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Biotechnology Patents: Safeguarding Human Health

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1. Introduction

Health related problems affect every human being in an interconnected way, between generations and between societies, through spatial and temporal transitions. This timeless and all-pervasive aspect of health makes biotechnology unique among all technologies. While the science that drives biotechnology has far to go before it reaches a comparable level of maturity of eighteenth century physics, nevertheless biology is now deeply rooted in science; it has taken huge strides from its humble beginnings as a classification science to cell biology, to molecular biology, and now modestly to quantum biology. Erwin Schrödinger, a pioneer of quantum mechanics, was among the first scientists to suggest, in his book *What is Life*? (Schrödinger, 1944), that quantum mechanics can provide deep insights into life's mechanisms. However, our current understanding of how such quantum phenomena as superposition, entanglement, collapse of the wavefunction, etc. affect the chemistry of life is nascent (Ball, 2011).

The links in the supply chain that support biotechnology products and services include knowledge creation in R&D laboratories, product creation in biotechnology and pharmaceutical industries, and the ultimate receiver of therapeutic remedies—a human patient, *inter alia*, communally bound by morality and ethics. The fact that this supply chain, in principle, must cater to every human being on our planet, demands that it be protected with utmost care. Perhaps the most vulnerable link in this chain is the patentable knowledge created through privately funded R&D, which, unless diligently protected, is easy prey to infringement and theft. The maintenance of this chain is astronomically expensive and complex as it must balance some extreme needs: huge funding for exploration-intensive, curiosity-driven, 'blue-sky' R&D; highly risky upfront investments by industry before going to market; enormous funds to protect its intellectual property, if necessary, through litigation; and the need to provide safe and affordable remedies to very large populations of indigent people in the world to keep them healthy.

This chapter is written for biotechnologists who wish to get an understanding of the role patents could play in protecting and advancing their research output in the service of mankind when commercial applications of that research is the optimal means of doing so. Here we discuss general principles of biotechnology patents and related issues, rather than country specific ones.

2. The promise of biotechnology

Biotechnology took roots more than 10,000 years ago. The 'old or traditional' methods of biotechnology were mainly fermentation (through the unwitting use of microbes) to produce such products as beer, wine, and cheese, and cross-breeding (through the unwitting use of genetic material) to modify plants and animals through progressive selection for desired traits. These methods were developed empirically, patiently, and over countless years (Darwin, 1872; Smith 2009). It was only during 1857 and 1876 that the fermentative ability of microorganisms was demonstrated by Louis Pasteur (Smith, 2009). The discovery by Alexander Fleming of the antibiotic penicillin in 1929 and its large-scale production in the 1940s created major advances in fermentation technology. Since then the technology has advanced rapidly not just in the production of antibiotics but in many other biochemical products including organic acids, polysaccharides, enzymes, vaccines, and hormones. Modern breeding methods now selectively move genes within the same species or between species.

The 'new or modern' biotechnology that emerged in the 1970s is (Lilly, 1997) "the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services." Its methods use microbial, animal or plant cells or enzymes for the purposes of breaking down, synthesizing, or transforming materials. The scientific foundation of biotechnology was laid in a remarkable paper by James D. Watson and Francis H. C. Crick in *Nature* (Watson & Crick, 1953), which elucidated the double-helix structure of cellular DNA[1] (deoxyribonucleic acid). It gave birth to molecular biology and paved the way for developing recombinant DNA and cell fusion techniques along with scientific versions of 'old' biotechnological processes of modern biotechnology. Advances such as the transformation of *Escherichia coli*[2]; cutting and joining DNA strands (recombinant DNA technology) (Cohen, et al, 1973)[3]; the rapid cloning of DNA strands (PCR technique) (Mullis, et al, 1986); the ability to make monoclonal antibodies (hybridoma technique) (Köhler & Milstein, 1975)[4], etc. have made possible the creation of genetically engineered life forms capable of manufacturing new and improved drugs, such as, human insulin, interferons, vaccines, and treatments for a host of human afflictions such as septic shock, anemia, diabetes, AIDS, cancer, hepatitis, and heart attack. Genetically engineered transgenic animals such as the Harvard mouse[5] and the SCID mouse[6] play an immensely important role in cancer and immunology research, respectively. Many other transgenic life forms such as bacteria, cows, pigs, goats, etc. play a crucial role in

[1] Formally known as B-DNA. Other forms of DNA, e.g., A-DNA, C-DNA, D-DNA, Z-DNA, DNA-triplex, DNA-quadruplex, etc. also exist. B-DNA is the most stable helical form adopted by random sequence DNA under physiological conditions

[2] This bacterium was discovered by Theodor Escherich (and named after him) in 1885.

[3] The method was protected by three patents, which have now expired.

[4] Amazingly, the method was never patented.

[5] In 1988, Philip Leder and Timothy Stewart of Harvard University inserted a cancer gene into mouse egg cells and produced the patented transgenic mouse (U.S. Patent No. 4,736,866, now expired). Transgenic mice have become an incredibly powerful cancer research tool.

[6] The SCID (*s*evere *c*ombined *i*mmuno*d*eficiency) mouse lacks T and B lymphocytes and immuno-globulins, either from inbreeding with an autosomal-recessive trait or from genetic engineering. It is used as a model for studies of the immune system.

the development of therapies and the manufacture of pharmaceuticals. Thus one of the main objectives of biotechnology is to find means of scaling-up biological processes.

The mapping of the human genome independently by the Human Genome Project and by Celera Genomics in 2001 was a remarkable breakthrough in data collection to aid studies of the human body.[7] A crucial step in providing personalized medical care was thus taken. The breakthrough creation of a bacterial cell controlled by a chemically synthesized genome was reported by Craig Ventor's team in May 2010 in *Science* (Gibson, et al, 2010). The team reported synthesizing the genome of the bacterium *Mycoplasma mycoides*, comprising some 1.1 million base pairs as a proof of principle that cells can be produced based upon genome sequences designed in the computer. There is, of course, much to be learnt before one can construct and transplant whole computer-designed genomes of higher life forms. Important limiting factors are insufficient scientific knowledge of gene structure and function, and of microRNAs.

The potential curative abilities of stem cells come from their remarkable ability to renew themselves through cell division, sometimes even after long periods of inactivity, and to develop into many different cell types in the body. When a stem cell divides, each new cell, under appropriate circumstances, may either remain a stem cell or become a specialized cell such as a muscle cell, a red blood cell, or a brain cell. This unique regenerative ability of stem cells offers new opportunities for treating diseases such as diabetes and heart disease. However, much remains to be understood about them before reliable cell-based therapies can be designed to treat diseases.

The strength of modern biotechnology comes from its interdisciplinary nature and the interactions it orchestrates between various parts of biology and engineering. It draws insights and knowledge from a wide range of fields: biochemistry, microbiology, molecular biology, cell biology, immunology, protein engineering, enzymology, breeding techniques, chemical engineering, mechanical engineering, computational methods, mathematical simulation, bioinformatics, etc. The products and processes it spawns are the results of intense R&D, astronomical funding, and the unique entrepreneurial spirit of the biotechnology community in converting R&D results into therapies and cures, diagnostic tools and tests for disease detection, etc.

At present, biotechnology produces a range of embryonic enabling technologies for which some applications are known and many more expected. It is sustained by an enormous faith that suites of these enabling technologies, when further refined and augmented, will eventually find vast new applications of tremendous value to society. So the main benefits essentially lie in the future. The expected benefits include novel personalized pharmaceutical drugs and therapies for many diseases based on individual genomic information, genetically engineered healthier food with longer shelf-life, and new energy-efficient techniques for protecting the environment. The biotechnology industry's

[7] The first analyses of the working draft human genome sequence were reported in the February 16, 2001 issue of *Science* and February 15, 2001 issue of *Nature*. The papers from *Nature* included initial sequence analyses generated by the publicly sponsored Human Genome Project, while *Science* publications focused on the draft sequence reported by the private company, Celera Genomics. The papers can be found at http://www.ornl.gov/sci/techresources/Human_Genome/project/journals/journals.shtml.

dependence on multi-nation patent protection for survival in the marketplace is therefore not at all surprising. In fact, it is imperative that every biotechnology researcher understands the circumstances when acquiring and protecting his research results by patents is crucial. Breakthrough R&D results by themselves are not enough; to serve society they must lead to commercially viable products and processes or find philanthropic hosts or find federal support. Of particular research interest are genes and their corresponding proteins as they are believed to represent the future of diagnostic and therapeutic medicine.

3. Basics of patent law

A patent is a limited period monopoly intellectual property right granted to an inventor of any country by a Government of any other or same country for an invention that fulfills prescribed statutory requirements of the granting country. Patent monopoly differs from market monopoly; a patent is a right to exclude, a right to prevent trespassing. In this sense it is no different from, say, the right to keep our house or car or any other personal possession free from trespassers. A patent grants inventors the right to exclude others from making, using, selling or offering to sell, and importing the claimed invention in the country of grant; it does not confer any right to practice the invention. This is because in practicing the invention, one may well need complementary patents held by others unwilling to cooperate or there may be other laws, rules or regulations that prevent its practice.

Patents are issued only to the first inventor (or group of joint inventors) of an invention who files a legally valid patent application; all others are barred, even if they independently created the invention. Consequently, those other inventors must get a license from the first inventor if they wish to practice the invention. Patents granted by a country, like its laws, have no extraterritorial effect; hence patents are unenforceable, if infringed, in another country where the invention in question is not patented. If multi-country patent protection is required, the invention must be patented in each desired country. There is no such thing as a "world-wide patent".

