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Biotechnology and intellectual property

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Through out the decades, biotechnology has emerged as research area which requires the understanding of the biological intricacies of nature. Much of the scientific knowledge has been imparted to transfer beneficial genetic traits from one species to another to enhance or protect an organism. In the field of medicine, these tasks have ranged from the production of proteins, such as insulin, to selective targeting and binding of specific cell types. Since the discovery in the year 1800 that the human body is composed of cells and proteins that are susceptible to infection but can also combat pathogenic microbes, the perceived battlefield has challenged our imagination to develop biopharmaceuticals – biologically based therapeutic products. As we enter the information age, the presence of excessive amount of biologic and genetic data, coupled with exponential growth in computing power, mean that the rate of developing novel biopharmaceuticals is not at all limited by the ability to identify targets and clone macromolecules. But after post GATT period, this research area has faced a lot of restrictions by the government to follow the patent protection of these biologically engineered products of plant or human cell origin. Thus, biotechnology which is usually defined as any technique that uses living organisms or substances from organisms to make or modify a product, to improve plants or animals or to develop microorganisms for specific uses, is facing serious constraints like lack of skilled human resources, funds to bear the cost of these projects, the sophisticated infrastructure and facilities and stringent government laws.

Key words: Biotechnology, patents, biomodulation, tissue.

INTRODUCTION

In early fifties, new interest in the field of cross fertilization between biology and physics, bionics and bioelectronics has come up, leading to convergence of several disciplines with biology. The history of this merged field is brought into light by the contribution of great biologists; Frederick Sager; who completely analyzed the protein insulin and J. Watson and F.H.C. Crick who discovered the double helix structure of DNA (Sanger and Thompson, 1953; Watson and Crick, 1953). Today also, biotechnology and genetics research have been the subject of extensive investment by both the public and private sectors with the resulting product and process making a significant and increasing contribution to human health. Health care biotechnologicals including genetic innovations have been the subject of intellectual property rights for many years. Over the last decades as the number of such innovations has increased their impact on health care has grown substantially. Recently the government and health care providers have shown concern regarding the licensing of these biologically engineered products to protect them from exploitation, particularly in health care field (Spranger, 2003). Although biotechnological research is becoming increasingly relevant in pharmaceutical applications, it is still only a small part of the pharmaceutical industry. New techniques such as hybridoma and gene transfer technologies are leading to the development of new strains with higher productivity and improved stability.

Advances in biotechnology may make it possible to follow a more enlightened pathway to develop the products necessary to fight off the massive disease problems of developing nations. Biotechnology would make it possible to economically produce orphan drugs, which are needed for specific treatment found in smaller number of populations. Through recombination technology higher yields of complex molecules such as proteins and antibodies, which cannot be produced by chemical means, can be achieved. Thus with the advent of recombinant technology exclusive production of an isomeric compound (Puchooa, 2004; Arathoon and Birch, 1986) and human therapeutic proteins in large quantities and of high purity is possible. Apart from the possibility to produce these biopharmaceuticals in a form identical to that naturally occurring in the body, designing a meaningful improvement

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in activity, stability and bioavailability has also been achieved. Such recombinant therapeutic products will also be free of the dangerous contaminants that have occasionally arisen if such products are extracted from animals e.g. human growth hormone extracted from cadaver is associated with Creutzfeldt-Jakob degenerative brain disease. Proteins therapeutics for pharmaceutical and clinical use cannot be consistently, sufficiently, safely and cost effectively applied without the recent milestones of biotechnology that include the basic principles of DNA and cell recombination and fermentation (Ahou and Liwan. 1999a). Almost all the biopharmaceuticals available today, other than nucleic acid based therapies, are proteins or peptides. Our ability to identify novel and effective therapeutic proteins and peptides has advances at such a rate that we are now limited by the human efforts and resources needed to develop and demonstrate the clinical efficacy and safety of these candidates.

