ERU. Together, the programme identified a number of specific genetic regions and markers that were implicated in RA. While this research achieved the aim to identify the non-HLA-specific risk factors for RA, none reached the genome wide threshold for "significant linkage".[13]

In addition, these papers also reflect on the rising importance of parallel work in identifying susceptibility genes in AS. Nominally, the AS research was subject to separate arc grants, but presented a clear overlap and relevance to the RA work. In particular, the project grant for the genetic mapping of non-HLA susceptibility genes in AS, which ran almost in parallel with this programme grant, needs to be considered as playing a major role in contributing to the primary outputs, as it was also a broader aim of the research to apply knowledge to other diseases. According to the PI, much of the technology which they were able to develop in this programme grant has also been applied to analysis of the genetic component of AS. Moreover, the PI claims that this programme grant laid the foundations for genetic research in both RA and AS and other rheumatic diseases. For example, collaboration with other groups allowed the PI to identify the chromosomal interval associated with familiar chondrocalcinosis.

On the basis of the specialisation in AS which (according to the PI) was attributable mostly to the fact that family samples were collected on-site, arc funded two further studies in this area. One was a project grant funded for two years (1998–2000) entitled: "Family studies in ankylosing spondylitis"; another was a programme grant that began in 1998 and finished in 2003, entitled "The genetic basis of ankylosing spondylitis".

Interestingly, the parallel work was one of the referees' concerns before the programme started; however, this may not necessarily present a criticism as the programme relied heavily on adequate family samples. Of course, this did cause a time delay, but it should not be interpreted necessarily as a shift of research efforts from the main programme. While the PI and the collaborators had difficulties in completing the research on time (see Stage 2: research process), the gene mapping exercise was completed. At the same time, the research conducted for RA in the latter stages seemed to gravitate towards the arc ERU in Manchester, indicating the PI's shifting interests towards the application of the gene mapping approach to AS, but also his desire to have more control over his work.

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[12] This possibly presents an overrepresentation of the papers as the PI did not identify the core of papers that attributed to the programme grant.

[13] arc 1999 end of year report.

13.6.1 Knowledge creation

As discussed in previous sections, the research was hampered generally by the scarcity of adequate numbers of sibling pair samples that were needed to carry out powerful statistical analyses.

By the end of 1996 the PI had analysed 170 sibling pair families, confirming linkage to HLA; in addition, 16 separate chromosomal localisations with some preliminary evidence of non-random segregation. The preliminary results showed positive linkage with 12 DNA regions. Also, the PI explored particular candidate regions, encoding the T cell receptor alpha and T cell receptor beta chains on two candidate genes. However, according to the PI, weak linkages such as this were common and did not constitute strong evidence of linkage. Following from this, these preliminary studies were extended to 300 sibling pair families to try to confirm previous potential linkages identified in the initial cohort of 170 families and also linkages with markets on specific genetic markers (chromosomes 3, 12 and 18) that were identified by another collaborating European group.

While over time there has been progress in using the genome-wide approach and associated technology development that has become more sophisticated, much of the knowledge created for the purposes of this programme grant remains tentative. Although there is evidence of linkage for a number of genes other than HLA, the levels of significance remain unclear. Sample size remains of major importance in continued efforts to identify genetic regions outside HLA that show susceptibility to RA. Taking account of other research efforts in this field, this research provides evidence for both overlap and discrepancies with previous genome screening in RA (Jawaheer and Gregersen 2002). Given the likely genetic heterogeneity of this disease, much of the ambiguity of results may be expected. Nevertheless, the work represents a major contribution to the knowledge base which may only come to fruition when more powerful analyses may be carried out, based on "global collaboration" (Jawaheer and Gregersen 2002).

13.6.2 Research targeting, capacity building and absorption

One of the strengths of this programme was that it enabled the establishment of research technology and methods that have since been used to study a range of rare and more common musculoskeletal diseases. These subsequent more successful applications of the techniques have contributed to advances in studies of RA, osteoporosis, chondrocalcinosis and rarer disorders such as fibrodysplasia ossificans progressiva, endosteal hyperostosis and Marfan syndrome.

This research programme clearly suffered from discontinuity in research capacity and left the programme "very exposed" (PI's comment). This may be a major reason why the programme (when viewed as a pillar in the overarching human genome centre) did not flourish as well as expected. According to the PI, the two research assistants who were employed initially for the first phase of the programme received substantial training, as they were involved in analysis, use of sophisticated software and "troubleshooting the semi-automated system". One of the research assistants continued her academic career and was later awarded a PhD in a separate institution.

Selected bibliometric indicators for case study M

Publication portfolio

Output

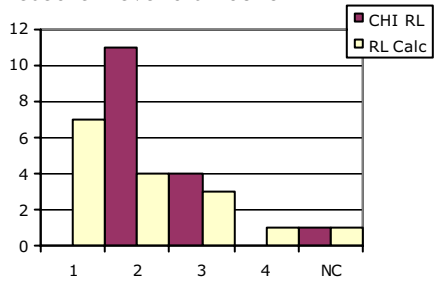
Number of papers	16

Collaboration

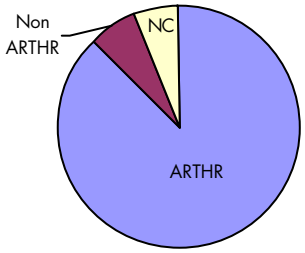
Mean number of authors	10.4
Mean number of addresses	5.0
% with non-UK addresses	62.5%

Type

Research level distribution



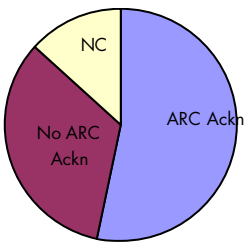
Field distribution



Funding

Mean number of acknowledgements	3.6

ARC funding acknowledgements



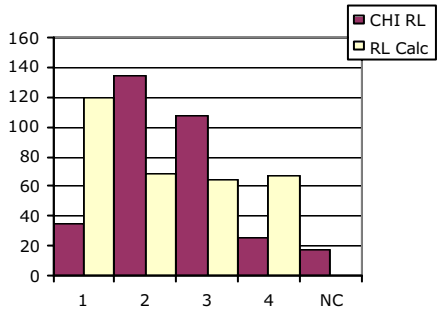
Knowledge flow

Strength

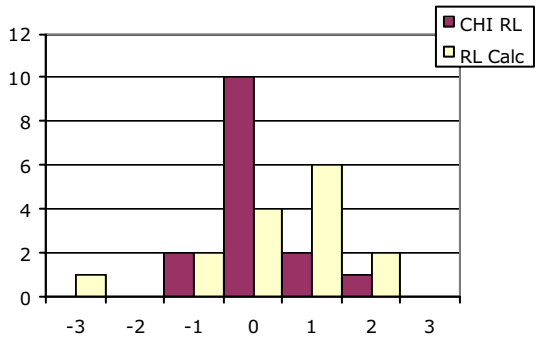
Mean citations per year (all papers)	22.8
Mean C0-4	15.1

Knowledge translation

Research level of citing papers



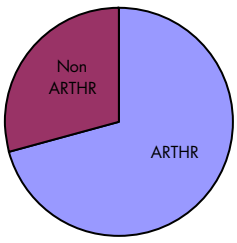
Relative research level



Knowledge diffusion

% of citations from the US	35%

Field distribution of citations



13.7 Interface B: Dissemination

There were several dissemination activities during the course of this programme, both nationally and internationally. For example, the PI organised a lecture tour incorporating several major rheumatology centres in Australia and Singapore. He arranged lectures at university hospitals, which were intended to help the establishment of a network to academic units recruiting families with AS and RA.

In 1996, the PI went to the US in order to present the work on the genome screen that arose from the arc programme to the American College of Rheumatology 60th National Meeting in Orlando.

The PI gained some media attention in the UK through newspaper articles on his work in AS. Other activities in the UK included meetings on the genetics of RA at local colleges and workshops to discuss some of the theory and practicalities surrounding the arc initiative to define the genetic component of susceptibility to RA more precisely.

13.8 Stage 4: secondary outputs – policymaking; product development

Because of the basic nature of this research, and the difficulty in identifying genes strongly linked to RA, this work has not yet fed directly into policymaking or product development.

13.9 Stage 5: adoption – by practitioners and public

To date there has been no opportunity for adoption as the research has not directly fed into policy or product development.

13.10 Stage 6: final outcomes

At the outset of the research, the PI's ambition was to set up a centre where RA genetic research could flourish in an environment with trained researchers and a capacity for technology development. However, in addition to the difficulty in identifying the genes associated with RA, and a range of process issues discussed above, this research was hampered by the fact that capacity was not available and sustainable to give sufficient impetus to this particular work.

Although this research has not led directly to any final outcomes, it has shown that it is very difficult to identify the underlying genes, and that there are genes that could be investigated further. In the work that grew out of this project, the PI shifted his focus onto specific subtypes of RA diseases such as AS and chondrocalcinosis; in the words of the PI these projects have shown more "satisfying results".

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CHAPTER 14 Case study N: Kennedy Institute core grant

14.1 Introduction to the research project

In osteoarthritis (OA), a complex range of biological processes and disorders lead to progressive damage of joint cartilage and bone, resulting in pain and the eventual failure of one or more joints. The arc Epidemiology Research Unit (arc ERU) estimates that at least 4.4 million people in the UK have X-ray-detectable evidence of moderate to severe OA in their hands, 550,000 have moderate to severe OA in their knees, and 210,000 have moderate to severe OA of the hip. Of OA sufferers, 55% report that the worst aspect of the disease is pain. The economic burden of OA is significant: in 1999–2000, the disease caused the loss of 36 million working days, equalling an estimated £3.197 billion in lost production (ARC ERU 2004).

The strands of institute research selected for this case study aimed to improve understanding of healthy cartilage and the mechanisms of its degeneration in OA. In particular, it explored the structure and changes of proteoglycans as a key structural element of functioning cartilage. Proteoglycans are macromolecules consisting of a core protein and carbohydrate chains (glycosaminoglycans), which are linked to the core like the bristles of a bottlebrush. They can be found almost everywhere in the body, both within and on the surface of cells. They are also a major component of the extracellular matrix in connective tissue, such as joint cartilage, sustaining tissue organisation, volume and resilience. The major proteoglycan in cartilage is aggrecan.

As the weight-bearing surface of the joint, articular cartilage is a major focus of damage in OA. Its degeneration, in turn, causes swelling, pain and deformation of the bone, leading to loss of function and disability. Cartilage is a highly specialised tissue with no blood vessels or nerve supply, whose large extracellular matrix is maintained by chondrocytes (cartilage cells). By the time of the beginning of the research discussed in this study, increased activity of these chondrocytes had emerged as a characteristic of early OA induced by injury.

The load-bearing capacity of cartilage is provided by its collagen fibres and proteoglycans. While collagen fibres give the cartilage shape, proteoglycans draw water into the collagen mesh, giving the cartilage the elastic deformation properties which are a key part of cartilage function. Ageing and disease result in marked changes in the size, content,

biosynthesis and organisation of proteoglycans in human articular cartilage. These changes and their effects on tissue properties and function were of central interest to the team led by the principal investigator (PI).

This study is based on an interview with the PI. It also draws on arc archive material, Institute archive material and annual reports, as well as the scientific publications resulting from the research described. The period examined reflects the time span between the allocation of the first five-year core grant to the PI's institute (a new arrangement that replaced previous annual grants), and the departure of the PI from the institute at the end of 1994. As the official date of the departure was embedded in a lengthy period of transition, the remainder of the academic year 1994–1995 has been included despite the PI's absence from the institute. The research strands chosen represent two elements of a much larger programme of research at the PI's division and institute.

14.2 Stage 0: topic/issue identification

The PI's interest in proteoglycans dated back to the days of his PhD research. Following the completion of this research, the PI moved to the institute which hosted the research discussed here. At the time, the institute was in the process of establishing itself as a leader in the field of proteoglycan research. By the time that this research was undertaken, the PI had become a head of the biochemistry division at the institute, and had published groundbreaking work showing that cartilage proteoglycans were aggregated by binding proteoglycan to hyaluronic acid, a long polysaccharide chain. Cross-links with hyaluronan helped to explain the heterogeneity of proteoglycan molecules in length and size.

The two strands of research discussed in this study continued the institute's tradition of work on the function of proteoglycans and in the wider field of cartilage biochemistry. In principle, the division's research plans sought to reflect the existing programme of work at the institute, the team's strength as relative to other researchers in the field, and areas of the greatest probable impact.

Strand A, "Modulation of the structure of CS-chains synthesised on aggrecan", investigated changes in the proteoglycan aggrecan whose biosynthesis, secretion and assembly is of major importance to cartilage function. The approach was based on the previous observation that OA chondrocytes are characterised by altered chondroitin sulphate (CS) chains on secreted aggrecan. The team proposed to monitor changes in aggrecan by using antibodies that recognise specific sequences of sulphation (epitopes)[1] in the molecule's CS-chains, as well as by using a range of other experimental assessment methods.

Strand B, "Molecular and cellular mechanisms that lead to cartilage damage", proposed to study the mechanisms of cartilage degradation by analysing the enhanced activity of chondrocytes in OA in culture models. This work built on previous studies of cellular and

[1] An epitope is a molecule or a portion of a molecule capable of binding to the combining site of an antibody.

A: … Until the development of monoclonal antibodies that recognise specific epitopes, the incidence and distribution of more unusual sequences … remained unexplored. Work with a number of tissues during development now suggests that the expression of many epitope sequences is closely controlled and chondroitin sulphate chains do not contain a random distribution of sulphated disaccharides, but mechanisms exist that provide them with specific chains sequences within their structure. As the expression of these patterns is developmentally regulated and changes with pathology, they may possess interesting biological properties by which the cell influences the matrix that surrounds it. The expression of CS-epitopes will also be investigated in a number of experimental systems using cartilage and chondrocytes. The effects of growth factors and cytokines[2] will be studied on explants of porcine articular cartilage. The expression of CS-epitopes will be identified by immunolocalisation on sections of the treated cartilage … The pattern of synthesis will also be investigated during recovery of cartilage explants from exposure to IL-1 or TNFa …

B: … The direction of this part of our programme has developed from our extensive work on experimental canine osteoarthritis. This is an important model of a disease process but it is expensive and the number of animals that can be handled limits its usefulness. If some of the articular cartilage changes can be mimicked *in vitro* then much more fundamental studies on the mechanisms involved in joint disease can be carried out. The responses of cartilage to mechanical loading or to locally released factors are likely to be responsible for many of the changes observed and the production of specific chondroitin sulphate markers will aid their detection. An intact cartilage on bone system, the sesamoid bone,[3] has been chosen for study … The study of chondrocytes in agarose[4] will establish if chondrocytes in an artificial matrix share similar responses to those in cartilage. The work will initially focus on validating the culture systems and establishing conditions for mechanical loading. These will be characterised using established methods for determining proteoglycan synthesis and turnover and release from the tissue, and also using in situ hybridisation to identify mRNA[5] for the major proteoglycan and collagen components. Two main developments are proposed in the range of assessments that will be applied to the chondrocytes. Firstly, the use of probes for metalloproteinases[6] and TIMP[7] and secondly, when they are available, the application of probes for cytokines and their receptors … will also be applied to tissue from experimental canine osteoarthritis in order to complete the characterisation of this model…

Box 14.1: Extracts from the strand-specific workplans in the Institute's core grant submission, December 1991

[2] Messenger molecules that control the activity of cells.

[3] Sesamoid bone: small bone formed in tendons, like the patella (knee) in humans.

[4] Agarose: a gel used in experiments; one of the constituents of agar, a gel consisting of polysaccharides derived from red algae.

[5] mRNA: a template for protein synthesis; the form of RNA carrying information from the DNA to the sites of protein synthesis in the cell.

[6] Metalloproteinase: member of a group of enzymes that can break down protein.

[7] TIMP: tissue inhibitors of metalloproteinases.

matrix changes in the joints of dogs whose anterior cruciate ligaments[8] had been cut. The proposed project aimed to replace the previous *in vivo* approach using dogs with a more manageable, less expensive *in vitro* system using pig bone and tissue. The extensive workplan submitted by the division for the first five-year extended core grant did not include abstracts; extracts from the division's submission are given in Box 14.1 above.

14.3 Interface A: project specification and selection

arc funding arrangements for the Kennedy Institute were reviewed in 1991–1992, resulting in a shift from annual core grants and research grants won in open competition to a five-year support grant subsuming individual research grants. The new funding arrangements were linked directly to an assessment of the quality of a five-year research plan, which included the research strands discussed in this study. The Institute submitted a review of current work and planned research in March 1991 which, at arc's request, was followed up by a more future-orientated and "scientifically focused" plan submitted in December 1991. The referees commented on this latter version.

The research proposal submitted by the Institute's biochemistry division was reviewed by five referees (A–E). Of these, one was based in the UK and the others abroad; all had a basic science background, although referee A had moved into the clinical field. While some referees made summary comments on the biochemistry programme, others differentiated between sections and work strands. A summary of their assessments is given in Table 14.1 (the letters A–E indicate the different referees' assessments).

Table 14.1: Summary of referees' comments in response to the Institute's core grant submission in December 1991

	High	Medium	Low	None
Overall value of the project	C, D	A, E	B	

(SOURCE: Institute archive)

Commenting on the section of the biochemistry programme to be led by the PI, referee A expressed concern about the apparent lack of clarity of the proposed work and its potential for producing relevant new information. He also pointed out a lack of scientific hypotheses to be tested, and insufficient details on collaboration arrangements. Finding these shortcomings difficult to reconcile with the PI's reputation and record of productivity, he wondered whether this impression was due to the elliptic presentation of the plans. He concluded with a cautious general endorsement of the proposed work.

Reviewing the biochemistry programme as a whole and using considerably sharper tones, referee B opened his remarks with a pessimistic assessment of the programme's likely contribution to the field. Summarising the nature of his concerns, he questioned whether the division had the "drive" to illuminate disease mechanisms rather than simply collect data. While expressing strong criticism of several other work strands in the programme, he

[8] Anterior cruciate ligament: the cruciate ligaments cross over the middle of the knee to keep it from sliding backwards and forward; the anterior cruciate ligament is located at the front.

did not comment specifically on the two work strands of interest here. However, his overall support for the programme was very low.

Referee C, who discussed the proposed work in four project clusters, took a distinctly more favourable view. Concerned that the proposed research was too global and ambitious, he referred to the team's outstanding research record as an assurance that, over time, efforts would be concentrated on the most promising areas of the proposed work. Moving on to strand-specific comments, he assessed the proteoglycan research as the "real strength of the programme", and commended work strand A (CS-epitopes) as an appropriate and promising extension of the team's previous work in the area. His opinion of the proposed work in cartilage and experimental disease was less unequivocal, as he was concerned that too many ambitious objectives would lead the research to deteriorate into "fishing expeditions". However, he concluded his assessment by stressing his "very high enthusiasm" for the work.

Referee D pointed out the team's record of pioneering work on molecular events in joint disease. The following, strand-specific comments were favourable throughout. With regard to strand A, he remarked that this work followed on from promising earlier work. Strand B, he highlighted, proposed "well conceived approaches" to study chondrocytes in OA. Therefore, his overall support was very strong.

Referee E submitted a comprehensive assessment that included detailed comments on each of the proposed work strands. Endorsement varied, with half of the strands ranked as "high", and one strand as "low". Support for both work strands of interest here was "moderate". While conceding that strand A contained "high potential" for revealing basic mechanisms of cellular response, the referee was concerned that there was very little preliminary data available in the area, and that the success of the proposed use of antibodies in assays was uncertain. With regard to strand B, the referee questioned whether there was evidence that the factors to be studied were really present in early experimental OA. He also questioned whether the loading protocols proposed for the *in vivo* model corresponded to the loading observed in animals.

In response to the referees' criticism that the proposed work was not sufficiently hypothesis-driven, the PI stated that this aspect was a notoriously contentious issue. He argued that such assessments underestimate the task of investigating a highly complex disease process such as OA or asthma. He argued that in these fields, where many different factors are involved, it is necessary to establish an overview of processes before formulating a hypothesis. Similarly, in the PI's opinion, comments that a team was taking on too much were often due to lack of familiarity with the techniques and procedures that were already established, whereas suggestions that the workplan was too diffuse were taken seriously.

The comments did not lead to a written reformulation of the proposed research plan, although the PI pointed out that the constructive comments were taken on board. The requested arc core funding was granted.

14.4 Stage 1: inputs to research

As is typical for research institutes and groups, the Institute's arc core funding and much of the funding from other public, charitable and industrial sources was pooled into one budget. This budget was divided up by the Institute's director and heads of division committee, of which the PI was a member. According to the interviewee, distribution was determined on the basis of the funding that was already in place, the budget available and new demands. No written records of the internal division of this "pot" have survived.

Until the period discussed here, arc funding for the Institute had been divided into annual core grants, individual projects and programme grants won in open competition. Following a major review of arc's funding arrangements for the Institute in 1991–1992, individual arc grants and core funding were rolled into one enlarged core grant. This core grant was fixed at £2.7 million for five years, from October 1992 to September 1997.[9] The amount reflected the total sum that the Institute had received from arc in previous years (eg in 1991–1992, a £1,819,000 core grant and an estimated £700,000 in individual grants),[10] but it was not calculated to take inflation into account.

The arrangement barred members of the Institute from applying for other, individual arc grants. While the Institute was successful in attracting other funding, arc remained the Institute's single most important sponsor. In the years studied, the arc core grant provided approximately 60–70% of the Institute's total income. This support was crucial to cover overheads: for example, in 1995 the Institute expected to spend £250,000 of the core grant on occupancy costs and £340,000 on laboratory expenses and consumables. In its annual report for 1993, the Institute explicitly acknowledged that its success in winning external funding was made possible by the Institute's arc core-funded staff and facilities. Between 1992 and 1995, annual income from research grants grew from £854,000 to £1,175,000.

For the reasons outlined above, the PI did not retain records to show the share of arc core funding allocated to work strands A and B. Typically, arc funding was used to support staff at the centre of the Institute, such as the director and support staff, rather than staff in the divisions.

According to the earlier core grant submission, completed in December 1991, the division's two senior scientists to work on strand A were to be supported by arc, while the two research assistants were to be funded by an industrial sponsor. The team researching strand B also included the division's two senior scientists. One postdoctoral researcher and one technician were to be funded by the MRC and one researcher was to be supported by a non-pharmaceutical commercial sponsor.

Recapitulating the history of arc funding received by the Institute, the PI highlighted the advantages of the move to a five-year core grant system. Previously, clear long-term leadership had been impeded by conflicting opinions within arc regarding financial support for the Institute. The allocation of funding on the basis of an annual vote had been unsatisfactory for the Institute, which already was handling a range of shorter-term

[9] In today's money: 1992–1993: £3,550,000; 1993–1994: £3,460,000; 1994–1995: 3,420,000; 1995–1996: £3,320,000.

[10] In today's money: £2,470,000 and £950,000 (= £3,420,000 total support from arc).

funding sources. Although the amount received by the Institute as a proportion of total arc expenditure had decreased in the past, from one-third of the arc budget in 1968 to 23% in 1978, there was pressure on arc to reduce this further. Although annual reports continued to be submitted, the five-year arrangement greatly facilitated longer-term planning and freed up time that had been spent previously on writing applications for individual arc grants.

14.4.1 **Human capital**

The PI had extensive experience in proteoglycan research and the wider field of cartilage biochemistry. The other senior researcher in the group, who collaborated on strands A and B, had set up a strong programme of study of the behaviour and turnover of human tissue, which contributed to the team's understanding of turnover methods both in terms of proteinase and molecular mechanisms. The postdoctoral researcher on strand B brought expertise in OA animal models and antibody technology to the project. The division also benefited from a highly skilled chief technician who had been long-established at the Institute.

14.4.2 **Techniques, reagents and equipment**

The PI's fellow senior researcher in the division had succeeded in building up an effective network to obtain human OA samples. Also, in the course of previous studies, he had created a database on the behaviour and turnover of tissue which was a valuable resource for the division. Monoclonal antibodies to detect changes in CS-epitopes (strand A) were provided by a collaborating department at an American university. This was one example of the many ways in which the team benefited from collaborations and a well-developed "sharing culture" in the field of proteoglycan research.

Reflecting on research conditions in terms of equipment, the PI remarked that his move to a large university department in the latter part of his career had given him access to a more extensive infrastructure than had been the case at the Institute. The impact of this difference in scale on research conditions had increased with the growth of high technology.

14.4.3 **Collaborations**

The division was involved in collaborations with the laboratories of the Wellcome Foundation, as well as national and international academic research departments, including a collaboration and exchange with a university in Thailand. A UK university department participated in work on proteoglycans in pre-OA synovial cartilage.

14.5 **Stage 2: research process**

The PI explained that the team worked at molecular level to understand cellular mechanisms and apply them to pathogenic mechanisms. While the team was productive in carrying out "good science" and expanding the knowledge of the field, progress in some areas was slower than expected due to unexpected findings and developments.

The PI pointed out, with hindsight, that the team working on CS-chains (strand A) was hindered by the absence of tools, which now would now enable them to undertake the

proposed work with success. For example, new methods have made it possible to identify unique structures in carbohydrates. The team tried to achieve this insight by using antibodies, but the necessary strong bindings to epitopes proved very hard to achieve. In the resulting absence of characterisations, insights into the molecules remained incomplete.

14.6 Stage 3: primary outputs from research

14.6.1 Knowledge creation

In response to the Institute's 1996 submission for a new core grant, one referee remarked that the connective tissue biology programme had led to "few publications in first class journals over the past five years" (comparison with bibliometrics).

The work on strand A, "Modulation of the structure of CS-chains synthesised on aggrecan", produced the following four key publications identified by the PI.

Hardingham and Fosang (1992) provided a review of the manifold sites and functions of proteoglycans, including cartilage. It explained the fundamentals of the heterogeneity of proteoglycan size and structure, due to variations in the number, length and sulphation of their glycosaminoglycan chains, and pointed out the role of these variations in responding to different biological needs.

Hardingham, Fosang, Hey and others (1994) threw light on patterns of sulphation in CS-chains but through monitoring the digestion of the bacterial enzyme chondroitinase by the proteoglycan aggrecan in pigs. Hazell and others (1995) investigated changes in proteoglycan structure by measuring levels of epitope on CS-chains and keratan sulphate (KS) chains of proteoglycan fragments present in the synovium of patients with OA caused by ligament or meniscus[11] damage. Results suggested that acute traumatic injury caused the body to respond with altered expression of CS-epitopes on cartilage proteoglycans, producing proteoglycans with lower KS content. Hardingham (1995) gave an overview of the group's findings on changes in CS-epitope expression in development, ageing and OA.

Strand B, "Molecular and cellular mechanisms that lead to cartilage damage", led to a larger output, including the following 12 key papers identified by the PI. Rather than focusing on the building structure of proteoglycans, these papers investigated mechanisms of the synthesis, degradation and turnover of proteoglycans.

Ratcliffe and others (1992) detected increased levels of components of proteoglycan aggregates released into the synovial fluid in dog joints with mechanically-induced OA. Carney and others (1992) compared the metabolism of newly-synthesised and established proteoglycans, revealing differences in breakdown mechanisms and breakdown products. Fosang and others (1993, 1994) focused on preferred molecular cleavage sites of collagenases (enzymes) in aggrecan. Hardingham, Fosang and Dudhia (1994) reviewed the composition, synthesis, function and turnover of aggrecan during development, age and disease.

[11] The crescent shaped cartilage between femur and tibia.

Hardingham and others (1992) investigated the respective fostering and inhibition of proteoglycan synthesis by growth factors and cytokines, revealing the potential importance of these factors in joint disease therapy. Venn and others (1993) compared the levels of cytokines, proteases and glycosaminoglycans in the synovial fluid of dog knee joints with early, mechanically-induced OA to the levels in the animals' opposite, healthy knees. The study revealed increased levels of cartilage proteoglycan synthesis and activity of the cytokine IL-6, which increases the degradation of proteoglycan in cartilage.

Rayan and Hardingham (1994) examined the rate of proteoglycan synthesis recovery after exposure to the cytokine IL-1 in pig cartilage explants, which was found to be extremely slow in the absence of serum. Lewthwaite and others (1994) tested the therapeutic potential of human IL-receptor antagonist in blocking inflammation and cartilage loss in early antigen-induced OA in rabbits, but found that this approach was not effective. Continuing work on the therapeutic potential of interleukin-1 receptor antagonist, Lewthwaite and others (1995) examined the tissue samples of rabbits treated with the antagonist. Results revealed a reversion of synovial fibrosis caused by IL-1.[12]

Turning to the role of the cytokine TNF-alpha, Lewthwaite and others (1995) injected rats with antigen-induced arthritis with a monoclonal anti-TNF antibody. This achieved reduction in joint inflammation and swelling, but neither the initial dose nor later increased doses and longer treatment periods were able to reduce the loss of proteoglycan form articular cartilage.

Venn and others (1995) demonstrated that the hypermetabolic activity observed in chondrocytes in mechanically-induced OA in dogs was reversible, by showing that in cartilage explants kept in culture, increased synthesis of proteoglycans subsides after two to three days.

The research described also underpinned the chapter on cartilage, which the PI co-authored initially for a leading textbook on rheumatology and extended as a single author in later editions (Campion and Hardingham 1993; Hardingham 1998).

14.6.2 **Research targeting, capacity building and absorption**

The team contributed significantly to the understanding of CS-chains which, the PI pointed out, has now been finally achieved. According to the PI, assessment of the impact of the work has to distinguish between two spheres of influence. Whereas in terms of reactions to papers this impact could be dispiritingly low, the same work had considerable influence on the strategic direction of the field of research. The PI's team entertained very good relationships with other scientists in the field of proteoglycan research, which had been very small at the start of the PI's career but eventually grew to a modest size.

Most of the scientists who worked on strands A and B remained in academia, with the exception of one postdoctoral member who left the field for personal reasons. A further postdoctoral member progressed into industry. The younger team members moved on to other research institutions. Three division members gained PhD degrees as a result of the research work discussed here.

[12] Fibrosis: formation of tissue as a reaction or repair process.

Selected bibliometric indicators for case study N

Publication portfolio

Output

Number of papers 16

Collaboration

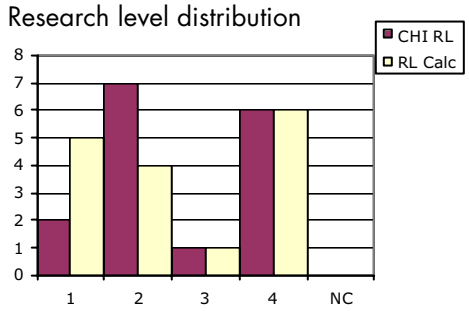
Mean number of authors 5.5

Mean number of addresses 2.8

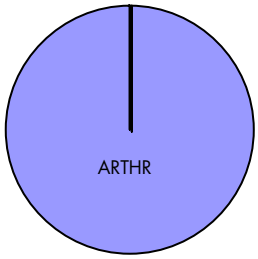
% with non-UK addresses 50.0%

Type

Research level distribution



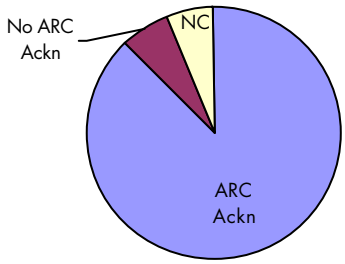
Field distribution



Funding

Mean number of acknowledgements 3.1

ARC Funding acknowledgements



Knowledge flow

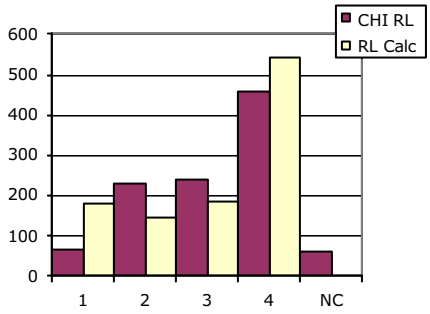
Strength

Mean citations per year (all papers) 75.0

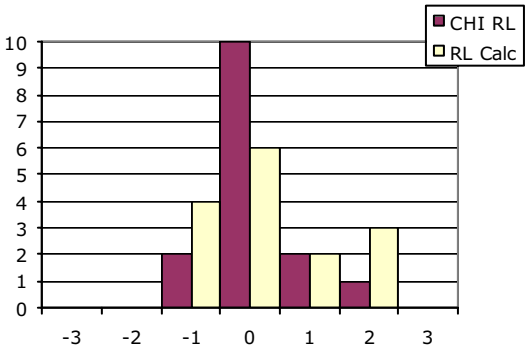
Mean C0-4 33.9

Knowledge translation

Research level of citing papers



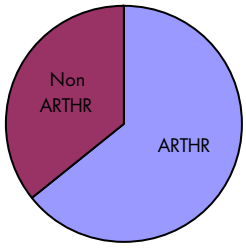
Relative research level



Knowledge diffusion

% of citations from the US 44%

Field distribution of citations



14.7 Interface B: dissemination

According to the PI, the team presented papers at UK and international conferences in order to disseminate the findings of their research. The PI himself contributed regularly to international meetings focusing on proteoglycans, pathogenic mechanisms and the surrounding area. For example, in 1994, he spoke at seven conferences in six countries. He also regularly submitted papers to, and attended the large three-day conferences hosted by, the US-based Orthopaedic Research Society.