The modern concept of patents dates back to the year 1421, when the Italian city-state Florence granted the first recorded patent to Fillippo Brunelleschi, for the design and use of a ship, the Badalone (seagoing monster; it was used to carry marble along the Arno river), for three years.[8] The Venetian Senate passed the first patent law on March 14, 1474, granting limited duration monopoly for original devices. That same Venice in 1594 granted Galileo[9] a "privilege" (what we know as a patent) on a machine which he had invented[10] "for raising water and irrigating land with small expense and great convenience," on the condition that it had never before been thought of or made by others. In his petition for the privilege he

[8] Christine MacLeod, Inventing the Industrial Revolution: The English Patent System. 1660-1800, Cambridge University Press, 2002, p. 11.

[9] Galileo Galilei (February 18, 1564 – January 8, 1642) is known as the father of modern science. He is perhaps the only scientist who is known by his first name rather than his last. In life sciences, Leonardo da Vinci, who preceded Galileo, is actually the unacknowledged "father of modern science" because of his remarkable studies of the human anatomy, and his empirical approach to science. See, e.g., Fritjof Capra, The Science of Leonardo, Doubleday, New York, 2007.

[9] Inkster, I., Potentially Global: A Story of Useful and Reliable Knowledge and Material Progress in Europe circa 1474-1912. Available at http://www.lse.ac.uk/collections/economicHistory/GEHN/GEHNPDF/PotentiallyGlobal-IInkster.pdf.

said, "it not being fit that this invention, which is my own, discovered by me with great labor and expense, be made the common property of everyone," adding further, that if he were granted the privilege, "I shall the more attentively apply myself to new inventions for universal benefit." Clearly, even the great scientist Galileo was not willing to divulge his invention for free exploitation by others without just compensation for his efforts. The Venetian Council granted Galileo a "privilege" for 21 years.

An invention is the creation of a new technical idea *and* of the physical means to accomplish or embody it. An idea *per se* is not an invention; a useful and successful implementation of an idea is. Four types of inventions are eligible for patents: process, machine, manufacture, or composition of matter, collectively known as statutory subject matter. They are subject to certain limitations that vary from country to country. However, there is universal agreement among nations that abstract ideas (e.g., mathematical formulas), laws of nature, natural phenomena, and products of nature are ineligible, but their application to a known structure or process may be eligible. What to exclude from patent monopoly is a national prerogative, largely derived from government policy decisions that accrue from the prevailing socio-economic conditions it must manage, and international treaty obligations.

Inventions that qualify as statutory subject matter must then face additional stringent statutory tests of substantial and credible utility (industrial application) in the eyes of an expert (such as a patent examiner in a patent office) in the field of the invention, novelty with respect to prior art (state-of-the-art) as it exists on the date of filing the patent application (in the United States there is some relaxation available), and nonobviousness, i.e., the invention has an inventive step that is unlikely to have been made by a person having ordinary skill in the art (PHOSITA), if required, assuming he would make the effort to study relevant prior art.

There is a *quid pro quo* attached to the grant of patents. To get a patent the inventor must put the invention in the public's possession. He must therefore fully describe his invention (written description requirement) in the patent application *before* the invention is formally examined by a patent examiner (examination typically takes two or more years). This description must be so clear and detailed as to enable a person skilled in the technologies related to the invention in question (an expert) to independently reproduce the invention (enablement requirement) without undue extra-solution activity, such as further research, data gathering, etc. on his part. In fact, this description should leave no doubt that the patent applicant was in possession of the claimed invention at the time of filing his application. Patents may be granted on improvements over existing inventions.

Patent laws of a country do not over-ride its other laws that might regulate the invention's use. For example, a new pharmaceutical cannot be marketed without the approval of appropriate authorities. Patent laws of a country may take into account moral, cultural, ethical, social, environmental, or scientific concerns of society.

In most countries with a patent regime, a pending patent application is placed in the public's possession 18 months after the first "priority" filing date[11] of the application or the

[11] The priority date of a patent application is the filing date of the first patent application (the priority document), which discloses the invention, and to which priority is properly claimed in the country of interest. The written description of the invention in the priority document should be detailed enough so as to enable one skilled in the relevant art to make and use the invention.

date of patent grant, whichever is earlier, by means of publication in print and world-wide-web enabled media. This gives an opportunity to others to improve upon the invention and possibly patent improvements (or focus on something else), without unduly stifling innovation. Limited period monopoly (usually 20 years from the priority filing date) is meant to prevent undue concentration of economic power, yet allow inventors (a rare breed) an opportunity to recover costs and earn profit from their long and expensive effort, not otherwise possible if others could reverse engineer the invention (often a far less expensive process) and duplicate it without penalty. The goal has been to get as many useful inventions into the public domain and in free use as soon as possible and thus enrich society as a whole without being unfair to the inventor. Patent protection is therefore a bargain struck by society on the premise that, in its absence there would be insufficient invention and innovation. Patent and other laws do not forbid an altruistic inventor (unless bound by a legal contract, say, to his employer) from freely placing his patentable inventions in the public domain without patent protection.

Patents are granted to inventors. The rights attached to a patent may be exercised by the patentee, his or her heirs or assigns during the term of the patent. A patent may be assigned (e.g., to one's employer) or licensed, with or without conditions attached, to one or more legal entities. A patent license to a licensee is an agreement that the patent owner will not enforce certain or all rights of exclusion against the licensee. Anyone else infringing the patent can be sued in a court of law by the patent's owner.

Limited period patent monopoly may provide an enormous first mover advantage to an entrepreneur, especially if it involves new technology. Alexander Graham Bell's two telephone patents—"Improvement in Telegraphy" (U.S. 174,465), granted on March 7, 1876, provided a monopoly on the basic principle of telephony, and "Improvement in Electric Telegraphy" (U.S. 186,787) granted on January 30, 1877, provided a monopoly on the telephone hardware—are outstanding examples. By the time the patents expired, American Bell (later to become AT&T) had acquired a "natural monopoly" in the telephone business.

An alternative to patent protection is to keep the invention a trade secret, which lasts as long as the secret is kept. This works if the invention's independent discovery is so unlikely that it can be monopolized indefinitely. Otherwise, independent discoverers of the secret can practice their invention with impunity, and worse, one of them may patent it and deny all others the use of the invention if not licensed from him. If one is keen to commercialize the invention, patent protection is much safer than trade secret, especially during negotiations with investors when detailed exposure of the invention may be necessary. At times, keeping marginal improvements of a patented invention as trade secrets may be preferred, especially if constrained by patenting costs.

3.1 Filing and prosecuting a patent application

To get a patent one must file a patent application at an appropriate office designated for the purpose, usually the patent office of the selected country. Each country has its own rules and regulations for filing and these must be strictly followed. To claim priority over others for an invention, it is necessary to be the "first to file" the application in accordance with the country's statutory requirements, which may include statutory grace periods. To claim

priority, one may file a provisional application which, at the minimum, fulfills the written description and enablement requirements, but it must be followed, within a year, by a proper application for the same invention as described in the provisional application, else the priority date is lost. Patent offices act only on proper applications. Provisional applications remain dormant during their life.

Prosecution is the process by which a (proper) patent application is defended before a patent office. The process often lasts several years. The application includes a complete description of the invention, a list of claims on statutory subject matter sought to be protected, and the requisite filled-in patent office forms, along with a filing fee. As prosecution proceeds, there may be other fees to be paid at various stages. For filing and prosecution details, visit the website of the desired patent office.

3.2 Patent claims

The legal core of a patent application is the list of claims. Each claim in this list covers and secures a process, a machine, a manufacture, a composition of matter, or a design, but never the function or result of either, nor the scientific explanation of their operation. The claims define the scope of a patent grant and function to forbid not only exact copies of an invention but also products that go to the heart of the invention but avoid the literal language of the claim by making a non-critical change. (See Section 4 below.) Whether a claim is allowed by a patent office is judged on the basis of novelty, nonobviousness, and utility (industrial applicability) of the invention being considered. Of course, claims are interpreted in light of the description of the invention provided in the patent application and information elicited during prosecution from the inventor, prior art and other sources. Almost all litigation related to patent infringement centers on the validity and scope of the claims.

In biotechnology, claims may be product claims, process claims, or product-by-process claims. Product claims may include such things as novel protein products, known but purified protein products, DNA sequence of a gene that encodes a particular protein, etc. Process claims may include preparation or use of recombinant DNA, the use of bacteria or cultured cells transformed with vectors containing DNA encoding a desired protein product, methods of use for proteins, methods for production or use of monoclonal antibodies, etc. Product-by-process claims deal with products that are too complex to be described conventionally (e.g., with reference to its composition, structure or some other testable parameter) and hence are described by the process with which it is made. By such claims it is not possible to use a new process to claim an old product. The focus here is the patentability of the product itself, not on the process used to describe it since the reference to a process serves only the purpose of defining the product.

There have been attempts by biotechnology inventors to get "reach-through claims" granted. Such claims seek to protect things which may not have been identified by the applicant in his patent application but which *may be* identified in the future by others by carrying out the invented process. This is different from the product-by-process claims as the products claimed in reach-through claims are speculative and hence do not fulfill the statutory requirements of disclosure and enablement. The purported justification for such broad extra-legal claims is that a pioneering invention paves the way for subsequent inventions and hence its inventor is "entitled" to capture some of the follow-on value based on the relative contribution of his pioneering invention. (Christie & Lim, 2005; IPO, 2009)

4. Infringement

Protecting an active patent when infringed can be a nightmare. It is time consuming, and hugely expensive (usually measured in millions of U.S. dollars) if it involves litigation. Alleged infringers, if challenged, are quite likely to counter-challenge by questioning the validity of the disputed patent. It is therefore imperative, especially in biotechnology where patents underpin business, that patent applications are prepared by experienced patent attorneys and that inventors work closely with them to minimize litigation possibilities. Considerations that go into the preparation of a fortified patent application include the doctrine of equivalent, prosecution history estoppel, reverse doctrine of equivalents, prior art or state-of-the-art, and the anticipated profile of the imaginary PHOSITA.