Today, because of the pressure on the industry to be more cost and time efficient, the discovery and development of new drugs within these companies occur in a highly integrated manner using new technologies and involving multidisciplinary project teams. The most significant discoveries fuelling the biotechnology industry occurred in the early 1970s, when Cohen and Boyer at Stanford University developed recombinant DNA technique and Kohler and Milstein produced monoclonal antibodies in Cambridge, U.K. (Stephen and Verhart, 1998). Thus, biotechnology is a frontier technology which has the the potential to provide substantial benefits to the society in a wide range of sectors such as agriculture, medical, health, forestry, animal husbandry and environment protection. Therefore, the strategy is to bring about change in biological science (including physiology, molecular biology, biochemistry and genetics). Unlike, other pharmaceutical fields, biotechnology are a field that can extend from agriculture to health care and to more innovative fields. And, with the perspective of an economist, this field after, information technology, can be the field for the product commercialisation and intellectual property rights (Murthy, 2004). Though it is very simple to say that the whole biotechnology is on molecular research but in reality this research involves number of issues to be discussed (EMEA, 1997, 1999b,) like, development of a suitable process at laboratory scale (especially for purity), scale up for technology transfer, production cost, compliance with the evolving FDA regulations and need for other regulatory approvals, compliance with the environmental restrictions and other environmentalist, availability of facilities and financing and documentation of process and quality controls.

Biotechnology research has been classified as basic research, translational research, applied research and beneficial research. This basic research generates knowledge i.e. the pathophysiology of any disease, the enzymatic invasion and the resultant cellular changes. The translational research involves engineered research i.e. engineering proteins for biosensor applications, engineered antibodies and engineered biomass such as tissue culture for biomass utilization for fuel, food and other purposes (Berthhold and Walter, 1994). Applied research involves improved techniques for detection of contamination, microorganism especially in animal cell lines, food and feeding stuffs. (Vasil et al., 1996). Beneficial research is the ultimate bioengineered product available to the public.

Due to the resources and viable government policies to help in achieving the developments in this field, the biotechnology areas can extend from high end point of floriculure to plant tissue culture. Products can be developed with high quality stands and effectiveness that they can compete in the global market and help bussiness realise maximum economic recovery (Allison and Lemley, 2002). Since biotechnology has the history of genomic research i.e. decoding of human genome to uncover the reasons for various diseases, the regulatory process is through biologic license establishments, which require that the data should be submitted in a new drug application. However, under the part of FDA modernization Act (passed in 1997), the regulatory agency has combined Establishment License Application (ELA) into one package called Biologic License Application (BLA). With the enactment of BLA process for biotechnology-based pharmacuticals, any faculty holding a current establishment license, can manufacture more than one recombinant product there by allowing a startup for this emerging field. In general, the relationship between the preclinical and clinical studies under BLA can be summarised (Watal 2002). With this advent, chances to illuminate protein interaction on molecular levels have shown to clear the mechanism of various drugs. More recently, the Bharat Biotech International Ltd (BBIL) has received the Genetic Engineering Approval Committee (GEAC) nod for conducting the Phase III clinical trial for its two novel recombitant products. It has also launched for the first time, the first line therapy for mycardial infarction (heart attack), deep vein thrombosis and pulmonary embolism, showing the promising hand of the government. Many products of nature (like specific antibiotics, microorganisms, protein etc.) have been successfully patented protecting the innovators right to reproduce. But it is debatable to categorize a naturally occurring substance as patentable, as it lacks novelty and inventive step. However if you enrich, purify or modify a product of nature in an industrially useful format, it is then patentable (WHO report, 2000). Considering the example of production of strain of Chinese Hamster Ovary (CHO) cells derived from cell line shows that validation is required at three stages namely A, B and C. Cell bank (stage A) could be like mycoplasm sterility, *in-vitro* virus, *in-vivo* virus, Bovine virus serum etc. Stage B involves validation of morphological and growth characteristics of the cellular productivity and stage C leads to end of production process which should be reproducible (DeRosnay, 1985). Therefore, validation for these biomodulated products require authenticity of source cells like adult stem cell, bone marrow cells or embryonic stem cells for generating tissues. All this data is provided to patent officers for filing and grant of patents. The development of the genetic resources of biodiversity which