14.8 Stage 4: secondary outputs – policymaking; product development

14.8.1 Informing policy and product development

The PI's departure from the Institute at the end of 1994 heralded a period of disintegration of the group, despite its traditional strengths. This process, which the PI described as evolutionary, culminated in the dissolution of the matrix biology group following the departure of the group's other leading scientist. However, the group was later reformed.

For the PI, the change from the Institute to a larger university academic setting led to a gradual refocusing of research interests. The transition was encouraged by the PI's award of seven years' funding from the Wellcome Trust for a position at a newly-created centre for cell and matrix research. While still working on cartilage, the PI moved away from work with animal models and the study of the causes of joint damage in favour of more fundamental biophysical research, although he continued to work on CS-epitopes. The PI was not accompanied by his former team members when moving to the new institution, as the senior scientists were tied to the location of the Institute. Several years later, the extensive experience in basic clinical collaboration and knowledge of mechanisms of cartilage destruction which the PI had gained at the Institute proved to be a decisive factor in the PI's selection to lead a large interdisciplinary research programme on methods of building new tissue. The area of tissue engineering, which holds greater promise for successful application, has since been the PI's central interest. The PI stressed that his government-funded work in tissue engineering, which recently has been favourably reviewed, is of direct relevance to arc's aims, while not taking up any of arc's resources.

Although other researchers have continued with the study of proteoglycans, so far (and in the words of the PI), work in the field has not come truly to fruition. There was hope that changes in CS-chains could be used as markers of OA in order to monitor disease and measure the success of treatments. The availability of a fast and accurate screening tool would have facilitated drug development greatly. Yet, while changes could be detected in most patients, this tool remained elusive as the difference between patients is wider than the range of change within individuals. However, a longstanding research collaborator of the PI in Thailand has succeeded in developing an antibody and new assay systems based on CS-epitopes, to be used for diagnostic purposes in joint diseases. This work was patented nationally and is currently under negotiation with a Swedish company with a view to producing a diagnostic kit.

At present, CS research is becoming active again, fuelled by an explosion of interest in signalling sequences. CS-chains contain recently-recognised growth factor/chemokine binding sequences which, in presenting such factors to cells, may act as co-factors in signalling.

The PI also pointed out that in industry there has been sustained interest in proteinase mechanisms. The PI contributed to this area by undertaking a small amount of research into the proteinases involved in degenerative mechanisms. A large pharmaceutical company (Dupont/Merck) succeeded in cloning proteinases called aggrecanases; however, beyond contributing to the field of research, the PI was not involved directly in this work. Although no drug has been developed yet, the PI reported that two aggrecanases and several related enzymes were currently in the pipeline for such development, with the aim of targeting the activation of enzymes in the disease process.

Work on basic structures has thrown light on the structure and shape of the complex cellular molecules involved in OA, but it has not led to any applications as yet. In conclusion, the PI stressed that the great desirability of a marker of early OA stood in melancholy contrast to sustained, yet less than rewarding, efforts in the area. At present, measuring the progression of OA still relies on X-rays.

The team's insights into the therapeutic potential of treatment with IL-1 receptor antagonist (IL-1ra) to block synovial fibrosis were not pursued further in the years following the period studied here, but have been taken up recently in the context of research into brain tissue repair and intervertebral disc degeneration at the PI's host institution.

14.9 Stage 5: adoption – by practitioners and public

As described, the team's research contributed indirectly to current research into drug development, but no registered products have resulted from the work. As a result, there has been no opportunity for adoption.

14.10 Stage 6: final outcomes

In the absence of registered products or procedures, it is not possible to identify any health gains derived from the research strands examined in this study. However, in throwing light on the fundamentals of molecular structure and functions in cartilage, the team's basic science work may be built upon successfully in the future.

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CHAPTER 15 Case study O: identification of non-HLA rheumatoid arthritis susceptibility genes

15.1 Introduction to the research project

This research project aimed to identify and characterise non-HLA rheumatoid arthritis (RA) susceptibility genes, and to evaluate their relative contribution to the aetiology[1] of the disease. The study was carried out at the arc Epidemiology Research Unit (arc ERU) in Manchester, in close collaboration with a laboratory in the Clinical School of the University of Oxford.

RA is one of the most common autoimmune diseases in caucasians, affecting approximately 1.2% of women and 0.4% of men in the United Kingdom (Symmons and others 2002). A genetic component to the development of RA clearly exists. For example, in twin studies, an increased concordance of RA has been observed in monozygotic twins compared with dizygotic twins, with an estimated heritability of disease liability of 60% (MacGregor and others 2000). By 1990, the association between RA disease risk and alleles of the HLA locus had been well established. However, this association was estimated to explain at best only 50% of the genetic component of RA. Therefore, the search for other RA susceptibility genes was deemed to be of fundamental importance.

Until the late 1980s, a systematic search for susceptibility genes in multigenic diseases such as RA was impossible. But due to several important advances in molecular biology techniques and the availability of well-characterised multi-case RA families (collected at the arc ERU in the UK National Repository for Storage of Family Study Material), identification of non-HLA rheumatoid arthritis susceptibility genes through linkage analysis had now become a realistic research proposition.[2]

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[1] Aetiology: the cause or origin of a disease or disorder as determined by medical diagnosis.

[2] Under Mendelian inheritance, for any marker locus with multiple alleles, siblings are expected to share a given parental allele 50% of the time. A significant distortion towards greater sharing of alleles in siblings affected with a disease such as RA is indicative of a genetic linkage with this disease (Ollier and Worthington 1997c).

A starting point for these studies was the long arm of chromosome 14, where some studies had suggested weak linkage already. In addition, other candidates were examined subsequently using the same approach, among which were chromosomes 7, 2 and X.

The general objective of the work proposed under the arc postdoctoral research fellowship was exactly that: to identify and characterise non-HLA susceptibility genes in RA through linkage analysis studies, and to evaluate their role in pathogenesis and relative contribution to the aetiology of the disease. In the project application, the following specific aims were articulated:

1. identification of new microsatellite sequences on the long arm of chromosome 14;
2. characterisation of microsatellite sequences and determination of allelic frequency in the normal population;
3. determination of whether linkage exists between selected microsatellites and RA, using affected sibling pairs; and
4. identification of putative susceptibility gene(s) by a detailed analysis of the region(s) of chromosome 14 shown to be in linkage with RA.

15.2 Stage 0: topic/issue identification

The postdoctoral research fellowship under examination in fact evolved out of another, large-scale arc ERU initiative: the establishment of a UK national repository for storage of family study material, which would draw together scientists around the country who were interested in the genetic aspects of rheumatic disease. This idea was developed by the new director of the arc ERU and his colleagues, in collaboration with researchers at the laboratory in Oxford. The lead researcher at the Oxford laboratory suggested that arc should establish a centralised national collection of multi-case families (ie families where at least two persons – ideally two siblings – are affected with RA). Then, this collection could form the basis for a systematic approach to genetic studies of RA.

Since the arc ERU in Manchester was – as the name conveys – an epidemiology unit, arc decided that this was the obvious location from which to coordinate this collection. Agreement was reached that the Oxford laboratory would concentrate on whole genomic screening (using relatively even-spaced microsatellites), whereas the arc ERU would focus on screening using candidate genes. Given the principal investigator's (PI) expertise, when she applied for a postgraduate research fellowship it seemed only logical to construct a research project that would build upon the valuable information that would be gathered gradually in the UK National Repository. In collaboration with senior staff, the PI decided to focus on the identification and characterisation of non-HLA RA susceptibility genes.

As stated in the previous section, the only well-established genetic link with RA was the association between RA disease risk and alleles of the HLA locus, and this was estimated to explain at best only 50% of the genetic component of RA. Therefore, it seemed scientifically challenging to begin searching for *non*-HLA RA susceptibility genes.

Unfortunately, a systematic search for susceptibility genes in oligogenic[3] diseases such as RA was virtually impossible until the late 1980s (which also explains why so little research had been done in this area). Three specific developments in molecular biology had led the process of studying non-HLA genes associated with RA to become more feasible in practice:

1. the polymerase chain reaction (PCR): this technique provided a major impetus for the characterisation of disease susceptibility genes, as it could be used to detect and amplify miniscule traces of specific DNA sequences;
2. identification of microsatellites: with the discovery that highly polymorphic microsatellite dinucleotide repeat sequences are present frequently throughout the genome (every 500kb), markers could be found now to enable linkage analysis studies to be performed in families with RA;
3. the cloning of large DNA inserts in yeast artificial chromosomes (YACs): the construction of DNA libraries in YACs enormously increased the size of DNA inserts that could be cloned in one single fragment. For the first time, YAC libraries provided a realistic means to search for informative microsatellite probes at specific sites in the human genome.

In the project application, the PI proposed to bring these three innovations together in order to construct a reverse genetics approach to identify susceptibility genes. The linkage studies suggested in the project are best applied to RA multi-case families where there are affected siblings and two living parents. In this respect, the UK National Repository for Storage of Family Study Material, which had been set up at the arc ERU in early 1990 as a resource for genetic studies, would provide the ideal material for this project.

The application was for a five-year project grant worth £181,238. The majority of the costs involved (£126,643) were for the PI's salary over these five years. In addition, a significant amount of funding (£46,745) was requested for the running expenses involved in utilising new and expensive molecular biology techniques such as PCR amplification, sequencing, and the use of oligonucleotides. Some funding (£7,850) was requested also to enable the purchase of two items of specialist equipment. Initially, however, arc approved the fellowship award for only two years (64,944). It would decide whether or not to continue based on a review that would take place after 18 months.

[3] A trait is considered to be oligogenic when few (two or more) genes work together to produce the phenotype. An oligogenic trait should be contrasted with a polygenic trait, which implies that many genes are involved in phenotype expression.

This application aims to utilise recent developments in molecular biology to identify non-HLA encoded RA susceptibility genes. The application of these techniques to the family material available from the ARC – National Repository of multicase RA families, will permit a novel approach to genetic mapping and the identification of susceptibility genes. This will initially be directed at the long arm of chromosome 14 although other candidate chromosomes will be investigated. A 3-stage PCR-based screen of YAC libraries of the human genome will be used to identify new microsatellite sequences and provide a detailed map of the long arm of chromosome 14. Polymorphism of newly-identified microsatellites will be determined in a normal population and the most polymorphic markers will then be subjected to linkage analysis in the multicase families. The establishment of linkage with specific chromosomal areas will be followed by a detailed investigation to identify putative RA susceptibility genes.

(SOURCE: arc archive)

Box 15.1: Abstract

15.3 Interface A: project specification and selection

arc's review process of the research proposal was a lengthy one. The proposal was reviewed by two formal referees (A and B), but in addition arc's evaluation committee requested two more informal expert reviews (C and D). After evaluating these four expert reviews, it consulted a fifth expert before reaching its final decision.

Referee A expressed some criticism with respect to the proposed research. First, he argued that more details could have been given about the number of families that would need to be sampled in order to reach significant results with their sibling pair linkage analysis (a target of 50 pairs was set in the proposal, and this was expected to be collected in the UK National Repository in time; but it was not clear in advance whether this would be sufficient). Second, he commented that more details should have been given concerning the number of genetic markers already characterised on the long arm of chromosome 14 (the proposed starting point of the analysis). It would indicate how many more of such markers would be needed for effective linkage studies, and thus be crucial to estimate whether the project could be completed in the proposed timescale (which was initially five years).

Referee B responded favourably to the pursuit of the project. She stated that the PI seemed to have a very suitable background and experience for the work. She also highlighted the originality of the work; at the time, the methods proposed were being used to look at many diseases, but to her knowledge no great amount of work was done in RA. In addition, she stressed that a successful outcome should be of enormous value to rheumatology, since it could provide another approach to managing the disease (apart from the HLA-related therapy). An added advantage was the collaboration with the researchers in Oxford, whom she expected to be able to support the project well with materials and experience. Her only caveat was that a "fishing expedition" such as this was likely to need either a large amount of luck or a tremendous input of financial and human resources (in other similar studies with which she was familiar, there were large teams of people devoting many years to the search). Therefore, referee B suggested that arc should understand that, aside from a lucky

chance, it was unlikely that a single worker (the PI) would progress very far. However, this did not mean that she thought a start should not be made; as stated, she expected it to be of great value for designing new approaches to patient treatment.[4]

Referee C worked at the same rheumatism research centre in Manchester where the PI had worked on a one-year arc-funded postdoctoral project on heat shock proteins. He strongly supported her application, but based this recommendation entirely on her track record and personal opinion of the candidate, rather than the details of the project application.

Lastly, the director of the arc ERU provided an evaluation in support of his unit's application for the fellowship (referee D). First, he stressed that although the arc ERU was primarily an epidemiology unit, it had developed a modern molecular biology facility. It had obtained substantial non-arc funding for equipment and recruited people with molecular biology experience within the group. Second, his argument was based on the link to the UK National Repository for Storage of Family Study Material; he stressed that it was applications of this type that justified the substantial grant that had been made available for the UK National Repository.

After consideration of these four evaluations, the Fellowship Panel agreed that it was difficult to assess the application without a reference from the director of the laboratory in Oxford. They not only wanted to know his opinion of the applicant and the proposed work, but also what his precise involvement would be during the project itself. The chairman of the panel spoke to the director personally twice. In these discussions, the director made clear that he was "willing to support [the PI] as an excellent research worker". However, he expressed the same concerns as referee A about the number of patient samples needed for the linkage studies. Moreover, he was concerned about the future of the work unless the PI received "some intensive training in the necessary technology".

The arc Fellowship Panel did not come to a final decision easily. It was convinced that the PI was a suitable person to be carrying out the proposed work, but it also felt that some of the concerns pointed out by the referees were not easily resolved. It stated that was a "delicate balance between [their] desire to give an 'ad hominem' award to [the PI] and these concerns as outlined above". On balance, the Panel decided that a two-year fellowship was appropriate at this stage. It suggested that progress would be assessed after 18 months, at which point it would be decided whether further funding would be made available an in what form.[5] Moreover, the Panel insisted that the PI should work in the Oxford laboratory for a period of at least six months to learn the necessary molecular biology techniques.

The director of the arc ERU accepted this decision and submitted his own written considerations in response to the referees' evaluations. He "fully supported" arc's requirement that the PI spend a period in Oxford for formal molecular biology training.

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[4] In this light, it is interested to note that referee B was slightly surprised that the PI did not envisage any patentable results upon success; she anticipated that pharmaceutical companies would be extremely interested in such information.

[5] In 1993, the work was incorporated into the arc ERU's core budget.

Also, he acknowledged the concern highlighted by referee A that it was difficult to estimate the number of families that would be needed to reach significant results in the study. However, he believed that the "planned sample size with its optional European additions [was] a reasonable estimate".

15.4 Stage 1: inputs to research

15.4.1 Funding

The budget requested for the postgraduate research fellowship consisted primarily of salary and running costs for the PI, who was already an experienced postdoctoral scientist and had been working on a Leverhulme project grant in the arc ERU. Funding was requested for a five-year period, the first two years of which would be spent on complete analysis of the long arm of chromosome 14. Several other candidate chromosomes would be investigated in the remaining period of the fellowship, depending on the success that was reached with chromosome 14 and the amount of follow-up work that would evolve from this.

The proposed work would be carried out at the arc ERU, where a well-equipped molecular biology laboratory already existed and most of the necessary technical equipment was available. However, two items of specialist equipment that were not present as yet were requested in the project application:

1. pulse field gel electrophoresis (PFGE) equipment, which is essential for the separation and purification of YACs; and
2. a hybridisation oven for use with radioactively labelled probes.

A sum total of £7,850 was requested for these pieces of equipment. Initially, however, this was not disbursed.

The requested running expenses reflect the high cost of the proposed molecular biology techniques at the time, particularly sequencing, PCR amplification and the use of synthetic oligonucleotide probes. These requests are in fact relatively modest, because some of the costs were absorbed by the arc ERU (such as the cost of running existing equipment, etc). Also, the UK National Repository was already fully funded by arc, so no costs would be incurred for DNA collection or preparation of DNA samples for the linkage studies.

Table 15.1 provides an overview of the total amount of financial support requested. As stated in section 15.2, initially arc decided to provide funding only for the first two years of the project. Depending on progress in this phase, additional funding would be disbursed (a review would take place after 18 months). In 1993, after a positive evaluation in the review, the project was incorporated into arc's core budget. No exact figures were available for the funding used during these years, but Table 15.1 is likely to give a reasonable estimate of the aggregate of financing spent.

Table 15.1: Requested annual project budgets 1991–1996 (in 1991 values)

(£)	1991–1992	1992–1993	1993–1994	1994–1995	1995–1996	Total
Salaries	23,433	24,366	25,301	26,280	27,263	126,643
Running expenses	8,195	8,950	9,350	9,925	10,325	46,745
Capital expenditure						7,850
Total cost of application	**31,628**	**33,316**	**34,651**	**36,205**	**37,588**	**181,238**

In addition to this core financing, some additional funding (£1,680) was disbursed in order to fund the PI's six-month internship in Oxford.

15.4.2 Human capital

Although the PI (and lead applicant) for the postgraduate research fellowship was still fairly junior at the time, she had built up a portfolio of expertise both outside and within the arc ERU that made her highly suitable for the work. There had been a "common theme" throughout everything she had done until then (and, in fact, after that point too): autoimmune diseases. She had done an Medical Research Council (MRC)-funded PhD on thyroid autoimmune diseases in London. Subsequently, she moved to Leicester and began working in molecular biology. The area she focused on was immune reaction to islet cells (which is important in diabetes). In her work, she used a mouse model for transplantation; the research group within which she worked was trying to achieve islet cell transplantation.

After finishing her postdoctoral research in Leicester, she heard about a researcher in Manchester who had a post available at this time to look at autoantigens in ankylosing spondilitis.[6] This work suited her quite well, but it was not a long-term position. Concurrently, another senior researcher was setting up a research portfolio in the arc ERU in Manchester, and the PI applied for arc funding to get involved in this work. While doing so, she actually received a Leverhulme trust grant to work at the arc ERU in the area of RA genetics research,[7] which she decided to accept.

The Leverhulme grant proved to be a very useful preparation for her subsequent arc postgraduate research fellowship application. Not only did she get the chance to prove that she was a good researcher, but she also established a good relationship with the (senior) researchers at the arc ERU. After approximately one year, it was decided that it would be a good career move for the PI to apply for a postgraduate research fellowship. Generally, it was seen to be a more prestigious career move than other options such as project grants, and at that time arc was the obvious place to apply for funding. When the idea for a project to identify non-HLA RA susceptibility genes was developed, the PI was the obvious person to take the lead in this research.

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[6] Ankylosing spondilitis (AS) is a painful, progressive, rheumatic disease. It mainly affects the spine but it can also affect other joints, tendons and ligaments. Other areas, such as the eyes, lungs, bowel and heart can also be involved (see: http://www.nass.co.uk/questions.htm). It is a debilitating condition affecting 175,000 people in the UK.

[7] According to the PI, the Leverhulme trust usually sponsors research that is fairly speculative, but does have potential commercial exploitation.

It should be noted that the expertise of novel molecular biology techniques at the laboratory in Oxford was an indirect but highly valuable input for the project. The knowledge of these techniques, which was gained by the PI during her six-month internship in Oxford, was crucial to the success of the project. In addition, this knowledge was transferred over the years to other researchers at the arc ERU, and now comprises an essential element of its genetics programme.

15.5 Stage 2: research process

When the PI began working on her postgraduate research fellowship, this field was rapidly progressing. The work started out as proposed by looking at chromosome 14, because this chromosome contained some good susceptibility gene candidates. The main thrust of the work was to identify markers that then would allow the team to analyse the families in the UK National Repository, in order to see whether there was evidence for a disease locus close to that marker.

At the time that the team were conducting this research at the arc ERU, the Centre d'Etude du Polymorphisme Humain (CEPH) in France was working in the same field, and initiated an "explosion" in the identification of microsatellite markers. This had a detrimental effect on the PI's work, as CEPH published their findings before the PI had the opportunity to do so herself. In fact, only two peer-reviewed papers came out of the core work that she did in the two years that were funded through the original postgraduate research fellowship.

However, a major positive of the work resided in the fact that the PI effectively transferred the technical expertise that she had learned in Oxford to the arc ERU in Manchester. After a period of difficult negotiations with arc and other funders (for reasons mentioned earlier, and explained further below), the arc ERU managed to get the funding to purchase the necessary equipment for microsatellite genotyping. This made it possible for the PI to establish the technology locally, and transfer the knowledge to other researchers in the unit.

The difficulties in acquiring the necessary funding for equipment and technology were caused by the fact that both the arc ERU in Manchester and the laboratory in Oxford were applying to arc to fund the same project. Both laboratories wanted to focus on the area of RA genetics in the early 1990s, and both were proposing to set up a cohort of patients from whom to collect DNA. The arc ERU proposed establishment of the National Repository for Storage of Family Study Material to arc before the laboratory in Oxford did, and secured funding for it. Understandably, the researchers in Oxford – who pushed for a similar repository – were disappointed, but an agreement was made that they would have access to the samples collected in Manchester.

In fact, arc decided that the two research groups in Oxford and Manchester would have to work together. The broad strategy it came up with to facilitate this was that the Oxford group would focus on whole genome screening, while the arc ERU would target candidate genes. Researchers at the arc ERU felt that this was a harsh decision, as they were collecting all the family material (through the UK National Repository), and had planned to do the whole genome screen themselves. But at the time the Oxford laboratory was a

very strong force in the field (especially because of the presence of the senior researcher previously mentioned). So the arc ERU agreed to the plan; it provided Oxford with DNA from the families, and continued with candidate gene screening.[8]

Interestingly, this division of labour worked to the benefit of the PI and the arc ERU. It transpired that candidate gene screening was a rather short, quick and straightforward process, whereas the whole genome screening that Oxford was doing, with the technology as it was at that time, was actually a very long and complex process. As a consequence, the arc ERU managed to produce a substantial number of publications, while the Oxford team was very unsuccessful (for the reasons explained below). While initially the PI had felt that the decision to divide the work up in this way had been disadvantageous to herself and the arc ERU, the situation worked out very favourably in the end. It helped her to launch her career, certainly in terms of publications.

The Oxford laboratory soon found out that the data collection in Manchester was progressing more slowly than expected. Therefore, it looked for other funders (the Wellcome Trust and Zeneca) to set up its own programme to examine the genetics of both osteoarthritis (OA) and RA. This led to problems between the arc ERU, the Oxford laboratory and arc. First, there was a dispute about ownership of the repository information, which had been funded largely by the arc: the arc felt that the Manchester material on which the Oxford centre depended was not properly acknowledged. In addition, around late 1994 to early 1995, it became apparent that the Oxford group had not been successful in its analysis of these DNA samples provided by the arc ERU. As a result, after a long period of extensive whole genome screening, no results had been published.

At that stage, the arc ERU suggested to the ARC that it was important that the results be published. The arc ERU indicated that it would like to have an opportunity to manage the whole genome screen. arc recognised their concern, and transferred more authority to the arc ERU, but it insisted on better cooperation between the two groups. The groups settled their differences and published a joint paper on the results of the whole genome screen in the journal *Arthritis & Rheumatism* (MacKay and others 2002). Nowadays, the Oxford laboratory focuses more on ankylosing spondilitis, while the arc ERU still investigates RA.

The PI pointed out that the time that was needed for the arc ERU and the Oxford group to establish a successful whole genome screen was a major disappointment. But it was eventually achieved largely through the efforts of the PI and her main colleague at Oxford to make the project work on a collaborative basis.[9]

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[8] It should be noted that the candidate genes that the arc ERU was using for its candidate gene analysis were not chosen on the basis of the whole genome screening that Oxford was doing, as this would have meant too long a lag before the arc ERU could have begun its analysis. The arc ERU researchers chose their own candidates – purely based on their knowledge of the biology of the condition. So the two strands of research were going on in parallel.

[9] In spite of initial tensions, the PI argues that this person turned out to be a very good collaborator; she "came on board and made the collaborative effort work".

15.5.1 **Knowledge creation**

As previously stated, the number of publications coming out of the PI's work initially was very limited. The early years of the postgraduate research fellowship resulted in only two publications (Worthington and others 1993, 1994). Soon after, this number picked up significantly. (The aggregate of publications that came out of the work done between 1990 and 1995 is summed up and discussed in Stage 3: primary outputs below.)

15.5.2 **Research targeting, capacity building and absorption**

As mentioned, a very fruitful knowledge transfer took place over the course of the postgraduate research fellowship and the years that followed. The expertise of molecular biology techniques that the PI picked up during her stay in Oxford, was effectively absorbed by the arc ERU research team, and continues to form an essential part of its skill set.

15.6 **Stage 3: primary outputs from research**

15.6.1 **Knowledge creation**

A total of 18 papers published in peer-reviewed journals have resulted from the postgraduate research fellowship and the three subsequent years of arc-funded work on identification of non-HLA RA susceptibility genes.

Worthington and others (1993, 1994) are the core publications resulting from the first two years of work under the postgraduate research fellowship. Worthington and others (1993) describes the identification of a dinucleotide repeat polymorphism at the alpha-1-antitrypsin (PI) locus. Worthington and others (1994) gives a summary of the pedigrees of the first 100 multi-case RA families with affected sibling pairs, with the intention to stimulate scientists to exploit the scientific gain from the effort involved in the establishment of the National Repository for Storage of Family Study Material.

Subsequent publications describe a lack of evidence that non-inherited maternal HLA contributes an additional susceptibility factor to RA (Silman and others 1995); suggest an interaction between genetic and reproductive risk factors in the aetiology of RA (Brennan and others 1996); and investigate linkage disequilibrium between various HLA disease susceptibility alleles and microsatellite markers close to the prolactin gene (Brennan and others 1996, 1997).

A group of papers investigates the role of tumor necrosis factor (TNF) microsatellite allele frequencies in RA, and associations between TNF microsatellites and RA-associated HLA specificities. Hajeer and others (1996) conclude that TNF microsatellites found to be associated with RA do not appear to be independent of class II HLA associations. Hajeer, John and others (1997) investigate whether TNF microsatellite polymorphisms are associated with sex and age at the onset of disease in RA, and finds that TNF microsatellite haplotypes are different in male and female patients with RA. Hajeer, Worthington and others (1997) suggest that TNF microsatellite alleles are not independent of HLA associations in systemic lupus erythematosis (SLE), and may be important in the expression of certain clinical features in SLE.

John, Hajeer and others (1997) discuss the candidate gene approach (as used at the arc ERU) as an alternative approach to whole genome screening for non-HLA susceptibility loci in RA. John, Marlow and others (1997) investigate whether there is any evidence of linkage between the natural resistance-associated macrophage protein gene, NRAMP1, and RA, and "suggest a role for NRAMP1 polymorphism in a subset of patients who do not possess HLA susceptibility alleles" (p. 452). Lazarus and others (1997) show that polymorphisms within the interleukin 10 (IL-10) gene promoter that are associated with high IL-10 levels may be important in the development of certain clinical features in SLE.

Marlow, John, Hajeer and others (1997) and Marlow, John and others (1997) describe attempts to compare the sensitivity of various analytical methods to detect linkage to known disease susceptibility loci in RA sibling pair families with complete (Marlow, John and others 1997) or incomplete (Marlow, John and others 1997; Marlow, John, Hajeer and others 1997) parental genotype information. The results show that sibling pair families with limited parental genotypes can be used to detect disease susceptibility loci, but also that the "informativeness" of the markers should be taken into account when selecting the method of analysis.

Ollier and Worthington (1997a, 1997b, 1997c) are review articles. Ollier and Worthington (1997a) is essentially a discussion of the importance of centrally collecting information of affected RA families (through the UK National Repository). It also highlights some of the main issues related to ethics and ownership at the Repository. Ollier and Worthington (1997b) was written in relation to the Fifth International Workshop on Rheumatoid Arthritis Genetics, which was held in Manchester on 13–15 March 1996. It discussed the potential of new approaches to complex disease investigation, based on using microsatellite genetic markers. Ollier and Worthington (1997c) goes into the specifics of whole genome screening, and discuss the advantages of affected sibling pair-based approaches over traditional linkage analysis.

Eyre and others (2004) attempted to replicate a previous whole genome scan of 182 UK RA-affected sibling pair families, which suggested linkage of RA to HLA and 11 other chromosome regions. Through replication in an independent cohort, they aimed to distinguish true linkages from false-positive linkages. It was found that none of the regions of linkage identified in the initial whole genome scan achieved statistical significance in the second cohort, supporting the notion that RA is a heterogeneous disorder. (In contrast, after stratification analysis – to account for gender, RA severity, etc – several regions did show nominal evidence of linkage.)

15.6.2 **Research targeting, capacity building and absorption**

Postgraduate research fellowships were introduced "to attract or retain talented scientists in rheumatological research and to provide a secure basis for their development at a critical point in their career". The senior faculty at the arc ERU felt that for these reasons, pursuing such a fellowship was a very good career opportunity for the PI.

The fellowship indeed turned out to be a very beneficial experience, both for the PI's career and the RA genetics research capacity at the arc ERU. As the PI indicated herself, the recommendation by arc to have her spend some time in Oxford was highly valuable. She

Selected bibliometric indicators for case study O

Publication portfolio

Output

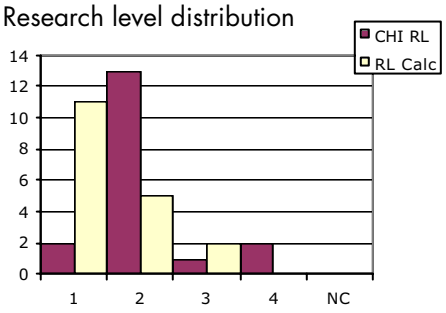
Number of papers	18

Collaboration

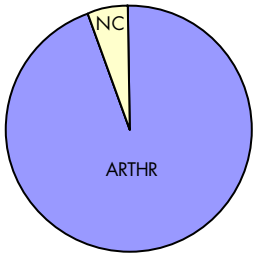
Mean number of authors	6.6
Mean number of addresses	1.6
% with non-UK addresses	5.6%

Type

Research level distribution



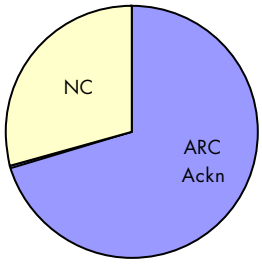
Field distribution



Funding

Mean number of acknowledgements	1.2

ARC funding acknowledgements



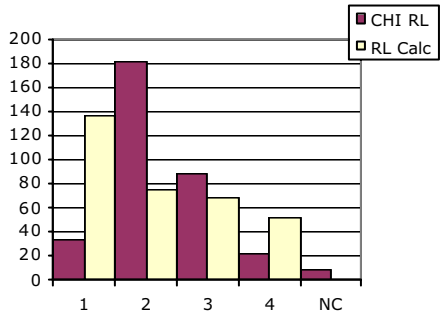
Knowledge flow

Strength

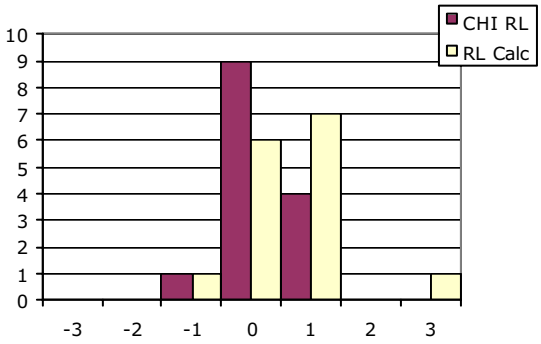
Mean citations per year (all papers)	23.6
Mean C0-4	15.4

Knowledge translation

Research level of citing papers



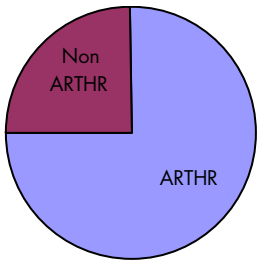
Relative research level



Knowledge diffusion

% of citations from the US	27%

Field distribution of citations



gained a lot of expertise by being part of the molecular biology group and by working closely with the experts.

Moreover, as stated in section 15.4.2, most of what the PI learned in Oxford was passed on to other people in the arc ERU in Manchester in subsequent years. For example, as soon as the PI returned to the arc ERU full-time, she taught the techniques that she had learned to a PhD student, who incorporated it into her own research. Through her arc fellowship, the PI thus facilitated a highly-effective technology transfer. Over the years, this knowledge that the PI gained through her period at the Oxford laboratory became of increasingly high importance to the work of the arc ERU in the field of RA genetics; the arc ERU now houses a centre for genotyping, which in a sense evolved entirely out of the work the PI did in Oxford 12 years ago. The fellowship therefore truly provided a starting point for the arc ERU to establish itself in the field of RA genetics.

The fellowship played an important role in the PI's personal career development as well, very much for the same reasons. After her period at the Oxford laboratory, she possessed a skill set that became crucial to the arc ERU's work in RA genetics. The fact that the grant was incorporated into the Institute funding after two years played a very important role in this. For reasons explained before (see Stage 2: research process), the concrete output that came out of the PI's the initial two years of work was rather disappointing. It resulted in only two publications over this period, which under most circumstances would have been regarded as unacceptable publication record. However, throughout this period the PI had had the time to create a post for herself, and to establish herself as a key person that would be needed to carry the whole project through to the end. As a result, her publication record became less significant.[10]

In other words, the fact that the work was subsequently rolled into the Institute's core funding allowed her to "absorb" the dip that she experienced in terms of publications during these first two years of work. In that sense, the longer time horizon for payoffs that the Institute could afford to have was highly beneficial to the PI. It turned out to be advantageous to the arc ERU because, as we observed in the previous subsection, after 1993 the number of publications picked up very rapidly. The PI still works in the field of RA genetics, but some things have happened that should be noted. Over the years, the arc ERU established excellent facilities, much due to the efforts of the PI and her team members. As a result, many people working in other areas from across the country and even the world have approached the arc ERU to seek their advice or use their facilities. As a result, the PI and many of her colleagues have become involved in various other strands of work. These areas usually appear completely unrelated to RA, but the PI finds it quite remarkable how often the advances in those areas turn out to be useful for other work that is done in RA.[11]

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[10] The fact that the PI had been working in the arc ERU for over a year before starting her fellowship contributed to this as well.