4.1 Doctrine of equivalents

Literal infringement of a valid active patent where the alleged infringer exactly or nearly exactly copies an invention without a licence from the patent owner is understandably rare. Generally, one tries to work around a patented invention by introducing differences and variations to avoid infringement. The question then is whether the modified product or process is remote enough from the patent that it will not infringe. Inadvertent infringement may arise if a product or process is invented in ignorance of an active patent whose existence is discovered only later, say, after a business commitment has been made to produce the product or use the process.

Such situations are partially dealt with by the judicially created doctrine of equivalents. This is a rule of claim interpretation under which a product or process, although not a literal infringement, is an infringement if it performs substantially the same function in substantially the same way to obtain the same result as a patented product or process. This doctrine, which has universal appeal, expands patent protection beyond the literal language of the claim. To determine what counts as an equivalent one must find a balance between two opposing public policies: (1) the importance of providing public notice as to what infringes by requiring clear and distinct claims, and (2) the need to prevent an infringer from avoiding liability by merely playing semantic games or by making only minor changes in the accused product or process to avoid the literal language of the claims (Belvis, 2003). In litigation, courts may seek expert opinion as to scientific or engineering facts and the decision may well depend on the most believable expert. Note that things that are equivalent for one purpose may not be so for other purposes. The Supreme Court of the United States sums it succinctly in *Graver Tank*[12]:

> What constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case. Equivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum. It does not require complete identity for every purpose and in every respect. In determining equivalents, things equal to the same thing may not be equal to each other and, by the same token, things for most purposes different may sometimes be equivalents. Consideration must be given to the purpose for which an ingredient is used in a patent, the qualities it has when combined with the other ingredients, and the

[12] *Graver Tank & Mfg. Co.* v. *Linde Air Products*, 339 U.S. 605 (1950). Available at http://supreme.justia.com/us/339/605/case.html.

> function which it is intended to perform. An important factor is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was.

In *Warner-Jenkinson*[13] the same Court then clarified and restricted the application of the doctrine of equivalents, holding that:

> Each element contained in a patent claim is deemed material to defining the scope of the patented invention, and *thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole*. It is important to ensure that the application of the doctrine, even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety. [Emphasis added]

This restriction on the doctrine of equivalents serves to eliminate one of the great mischiefs that could be played in patent law. Absent this rule, one could attempt to use the doctrine of equivalents to subvert patent claims. Rather than focusing on specific claim language and elements of the claim, the case could be tried based on how the accused device was equivalent to that claim as a whole. The Court further held that the equivalence determination was to be made at the time of the alleged infringement and not at the time the patent issued. It is likely that the less certain and more complex the courts perceive a scientific field underlying a technology to be (as is the case with biotechnology), the less scope will be given to patents under the doctrine of equivalents. If the patent is a pioneer in a whole new field, it will generally receive a broader range of equivalents than one for a narrow improvement to existing technology (Blenko, 1990). There are a few other restrictions that circumscribe the doctrine of equivalents: prosecution history estoppel, the reverse doctrine of equivalents, and prior art.

4.2 Prosecution history estoppel

During prosecution, quite likely, one or more claims will be rejected or require amendment to become narrower and detailed, in view of prior art. If a claim is allowed after being narrowed to avoid prior art, the patentee is barred from asserting the narrowed claim in its earlier broader sense under the doctrine of equivalents. This means that broad claims that have to be amended during prosecution can be difficult to enforce, if infringed. In short, rejected or narrowed claims cannot be expanded to their earlier scope under the doctrine of equivalents. In fact, such claims practically forego any benefit that could have accrued under the doctrine of equivalents in infringement cases.

4.3 Reverse doctrine of equivalents

A further restriction on the doctrine of equivalents is the *reverse doctrine of equivalents*. As noted by the Supreme Court of the United States in the *Graver Tank* case:

> The wholesome realism of this doctrine [of equivalence] is not always applied in favor of a patentee but is sometimes used against him. Thus, where a device is so far changed

[13] *Warner-Jenkinson Co.* v. *Hilton Davis Chemical Co.*, 520 U.S. 17 (1997). Available at http://supreme.justia.com/us/520/17/case.html.

> in principle from a patented article that it performs the same or similar function in a substantially different way, but nevertheless falls within the literal words of the claim, the doctrine of equivalents may be used to restrict the claim and defeat the patentee's action for infringement. [Citations omitted]

Thus, where an invention relies on the fundamental concept embodied in a patent but is more sophisticated than the patented device due to "a significant advance," the accused device does not infringe by virtue of the reverse doctrine of equivalents. Once a patentee establishes literal infringement, the burden is on the alleged infringer to establish non-infringement under the reverse doctrine of equivalents. This is an untested area of patent law but may become important in biotechnology with respect to certain pioneering technologies, such as, synthetic cell technology.

4.4 Prior art

Prior art or state-of-the-art is all information, available in any form, in the public domain. It does not include secret information, such as trade secrets. The existing reservoir of ideas and their expression form the foundation on which new intellectual property is built. Normally, prior art does not include unpublished work or mere conversations (although in the European Patent Convention, oral disclosures do form prior art[14]). There is a continuing effort by various countries to document their respective traditional knowledge, such as medicinal properties of plants, and make that knowledge available as searchable prior art. The doctrine of equivalents excludes whatever is already prior art.

4.5 The PHOSITA in biotechnology

In examining a patent application, the patent examiner faces an immediate problem. How to define the relevant PHOSITA? In patent law the PHOSITA is a legal fictional character or a team of characters analogous to the "reasonable person" in the common law of torts. The PHOSITA is a statistical concept in the sense that there is a very high probability that no one from the community of ordinarily skilled persons in the relevant technical field(s) will be able to come up with the invention in question or its close equivalent or a superior one if the community was required to do so. So the PHOSITA, by definition, is neither a genius nor a layperson, but one possessing normal skills and knowledge in the required technical field. In this sense he serves as a litmus test for deciding if an invention is nonobvious or involves an inventive step. If the PHOSITA is deemed capable of coming up with the invention by applying his mind, knowledge, skill, and common sense, that particular invention is deemed unpatentable. In short, a "person of ordinary skill is also a person of ordinary creativity, not an automaton."[15]

Unfortunately, "ordinary skill" must be determined on a case-by-case basis, depending on the sophistication and technological features of the invention. Clearly, the ordinary skills of

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[14] Art. 54(2) EPC: "The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application."

[15] *KSR International Co.* v. *Teleflex Inc. et al*, 550 U.S.__ (2007). Availlable at http://supreme.justia.com/us/550/04-1350/

a nuclear physicist are different from those of a chef or a cobbler or a molecular biologist. Factors used in determining ordinary skill include the time frame of the invention; education level of the inventor, education level of active workers in the field of the invention, and the type of problems generally encountered in the field; prior art solutions relevant to the invention; rapidity with which innovations are made in the field; sophistication of the technology; etc. Further, with time, the profile of a PHOSITA, in advancing technologies, will only improve due to the infusion of new knowledge and skills. Therefore, in rapidly advancing fields, such as biotechnology, determining the profile of a PHOSITA requires great skill and frequent revision.

The PHOSITA's role is crucial in several places—in the enablement requirement, the nonobviousness requirement, the utility requirement (the invention must operate as described if he is to be enabled), and the written description requirement, as compliance with these requirements is measured from his perspective. Therefore, claims must be written so that a PHOSITA would understand the bounds of the patent, including the territory covered by the doctrine of equivalents. A fundamental test for the doctrine of equivalents is whether a PHOSITA would reasonably interchange the elements in a claim at issue in an infringement case. What is not clear is that as higher education spreads and the PHOSITAs learn to solve problems at conceptual levels, how that will affect the doctrine of equivalents.

The enablement and non-obviousness questions arise before the issuance of a patent while the question of interchangeability arises at the time of infringement. Note that while biotechnology patent examiners are experts in biotechnology, infringement and validity cases are decided by judges who are not. So there is often a misalignment of the PHOSITA's profile separately conjured by the examiner and the judge in any given biotechnology patent case. In fact, it is rather difficult for courts to insert, in their decisions, the role of "common sense" a PHOSITA might routinely employ in his day-to-day work.

In infringement cases, the cut-off date chosen to ascertain prior art and the PHOSITA's profile can become a critical factor even when the dates differ by only a few weeks. Scientific breakthroughs and pioneer inventions suddenly appearing on the scene around the cut-off date can complicate matters tremendously. In the fast changing world of biotechnology, what is nonobvious today may well be obvious next year or next week!

5. Patentability conditions in biotechnology

Large scale patenting of living matter is recent. Indeed, prior to 1980, few patents had been granted on non-living biological matter and biologically pure cultures of micro-organisms as they did not exist in nature in their pure form; they could only be produced in carefully controlled laboratory environments. Patent laws around the world till then had assumed that higher life forms were not patentable as they were deemed products of nature. An abrupt change in legal thinking occurred when the Supreme Court of the United States in its June 16, 1980 decision in *Diamond* v. *Chakrabarty* held that "a live, human-made micro-organism is patentable subject matter" under the U.S. Patent Act of 1952. Recall that recombinant DNA technology was already well known in 1980. The Court reasoned that Chakrabarty's microorganism was a "nonnaturally occurring manufacture or composition of matter—a product of human ingenuity" worthy of liberal encouragement under the

patent system. It declared that "the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions." The floodgates for biotechnology patents were thus opened in the United States,[16] and eventually, using similar reasoning, patents on living matter were allowed in other countries. In 1988, the United States Patent and Trademark Office (USPTO) issued the first transgenic animal patent on the now famous Harvard mouse[17], a mouse genetically engineered to be particularly susceptible to tumor growth. Patents have since been issued on many other genetically engineered plants and animals.

The nature of biotechnology and its close working association with bioinformatics and molecular biology has added a new and complex dimension in patenting. The DNA is both a material molecule as well as a literal embodiment of coded information (the book of life). The courts are still trying to understand this deep two-facedness of DNA. For example, can artificially created DNA or gene sequences be copyrighted?

