

Open innovation in neuroscience research and drug discovery

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Abstract

The pressures on the pharmaceutical industry have incentivised a number of new collaborative models of research and development which can be categorised as open innovation. Examples of the different types of models employed are discussed and some, but not all, of these have been used to promote research and drug discovery for central nervous system disorders. Some are completely open access, while others have some intellectual property restrictions. Going forward, more ways of promoting open innovation and the sharing of best practice, especially in the neurosciences, will stimulate research and hopefully accelerate new medicines development.

Keywords

Open innovation, central nervous system disorders, precompetitive collaboration

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What is open innovation?

Open innovation is a term that was first coined by Henry Chesborough (2003) although some of its principles were already in operation and use by companies in the early 1990s, most notably Procter and Gamble (Davila et al., 2012). A recent report by Pigott et al. (2014) defines open innovation as,

The process of innovating with others for shared risk and reward to produce mutual benefits for each organisation, creating new products, processes or ideas that could not otherwise have been achieved alone, or enabling them to be achieved more quickly, cheaply or efficiently.

For a company, this means taking the best and most effective route to moving an idea from concept to product or service whether it is using internal or external resources. In this regard, it differs from closed innovation where a company would keep control of all aspects of innovation, with all the necessary capabilities and resources required held internally in the company. Companies that excel in open innovation such as Philips, Unilever and Procter and Gamble create the culture and environment that allows ideas to be channelled down the most appropriate route. This can include spinning ideas out into new companies, in-licencing and out-licencing as well as making them freely available for anyone to exploit. In this way, open innovation can be seen as a proactive form of intellectual property (IP) management (Davila et al., 2012). It is important to note that open innovation is not synonymous with open access. Open access is a

form of open innovation but there are many different forms of open innovation as shown in Table 1.

Open innovation and pharmaceutical companies

For all governments and most medical consumers – private or public, the cost of novel drug development is becoming unaffordable (Munos, 2014). The direct (by illness) or indirect (support of patient by carers, families and friends) impact on economic productivity is escalating. Lifestyle and demographic changes, including a decrease in the relative proportion of carers in the coming decades, will exacerbate this crisis in healthcare as the incidence of long-term chronic diseases continues to increase. As the budgets for care provision come under ever more intense strain, with an increasing percentage of GDP devoted to healthcare in western economies, the crisis in healthcare will grow. The pharmaceutical industry in general, and its neuroscience drug discovery in particular, has been through a large amount of change over the previous decades with countless mergers, down-sizing of R&D functions within

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Table 1. Main types of open innovation initiatives.

Type of open innovation	IP model	Type of participants	Example	Neuroscience-related example
Precompetitive collaboration	Background IP can be shared among participants	Primarily companies and/or academia	Innovative Medicines Initiative (IMI)	NEWMEDS for schizophrenia
Restricted sharing of tools and reagents (e.g. compounds)	Originator of tool or reagent usually retains some IP	Company to company or company to academia	Lilly Open Innovation Drug Discovery programme	NCATS compound list has neuroscience-related molecules
Use of facilities and capital equipment	Variable depending on initiative	Primarily companies and academia or biotech	GSK Open Lab at Tres Cantos	No specific neuroscience example
Crowdsourcing	Variable depending on initiative	One pharma company and academia/biotech	Bayer Grants4Targets	DREAM ALS Stratification Prize4Life Challenge
Crowdfunding	Variable depending on initiative	Biotech/academia and general public	FutSci funding of cancer trial	ALS Ice bucket challenge
Open sharing of data	No IP rights usually	Primarily academic but some industry	GSK and Novartis data sharing for anti-malarial drug discovery	PRO-ACT database of ALS patient data
Open Source sharing of tools and reagents	No IP rights	Primarily companies and/or academia	Structural Genomics Consortium (SGC)	The NeuroSGC for PD and ALS Prize4Life