[11] An example can be found in the work of the PI looking at Attention Deficit Disorder (ADD) in children. For this work, a number of neurotransmitters have been investigated, some of which the PI and her colleagues are now planning to investigate in relation to RA. Thanks to the previous work, all the necessary information and background is in place for this.

However, in recent years the PI has tried to pull back from the non-RA activities in which she was involved. Her main focus outside of RA is now psoriasis[12] and psoriatic arthritis (a combination of psoriasis and arthritis). This area has grown substantially over the past few years, thanks in part to the fruitful collaboration with Hope Hospital (Manchester), which has a strong reputation in the field of psoriasis genetics. The PI now has an ARC-funded PhD student working in the field and a clinical fellow; another PhD student will soon be starting. Another MRC-funded clinical fellow, who obtained her PhD in psoriatic arthritis, is active in this area as well. In addition, the PI is moving increasingly into the area of genetics of drug response. This topic straddles her RA work and psoriasis and psoriatic arthritis work, bringing these strands together.

The work carried out under, and evolving out of, the PI's postgraduate research fellowship during 1990–1995 was important to the careers of two other people working at the arc ERU during that period. One of these was a PhD student at the time (1992–1995), under the PI's supervision. She subsequently left to work at New York University, under the supervision of a senior rheumatologist who continues to speak highly of her. Recently, she has left New York to return to her native Mauritius, where she has set up a genetics laboratory. The other person, who came to the arc ERU with an MSc in statistical genetics, joined the arc ERU towards the end of the period under analysis to assist in the whole genome screening. She later left for Oxford, and has continued to work in genetics.

It can be seen that the number of people that developed their career under the auspices of the PI during this period was rather limited. According to the PI, this is quite easily explained; she was awarded this arc postgraduate research fellowship in an early stage in her career. As a result, the number of people working for her was limited in the first few years. (This number expanded substantially in the second half of the 1990s, as the PI grew to become one of the central people in the arc ERU.)

15.7 Interface B: dissemination

Apart from publications and occasional presentations, no real attempts were made to disseminate the research findings to academic audiences. First, this had to do with the fact that there were not that many findings to disseminate, especially in the initial years. Second, the team working on this strand of research was rather small. As a consequence, the people engaged were involved primarily in doing the actual research, which did not leave much room for additional activities. Towards the end of the period under investigation, as the number of publications picked up and the work gained momentum, the notion of disseminating findings gradually received some more attention. This is reflected by the three review articles that were published in relation to the work (Ollier and Worthington 1997a, 1997b, 1997c).

Outside of the academic realm, there was not much engagement with the public. Attempts to reach the broader public were made, but mainly with the aim of recruiting people for the UK National Repository (through press releases in the local press, talking to medical

[12] An autoimmune disease of the skin.

consultants, etc). In other words, the emphasis was on getting patients, not on improving public knowledge about the disease or the research being done in the area.

15.8 Stage 4: secondary outputs – policymaking; product development

15.8.1 Informing policy and product development

The work performed by the PI during 1990–1995 has not fed directly into policies, clinical guidelines or standards of treatment. The more recent work carried out by the arc ERU in the field of RA genetics is getting closer to this point, but still has not resulted in anything concrete. It is easier to envisage how this may occur in the near future, now that the arc ERU has moved into pharmacogenetics. But in the field of genetics, there are two options: (1) identifying novel pathways; and (2) understanding more about the genetic basis of the disease in general, to improve prognosis. The increases that are made in both these fields have in a way built upon the techniques that were developed in the PI's early work, but no breakthroughs have been made directly as a result. Currently, some of the knowledge obtained in those early years is used to improve aspects of another strand of work coordinated by the arc ERU: the Norfolk Arthritis Register (NOAR – case study P).

The arc ERU did not have any industrial collaborations in the period under examination (1990–1995). However, as the reputation of the unit in RA genetics has grown over the years, pharmaceutical companies have become increasingly interested in its activities. In recent years, the arc ERU has had some collaborative schemes with AstraZeneca, as well as several other companies.

The PI does not think that initially there was less interest from industry for their work, because it had less direct relevance to treatment and patient care. She points out that even at that stage, the arc ERU was doing linkage studies based on a richness of data that a pharmaceutical company would never be able to collect.[13] In that sense, their activities have always been attractive. The main issue was the laboratory's reputation in the field. The Oxford laboratory, for example, did have some collaborations with industry at that time. Since the arc ERU has taken over the leading role in the field of RA genetics since then, it receives more attention from industry now.

15.9 Stage 5: adoption – by practitioners and public

As no policies or products have been developed from the work, there has been no opportunity for adoption.

[13] Pharmaceutical companies could probably recruit the people with RA to do a similar study, but it would be virtually impossible to attract expert rheumatologists that really understand this complex, heterogeneous disease.

15.10 Stage 6: final outcomes

There have been no final outcomes as no policies or products have yet been developed from the work.

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CHAPTER 16 Case study P: the Norfolk Arthritis Register (NOAR)

16.1 Introduction to the research project[1]

The Norfolk Arthritis Register (NOAR) was set up in 1990 as a means to study new cases of inflammatory arthritis as they occur in the community, and to follow these patients prospectively in order to investigate the natural history of the condition. It was the first primary care-based register of incident cases of inflammatory arthritis (arc archives; Symmons and others 1994). NOAR was developed by the arc Epidemiology Research Unit (arc ERU) in Manchester. The day-to-day management was organised from within St Michael's Hospital in Aylsham, Norfolk. In 2001, NOAR moved to the Department of Rheumatology of the new Norfolk and Norwich Hospital.

In 1990, at the onset of the NOAR, epidemiological studies of the prevalence of rheumatoid arthritis (RA) in adult caucasian populations had led consistently to results of approximately 1% (Hochberg and Spector 1990; Spector 1990). The only substantive study that had been done in the UK was conducted by Lawrence over 25 years before then; it indicated a prevalence of definite RA of 1.1% (Lawrence 1961). However, prevalence studies are regarded as a poor guide to the true pattern of RA in the community, because patients with chronic stable disease are overrepresented. Patients whose disease goes into remission pass much more rapidly through the prevalent pool, even though these cases are likely to be a rich source of information about the aetiology and prognosis of RA. Furthermore, people that die prematurely from the disease will be underrepresented in the prevalent pool. Therefore, the only way to gain an accurate understanding of RA is to study incident cases (Symmons and others 1994).[2]

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[1] A complication with institute grants is that in most cases, these grants do not fund one neatly-defined strand of research. This is especially problematic in this case study, where the principal investigator has used the arc institute grant for such a diverse range of research projects that it is impossible to examine each of them exhaustively. Therefore, one specific strand of work completely covered by the institute grant has been selected for analysis: NOAR.

[2] "Incidence" is defined as the number of new cases of a disease in a defined population over a specific period of time, whereas 'prevalence' represents the number of cases of a disease existing in a given population at a specific period of time (or at a particular moment in time).

Before 1990 there had been few studies of the incidence of RA, mainly due to the methodological difficulties involved in such research; the disease is so rare that in order to gather 50 cases per year, one would have to monitor approximately 200,000 adults. There had been no studies in the world that used prospective notification of population-based cases of RA.

In January 1990, NOAR was established to fill this void. It began with three aims:

1. to establish the current incidence and descriptive epidemiology of RA, in space and with time;
2. to look for risk factors for disease onset; and
3. to look for predictors early in the disease of either a good or poor prognosis.

More specifically, NOAR set itself the following objectives for the first five years of the programme:

- to initiate a community-based register of patients with inflammatory joint disease;
- to establish the incidence of inflammatory joint disease presenting to primary care within the target population;
- to determine the proportion of those individuals that would satisfy currently accepted criteria for RA – the 1987 ARA criteria (Arnett and others 1988) – at various time points;
- to look for evidence of clustering of the onset of cases either in time or within geographical areas;
- to assemble an inception cohort with a view to assessing the long-term prognosis of incident cases; and
- to determine whether the associations described in clinic-based patients between HLA class II genes and RA are observed within these recent-onset population-derived cases.

The arc ERU chose the Norwich Health Authority as a setting for the project for a number of reasons:

- the population comprises both rural and urban inhabitants, and is reasonably stable (which facilitates follow-up studies);
- the main referral hospitals for rheumatology and orthopaedic patients are situated in the centre of the authority (Norwich and Aylsham);
- there are excellent links between primary and secondary care in the region;
- the local rheumatologists were enthusiastic about the project;[3] and

[3] The principal investigator (PI) for the project had been informed by a fellow rheumatologist in Norfolk that this region would be a very suitable setting for a prospective arthritis register.

- the population is of an appropriate size (around 480,000) to yield reliable estimates of RA incidence and predictors of prognosis.

The principal aim was for the programme to become a valuable contribution to the epidemiology literature, and to provide a resource for the study of the ecology and natural history of the disease in a population sample. As explained above, incidence is a much more useful measure than prevalence, especially for diseases such as RA whose course runs from relapse to remission. Hence, NOAR is a highly valuable study for improving our understanding of both the aetiology and prognosis of RA, and also for health services planning.

16.2 Stage 0: topic/issue identification

The idea for NOAR originated several years before it was put in practice at the arc ERU. The principal investigator (PI) worked as a senior lecturer at the London Hospital Medical College at that time, where he had built up a portfolio of research activities in rheumatology and epidemiology.[4] During this time, he had become aware of what had been learned about cancer through the use of population-based cancer registers (cancer registering is a nationwide standardised process in the UK),[5] and strongly believed that such a study could be extremely valuable for RA as well. According to the PI, "one cannot just rely on patient data from hospitals in order to find out what is going on in a disease such as RA". By capturing every incidence of RA in a population, at an early stage of the disease, one could look at risk factors at the time of onset, separating out the factors associated with getting the disease and those associated with having a severe case and being hospitalised. An additional advantage would be that instead of relying on case notes – which are known to be imperfect – there would be a standardised assessment.

When the director of the arc ERU in Manchester retired early and this post became vacant, the PI applied for the position. This post was made available on the condition that applicants would bring their own research portfolio to the table. In his review process, the PI suggested that the arc ERU would focus on three strands of work:

1. an RA genetics programme;
2. a programme on pain research; and
3. an arthritis register.

The appointment committee was enthused by the suggested research portfolio, as well as the enormous potential of the PI in the field, and appointed him as the new director of the arc ERU in 1988.

The idea evolved out of a series of discussions between the PI and two colleagues who were active also in the field of rheumatology and who had worked in Birmingham together.

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[4] The London Hospital Medical College, England's oldest medical college, was established in 1785. In 1995, it merged with St Bartholomew's Hospital Medical College ("Barts"), established in 1843, to form Queen Mary's School of Medicine and Dentistry (see http://www.mds.qmw.ac.uk/).

[5] See http://www.doh.gov.uk/cancer/cancer-registries.htm (accessed 4 March 2004).

One of them had accepted a position as a consultant rheumatologist in Norfolk in February 1988. All three agreed that the Norwich health district would be a highly suitable place to build such a register: it was isolated, had a stable population, a central hospital and very good links with primary care. Therefore, Norfolk quickly became an obvious place to set up the register. But, as the Norfolk rheumatologist indicated himself, although the fact that he worked in the area was of enormous value to the feasibility of the project, "the number one reason was geography".

Soon after his appointment, the PI got together with his two collaborators and a select group of other experts to examine the practical issues of setting up an arthritis register. This is where the option to start the register in Norfolk was discussed and basically decided. The initiative for NOAR was driven mainly by these kinds of semi-informal discussions between the PI and several fellow researchers active in the field of rheumatology and epidemiology, who all shared the vision that there was a unique opportunity to fill a knowledge gap in the literature by setting up a population-based arthritis register.[6]

The development of such a register was expected to be of enormous potential value for development of a further understanding of the epidemiology, aetiology and prognosis of RA. Therefore, although other funders could have stepped in, arc was an obvious place to apply for financial support for the project.

Since no formal application for the NOAR project was ever reviewed (see Interface A) no direct estimates exist of the amount of funding that was expected to go into NOAR in the years that we examine here (1990–1995). However, in the proposed Institute budget for the year 1990–1991 – which was set at a total of £729,315 – an amount of £76,470 was secured for NOAR. This was expected to rise by 10–15% per annum, as the size of the register, and the pool of cases to be monitored, would expand.

There are no reliable figures on the incidence of rheumatoid arthritis (RA) in the UK. The latest figures for the prevalence of RA are over 30 years old. The Norfolk Arthritis Register (NOAR) has been set up to provide reliable data on the incidence of RA on a continuing basis. It has 2 additional aims: to look for clustering of cases geographically and in time; and to look for features at presentation which will predict either a good or a poor prognosis.

All the GPs in the Norwich Health Authority (n = 266) have agreed to notify NOAR of all adult patients with inflammatory arthritis (>1 joint) lasting more than 4 weeks with an onset since 1 January 1989. The patient is then visited at home by a metrologist trained to gather relevant demographic, clinical and epidemiological data; to examine joints and to take blood. The patients' records are tagged so that subsequent hospital referral will be reviewed annually to assess the pattern of inflammation and the development of disability and deformity. Completeness of notification is validated in part by parallel reporting from hospital clinics.

(SOURCE: arc archive)

Box 16.1: Abstract

[6] Neither of the other two rheumatologists from Norfolk was involved in the development of NOAR at the time, because they would both retire within a few years, and thus not be around long enough to participate actively.

16.3 Interface A: project specification and selection

The assessment procedure for NOAR was quite different from the standards that arc adheres to in case of project or programme grants; its merit was not assessed through a formal process of peer review. As part of all the three core strands of work proposed by the PI, it was evaluated by the appointment committee as an integral part of his application for directorship of the arc ERU. Candidates for this position were asked to come up with their own research portfolio. Not only did this include an indication of the focal areas of research, but also some estimates of the budgeting involved.

In a sense, the peer-review process for NOAR was rather informal. As the PI conceded, it was unclear whether the appointment committee had been truly able to evaluate the potential of the research programme – yet they did not bring in any external experts to do this. However, an added complication was that the PI's proposed research team had a unique set of expertise. This was why the appointment committee was so interested in his application in the first place, but as a consequence there were not many experts in the UK, or even worldwide, who could evaluate the details of the proposed research. Notwithstanding this, the members of the appointment committee agreed that the team were at the forefront of research in their area, and considered the proposal to be highly promising. They were impressed by the PI's track record, enthusiasm and leadership skills, and decided to appoint him to the position, believing that if any research team would have the know-how to effectively undertake this research, it would be this one.

Soon after his appointment, the PI and new director of the arc ERU set up his own formal review process. A first site visit to arc ERU was conducted on 15 March 1990, at his request. The site visit team, composed of four international experts and guided by the arc scientific officer, was "particularly impressed" by NOAR. It reported that NOAR had "major potential" and that "it might prove to answer many important questions about the aetiology of rheumatoid arthritis". Moreover, the experts all saw the PI as a future world leader in the area:

> Naturally, he does not yet see himself in that light, but he has begun to do important work as an international advisor and educator. We hope that the ARC will do everything possible to encourage him towards world leadership.

However, the site visit team had been surprised to learn that the arc ERU had not been subject to regular peer review during the two decades that the previous director had been heading the unit. They saw this as a serious error and suggested to arc that site visits would be arranged in the future. Soon after the recommendations of this first site visit team were made, a regular five-yearly peer review process was set up for the arc ERU. The first formal review that was carried out in this context took place on 3 June 1993. The working group undertaking the review was chaired by a leading rheumatology professor from the Kennedy Institute of Rheumatology in London, and also involved an expert in the field of cancer epidemiology from the University of Nottingham Medical School. The PI strongly approved of his inclusion in the working group, as it has always been his conviction that "it is important to bring top-notch non-RA epidemiologists into the review process".

The working group reported that NOAR was an "important and unique study" which needed to be done and which should continue. However, it did point out that there appeared to be "a weakness regarding the selection of appropriate controls and eliciting of

hormone exposures". Therefore, it was recommended that "advice should urgently be sought from an epidemiologist with experience of large etiological studies" (arc archives). When we notified the PI of this information, he responded by saying he could not recall having been confronted with this criticism at that time. Moreover, he stated that even if he had, it would be unlikely that he had responded to it. The remarks did not make any scientific sense to him, and did "not seem relevant to what was going on at NOAR at that time".

16.4 Stage 1: inputs to research

16.4.1 Funding

Table 16.1: NOAR annual budgets 1990–1995 (in 1990 values)

(£)	1990/91	1991/92	1992/93	1993/94	1994/95
Salaries	59,970	72,456	93,783	115,263	125,140
Consumables	16,500	16,500	19,060	21,000	24,650
Capital expenditure	-	-	2,100	-	-
TOTAL	**76,470**	**88,956**	**114,943**	**136,269**	**149,790**

The arc ERU devoted a specific part of its institute budget to NOAR every year. In the period from 1990 until 1995, this amounted to a total of £566,428 (see Table 16.1 above). Most of this funding was spent on the salaries of the staff involved (£466,612). In addition, consumables accounted for roughly 17% of the budget (£97,710). Hardly any of the funds were spent on capital expenditure (£2,100), as most of the necessary equipment was already present at the arc ERU.

The manager and as the four metrologists "on the ground" in Norwich were all funded through the arc ERU. However, the lead rheumatologist never received any arc ERU or arc financing for his involvement in NOAR. He acted out of a scientific interest and loyalty to his colleagues, and also because he expected to gain a lot from being engaged with the programme on the long term.

NOAR was offered interest-free accommodation in St Michael's Hospital in Aylsham, within the Department of Rheumatology. (Later, when the Department of Rheumatology moved to the Norfolk and Norwich Hospital in 1996, NOAR followed and became situated in this new location. It is still run from the Department of Rheumatology in the new Norfolk and Norwich Hospital.)

16.4.2 Human capital

At the onset of the NOAR project, the PI had built up a very strong track record in the field of rheumatology and epidemiology. After qualifying in medicine, and doing some work as a junior doctor, he had received epidemiology training at London University. He subsequently spent nine years as a lecturer (and later as a senior lecturer) at the London Hospital Medical College, in broad areas of epidemiology and rheumatology. During this time, he had cultivated a strong portfolio of research activities and developed a vision about the core strands of work on which he wanted to focus.

Upon his appointment at the arc ERU the PI used this vision, as well as his connections with fellow rheumatologists in Birmingham and Norwich, in order to develop the necessary infrastructure of skilled people (both around him at the arc ERU and the Norwich Health Authority). In practical terms, this worked very effectively right from the onset. This was also much to the credit of the lead clinician in Norwich, who was highly skilled and motivated and managed to set up a solid team that truly functioned as a satellite unit of the arc ERU.

16.4.3 Techniques, reagents and equipment

As previously stated, the part of the NOAR budget spent on equipment was negligible. The main reason for this was that the necessary equipment for analysing the samples collected was already present at the ERU.

16.4.4 Benefits of institute funding

The PI indicated that the institute funding provided to the arc ERU by arc was crucial to the success of the NOAR project, for two main reasons. First, institute funding offers long-term stability. A project such as NOAR needs several years to develop before any substantial outputs begin to emerge. It takes several years to set up the institutional infrastructure, and building up the patient base and the experience takes even longer. The value of projects such as NOAR therefore increases enormously after a few years have passed. Had the arc ERU only received five-year funding (eg through a project grant) it was hardly likely to have led to any valuable results. This is illustrated by the portfolio of NOAR publications: in the initial period, the number of papers that sprung from NOAR was very small, but this picked up enormously after several years. Moreover, institute funding allows large-scale projects to be developed. Research endeavours such as NOAR involve very high costs; the investment is long-term and large-scale. Again, institute funding offers the stability and security that are crucial in allowing such projects to develop and thrive; it also allows lead researchers to promise their staff that such long-term support exists in return for their commitment.[7]

This aspect of long-term stability is also a crucial one from a human resource perspective. The NOAR project requires a diverse pool of very different types of expertise, focused on one area. Much of this expertise is very scarce in this country, in particular high-quality researchers into epidemiology. The nature of working in epidemiology means that the timescale on which scientific rewards can be obtained is much longer and harder to predict. In more traditional, laboratory-based research (such as molecular biology), people virtually know that they will have publishable results within three years, but in epidemiology research this is much less certain. For this reason, both funders and research staff have to be engaged for the long-term.

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[7] This point was reiterated in one of the first publications that came out of NOAR: "This paper reports the first reliable incidence figures for RA in the UK. The greatest potential achievements for NOAR are likely, however, to lie in the future. The study design will enable us to monitor secular trends in the incidence of RA, to look for time-space clustering of cases, and to investigate prognostic indicators" (Symmons and others 1994).

16.5 Stage 2: research process

Upon the successful completion of a pilot study, NOAR was launched. In 1989 a clinical manager, a part-time secretary and four part-time metrologists were appointed. They spent the autumn of that year visiting all the 276 general practitioners (GPs) in 76 practices in the Norwich Health Authority, to inform them about the study and provide them with the necessary supporting information. The study went live with a press conference on 3 January 1990 (arc archives). After that date, GPs notified NOAR of all the adults who developed an inflammatory arthritis (more than one joint) lasting for more than four weeks.

According to the PI, the project benefited enormously from having good communication between the people in Manchester and those in Norwich. From the onset, the fieldwork in Norwich functioned very effectively as a satellite of the arc ERU – which it still does. The rheumatologist (who initially worked in Birmingham, and had moved to the arc ERU in Manchester in 1989) travelled to Norwich often to talk with the metrologists, manager and her former colleague. In the initial years, the PI travelled there on a monthly basis, which – according to the rheumatologist in Norwich – was of enormous importance to getting NOAR on track.

In addition, there were intermittent meetings in Norfolk or at the arc ERU where the two teams came together to discuss results and progress. Further, there was a local management committee in Norwich that met (and still meets) once a year, as well as a scientific committee in Manchester that convenes on a yearly basis. In other words, several arrangements – both formal and informal – were put in place to ensure that NOAR was progressing as planned.

As stated in Interface A: project specification and selection, the progress in the NOAR project was first evaluated in a site visit to the ERU, which was conducted on 15 March 1990. The site visit team was highly impressed by the project at that time, and considered it to have major potential. It did not propose any changes to the management of the project.

Before 1991, although the arc ERU had been situated on the University of Manchester campus, it had been independent of it. The director and PI had sought to change this status, for several reasons. First, the ERU had begun to work increasingly closely with many departments within the university. Second, recruitment and career development of arc ERU staff would be enhanced by the ability to confer appropriate academic titles. Third, it would enable the unit to compete with other university departments for funding from other bodies than arc. Lastly, the unit had rapidly grown out of its allocated space, and there was no clear mechanism by which it could negotiate for an increase.

This effort was successful and from late 1991 onwards, the arc ERU became recognised as an independent entity within the School of Public Health Sciences and Epidemiology, one of the five schools of the Faculty of Medicine. Soon after this transition, a general sentiment arose that the "amalgamation was valuable to both the Unit and the University". Although there were no obvious direct implications for NOAR, the arc ERU's new status had at least some indirect positive effects on the operations of this project also.

In the arc ERU's Report of Scientific Activities 1989–1992, it was reported that NOAR had achieved its initial objectives. By this time, the register was "successfully up and running" and recruitment of new cases had been at a fairly high and rising level. Also, the first estimates of RA and inflammatory polyarthritis (IP) had been derived and published (see Symmons and others 1992), and they were broadly in line with other published estimates based on less robust data. Even a fifth metrologist had been added to the team in late 1992. But again, it was pointed out in the report that NOAR "has to be considered as a long-term study. Even after three years of intensive data collection it is only possible to make preliminary analyses on the data collected".

Despite its overall success, there were several aspects of the NOAR project that did not go entirely as planned. First, at the time that NOAR was set up, the PI and his co-applicants expected that it would be easy to distinguish early on which patients had RA and which did not. In the event, this did not turn out to be the case and so most of the publications from NOAR are based on all the cases of inflammatory arthritis put together.

Second, perhaps the largest drawback of NOAR resided in the problems that it encountered after the period we examine here. There were enormous difficulties in keeping all the GPs in the Norwich Health Authority engaged in monitoring the cases of RA after the first five years. Because of this, NOAR has diminished gradually from a register keeping track of the whole Norwich health district of a population of half a million, to one that now monitors only a subset of approximately 200,000 people. The simple reason for this is that only part of the GPs kept reporting and monitoring all the cases of RA that they encountered systematically; some did sporadically and others did not at all.[8]

Third, a problem which became more apparent as NOAR progressed is that the population in the Norwich health district – although very stable – was not as stable as one would have liked it to be. Over the 15 years of NOAR's operation, significant numbers of patients have moved into or out of the region.

In spite of these difficulties, the results that have come out of NOAR are considered generally to be hugely successful, as we will see in the next section.

16.6 Stage 3: primary outputs from research

16.6.1 Knowledge production (payback category A)

One of the main primary outputs of the early work on NOAR has been a widening of the scientific knowledge base through the publication of peer-reviewed papers. However, when determining which publications came out of the work that was done on NOAR between 1990 and 1995, a fundamental problem is encountered. NOAR still exists, and many of the recent studies that are done on the basis of the community-based cohort that it contains link back at least partially to the data that was gathered in the initial years of operation. As a project of this kind has to go through at least five years of intensive data

[8] Cancer registers tend to work better in this respect. GPs need tissue samples for their diagnosis in any event, and once this is obtained, registration is very straightforward. With diseases such as RA, which require a clinical diagnosis, this is harder to manage.

collection before any substantial analyses can be carried out, the papers that have been published only very recently may be based heavily on the data that was collected in the period examined in this study.[9]

In an attempt to find a practical solution to deal with this problem, it was decided – in agreement with the PI – to expand the window of analysis to include all papers related to NOAR published between 1990 and 1997. In addition, a selection of more recent papers that rely heavily on the oldest cases in the register will be included. Some of the most important studies in this sample are discussed briefly here.

The studies carried out on the register explore various topics. First, several studies have been undertaken to establish the occurrence of RA. The first incidence data were published in 1992 (Symmons and others 1992) and 1994 (Symmons and others 1994). They were followed by a five-year follow-up study, which refined the annual incidence estimates to 54.0 per 100,000 for women and 24.5 per 100,000 for men (Wiles, Symmons and others 1999).

Second, since NOAR cases were monitored continuously from a defined population, it was possible to look for evidence of clustering of cases in time and space. It was found that, in general, there is no evidence that new cases of RA occur in clusters (Silman and others 1997). However, although the majority of cases cannot be explained through clustering, three small clusters of cases in space have more recently been observed (Silman and others 2000). But it remains difficult to say whether or not these are true clusters; they may have occurred by chance.

In 1996, a paper was published which had found no evidence of an influence of socioeconomic status on the incidence of RA (Bankhead and others 1996). A year later, another study confirmed the observation of various other studies; it reported a protective effect for the development of IP in women using the oral contraceptive pill (Brennan and others 1997). Two other studies showed that, although it had been found that psoriasis and immunisation are potential triggers of IP, there was no evidence that the pattern of arthritis at presentation or the short-term outcome was any different in patients whose IP might have been triggered by psoriasis (Harrison, Silman and others 1997) or immunisation (Harrison, Thomson and others 1997) than in those without triggers.

Lastly, the design of NOAR also made it possible to distinguish between the genetic factors that influence susceptibility to RA or IP and those that influence persistence or disease severity. In 1993, a family study was performed amongst patients newly-notified to NOAR, using their friends as controls. The study showed that the occurrence of RA was not increased in the first-degree relatives of these NOAR cases (Jones and others 1996). Another paper investigated the allele frequencies of HLA-DR4 and DR1 – two potential markers for susceptibility and/or severity to RA – in a series of 208 patients classified as having either RA or undifferentiated IP. The frequency of occurrence of DR4 in these patients with RA did not differ significantly from that in controls (42 vs 37%). HLA-DR1 was increased in the group with IP (25 vs 18%). The fact that the frequency of DR4 was

[9] An example is the recently published paper by Goodson and others (2002), which examines mortality in early IP. This paper relies heavily on the data gathered in 1990–1995, as most of the deaths are likely to have occurred among the oldest cases.

not increased supports the hypothesis that DR4 is less important as a marker for susceptibility to RA than it is for diseasepersistence or severity.

In the years following our period of analysis, the number of studies that have evolved out of NOAR have only increased. The PI firmly believes that the register has a national and international reputation, as it "has provided groundbreaking work in the understanding of how common RA is, and what factors are associated with it".

16.6.2 **Research targeting, capacity building and absorption (payback category B)**

The NOAR project has helped a number of people to build their career in the field of epidemiology and rheumatology, both at the University of Manchester as well as in Norfolk. At the arc ERU, most notably there is the PI himself, of which NOAR was one of the three main pillars of his work. The register has been lauded – much to his credit – as an "invaluable epidemiological service to researchers working on inflammatory arthritis" (ARC 1999). Another key person in setting up the NOAR project, the lead co-applicant at the arc ERU, has developed her career within the arc ERU mainly on the basis of NOAR, and is now a professor of rheumatology in Manchester. arc has continued to play an important role in her research; roughly 80% of the research she does is funded by arc.

In addition, NOAR has been the setting for three clinical research fellows to obtain PhDs, one health economist and one nutritionist to obtain PhDs, one epidemiologist to obtain a PhD, one research assistant to obtain an MSc in Epidemiology and Medical Science and another research assistant to obtain an MHSc. All of these individuals have continued to use the research skills gained while working on the NOAR Project. One of the main statisticians for NOAR has gone through a very good career trajectory. He obtained his PhD on NOAR and is now a lead researcher at an international agency for research in cancer in Lyon, France. The research assistant who received an MSc degree moved to the University of Oxford in 1996, where she is now a research fellow. Over the last five years, she has been working in the field of breast and cervical cancer screening and on factors that influence attendance for screening. Two of the clinical fellows are now consultant rheumatologists with an ongoing interest in early arthritis. The other fellow is still in training.

The rheumatologist for NOAR in Norfolk also has built a very successful career out of his work for NOAR. His involvement in NOAR changed his research agenda significantly, and moved it much more into epidemiology. Vasculitis[10] remained his main area of interest, but he began to study the epidemiology of this disease based on his experience with NOAR.[11] Partly to his and NOAR's credit, the University of East Anglia has developed into one of the leading centres for research into rheumatic diseases in the country (as will be discussed in Section 4: secondary outputs).

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[10] Inflammation of blood vessels.

[11] His work has resulted in over 200 publications, and although most of those focus on vasculitis, all the more recent ones are attached to epidemiology. He conceded that this was very much due to his involvement in NOAR.

Selected bibliometric indicators for case study P

Publication portfolio

Output

Number of papers 27

Collaboration

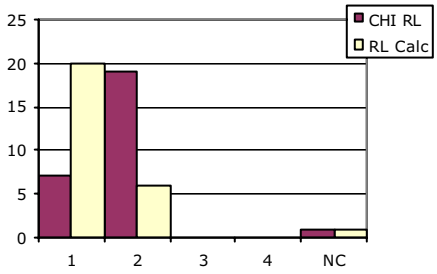
Mean number of authors 5.4

Mean number of addresses 2.2

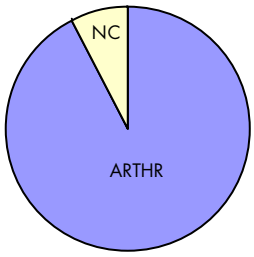
% with non-UK addresses 11.1%

Type

Research level distribution



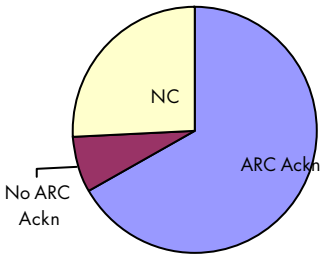
Field distribution



Funding

Mean number of acknowledgements 0.9

ARC funding acknowledgements



Knowledge flow

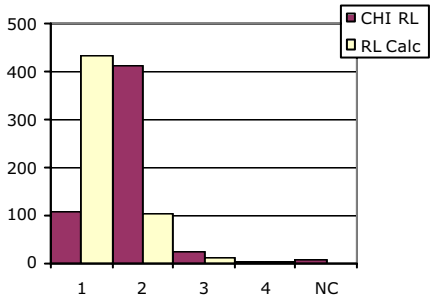
Strength

Mean citations per year (all papers) 39.7

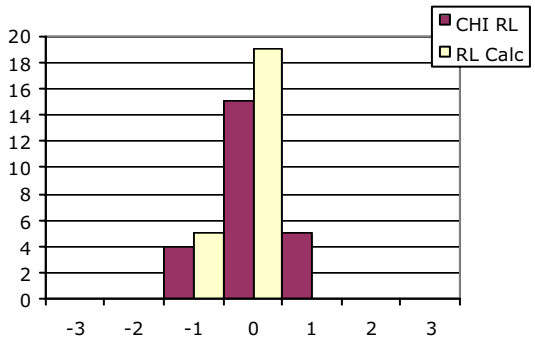
Mean C0-4 15.9

Knowledge translation

Research level of citing papers



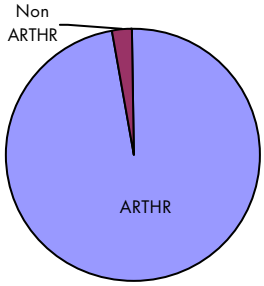
Relative research level



Knowledge diffusion

% of citations from the US 20%

Field distribution of citations



16.6.3 **Informing policy and product development (payback category C)**

The work done on NOAR in the period examined has had no direct impact on policies or products (such as clinical guidelines, standards of treatment, etc). But recently, work on NOAR has been moving closer to the types of output that do have policy implications. For example, two important studies published in 2001 and 2003 respectively, indicated that early treatment of RA is good and late treatment is bad (Bukhari and others 2003; Wiles and others 2000).[12] The former example is a good indication of how NOAR influences policies and treatment. Its impact on clinical guidelines, policies and treatment procedures is indirect; it delivers data that underpin or support changes in treatment – for example, through studies indicating that early treatment is beneficial – but it does not lead them; these changes are also driven by other evidence. but in the area of education and information campaigning about RA, NOAR has truly lead developments.