Finally, when filing a biotechnology patent application, particular attention should be paid to meeting the legal requirements of (1) statutory subject matter, (2) utility, (3) novelty, (4) nonobviousness, and (5) specification (description, enablement, and claims). The vast majority of litigation cases revolve around these statutory requirements.

5.1 Statutory subject matter

Biotechnology deals with bio-matter itself (including products of biotechnology living or non-living) and processes of making bio-matter. Examples of non-living bio-matter are amino acids, peptides, proteins, fats and fatty acids, and nucleic acids. They are all chemical compounds and are usually better known in the form of antibodies, hormones, enzymes, antibiotics, steroids, cholesterol, DNA molecules, etc.

The primary entity in living bio-matter is the cell, the smallest reproducible unit of life. A wide range of biotechnology product inventions, e.g., proteins, antibodies, intracellular components of plant and animal cells (DNA fragments, DNA constructs, DNA promoters, plasmids, vectors, RNAs, ribosomes, chloroplasts, mitochondria, Golgi bodies, etc.) and living matter *per se*, such as cell lines, fused cells, plant seeds, tissue cultures, microorganisms, plants and nonhuman animals, are patentable subject matter.

Biotechnology process inventions include processes for sequencing DNA, RNA or proteins; processes for genetically manipulating cells, plants or animals; processes for recovering proteins produced by cell lines or animals; processes for detecting and characterizing mutagenic agents; processes for culturing tissue or cells; processes for diagnosing or detecting biological states; fermentation, chemical and diagnostics methods; methods of treating human or animal bodies; methods of controlling pests; etc. Biotechnology processes also provide the potential for creating genetically altered bio-matter itself. In the early to mid-1980s researchers were already creating genetically altered transgenic mice, hamsters, rats, hogs, poultry, cattle, sheep, and fish. In 2010, the first synthetic cell capable of

[16] Chakrabarty was granted U.S. Patent No. 4,259,444, Microorganisms having multiple compatible degradative energy-generating plasmids and preparation thereof, filed on June 7, 1972, issued on March 31, 1981. The patent has now expired.

[17] This was U.S. Patent No. 4,736,866, Transgenic non-human mammals, issued April 12, 1988 to Philip Leder and Timothy A. Stewart. The patent has now expired.

continuous self-replication was created, a cell that was completely controlled by a computer designed synthetic chromosome.

5.2 The utility requirement (genetic materials)

A patent examiner will accept a utility asserted by an applicant unless there is evidence or sound scientific reasoning against it. Clinical trials of a new pharmaceutical are not required to establish its utility[18]. Transgenic animals are generally created with a specific use in mind, so their utility is usually obvious. For gene sequences a nontrivial utility of the protein it will produce must be shown. Citing generic useful functions such as a marker, probe, or primer for various genetic researchers may likely be considered trivial given the present state-of-the-art in gene research.

New processes related to genetic materials must show utility for the product of a process as well as the process itself, otherwise one could end in patenting a process which yielded an unpatentable product. "Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area."[19] Less this constraint, the patentable field would be too broad. Therefore, to assert utility, say, for a process for making a protein, one must establish that the protein itself has substantial and specific utility in currently available form.

General utility is disallowed because it would embrace a broad class of an invention. For example, regarding ESTs (expressed sequence tags), "a claim to a polynucleotide whose use is disclosed simply as a 'gene probe' or 'chromosome marker' would not be considered to be *specific* in the absence of a disclosure of a specific DNA target."[20] An EST does not explain the purpose and use of the gene. Therefore an EST patent "would amount to a hunting license"[21] for performing research that may lead nowhere. Likewise, cDNA fragments used as probes for finding full-length genes lacks specific utility because, "[a]ny partial nucleic acid prepared from any cDNA may be used as a probe in the preparation and or identification of a full-length cDNA." [22] Biotechnology patents must present a higher degree of utility than for most other types of patents, say, in mechanical or electrical engineering.

5.3 The novelty requirement

Non-naturally occurring life forms such as transgenic animals that are "man-made" or "man-altered" for the first time satisfy the novelty requirement. Gene sequences, either artificially created or purified and altered from their natural state, say, by deleting the introns and retaining the protein coding exons, may fulfill the novelty requirement.

[18] See, e.g., *In Re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Available at http://law.justia.com/cases/federal/appellate-courts/F3/51/1560/618133/.
[19] *Brenner* v. *Mansion*, 383 U.S. 519 (1966). Available at http://supreme.justia.com/us/383/519/case.html.
[20] USPTO, Revised Interim Utility Guidelines Training Materials (1999) at 5. Available at http://www.uspto.gov/web/menu/utility.pdf.
[21] *In re Fisher*, 421 F.3d 1365, 1376-77 (Fed. Cir. 2005). Available at http://www.cafc.uscourts.gov/images/stories/opinions-orders/04-1465.pdf.
[22] USPTO, Revised Interim Utility Guidelines Training Materials (1999) at 51.

However, the current state-of-the-art in human gene sequencing and its rate of advance are such that in future litigation courts may well set a more stringent criterion for novelty. This is perhaps inevitable given that many of the products of interest to the biotechnology industry are synthetic versions of substances that already exist in nature, and creating those synthetic versions is within the capabilities of a PHOSITA. Under these circumstances, can a synthetic version be called "new"? While methods of use of "new" sequences may be novel, claiming those sequences as new compositions may not be easily allowed.[23]

5.4 The nonobviousness requirement

The nonobviousness requirement is an important policy lever by which governments can efficiently control the transfer of intellectual wealth to promote industrial products and processes. This is particularly important when dealing with innovative medical products and diagnostic tools being produced and mass marketed by multinational pharmaceutical and biotechnology firms.

The core of a researcher's activity is hypotheses testing. This is what many biotechnology PHOSITA do routinely. Scientific inventions in biotechnology rarely come about *de novo*. Thus how much of the experimental research or testing conducted in the lead-up to an invention is attributable to a PHOSITA is central to the obviousness test. Routine, ordinary, logical, or workshop activity is not deserving of patent monopoly. "The results of ordinary innovations are not the subject of exclusive rights under patent law;" otherwise "patents might stifle rather than promote the progress of useful arts."[24] Thus routine testing in the lead-up period to invention in anticipation of reasonable expectation of success should be expected of an ordinarily creative PHOSITA.

Setting obviousness standards for gene patents is difficult because scientists use similar techniques to isolate different gene sequences, even though the gene may be new. A related question immediately arises. If homology-based utility satisfies the requirement of utility, would the invention be considered obvious? The USPTO's view[25], obviously in the context of U.S. patent law, is that nonobviousness and utility requirements are separate. This is because even though a claim to a nucleic acid is supported by a homology-based utility over a set of nucleic acids, that utility is not *prima facie* obvious. Homology-based deductions may provide a reason or motivation to make the claimed composition, but it would still be necessary to establish a fact-intensive comparison of the claim with the prior art rather than the mechanical application of one or another *per se* rule. In short, "obvious-to-try" and obviousness is not always the same thing (rules of thumb are not rules of law). The mere fact that something is "obvious to try" in view of known prior art does not automatically imply that the invention resulting therefrom is obvious. This is especially true where the prior art does not contain any suggestion or teaching that might suggest how the invention might be accomplished or any basis for reasonable expectation that beneficial results will accrue by proceeding along the lines taken by an inventor.

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[23] *In re Gleave*, 560 F.3d 1331 (Fed. Cir. 2009). Available at http://www.cafc.uscourts.gov/images/stories/opinions-orders/08-1453.pdf.

[24] *KSR International Co.* v. *Teleflex Inc. et al*, 550 U.S. __ (2007), at 24.

[25] Utility Examination Guidelines, USPTO, Federal Register, Vol. 66, No. 4, January 5, 2001, Notices, pp. 1092-1099. Available at http://www.uspto.gov/web/offices/com/sol/notices/utilexmguide.pdf.

To assess nonobviousness requires profiling a PHOSITA, who in biotechnology usually holds a PhD and is therefore an expert in common perception. Moreover, this PHOSITA is more likely to be a team of experts rather than a "mythical individual". So how does one reasonably determine this mythical PHOSITA at a point in time in an area of technology which is advancing so rapidly that the profile would need to be updated, at times, on a weekly basis? How are questions related to the doctrine of equivalents to be handled, especially if the invention is a synthetic version of a 'product of nature'? After all, Nature too is experimenting constantly with its own creations, including the destruction and creation of new species in the predator-prey game of "survival of the fittest" or "natural selection". These are extremely difficult questions to deal with in litigation.

5.5 The specification requirement

A specification is targeted at an expert in the field of the invention. Therefore, it is unnecessary for an applicant to spell out every detail but only enough to convince an expert that the inventor possessed the invention as of the filing date, and to enable a PHOSITA to make and use the invention without undue experimentation[26]. For example, in a gene related patent, a written description doesn't need a recitation or incorporation by reference of genes and sequences that are well documented in the prior art. An adequate description of the invention therefore depends on the nature and scope of the invention, not the description's length. Furthermore, an actual reduction to practice is *not* required. An invention can be "complete" even without an actual reduction. The Court of Appeals for the Federal Circuit in the United States, in *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006)[27] has succinctly stated: "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met … even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macro-molecule must contain a recitation of known structure."

Our current knowledge depicts living matter as incredibly complex (almost like a black-box) and therefore not describable either completely or accurately as required under the written description requirement. Inventions involving biological materials such as cell lines, cloning vectors, hybridomas, plasmids, microorganisms, etc., are sometimes impossible to describe adequately in words and reproducing them is not always a completely repeatable process. This problem is addressed by depositing appropriate biological materials with a recognized repository which provides permanence and availability to other researchers on demand (Berns, et al, 1996). This removes any uncertainty regarding the precise characterization of the material, such as a microorganism or cell line claimed in the invention, while ensuring that others will be able to practice the invention completely. In cases where the deposit requirement applies to higher-life forms, such as transgenic animals, the requirements may be satisfactorily fulfilled if a deposit of the lowest common denominator of a higher life form, e.g., the sperm, egg, fertilized egg, embryo, etc. is deposited. As on June 03, 2011, 75 Contracting Parties had signed the Budapest Treaty on the International Recognition of the

[26] If the profiled PHOSITA is generally expected to perform complex experimental tasks, then such tasks will not be considered as "undue".