IP: intellectual property; NCATS: National Center for Advancing Translational Sciences; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis.

companies and closure of sites coupled with the opening of hubs in centres of academic excellence, for example, Astra Zeneca at Cambridge, UK, and Johnson and Johnson's Innovation Centres in San Francisco, Boston, London and Shanghai (Gautam and Pan, 2016). Many companies have either closed (e.g. GSK) or significantly down-sized (e.g. AstraZeneca) their neuroscience R&D in the United States and Europe. However, there is still a high unmet need in both neurological and psychiatric disorders as discussed by Nutt and Attridge (2014). Recent information (Mullard, 2016) that the likelihood of reaching approval for a drug entering Phase I for both neurology (8.4%) and psychiatry (6.2%) was lower than average across all indications (9.6%) means that new business models for pharmaceutical R&D are even more imperative for central nervous system (CNS) disorders. The lack of R&D in psychiatric disease is a reflection, in part, of the lack of validated biomarkers and animal models as well poor disease understanding (Cook et al., 2014). This complexity coupled with the plethora of potential biological targets that have arisen from genomic research makes the selection of the best target a significant challenge. Furthermore, massive duplication of effort, due to secrecy fuelled by current patenting strategies in both the drug discovery industry and academia, has effectively reduced the number of drug targets and hypothesis that can be efficiently tested with finite global public and private investment (Edwards et al., 2011).

Compared to several years ago (Hunter and Stephens, 2010), a large number of pharmaceutical companies have now declared that they have adopted an open innovation strategy and 55% of the top 20 pharmaceutical companies of 2016 by revenue have links to open innovation portals on their web pages. An analysis by Schuhmacher et al. (2013) showed that just under 50% the pipeline products of 13 multinational pharmaceutical companies were externally sourced indicating a greater receptivity to external innovation coupled with an 'introverted innovation management'. By this, the authors meant that the companies had a tendency to use internal know-how and expertise when managing R&D activities. A natural extension of this is that although

pharmaceutical companies are externally focussed, a lot of the management culture in terms of how these collaborative and precompetitive activities are managed is still along very traditional lines with a fear of 'loss of control'. Nevertheless, there are a wide range of types of initiatives that companies are engaged in that fall under the banner of open innovation and the most common of these will be discussed and the involvement of neuroscience drug discovery specifically in them examined.

Precompetitive research collaborations

One of the earliest examples of precompetitive collaboration between companies and academia is the Division of Signal Transduction Therapy (DSTT) at Dundee University, formerly known as the Dundee Kinase Consortium. This was formed in 1998 and currently consists of AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck KGaA, Pfizer and 20 academic research teams. In this collaboration, all unpublished results are shared between the collaborators, along with reagents, technology and technical know-how. Academic staff involved in DSTT sign confidentiality agreements protecting the companies' IP, although they can still publish papers based on the collaboration's research. Once a company takes on a programme internally, then subsequent data do not have to be shared with collaborators (Savage, 2016).

Precompetitive collaborations of this type are probably the area of open innovation that has seen the most growth over the past decade (Wang et al., 2015). The largest example of a pharmaceutical-based precompetitive research collaboration is the Innovative Medicines Initiative (IMI). The first IMI programme was funded by the EU Framework 7 programme which committed 1 billion euros from the Commission together with 1 billion euros worth of funding from industry. There were two important features of this public-private partnership. The first is that the industry funding was

Table 2. Neuroscience-specific projects in the IMI (2008–2014).