What NOAR has done through examining RA at the primary care level is to prompt people to reconsider what RA really is. It is now recognised as being a much wider disease than was the case only 10 to 15 years ago. In that sense, NOAR really has opened the debate about how arthritis should be defined.

16.6.4 **Health benefits (payback category D)**

No evidence for this has been found. Although no formal review has ever been conducted, there are some indications that awareness of RA has increased amongst clinicians in the Norwich area. In turn, this may have had a positive effect on patient care. In fact, according to the PI, patients in Norfolk have tended to have relatively milder cases of the disease in the long-term. However, it is unclear whether this reflects an improvement in treatment or simply a trend towards milder disease. This has not been examined yet.[13]

16.6.5 **Broader economic benefits (payback category E)**

No direct economic benefits have resulted.

16.7 **Interface B: dissemination**

The PI and his collaborators have undertaken various activities to disseminate information about NOAR in the scientific community. All of them have given a range of presentations that directly or indirectly relate to NOAR at meetings both in the UK and overseas, and have travelled extensively to present material about it (for example, at the annual meeting of the Italian Rheumatology Society). Moreover, they have written a few articles for *Arthritis Today*, arc's quarterly publication, and some of the more recent studies nested within NOAR have been the subject of arc press releases.

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[12] Another example is related to the fact that last year it was found that cardiovascular disease is a leading cause of death in RA. Studies around NOAR have contributed to this debate. Obviously, this discovery should feed directly into policy; it should give RA patients a focus on living and eating healthily, monitoring their cholesterol levels regularly, etc.

[13] For the NOAR studies, in a way it would be troublesome if treatment had indeed improved, because the goal of these studies is to measure the natural history of the disease, which ideally should be unaffected through other variables such as management.

Hardly any dissemination activities for NOAR were undertaken outside of the scientific field.

16.8 Stage 4: secondary outputs – policymaking; product development

16.8.1 Knowledge creation

The information which has come out of NOAR on the occurrence of RA has had a major impact and has been a useful starting point for many other researchers. Information on predictors of outcome and the aetiology of the disease has been widely quoted. For example, information from NOAR showed that smoking is a risk factor for the development of RA (Symmons and others 1997). Other subsequent publications have confirmed this association, and this has now become an accepted risk factor for the development of the disease. Similarly, the hypothesis that many patients with RA die prematurely from cardiovascular disease (Goodson and others 2002) has been confirmed by others and is now an area of intense interest within the rheumatological community.

16.8.2 Research targeting, capacity building and absorption

As the PI pointed out, "NOAR has definitely increased research capacity locally" in Norfolk. The area has developed into one of the leading centres for research into rheumatic diseases. During the second half of the 1990s

> a number of key people and disciplines have converged in Norwich from other leading centres, and the result has been a flowering of clinical and scientific research, with major implications for the treatment and care for people with arthritis. (ARC 1999, p.1).

This was confirmed by the lead rheumatologist at Norfolk and Norwich Hospital, who had been involved in NOAR from the onset. He gave the example that in the new medical school, epidemiology and rheumatology receive a lot of attention in the curriculum as well as in the research portfolio – much more than they would normally get in a provincial hospital. To a large extent, this is due to his good track record in those fields and, in turn, based significantly on NOAR. So NOAR has had a huge, but largely indirect, effect on developments in the region.

These developments have been indeed much to the credit of the lead rheumatologist in Norfolk and Norwich Hospital. Not only has he done a terrific job at managing and coordinating the NOAR project right from the onset, but also has managed to build up a cutting-edge rheumatology department in the Norfolk and Norwich Hospital. In 1998, this department won the Searle Rheumatology Team of the Year Award for its innovative clinical practice and overall performance. A third major centre of rheumatology research is situated in the University of East Anglia (UEA), where most of the arc funding is concentrated. arc funds several PhD and postdoctoral positions in the laboratories of the UEA's School of Biological Sciences (ARC 1999).

Furthermore, NOAR has functioned as an example for several other population-based registers in Europe. For example, both the PI and the rheumatologist in Norwich indicated

that they had been involved as advisers in the process of setting up registers based on a model similar to NOAR.[14]

The Danes have set up a similar programme to NOAR. According to the PI, the Danish National Institute of Health had stated to him that this initiative had been set up as a result of their enthusiasm about what had been achieved with NOAR.

16.8.3 Informing policy and product development

As stated previously, although the work done on NOAR in the initial years has not fed directly into policy changes or clinical guidelines, more recent studies – many of which are at least partially based upon the work done in the first period – are moving in this direction.

The incidence and prevalence figures from NOAR are widely cited in many clinical guidelines as a benchmark of the occurrence of RA. In addition, the arc ERU published a paper on the physical and emotional outcomes of RA at five years, which was intended specifically to act as a benchmark against which others could measure their patients' progress.

16.8.4 Health benefits

A similar argument can be made for health benefits. According to the PI, "nothing has had a substantial effect at a patient level yet", but research is moving steadily in this direction. Moreover, a lot of research has been started up in recent years that is not directly related to NOAR but has certainly evolved out of it. Good examples of this are the health economic evaluations that are undertaken at the UEA; several researchers at the UEA's Department of Health Policy have been investigating the financial cost of arthritis to the patient. For example, one person at UEA wrote a PhD on the costs of early arthritis, which led to three publications. It showed evidence that suggested direct health service costs represent only 20% of the total costs for treatment of early RA.[15]

16.8.5 Broader economic benefits

No indications of any economic benefits that have indirectly evolved out of NOAR have been found.

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[14] One of the PI's contributions was a talk about NOAR, which he gave at a conference that was organised as a brainstorming session on how to build a similar Swedish register. The people there were setting up a register that was somewhat different, being based on primary care rather than attending hospital patients, but highly similar in many other ways. The rheumatologist in Norfolk indicated his involvement in other similar activities, although mostly in relation to vasculitis registers.

[15] According to the rheumatologist in Norwich, this study needs to be repeated, as the amount of data available was very limited at that time. The data were heavily skewed, as the sample contained a very small number of patients that were extremely expensive to health services due to inpatient care.

16.9 Stage 5: adoption – by practitioners and public

16.9.1 Informing policy and product development

Data from NOAR on the benefit of the early treatment of arthritis with regards to outcome have become part of the evidence base quoted when arguing for early referral and early treatment of RA. NOAR has not been the only project to produce this evidence, but it has certainly played its part in the shift towards early recognition and treatment of this disease.

16.10 Stage 6: final outcomes

16.10.1 Informing policy and product development

The prognosis of patients developing RA today is much better than it was when the NOAR project was initiated in 1989. Advances in treatment are one reason for this. Better understanding of the need for early treatment and of which patients are likely to do badly has contributed also. NOAR has played an important part in contributing to the evidence base. Recognition of the benefit of the early treatment of RA means that nowadays, patients are more likely to be referred early and to be seen within a short timeframe. Early referral of RA patients is one of the two quality standards set for rheumatology by the Royal College of Physicians.

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Annex A: Bibliometrics results tables

Case Study	Year	Authors	Title	Full Reference	Authorship # authors	Authorship # addr	Authorship # Non UK addr	Funding ARC Ackn	Funding # Ackn	Area Within ARTHR	Area Cites within ARTHR	90	91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	Total	N Art/Not	Cites by Reviews	Self Cites	AU	CA	CH	DE	ES	FR	IT	JP	NL	SE	UK	US	C0-4 (actual)	C0-4 (journal)	CHI Level Orig Jrnl	CHI Citing Papers 1	CHI Citing Papers 2	CHI Citing Papers 3	CHI Citing Papers 4	CHI Citing Papers NC	Orig Jrnl	Citing Papers 1	Citing Papers 2	Citing Papers 3	Citing Papers 4	Citing Papers NC	Citation by Guidelines Any	Citation by Guidelines Arth Rltd
A	1996	Torgerson-DJ Klabermoffett-J Russell-IT	Patient preferences in randomised trials: threat or opportunity?	Journal of Health Services Research & Policy, 1996, Vol 1, pp 194-197	3			1			1							0	2	2	5	3	2	3	2	19	16		3	2	1			1				1		16	3	12			11	3	2	0	3		18	1	0	0			
A	1999	Frankel-BS Moffett-JK Keen-S Jackson-D	Guidelines for low back pain: changes in GP management	Family Practice, 1999, Vol 16, pp 216-222	4			0																																																	
A	1999	Keen-S Dowell-AC Hurst-K Klabermoffett-JA Tovey-P Williams-R	Individuals with low back pain: how do they view physical activity?	Family Practice, 1999, Vol 16, pp 39-45	6			0																																																	
A	1999	Moffett-JK Torgerson-D Bellsyer-S Jackson-D Llewlynphillips-H Farrin-A Barber-J	Randomized Controlled Trial of Exercise for Low-Back-Pain - Clinical Outcomes, Costs, and Preferences	BRITISH MEDICAL JOURNAL, 1999, Vol 319, Iss 7205, pp 279-283	7	3	0	1		0	5										1	6	10	6	3	26	19	5	3	3	1	1	1				1		1	7	8	26	14.4	1	8	7	4	0	7	1	21	5	0	0		0	0
A	2000	Bellsyer-SE Moffett-JA	Recruiting patients to randomized trials in primary care: principles and	Family Practice, 2000, Vol 17, pp 187-191	2			1																																																	
A	2001	Garratt-AM Klabermoffett-J Farrin-AJ	Responsiveness of generic and specific measures of health outcome in	Spine, 2001, Vol 26, pp 71-77	3			1			1											0	1	0	1	2	2			1	1										1				0	1	1	0	0		0	2	0	0			
B	1996	Cooper-C Campbell-L Byng-P Croft-P Coggon-D	Occupational Activity and the Risk of Hip Osteoarthritis	ANNALS OF THE RHEUMATIC DISEASES, 1996, Vol 55, Iss 9, pp 680-682	5	2	0	0	0	1	5							0	0	1		1	2	0	1	5	5		1		1				1			1		3	1	2	8.3	2	2	3	0	0	0	1	5	0	0	0		0	0
B	1998	Coggon-D Kellingray-S Inskip-H Croft-P Campbell-L Cooper-C	Osteoarthritis of the Hip and Occupational Lifting	AMERICAN JOURNAL OF EPIDEMIOLOGY, 1998, Vol 147, Iss 6, pp	6	2	0	0	0	1	16									1	0	6	1	6	4	18	14	3	5		1						2	2	1	6	5	14	15.1	2	3	13	0	0	2	1	16	1	1	0		0	0
B	1998	Cooper-C Inskip-H Croft-P Campbell-L Smith-G Mclaren-M Coggon-D	Individual Risk-Factors for Hip Osteoarthritis - Obesity, Hip Injury and Physical-Activity	AMERICAN JOURNAL OF EPIDEMIOLOGY, 1998, Vol 147, Iss 6, pp	7	3	0	0	1	1	26									2	2	12	2	7	7	32	26	4	5				1		1		1	1	1	9	13	25	15.1	2	7	17	2	1	5	1	27	2	3	0		0	0
B	1998	Dennison-EM Arden-NK Kellingray-S Croft-P Coggon-D Cooper-C	Hormone Replacement Therapy, Other Reproductive Variables and Symptomatic Hip Osteoarthritis in Elderly White Women - A Case-Control	BRITISH JOURNAL OF RHEUMATOLOGY, 1998, Vol 37, Iss 11, pp 1198-1202	6	2	0	0	0	1	11									0	0	4	4	3	4	15	10	5		3	1		1		2	1		1		3	5	11	11.7	1	6	5	0	2	2	1	11	1	1	2		0	0
B	2000	Yoshimura-N Sasaki-S Iwasaki-K Danjoh-S Kinoshita-P Yasuda-T Tamaki-T Hashimoto-T Kellingray-S Croft-P Coggon-D Cooper-C	Occupational Lifting Is Associated with Hip Osteoarthritis - A Japanese Case-Control Study	JOURNAL OF RHEUMATOLOGY, 2000, Vol 27, Iss 2, pp 434-440	12	4	1	0	0	0	8											1	2	3	4	10	8	1			1							2		1	5		10.9	2	2	7	0	0	1	1	9	1	0	0		0	0
B	2002	Croft-P Lewis-M Wynnjones-C Coggon-D Cooper-C	Health-Status in Patients Awaiting Hip-Replacement for Osteoarthritis	RHEUMATOLOGY, 2002, Vol 41, Iss 9, pp 1001-1007	5	3	0	0	0	0	1												0	0	2	2	2		2											2			9.9	1	0	2	0	0	0	1	2	0	0	0		0	0
C	1991	Ward-RV Hembry-RM Reynolds-JJ Murphy-G	The Purification of Tissue Inhibitor of Metalloproteinases-2 from Its 72 kDa Progelatinase Complex - Demonstration of the Biochemical Similarities of Tissue Inhibitor of Metalloproteinases-2 and Tissue Inhibitor of	BIOCHEMICAL JOURNAL, 1991, Vol 278, Iss AUG, pp 179-187	4	1	0	0	1	0	19			11	11	20	18	16	11	12	12	9	8	4	2	134	120	13	45	8	12	3	9	1	12	3	24		1	61	37	60	16.4	4	5	16	36	74	3	4	12	12	28	82		0	0
C	1991	Ward-RV Atkinson-SJ Slocombe-PM Docherty-AJP Reynolds-JJ Murphy-G	Tissue Inhibitor of Metalloproteinases-2 Inhibits the Activation of 72 kDa Progelatinase by Fibroblast Membranes	BIOCHIMICA ET BIOPHYSICA ACTA, 1991, Vol 1079, Iss 2, pp 242-246	6	2	0	1	3	0	11			9	20	30	22	24	23	22	17	12	8	2	4	193	170	23	33	3	8	1	12	4	13	6	38	2	0	56	89	81	11.32	4	7	22	44	117	3	4	22	16	32	123		0	0
C	1992	Atkinson-SJ Ward-RV Reynolds-JJ Murphy-G	Cell-Mediated Degradation of Type-IV Collagen and Gelatin Films Is Dependent on the Activation of Matrix Metalloproteinases	BIOCHEMICAL JOURNAL, 1992, Vol 288, Iss DEC, pp 605-611	4	1	0	0	3	0	1			0	3	2	1	6	4	5	2	1	0	0	1	25	21	4	3		1		1		1	3	6			5	9	12	16.7	4	3	1	5	16	0	4	3	1	5	16		0	0
C	1992	Knight-CG Willenbrock-F Murphy-G	A Novel Coumarin-Labeled Peptide for Sensitive Continuous Assays of the Matrix Metalloproteinases	FEBS LETTERS, 1992, Vol 296, Iss 3, pp 263-266	3	2	0	0	1	0	41			3	9	22	26	27	37	30	48	44	42	26	38	352	336	14	40	4	13	9	35	7	21	13	53	8	2	92	150	87	14.5	4	3	15	82	239	13	4	12	13	36	291		0	0
C	1992	Murphy-G Atkinson-S Ward-R Gavrilovic-J Reynolds-JJ	The Role of Plasminogen Activators in the Regulation of Connective-Tissue Metalloproteinases	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1992, Vol 667, Iss DEC, pp	5	1	0	0	0	0	14			1	2	6	12	18	15	18	15	10	13	8	8	126	110	16	6	3	1	2	5	2	7	6	9	7	3	24	54	39	4.5	4	10	19	53	42	2	3	21	17	33	55		0	0
C	1992	Murphy-G Willenbrock-F Ward-RV Cockett-MI Eaton-D Docherty-AJP	The C-Terminal Domain of 72-kDa Gelatinase-A Is Not Required for Catalysis, But Is Essential for Membrane Activation and Modulates Interactions with Tissue Inhibitors of Metalloproteinases	BIOCHEMICAL JOURNAL, 1992, Vol 283, Iss MAY, pp 637-641	6	2	0	0	1	0	15			4	16	33	31	34	23	20	18	12	12	14	10	227	189	34	53	7	14	1	20	2	12	9	21	2	1	72	112	118	16.7	4	5	18	48	153	3	4	15	10	33	169		0	0
C	1992	Murphy-G Ward-R Gavrilovic-J Atkinson-S	Physiological mechanisms for metalloproteinase activation	MATRIX SUPPLEMENT, 1992, Vol 1, pp	4						21			2	2	10	15	15	8	13	6	6	6	5	6	94	78	15	7	7	2	1	9	2	2	4	5	3	7	20	42	44			7	10	32	42	3		16	9	14	55			
C	1993	Tolley-S Murphy-G Oshea-M Ward-R Docherty A Cockett-M Rawas-A Davies-G	Crystallization and Preliminary-X-Ray Analysis of a Truncated Tissue Metalloproteinase Inhibitor-Delta-128-194 Timp-2	JOURNAL OF MOLECULAR BIOLOGY, 1993, Vol 229, Iss 4, pp 1163-1164	8	4	0	1	5	0	1				2	3	1								1	7	5	1	3	0	0	0	0	0	0	0	0	0	0	4	3	6	24.93	4		2	2	3		4	2	1	1	3		0	0
C	1994	Murphy-G Willenbrock-F Crabbe-T Oshea-M Ward-R Atkinson-S Oconnell-J Docherty-A	Regulation of Matrix Metalloproteinase Activity	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1994, Vol 732, pp 31-41	8	3	0	0	0	0	6					0	0	10	12	12	12	12	9	8	9	84	70	11	3	4	3	2	8	1	4	1	8	1		12	48	34	4.1	4	4	15	30	33	2	3	15	5	18	46		0	0
C	1994	Ward-RV Atkinson-SJ Reynolds-JJ Murphy-G	Cell Surface-Mediated Activation of Progelatinase-A - Demonstration of the Involvement of the C-Terminal Domain of Progelatinase-A in Cell-Surface Binding and Activation of Progelatinase-A by Primary Fibroblasts	BIOCHEMICAL JOURNAL, 1994, Vol 304, Iss NOV, pp 263-269	4	1	0	0	1	0	4					0	4	16	12	17	7	4	4	5	1	70	56	14	18	4	5	1	8	2	3	3	11	3		21	32	49	15.7	4	2	2	17	46	3	4	4	5	8	53		0	0
C	1994	Hayakawa-T Fujimoto-N Ward-RV Iwata-K	Interaction Between Progelatinase-A and Timp-2	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1994, Vol 732, pp 389-391	4	3	1	0	2	0	0										1					1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	4.06	4				1		3			1			0	0
C	1995	Atkinson-SJ Crabbe-T Cowell-S Ward-RV Butler-MJ Sato-H Seiki-M Reynolds-JJ	Intermolecular Autolytic Cleavage Can Contribute to the Activation of Progelatinase-A by Cell-Membranes	JOURNAL OF BIOLOGICAL CHEMISTRY, 1995, Vol 270, Iss 51, pp 30479-30485	9	3	1	0	1	0	8						0	10	18	22	18	18	15	20	11	132	122	10	41	6	7	5	10	4	14	3	30	2	1	33	50	68	29.8	4	6	15	29	80	2	4	9	10	20	93		0	0
C	1996	Fujimoto-N Ward-RV Shinya-T Iwata-K Yamashita-K Hayakawa-T	Interaction Between Tissue Inhibitor of Metalloproteinases-2 and Progelatinase-A - Immunoreactivity Analyses	BIOCHEMICAL JOURNAL, 1996, Vol 313, Iss FEB, pp 827-833	6	3	1	0	3	0	1								3	1			1	1	1	7	5	1	0	0	1	0	1	0	1	0	0	0	0	1	5	4	14.9218	4		1	2	4		4	1	1		5		0	0
E	1992	Cooper-C Cushnaghan-J Kirwan-JR Dieppe-PA Rogers-J Mcalindon-T Mccrae-F	Radiographic Assessment of the Knee-Joint in Osteoarthritis	ANNALS OF THE RHEUMATIC DISEASES, 1992, Vol 51, Iss 1, pp 80-82	7	2	1	1	1	1	31			3	4	4	6	5	2	3	4	2	0	1	0	34	31	1	10	1	1	0	3	0	3	0	0	0	3	17	6	22	7.2	2	1	28	1	0	4	1	30	1	3	0		0	0
E	1992	Ismaiel-S Atkins-RM Pearse-MF Dieppe-PA Elson-CJ	Susceptibility of Normal and Arthritic Human Articular-Cartilage to Degradative Stimuli	BRITISH JOURNAL OF RHEUMATOLOGY, 1992, Vol 31, Iss 6, pp 369-373	5	4	1	1	1	1	21			0	4	3	0	2	2	3	2	2	1	1	1	21	20	1	6	1	2	0	2	0	0	0	0	2	0	12	5	9	8.3	1	2	12	2	2	3	1	12	3	4	2		0	0
E	1992	Mcalindon-TE Cooper-C Kirwan-JR Dieppe-PA	Knee Pain and Disability in the Community	BRITISH JOURNAL OF RHEUMATOLOGY, 1992, Vol 31, Iss 3, pp 189-192	4	2	1	1	1	1	58			1	3	4	7	8	4	8	4	8	8	7	5	67	60	4	14	0	11	2	1	0	0	1	5	4	1	31	17	23	8.3	1	17	43	5	0	2	1	61	6	0	0		0	0
E	1992	Mccrae-F Shouls-J Dieppe-P Watt-I	Scintigraphic Assessment of Osteoarthritis of the Knee-Joint	ANNALS OF THE RHEUMATIC DISEASES, 1992, Vol 51, Iss 8, pp 938-942	4	3	1	1	2	1	23			0	2	1	4	2	2	5	3	2	4	0	2	27	24	3	5	1	1	0	0	0	1	0	3	1	4	9	7	9	7.2	2	7	15	1	0	4	1	20	3	4	0		0	0
E	1992	Westacott-CI Taylor-G Atkins-R Elson-C	Interleukin-1-Alpha and Interleukin-1-Beta Production by Cells Isolated from Membranes Around Aseptically Loose Total Joint Replacements	ANNALS OF THE RHEUMATIC DISEASES, 1992, Vol 51, Iss 5, pp 638-642	4	3	1	1	1	1	12			0	0	2	2	4	3	4	0	2	1	2	0	20	16	3	7	0	0	0	1	0	2	0	2	0	0	13	2	8	7.2	2	8	9	3	0	0	1	16	1	3	0		0	0
E	1993	Dieppe-P Cushnaghan-J Young-P Kirwan-J	Prediction of the Progression of Joint Space Narrowing in Osteoarthritis of the Knee by Bone-Scintigraphy	ANNALS OF THE RHEUMATIC DISEASES, 1993, Vol 52, Iss 8, pp 557-563	4	2	1	1	1	1	96				0	1	12	13	15	9	11	14	10	13	10	108	87	12	11	3	6	0	0	0	12	4	4	4	13	32	34	41	7.2	2	22	63	4	2	17	1	74	12	18	4		0	0
E	1993	Hollander-AP Dieppe-PA Atkins-RM Elson-CJ	Hypothesis - Cartilage Catabolic Cofactors in Human Arthritis	JOURNAL OF RHEUMATOLOGY, 1993, Vol 20, Iss 2, pp 223-224	4	3	1	1	1	1	11				0	1	3	1	1	1	3	1	0	0	0	11	10	0	2	4	0	0	1	0	0	0	0	1	0	4	4	6	7.8	2	2	6	2	1	0	1	6	2	0	3		0	0
E	1993	Mcalindon-TE Teale-JD Dieppe-PA	Levels of Insulin Related Growth Factor-I in Osteoarthritis of the Knee	ANNALS OF THE RHEUMATIC DISEASES, 1993, Vol 52, Iss 3, pp 229-231	3	4	1	1	1	1	17				0	1	3	7	3	1	0	1	1	0	0	17	13	3	2	0	0	0	0	0	1	2	1	0	0	2	12	14	7.2	2	1	10	4	0	2	1	10	3	4	0		0	0
E	1993	Rogers-JM Dieppe-PA	Ridges and grooves on the bony surfaces of osteoarthritic joints	OSTEOARTHRITIS AND CARTILAGE, Vol 1, pp167 70	1					0																																		0						0							
E	1993	Seed-MP Ismaiel-S Cheung-CY Thomson-TA Gardner-CR Atkins-RM Elson-CJ	Inhibition of Interleukin 1-Beta Induced Rat and Human Cartilage Degradation Invitro by the Metalloproteinase Inhibitor U27391	ANNALS OF THE RHEUMATIC DISEASES, 1993, Vol 52, Iss 1, pp 37-43	7	5	1	0	2	1	21				0	6	3	5	5	3	2	0	1	0	0	25	23	2	0	5	0	2	5	0	2	2	1	1	0	8	11	19	7.2	2	2	7	6	10	0	1	6	3	3	13		0	0
E	1994	Cooper-C Mcalindon-T Snow-S Vines-K Young-P Kirwan-J Dieppe-P	Mechanical and Constitutional Risk-Factors for Symptomatic Knee Osteoarthritis - Differences Between Medial Tibiofemoral and	JOURNAL OF RHEUMATOLOGY, 1994, Vol 21, Iss 2, pp 307-313	7	3	1	1	2	1	48					1	3	8	8	2	5	9	6	7	3	52	44	6	11	5	0	1	1	0	0	1	1	2	3	22	18	22	9.2	2	13	32	4	0	3	1	41	5	6	0		0	0
E	1994	Creamer-P Sharif-M George-E Meadows-K Cushnaghan-J Shinmei-M Dieppe-P	Intra articular hyaluronic acid in osteoarthritis of the knee: an investigation into mechanisms of action	OSTEOARTHRITIS AND CARTILAGE, 1994, Vol 2, pp 133-140	7					0	20					0	1	5	1	3	1	2	3	2	2	20	17	2	12	0	1	0	0	0	1	2	0	0	3	13	1	10	8.6	0	5	10	2	0	3	0	14	3	3	0		0	0
E	1994	Cushnaghan-J Mccarthy-C Dieppe-P	Taping the Patella Medially - A New Treatment for Osteoarthritis of the Knee-Joint	BRITISH MEDICAL JOURNAL, 1994, Vol 308, Iss 6931, pp 753-755	3	2	1	1	1	1	24					0	2	2	3	3	2	5	4	4	4	29	25	2	3	7	0	1	1	0	1	1	0	0	1	10	6	10	15.5	1	14	14	0	0	1	1	28	1	0	0			
E	1994	Dieppe-P Kirwan-J	The Localization of Osteoarthritis	BRITISH JOURNAL OF RHEUMATOLOGY, 1994, Vol 33, Iss 3, pp 201-203	2	2	1			1	31					2	7	8	3	1	2	6	0	2	1	32	24	6	10	1	0	0	2	0	0	0	2	0	2	16	12	21	8.2	1	10	14	5	0	3	1	23	1	5	3		0	0
E	1994	George-G Creamer-P Dieppe-P	Clinical Subsets of Osteoarthritis	JOURNAL OF MUSCULOSKELETAL MEDICINE, 1994, Vol 11, pp 14-30	3					0																																															
E	1994	Mccarthy-C Cushnaghan-J Dieppe-P	The predictive role of scintigraphy in radiographic osteoarthritis of the hand	OSTEOARTHRITIS AND CARTILAGE, 1994, Vol 2, pp 25-28	3					0	2					0	1	0	1	0	0	0	0	1	0	3	2	0	0	0	0	0	0	0	0	0	0	0	0	3	1	2	8.6	0	0	3	0	0	0	0	2	1	0	0			
E	1994	Poole-AR Ionescu-M Swan-A Dieppe-PA	Changes in Cartilage Metabolism in Arthritis Are Reflected by Altered Serum and Synovial-Fluid Levels of the Cartilage Proteoglycan Aggrecan -	JOURNAL OF CLINICAL INVESTIGATION, 1994, Vol 94, Iss 1, pp 25-33	4	4	1	1	3	1	55					0	7	4	7	8	8	6	14	4	1	59	47	9	25	1	27	0	0	0	6	3	5	4	9	9	27	26	39.8	3	10	20	13	6	10	4	18	15	13	13		0	0
E	1994	Rogers-JM Dieppe-P	Is Tibiofemoral Osteoarthritis in the Knee-Joint a New Disease	ANNALS OF THE RHEUMATIC DISEASES, 1994, Vol 53, Iss 9, pp 612-613	2	2	1	1	2	1	9					0	1	5	2	0	0	1	1	0	0	10	8	1	2	0	1	0	0	0	1	0	1	0	1	5	3	8	10.0	2	4	4	1	1	0	1	8	1	1	0		0	0
E	1994	Swan-A Chapman-B Heap-P Seward-H Dieppe-P	Submicroscopic Crystals in Osteoarthritic Synovial-Fluids	ANNALS OF THE RHEUMATIC DISEASES, 1994, Vol 53, Iss 7, pp 467-470	5	4	1	1	3	1	19					0	0	2	1	2	3	5	2	5	0	20	13	4	1	0	0	0	0	0	2	0	0	1	0	3	11	5	10.0	2	3	12	1	1	3	1	17	0	2	1		0	0
E	1995	Dieppe-P Brandt-KD Lohmander-S Felson-DT	Detecting and Measuring Disease Modification in Osteoarthritis - The Need for Standardized Methodology	JOURNAL OF RHEUMATOLOGY, 1995, Vol 22, Iss 2, pp 201-203	4	5	1			1	16						2	7	2	0	1	1	1	2	1	17	13	1	5	0	2	0	0	0	9	0	0	0	4	1	5	12	9.2	2	3	10	1	0	3	1	13	1	3	0		0	0
E	1995	Dieppe-P	Recommended methology for assessing the progression of osteoarthritis of the hip and knee joints	OSTEOARTHRITIS AND CARTILAGE, 1995, Vol 3, pp 73-77	1					0	20						0	1	3	2	5	3	4	4	0	22	20	2	0	0	0	0	1	0	7	0	1	0	3	9	5	11	8.6	0	3	14	0	0	5	3	17	0	5	0			