[27] Available at http://law.justia.com/cases/federal/appellate-courts/F3/448/1357/637048/.

Deposit of Micro-organisms for the Purposes of Patent Procedure[28] (done at Budapest on April 28, 1977, and amended on September 26, 1980). The Treaty specifically requires the following:

> Contracting States which allow or require the deposit of microorganisms for the purposes of patent procedure shall recognize, for such purposes, the deposit of a microorganism with any international depositary authority. Such recognition shall include the recognition of the fact and date of the deposit as indicated by the international depositary authority as well as the recognition of the fact that what is furnished as a sample is a sample of the deposited microorganism. (Article 3(1)(a))
> As far as matters regulated in this Treaty and the Regulations are concerned, no Contracting State may require compliance with requirements different from or additional to those which are provided in this Treaty and the Regulations. (Article 3(2))

The satisfaction of the specification requirement is largely a procedural matter and depends on the skill of the patent counsel and the inventor's cooperation in preparing the patent application. On the other hand, fulfilling the requirements of utility, novelty, and non-obviousness depend more on the substantive merits of the invention itself.

6. Patent related treaties & agreements

Grant of patents and their enforcement, if infringed, rests with national governments. Differing national economic and geopolitical needs have resulted in wide differences among national patent systems that, at times, have led to odious disharmonies in patent enforcement and flow of trade and commerce. There has been a long-felt need for harmonized patent laws, especially by those who need their inventions protected concurrently in major world markets. Since the 1880s, limited harmonization among groups of nations, mainly related to procedural matters, has been achieved through various international treaties. The important ones are: (1) Paris Convention for the Protection of Industrial Property (1883),[29] (2) Patent Cooperation Treaty (1970),[30] (3) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) (The Agreement is Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994),[31] and (4) The Trilateral Cooperation (1983)[32] agreement among the patent offices of the United States, Europe, and Japan.

6.1 The Paris Convention

The Paris Convention (1883), now administered by the World Intellectual Property Organization (WIPO)[33], has shaped the patent laws of various countries, especially those of its member States called Contracting Parties. It was the first important international treaty designed to help people of one country obtain protection in another for their intellectual

[28] Available at http://www.wipo.int/treaties/en/registration/budapest.
[29] Available at http://www.wipo.int/treaties/en/ip/paris/trtdocs_wo020.html.
[30] Available at http://www.wipo.int/pct/en/texts/pdf/pct.pdf.
[31] Available at http://www.wto.org/english/docs_e/legal_e/27-trips.pdf.
[32] Website: http://www.trilateral.net/index.html.
[33] WIPO "is responsible for the promotion of the protection of intellectual property throughout the world through cooperation among States". Website: http://www.wipo.int//portal/index.html.en.

creations in the form of inventions (patents), trademarks, and industrial designs. As on July 15, 2011, there were 173 member States[34]. The Convention does not allow Contracting Parties to discriminate between their own nationals and nationals of other Contracting Parties as regards the protection of industrial property. *Inter alia*, the Convention lays down the common basic structure for patent protection to which the Contracting Parties are bound. This basic structure does not unduly trespass on the sovereign rights of Contracting Parties or compromise their national interests. In fact, Article 19, of the Convention states that Contracting Parties "reserve the right to make separately between themselves special agreements for the protection of industrial property, in so far as these agreements do not contravene the provisions of this Convention." Because of this, patent laws of respective member States share a substantial common core.

The Paris Convention forms the foundation for two other important treaties related to patents—the Patent Cooperation Treaty (1970) and the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) (1995).

6.2 Patent Cooperation Treaty (PCT)

The *Patent Cooperation Treaty* (PCT), administered by WIPO, became operational on June 1, 1978. As of September 23, 2011, the PCT had 144 signatories[35]. While the Paris Convention provides a means of access into different countries' patent systems, a patent application once filed, must be prosecuted through each national patent system. Under the PCT, patent applicants from Contracting States enjoy a relatively simple way of commencing patent applications in a number of countries simultaneously. This provision has since been encoded in the patent laws of most Contracting States.

The PCT provides a centralized mechanism for filing patent applications, prior art search and preliminary examination of the patent application; it does *not* grant patents. PCT Contracting States are bound by Chapter II of the PCT relating to the international preliminary examination of patent applications. An applicant can designate specific countries or regional conventions for grant of patent by filing an international patent application in the appropriate receiving office. After an international search report and a non-binding preliminary opinion on patentability has been provided, the applicant must still apply separately and individually to each jurisdiction where patent protection is required. While the search and the preliminary opinion might reduce subsequent search-related workload of national patent offices examining the patent application, the main and substantial workload still belongs to the national patent office. Every biotechnologist should become familiar with the process of filing a patent application under the PCT.

6.3 TRIPS

Of all the treaties in force, TRIPS is the most ambitious. Ratification of TRIPS is a prerequisite for a country to become a member of the World Trade Organization (WTO)[36]. As on October 4, 2011, WTO had 153 members. TRIPS entered into force on January 1, 1996, and covers various forms of intellectual property rights, including patents. It introduced

[34] Visit http://www.wipo.int/export/sites/www/treaties/en/documents/pdf/paris.pdf for updates.
[35] Visit http://www.wipo.int/pct/guide/en/gdvol1/annexes/annexa/ax_a.pdf for updates.
[36] Web site: http://www.wto.org/.

intellectual property law into the international trading system for the first time. It was negotiated at the end of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) in 1994. TRIPS nudged signatory countries towards a level of uniformity, which most are still struggling to cope with even though it was sweetened with some concessions for developing and underdeveloped countries. For example, art. 1.1 leaves member states "free to determine the appropriate method of implementing the provisions of this Agreement within their own legal system and practice" and a November 2005 decision of the Council for TRIPS allowed least-developed country members to postpone implementation of many TRIPS obligations until 2013.[37] The difficulties faced by developing countries are not just due to their inferior stages of technological advancement but also due to social, administrative, infrastructural, and other costs incurred in implementing TRIPS. This is particularly visible in the case of pharmaceutical products.[38]

Under the TRIPS Agreement, member countries are required to make patents available "for any invention, whether products or processes, in all fields of technology" without discrimination, subject to certain legal requirements being met. These requirements are that they must fulfill the member country's legislated criteria for novelty, inventiveness, and industrial applicability. Further, once patent rights are granted, the owner of the patent should be able to enjoy those rights in the member country without discrimination as to the place of invention and whether products are imported or locally produced. The above is subject to three exceptions: (1) the invention should not be contrary to *ordre public* or morality; (2) inventions related to diagnostic, therapeutic and surgical methods for the treatment of humans or animals may be excluded from being patented; and (3) inventions related to plants and animals other than micro-organisms and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes may be excluded. However, when such exclusions are made in the patent system for plant varieties, an effective *sui generis* system of protection must be provided. Subsequent to the Doha Round which took several years to negotiate, TRIPS permits countries to issue compulsory licenses to meet the health needs of nations unable to produce locally needed medicines.[39] This, however, means little to countries which lack the ability to manufacture pharmaceuticals locally.

Several TRIPS articles remain open to wide interpretation to allow each member country freedom to tailor its patent system according to its domestic needs, present state of development, and growth potential. For example, while TRIPS lists an "inventive step" as one of the requirements for patentable subject matter (art. 27(1)), it does not define the term. Likewise it defines the scope of a patent in terms of the nature of the rights conferred (art. 28), but does not set out the breadth of the technological terrain a patent must cover. This allows member states to supply their own definitions of "inventive step" and determine the scope of patent protection.

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[37] For developing countries, the patent standards (articles 27-34) of the TRIPS Agreement became generally operational on January 1, 2000. Those developing countries that did not allow product patents on pharmaceutical and agricultural chemical products were given a grace period of five years to cover them, subject to a "mail box" provision for patents arising in the meantime.

[38] See, *e.g.*, Janice M. Mueller, *Taking TRIPS to India – Novartis, Patent Law, and Access to Medicines*, 356 New England Journal of Medicine, 541, 541 (2007).

[39] Declaration on the TRIPS Agreement and Public Health (adopted on November 14, 2001). Available at http://docsonline.wto.org/DDFDocuments/t/WT/Min01/DEC2.doc.

6.4 The Trilateral Cooperation

The Trilateral Cooperation was set up in 1983 between the USPTO, the European Patent Office and the Japan Patent Office (collectively known as the Trilateral Offices) to overcome certain problems arising due to a dramatic rise in the number of patent filings in the early 1980s. These Offices process the greater part of all patent applications filed worldwide including PCT applications. Under the Cooperation, the Offices focus on addressing global patent workload challenges, e.g., decreasing pendency and examination backlogs, improving patent quality, and leveraging IT solutions to accelerate processing of patent applications. Through work sharing arrangements the Offices leverage work done earlier by another Office to improve their own search and examination practices. One of their goals is to eventually develop a paperless administration of the patent procedure, the exchange of documents, and electronic filing of applications.

6.5 Hurdles in the path of harmonization

Attempts to harmonize different national patent systems face major hurdles: the standards to be followed for utility, novelty, and nonobviousness; defining circumstances when research exemption and compulsory licensing are appropriate; setting objective standards for analyzing infringement and award of relief; etc. These issues are dealt with in widely differing ways by different countries. Any debate on global harmonization must also consider alternative mechanisms for encouraging technological innovation, not just the patent system, and account for the fact that different countries are at different stages of transition—from the industrial age to the information age. A recent paper (Reichman and Dreyfuss, 2007) succinctly notes:

> [T]he worldwide intellectual property system has entered a brave new scientific epoch, in which experts have only tentative, divergent ideas about how best to treat a daunting array of emerging new technologies. The existing system has become increasingly dysfunctional because it operates with a set of rudimentary working hypothesis that have not kept pace with technical change.