Acronym	Full title	Website	Disease area covered
AETIONOMY	Organising mechanistic knowledge about neurodegenerative diseases for the improvement of drug development and therapy	www.aetionomy.eu	Alzheimer's disease and Parkinson's disease
EMIF	European Medical Information Framework	www.emif.eu	Alzheimer's disease (also metabolic disease)
EPAD	European Prevention of Alzheimer's Dementia Consortium	www.ep-ad.org	Alzheimer's disease
EU-AIMS	European Autism Interventions – A Multicentre Study for Developing New Medications	www.eu-aims.eu	Autism
EuroPain	Understanding chronic pain and improving its treatment	www.imieuropain.org	Chronic pain
NEWMEDS	Novel Methods leading to New Medications in Depression and Schizophrenia	www.newmeds-europe.com	Schizophrenia and depression
PharmaCog	Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in the early clinical development	www.alzheimer-europe.org/Research/PharmaCog	Alzheimer's disease

IMI: Innovative Medicines Initiative.

Extracted from Innovative Medicines Initiative: Key Facts and Figures (https://www.imi.europa.eu/projects-results/project-factsheets?keywords=&status=All&tags=All&im_i=1&call=All).

provided not as cash but as ‘in-kind’ contributions, for example, people and technology. This meant that the quality of interactions between people on the projects was high and that there had to be long-term commitment to the area on the part of the companies involved. The important feature was that the problems to be addressed, the research questions if you will, were set by the group of industry representatives that constituted the European Federation of Pharmaceutical Industries and Associations (EFPIA) Research Directors Group. This meant that these topics were of interest to more than one company and again represented problems that companies had a long-term commitment to solving. Once the call topics were agreed, outline proposals were invited from consortia of academia, patient groups, small and medium-sized enterprises (SMEs) and so on to address the topics set out in the call. The proposals were peer reviewed and a final winning proposal was selected to work up a full proposal with the pharmaceutical industry partners.

The IMI allocated about 10% of the funding available directly to brain disorders over the 6 years of the project (*Nature News*, 2014) and involved contributions from 25 pharmaceutical companies. A list of the specific neuroscience-related projects is given in Table 2. There have already been important outcomes from these projects. For example, the Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS) project has come up with a more efficient design for new antipsychotics (Rabinowitz et al., 2014) but also highlighted a number of issues in clinical trial design, for example, the effect of inclusion criterion definitions (Rabinowitz et al., 2013). Additional outputs include a range of tools useful not only in schizophrenia and depression but also for other indications, for example, DupCheck, to check whether patients are already enrolled in clinical trials and a machine learning tool box for pharmacological imaging and pattern recognition (see <http://www.newmeds-europe.com/en/9729.php>).

Compound sharing

This has sometimes been referred to as a form of crowdsourcing molecules although frequently it happens among limited participants (McGilvray 2016). There are good reasons for that since a

company's chemical collection can be considered a very valuable asset. Limited sharing however allows some monetisation of that asset (Reichman and Simpson, 2016). Preclinical compound sharing has been carried out in a variety of ways. In some instances, drug companies have portals where academics can submit their molecules for screening by the company in the companies' assays, for example, Lilly Open Innovation Drug Discovery programme. For clinical compounds, several repositories have been established – the first was the National Center for Advancing Translational Sciences' (NCATS) New Therapeutic Uses programme (<https://ncats.nih.gov/ntu>) with over 20 compounds in the 2014 list. The second initiative has been funded by the Medical Research Council with a range of compounds from seven pharmaceutical companies (<https://www.mrc.ukri.org/documents/xls-csv/mrc-industry-asset-sharing-initiative-compound-list-2016>). Both of these programmes include drugs that could be useful for CNS indications, for example, cannabinoid agonists and H3 antagonists.