Details of Paper					Authorship			Funding		Area		Citation Numbers: Number of cites by year																		Summary Figures: Citing countries														Research Level: CHI Level												Citation by Guidelines	
Case Study	Year	Authors	Title	Full Reference	# authors	# addr	# Non UK addr	ARC Ackn	# Ackn	Within ARTHR	Cites within ARTHR	90	91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	Total	N Art/Not	Cites by Reviews	Self Cites	AU	CA	CH	DE	ES	FR	IT	JP	NL	SE	UK	US	C0-4 (actual)	C0-4 (journal)	Orig Jrnl	Citing Papers 1	2	3	4	NC	Orig Jrnl	Citing Papers 1	2	3	4	NC	Any	Arth Rltd
E	1995	Lim-KKT Rogers-J Shepstone-L Dieppe-PA	The Evolutionary Origins of Osteoarthritis - A Comparative Skeletal Study of Hand Disease in 2 Primates	JOURNAL OF RHEUMATOLOGY, 1995, Vol 22, Iss 11, pp 2132-2134	4	2	1	1	2	1	4						0	2	1	0	0	0	0	2	0	5	3	2	1	0	1	0	0	0	0	0	0	0	1	2	3	3	9.2	2	0	3	1	1	0	1	3	1	1	0		0	0
E	1995	Sharif-M George-E Dieppe-PA	Correlation Between Synovial-Fluid Markers of Cartilage and Bone Turnover and Scintigraphic Scan Abnormalities in Osteoarthritis of the	ARTHRITIS AND RHEUMATISM, 1995, Vol 38, Iss 1, pp 78-81	3	2	1	1	1	1	31						2	4	6	3	4	5	4	4	2	34	27	7	6	2	3	1	0	0	2	3	0	0	3	9	12	19	21.4	2	6	17	4	1	6	2	18	8	7	1		0	0
E	1995	Sharif-M Saxne-T Shepstone-L Kirwan-JR Elson-CJ Heinegard-D Dieppe-PA	Relationship Between Serum Cartilage Oligomeric Matrix Protein-Levels and Disease Progression in Osteoarthritis of the Knee-Joint	BRITISH JOURNAL OF RHEUMATOLOGY, 1995, Vol 34, Iss 4, pp 306-310	7	5	1	1	9	1	72						1	5	12	13	7	5	11	15	6	75	63	9	16	0	6	5	9	1	9	4	5	4	15	14	30	38	8.2	1	12	41	4	6	12	1	36	19	14	6		0	0
E	1995	Sharif-M George-E Shepstone-L Knudson-W Thonar-EJMA Cushnaghan-J Dieppe-P	Serum Hyaluronic-Acid Level as a Predictor of Disease Progression in Osteoarthritis of the Knee	ARTHRITIS AND RHEUMATISM, 1995, Vol 38, Iss 6, pp 760-767	7	3	1	1	1	1	48						0	8	12	7	9	4	6	3	3	52	39	9	12	2	2	0	3	0	9	2	4	1	7	12	19	36	21.4	2	7	32	3	2	8	2	30	12	8	2		0	0
E	1996	Sharif-M George-E Dieppe-PA	Synovial-Fluid and Serum Concentrations of Aminoterminal Propeptide of Type-III Procollagen in Healthy-Volunteers and Patients with Joint Disease	ANNALS OF THE RHEUMATIC DISEASES, 1996, Vol 55, Iss 1, pp 47-51	3	2	1	1	1	1	7							0	1	3	1	0	1	0	1	7	5	2	1	0	0	0	1	0	1	1	0	0	1	1	2	5	8.3	2	1	5	1	0	0	1	5	2	0	0		0	0
E	1996	Sharif-M Osborne-DJ Meadows-K Woodhouse SM Colvin-EM Shepstone-L Dieppe-PA	The Relevance of Chondroitin and Keratan Sulfate Markers in Normal and Arthritic Synovial-Fluid	BRITISH JOURNAL OF RHEUMATOLOGY, 1996, Vol 35, Iss 10, pp 951-957	7	3	1	1	2	1	15							0	3	2	4	2	4	3	0	18	13	4	2	0	1	0	1	0	2	0	6	0	0	8	2	11	9.9	1	1	9	8	0	0	1	5	5	4	4		0	0
E	1997	Dieppe-PA Cushnaghan-J Shepstone-L	The Bristol 'OA500' study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee	OSTEOARTHRITIS AND CARTILAGE, 1997, Vol 5, Iss 2, pp87-97	1						35								2	1	2	9	10	7	5	36	28	5	0	2	0	1	0	0	6	5	2	0	0	12	15	24	10.5	0	5	23	2	0	6	3	25	3	8	0			
E	1997	Rogers-J Shepstone-L Dieppe-P	Bone Formers - Osteophyte and Enthesophyte Formation Are Positively Associated	ANNALS OF THE RHEUMATIC DISEASES, 1997, Vol 56, Iss 2, pp 85-90	3	2	1	0	0	1	6								1	0	2	3	0	1	0	7	6	0	2	0	0	0	0	0	0	0	0	0	0	4	1	6	8.3	2	0	7	0	0	0	1	6	1	0	0		0	0
E	1997	Sharif-M Elson-CJ Dieppe-PA Kirwan-JR	Elevated Serum C-Reactive Protein-Levels in Osteoarthritis	BRITISH JOURNAL OF RHEUMATOLOGY, 1997, Vol 36, Iss 1, pp 140-141	4	3	1			1	4								0	0	1	2	0	1	0	4	4	0	1	0	1	0	0	0	0	0	0	0	0	1	3	3	9.9	1	1	1	0	0	2	1	2	0	2	0		0	0
E	1997	Webb-GR Westacott-CI Elson-CJ	Chondrocyte tumor necrosis factor receptors and focal loss of cartilage in osteoarthritis	OSTEOARTHRITIS AND CARTILAGE, 1997, Vol 5, Iss 6, pp 427-437	1						12								0	1	3	3	0	4	1	12	9	2	1	0	0	0	0	0	0	0	0	0	0	5	6	7	10.5	0	0	2	1	3	6	3	1	1	7	3			
E	1997	Westacott-CI Webb-GR Warnock-MG Sims-JV Elson-CJ	Alteration of Cartilage Metabolism by Cells from Osteoarthritic Bone	ARTHRITIS AND RHEUMATISM, 1997, Vol 40, Iss 7, pp 1282-1291	5	3	1	1	3	1	34								0	3	9	8	3	7	5	35	28	3	2	0	9	0	1	0	3	4	0	1	0	7	10	23	19.9	2	1	17	13	4	0	2	13	4	13	5		0	0
E	1998	Elson-CJ Mortuza-FY Perry-MJ Warnock-MG Webb-GR Westacott-CI	Cytokines and Focal Loss of Cartilage in Osteoarthritis	BRITISH JOURNAL OF RHEUMATOLOGY, 1998, Vol 37, Iss 1, pp 106-107	6	2	1			1	6									1	0	3	1	1	0	6	5	0	4	0	0	0	1	0	0	0	0	0	0	5	1	6	11.7	1	1	2	0	0	3	1	3	0	3	0		0	0
E	1998	Pitts-SA Olomolaiye-OO Elson-CJ Westacott-CI Bidwell-JL	An Mspa1-I Polymorphism in Exon-1 of the Human TNF Receptor-Type (P55) Gene	EUROPEAN JOURNAL OF IMMUNOGENETICS, 1998, Vol 25, Iss 2-3,	5	2	1	0	2	0	4									0	1	0	2	2	3	8	7	1	1	0	0	0	0	0	0	1	1	1	0	3	2	5	3.4	3	1	3	4	0	0	3	3	2	2	1		0	0
E	1998	Pitts-SA Olomolaiye-OO Elson-CJ Westacott-CI Bidwell-JL	Identification of a Rare bG/II Polymorphism in the Promoter Region of the Human TNF Receptor-Type-I (P55) Gene	EUROPEAN JOURNAL OF IMMUNOGENETICS, 1998, Vol 25, Iss 2-3,	5	2	1	0	3	0	2									0	1	1	0	1	2	5	5	0	1	0	0	0	0	0	0	0	2	0	0	2	1	3	3.4	3	0	4	1	0	0	3	1	1	3	0		0	0
E	1998	Webb-GR Westacott-CI Elson-CJ	Osteoarthritic Synovial-Fluid and Synovium Supernatants Up-Regulate Tumor-Necrosis-Factor Receptors on Human Articular Chondrocytes	OSTEOARTHRITIS AND CARTILAGE, 1998, Vol 6, Iss 3, pp 167-176	3	2	1	1	2	1	14									0	1	4	3	5	1	14	13	0	4	0	0	0	1	0	2	2	1	0	0	4	5	13	12.0	0	1	4	1	5	3	3	4	1	4	5		0	0
E	1999	Sitara-D Olomolaiye-O Wood-N Keen-L Morse-H Elson-C Westacott-C Bidwell-J	Identification of novel single nucleotide polymorphisms in intron 1B and exon 1C of the human interleukin 1 receptor type I (IL 1RI) gene	GENES AND IMMUNITY, 1999, Vol 1, Iss 2, pp 161-3	1						0										0	1	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0.0		0	0	1	0	0		0	0	1	0			
E	2000	Cooper-C Snow-S Mcalindon-TE Kellingray-S Stuart-B Coggon-D Dieppe-PA	Risk-Factors for the Incidence and Progression of Radiographic Knee Osteoarthritis	ARTHRITIS AND RHEUMATISM, 2000, Vol 43, Iss 5, pp 995-1000	7	3	1	1	1	1	16											1	2	12	3	18	13	3	3	1	0	0	1	0	0	3	2	0	1	5	8	0	24.3	2	3	10	2	0	3	2	13	3	2	0		0	0
E	2000	Dieppe-P Cushnaghan-J Tucker-M Browning-S Shepstone-L	The Bristol Oa500 Study - Progression and Impact of the Disease After 8 Years	OSTEOARTHRITIS AND CARTILAGE, 2000, Vol 8, Iss 2, pp 63-68	5	2	1	1	1	1	6											1	1	1	3	6	5	1	0	0	0	0	1	0	0	2	0	0	0	1	4	0	12.0	0	0	3	1	0	2	3	3	1	2	0		1	1
E	2000	Kirwan-JR Elson-CJ	Is the Progression of Osteoarthritis Phasic - Evidence and Implications	JOURNAL OF RHEUMATOLOGY, 2000, Vol 27, Iss 4, pp 834-836	2	3	1			1	5											0	0	2	3	5	4	1	0	0	0	0	0	0	0	2	0	0	0	1	4	0	10.9	2	0	2	1	0	2	1	3	0	2	0		0	0
E	2000	Sharif-M Shepstone-L Elson-CJ Dieppe-PA Kirwan-JR	Increased Serum C-Reactive Protein May Reflect Events That Precede Radiographic Progression in Osteoarthritis of the Knee	ANNALS OF THE RHEUMATIC DISEASES, 2000, Vol 59, Iss 1, pp 71-74	5	5	1	0	1	1	8											1	3	2	2	8	4	1	2	0	2	0	1	0	0	0	1	0	1	2	5	0	8.5	2	1	5	0	0	2	1	4	2	2	0		0	0
E	2000	Westacott-CI Barakat-AF Wood-L Perry-MJ Neison-P Bisbinas-I Armstrong-L Millar-AB	Tumor-Necrosis-Factor-Alpha Can Contribute to Focal Loss of Cartilage in Osteoarthritis	OSTEOARTHRITIS AND CARTILAGE, 2000, Vol 8, Iss 3, pp 213-221	9	5	1	1	5	1	11											0	1	5	5	11	9	1	2	0	1	0	2	0	0	1	1	0	0	6	3	0	12.0	0	0	5	2	2	2	3	1	3	4	3		0	0
E	2002	Barakat-AF Elson-CJ Westacott-CI	Susceptibility to Physiological Concentrations of IL-1-Beta Varies in Cartilage at Different Anatomical Locations on Human Osteoarthritic Knee	OSTEOARTHRITIS AND CARTILAGE, 2002, Vol 10, Iss 4, pp 264-269	3	3	1			1	1													0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	12.0	0	0	1	0	0	0	3	0	1	0	0		0	0
E	2002	Westacott-CI Urban-JPG Goldring-MB Elson-	The Effects of Pressure on Chondrocyte Tumor-Necrosis-Factor Receptor	BIORHEOLOGY, 2002, Vol 39, Iss 1-2, pp	4	4	1			1																																		3						3						0	0
F	1990	Thomas-JT Boothandford-RP Marriott-A Kwan-APL Ayad-S Grant-ME	Isolation of cDNAs Encoding Bovine Type-X Collagen	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1990, Vol 580, Iss FEB, pp	6	2	1	0	0	0	2		3	0	0	0	0	0	0	0	0	0	0	0	0	3	3	0	1	0	0	0	0	0	0	0	0	0	0	3	0	3	4.4	4	0	0	0	3	0	3	0	0	0	3		0	0
F	1991	Hoyland-JA Thomas-JT Donn-R Marriott-A Ayad-S Boothandford-RP Grant-ME Freemont-	Distribution of Type-X Collagen Messenger-RNA in Normal and Osteoarthritic Human Cartilage	BONE AND MINERAL, 1991, Vol 15, Iss 2, pp 151-163	8	3	1	0	0	1	54		0	1	7	7	9	8	7	5	5	4	6	4	2	65	59	6	14	1	6	4	17	2	2	0	1	0	3	23	25	24	9.0	3	2	15	17	27	4	3	7	6	21	31		0	0
F	1991	Thomas-JT Cresswell-CJ Rash-B Hoyland-J Freemont-AJ Grant-ME Boothandford-RP	The Human Collagen-X Gene - Complete Primary Sequence and Reexpression in Osteoarthritis	BIOCHEMICAL SOCIETY TRANSACTIONS, 1991, Vol 19, Iss 4, pp	7	3	1	1	3	1	4		1	0	1	1	2	0	0	0	1	0	0	0	0	6	5	1	2	0	0	0	0	0	0	0	0	0	0	2	3	5	4.9	4	0	3	1	2	0	4	2	0	2	2		0	0
F	1991	Thomas-JT Kwan-APL Grant-ME Boothandford-RP	Isolation of cDNAs Encoding the Complete Sequence of Bovine Type-X Collagen - Evidence for the Condensed Nature of Mammalian Type-X	BIOCHEMICAL JOURNAL, 1991, Vol 273, Iss JAN, pp 141-148	4	2	1	0	1	0	19		8	6	9	6	5	4	2	1	1	1	1	1	0	45	41	4	10	2	5	0	6	1	2	0	1	1	0	19	15	34	16.4	4	0	2	6	37	0	4	1	0	9	35		0	0
F	1991	Thomas-JT Cresswell-CJ Rash-B Nicolai-H Jones-T Solomon-E Grant-ME Boothandford-	The Human Collagen X-Gene - Complete Primary Translated Sequence and Chromosomal Localization	BIOCHEMICAL JOURNAL, 1991, Vol 280, Iss DEC, pp 617-623	8	3	1	1	4	0	14		0	5	6	11	9	9	4	8	4	4	2	3	1	66	59	6	11	6	5	1	9	1	4	0	8	0	0	20	23	31	16.4	4	1	6	13	45	1	4	5	4	12	45		0	0
F	1992	Brass-A Kadler-KE Thomas-JT Grant-ME Boothandford-RP	The Fibrillar Collagens, Collagen-VIII, Collagen-X and the C1Q Complement Proteins Share a Similar Domain in Their C-Terminal	FEBS LETTERS, 1992, Vol 303, Iss 2-3, pp 126-128	5	2	1	0	0	0	5			0	2	5	9	5	4	7	6	3	3	3	3	50	39	11	6	8	0	1	5	3	10	1	7	1	0	14	8	21	14.5	4	1	1	6	42	0	4	1	1	5	43		0	0
F	1992	Sweetman-WA Rash-B Sykes-B Beighton-P Hecht-JT Zabel-B Thomas-JT Boothandford-R Grant-ME Wallis-GA	Sscp and Segregation Analysis of the Human Type-X Collagen Gene (Col10A1) in Heritable Forms of Chondrodysplasia	AMERICAN JOURNAL OF HUMAN GENETICS, 1992, Vol 51, Iss 4, pp 841-849	10	6	1	1	8	0	5			0	2	10	2	3	0	2	0	1	1	2	0	23	18	5	7	1	1	0	2	0	2	0	3	0	0	6	10	17	26.2	3	1	4	8	10	0	3	3	5	9	6		0	0
F	1993	Kong-RYC Kwan-KM Lau-ET Thomas-JT Boothandford-RP Grant-ME Cheah-KSE	Intron-Exon Structure, Alternative Use of Promoter and Expression of the Mouse Collagen X-Gene, Col10A-1	EUROPEAN JOURNAL OF BIOCHEMISTRY, 1993, Vol 213, Iss 1, pp	7	3	1	1	3	0	11				0	3	3	3	2	2	2	1	2	4	2	24	23	1	8	6	3	0	2	0	1	0	4	1	0	8	10	11	15.2	4	1	0	7	14	2	4	1	0	8	15		0	0
F	1993	Wallis-GA	Here today bone tomorrow. The effects of mutations of the type X collagen gene in mice and man establish a role for this extracellular matrix protein	CURRENT BIOLOGY, 1993, Vol 3, pp687-689	1					0	7				0	0	0	0	4	1	6	0	1	0	0	12	11	1	0	3	4	0	0	0	1	0	0	0	0	4	3	4	26.8	0	0	0	2	8	2	0	0	0	2	10			
F	1994	Rash-B Sweetman-W Sykes-B Thomas-T Grant-M Boothandford-R Wallis-G	7 Polymorphisms at the Col10A1 Locus	HUMAN MOLECULAR GENETICS, 1994, Vol 3, Iss 6, pp 1032-1032	7	3	1			0	0					0	0	1	0	1	0	0	0	0	0	2	2	0	1	0	0	0	1	0	1	0	0	0	0	1	1	2	20.9	4	0	1	0	1	0	3	0	2	0	0		0	0
F	1994	Thomas-JT Ayad-S Grant-ME	Cartilage Collagens - Strategies for the Study of Their Organization and Expression in the Extracellular-Matrix	ANNALS OF THE RHEUMATIC DISEASES, 1994, Vol 53, Iss 8, pp 488-496	3	2	1	0	0	1	11					0	3	3	2	0	3	1	2	1	0	15	14	1	0	0	1	1	0	0	0	0	0	1	1	7	5	8	10.0	2	1	3	4	6	1	1	5	1	3	6		0	0
F	1994	Wallis-GA Rash-B Sweetman-WA Thomas-JT Super-M Evans-G Grant-ME Boothandford-RP	Amino-Acid Substitutions of Conserved Residues in the Carboxyl-Terminal Domain of the Alpha-L(X) Chain of Type-X Collagen Occur in 2 Unrelated Families with Metaphyseal Chondrodysplasia Type Schmid	AMERICAN JOURNAL OF HUMAN GENETICS, 1994, Vol 54, Iss 2, pp 169-178	8	4	1	1	1	0	14					5	8	19	4	5	5	2	1	2	1	52	43	6	3	7	1	0	6	1	5	1	4	0	0	11	25	41	28.0	3	4	8	11	27	2	3	9	4	12	27		0	0
F	1995	Thomas-JT Sweetman-WA Cresswell-CJ Wallis-GA Grant-ME Boothandford-RP	Sequence Comparison of 3 Mammalian Type-X Collagen Promoters and Preliminary Functional-Analysis of the Human Promoter	GENE, 1995, Vol 160, Iss 2, pp 291-296	6	2	1	1	1	0	4						0	3	2	3	3	0	1	3	0	15	15	0	2	0	5	0	3	1	0	0	0	0	0	3	7	11	9.2	4	0	1	2	12	0	4	0	0	5	10		0	0
F	1996	Chambers-D Thomas-JT Boam-D Wallis-GA Grant-ME Boothandford-RP	Sequence Elements Within Intron-1 of the Human Collagen-X Gene Do Not Contribute to the Regulation of Gene-Expression	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1996, Vol 785, pp 227-230	6	2	1			0	0							0	0	0	0	0	0	2	0	2	2	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0	5.0	4	0	0	0	2	0	3	0	0	0	2		0	0
F	1996	Hillarby-MC King-KE Brady-G Grant-ME Wallis GA Boothandford-RP	Localization of Gene-Expression During Endochondral Ossification	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1996, Vol 785, pp 263-266	6	2	1			0	4							0	1	1	0	2	1	0	0	5	4	1	3	0	0	0	2	0	0	0	0	0	0	4	2	4	5.0	4	0	0	4	1	0	3	0	0	3	2		0	0
F	1996	Salo-LA Hoyland-J Ayad-S Kielty-CM Freemont-A Pirttiniemi-P Kantomaa-T Grant-	The Expression of Type-X and Type-VI Collagen and Fibrillin in Rat Mandibular Condylar Cartilage - Response to Mastication Forces	ACTA ODONTOLOGICA SCANDINAVICA, 1996, Vol 54, Iss 5, pp 295-302	9	4	1	0	1	1	2							0	1	1	0	0	0	1	2	5	5	0	0	0	0	0	0	0	0	0	2	0	0	0	1	2	2.6	2	1	1	1	2	0	1	2	0	1	2		0	0
F	1996	Wallis-GA Rash-B Sykes-B Bonaventure-J Maroteaux-P Zabel-B Wynnedavies-R Grant-ME Boothandford-RP	Mutations Within the Gene Encoding the Alpha-1(X) Chain of Type-X Collagen (Col10A1) Cause Metaphyseal Chondrodysplasia Type Schmid But Not Several Other Forms of Metaphyseal Chondrodysplasia	JOURNAL OF MEDICAL GENETICS, 1996, Vol 33, Iss 6, pp 450-457	9	6	1	1	4	0	7							1	0	5	3	6	2	3	1	21	17	3	4	7	0	2	1	0	2	1	2	0	0	5	7	15	9.9	2	2	7	3	8	1	2	6	4	3	8		0	0
F	2000	Green-H Canfield-AE Hillarby-MC Grant-ME Boothandford-RP Freemont-AJ Wallis-GA	The Ribosomal-Protein Qm Is Expressed Differentially During Vertebrate Endochondral Bone-Development	JOURNAL OF BONE AND MINERAL RESEARCH, 2000, Vol 15, Iss 6, pp 1066-	7	4	1	1	3	1	4											1	1	2	1	5	5	0	3	0	0	0	0	0	0	0	0	0	0	3	3	0	23.0	3	0	0	2	3	0	3	0	0	2	3		0	0
F	2000	Gregory-CA Zabel-B Grant-ME Boothandford-RP Wallis-GA	Equal Expression of Type-X Collagen Messenger-RNA from Mutant and Wild-Type Col10A1 Alleles in Growth-Plate Cartilage from a Patient with Metaphyseal Chondrodysplasia Type Schmid	JOURNAL OF MEDICAL GENETICS, 2000, Vol 37, Iss 8, pp 627-629	5	4	1			1	1											0	0	1	2	3	3	0	0	1	0	0	0	0	0	1	0	0	0	0	1	0	9.3	2	0	0	0	3	0	2	1	0	0	2		0	0
F	2001	Cheung-JOP Hillarby-MC Ayad-S Hoyland-JA Jones-CJP Denton-J Thomas-JT Wallis-GA	A Novel Cell-Culture Model of Chondrocyte Differentiation During Mammalian Endochondral Ossification	JOURNAL OF BONE AND MINERAL RESEARCH, 2001, Vol 16, Iss 2, pp 309-	9	5	1	0	4	1																																		3						3						0	0
F	2001	Newman-B Gigout-LL Sudre-L Grant-ME Wallis-GA	Coordinated Expression of Matrix Gla Protein Is Required During Endochondral Ossification for Chondrocyte Survival	JOURNAL OF CELL BIOLOGY, 2001, Vol 154, Iss 3, pp 659-666	5	4	1	1	3	1	2													2	4	6	4	2	1	0	1	1	0	0	2	0	1	0	0	1	3	0	53.4	4	1	1	1	3	0	4	1	1	1	3		0	0
F	2002	Chambers-D Young-DA Howard-C Thomas-JT Boam-DS Grant-ME Wallis-GA Boothandford-	An Enhancer Complex Confers Both High-Level and Cell-Specific Expression of the Human Type-X Collagen Gene	FEBS LETTERS, 2002, Vol 531, Iss 3, pp 505-508	8	2	1			0																																		4						4						0	0

Case Study	Year	Authors	Title	Full Reference	Authorship # authors	Authorship # addr	Authorship # Non UK addr	Funding ARC Ackn	Funding # Ackn	Area Within ARTHR	Area Cites within ARTHR	90	91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	Total	N Art/Not	Cites by Reviews	Self Cites	AU	CA	CH	DE	ES	FR	IT	JP	NL	SE	UK	US	C0-4 (actual)	C0-4 (journal)	CHI Level Orig Jrnl	Citing Papers 1	Citing Papers 2	Citing Papers 3	Citing Papers 4	Citing Papers NC	Orig Jrnl	Citing Papers 1	Citing Papers 2	Citing Papers 3	Citing Papers 4	Citing Papers NC	Citation by Guidelines Any	Citation by Guidelines Arth Rltd
F	2003	Cheung-JOP Grant-ME Jones-CJP Hoyland-JA Freemont-AJ Hillarby-MC	Apoptosis of Terminal Hypertrophic Chondrocytes in an in-Vitro Model of Endochondral Ossification	JOURNAL OF PATHOLOGY, 2003, Vol 201, Iss 3, pp 496-503	6	4	1			1																																		3						3						0	0
G	1993	Beynon-HLC Haskard-DO Davies-KA Haroutunian-R Walport-MJ	Combinations of Low Concentrations of Cytokines and Acute Agonists Synergize in Increasing the Permeability of Endothelial Monolayers	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 1993, Vol 91, Iss 2, pp 314-	5	2	1	0	0	1	5				0	2	1	5	3	2	0	2	3	4	1	23	21	2	3	0	0	0	2	1	1	2	1	0	1	4	13	11	11.2	2	5	6	9	3	0	3	7	4	5	7		0	0
G	1993	Davies-KA Erlendsson-K Beynon-HLC Peters-AM Steinsson-K Valdimarsson-H Walport-MJ	Splenic Uptake of Immune-Complexes in Man Is Complement-Dependent	JOURNAL OF IMMUNOLOGY, 1993, Vol 151, Iss 7, pp 3866-3873	7	3	1	1	1	1	31				0	2	8	4	3	8	1	9	6	4	1	46	35	10	21	0	0	3	0	0	2	0	0	0	3	17	15	17	30.7	3	4	12	26	4	0	4	12	4	10	20		0	0
G	1993	Tonoli-M Davies-KA Norsworthy-PJ Cohen-J Walport-MJ	The Anti-Lipid-A Antibody Ha-1A Binds to Rough Gram-Negative Bacteria, Fixes Complement and Facilitates Binding to Erythrocyte Cr-1 (Cd35)	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 1993, Vol 92, Iss 2, pp 232-	5	2	1	0	0	0	3				0	4	3	2	1	0	0	1	0	1	0	12	8	3	5	0	0	1	0	0	1	0	0	2	0	5	4	10	11.2	2	1	4	6	1	0	3	4	2	4	2		0	0
G	1994	Beynon-HLC Davies-KA Haskard-DO Walport-MJ	Erythrocyte Complement Receptor-Type-1 and Interactions Between Immune-Complexes, Neutrophils, and Endothelium	JOURNAL OF IMMUNOLOGY, 1994, Vol 153, Iss 7, pp 3160-3167	4	2	1	1	2	1	7					0	4	3	3	3	1	0	3	1	0	18	14	4	3	0	0	0	0	0	0	0	0	0	0	4	11	13	28.3	3	1	3	11	3	0	4	3	3	3	9		0	0
G	1994	Bowness-P Davies-KA Norsworthy-PJ Athanassiou-P Taylorwiedeman-J Borysiewicz-LK Meyer-PAR Walport-MJ	Hereditary C1Q Deficiency and Systemic Lupus-Erythematosus	QUARTERLY JOURNAL OF MEDICINE, 1994, Vol 87, Iss 8, pp 455-464	8	6	1	1	1	1	54					0	0	9	10	8	11	12	7	10	2	69	46	18	9	0	1	1	9	1	1	0	2	2	5	17	32	27	11.8	2	6	22	33	7	1	1	23	6	8	32		0	0
G	1994	Davies-KA Schifferli-JA Walport-MJ	Complement Deficiency and Immune-Complex Disease	SPRINGER SEMINARS IN IMMUNOPATHOLOGY, 1994, Vol 15, Iss 4, pp 397-416	3	3	1	0	0	1	15					1	0	6	6	1	4	4	3	2	1	28	26	2	6	0	0	0	1	0	0	0	0	1	0	10	13	14	12.7	2	2	4	17	4	1	3	4	1	8	15		0	0
G	1994	Davies-KA Beynon-HLC Walport-MJ	Long-Term Management After Splenectomy - Consider Prophylaxis in Systemic Lupus-Erythematosus	BRITISH MEDICAL JOURNAL, 1994, Vol 308, Iss 6921, pp 133-133	3	2	1			1	4					0	0	1	0	0	0	1	0	2	0	4	2	1	3	0	0	0	0	0	0	0	0	0	0	3	0	1	15.5	1	2	2	0	0	0	1	4	0	0	0		0	0
G	1994	Davies-KA Athanassiou-P Norsworthy-PJ Loizou-S Walport-MJ	Anti C1q antibodies in SLE	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 1994, Vol 97, Iss 2, pp28	5					0	1					0	0	1	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	1	11.4	2	1	0	0	0	0	3	1	0	0	0			
G	1994	Robson-MG Walport-MJ Davies-KA	Systemic Lupus-Erythematosus and Acute Demyelinating Polyneuropathy	BRITISH JOURNAL OF RHEUMATOLOGY, 1994, Vol 33, Iss 11, pp 1074-1077	3	2	1	0	0	1																																		1						1						0	0
G	1994	Vyse-TJ Spath-PJ Davies-KA Morley-BJ Philippe-P Athanassiou-P Giles-CM Walport-	Hereditary Complement Factor-I Deficiency	QUARTERLY JOURNAL OF MEDICINE, 1994, Vol 87, Iss 7, pp 385-401	8	4	1	0	1	1	11					2	0	6	3	0	2	4	2	1	2	22	17	5	8	0	0	3	1	1	0	1	0	1	0	8	4	11	11.8	2	3	6	10	2	1	1	6	3	5	8		0	0
G	1994	Walport-MJ Davies-KA Botto-M Naughton-MA Isenberg-DA Biasi-D Powell-RJ Cheung-NT Struthers-GR	C3 Nephritic Factor and SLE - Report of 4 Cases and Review of the Literature	QUARTERLY JOURNAL OF MEDICINE, 1994, Vol 87, Iss 10, pp 609-615	9	6	1	1	1	1	8					0	1	0	2	1	2	5	3	1	2	17	10	6	5	0	3	0	0	0	0	1	1	0	1	7	2	4	11.8	2	3	8	4	2	0	1	10	1	2	4		0	0
G	1995	Athanassiou-P Ioakimidis-D Weston-J Georganas-K Kontomerkos-T Davies-KA	Type-1 Cryoglobulinemia Associated with a Thymic Tumor - Successful Treatment with Plasma-Exchange	BRITISH JOURNAL OF RHEUMATOLOGY, 1995, Vol 34, Iss 3, pp 285-289	6	4	1	1	2	1																																		1						1						0	0
G	1995	Davies-KA Chapman-PT Norsworthy-PJ Jamar-F Athanassiou-P Keelan-ETM Harrison-AA Binns-RM Haskard-DO Walport-MJ	Clearance Pathways of Soluble Immune-Complexes in the Pig - Insights into the Adaptive Nature of Antigen Clearance in Humans	JOURNAL OF IMMUNOLOGY, 1995, Vol 155, Iss 12, pp 5760-5768	10	3	1	1	6	1	3						0	2	0	1	1	0	1	2	1	8	8	0	3	0	0	1	1	0	0	0	0	0	0	4	3	4	28.3	3	0	2	4	2	0	4	0	2	3	3		0	0
G	1995	Seelen-MA Athanassiou-P Lynn-WA Norsworthy-P Walport-MJ Cohen-J Davies-KA	The Anti-Lipid-A Monoclonal-Antibody E5 Binds to Rough Gram-Negative Bacteria, Fixes C3, and Facilitates Binding of Bacterial Immune-Complexes to Both Erythrocytes and Monocytes	IMMUNOLOGY, 1995, Vol 84, Iss 4, pp 653-661	7	3	1	1	2	1	2						0	4	0	2	1	3	0	0	0	10	7	3	2	0	1	0	1	0	1	0	2	0	0	2	1	7	12.3	3	4	4	2	0	0	4	6	2	1	1		0	0
G	1995	Wright-AH Douglass-WA Taylor-GM Lau-YL Higgins-D Davies-KA Law-SKA	Molecular Characterization of Leukocyte Adhesion Deficiency in 6 Patients	EUROPEAN JOURNAL OF IMMUNOLOGY, 1995, Vol 25, Iss 3, pp 717-722	7	6	1	0	1	0	1						0	0	1	3	2	7	4	1	1	19	16	3	10	0	0	1	0	1	1	0	0	4	0	12	7	6	24.0	3	1	4	9	4	1	4	4	1	5	9		0	0
G	1996	Bottto-M Theodoridis-E Thompson-EM Beynon-HLC Briggs-D Isenberg-DA Walport-	Fc-Gamma-Riia Polymorphism in Systemic Lupus-Erythematosus (SLE) - No Association with Disease	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 1996, Vol 104, Iss 2, pp	8	5	1	1	1	1	48							1	5	11	10	8	7	11	10	63	49	13	3	0	1	0	5	3	2	1	7	8	2	9	27	35	11.0	2	3	35	23	1	1	3	18	21	10	14		0	0
G	1996	Davies-KA	Complement, Immune-Complexes and Systemic Lupus-Erythematosus	BRITISH JOURNAL OF RHEUMATOLOGY, 1996, Vol 35, Iss 1, pp 5-23	1	2	1	1	1	1	12							0	1	4	5	3	0	2	2	17	10	7	0	0	0	0	2	0	0	0	1	1	0	6	5	13	9.9	1	4	6	7	0	0	1	9	1	0	7		0	0
G	1996	Hogarth-MB Norsworthy-PJ Allen-PJ Trinder-PKE Loos-M Morley-BJ Walport-MJ Davies-	Autoantibodies to the Collagenous Region of C1Q Occur in 3 Strains of Lupus-Prone Mice	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 1996, Vol 104, Iss 2, pp	8	3	1	1	3	1	5							0	0	1	0	0	3	2	1	7	4	3	2	0	0	0	0	0	0	0	0	3	0	2	3	1	11.0	2	0	1	6	0	0	3	1	0	1	5		0	0
G	1996	Vyse-TJ Morley-BJ Bartok-I Theodoridis-EL Davies-KA Webster-ADB Walport-MJ	The Molecular-Basis of Hereditary Complement Factor-I Deficiency	JOURNAL OF CLINICAL INVESTIGATION, 1996, Vol 97, Iss 4, pp 925-933	7	3	1	1	2	1	1							1	1	4	2	2	3	1	1	15	12	3	0	0	2	1	3	1	0	0	0	0	0	2	3	10	40.1	3	1	3	6	3	2	4	2	2	4	7		0	0
G	1996	Walport-MJ Davies-KA	Complement and Immune-Complexes	RESEARCH IN IMMUNOLOGY, 1996, Vol 147, Iss 2, pp 103-109	2	2	1	0	0	1	4							0	0	3	3	1	2	2	0	11	9	2	2	3	0	1	0	0	0	0	0	0	0	2	4	7	7.3	3	1	0	9	1	0	4	1	1	3	6		0	0
G	1996	Mitchell-TJ Naughton-M Norsworthy-P Davies-KA Walport-MJ Morley-BJ	IFN-Gamma Up-Regulates Expression of the Complement Components C3 and C4 by Stabilization of Messenger-RNA	JOURNAL OF IMMUNOLOGY, 1996, Vol 156, Iss 11, pp 4429-4434	6	2	1	1	2	1	3							0	2	4	5	5	2	3	0	21	18	3	2	1	0	2	2	0	0	1	2	0	0	3	13	16	28.6	3	0	2	14	5	0	4	0	0	3	18		0	0
G	1997	Walport-MJ Davies-KA Morley-BJ Botto-M	Complement Deficiency and Autoimmunity	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1997, Vol 815, pp 267-281	4	2	1			1	18								0	3	5	6	3	7	6	30	19	10	3	1	1	0	3	0	1	1	0	1	1	8	15	17	5.0	4	4	10	12	4	0	3	8	3	6	13		0	0
G	1998	Cutler-AJ Botto-M Vanessen-D Rivi-R Davies-KA Gray-D Walport-MJ	T-Cell-Dependent Immune-Response in C1Q-Deficient Mice - Defective Interferon-Gamma Production by Antigen-Specific T-Cells	JOURNAL OF EXPERIMENTAL MEDICINE, 1998, Vol 187, Iss 11, pp 1789-1797	7	4	1	1	2	1	12									2	0	9	10	10	3	34	23	11	10	1	0	3	4	0	2	0	0	0	1	15	14	31	59.1	3	2	3	26	3	0	4	4	3	3	24		0	0
G	1998	Devi-BS Vannoordin-S Krausz-T Davies-KA	Peripheral-Blood Lymphocytes in SLE - Hyperexpression of Cd154 on T-Lymphocytes and B-Lymphocytes and Increased Number of Double-	JOURNAL OF AUTOIMMUNITY, 1998, Vol 11, Iss 5, pp 471-475	4	3	1	0	0	1	13									0	3	5	3	5	2	18	10	8	0	0	0	0	0	0	0	1	0	0	0	0	15	16	8.7	3	0	5	9	3	1	3	3	3	3	9		0	0
G	1998	Hogarth-MB Slingsby-JH Allen-PJ Thompson-EM Chandler-P Davies-KA Simpson-E Morley-BJ Walport-MJ	Multiple Lupus Susceptibility Loci Map to Chromosome-1 in Bxsb Mice	JOURNAL OF IMMUNOLOGY, 1998, Vol 161, Iss 6, pp 2753-2761	9	4	1	1	5	1	18									0	5	6	8	4	5	28	18	10	4	1	2	1	0	0	1	1	2	0	3	8	15	23	27.5	3	1	3	18	5	1	4	1	3	4	20		0	0
G	1998	Walport-MJ Davies-KA Botto-M	Clq and Systemic Lupus-Erythematosus	IMMUNOBIOLOGY, 1998, Vol 199, Iss 2, pp	3	2	1	0	0	1	39									0	7	22	21	11	4	65	33	23	4	0	1	2	5	0	5	1	2	5	2	18	21	61	12.0	3	8	20	29	7	1	4	20	8	7	30		0	0
G	1999	Norsworthy-P Theodoridis-E Botto-M Athanassiou-P Beynon-H Gordon-C Isenberg-D Walport-MJ Davies-KA	Overrepresentation of the Fc-Gamma Receptor-Type Iia R131/R131 Genotype in Caucasoid Systemic-Lupus-Erythematosus Patients with Autoantibodies to C1Q and Glomerulonephritis	ARTHRITIS AND RHEUMATISM, 1999, Vol 42, Iss 9, pp 1828-1832	9	5	1	1	1	1	25										0	5	7	10	7	29	23	5	5	0	0	0	1	0	0	0	0	6	2	7	13	29	24.3	2	4	16	8	1	0	2	12	10	2	5		0	0
G	2000	Davies-KA Norsworthy-P	Autoantibodies to complement components	METHODS IN MOLECULAR BIOLOGY, 2000, Vol 150, pp173-192	2					0																																														
G	2000	Nash-JT Davies-KA	Complement and immune complexes	METHODS IN MOLECULAR BIOLOGY, 2000, Vol 150, pp203-214	2					0																																														
G	2001	Nash-JT Taylor-PR Botto-M Norsworthy-PJ Davies-KA Walport-MJ	Immune-Complex Processing in C1Q-Deficient Mice	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 2001, Vol 123, Iss 2, pp	6	2	1	1	3	1	5													4	2	8	7	0	2	1	1	1	1	0	0	0	0	0	0	2	4	0	10.6	2	0	2	3	2	1	3	1	0	3	4		0	0
G	2002	Botto-M Walport-MJ	C1Q, Autoimmunity and Apoptosis	IMMUNOBIOLOGY, 2002, Vol 205, Iss 4-5, pp 395-406	2	2	1			1	0													0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	12.0	3	0	1	0	0	0	4	0	0	1	0		0	0
G	2002	Davies-KA Robson-MG Peters-AM Norsworthy P Nash-JT Walport-MJ	Defective Fc-Dependent Processing of Immune-Complexes in Patients with Systemic-Lupus-Erythematosus	ARTHRITIS AND RHEUMATISM, 2002, Vol 46, Iss 4, pp 1028-1038	6	2	1			1	4													1	4	5	4	1	0	0	0	0	0	0	0	0	1	0	1	1	1	0	24.3	2	0	4	1	0	0	2	2	1	2	0		0	0
H	1994	Akbar-AN Savill-J Gombert-W Bofill-M Borthwick-NJ Whitelaw-F Grundy-J Janossy-G	The Specific Recognition by Macrophages of CD8(+),Cd45Ro(+) T-Cells Undergoing Apoptosis - A Mechanism for T-Cell Clearance During	JOURNAL OF EXPERIMENTAL MEDICINE, 1994, Vol 180, Iss 5, pp 1943-1947	9	5	1	1	4	1	13					0	7	12	13	5	4	7	3	5	1	57	49	8	24	0	0	1	4	0	3	3	2	0	0	28	23	37	62.2	3	1	6	38	12	0	4	4	5	10	38		0	0
H	1994	Bofill-M Akbar-AN Salmon-M Robinson-M Burford-G Janossy-G	Immature CD45RA(Low)Ro(Low) T-Cells in the Human Cord-Blood .1. Antecedents of CD45RA(+) Unprimed T-Cells	JOURNAL OF IMMUNOLOGY, 1994, Vol 152, Iss 12, pp 5613-5623	6	3	1	1	3	1	3					1	6	5	5	7	5	7	3	2	1	42	37	5	4	0	4	1	3	1	6	5	3	2	1	12	7	24	28.3	3	0	12	26	4	0	4	9	7	10	16		0	0
H	1994	Salmon-M Pilling-D Borthwick-NJ Viner-N Janossy-G Bacon-PA Akbar-AN	The Progressive Differentiation of Primed T-Cells Is Associated with an Increasing Susceptibility to Apoptosis	EUROPEAN JOURNAL OF IMMUNOLOGY, 1994, Vol 24, Iss 4, pp 892-899	7	3	1	1	4	1	36					11	17	37	20	16	15	20	8	6	5	155	125	27	29	5	7	3	12	2	11	11	7	5	1	61	46	101	24.0	3	5	15	114	21	0	4	14	8	33	100		0	0
H	1996	Akbar-AN Borthwick-NJ Wickremasinghe-RG Panayiotidis-P Pilling-D Bofill-M Krajewski-S Reed-JC Salmon-M	Interleukin-2 Receptor Common Gamma-Chain Signaling Cytokines Regulate Activated T-Cell Apoptosis in Response to Growth-Factor Withdrawal - Selective Induction of Anti-Apoptotic (Bcl-2, Bcl-X(L)) But Not	EUROPEAN JOURNAL OF IMMUNOLOGY, 1996, Vol 26, Iss 2, pp 294-299	9	5	1	1	5	1	31							4	30	44	33	27	28	20	16	202	181	20	30	8	2	7	15	7	29	18	14	1	1	45	78	138	21.0	3	2	19	132	48	1	4	5	14	44	139		0	0
H	1996	Gombert-W Borthwick-NJ Wallace-DL Hyde-H Bofill-M Pilling-D Beverley-PCL Janossy-G Salmon-M Akbar-AN	Fibroblasts Prevent Apoptosis of IL-2-Deprived T-Cells Without Inducing Proliferation - A Selective Effect on Bcl-X(L) Expression	IMMUNOLOGY, 1996, Vol 89, Iss 3, pp 397-404	10	4	1	1	3	1	11							0	6	6	5	10	6	1	2	36	28	5	15	1	0	0	3	0	2	0	0	0	0	18	8	27	10.8	3	2	4	22	7	1	4	6	2	7	21		0	0
H	1996	Pilling-D Akbar-AN Bacon-PA Salmon-M	CD4(+) CD45RA(+) T-Cells from Adults Respond to Recall Antigens After Cd28 Ligation	INTERNATIONAL IMMUNOLOGY, 1996, Vol 8, Iss 11, pp 1737-1742	4	3	1	1	2	1	6							0	1	2	10	5	6	6	0	30	24	5	4	0	1	0	3	1	0	1	0	1	0	20	8	18	13.1	3	2	4	22	2	0	4	3	3	7	17		0	0
H	1997	Borthwick-NJ Akbar-AN Maccormac-LP Lowdell-M Craigen-JL Hassan-I Grundy-JE Salmon-M Yong-KL	Selective Migration of Highly Differentiated Primed T-Cells, Defined by Low Expression of Cd45Rb, Across Human Umbilical Vein Endothelial-Cells - Effects of Viral-Infection on Transmigration	IMMUNOLOGY, 1997, Vol 90, Iss 2, pp 272-280	9	4	1	0	3	1	5								2	2	2	1	4	0	1	12	11	1	3	0	0	0	2	0	0	0	0	0	0	4	6	11	10.8	3	0	5	5	2	0	4	3	3	0	6		0	0
H	1997	Hyde-H Borthwick-NJ Janossy-G Salmon-M Akbar-AN	Up-Regulation of Intracellular Glutathione by Fibroblast-Derived Factor(S) - Enhanced Survival of Activated T-Cells in the Presence of Low Bcl-2	BLOOD, 1997, Vol 89, Iss 7, pp 2453-2460	5	3	1	1	2	1	1								0	3	1	7	3	1	1	16	12	4	2	0	0	1	1	3	0	0	1	1	1	3	3	14	31.2	3	0	1	8	7	0	3	1	2	5	8		0	0