Any attempt to push harmonization beyond TRIPS would require great care. At the least, individual nations must be clear about the patent system that would best serve their interests in the new knowledge economy. The daunting nature of the task becomes evident from the experience of the United States, which after six years of feet-dragging and several aborted attempts at reforming its Patent Act, finally enacted the Leahy-Smith America Invents Act, 2011[40] on September 16, 2011. It is seen as "a jobs creation bill." The Act, most importantly, changes the earlier "first-to-invent" system to a "first-to-file" system to make it compatible with the rest of the world, raises patentability standards, makes injunctions and damages harder to obtain, provides new options for challenging bad patents, provides enhanced funding of PTO operations, provides for expedited examination of patent applications (for a fee), etc. Full implementation of the new law will take several months. A lack of political will to sink differences to bring about change was evident throughout.

[40] Available at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=112_cong_bills&docid=f:s23es.txt.pdf.

7. Societal impact of biotechnology patents

Since the 1970s the spotlight has shifted from technological advances of the industrial revolution (driven by Newton's laws of motion and Maxwell's laws of electromagnetism) to advances in biotechnology (driven by molecular biology and biochemistry). Towards the end of the twentieth century, conventional wisdom asserted that while that century belonged to physics and chemistry, which led to huge industrialization and consequent megacities, the twenty-first century will belong to biology and associated technologies. Its impact on society is expected to be phenomenal, affecting every inhabitant on our planet in an intimate way. The nature of the impact will crucially depend on how society accepts or rejects new technical innovations in biotechnology (Smith, 2009). Even though, since the 1980s, biotechnology has been recognized and welcomed as a highly promising strategic technology by many industrialized nations (Bera, 2009c), it has not resulted in automatic acceptance by society. The rate at which R&D results can be assimilated will depend less on scientific or technical considerations but more on such factors as availability of venture capital, the ability to acquire and protect patents, marketing skills, the efficacy and cost-effectiveness of new technologies, and possibly of far greater importance, public perception and acceptance. Perhaps no other industry is as heavily dependent on patents as the biotechnology industry and on public trust.

The emergence of the modern biotechnology industry in the 1970s as an intermediate sector between academic research institutions and Big Pharma was novel. Academic researchers played an important role in the founding of many biotechnology companies; some participated in both worlds, some turned into entrepreneurs. University-industry collaboration became a critical factor in commercial success as did the foresight of some venture capitalists who were willing and able to support inexperienced companies entering a market with a seven- to ten-year product development cycle. Indeed, without patent rights in areas such as isolation and purification of proteins, DNA sequences, monoclonal antibodies, transgenic organisms and gene expression systems, etc., many biotechnology companies could not exist (Bera, 2009b; Williams, 2005).

7.1 New technologies spark patenting debates

Historically, the birth of each new technology tends to spark a patenting debate. In the early 20th century the debate was whether agricultural inventions could be patented on the grounds that agriculture was not an industry. In the 1970s, it was argued that pharmaceutical patents were unethical. In the 1980s, the biotechnology industry faced hostility over "patenting of life". Even now, bioethical, social, and legal questions related to biotechnology patents are far from being over, as are issues related to intellectual property, scientific integrity, and conflicts of interest in research. For a satisfactory resolution, the debate must involve experts from diverse fields: science, engineering, theology, and philosophy. Finally, since the 1990s, the computer revolution and the Internet have produced many controversies related to software and business method patents (Poynder, 2000). An apparently persuasive argument against biotechnology patents is the field's rapid pace of development. For example, a few decades ago, finding a gene may have taken ten years, but now one can be found within seconds using a computer search and gene maps (Demaine & Fellmeth, 2002). If invention is inevitable, does it merit reward of exclusivity? If yes, for how long? A long period may spur innovation but also limit the spread of new and useful products and processes and make them more expensive. On the other hand, rapid

discovery of genes does not imply rapid availability of useful and safe applications based on those genes. Those applications come from creative geniuses. Should they not be rewarded with patents? For inventions, such as vaccines for public health, the balancing act is never easy, given the enormous R&D costs of developing them and the crucial role of Nobel class researchers who make them possible. As Todd Dickinson (former director of the USPTO) once remarked, "there are so many chemicals in the human body that, if we ruled them all off limits to patenting, we would rule out an extraordinary number of valuable and important inventions. … Without the funding and incentives that are provided by the patent system, research into the basis of genetic diseases and the development of tools for the diagnosis and treatment of such diseases would be significantly curtailed." (Dickinson, 2000)

Another objection is that the "current model rewards particular kinds of creative effort, namely those which result in commercial gain. It is therefore likely to hinder innovation of products that have limited market value, but which have huge social benefit."[41] This flawed argument overlooks the obvious fact that intellectual property laws *were* meant to encourage commercial gain. There are other laws which encourage social benefit and one does not criticize those laws for hindering innovation that lead to commercial gains. The correct approach, if providing social benefit which have limited market value is the objective, is to elect governments that will act more enthusiastically in providing social benefits (of course, the government will have to increase taxes to do so), encourage the general population to contribute to philanthropic activity by donating time and service to community activities, including creating intellectual property. There are no laws against such philanthropic activities, but there is a huge lack of enthusiasm on the part of the general population to help itself. That same population works more energetically when it gets a share of "commercial gains" in terms of employment opportunities and wages. Commenting on the allegation that the global intellectual property regime denies poor people access to drugs, Alasdair Poore said, "Without an effective patent system, who would have made the necessary investment to discover and manufacture those drugs? It's politics and economics that block access to drugs for the world's poor, not the IP system." (Prowse, 2009)

On closer inspection, one finds that the broadest debates concern ethical and societal aspects of patenting genetic materials, the perceived rights of indigenous communities that have shaped their environment and its organisms and thus the genetic resource embodied therein, and the manner in which the bioindustry prospects (or allegedly pirates) biological resources of poor countries and commercializes the products it derives through patents (Koopman, 2003). At another level, while patenting of biotechnology inventions is being criticized, it is really the science behind it that the opponents seem to be against.

7.2 Knowledge is commercial power

An important, although not the only, measure of a technology's success is its embodiment in products and processes that generate a profitable commercial market through public acceptance. Public acceptance is a factor *only* if there is a supplier willing to assume business risks and enter the market. One might then assume that if a suite of patentable products and

[41] See, e.g., Who Owns Science? The Manchester Manifesto, Institute for Science, Ethics and Innovation, The University of Manchester, 2009. Available at http://www.isei.manchester.ac.uk/TheManchesterManifesto.pdf.

processes, paid for out of the public purse, were owned by the government and made available free or at a nominal cost for commercial exploitation, business risks would be lowered. That such is not the case was the genesis of the Bayh-Dole Act[42] of 1980 in the United States. What the government found was that discoveries made in the universities with federal funds were grossly underutilized[43] because government policy required that it take title to all such inventions and license them non-exclusively. The vast majority of university discoveries, as expected, were early stage discoveries that required substantial additional investment to turn them into a marketable product. It was estimated in 2002 that a "dollar's worth of academic invention or discovery require[d] upwards of $10,000 of private capital to bring to market."[44] (The government funds the 'inspiration' while the private sector funds the 'perspiration'!) "New drug development costs have risen from $0.8 billion (1997) to an expected $1.9 billion (2013)."[45] Without the protection of an exclusive license, companies were reluctant to invest huge sums when the resulting products could easily be appropriated by competitors.[46]

The Bayh-Dole Act was a bold, against-the-grain, initiative meant to rejuvenate the U.S. economy. Under Bayh-Dole, the government relinquished its intellectual property rights on the outputs of federally funded research and permitted universities and small businesses to acquire title to inventions created with federal funds. It also allowed exclusive licensing of patents thus acquired, to industry since, without it, companies were wary of investing in the further development of university developed technologies. In addition, descriptions of inventions were given legal protection from public dissemination and from requests under the *Freedom of Information Act*[47] for a reasonable period to enable patent applications to be filed. In return, the government retained a royalty-free, non-exclusive license to practice the patented inventions coming out of federally funded research throughout the world (including use by government contractors) and held 'march-in rights', which allowed the government to take back the title if the patent owner failed to commercialize the invention. However, the exercise of march-in rights was made substantially difficult and appealable in courts. The march-in rights were basically introduced to prevent companies from licensing university patents with the sole intention of blocking rival companies from doing so. The

[42] University and Small Business Patent Procedure Act of 1980, (Pub. L. 96-517), §6(a), Dec. 12, 1980, 94 Stat. 3018 (35 U.S.C. 200 et seq.). Also known as the Bayh-Dole Act of 1980, it was given effect from July 1, 1981, "to use the patent system to promote the utilization of inventions arising from federally funded research or development."

[43] In 1980, the Federal Government held title to approximately 28,000 patents. Fewer than 5% of these were licensed to industry for development of commercial products. (See The Bayh-Dole Act: A Guide to the Law and Implementing Regulations, Council on Governmental Relations, October 1999, p. 2. Available at http://www.cogr.edu/docs/Bayh_Dole.pdf.)

[44] Innovation's golden goose, The Economist, December 14, 2002, p. 3.

[45] Wai Lang Chu, CRO's drug R&D contribution never been more significant, 25 September 2006. Available at http://www.outsourcing-pharma.com/Preclinical-Research/CRO-s-drug-R-D-contribution-never-been-more-significant.

[46] The Bayh-Dole Act: Important to our Past, Vital to our Future, 2006. Sense of Congress resolution passed by the U.S. House of Representatives on December 6, 2006. Available at http://www.autm.net/Content/NavigationMenu/About/PublicPolicy/BDTalkPts031407.pdf.