Sharing of facilities or equipment

There are fewer examples of this in the drug discovery sector than in other sectors such as electronics. Many of these occur within the confines of innovation hubs or science parks where expensive biomedical instruments, for example, electron microscopes and nuclear magnetic resonance (NMR) machines, are usually centralised and shared. One of the earliest examples of sharing of facilities and expertise is the GSK Open Lab at Tres Cantos in Spain (<http://www.openlabfoundation.org/about/partners.html>). This facility is dedicated to developing new medicines for diseases of the developing world. It was established in 2010 and to date has received £10 million of funding from GSK. Visiting scientists have access to expertise, for example, in medicinal chemistry, pharmacology, preliminary toxicology and biochemistry as well as facilities like NMR and liquid chromatography–mass spectrometry (LC/MS) spectrometry and high-containment laboratories. In 2012, Bayer started its first pharmaceutical CoLaborator in San Francisco and by 2018 it had

four – the additional three are located in Kobe, Berlin and Moscow (<https://www.colaborator.bayer.com/>). The aim of these is to give entrepreneurs and young life science companies suitable laboratory and office infrastructure and access to the company's research expertise and infrastructure as well as a first point of contact in the search for partnering options.

Because of the huge savings to be made in equipment sharing, especially for early-stage drug discovery companies, many science parks such as the Babraham Campus near Cambridge in the United Kingdom do make facilities available. Much of the work carried out both at the Babraham Research Institute and the companies on the Babraham Campus is relevant to neuroscience and thus the sharing of facilities should benefit neuroscience drug discovery in the long term. These include the Technology Development Laboratory (TDL), which provides access to resources, equipment and space so that early-stage concepts can be developed to commercially viable opportunities. The TDL staff also offer fee-for-service scientific assistance across many fields including molecular biology, protein biochemistry, cell biology and immunology. Companies located on the Campus also have access to the Babraham Institute's facilities including bioinformatics, imaging, mass spectrometry, next-generation sequencing and flow cytometry as well as access to *in vivo* laboratories.

In Sweden, the Swedish government allocated money to establish a platform that academics could use to support their drug discovery efforts – the Science for Life Laboratory Drug Discovery and Development (SciLifeLabDDD) platform. The lab was established at two nodes, Uppsala and Stockholm, in 2014 and it has all the technologies needed for small molecule and protein therapeutic drug discovery, for example, medicinal chemistry, protein expression, screening, compound handling, systems pharmacology and drug safety (Arvidsson et al., 2016). Currently, there are at least three neuroscience-based projects being run at the platform (2018: <https://www.scilifelab.se/platforms/ddd>).

Crowdsourcing

Crowdsourcing is a term that was first coined in 2006 as an Internet-enabled business model that harnessed the creative ability of agents external to an organisation (Bentzien et al., 2015). Some companies run their own crowdsourcing challenges – for example, Bayer started with two global crowdsourcing programmes. The first, Grants4targets (www.grants4targets.com), was introduced in 2009. It supports research on novel drug targets for applications in Bayer's focus areas – oncology, gynaecology, cardiology, haematology and ophthalmology – through funding and through expertise and technologies in drug discovery. Proposals are submitted online and two types of grants are available: Support Grants (EUR 5000–10,000) for research on targets at the early stages of discovery and Focus Grants (EUR 10,000–125,000) for more mature ideas as a first step towards transferring a target to the drug discovery process. This has proved so successful that in 2016 a second programme, Grants4Indications, was announced (www.grants4indications.bayer.com). While the first initiative clearly had no relevance to neuroscience, the second seeks to look for new indications for Bayer compounds and clearly these could include neurological or psychiatric diseases. More challenges have followed such as Grants4indications in 2017 (<https://grants4indications.bayer.com/home/>) which looks at new indications for Bayer drugs.

Other pharmaceutical companies have used crowdsourcing providers, and Astra Zeneca has used Innocentive (which was a crowdsourcing company originally spun out of Lilly) to seek potential solutions to two neuroscience challenges – novel biomarkers for neuropathic pain (ideation) and seeking substances with activity on the nicotinic acetylcholine receptor (reduction to practice; Bentzien et al., 2015).