Case Study	Year	Authors	Title	Full Reference	Authorship # authors	Authorship # addr	Authorship # Non UK addr	Funding ARC Ackn	Funding # Ackn	Area Within ARTHR	Area Cites within ARTHR	90	91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	Total	N Art/Not	Cites by Reviews	Self Cites	AU	CA	CH	DE	ES	FR	IT	JP	NL	SE	UK	US	C0-4 (actual)	C0-4 (journal)	CHI Level Orig Jrnl	CHI Citing Papers 1	2	3	4	NC	Citing Papers Orig Jrnl	Citing Papers 1	2	3	4	NC	Citation by Guidelines Any	Arth Rltd
H	1997	Salmon-M Scheeltoellner-D Huissoon-AP Pilling-D Shamsadeen-N Hyde-H Dangeac-AD Bacon-PA Emery-P Akbar-AN	Inhibition of T-Cell Apoptosis in the Rheumatoid Synovium	JOURNAL OF CLINICAL INVESTIGATION, 1997, Vol 99, Iss 3, pp 439-446	10	4	1	1	3	1	46								3	9	14	19	15	11	7	78	59	14	17	3	2	3	6	1	7	4	7	6	0	25	23	60	40.1	3	6	19	39	12	2	4	15	12	12	39		0	0
H	1998	Orteu-CH Poulter-LW Rustin-MHA Sabin-CA Salmon-M Akbar-AN	The Role of Apoptosis in the Resolution of T-Cell-Mediated Cutaneous Inflammation	JOURNAL OF IMMUNOLOGY, 1998, Vol 161, Iss 4, pp 1619-1629	6	5	1	0	2	1	6									0	3	10	10	5	2	30	28	0	11	0	0	0	3	0	5	1	2	3	1	16	2	28	27.5	3	1	7	17	5	0	4	4	1	10	15		0	0
H	1998	Soares-MVD Borthwick-NJ Maini-MK Janossy-G Salmon-M Akbar-AN	IL-7-Dependent Extrathymic Expansion of CD45RA(+) T-Cells Enables Preservation of a Naive Repertoire	JOURNAL OF IMMUNOLOGY, 1998, Vol 161, Iss 11, pp 5909-5917	6	5	1	0	3	1	8									0	3	9	15	18	10	55	50	4	4	1	0	2	3	1	9	3	0	1	0	8	28	45	27.5	3	1	8	41	5	0	4	4	5	23	23		0	0
H	1999	Bird-IN Taylor-V Newton-JP Spragg-JH Simmons-DL Salmon-M Buckley-CD	Hemophilic Pecam-1(Cd31) Interactions Prevent Endothelial-Cell Apoptosis But Do Not Support Cell Spreading or Migration	JOURNAL OF CELL SCIENCE, 1999, Vol 112, Iss 12, pp 1989-1997	7	4	1	1	4	1	1										1	3	5	6	7	22	15	7	1	1	1	3	3	1	0	1	2	0	0	2	11	22	22.2	4	0	2	10	8	2	4	0	3	7	12		0	0
H	1999	Buckley-CD Pilling-D Henriquez-NV Parsonage-G Threlfall-K Scheeltoellner-D Simmons-DL Albar-AN Lord-JM Salmon-M	RGD Peptides Induce Apoptosis by Direct Caspase-3 Activation	NATURE, 1999, Vol 397, Iss 6719, pp 534-539	10	6	1	1	5	0	11										15	29	24	26	19	113	79	30	5	2	8	1	7	5	5	5	13	4	1	12	56	113	100.6	4	5	15	35	54	4	4	13	9	22	69		0	0
H	1999	Faint-JM Pilling-D Akbar-AN Kitas-GD Bacon-PA Salmon-M	Quantitative Flow-Cytometry for the Analysis of T-Cell Receptor V-Beta Chain Expression	JOURNAL OF IMMUNOLOGICAL METHODS, 1999, Vol 225, Iss 1-2, pp 53-60	6	3	1	1	1	1	0										0	0	0	0	2	2	2	0	0	0	1	0	0	0	0	0	0	0	0	0	2	2	8.8	3	0	0	2	0	0	4	0	1	0	1		0	0
H	1999	Pilling-D Akbar-AN Girdlestone-J Orteu-CH Borthwick-NJ Amft-N Scheeltoellner-D Buckley	Interferon-Beta Mediates Stromal Cell Rescue of T-Cells from Apoptosis	EUROPEAN JOURNAL OF IMMUNOLOGY, 1999, Vol 29, Iss 3, pp 1041-1050	9	3	1	1	6	0	18										4	20	18	5	9	56	47	9	21	1	0	0	6	0	5	1	5	1	2	32	9	56	22.5	3	3	10	33	9	1	4	7	6	11	32		0	0
H	1999	Scheeltoellner-D Pilling-D Akbar-AN Hardie-D Lombardi-G Salmon-M Lord-JM	Inhibition of T-Cell Apoptosis by IFN-Beta Rapidly Reverses Nuclear Translocation of Protein-Kinase C-Delta	EUROPEAN JOURNAL OF IMMUNOLOGY, 1999, Vol 29, Iss 8, pp 2603-2612	7	4	1	1	3	0	8										1	16	6	9	9	41	33	8	17	2	1	0	4	0	5	1	1	1	1	21	11	41	22.5	3	0	4	18	19	0	4	0	1	9	31		0	0
H	1999	Shields-PL Morland-CM Salmon-M Qin-SX Hubscher-SG Adams-DH	Chemokine and Chemokine Receptor Interactions Provide a Mechanism for Selective T-Cell Recruitment to Specific Liver Compartments Within	JOURNAL OF IMMUNOLOGY, 1999, Vol 163, Iss 11, pp 6236-6243	6	4	1	1	7	1	6										0	9	26	25	27	87	64	16	11	7	4	1	13	2	4	8	13	2	1	18	28	87	27.5	3	2	34	40	11	0	4	10	15	27	35		0	0
H	2000	Buckley-CD Amft-N Bradfield-PF Pilling-D Ross-E Arenzanaseisdedos-F Amara-A Curnow-SJ Lord-JM Scheeltoellner-D Salmon-	Persistent Induction of the Chemokine Receptor Cxcr4 by TGF-Beta-1 on Synovial T-Cells Contributes to Their Accumulation Within the Rheumatoid Synovium	JOURNAL OF IMMUNOLOGY, 2000, Vol 165, Iss 6, pp 3423-3429	11	3	1	1	6	1	20											0	13	18	8	39	30	7	5	0	3	0	4	3	1	3	5	0	0	12	16	0	27.5	3	2	11	21	4	1	4	5	6	6	22		0	0
H	2000	Lombardi-G Dunne-PJ Scheeltoellner-D Sanyal-T Pilling-D Taams-LS Life-P Lord-JM Salmon-M Akbar-AN	Type-1 IFN Maintains the Survival of Anergic CD4(+) T-Cells	JOURNAL OF IMMUNOLOGY, 2000, Vol 165, Iss 7, pp 3782-3789	10	5	1	1	7	0	5											0	3	6	4	13	11	2	3	0	0	0	0	0	2	0	1	2	0	5	4	0	27.5	3	2	3	7	1	0	4	3	0	2	8		0	0
H	2001	Plunkett-FJ Soares-MVD Annels-N Hislop-A Ivory-K Lowdell-M Salmon-M Rickinson-A	The Flow Cytometric Analysis of Telomere Length in Antigen-Specific CD8(+) T-Cells During Acute Epstein-Barr-Virus Infection	BLOOD, 2001, Vol 97, Iss 3, pp 700-707	9	6	1	0	2	1	1													10	7	21	14	4	2	0	2	1	3	0	0	1	0	1	0	5	9	0	30.4	3	0	1	17	3	0	3	1	1	11	8		0	0
I	1992	Jones-A Maddison-P Doherty-M	Teaching Rheumatology to Medical-Students - Current Practice and Future Aims	JOURNAL OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON, 1992, Vol 26, Iss 1, pp 41-43	3	1	0	1	2	1	5			0	0	0	1	1	0	0	1	1	0	2	0	6	5	0	0	0	0	0	0	0	0	0	0	0	0	6	0	2	3.0	1	4	2	0	0	0	1	6	0	0	0		0	0
I	1992	Jones-A Hopkinson-N Pattrick-M Berman-P Doherty-M	Evaluation of a Method for Clinically Assessing Osteoarthritis of the Knee	ANNALS OF THE RHEUMATIC DISEASES, 1992, Vol 51, Iss 2, pp 243-245	5	2	0	1	2	1	8			0	2	0	3	0	1	2	1	0	0	0	1	10	9	1	4	0	0	0	1	0	0	0	0	0	1	8	1	5	7.2	2	3	7	0	0	0	1	9	1	0	0		0	0
I	1992	Jones-AC Chuck-AJ Arie-EA Green-DJ Doherty-M	Diseases Associated with Calcium Pyrophosphate Deposition Disease	SEMINARS IN ARTHRITIS AND RHEUMATISM, 1992, Vol 22, Iss 3, pp 188-	5	3	0	1	1	1	29			0	1	3	5	5	3	4	3	2	3	3	2	34	26	6	5	2	1	1	2	4	2	2	1	3	0	6	15	14	9.0	2	2	21	7	3	1	1	21	6	5	2		0	0
I	1992	Cope-AP Aderka-D Doherty-M Engelmann-H Gibbons-D Jones-AC Brennan-FM Maini-RN Wallach-D Feldmann-M	Increased Levels of Soluble Tumor-Necrosis-Factor Receptors in the Sera and Synovial-Fluid of Patients with Rheumatic Diseases	ARTHRITIS AND RHEUMATISM, 1992, Vol 35, Iss 10, pp 1160-1169	10	4	1	1	3	1	120			1	8	20	32	28	13	16	20	16	8	12	10	184	142	35	38	7	7	5	10	1	6	7	12	17	2	43	46	89	19.9	2	21	81	70	9	3	2	78	26	23	57		0	0
I	1992	Jones-AC Doherty-M	The Treatment of Osteoarthritis	BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, 1992, Vol 33, Iss 4, pp	2	1	0	1	1	1	8				1	1	2		2		1	1		2	1	11	7	2	0	1	2	0	0	0	0	0	0	0	0	5	4	4	8.68	2	3	3	5			1	7		1	3		0	0
I	1992	Jones-AC Berman-P Doherty-M	Nonsteroidal Antiinflammatory Drug Usage and Requirement in Elderly Acute Hospital Admissions	BRITISH JOURNAL OF RHEUMATOLOGY, 1992, Vol 31, Iss 1, pp 45-48	3	2	0	0	0	1	19			1	3	3	3	3	1	2	1		2	2	1	22	16	4	2	2	2	0	0	0	0	1	0	0	0	6	10	13	8.26	1	6	14		1	1	1	21			1		0	0
I	1993	Jones-A Regan-M Ledingham-J Pattrick-M Manhire-A Doherty-M	Importance of Placement of Intraarticular Steroid Injections	BRITISH MEDICAL JOURNAL, 1993, Vol 307, Iss 6915, pp 1329-1330	6	2	1	1	1	1	40				0	0	1	7	5	4	4	5	6	4	13	49	38	5	2	3	6	0	2	1	5	1	0	4	2	16	6	13	13.6	1	16	28	1	0	4	1	43	4	2	0		0	0
I	1993	Jones-AC Ledingham-J Mcalindon-T Regan-M Hart-D Macmillan-PJ Doherty-M	Radiographic Assessment of Patellofemoral Osteoarthritis	ANNALS OF THE RHEUMATIC DISEASES, 1993, Vol 52, Iss 9, pp 655-658	7	3	0	1	1	1	23				0	0	2	6	2	4	2	3	0	2	2	23	22	1	10	1	1	0	1	0	1	0	0	1	5	12	1	10	7.2	2	4	17	0	0	2	1	21	0	2	0		0	0
I	1993	Samanta-A Jones-A Regan-M Wilson-S Doherty-M	Is Osteoarthritis in Women Affected by Hormonal Changes or Smoking	BRITISH JOURNAL OF RHEUMATOLOGY, 1993, Vol 32, Iss 5, pp 366-370	5	3	0	1	1	1	48				0	0	2	6	6	4	8	4	7	7	8	52	39	10	0	4	1	0	3	0	1	0	0	0	3	11	25	14	8.3	1	12	33	1	0	6	1	40	10	2	0		0	0
I	1996	Jones-A Doherty-M	Intraarticular Corticosteroids Are Effective in Osteoarthritis But There Are No Clinical Predictors of Response	ANNALS OF THE RHEUMATIC DISEASES, 1996, Vol 55, Iss 11, pp 829-832	2	1	0	0	0	1	29							0	3	2	2	6	5	2	9	29	25	3	5	0	4	2	2	2	8	2	0	3	3	9	10	13	8.3	2	8	17	1	1	2	1	23	4	0	2		0	0
I	2002	Jones-AC Coulson-L Muir-K Tolley-K Lophatananon-A Everitt-L Pringle-M Doherty-	A Nurse-Delivered Advice Intervention Can Reduce Chronic Nonsteroidal Antiinflammatory Drug-Use in General-Practice - A Randomized Controlled	RHEUMATOLOGY, 2002, Vol 41, Iss 1, pp 14-21	8	2	0	0	1	1	0													1		1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0		0	1		1				1	1					0	0
J	1993	Beard-DJ Kyberd-PJ Fergusson-CM Dodd-CAF	Proprioception After Rupture of the Anterior Cruciate Ligament - An Objective Indication of the Need for Surgery	JOURNAL OF BONE AND JOINT SURGERY-BRITISH VOLUME, 1993, Vol	4	2	0	0	3	0	8				0	4	2	5	2	3	10	5	11	6	7	55	50	3	4	3	4	2	5	1	0	1	7	1	3	10	17	13	6.2	1	21	13	7	2	12	1	47	3	4	1		0	0
J	1994	Beard-DJ Kyberd-PJ Oconnor-JJ Fergusson-CM Dodd-CAF	Reflex Hamstring Contraction Latency in Anterior Cruciate Ligament Deficiency	JOURNAL OF ORTHOPAEDIC RESEARCH, 1994, Vol 12, Iss 2, pp 219-	5	6	0	0	3	0	4					1	0	3	2	2	4	2	6	2	3	25	20	4	3	1	3	0	1	0	0	0	3	1	0	4	13	8	7.5	2	11	4	2	1	7	3	22	0	3	0		0	0
J	1994	Beard-DJ Dodd-CAF Trundle-HR Simpson-AHRW	Proprioception Enhancement for Anterior Cruciate Ligament Deficiency - A Prospective Randomized Trial of 2 Physiotherapy Regimes	JOURNAL OF BONE AND JOINT SURGERY-BRITISH VOLUME, 1994, Vol	4	2	0	1	2	0																																	0.8	1						1						0	0
J	1994	Beard-DJ Dodd-CAF Zavatsky-AB Murray-DW Dowdall-MJ O'Connor-JJ	Is leg lifting in full extension safe following anterior cruciate ligament reconstruction?	PHYSIOTHERAPY, 1994, Vol 80, Iss 7 pp437-8	1																																							0.0														
J	1994	Zavatsky-AB Beard-DJ O'Connor-JJ	Cruciate ligament loading during isometric muscle contractions: A theoretical basis for rehabilitation	AMERICAN JOURNAL OF SPORTS MEDICINE, 1994, Vol 22, Iss 3, pp418-23	2						1					0	0	1	0	1	2	0	1	1	0	6	5	1	2	0	0	0	0	0	0	0	0	0	1	3	2	2	8.4	0	2	2	0	1	1	0	4	1	1	0			
J	1996	Ainslie-T Beard-DJ	Quantification of quadriceps passive resistance using isokinetic dynamometry.	PHYSIOTHERAPY, 1996, Vol 82, pp628-630.	2																																																					
J	1996	Beard-DJ Soundarapandian-RS O'Connor-JJ Dodd-CAF	Gait and electromyographic analysis of anterior cruciate ligament deficient subjects.	GAIT & POSTURE, 1996, Vol 4, pp83-88.	1						0							0	0	2	1	0	2	0	6	11	11	0	1	0	3	0	1	0	0	1	0	0	2	1	4	3	4.0	0	1	0	1	3	6	1	8	3	0	0			
J	1997	Esposito-IJ- Beard-DJ Dodd-CAF Shafigan-B	Rehabilitation following patellar tendon or ABC prosthetic ligament reconstruction for chronic anterior cruciate ligament deficient knees..	KNEE, 1997, Vol 4, pp81-86	2																																							0.0	0													
J	1997	Wallace-DA Beard-DJ Gill-RHS Carr-AJ	Reflex Muscle-Contraction in Anterior Shoulder Instability	JOURNAL OF SHOULDER AND ELBOW SURGERY, 1997, Vol 6, Iss 2, pp 150-155	4	2	0			0	1								0	0	0	0	0	1	3	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0.0	0	0	1	0	0	3	1	3	1	0	0		0	0
J	1998	Beard-DJ	Home or supervised rehabilitation following anterior cruciate ligament reconstruction: a randomised controlled trial	JOURNAL OF ORTHOPAEDIC & SPORTS PHYSICAL THERAPY	1																																							0.0	0						0							
J	2000	Beard-DJ Dodd-CAF Simpson-HARW	Sensorimotor Changes After Anterior Cruciate Ligament Reconstruction	CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, 2000, Iss 372, pp	3	2	1	1	1	0																																		0.4	2						1						0	0
J	2001	Beard-DJ Anderson-JL Davies-S Price-AJ Dodd-CA	Hamstring vs patella tendon for anterior cruciate ligament reconstruction a randomised controlled trial	KNEE, 2001, Vol 8, Iss 1, pp45-50	1						2												0	1	1	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0.0	0	2	0	0	0	0		2	0	0	0			
J	2002	Anderson-JL Lamb-SE Barker-KL Davies-S Dodd-CA Beard-DJ	Changes in Muscle Torque Following Anterior Cruciate Ligament Reconstruction - A Comparison Between Hamstrings and Patella Tendon	ACTA ORTHOPAEDICA SCANDINAVICA, 2002, Vol 73, Iss 5, pp 546-552	6	3	0			0																																		4.0	1						1						0	0
K	1995	Rai-RS Clifford-K Cohen-H Regan-L	High Prospective Fetal Loss Rate in Untreated Pregnancies of Women with Recurrent Miscarriage and Antiphospholipid Antibodies	HUMAN REPRODUCTION, 1995, Vol 10, Iss 12, pp 3301-3304	4	2	0	1	2	1	35							2	8	7	8	11	9	6	2	53	39	10	14	1	1	0	0	5	6	3	2	1	0	22	6	25	10.83	2	9	30	12	1	1	2	28	17	6	2		0	0
K	1997	Rai-R Cohen-H Dave-M Regan-L	Randomized Controlled Trial of Aspirin and Aspirin Plus Heparin in Pregnant-Women with Recurrent Miscarriage Associated with Phospholipid Antibodies (or Antiphospholipid Antibodies)	BRITISH MEDICAL JOURNAL, 1997, Vol 314, Iss 7076, pp 253-257	4	2	0	1	1	1	110								15	27	31	29	38	39	27	206	145	34	24	7	11	0	5	10	16	13	4	7	1	80	39	140	17.3	1	49	105	39	6	7	1	138	46	18	4		1	1
K	1997	Rai-R	Obstetric complications of antiphospholipid antibodies								5										1		4	3	3	11	11	0	2	0	1	0	1	0	2	1	0	1	0	4	1	5	0	0	4	3	2	1	1	0	6	3	1	1			
K	1998	Rai-R Regan-L	Antiphospholipid Syndrome and Pregnancy Loss	HOSPITAL MEDICINE, 1998, Vol 59, Iss 8, pp 637-639	2	2	0	0	0	1	1										1	1		1	2	5	2	3	1	2	1	0	0	0	0	0	0	0	0	2	0	3	0	1	1	2		2		1	3	1		1		0	0
K	1999	Backos-M Rai-R Baxter-N Chilcott-IT Cohen-H Regan-L	Pregnancy Complications in Women with Recurrent Miscarriage Associated with Antiphospholipid Antibodies Treated with Low-Dose Aspirin	BRITISH JOURNAL OF OBSTETRICS AND GYNAECOLOGY, 1999, Vol 106, Iss 2, pp	6	2	0	0	0	1	24										2	6	17	10	7	42	31	11	10	0	0	0	1	3	5	4	2	0	0	20	4	42	11.7	2	10	16	14	1	1	1	26	8	8	0		0	0
K	1999	Backos-M Rai-R Thomas-E Murphy-M Dore-C Ragan-L	Bone-Density Changes in Pregnant-Women Treated with Heparin - A Prospective, Longitudinal-Study	HUMAN REPRODUCTION, 1999, Vol 14, Iss 11, pp 2876-2880	6	4	0	0	0	0	6											2	2	4	3	11	9	1	3	0	0	0	0	0	1	1	0	0	1	5	2	11	10.67	2	2	4	5			2	5	2	3	1		0	0
K	2003	Sebire-NJ Backos-M Elgaddal-S Goldin-RD Regan-L	Placental Pathology, Antiphospholipid Antibodies, and Pregnancy Outcome in Recurrent Miscarriage Patients	OBSTETRICS AND GYNECOLOGY, 2003, Vol 101, Iss 2, pp 258-263	5	2	0			1	0														1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0		9.19	1	1					1	1					0	0