[47] Available at http://usgovinfo.about.com/library/foia/blfoiacode.htm.

rights were meant to ensure fair competition and to meet the needs of U.S. citizens; they were not meant for the government to set prices, as some have tried to claim.[48]

So, post-Bayh-Dole, we now witness the hitherto unimagined situation where innovations, already paid for by the public, can be brought to the market only if those innovations are privatized and resold to the public via patents acquired by commercial entities. Otherwise certain markets will likely vanish on their own because the risks are too high! The biotechnology industry, through university-industry collaboration, has shown that knowledge is a phenomenal commercial power. The emulation of the Act by other countries, although common now, will not necessarily have the same impact that has been visible in the U.S. because of dissimilar national circumstances, or the absence of world-class research universities.

Patent laws never anticipated that together "blue sky" research *and* living matter would play such a fundamental role in late 20th century commerce with such speed, and economists and policy makers never imagined the deep post-1980 university-industry (or generally, public-private) collaborations that rapidly gained momentum in the biotechnology sector following three signal events in 1980 in the United States: the Bayh-Dole Act, grant of the Cohen-Boyer patent, and the Chakrabarty court decision (Bera, 2009d). These rapid changes have bewildered lawmakers, patent offices, the judiciary, and relevant enforcement agencies. To older generations it is sacrilege that "even the pure quest for knowledge is subverted by the need for profit."[49] To the new generation it is the welcome emergence of a new and refreshing paradigm where pure knowledge is rapidly converted to applications to serve consumers through conventional market mechanisms of demand and supply. The future may see the emergence of other market mechanisms, whose advent no economist will likely anticipate, because they will occur to accommodate needs triggered by innovation alongside need inspired innovations.

The writing on the wall is clear; the times are changing, and so must the way we teach, create, use, and protect knowledge and the innovations they spawn. Initially, important chunks of that knowledge in biotechnology coming from universities will be tacit and scarce, hence university-industry collaboration will be crucial for technology transfer and commercial success. The relative youth of the biotechnology industry and its dependence on scientific breakthroughs means that star scientists—their accessibility, location, motivation to collaborate at the bench-science level with scientists in industry in converting basic scientific knowledge into commercially viable products and processes—will be crucial in determining the pace of diffusion of tacit scientific knowledge (Zucker & Darby, 1996). To remain relevant in an economically global world, the social role of universities and government research laboratories must change as must our understanding of morality, ethics, and citizenship.

It is mainly due to the university-industry collaboration example set by the United States that universities elsewhere are now expected to transform themselves into engines of economic growth, rather than remain as not-for-profit ivory towers. This is an enormous social transformation, and an enormous opportunity for universities to help the world settle down in the new era of a knowledge-intensive global economy. In this world, university-

[48] Statement of Senator Birch Bayh to the National Institute's of Health, May 25, 2004. Available at http://www.ott.nih.gov/policy/meeting/Senator-Birch-Bayh.pdf.

[49] The quote is from John Sulston, How science is shackled by intellectual property, The Guardian, 26 November 2009.

industry collaborative research is a natural means of providing continuing education to knowledge workers throughout their professionally productive life. It is also a natural means of mutual technology transfers between academic researchers and applied industry researchers, especially of tacit knowledge. Donald Kennedy of Stanford University was spot on when he said, "Technology transfer is the movement of ideas in people."[50] This movement in biotechnology must frequently happen under the protective cover of patents. One of the outstanding examples of technology transfer between university and industry is the licensing policy adopted by Stanford University with respect to the Cohen-Boyer patents[51] (Bera, 2009a). No doubt, other technology transfer models to fulfill emerging needs will evolve as the biotechnology sector matures.

Modern science-based industries (SBIs) critically depend on monetary funds, star scientists (human capital), and protected intellectual property (intellectual capital). Where and when star scientists publish also has a determining effect on the commercial adoption of new technologies. Geographically, SBIs tend to nucleate in close proximity of universities hosting a star group of scientists active in the relevant science, as it greatly improves mutual accessibility of both people and research facilities. This has generally been the case for biotechnology, especially in the United States (Zucker & Darby, 1996). Governments must bear this in mind when framing policies for economic and industrial growth and providing infrastructure. Once nucleation is complete and substantial diffusion of tacit knowledge of the stars has taken place, further expansion of the industry can spread to far-off places, especially of manufacturing units and support R&D groups.

7.3 Gene patents (unresolved issues)

A recent gene patent case, *Association for Molecular Pathology* v. *the USPTO and Myriad Genetics*, No. 10-1406 (Fed. Cir. 2011)[52], decided by the United States Court of Appeals for the Federal Circuit, has gained extraordinary attention. In this case, the validity of a series of patents that claim isolated DNA compositions and methods for testing the presence of genetic mutations that are correlated with an increased risk of certain breast and ovarian cancers (the BRCA1 and BRCA2 genes) was challenged. Myriad owns or is the exclusive licensee of these patents. Opponents of the patents argued that the patent claims encompass patent-ineligible subject matter, e.g., products of nature. At issue were such fundamental questions as to whether isolated DNA should be eligible for a patent, and whether the patenting of genes promotes or stifles innovation and development of new diagnostics and therapies. The Court stated expressly that an isolated partial DNA fragment, not just cDNA has a "markedly different structure to native DNA" and so reaffirmed that isolated gene sequences are patentable. Patentability of DNA sequences as diagnostics remains uncertain. Whether the Supreme Court of the United States will entertain an appeal in the Myriad case is not yet known.

Quite independent of how this case eventually ends, patent law will need to revisit the grant of gene patents. We now know that the one-gene-one-protein assumption of yore is no

[50] As quoted in Zucker & Darby, 1996.
[51] Stanford University, which owned the patents, granted non-exclusive licenses to 467 companies and amassed licensing revenues of $255 million. The patents expired in 1997.
[52] Available at http://www.cafc.uscourts.gov/images/stories/opinions-orders/10-1406.pdf.

longer true. The proteome is larger than the genome—there are more proteins than genes due to alternative splicing of genes and post-translation modifications like glycosylation and phosphorylation. The cause of most disorders and diseases is a combination of genetic and environmental factors and this raises important questions about the adequacy, scope and purpose of patent law in view of rapidly advancing knowledge in biotechnology and related fields. It is amply possible that under present laws, a single gene or a short DNA sequence, if patented, could result in a near monopoly on diagnostic tests and treatments for widespread and serious ailments, such as, diabetes, cancer, multiple sclerosis, and Alzheimer's disease. Can such patents be considered as serving human society if the patent owner cannot pursue all known downstream opportunities and blocks others from pursuing those or new ones? If such patents are inevitable, what steps should be taken to ensure that they do not obstruct others ready to pursue opportunities not pursued by the patent owner. Even otherwise, courts and administrative agencies continue to struggle with issues raised by gene patents and their predecessors—chemical patents—as to when and how patents should be granted on biochemicals in their natural and modified states under existing patent laws.

The fact that creation of transgenic humans is, in principle, possible, inevitably raises questions of human dignity, and moral and ethical issues. There appears to be a general consensus that transgenic humans are not patentable. Yet, no unambiguous definition of a transgenic human exists. Given that the genomic DNA differences between human and chimpanzee is only about 1.2%, the possibility of creating a patentable transgenic talking chimpanzee that can communicate with humans is not a fantasy. Such a chimpanzee might actually be able to speak and be capable of making connections between human words, objects, and even emotions. For the first time we may then be able to establish verbal communication with another species and derive remarkable insights about the animal kingdom. Should this possibility be denied to the human race because the transgenic chimpanzee is also a transgenic human? (Bera, 2009d)

The owner of a gene patent does not "own" any organism containing that gene. Thus, a person whose body contained a patented gene would not infringe the patent. However, if a gene, patented or not, is inserted into a living organism that organism may become patentable and then commercially exploited. Ownership and commercial exploitation of plants and animals, such as buying and selling them, is widely accepted in our society, but not of humans in *today's* world. Finally, animal breeding is not new and has been practiced since virtually the beginning of agriculture. Human breeding through marriage customs is also not new. Clearly, when one discusses moral issues related to patents, it is not the invention that is morally repugnant but its use in certain unintended ways. No one in the patent system—inventors, patent examiners, judges, or even legislatures (representing the people) can anticipate all uses of a particular patent that may eventually turn out to be, on a statistical balance, detrimental or beneficial to society. Any premeditated restrictions on the grant of patents must carefully consider the possibility that such restrictions may undermine the patent law's primary objective of promoting technical innovation.

8. Concerns over biopiracy

A paradigm shift inevitably entails shifts of power. The rise of biotechnology has sharpened the divide between the science-based industrial nations, and the genetically endowed but less-developed nations whose genetic resources are prospected by the former. The

conflicting issues being debated include the proprietary character of natural genetic material and the nature of commercial exploitation of the value added to those materials through R&D. Natural genetic resources abound in developing countries with a tropical climate, e.g., Brazil, Peru, Costa Rica, and India, in the form of gene pools, organisms, and ecosystems. Biotechnologists are obviously interested in these resources and related 'traditional knowledge' held by indigenous communities as inputs to research while the biotechnology industry is interested in prospecting those resources for potential commercial exploitation.

The methodology and approach of traditional knowledge is holistic and applied according to notions of biocentricism (a political or ethical stance which asserts the value of non-human life in nature), co-evolution and equality; it does not rely on empirical verification, rather it seeks connections between the physiological characteristics of organisms (visible phenotypic properties) with their spiritual ones. In contrast, modern biotechnology concentrates on biochemical genotypic properties. Nevertheless, traditional knowledge can be a valuable starting point for biotechnologists by indicating to them specific organisms and their known medical usage (Koopman, 2003). The enormous gap in terms of effectiveness and use between products and processes derived from traditional knowledge and from modern biotechnology must be filled by very expensive R&D, which is clearly outside the capabilities of indigenous communities. These are uncontested facts.