A different type of crowdsourcing, which has already been used for a neuroscience indication, is obtaining data directly from patients using an app on their mobile phone. In 2017, Novartis partnered with Sage Bionetworks (who run a number of crowdsourcing projects) to do just this in multiple sclerosis (MS). This study, called the 'Evaluation of Evidence from Smart Phone Sensors and Patient-Reported Outcomes in Participants with Multiple Sclerosis (elevateMS)', will collect sensor-based data from physical tasks and symptoms, thereby providing objective real-world evidence about the issues for patients with MS. The mobile app was designed with input from patients, neurologists and advocates. Patients fed back on the app's user interface, what the study should measure, and how the app should track patient activity and disease symptoms. This type of evidence gathering can be used in a number of different CNS diseases and ultimately in the trials of new therapeutics.

Crowdfunding

Crowdfunding has been used with some success to fund clinical trials (Sharma et al., 2015) and are probably the most useful, because of the smaller amounts raised, for pilot studies. A search of neuroscience-related research projects on the experiment platform, a scientific crowdfunding website (<https://experiment.com/discover/neuroscience>) revealed a wide range of projects (sensors, clinical trials, basic research) and amounts sought and raised (from US\$460 to US\$5 million).

Open source sharing of tools and reagents

Recently, several open source precompetitive public-private partnerships have catalysed discoveries in pioneer, high-risk areas of early-stage drug discovery. In the area of neuropsychiatry, emerging initiatives are aiming at more efficient structuring of early- and late-stage discovery platforms, with a strong emphasis on the open science (Edwards et al., 2011; Norman et al., 2011; Scott, 2016). This is further reinforced by a recent report from the NY Academy of Science (2013) recommending the adoption of open, precompetitive initiatives to accelerate the rate of discoveries.

One such example is the Structural Genomics Consortium (SGC), formed in 2003 with the open access ethos as its core tenet. It has since catalysed research in new areas of human biology and drug discovery by focusing to a large extent on less well-studied areas of human biology and disease. The SGC, strongly supported by its pharmaceutical industry partners, places all its research output and reagents, including industry-standard small molecule chemical inhibitors (probes) in the public domain without restriction on use. These are used widely to interrogate protein targets and signalling pathways to further our understanding of disease mechanisms, for instance.

The establishment of a precompetitive and patent-free Consortium has had many advantages; some were obvious and others unexpected. What was clear at the outset was that adhering to open access principles allowed cross-leveraging of public and private funds to explore novel areas of human biology in an organised way, thus reducing duplication and sharing the risks and costs that no single institution could bear alone. It was also clear that it would place the emphasis on the science and on accelerating the transfer of knowledge to the scientific community, rather than on commercial interests. The SGC has disseminated tens of thousands of cDNA clones and thousands of samples of several chemical inhibitors, with hardly any transactional costs. Hundreds of academic papers report the use of SGC-generated reagents, and across the pharmaceutical and biotechnology sectors, SGC reagents are used daily to advance internal drug discovery programmes.

What was less appreciated was the extent to which the consortium's position would resonate with the academic and clinical communities. The SGC collaborative network now comprises scientists in hundreds of institutions around the world – all of whom have committed to the open access principles and who contribute their ideas and results to the public domain (Lee, 2014).

This has enabled an unprecedented acceleration in discoveries of new drug targets, backed by robust, reproducible and diversified data, and culminating in pioneer clinical trials in less than 3 years – compared to the typical range of 6–30 years observed in the closed model (Knapp and Sundstrom, 2014), and at a minimal fraction of the usual investment. Some preliminary studies have analysed the SGC's model although most are narrowly focused in more immediate aspects, such as increases in industrial productivity (Jones et al., 2014; Marcello, 2015).

In an effort to further accelerate and amplify the impact of open access/open source data and reagents, the SGC initiated two novel programmes – one focused on an open patient-derived cell platform and another working closely with patient and disease foundations in early-stage drug discovery. The first one is driven by an important scientific need: predictive assays based on human tissue and primary cells. Preclinical studies with conventional proliferating cell lines and animal models of disease have usually proven unable to predict drug efficacy in human trials, especially in neurosciences. The aim is to identify and validate pioneer targets by profiling the highest-quality chemical and antibody tools in the most relevant, highest-quality assays based on patient cells (primary or induced pluripotent stem cells) and tissues (Edwards et al., 2015) – with results being anonymised and then shared openly without restrictions on its use.