is known as biotechnology is currently in a state of Intellectual Property Protection which protects the application of thoughts, ideas and information which are of commercial value. Under this protection earlier living organisms were largely excluded from protection but now attitudes are changing and biotechnology is receiving some form of protection. Till today, there is no clear international consensus on how biotechnology should be treated. However, bodies such as the Wild Intellectual Property Organization (WIPO), the United Nation permanent body responsible for intellectual property, and the Organization for Economic Cooperation and Development (OECD) have conducted separate studies and produced reports to make the government aware of potential problems and have offered some suggestions. United State Patent and Trademark Office (USPTO) have granted patents for the pure cultures of specific microorganism as well as medically important proteins. However, the main problem with this form of protection is that the secret generally becomes public once biotechnology is used commercially and thus the protection is lost. Some of the products of nature, which are generally patentable under US patent law, are given below (Weng and Delisi, 2000):

a) A pure microbial culture
b) Isolated virus
c) Specific purified proteins (erythropoietin)
d) Purified nucleic acid sequences (indulging isolated genes)
e) Other purified biomolecules (e.g. antibiotic, vitamin etc.)

In the late 1980s, the USPTO confirmed that they would consider issuing patents for non-human multicellular organisms. Some patents have been issued for some human genes, largely on the basis of use of cloned products. Patenting DNA sequences came under heavy legal and public scrutiny in 1992, when US National Institute of Health filed patent aplication on partial human sequences of DNA. This patent was rejected on the consensus that the patent protection should only be considered for nucleotide sequences that serve as diagnostic markers or code for proteins. The issue of patenting genetic material or transgenic plants/ animals remains a contentious one. The debate is not confined to technical and legal argument but has encompassed ethical and political issues, including public opinion. The increasing technical complexity and sophistication of the biological principles and processes upon which biotechnological innovations are based, has also made patent issues more difficult (Roychowdhury, 2005). Table 1 shows the tissue engineered patented products which are in the market:

In general, biological materials (specific cell proteins, genes, and nucleoside) which previously existed in nature are patentable provided they must be isolated/purified from natural environment and must confirm to the general patentability principles regarding novelty, non-obviousness, utility and sufficiency of disclosure.

The utility condition therefore prevents patenting of gene/genome function. Thus, it is not possible to patent human body, cloning of humans, use of human embryos for commercial purposes, modifying germ line identified in humans, modifying the genetic complement of an animal in relation of suffering to benefits. Secondly, manufacturing process used to produce a recombinant biological product is complex than the synthetic drug products and it includes numerous extraction, purification and concentration steps which further retards the process of patenting and the expiry period (usually 17-20 years) from the date of invention is too little for such invention leading to lack of rewards. Table 2 shows the patent expiry of various recombinant biologics (Schellekens, 2004; Rudin. and Weissleder, 2003).

The revolution in biotechnology has several implications for medicine and agriculture. The definition of biotechnology, according to technology assessment of United States Congress is any technique that uses living organisms or substances from other living organisms to modify the product, to improve plants or animals or to develop microorganism for specific uses. Therefore, biomodulation encompasses recombinant DNA technology. Now this technique has included many areas of plant and animal research. It has offered hope to restore the environment and protecting the endangered species as well as wastes from industries and oil mills (Daar et al., 2002).