Case Study	Year	Authors	Title	Full Reference	Authorship # authors	# addr	# Non UK addr	Funding ARC Ackn	# Ackn	Area Within ARTHR	Cites within ARTHR	90	91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	Total	N Art/Not	Cites by Reviews	Self Cites	AU	CA	CH	DE	ES	FR	IT	JP	NL	SE	UK	US	C0-4 (actual)	C0-4 (journal)	CHI Level Orig Jrnl	Citing Papers 1	2	3	4	NC	Orig Jrnl	Citing Papers 1	2	3	4	NC	Citation by Guidelines Any	Arth Rltd
L	1992	Brennan-FM Gibbons-DL Mitchell-T Cope-AP Maini-RN Feldmann-M	Enhanced Expression of Tumor-Necrosis-Factor Receptor Messenger-RNA and Protein in Mononuclear-Cells Isolated from Rheumatoid-Arthritis	EUROPEAN JOURNAL OF IMMUNOLOGY, 1992, Vol 22, Iss 7, pp 1907-1912	6	2	0	1	3	1	49			3	7	7	14	10	4	4	1	4	3	4	4	65	49	16	21	2	2	4	2	0	3	6	7	0	1	24	10	41	22.5	3	3	26	32	4	0	4	17	9	11	28		0	0
L	1992	Brennan-FM Maini-RN Feldmann-M	TNF-Alpha - A Pivotal Role in Rheumatoid-Arthritis	BRITISH JOURNAL OF RHEUMATOLOGY, 1992, Vol 31, Iss 5, pp 293-298	3	2	0	1	1	1	141			1	11	16	31	23	15	18	16	13	13	16	8	181	147	31	24	9	5	12	11	0	10	9	10	10	3	60	54	82	8.3	1	15	82	66	15	3	1	62	37	26	56		0	0
L	1992	Chu-CQ Field-M Allard-S Abney-E Feldmann-M Maini-RN	Detection of Cytokines at the Cartilage Pannus Junction in Patients with Rheumatoid-Arthritis - Implications for the Role of Cytokines in Cartilage	BRITISH JOURNAL OF RHEUMATOLOGY, 1992, Vol 31, Iss 10, pp 653-661	6	2	0	1	3	1	123			0	3	7	22	16	16	18	13	9	12	5	8	129	106	22	16	9	3	4	12	1	7	5	9	18	3	34	36	48	8.3	1	19	66	32	10	2	1	58	25	16	30		0	0
L	1992	Cope-AP Aderka-D Doherty-M Engelmann-H Gibbons-D Jones-AC Brennan-FM Maini-RN Wallach-D Feldmann-M	Increased Levels of Soluble Tumor-Necrosis-Factor Receptors in the Sera and Synovial-Fluid of Patients with Rheumatic Diseases	ARTHRITIS AND RHEUMATISM, 1992, Vol 35, Iss 10, pp 1160-1169	10	4	1	1	3	1	120			1	8	20	32	28	13	16	20	16	8	12	10	184	142	35	38	7	7	5	10	1	6	7	12	17	2	43	46	89	19.9	2	21	81	70	9	3	2	76	29	22	57		0	0
L	1992	Deleuran-BW Chu-CQ Field-M Brennan-FM Katsikis-P Feldmann-M Maini-RN	Localization of Interleukin-1-Alpha, Type-1 Interleukin-1 Receptor and Interleukin-1 Receptor Antagonist in the Synovial-Membrane and Cartilage Pannus Junction in Rheumatoid-Arthritis	BRITISH JOURNAL OF RHEUMATOLOGY, 1992, Vol 31, Iss 12, pp 801-809	7	2	0	1	2	1	94			0	2	6	18	9	13	14	5	11	8	8	5	99	82	16	11	12	1	5	5	3	5	2	6	16	3	20	34	35	8.3	1	11	55	22	8	3	1	45	18	10	26		0	0
L	1992	Deleuran-BW Chu-CQ Field-M Brennan-FM Mitchell-T Feldmann-M Maini-RN	Localization of Tumor-Necrosis-Factor Receptors in the Synovial Tissue and Cartilage Pannus Junction in Patients with Rheumatoid-Arthritis - Implications for Local Actions of Tumor-Necrosis-Factor-Alpha	ARTHRITIS AND RHEUMATISM, 1992, Vol 35, Iss 10, pp 1170-1178	7	2	0	1	3	1	112			1	12	10	30	10	12	9	12	10	7	6	7	126	97	27	28	9	7	8	7	1	6	5	5	8	1	35	35	63	19.9	2	17	63	39	7	0	2	62	16	13	35		0	0
L	1992	Feldmann-M Brennan-FM Williams-RO Cope-AP Gibbons-DL Katsikis-PD Maini-RN	Evaluation of the role of cytokines in autoimmune disease: importance of TNF in rheumatoid arthritis	PROGRESS IN GROWTH FACTOR RESEARCH ,1992, Vol 4, Iss 3, pp247-55	2						14			0	0	2	5	1	3	4	3	2	2	0	2	24	19	5	0	0	2	1	3	0	0	1	3	1	0	3	11	8	0.0		1	5	17	1	0		4	1	3	16			
L	1992	Williams-RO Feldmann-M Maini-RN	Antitumor Necrosis Factor Ameliorates Joint Disease in Murine Collagen-Induced Arthritis	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1992, Vol	3	1	0			1	352			1	18	34	55	46	48	36	65	42	33	40	22	440	366	66	83	17	9	18	27	2	17	14	47	36	19	130	155	154	43.0	4	25	168	194	46	7	4	103	68	59	210		0	0
L	1992	Zheng-RQH Abney-ER Chu-CQ Field-M Maini-RN Lamb-JR Feldmann-M	Detection of Invivo Production of Tumor-Necrosis-Factor-Alpha by Human Thyroid Epithelial-Cells	IMMUNOLOGY, 1992, Vol 75, Iss 3, pp 456-462	7	4	0	1	5	1	2			2	2	7	11	5	3	3	5	5	2	1	0	46	35	10	3	0	1	0	4	3	1	3	7	2	1	13	11	27	12.4	3	0	13	27	6	0	4	5	14	12	15		0	0
L	1992	Chu-CQ Field-M Andrew-E Haskard-D Feldmann-M Maini-RN	Detection of Cytokines at the Site of Tuberculin-Induced Delayed-Type Hypersensitivity in Man	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 1992, Vol 90, Iss 3, pp 522-	6	3	0	1	3	0	4			0	1	0	3	7	3	3	3	3	2	3	3	31	28	2	2	1	0	1	1	0	0	0	1	5	4	10	9	11	11.2	2	4	7	16	4	0	3	6	4	7	14		0	0
L	1993	Aderka-D Wysenbeek-A Engelmann-H Cope-AP Brennan-F Molad-Y Hornik-V Levo-Y Maini RN Feldmann-M Wallach-D	Correlation Between Serum Levels of Soluble Tumor-Necrosis-Factor Receptor and Disease-Activity in Systemic Lupus-Erythematosus	ARTHRITIS AND RHEUMATISM, 1993, Vol 36, Iss 8, pp 1111-1120	11	6	1	0	5	1	52				1	9	14	17	13	6	14	8	6	6	6	100	80	17	9	3	1	7	7	0	11	6	4	2	4	11	22	54	19.9	2	15	50	28	5	2	2	51	17	14	18		0	0
L	1993	Cope-AP Gibbons-DL Aderka-D Foxwell-BM Wallach-D Maini-RN Feldmann-M Brennan-	Differential Regulation of Tumor-Necrosis-Factor Receptors (TNF-R) by IL-4, Up-Regulation of P55 and P75 TNF-R on Synovial Joint Mononuclear-	CYTOKINE, 1993, Vol 5, Iss 3, pp 205-212	8	4	1	1	8	1	20				0	4	5	6	1	2	2	3	1	2	0	26	22	4	9	4	3	3	2	0	1	1	0	0	0	9	3	16	13.6	4	2	7	15	2	0	4	7	2	2	15		0	0
L	1993	Elliott-MJ Maini-RN Feldmann-M Longfox-A Charles-P Katsikis-P Brennan-FM Walker-J Bijl-H Ghrayeb-J Woody-JN	Treatment of Rheumatoid-Arthritis with Chimeric Monoclonal-Antibodies to Tumor-Necrosis-Factor-Alpha	ARTHRITIS AND RHEUMATISM, 1993, Vol 36, Iss 12, pp 1681-1690	11	4	1	1	4	1	398				0	37	77	61	56	45	68	49	35	39	34	501	363	116	92	32	16	15	55	9	16	10	32	49	9	144	169	231	19.9	2	65	226	148	46	16	2	223	66	62	150		1	1
L	1993	Maini-RN Brennan-FM Williams-R Chu-CQ Cope-AP Gibbons-D Elliott-M Feldmann-M	TNF-Alpha in Rheumatoid-Arthritis and Prospects of Anti-TNF Therapy	CLINICAL AND EXPERIMENTAL RHEUMATOLOGY, 1993, Vol 11, Iss S8, pp S173-S175	8	2	0	1	1	1	24				0	8	12	3	3	0	1	1	3	2	2	35	29	6	5	1	4	1	4	0	2	0	0	5	0	10	16	26	5.8	2	2	16	13	3	1	2	10	5	10	10		0	0
L	1993	Maini-RN	Is tumour necrosis factor-a (TNF-a) a potential therapeutic target in Rheumatoid Arthritis? Concept validation studies	SEMINARS IN CLINICAL IMMUNOLOGY, 1993, Vol 6, pp5	1						2				0	0	1	1	0	0	0	0	0	0	0	2	1	1	0	0	0	0	1	0	0	0	0	0	0	1	0	2	0.0		1	0	1	0	0		1	0	0	1			
L	1993	Williams-RO Williams-DG Feldmann-M Maini-RN	Increased Limb Involvement in Murine Collagen-Induced Arthritis Following Treatment with Anti-Interferon-Gamma	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 1993, Vol 92, Iss 2, pp 323-	4	1	0	1	3	1	29				0	4	3	4	5	3	3	1	3	2	5	33	26	7	5	0	0	2	2	0	3	1	5	1	2	8	13	16	11.2	2	2	8	21	2	0	3	5	2	6	20		0	0
L	1994	Cope-AP Londei-M Chu-NR Cohen-SBA Elliott MJ Brennan-FM Maini-RN Feldmann-M	Chronic Exposure to Tumor-Necrosis-Factor (TNF) in-Vitro Impairs the Activation of T-Cells Through the T-Cell Receptor CD3 Complex - Reversal in-Vivo by Anti-TNF Antibodies in Patients with Rheumatoid-Arthritis	JOURNAL OF CLINICAL INVESTIGATION, 1994, Vol 94, Iss 2, pp 749-760	8	1	0	1	6	1	68					3	9	17	11	5	15	8	15	12	7	102	78	21	20	3	4	2	5	2	6	3	6	13	7	30	31	45	39.8	3	11	45	41	4	1	4	40	12	19	31		0	0
L	1994	Elliott-MJ Maini-RN	New Directions for Biological Therapy in Rheumatoid-Arthritis	INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, 1994, Vol 104, Iss 2,	2	1	0	1	1	1	26					2	11	6	2	3	2	1	1	1	0	29	19	8	8	0	0	1	3	0	0	3	1	3	0	9	15	24	7.0	3	3	16	10	0	0	3	15	4	4	6		0	0
L	1994	Elliott-MJ Maini-RN Feldmann-M Kalden-JR Antoni-C Smolen-JS Leeb-B Breedveld-FC Macfarlane-JD Bijl-H Woody-JN	Randomized Double-Blind Comparison of Chimeric Monoclonal-Antibody to Tumor-Necrosis-Factor-Alpha (Ca2) Versus Placebo in Rheumatoid-Arthritis	LANCET, 1994, Vol 344, Iss 8930, pp 1105-1110	11	7	1	1	3	1	535					4	60	86	105	91	99	86	90	88	58	767	543	168	124	32	27	24	85	6	32	21	46	83	21	171	289	346	44.6	2	102	351	216	70	28	1	353	115	90	209		1	1
L	1994	Elliott-MJ Maini-RN Feldmann-M Longfox-A Charles-P Bijl-H Woody-JN	Repeated Therapy with Monoclonal-Antibody to Tumor-Necrosis-Factor-Alpha (Ca2) in Patients with Rheumatoid-Arthritis	LANCET, 1994, Vol 344, Iss 8930, pp 1125-1127	7	3	1	1	3	1	236					4	24	31	40	43	62	42	35	37	24	342	227	94	45	9	12	10	45	7	16	6	22	32	8	98	120	142	44.6	2	51	141	100	34	16	1	152	37	48	105		0	0
L	1994	Feldmann-M Elliott-MJ Brennan-FM Maini-RN	Use of Antitumor Necrosis Factor Antibodies in Rheumatoid-Arthritis	JOURNAL OF INTERFERON RESEARCH, 1994, Vol 14, Iss 5, pp 299-300	4	1	0	1	1	1	1					0	0	0	1	0	1	1	0	0	0	3	2	1	0	0	0	0	1	0	0	0	0	0	0	0	2	1	5.8	4	0	1	2	0	0	4	1	0	0	2		0	0
L	1994	Feldmann-M Brennan-FM Elliott-M Katsikis-P Maini-RN	TNF-Alpha as a Therapeutic Target in Rheumatoid-Arthritis	CIRCULATORY SHOCK, 1994, Vol 43, Iss 4, pp 179-184	5	1	0	1	1	1	10					0	0	5	4	3	2	2	3	2	3	24	19	5	1	4	1	0	1	0	0	0	1	0	0	3	13	12	8.3	3	1	7	7	9	0	3	5	3	2	14		0	0
L	1994	Feldmann-M Maini-RN	From the laboratory to the clinic: Evaluation of cytokines in rheumatoid arthritis has led to a new therapeutic target, TNFa	THE IMMUNOLOGIST, 1994, Vol 2, pp 172	2						3					0	0	2	0	0	1	0	1	0	0	4	4	0	0	0	0	0	0	0	0	0	1	0	0	0	2	2	0.0		0	0	3	1	0		1	0	1	2			
L	1994	Katsikis-PD Chu-CQ Brennan-FM Maini-RN Feldmann-M	Immunoregulatory Role of Interleukin-10 in Rheumatoid-Arthritis	JOURNAL OF EXPERIMENTAL MEDICINE, 1994, Vol 179, Iss 5, pp 1517-1527	5	1	0	1	1	1	215					4	33	53	27	44	32	30	27	12	12	274	230	39	41	11	9	8	18	2	26	14	22	21	8	69	67	161	62.2	3	21	115	118	17	3	4	82	42	43	107		0	0
L	1994	Maini-RN Elliott-M Brennan-FM Williams-RO Feldmann-M	Targeting TNF-Alpha for the Therapy of Rheumatoid-Arthritis	CLINICAL AND EXPERIMENTAL RHEUMATOLOGY, 1994, Vol 12, Iss S11, pp S63-S66	5	1	0	1	1	1	5					0	0	0	1	0	3	0	3	1	1	9	7	1	0	0	0	1	3	0	1	0	1	1	0	0	3	1	4.9	2	4	3	1	0	1	2	5	2	1	1		0	0
L	1994	Maini-RN Elliott-MJ Charles-PJ Feldmann-M	Immunological Intervention Reveals Reciprocal Roles for Tumor-Necrosis-Factor-Alpha and Interleukin-10 in Rheumatoid-Arthritis and Systemic Lupus-Erythematosus	SPRINGER SEMINARS IN IMMUNOPATHOLOGY, 1994, Vol 16, Iss 2-3, pp 327-336	4	2	0	1	1	1	17					0	2	6	4	2	3	2	2	0	0	21	12	7	8	0	0	0	3	0	0	0	0	1	0	9	7	14	12.7	2	2	9	9	1	0	3	7	3	5	6		0	0
L	1994	Maini-RN	Are There Special Considerations Relevant to Trials of Biologic Agents - Comment	JOURNAL OF RHEUMATOLOGY, 1994, Vol 21, Iss S41, pp 47-48	1	1	0			1	1					0	1	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	1	9.2	2	0	1	0	0	0	1	1	0	0	0		0	0
L	1994	Maini-RN	Testing immunological concepts by clinical trials in rheumatoid arthritis	THE IMMUNOLOGIST, 1994, Vol 2, pp 147	1																																						0.0														
L	1994	Sohi-MK Sutton-BJ Corper-AL Wan-T Maini-RN Brown-C Rijnders-T Beale-D Feinstein-A Humphreys-AS Taussig-MJ	Crystallization and Preliminary-X-Ray Analysis of the Fab Fragment of a Human Monoclonal IgM Rheumatoid-Factor (2A2)	JOURNAL OF MOLECULAR BIOLOGY, 1994, Vol 242, Iss 5, pp 706-708	11	4	1	1	3	1	2					0	0	1	1	0	0	1	3	0	0	6	6	0	5	1	0	0	0	0	3	0	0	0	0	5	4	2	20.4	4	0	2	1	3	0	4	0	0	0	6		0	0
L	1994	Williams-RO Mason-LJ Feldmann-M Maini-RN	Synergy Between Anti-CD4 and Antitumor Necrosis Factor in the Amelioration of Established Collagen-Induced Arthritis	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1994, Vol	4	1	0			1	116					3	17	25	17	25	13	10	9	6	5	130	93	28	36	2	5	2	12	2	5	4	10	8	0	52	42	87	43.2	4	16	54	49	8	3	4	51	19	11	49		0	0
L	1995	Brennan-FM Maini-RN Feldmann-M	Cytokine Expression in Chronic Inflammatory Disease	BRITISH MEDICAL BULLETIN, 1995, Vol 51, Iss 2, pp 368-384	3	1	0	1	1	0	20						0	0	6	9	8	9	5	6	4	47	40	7	2	0	0	1	1	2	4	0	4	2	0	15	12	23	9.2	3	3	15	18	10	1	1	15	4	6	22		0	0
L	1995	Brown-CMS Fitzgerald-KJ Moyes-SP Mageed-RA Williams-DG Maini-RN	Sequence-Analysis of Immunoglobulin Heavy-Chain Variable Region Genes from the Synovium of a Rheumatoid-Arthritis Patient Shows Little Evidence of Mutation But Diverse Cdr3	IMMUNOLOGY, 1995, Vol 84, Iss 3, pp 367-374	6	1	0	1	3	1	10						0	2	5	0	0	2	1	0	0	10	10	0	3	0	0	1	0	0	1	0	0	0	0	5	2	7	12.3	3	0	2	5	3	0	4	0	0	3	7		0	0
L	1995	Butler-DM Maini-RN Feldmann-M Brennan-FM	Modulation of Proinflammatory Cytokine Release in Rheumatoid Synovial-Membrane Cell-Cultures - Comparison of Monoclonal Anti TNF-Alpha Antibody with the Interleukin-1 Receptor Antagonist	EUROPEAN CYTOKINE NETWORK, 1995, Vol 6, Iss 4, pp 225-230	4	1	0	1	3	1	64						0	4	6	9	10	9	14	11	11	74	53	19	24	4	2	2	7	0	0	2	5	2	1	29	29	29	9.6	3	7	32	21	8	6	4	30	12	9	23		0	0
L	1995	Cohen-SBA Katsikis-PD Chu-CQ Thomssen-H Webb-LMC Maini-RN Londei-M Feldmann-M	High-Level of Interleukin-10 Production by the Activated T-Cell Population Within the Rheumatoid Synovial-Membrane	ARTHRITIS AND RHEUMATISM, 1995, Vol 38, Iss 7, pp 946-952	8	1	0	1	5	1	69						2	10	16	18	18	11	8	3	1	87	72	14	17	3	2	3	5	1	13	10	7	9	2	24	24	64	21.4	2	7	38	37	3	2	2	29	11	14	33		0	0
L	1995	Williams-RO Ghrayeb-J Feldmann-M Maini-RN	Successful Therapy of Collagen-Induced Arthritis with TNF Receptor-IgG Fusion Protein and Combination with Anti-CD4	IMMUNOLOGY, 1995, Vol 84, Iss 3, pp 433-439	4	2	1	1	4	1	42						2	6	9	16	8	5	3	5	3	57	41	15	20	2	0	1	4	0	2	0	1	3	0	30	20	41	12.3	3	6	19	26	4	2	4	15	7	9	26		0	0
L	1995	Brennan-FM Gibbons-DL Cope-AP Katsikis-P Maini-RN Feldmann-M	TNF Inhibitors Are Produced Spontaneously by Rheumatoid and Osteoarthritic Synovial Joint Cell-Cultures - Evidence of Feedback-Control	SCANDINAVIAN JOURNAL OF IMMUNOLOGY, 1995, Vol 42, Iss 1, pp 158-	6	1	0	1	4	1	21						0	7	3	1	8	3	3	1	2	28	20	8	4	1	4	2	2	0	0	0	0	1	0	7	14	19	7.1	3	3	12	11	2	0	4	10	7	5	6		0	0
L	1995	Cope-AP Maini-RN	Soluble Tumor-Necrosis-Factor Receptors in Arthritis	JOURNAL OF RHEUMATOLOGY, 1995, Vol 22, Iss 3, pp 382-384	2	3	1			1	14						0	4	3	2	1	1	1	2	1	15	11	3	0	0	0	0	1	0	0	4	1	2	0	0	3	10	9.2	2	2	11	1	0	1	1	11	3	1	0		0	0
L	1996	Feldmann-M Brennan-FM Maini-RN	Rheumatoid-Arthritis	CELL, 1996, Vol 85, Iss 3, pp 307-310	3	1	0	0	0	1	194							6	23	32	37	41	32	34	37	242	207	25	12	4	4	10	29	2	13	16	57	14	8	34	87	139	148.1	4	10	89	98	40	5	4	46	42	35	119		0	0
L	1996	Paleolog-EM Hunt-M Elliott-MJ Feldmann-M Maini-RN Woody-JN	Deactivation of Vascular Endothelium by Monoclonal Antitumor Necrosis Factor-Alpha Antibody in Rheumatoid-Arthritis	ARTHRITIS AND RHEUMATISM, 1996, Vol 39, Iss 7, pp 1082-1091	6	2	1	1	4	1	92							5	17	20	16	10	16	13	10	107	69	31	25	6	4	2	12	1	2	2	3	16	5	36	25	68	19.9	2	17	56	21	8	5	2	49	23	13	22		0	0

Case Study	Year	Details of Paper: Authors	Title	Full Reference	Authorship: # authors	# addr	# Non UK addr	Funding: ARC Ackn	# Ackn	Area: Within ARTHR	Cites within ARTHR	90	91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	Total	N Art/Not	Cites by Reviews	Self Cites	AU	CA	CH	DE	ES	FR	IT	JP	NL	SE	UK	US	C0-4 (actual)	C0-4 (journal)	CHI Level: Orig Jrnl	Citing Papers: 1	2	3	4	NC	Orig Jrnl	Citing Papers: 1	2	3	4	NC	Citation by Guidelines: Any	Arth Rltd
L	1996	Tak-PP Taylor-PC Breedveld-FC Smeets-TJM Daha-MR Kluin-PM Meinders-AE Maini-RN	Decrease in Cellularity and Expression of Adhesion Molecules by Antitumor Necrosis Factor-Alpha Monoclonal-Antibody Treatment in	ARTHRITIS AND RHEUMATISM, 1996, Vol 39, Iss 7, pp 1077-1081	8	2	1	1	2	1	123							0	18	20	23	21	28	16	15	141	100	30	40	15	2	2	17	1	3	2	3	32	9	31	32	82	19.9	2	32	76	21	7	5	2	81	30	12	18		0	0
L	1996	Williams-LM Gibbons-DL Gearing-A Maini-RN Feldmann-M Brennan-FM	Paradoxical Effects of a Synthetic Metalloproteinase Inhibitor That Blocks Both P55 and P75 TNF Receptor Shedding and TNF-Alpha Processing in RA Synovial-Membrane Cell-Cultures	JOURNAL OF CLINICAL INVESTIGATION, 1996, Vol 97, Iss 12, pp 2833-2841	6	2	0	1	5	1	29							2	15	16	10	9	11	12	2	77	58	16	8	1	0	2	8	1	4	4	8	6	1	24	25	52	40.1	3	3	20	32	20	2	4	16	9	8	44		0	0
M	1995	Wordsworth-P	Genes and Arthritis	BRITISH MEDICAL BULLETIN, 1995, Vol 51, Iss 2, pp 249-266	1	1	0	0	0	1	16						1	1	4	5	3	3	1	2	0	20	16	4	4	1	0	0	4	1	1	1	1	3	0	8	4	14	9.2	3	2	11	5	2	0	1	8	6	1	5		0	0
M	1996	Hall-FC Weeks-DE Camilleri-JP Williams-LA Amos-N Darke-C Gibson-K Pile-K Wordsworth BP Jessop-JD	Influence of the HLA-Drb1 Locus on Susceptibility and Severity in Rheumatoid-Arthritis Influence of the HLA-Drb1 Locus on Susceptibility and Severity in Rheumatoid-Arthritis	QJM-MONTHLY JOURNAL OF THE ASSOCIATION OF PHYSICIANS, 1996, Vol 89, Iss 11, pp 821-829	10	6	1	1	3	1	24							0	2	1	6	6	3	8	3	29	21	8	6	2	1	0	2	0	0	0	1	1	0	11	11	15	9.2	2	6	15	8	0	0	1	18	6	5	0		0	0
M	1996	Rudwaleit-M Tikly-M Khamashta-M Gibson-K Klinke-J Hughes-G Wordsworth-P	Interethnic Differences in the Association of Tumor-Necrosis-Factor Promoter Polymorphisms with Systemic Lupus-Erythematosus	JOURNAL OF RHEUMATOLOGY, 1996, Vol 23, Iss 10, pp 1725-1728	7	3	1	1	2	1	16							0	1	5	5	6	11	2	2	33	24	8	2	3	0	0	2	0	2	1	5	1	1	9	8	17	8.4	2	3	14	13	2	1	1	12	9	7	5		0	0
M	1997	Cornelis-F Hardwick-L Flipo-RM Martinez-M Lasbleiz-S Prudhomme-JF Tran-TH Walsh-S Delaye-A Nicod-A Loste-MN Lepage-V Gibson-K Pile-K Djoulah-S Danze-PM Liote-F Charron D Weissenbach-J Kuntz-D Bardin-T	Association of Rheumatoid-Arthritis with an Amino-Acid Allelic Variation of the T-Cell Receptor	ARTHRITIS AND RHEUMATISM, 1997, Vol 40, Iss 8, pp 1387-1390	22	6	1	1	6	1	12								1	5	3	1	1	3	0	14	10	3	5	0	0	1	0	0	0	1	0	0	0	7	6	11	19.9	2	1	9	4	0	0	2	5	2	5	2		0	0
M	1997	Hall-FC Brown-MA Weeks-DE Walsh-S Nicod-A Butcher-S Andrews-LJ Wordsworth-BP	A Linkage Study Across the T-Cell Receptor-A and T-Cell Receptor-B Loci in Families with Rheumatoid-Arthritis	ARTHRITIS AND RHEUMATISM, 1997, Vol 40, Iss 10, pp 1798-1802	8	2	1	1	3	1	4								0	2	1	1	0	1	0	5	1	3	2	0	0	0	0	0	0	0	0	0	0	3	2	4	19.9	2	0	3	1	0	1	2	1	0	4	0		0	0
M	1997	Hardwick-LJ Walsh-S Butcher-S Nicod-A Shatford-J Bell-J Lathrop-M Wordsworth-BP	Genetic-Mapping of Susceptibility Loci in the Genes Involved in Rheumatoid-Arthritis	JOURNAL OF RHEUMATOLOGY, 1997, Vol 24, Iss 1, pp 197-198	8	3	0	0	0	1	13								1	2	4	4	2	4	3	20	11	8	0	0	1	0	1	3	3	2	0	2	3	7	5	13	8.4	2	2	9	6	3	0	1	5	6	4	5		0	0
M	1998	Brown-MA Pile-KD Kennedy-LG Campbell-D Andrew-L March-R Shatford-JL Weeks-DE Calin-A Wordsworth-BP	A Genome-Wide Screen for Susceptibility Loci in Ankylosing-Spondylitis	ARTHRITIS AND RHEUMATISM, 1998, Vol 41, Iss 4, pp 588-595	10	5	1	1	7	1	59									6	13	17	15	8	13	72	50	15	18	4	6	0	6	7	6	1	3	3	0	26	23	59	24.3	2	9	32	20	6	5	2	36	12	9	15		0	0
M	1998	Eskdale-J Mcnicholl-J Wordsworth-P Jonas-B Huizinga-T Field-M Gallagher-G	Interleukin-10 Microsatellite Polymorphisms and IL-10 Locus Alleles in Rheumatoid-Arthritis Susceptibility	LANCET, 1998, Vol 352, Iss 9136, pp 1282-1283	7	5	1	0	1	1	18									0	4	4	9	7	6	30	22	6	10	0	0	0	7	2	1	1	2	7	1	9	6	24	29.7	2	6	15	9	0	0	1	13	8	3	6		0	0
M	1998	Hall-FC Thomson-K Procter-J Mcmichael-AJ Wordsworth-BP	TCR-Beta Spectratyping in RA - Evidence of Clonal Expansions in Peripheral-Blood Lymphocytes	ANNALS OF THE RHEUMATIC DISEASES, 1998, Vol 57, Iss 5, pp 319-322	5	3	0	0	2	1	6									0	1	2	5	6	1	15	12	3	0	0	0	0	2	0	0	1	1	2	0	2	8	14	8.5	2	0	3	10	1	1	1	2	1	7	5		0	0
M	1998	Ibberson-M Peclat-V Guerne-PA Tiercy-JM Wordsworth-P Lanchbury-J Camilleri-J So-AK	Analysis of T-Cell-Receptor-V Alpha Polymorphisms in Rheumatoid-Arthritis	ANNALS OF THE RHEUMATIC DISEASES, 1998, Vol 57, Iss 1, pp 49-51	8	7	1	1	4	1										0	2	1	0	0	0	3	1	2	0	0	0	0	0	0	0	0	0	0	0	3	0	3	8.5	2	0	1	0	2	0	1	0	1	1	1		0	0
M	1998	Wordsworth-BP	T-Cell Genetics and Rheumatoid-Arthritis (RA)	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 1998, Vol 111, Iss 3, pp 469	1	1	0			1	2									0	0	0	1	1	0	2	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	2	10.6	2	0	1	1	0	0	3	1	0	1	0		0	0
M	1999	Andrew-LJ Brancolini-V Delapena-LS Devoto-M Caeiro-F Marchegiani-R Reginato-A Gaucher-A Netter-P Gillet-P Loeuille-D Prockop-DJ Carr-A Wordsworth-BF Lathrop-M Butcher-S Considine-E Everts-K Nicod-A	Refinement of the Chromosome 5P Locus for Familial Calcium Pyrophosphate Dihydrate Deposition Disease	AMERICAN JOURNAL OF HUMAN GENETICS, 1999, Vol 64, Iss 1, pp 136-145	21	7	1	0	2	1	13										2	4	3	5	2	16	10	6	7	2	1	1	2	0	1	0	0	0	0	6	11	16	34.5	3	1	5	4	2	4	3	8	2	3	3		0	0
M	1999	Baerwald-CGO Mok-CC Fife-MS Tikly-M Lau-CS Wordsworth-BP Ollier-B Panayi-GS	Distribution of Corticotropin-Releasing Hormone Promoter Polymorphism in Different Ethnic-Groups - Evidence for Natural-Selection in Human-	IMMUNOGENETICS, 1999, Vol 49, Iss 10, pp 894-899	9	6	1	1	7	1	2										0	1	1	2	0	4	3	1	2	0	0	0	2	0	0	1	0	0	1	0	2	4	9.0	3	1	1	1	1	0	4	2	1	1	0		0	0
M	2001	Merriman-TR Cordell-HJ Eaves-IA Danoy-PA Coraddu-F Barber-R Cucca-F Broadley-S Sawcer-S Comptson-A Wordsworth-P Shatford-J Laval-S Jirholt-J Holmdahl-R Theofilopoulos-AN Kono-DH Tuomilehto-J Tuomilehtowolf-E Buzzetti-R Marrosu-MG Undlien-DE Ronningen-KS Ionescotirgoviste-C Shield-JP Pociot-F Nerup-J Jacob-CO	Suggestive Evidence for Association of Human-Chromosome-18Q12-Q21 and Its Orthologue on Rat and Mouse-Chromosome-18 with Several Autoimmune-Diseases	DIABETES, 2001, Vol 50, Iss 1, pp 184-194	31	18	1	1	10	0	12												6	11	8	25	14	8	6	1	1	0	2	0	1	1	1	0	2	8	12	0	29.6	3	1	4	13	3	4	3	2	7	5	11		0	0
M	2002	Mackay-K Eyre-S Myerscough-A Milicic-A Barton-A Laval-S Barrett-J Lee-D White-S John-S Brown-MA Bell-J Silman-A Ollier-W	Whole-Genome Linkage Analysis of Rheumatoid-Arthritis Susceptibility Loci in 252 Affected Sibling Pairs in the United-Kingdom	ARTHRITIS AND RHEUMATISM, 2002, Vol 46, Iss 3, pp 632-639	16	2	0	n/a		1	30													7	25	32	20	9	4	0	0	0	1	2	1	0	4	1	3	6	13		24.3	2	3	11	12	4	2	2	7	8	8	9	0	0	0
M	2004	Newton-JL Harney-SM Wordsworth-BP Brown-MA	A review of the MHC genetics of Rheumatoid Arthritis	GENES AND IMMUNITY, 2004, Vol 5, Iss 3, pp151-157	2																																																					
N	1992	Carney-SL Billingham-MEJ Caterson-B Ratcliffe-A Bayliss-MT Hardingham-TE Muir-H	Changes in Proteoglycan Turnover in Experimental Canine Osteoarthritic Cartilage	MATRIX, 1992, Vol 12, Iss 2, pp 137-147	7	4	1	1	4	1	39			0	5	5	10	3	4	2	2	2	5	3	2	43	39	4	16	7	3	0	1	1	3	0	0	3	5	9	15	23	8.5	4	5	15	7	11	5	4	12	9	8	14		0	0
N	1992	Hardingham-TE Bayliss-MT Rayan-V Noble-DP	Effects of Growth-Factors and Cytokines on Proteoglycan Turnover in Articular-Cartilage	BRITISH JOURNAL OF RHEUMATOLOGY, 1992, Vol 31, Iss S1, pp 1-6	4	1	0	1	2	1	42			0	0	10	4	8	4	2	3	6	2	2	3	44	42	2	1	0	0	1	2	0	2	0	1	9	4	10	19	22	8.3	1	5	13	13	12	1	1	14	8	7	15		0	0
N	1992	Hardingham-TE Fosang-AJ	Proteoglycans - Many Forms and Many Functions	FASEB JOURNAL, 1992, Vol 6, Iss 3, pp 861-870	2	2	1	1	2	1	240			2	44	60	66	58	53	55	45	40	37	36	23	519	430	84	12	23	38	18	57	9	23	16	55	13	13	60	210	230	52.3	4	14	74	126	286	19	4	44	61	93	321		0	0
N	1992	Ratcliffe-A Billingham-MEJ Saednejad-F Muir-H Hardingham-TE	Increased Release of Matrix Components from Articular-Cartilage in Experimental Canine Osteoarthritis	JOURNAL OF ORTHOPAEDIC RESEARCH, 1992, Vol 10, Iss 3, pp 350-	5	3	1	1	4	1	42			1	9	4	7	6	3	4	4	2	5	0	0	45	44	1	13	1	4	0	0	0	0	0	1	1	6	4	35	27	7.9	2	5	22	9	5	4	3	15	15	11	4		0	0
N	1993	Fosang-AJ Last-K Knauper-V Neame-PJ Murphy-G Hardingham-TE Tschesche-H	Fibroblast and Neutrophil Collagenases Cleave at 2 Sites in the Cartilage Aggrecan Interglobular Domain	BIOCHEMICAL JOURNAL, 1993, Vol 295, Iss OCT, pp 273-276	8	5	1	1	5	1	64				0	8	15	10	12	13	14	8	7	9	3	99	93	6	14	13	7	3	13	1	0	1	7	8	5	16	58	45	16.7	4	6	15	20	51	7	4	15	9	13	62		0	0
N	1993	Venn-G Nietfeld-JJ Duits-AJ Brennan-FM Arner-E Covington-M Billingham-MEJ	Elevated Synovial-Fluid Levels of Interleukin-6 and Tumor-Necrosis-Factor Associated with Early Experimental Canine Osteoarthritis	ARTHRITIS AND RHEUMATISM, 1993, Vol 36, Iss 6, pp 819-826	8	5	1	1	3	1	36				1	0	8	5	4	5	7	3	6	3	1	43	36	7	1	3	4	1	1	0	2	1	3	1	2	10	16	18	19.9	2	6	20	12	3	2	2	17	12	6	8		0	0
N	1994	Fosang-AJ Last-K Neame-PJ Murphy-G Knauper-V Tschesche-H Hughes-CE Caterson	Neutrophil Collagenase (MMP-8) Cleaves at the Aggrecanase Site E(373)-A(374) in the Interglobular Domain of Cartilage Aggrecan	BIOCHEMICAL JOURNAL, 1994, Vol 304, Iss DEC, pp 347-351	9	6	1	1	8	1	48					0	7	12	14	11	9	5	5	6	4	73	62	7	24	12	5	1	11	1	1	1	6	6	1	16	34	44	15.7	4	3	11	15	40	4	4	9	5	12	47		0	0
N	1994	Hardingham-TE Fosang-AJ Hey-NJ Hazell-PK Kee-WJ Ewins-RJF	The Sulfation Pattern in Chondroitin Sulfate Chains Investigated by Chondroitinase ABC and Acii Digestion and Reactivity with Monoclonal-	CARBOHYDRATE RESEARCH, 1994, Vol 255, Iss MAR, pp 241-254	6	1	0	1	2	1	12					0	4	3	2	1	1	0	1	1	0	13	13	0	1	1	2	0	1	0	2	0	3	0	1	1	6	10	6.3	4	2	1	1	9	0	4	2	0	2	9		0	0
N	1994	Hardingham-TE Fosang-AJ Dudhia-J	The Structure, Function and Turnover of Aggrecan, the Large Aggregating Proteoglycan from Cartilage	EUROPEAN JOURNAL OF CLINICAL CHEMISTRY AND CLINICAL BIOCHEMISTRY, 1994, Vol 32, Iss 4, pp	3	2	1	1	2	1	32					1	1	5	3	8	5	6	6	6	5	46	41	5	4	0	5	1	6	0	1	0	1	0	1	9	17	18	4.2	3	4	4	9	27	2	2	6	3	8	29		0	0
N	1994	Lewthwaite-J Blake-SM Hardingham-TE Warden-PJ Henderson-B	The Effect of Recombinant Human Interleukin-1 Receptor Antagonist on the Induction-Phase of Antigen-Induced Arthritis in the Rabbit	JOURNAL OF RHEUMATOLOGY, 1994, Vol 21, Iss 3, pp 467-472	5	2	0	1	3	1	33					1	10	4	0	10	5	3	2	2	0	37	31	6	3	1	0	2	7	1	0	1	0	9	1	8	15	25	9.2	2	6	19	10	2	0	1	20	5	1	11		0	0
N	1994	Rayan-V Hardingham-T	The Recovery of Articular-Cartilage in Explant Culture from Interleukin-1-Alpha - Effects on Proteoglycan Synthesis and Degradation	MATRIX BIOLOGY, 1994, Vol 14, Iss 3, pp 263-271	2	1	0			1	19					1	2	1	4	3	1	3	1	2	1	19	16	3	3	1	0	0	4	0	0	0	0	6	1	5	7	11	22.8	4	2	6	3	6	2	4	5	4	3	7		0	0
N	1995	Hardingham-T	Changes in Chondroitin Sulfate Structure Induced by Joint Disease	ACTA ORTHOPAEDICA SCANDINAVICA, 1995, Vol 66, Iss S266, pp 107-110	1	1	0	0	1	1																																	4.98	1						1						0	0
N	1995	Hazell-PK Dent-C Fairclough-JA Bayliss-MT Hardingham-TE	Changes in Glycosaminoglycan Epitope Levels in Knee-Joint Fluid Following Injury	ARTHRITIS AND RHEUMATISM, 1995, Vol 38, Iss 7, pp 953-959	5	2	0	1	2	1	31								5	3	7	2	5	4	5	31	29	2	5	3	4	0	1	0	1	0	3	0	2	10	12	15	21.44	2	1	14	4	5	7	2	9	6	11	5		0	0
N	1995	Lewthwaite-J Blake-S Thompson-RC Hardingham-TE Henderson-B	Antifibrotic Action of Interleukin-1 Receptor Antagonist in Lapine Monoarticular Arthritis	ANNALS OF THE RHEUMATIC DISEASES, 1995, Vol 54, Iss 7, pp 591-596	5	3	1	1	2	1	4							1	1	1	1		1			5	3	2	0	0	0	1	1	1	0	0	0	0	0	0	3	4	10.02	2		3		1	1	1	3	1		1		0	0
N	1995	Lewthwaite-J Blake-S Hardingham-T Foulkes-R Stephens-S Chaplin-L Emtage-S Catterall-C Short-S Nesbitt-A Allen-R Bodmer-M Brown-D Andrew-D Henderson-B	Role of TNF-Alpha in the Induction of Antigen-Induced Arthritis in the Rabbit and the Antiarthritic Effect of Species-Specific TNF-Alpha Neutralizing Monoclonal-Antibodies	ANNALS OF THE RHEUMATIC DISEASES, 1995, Vol 54, Iss 5, pp 366-374	15	3	0	1	3	1	16						1		4		6	4	1	1	1	18	15	3	1	2	1	1	5	0	0	0	1	1	1	5	6	11	10.02	2	2	6	9	1		1	5	3	1	9		0	0
N	1995	Venn-G Billingham-MEJ Hardingham-TE	Increased Proteoglycan Synthesis in Cartilage in Experimental Canine Osteoarthritis Does Not Reflect a Permanent Change in Chondrocyte	ARTHRITIS AND RHEUMATISM, 1995, Vol 38, Iss 4, pp 525-532	3	3	0	1	3	1	16							1		2	3	4	2	1	3	16	14	2	0	0	3	0	0	0	1	0	0	1	3	1	6	6	21.44	2	2	5	1	1	7	2	5	2	8	1		0	0
O	1993	Worthington-J Pearson-C Julier-C Bell-J Cornelis-FB	Dinucleotide Repeat Polymorphism at the Pi Locus	HUMAN MOLECULAR GENETICS, 1993, Vol 2, Iss 12, pp 2203-2203	5	3	1			1																																	17.1	4						3						0	0
O	1994	Worthington-J Ollier-WER Leach-MK Smith-I Hay-EM Thomson-W Pepper-L Carthy-D Farhan-A Martin-S Dyer-P Davison-J Bamber-	The Arthritis-and-Rheumatism-Councils National Repository of Family Material - Pedigrees from the 1st 100 Rheumatoid-Arthritis Families Containing Affected Sibling Pairs	BRITISH JOURNAL OF RHEUMATOLOGY, 1994, Vol 33, Iss 10, pp 970-976	14	2	0	1	1	1	24					0	3	4	7	4	2	2	2	2	0	26	23	1	14	0	0	0	0	0	0	0	1	0	1	24	9	18	8.2	1	0	17	5	4	0	1	11	7	4	4		0	0