The second one builds disease-specific, patient-driven organisations who are increasingly frustrated at the lack of progress and success of the current drug discovery and development model. These organisations have developed into fully fledged research-oriented organisations, moving beyond the historical reactive grant-giving model to organisations that are driving, leading and funding cutting-edge, patient-centric disease-specific research agendas. Through collaborations, the SGC and disease foundations like the Alzheimer's Disease UK have the potential of bringing together matured and sophisticated research capability and platforms from either side to multiply their impacts: the SGC's disease-agnostic approach with all the novel targets and technologies

developed in its extensive preclinical research platform implemented in six leading academic institutions across the globe with the disease-specific knowledge, research infrastructure and tools as well as the clinical network, drive, passion and sense of urgency from disease foundations and its supporters – all committed to work in cooperation and sharing results and data to accelerate discoveries (<http://oxford-ddi.alzheimersresearchuk.org/news/alzheimers-research-uk-drug-discovery-alliance-sgc-announce-collaboration-dementia-research/>).

More recently, the SGC has initiated two strategic partnerships of direct relevance to neuroscience drug discovery. The first one – called the NeuroSGC – has the SGC and the Montreal Neurological Institute and Hospital (aka 'The Neuro') partnering to discover new targets for drug development for neurological diseases. The NeuroSGC will initially focus on Parkinson's disease and amyotrophic lateral sclerosis (ALS) and aims to use patient-derived samples to identify new potential targets and drug treatments. Because of its dual nature as a hospital and research institute, The Neuro has access to samples from ALS and Parkinson's disease patients who believe that being part of the research discovery process is critically important. The Neuro's Open Drug Discovery Platform, part of the Tanenbaum Open Science Institute (Poupon et al., 2017), develops human-induced pluripotent stem cells (hiPSCs) from these samples that can then be genetically reprogrammed to become any cell in the human body. The role of the NeuroSGC team will be to implement and run the cell- and tissue-based assays at The Neuro, ensuring that they are reproducible, robust and relevant to the disease. The Centre for Drug Research and Development will help the NeuroSGC develop the automated and high-content screening part of the assays. The NeuroSGC will also do the initial analysis on the assays, identifying the most promising targets for further research (<https://www.mcgill.ca/neuro/channels/news/new-open-science-partnership-will-pave-way-better-treatments-faster-283247>).

In its second neurosciences partnership, the SGC and three of the leading research foundations for ALS – the ALS Association (US), the Motor Neurone Disease Association (UK) and ALS Society of Canada – have created the open access ALS Reproducible Antibody Platform (ALS-RAP – <https://www.thesgc.org/news/als-rap>). This is in response to the lack of a common and transparent validation framework, leading to antibodies with high variability and low specificity – yielding questionable results, wasting time and resources and, more importantly, compromising steady scientific progress to understand this challenging disease. The ALS-RAP will generate antibodies for novel ALS-associated genes, as nominated by the international ALS research community, as well as establish validation for novel and existing (commercial and academic) renewable antibodies to support the generation of reproducible data to uncover ALS biology.

Conclusion

It is clear that the nature of collaboration and interactions between academia and the pharmaceutical industry is evolving. Although there are some really positive examples such as the IMI and the SGC, the pace of change really needs to accelerate if new therapeutics for neurological and psychiatric diseases are going to be developed in the near term. This means that there needs to be good cooperation and understanding not just between academia

and industry but between regulators, payors and patients as well. The brain is a highly efficient organ that develops through growing new connections and then pruning those that are not efficient and strengthening those that work well; perhaps, we should emulate that model in developing and learning from new and past collaborations.

Declaration of conflicting interests

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