The biopiracy debate then essentially revolves around ethical and societal values as viewed from two widely different cultures over the patenting of genetic material whose natural inputs were prospected in and transported from indigenous communities on the basis of their traditional knowledge, with next to nothing in return in terms of acknowledgement or affordable products and processes or sharing of R&D knowledge. In short, the indigenous communities see this as blatant biopiracy. This is a clash between two cultures—of shared community rights against privately held individual rights. Indigenous communities seldom recognize the concepts of individual ownership, exclusion and competition that underlie the Western concepts of property law regimes.

Such irreconcilable differences have found palatable compromises in the form of the Convention on Biological Diversity[53] and TRIPS, where each culture makes concessions to the other. Countries providing access to genetic resources or traditional knowledge are permitted, and some have implemented, *sui generis* systems where they provide access on certain conditions, such as, getting prior informed consent of a national office dealing with such matters, benefit sharing arrangements (e.g., sharing of proceeds derived from commercial exploitation, training in R&D, transfer of technology under 'fair and most favorable terms' consistent with the 'adequate and effective protection of intellectual property rights'), and treating certain violations of the statutes as criminal offenses, in exchange for biological samples and traditional knowledge. In a subtle way, these *sui generis* systems are enforcing "reach through claims" on others for advantages nature has endowed indigenous communities with and the traditional knowledge they have developed long ago. The debate never mentions the tremendous unpatentable scientific knowledge of Newton, Maxwell, Einstein, and others which has been freely bestowed on the world without seeking rents, and which has allowed such dreams as putting a man on the moon possible.

[53] Available at http://www.cbd.int/doc/legal/cbd-en.pdf.

9. Conclusions

Our new understanding of living matter is leading us to uncharted territories. Recombinant DNA technology, transgenic animals, synthetic cells are just the tip of the iceberg. Creation of computer designed, engineered life is no longer science fiction but a potential reality. Will surreptitiously created transgenic humans one day enslave natural humans and rule the world. Can such an event be stalled? What will a world dominated by transgenic humans be like? Will it be more humane than ours? Will they rule more by the head and less by the heart or the other way round? We have no way of knowing.

While patent laws forbid patenting of abstract ideas, thought processes, laws of nature, natural phenomena, and products of nature so as not to stifle advancement of knowledge, the laws do recognize, as they did for Galileo, that certain down-to-earth inventions, conjured through human ingenuity by applying these forbidden things, go beyond philosophical musings and have potential commercial value, because of their utility to humans. In such cases, a *quid pro quo* system that provides limited period monopoly with commercial advantage in the form of patents, in exchange for a full public disclosure of the invention not later than the date of patent grant, encourages further creation of new inventions or improvements over old ones. Patent laws were meant to encourage commercial gain in an equitable manner. There are other laws and practices that encourage material and spiritual contributions to society through raised taxes, philanthropy, free social service, open-source, etc., which are not motivated by commercial gain. Patent laws do not interfere with these other laws and practices. Outside of contractual obligations to, say, his employer, a biotechnologist can choose to patent or not patent. Patent laws do not operate in isolation. Their purpose is to benefit society on the whole so that the positives outweigh the negatives in a statistical sense. There is no denying that countries with a thriving patent system, with all its faults, have advanced technologically more rapidly than all other countries and provided a better quality of life to their citizens. It is hoped that this chapter will help the reader decide when patenting is appropriate in light of other alternatives.

10. References

Ball, P., The dawn of quantum biology, *Nature*, Vol. 474, 16 June 2011, pp. 272-274.

Belvis, G. (2003). Chapter 2 Overview of the Doctrine of Equivalents and § 112, 6 Equivalents, In: *Intellectual Property Law Update*, G. Belvis, pp. 35-66, Aspen Publishers, Retrieved from http://www.brinkshofer.com/files/102.pdf

Bera, R.K. (2009a). The Story of the Cohen-Boyer Patents. *Current Science*, Vol. 96, No. 6, (25 March 2009), pp. 760-763.

Bera, R.K. (2009b). The Changing role of Universities and Research Institutions in a Global Economy: Lessons Drawn from the U.S. Biotechnology Sector. *Current Science*, Vol. 96, No. 6, (25 March 2009), pp. 774-778.

Bera, R.K. (2009c). Intellectual Property Fuels a Global Sense of Competitiveness. *Current Science*, Vol. 96, No. 7, (10 April 2009), pp. 898-903.

Bera, R.K. (2009d). Post-1980 World of Biotechnology Patents in the U.S. *Current Science*, Vol. 96, No. 10, (25 May 2009), pp. 1343-1348.

Berns, K.I., Bond, E.C., & Manning, F.J. (Eds.). (1996). *Resource Sharing in Biomedical Research*, National Academy Press, Washington.

Blenko, Jr., W.J. (1990). The Doctrine of Equivalents in Patent Infringement, *JOM*, Vol. 42, No. 5, (May 1990), p. 59.

Cohen, S. N., Chang, A. C. Y., Boyer, H. W., & Helling, R. B. (1973). Construction of Biologically Functional Bacterial Plasmids In Vitro, *Proc. Nat'l Acad. Sci.*, Vol. 70, No. 11, (November 1973), pp. 3240-3244.

Christie, A. F. & Lim, A. (2005). Reach-through Patent Claims in Biotechnology: An Analysis of the Examination Practices of the United States, European and Japanese Patent Offices. *Intellectual Property Quarterly*, Vol. 3, (2005), pp. 236-266.

Darwin, C. (1872). *The Origin of Species*, 6th edition, Modern Library, ISBN 0451625587.

Demaine, L.J., & Fellmeth, A.X. (2002). Reinventing the double helix: a novel and nonobvious reconceptualization of the biotechnology patent, *Stanford Law Review*, Vol. 55, No. 2 (November 2002), pp. 303-462.

Dickinson, T. (2000). Gene Patents and Other Genomic Inventions: Hearing before the Subcommittee on Courts & Intellectual Property of the Committee on the Judiciary, House of Representative, *106th Congress*, (July 13, 2000), Retrieved from http://commdocs.house.gov/committees/judiciary/hju66043.000/hju66043_0f.htm

Gibson, D.G., *et al*. (2010). Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome, *Science*, (20 May 2010), pp. 1-12.

IPO (2009). Examination Guidelines for Patent Applications relating to Biotechnological Inventions in the Intellectual Property Office, *IPO*, U.K., (April 2009).

Koopman, J. (2003). Biotechnology, Patent Law and Piracy: Mirroring the Interests in Resources of Life and Culture, *Electronic Journal of Comparative Law*, Vol. 7.5, (December 2003), pp. 1-19, Available from http://www.ejcl.org/ejcl/75/art75-7.html

Köhler, G, & Milstein C. (1975). Continuous cultures of fused cells secreting antibody of predefined specificity, *Nature*, Vol. 256, Issue 5517, (07 August 1975), pp. 495-7.

Lilly, M.D. (1997). The development of biochemical engineering science in Europe, *Journal of Biotechnology*, Vol. 59, Issues 1-2, (17 December 1997), pp. 11-18.

Mullis, K.B. et al. (1986). Specific enzymatic amplification of DNA in vitro: the polymerase chain reaction, *Cold Spring Harbor Symp. Quant. Biol.*, Vol. 51, pp. 263-73.

Poynder, R. (2000). Internet sparks patenting controversy, *IP Matters*, (30 April 2001), Available from http://www.richardpoynder.co.uk/internet_sparks.htm

Prowse, P. (2009). Patent profession welcomes Manchester Manifesto on science but slams 'misleading' comments on IP, (November 27, 2009), Retrieved from http://www.cipa.org.uk/pages/press/article?D5C2CBED-894B-488B-ACD2-07B01E204A06

Reichman, J.H. & Dreyfuss, R.C. (2007). Harmonization without Consensus: Critical Reflections on Drafting a Substantive Patent Law Treaty, *Duke Law Journal*, Vol. 57, No. 1, pp. 85-130.

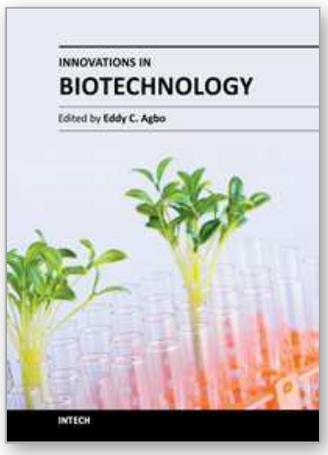
Schrödinger, E. (1944). What is Life? Cambridge University Press, Cambridge, Retrieved from http://whatislife.stanford.edu/LoCo_files/What-is-Life.pdf

Smith, J.E. (2009). *Biotechnology*, (5th edition), Cambridge University Press, Cambridge.

Watson, J.D., and Crick, F.H.C. (1953). Molecular structure of nucleic acids, *Nature*, Vol. 171, No. 4356, (April 25, 1953), pp. 737-738.

Williams, A. (2005). The New Innovation: Rethinking Intellectual Property for the ONE Big Idea, New Paradigm Learning Corporation, (June 2005).

Zucker, L.G., & Darby, M.R. (1996) Star scientists and institutional transformation: Patterns of invention and innovation in the formation of the biotechnology industry, *Proc. Natl. Acad. Sci. USA*, Vol. 93, November 1996, pp. 12709-12716.



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Innovations in Biotechnology provides an authoritative crystallization of some of the evolving leading-edge biomedical research topics and developments in the field of biotechnology. It is aptly written to integrate emerging basic research topics with their biotechnology applications. It also challenges the reader to appreciate the role of biotechnology in society, addressing clear questions relating to biotech policy and ethics in the context of the research advances. In an era of interdisciplinary collaboration, the book serves an excellent indepth text for a broad range of readers ranging from social scientists to students, researchers and policy makers. Every topic weaves back to the same bottom line: how does this discovery impact society in a positive way?

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