The existence of microorganism and their role in contaminating foods are quite recent discoveries, dating back some hundred years. The Fermentation of foods and beverages was an art practiced without scientific knowledge for guidance. Fermentation is typically affected by bacteria and yeasts and facilitates preservation and storage (Ahmed et al., 2000; Steinkraur, 1983). It markedly improves nutritional and health quality in food products. Protein content of certain grain foods is increased by fermentation. Furthermore, fermentation and staling result in modification of starches which are associated with protection against colon cancer and gastrointestinal disease. Improvement and optimization of fermentation and bioprocessing is applicable in improving quality and functionality of foods. For example, milk undergoes fermentation when bacterial action causes it to curd, thus separating it from the thin watery whey. Modern cheese makers inoculate the milk with lactic acid bacteria (*Lactobacilli*) and other enzymes such as rennet to curdle the casein. This rennet is found in gastric juices produce in the fourth stomach of calves and other animals. Beverages and wine are also manufactured by action of yeasts. Many primary metabolites such as aminoacids, pharmaceutical compounds and a variety of chemicals, hormones and pigments are produced by industrial fermentation for commercial use. Some of the examples are given in Table 3. Another applicable enzyme like cellulase, which hydrolyses cellulose is produced by microorganism *Trichoderma konigi*, this enzyme aids in digestion. Based on this research, a library of DNA fragments have been compiled which contains the isolated genomes of variety of organisms. This collection of fragments is used to isolate specific genes from transgenic crop plants or weeds or insect, microorganisms or pests that may cause problems. One challenge in creating transgenic transgenic animals is to ensure that the transgene turns on

Table 1. Tissue engineered products currently marketed. (Galbraith, 2004)

Product name	Manufacturer and address	Cell type	Clinical use
Epicell ®	Genzyme (cambridge, MA, USA)	Keratinocytes	Burns
Apligrof ®	Organogeniesis (canton, MA, USA)	Fibroblasts/ Keratinocytes	Ulceration of skin
Epidex ®	IsoTis (Luranne, Switzerland)	Keratinocytes	Ulceration of skin
Transcyte ®	Smith and Nephew (Memphis, IN, USA	Fibroblasts	Burns

Table 2. Patent expiry dates for recombinant biologics of US and Europe (Schellekens, 2004).

Product	Innovator	Market exclusivity expiry -US	Market exclusivity expiry -Europe
Somatroptin	Genentech	Expired	Expired
Insulin	EliLilly	Expired	Expired
Interferon alpha 2	Biogen / Roche	2002	2003-2007
Erythropoietin-alpha	Amgen	2013	2004

Table 3. Drugs derived from tissue culture (Karadikar and Ghaskadbi, 2005).

Drug	Cell model	Action
Procainamide Hydrochloride	Chick Embryo	Antiarrhythmic Drug
Gooseecoid*	White Leghorn chick eggs	Molecular modulation of mesodermal structures.
Equine antitoxin	Monoclonal antitoxins	Therapy for botulism
Ciprofloxacin	Recombinant antibody	Therapy for inhalation anthrax

*An important protein that controls cell migration during gastrulation.

at the right time and in the right tissue. Microinjection, the first developed by US in the mouse, has been the method of choice for most transgenic research (For review, see Allison and Lemley, 2002; Karandikar and Ghaskadbi, 2005**;** Yoshiyama et al; 2004; Doelle, 1984). Some microinjected fertilized eggs must be cultured *in vitro* until they reach a certain stage and others are transferred to hosts almost immediately after microinjection. Winning appoval of genetically engineered animals is the most recent victory for biotechnological companies, which otherwise had been a long struggle. In 1930, the US patents were granted for innovation in horticulture involving asextually propogated plant varieties then the term" invention" was given to this technique involved a living organism. The consensus related to the invention was upon that non naturally occurring non human multicellular organism are patentable and the first patent was granted to "Harvard Mouse" which is a genetically altered mouse, used as model to study breast cancer. Lawmakers seeking ways to protect intellectual property, which include patents, copyright, trade secrets and trademarks, have also addressed the issue of patenting genetically engineered animals. The patent debates have extended beyond the appropriateness of animals. It now encompasses questions about the consequences of commercial uses of patented organisms and about the merits of the technology itself. The open discussion of ethical, social and legal implications will be required to ensure that the end product of modern technology will contribute in a positive way towards a better world. Many products of nature (like specific antibiotics, microorganisms, proteins etc,) have been successfully patented (Reuter, 2005). Further, the stem cell research which has shown an immense diagnostic and therapeutic potential based on human stem cells seem to allow new medical treatments for serious diseases like Parkinson's, Alzheimer's diseases, leukemia or diabetes, but no industry would like to invest heavily on this technique unless the protection is there. Though the law on International Patent has shown protection for invention in biologicals for a period of 160 years but stem cells and DNA or any part of human body is not under this protection (Spranger, 2003). Based on this gene transfer method, drugs have been discovered for which transmitters (targets) have been located based on the biotechnological approaches (Karandikar and Ghaskadbi, 2005; Yoshiyama, et al., 2004; Ronald and Michael, 2003). A few examples are highlighted in Table 3.