Case Study	Year	Authors	Title	Full Reference	Authorship # authors	Authorship # addr	Authorship # Non UK addr	Funding ARC Ackn	Funding # Ackn	Area Within ARTHR	Area Cites within ARTHR	90	91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	Total	N Art/Not	Cites by Reviews	Self Cites	AU	CA	CH	DE	ES	FR	IT	JP	NL	SE	UK	US	C0-4 (actual)	C0-4 (journal)	CHI Level Orig Jrnl	CHI Citing Papers 1	2	3	4	NC	Orig Jrnl	Citing Papers 1	2	3	4	NC	Citation by Guidelines Any	Arth Rltd
O	1995	Silman-AJ Hay-EM Worthington-J Thomson-W Pepper-L Davidson-J Dyer-PA Ollier-WER	Lack of Influence of Noninherited Maternal HLA-Dr Alleles on Susceptibility to Rheumatoid-Arthritis	ANNALS OF THE RHEUMATIC DISEASES, 1995, Vol 54, Iss 4, pp 311-313	8	2	0	1	2	1	4						0	0	0	3	0	1	1	0	2	7	4	1	0	0	0	0	2	2	2	2	0	4	0	0	0	3	10.0	2	0	5	2	0	0	1	3	3	1	0		0	0
O	1996	Brennan-P Ollier-B Worthington-J Hajeer-A Silman-A	Are Both Genetic and Reproductive Associations with Rheumatoid-Arthritis Linked to Prolactin	LANCET, 1996, Vol 348, Iss 9020, pp 106-109	5	1	0	1	1	1	19							0	3	5	5	3	2	1	1	20	15	5	4	1	0	2	0	3	0	0	1	1	1	6	4	16	37.5	2	1	15	3	1	0	1	11	4	3	2		0	0
O	1996	Hajeer-AH Worthington-J Silman-AJ Ollier-WER	Association of Tumor-Necrosis-Factor Microsatellite Polymorphisms with HLA-Drb1(Asterisk)04-Bearing Haplotypes in Rheumatoid-Arthritis Patients	ARTHRITIS AND RHEUMATISM, 1996, Vol 39, Iss 7, pp 1109-1114	4	1	0	1	1	1	48							1	7	7	12	16	7	11	1	62	49	8	18	1	2	0	2	7	3	3	3	3	2	31	12	43	19.9	2	7	37	12	5	1	2	29	13	14	6		0	0
O	1997	Brennan-P Hajeer-A Ong-KR Worthington-J John-S Thomson-W Silman-A Ollier-B	Allelic Markers Close to Prolactin Are Associated with HLA-Drb1 Susceptibility Alleles Among Women with Rheumatoid-Arthritis and	ARTHRITIS AND RHEUMATISM, 1997, Vol 40, Iss 8, pp 1383-1386	8	1	0	1	1	1	22								0	5	7	3	5	3	3	26	16	10	4	1	0	3	1	0	0	1	3	0	0	6	8	20	19.9	2	3	14	7	2	0	2	6	9	8	3		0	0
O	1997	Hajeer-A John-S Ollier-WE Silman-AJ Dawes-P Hassell-A Mattey-D Fryer-A Strange-R	Tumor-Necrosis-Factor Microsatellite Haplotypes Are Different in Male and Female-Patients with RA	JOURNAL OF RHEUMATOLOGY, 1997, Vol 24, Iss 1, pp 217-219	10	3	0	1	1	1	12								2	1	4	4	3	3	0	17	14	3	4	0	1	0	2	1	1	0	0	1	2	6	7	14	8.4	2	1	11	3	1	1	1	6	6	3	2		0	0
O	1997	Hajeer-AH Worthington-J Davies-EJ Hillarby-MC Poulton-K Ollier-WER	TNF Microsatellite A2, B3 and D2 Alleles Are Associated with Systemic Lupus-Erythematosus	TISSUE ANTIGENS, 1997, Vol 49, Iss 3, pp 222-227	6	1	0	1	1	1	12								0	5	1	6	5	1	1	19	10	8	6	1	1	0	0	2	1	1	3	0	0	8	4	17	10.2	3	0	12	6	1	0	3	7	1	7	4		0	0
O	1997	John-S Hajeer-A Marlow-A Myerscough-A Silman-AJ Ollier-WER Worthington-J	Investigation of Candidate Disease Susceptibility Genes in Rheumatoid-Arthritis - Principles and Strategies	JOURNAL OF RHEUMATOLOGY, 1997, Vol 24, Iss 1, pp 199-201	7	1	0	1	1	1	12								2	0	2	3	3	1	3	14	11	2	2	1	0	0	1	1	0	0	0	0	0	6	5	10	8.4	2	4	4	6	0	0	1	7	3	2	2		0	0
O	1997	John-S Marlow-A Hajeer-A Ollier-W Silman-A Worthington-J	Linkage and Association Studies of the Natural-Resistance Associated Macrophage Protein-1 (Nramp1) Locus in Rheumatoid-Arthritis	JOURNAL OF RHEUMATOLOGY, 1997, Vol 24, Iss 3, pp 452-457	6	1	0	1	2	1	7								0	2	1	3	1	3	0	10	6	4	1	0	2	0	0	1	0	0	0	0	1	4	4	7	8.4	2	0	5	4	0	1	1	3	3	3	1		0	0
O	1997	Lazarus-M Hajeer-AH Turner-D Sinnott-P Worthington-J Ollier-WER Hutchinson-IV	Genetic-Variation in the Interleukin-10 Gene Promoter and Systemic Lupus Erythematosus	JOURNAL OF RHEUMATOLOGY, 1997, Vol 24, Iss 12, pp 2314-2317	7	3	0	1	1	1	38								1	5	15	12	18	13	13	77	60	11	6	3	0	0	5	2	3	3	3	6	5	28	18	51	8.4	2	12	38	22	3	2	1	31	18	15	13		0	0
O	1997	Marlow-AJ John-S Worthington-J	Multipoint analysis of quantitative traits	GENETIC EPIDEMIOLOGY, 1997, Vol 14, Iss 6, pp845-850	2																																						6.1	4						2							
O	1997	Marlow-A John-S Hajeer-A Ollier-WER Silman-AJ Worthington-J	The Sensitivity of Different Analytical Methods to Detect Disease Susceptibility Genes in Rheumatoid-Arthritis Sibling Pair Families	JOURNAL OF RHEUMATOLOGY, 1997, Vol 24, Iss 1, pp 208-211	6	1	0	1	1	1	7								2	2	0	2	2	0	0	8	6	1	4	0	0	0	0	2	1	1	0	1	0	4	2	8	8.4	2	1	6	1	0	0	1	7	0	1	0		0	0
O	1997	Ollier-B Worthington-J	Happy Families	ANNALS OF THE RHEUMATIC DISEASES, 1997, Vol 56, Iss 3, pp 149-150	2	1	0	1	1	1	1								0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	8.3	2	0	0	0	0	1	1	1	0	0	0		0	0
O	1997	Ollier-W Worthington-J	Small Fish in a Big Pond	BRITISH JOURNAL OF RHEUMATOLOGY, 1997, Vol 36, Iss 9, pp 931-932	2	1	0			1	7								0	1	0	3	2	0	1	7	4	0	3	0	0	0	0	2	1	1	0	1	0	5	0	6	9.9	1	1	5	1	0	0	1	6	0	0	1		0	0
O	1997	Ollier-WER Worthington-J	New Horizons in Rheumatoid-Arthritis Genetics	JOURNAL OF RHEUMATOLOGY, 1997, Vol 24, Iss 1, pp 193-193	2	1	0			1	5								0	0	0	2	0	1	2	5	4	1	0	0	0	0	0	1	0	0	0	0	0	0	4	2	8.4	2	0	1	4	0	0	1	1	0	0	4		0	0
O	2002	Mackay-K Eyre-S Myerscough-A Milicic-A Barton-A Laval-S Barrett-J Lee-D White-S John-S Brown-MA Bell-J Silman-A Ollier-W	Whole-Genome Linkage Analysis of Rheumatoid-Arthritis Susceptibility Loci in 252 Affected Sibling Pairs in the United-Kingdom	ARTHRITIS AND RHEUMATISM, 2002, Vol 46, Iss 3, pp 632-639	16	2	0	n/a		1	30													7	25	32	20	9	4	0	0	0	1	2	1	0	4	1	3	6	13		24.3	2	3	11	12	4	2	2	7	8	8	9	0	0	0
O	2003	Brown-MA Brophy-S Bradbury-L Hamersma-J Timms-A Laval-S Cardon-L Calin-A	Identification of Major Loci Controlling Clinical-Manifestations of Ankylosing Spondylitis	ARTHRITIS AND RHEUMATISM, 2003, Vol 48, Iss 8, pp 2234-2239	9	2	0			1																																	24.3	2						2						0	0
P	1990	Symmons-DPM Barrett-EM Scott-DGI Silman-AJ	The Norfolk Arthritis Register – a study of the incidence of RA	BRITISH JOURNAL OF RHEUMATOLOGY, 1990, Vol 29, suppl, pp79	2						9	0	0	3	2	1	1	1	1	0	0	0	0	0	0	9	5	2	4	0	0	0	0	0	1	0	0	0	0	8	1	6	6.7	1	2	6	1	0	0	1	9	0	0	0			
P	1990	Symmons-DPM	General practice – the ideal setting for modern epidemiological research	RHEUMATOLOGY AND GASTRENTEROLOGY IN PRACTICE, 1990, Vol 1, pp35-36	2																																						0.0														
P	1992	Chakravorty-K Symmons-DPM Barrett-EM Scott-DGI	Arthritis Following Immunization - A Report of 21 Cases	BRITISH JOURNAL OF RHEUMATOLOGY, 1992, Vol 31, Iss S2, pp 116-116	4	2	0			1																																	8.3	1						1						0	0
P	1992	Symmons-DPM Barrett-EM Chakravorty-K Scott-DGI Silman-AJ	The Incidence of Rheumatoid-Arthritis in Norfolk, England	ARTHRITIS AND RHEUMATISM, 1992, Vol 35, Iss 9, pp S126-S126	5	2	0			1	2			0	0	1	0	0	0	0	0	1	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	19.9	2	0	2	0	0	0	2	2	0	0	0		0	0
P	1993	Symmons-DPM Chakravarty-K	Can Immunization Trigger Rheumatoid-Arthritis	ANNALS OF THE RHEUMATIC DISEASES, 1993, Vol 52, Iss 12, pp 843-844	2	2	0			1	19				0	2	1	1	5	1	2	4	1	4	1	22	18	2	7	0	1	0	0	0	7	0	0	0	0	9	2	9	7.2	2	5	14	3	0	0	1	18	1	3	0		0	0
P	1993	Thomson-W Pepper-L Payton-A Carthy-D Scott-D Ollier-W Silman-A Symmons-D	Absence of an Association Between HLA-Drb1-Asterisk-04 and Rheumatoid-Arthritis in Newly-Diagnosed Cases from the Community	ANNALS OF THE RHEUMATIC DISEASES, 1993, Vol 52, Iss 7, pp 539-541	8	2	0	1	1	1	52				3	1	6	7	8	3	10	7	2	1	4	52	44	7	14	1	3	3	3	1	2	2	2	4	1	21	7	25	7.2	2	8	36	7	1	0	1	38	8	5	1		0	0
P	1994	Symmons-DPM Barrett-EM Bankhead-CR Scott-DGI Silman-AJ	The Incidence of Rheumatoid-Arthritis in the United-Kingdom - Results from the Norfolk Arthritis Register	BRITISH JOURNAL OF RHEUMATOLOGY, 1994, Vol 33, Iss 8, pp 735-739	5	2	0	1	1	1	102					4	7	11	9	8	10	17	8	16	16	106	89	11	62	0	2	0	5	0	0	0	2	7	2	67	17	39	8.2	1	23	75	6	1	1	1	82	21	2	1		0	0
P	1996	Bankhead-C Silman-A Barrett-B Scott-D Symmons-D	Incidence of Rheumatoid-Arthritis Is Not Related to Indicators of Socioeconomic Deprivation	JOURNAL OF RHEUMATOLOGY, 1996, Vol 23, Iss 12, pp 2039-2042	5	3	0	1	1	1	15							0	1	0	2	4	2	2	4	15	12	2	4	0	0	0	0	0	0	0	0	1	3	5	2	7	8.4	2	3	11	0	0	1	1	14	1	0	0		0	0
P	1996	Brennan-P Harrison-B Barrett-E Chakravarty-K Scott-D Silman-A Symmons-D	A Simple Algorithm to Predict the Development of Radiological Erosions in Patients with Early Rheumatoid-Arthritis - Prospective Cohort Study	BRITISH MEDICAL JOURNAL, 1996, Vol 313, Iss 7055, pp 471-476	7	2	0	1	1	1	37							1	6	4	6	3	3	3	11	37	21	7	13	2	1	0	1	1	1	0	1	5	0	22	8	20	17.3	1	7	28	2	0	0	1	27	9	1	0		0	0
P	1996	Harrison-BJ Symmons-DPM Brennan-P Bankhead-CR Barrett-EM Scott-DGI Silman-	Inflammatory Polyarthritis in the Community Is Not a Benign Disease - Predicting Functional Disability One-Year After Presentation	JOURNAL OF RHEUMATOLOGY, 1996, Vol 23, Iss 8, pp 1326-1331	7	2	0	1	1	1	32							0	1	4	5	7	7	4	4	32	22	9	8	1	0	1	1	0	4	0	0	7	3	18	6	17	8.4	2	6	25	1	0	0	1	26	6	0	0		0	0
P	1996	Harrison-BJ Symmons-DPM Brennan-P Barrett-EM Silman-AJ	Natural Remission in Inflammatory Polyarthritis - Issues of Definition and Prediction	BRITISH JOURNAL OF RHEUMATOLOGY, 1996, Vol 35, Iss 11, pp 1096-1100	5	2	0	1	1	1	33							1	0	3	3	9	6	3	8	33	18	7	9	1	1	3	1	0	2	0	0	9	2	14	5	16	9.9	1	13	19	1	0	0	1	27	6	0	0		0	0
P	1996	Jones-MA Silman-AJ Whiting-S Barrett-EM Symmons-DPM	Occurrence of Rheumatoid-Arthritis Is Not Increased in the First Degree Relatives of a Population-Based Inception Cohort of Inflammatory	ANNALS OF THE RHEUMATIC DISEASES, 1996, Vol 55, Iss 2, pp 89-93	5	2	0	1	1	1	12							0	1	0	2	4	3	1	2	13	9	3	4	0	0	0	0	3	2	2	0	4	0	4	4	7	8.3	2	4	7	1	0	1	1	11	2	0	0		0	0
P	1997	Brennan-P Bankhead-C Silman-A Symmons-D	Oral-Contraceptives and Rheumatoid-Arthritis - Results from a Primary Care-Based Incident Case-Control Study	SEMINARS IN ARTHRITIS AND RHEUMATISM, 1997, Vol 26, Iss 6, pp 817-	4	1	0	1	1	1	20								0	2	6	8	2	2	3	23	14	8	4	1	1	0	1	0	0	5	0	0	1	5	10	18	13.2	2	6	16	0	1	0	1	20	2	1	0		0	0
P	1997	Harrison-BJ Silman-AJ Barrett-EM Scott-DGI Symmons-DPM	Presence of Psoriasis Does Not Influence the Presentation or Short-Term Outcome of Patients with Early Inflammatory Polyarthritis	JOURNAL OF RHEUMATOLOGY, 1997, Vol 24, Iss 9, pp 1744-1749	5	1	0	1	1	1	19								0	0	0	2	5	5	7	19	11	4	9	1	0	0	0	0	4	1	0	4	0	9	2	7	8.4	2	6	12	0	0	1	1	18	1	0	0		0	0
P	1997	Harrison-BJ Thomson-W Pepper-L Ollier-WER Chakravarty-K Barrett-EM Silman-AJ	Patients Who Develop Inflammatory Polyarthritis (Ip) After Immunization Are Clinically Indistinguishable from Other Patients with Ip	BRITISH JOURNAL OF RHEUMATOLOGY, 1997, Vol 36, Iss 3, pp 366-369	8	3	0	1	1	1	10								2	0	2	2	0	1	3	10	7	1	5	0	0	0	0	0	4	0	0	2	0	5	1	6	9.9	1	2	8	0	0	0	1	9	1	0	0		0	0
P	1997	Silman-A Bankhead-C Rowlingson-B Brennan-P Symmons-D Gatrell-A	Do New Cases of Rheumatoid-Arthritis Cluster in Time or in-Space	INTERNATIONAL JOURNAL OF EPIDEMIOLOGY, 1997, Vol 26, Iss 3, pp	6	2	0	1	1	1	11								0	0	1	2	5	1	2	11	9	1	5	0	0	0	0	0	0	0	0	0	0	5	3	8	7.1	1	1	10	0	0	0	1	9	2	0	0		0	0
P	1997	Symmons-DPM Bankhead-CR Harrison-BJ Brennan-P Barrett-EM Scott-DGI Silman-AJ	Blood-Transfusion, Smoking, and Obesity as Risk-Factors for the Development of Rheumatoid-Arthritis - Results from a Primary Care-Based Incident Case-Control Study in Norfolk, England	ARTHRITIS AND RHEUMATISM, 1997, Vol 40, Iss 11, pp 1955-1961	7	2	0	1	1	1	55								0	2	8	10	11	16	11	58	42	8	12	2	2	0	0	0	1	1	0	1	7	26	16	31	19.9	2	6	47	4	0	1	2	36	18	1	3		0	0
P	1998	Harrison-BJ Symmons-DPM Barrett-EM Silman-AJ	The Performance of the 1987 ARA Classification Criteria for Rheumatoid-Arthritis in a Population-Based Cohort of Patients with Early Inflammatory	JOURNAL OF RHEUMATOLOGY, 1998, Vol 25, Iss 12, pp 2324-2330	4	2	0	1	1	1	40									0	4	12	7	9	8	40	23	4	13	2	1	0	1	0	7	1	0	8	0	20	7	32	10.9	2	4	36	0	0	0	1	28	12	0	0		1	1
P	1999	Wiles-N Barrett-J Barrett-E Silman-A Symmons-D	Disability in Patients with Early Inflammatory Polyarthritis Cannot Be Tracked from Year-to-Year - An Examination of the Hypothesis Underlying	JOURNAL OF RHEUMATOLOGY, 1999, Vol 26, Iss 4, pp 800-804	5	2	0	1	1	1	10										0	3	2	3	2	10	6	2	2	1	0	0	0	0	2	0	0	0	3	7	1	10	10.9	2	3	7	0	0	0	1	9	1	0	0		1	1
P	1999	Wiles-N Symmons-DPM Harrison-B Barrett-E Barrett-JH Scott-DGI Silman-AJ	Estimating the Incidence of Rheumatoid-Arthritis - Trying to Hit a Moving Target	ARTHRITIS AND RHEUMATISM, 1999, Vol 42, Iss 7, pp 1339-1346	7	2	1	1	1	1	28											7	7	5	9	28	17	3	14	1	0	0	0	0	1	0	0	3	2	16	5	28	24.34	2	3	24			1	2	21	7				1	0
P	2000	Wiles-N Dunn-G Barrett-E Silman-A Symmons D	Associations Between Demographic and Disease-Related Variables and Disability over the First 5 Years of Inflammatory Polyarthritis - A Longitudinal Analysis Using Generalized Estimating Equations	JOURNAL OF CLINICAL EPIDEMIOLOGY, 2000, Vol 53, Iss 10, pp 988-996	5	3	1	0	0	1	5											0	1	0	4	5	3	2	2	0	0	0	0	0	0	0	0	0	0	3	2	0	12.1	2	0	5	0	0	0	1	5	0	0	0		0	0
P	2000	Wiles-NJ Dunn-G Barrett-EM Harrison-BJ Silman-AJ Symmons-DPM	One-Year Follow-Up Variables Predict Disability 5 Years After Presentation with Inflammatory Polyarthritis with Greater Accuracy Than at Base-Line	JOURNAL OF RHEUMATOLOGY, 2000, Vol 27, Iss 10, pp 2360-2366	6	3	0	1	1	1	7											0	2	0	5	7	7	0	2	0	0	0	0	0	2	0	0	0	2	2	1	0	10.9	2	1	6	0	0	0	1	7	0	0	0		1	1
P	2000	Silman-A Harrison-B Barrett-E Symmons-D	The Existence of Geographical Clusters of Cases of Inflammatory Polyarthritis in a Primary-Care Based Register	ANNALS OF THE RHEUMATIC DISEASES, 2000, Vol 59, Iss 2, pp 152-154	4	2	0	1	1	1	2														2	2	1	0	2	0	0	0	0	0	0	0	0	0	0	2	0		8.54	2		2				1	2					0	0
P	2001	Wiles-NJ Lunt-M Barrett-EM Bukhari-M Silman AJ Symmons-DPM Dunn-G	Reduced Disability at 5 Years with Early Treatment of Inflammatory Polyarthritis - Results from a Large Observational Cohort, Using	ARTHRITIS AND RHEUMATISM, 2001, Vol 44, Iss 5, pp 1033-1042	7	2	0	1	1	1	12												1	5	6	12	11	0	3	0	0	0	0	0	0	1	0	1	0	3	5	0	24.3	2	2	10	0	0	0	2	10	2	0	0		0	0
P	2001	Wiles-NJ Scott-DGI Barrett-EM Merry-P Arie-E Gaffney-K Silman-AJ Symmons-DPM	Benchmarking - The 5-Year Outcome of Rheumatoid-Arthritis Assessed Using a Pain Score, the Health Assessment Questionnaire, and the Short Form-36 (Sf-36) in a Community and a Clinic-Based Sample	ANNALS OF THE RHEUMATIC DISEASES, 2001, Vol 60, Iss 10, pp 956-961	8	3	0	0	0	1	3												1	1	1	3	3	0	1	0	0	0	0	0	0	0	0	0	0	2	2	0	8.5	2	1	2	0	0	0	1	3	0	0	0		0	0
P	2002	Goodson-NJ Wiles-NJ Lunt-M Barrett-EM Silman-AJ Symmons-DPM	Mortality in Early Inflammatory Polyarthritis - Cardiovascular Mortality Is Increased in Seropositive Patients	ARTHRITIS AND RHEUMATISM, 2002, Vol 46, Iss 8, pp 2010-2019	6	3	1			1	7														7	7	3	1	2	0	0	0	0	0	0	0	0	0	0	2	4		24.34	2		7				2	5	2				0	0
P	2003	Bukhari-MAS Wiles-NJ Lunt-M Harrison-BJ Scott-DGI Symmons-DPM Silman-AJ	Influence of Disease-Modifying Therapy on Radiographic Outcome in Inflammatory Polyarthritis at 5 Years - Results from a Large Observational	ARTHRITIS AND RHEUMATISM, 2003, Vol 48, Iss 1, pp 46-53	7	2	0			1																																	24.34	2						2							

Annex B: Assessors' report form

IN CONFIDENCE

Research Subcommittee of The Arthritis & Rheumatism Council

Assessor's Report on Application from: .....

OVERALL ASSESSMENT

Please indicate your opinion by placing ticks in the appropriate columns; if you do not wish to comment on a particular aspect please leave that line blank.

	high	medium	low	none
i) **originality of project**				
ii) **potential value to rheumatology**				
iii) **potential practical value**				
iv) **appropriateness of overall project design**				
v) **suitability of methods**				
vi) **feasibility within time proposed**				
vii) **standing of applicant in this field**				

on the information at present available, I therefore recommend:

A (strong support)	**B** (possible support)	**C** (no support)	**X** (uncertain until information requested below is available)
☐	☐	☐	☐

If you recommend a category other than **C**, *please answer the folowing questions:*

1. Duration of support acceptable ☐ *or* modify as indicated ☐

.....

.....

.....

2. Rate for salaries, expenses, etc. acceptable ☐ *or* modify as indicated ☐

.....

.....

.....

3. Other aspects Are there any factors concerning the career future of anyone mentioned in the application, or of the administrative proposals, that require special consideration or clarification?

no ☐ *or* yes, as indicated ☐

.....

.....

.....

4. Additional information Is any further information required? (It would be helpful if any suggestions could be worded so as to be suitable for transmission verbatim to the applicant.)

no ☐ *or* yes, as indicated ☐

.....

.....

.....

.....

.....

5. Interview Is an interview necessary to arrive at a fair assessment?

no ☐ *or* yes ☐

GENERAL COMMENTS Please give any general comments you may have overleaf.

Date ..... Signature .....

There is increasing pressure for research funders to demonstrate, and seek to maximise, the payback from the research they fund. This report, prepared for and funded by the Arthritis Research Campaign (**arc**), presents the results of an evaluation of 16 research grants awarded by **arc** in the early 1990s. The main objective was to develop a system for evaluating arthritis research, with a view to allowing arc to stimulate and manage the exploitation of research advances so that they translate into outcomes of practical benefit to people with arthritis.

This is the Volume 2 of the report and presents a collection of the case studies used in the study. These case studies all follow a similar format based on the conceptual model and provide a rich and detailed narrative on the payback of each research grant.

Volume 1 of the report presents a framework that conceptualises the relationship between research inputs, process, output and outcomes. Using this framework, we catalogue a diverse range of research output and outcomes arising from these 16 grants and make a series of quantitative and qualitative assessments comparing, for example, payback from project grants versus programme grants. In conclusion, we make six observations:

- There is a diversity of research payback.
- The researcher is the key driver of research translation.
- Short, focused project grants seem to provide value for money.
- Intended and unintended flexibility in funding is used advantageously.
- Referees' contributions to the peer-review process are of variable benefit.
- The payback framework could be operationalised and embedded by arc.

Both volumes of the report are available, as PDF files, from http://www.rand.org.

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