Pharmaceutical biotechnology (Bogunia and Sugisaka, 2002) has introduced chemical transformations that yield products with important therapeutic value. For example conversion of cholesterol to other steroids such as cortisone and sex hormones. This research field involves the ability of microorganism to synthesize a wide variety of compounds and unusual substances to exploit comercially. Novel areas of pharmaceutical biotechnology involve the drug targeting to specific sites. Such application encompasses:

(a) Liposomal drug delivery: It includes microscopic spheres

with aqueous layer surrounded by shells. These are related to delivering protiens and peptides in various immune related diseases.
(b) Erythrocytes for loading human erythropoietin loaded by encapsulation and releasing the medicament by isotonic releasing procedure.
(c) Monoclonal antibodies: These are termed as magic bullets to diagnose and cure the immune response especially for cancer diagnosis and pregnancy detection like HCG in urine.

While a recent survey of scientific experts around the world indicated that the top biotechnological need for developing countries was technology for diagnosis of infectious disease apart from needs such as vaccines and increased nutrient content of food crops. It is required that without biomodulation, the yields and availability of food crops in developing countries is not possible therefore various ways in which biotechnology and genetic medication can be exploited for consumer benefits is supported (Bouis et al, 2003; William, 2003; Yan and Kerr, 2002; Chandler and Thorpe, 1986). In certain areas of biotechnology, techniques applied in genetic modification include mutation breeding, improved conventional breeding, transgenic modifications, DNA insertion, gene transfer and somatic hyberdization. These techniques provide insight into the potential for application of biotechnology in developing improved quality and functional foods for human nutrition and health, rather than simply for use in agricultural technology for improved yield and pest resistance. The production of increased levels of betacarotene (the precursor, lycopene) is shown to have physiological chemopreventive effects with regards to various cancers. Lycopene, commonly found in various carotenoid containing plants such as tomatoes and carrots, is an essential ingredient in maintaining eye health and vision and its increased production is a result of this research only. Utilization of plants as bio-factories for the production of vaccines in developing countries has been examined (Brink et al., 1998). This is attainable by transgenic plants for the production of adequate levels of desired vaccines and facilitates distribution to target populations who may otherwise not have access to such vaccines. It is purported that without biotechnology, the yields and availability of food crops in developing countries particularly in Sub-Saharan Africa would be heavily compromised, leading to inadequate supplies by the year 2025 (Dyson, 1999). Modifications that have been targeted and developed by various biotechnology companies include improvement in the oil content and composition of oil seeds such as legumes (Altman, 1999). Improvement in soybean oil quality is achieved by stabilization of the unsaturated fatty acids by increasing levels of the antioxidant, vitamin E.

Not only this, biotechnology in plant includes techniques like micropropogation for increased production of plants like sugarcane, bananas and Anthurium. Furthermore, for crop breeding and diagnosis of plant diseases, identification of pathogens carried out by serological tests based on the detection of monoclonal and recombinant antibodies or by using nucleic acid sequence based technology (Puchooa, 2004).

Conclusion

Though the literature has supported that biotechnology and biomodulation have not been in picture quite recently, but the sophistication involved and the sensitivity of cultured tissues have limited the scope of this emerging field to a few nations only. Furthermore, the evolution in this field is evidenced by making a mouse crucible of genetic manipulation and a remedy to human diseases by human embryonic stem cells through knock out/knock in gene system, a system where certain genes are removed and certain genes are inserted to have manipulated effect.

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