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THE RACE TO PATENT THE GENOME: FREE RIDERS, HOLD UPS, AND THE FUTURE OF MEDICAL BREAKTHROUGHS

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*222 Introduction

Genes tell us who our parents were, who we are, and who our children will be. Genes hold the key to why one person is bald, another is tall, and another has a fatal heart attack. In order to understand health and battle disease, scientists seek an understanding of these genes, hoping to improve our lives and cure the diseases that plague us. The complete sequencing of the human genome offers unprecedented opportunities for scientific advancement and medical breakthroughs. However, scientists now stumble over corporate-owned gene patents as they seek to utilize newly identified genetic material and the information encoded therein. This patenting of genes creates dissension and often passionate debate between the academic and corporate communities of scientists regarding the proper place of such patents. It is this debate that this article seeks to explore and examine.

While the scientists clash loudly in the foreground of this debate, its backbone is the Constitution itself. According to the Constitution, patents promote the progress of science and the useful arts by rewarding inventors of new and useful inventions with a monopoly of limited duration.[1] The patent monopoly offers the inventor an incentive to invent and to disclose the invention by granting him the sole right to exploit the invention. In other words, a largely economic basis provides support for these patent incentives. So, what if other incentives not obviously ***223** within the scope of the patent grant of the Constitution play a significant role in the inventions? Academic scientists argue that basic science researchers pursue gene identification principally for individual achievement and peer recognition, an ethic that demands full disclosure and free access to scientific knowledge. Moreover, patents on the backbone of health and disease (i.e., genes and genetic material) create opportunities to block or hold up research efforts through the imposition of licensing negotiations and fees. Others

argue that the Constitution does not embrace gene patents because genes are not inventions but are products of nature outside the scope of patentable subject matter. Corporate scientists, on the other hand, argue that patenting provides the necessary economic incentives to encourage risky and expensive research to identify and characterize new genes. The absence of patents then encourages free riding (the taking of a costly new gene and its information by someone who did not invest in its discovery). Free riding creates a strong disincentive to the innovation and investment required for genetic research. This clash of incentives and definitions underlies the debate and dissension surrounding gene patents.

This article sets forth a framework for the debate surrounding gene patents and analyzes a series of potential patent reforms. Part I of this article surveys the basic scientific concepts of genes and discusses some illustrative examples of medical uses for genes and genetic information, namely gene therapy, diagnostic genetic testing, and purified protein production. Part II considers the current state of the law regarding the patentability of a gene, the various requirements for a gene patent, and the resultant scope of patent protection given to a gene. In Part III of this article, various economic rationales supporting gene patenting are discussed and contrasted with the rationale that opposes gene patentability on the grounds that genes are products of nature. Part IV briefly describes the importance of gene patents to the public and to scientists and discusses the potential anticommons looming for such patents. Part V analyzes various patent reforms in the context of gene patents, highlights the complexity of gene patenting, underscores a potential for free riders and hold ups, and offers a tentative framework for restructuring the current gene patent system. Finally, the article concludes by highlighting the urgency of the debate and the need for a timely and definitive resolution as to the proper role, if any, for gene patents.

I. Science and the Human Genome Project

A critical analysis of gene patents requires a basic understanding of the biology of the gene. This section provides a brief overview of basic genetic concepts so that the reader may fully analyze the issues in the gene patent debate.

A. Basic Scientific Concepts

Genes are the language that gives a cell, and ultimately our bodies, life and meaning. While a cell is the fundamental unit of an organism, genes provide all of ***224** the instructions for the functions and machinery of each cell.[2] These instructions lie in a long sequence of four chemicals, known as nucleotides, bound together in a unique pattern.[3] Sequences of these nucleotides are known as deoxyribonucleic acid or DNA.[4] The identification of the pattern of these four nucleotides constitutes a cell's DNA sequence or genetic code.[5] The human genome consists of the genetic code of all the genes, gene control sequences, and genetic code with unknown or silent functions.[6] The genome is largely contained in the chromosomes of the cell and is approximately three billion nucleotide pairs.[7] Genes comprise about 2% of the human genome and number approximately 30,000 to 40,000.[8]

The DNA sequence of a gene is translated into a protein through an intermediate form called messenger ribonucleic acid (mRNA).[9] The sequence of a newly transcribed mRNA molecule is a mirror image, or complementary sequence of the gene sequence.[10] This immature mRNA molecule undergoes a splicing reaction where non-protein encoding DNA sequences (i.e., introns) are removed.[11] The remaining protein-encoding sequences (i.e., exons) constitute the mature mRNA molecule that is subsequently transported from the nucleus to the cytoplasm of the cell where it directs the building of proteins.[12] The mature mRNA molecule is the form typically cloned from a cell and then transcribed back into DNA for use as a research tool.[13] The DNA copied from mRNA is known as complementary DNA (cDNA).[14]

Final assembly of the protein occurs using the mature mRNA molecule as a template.[15] Once the protein is completely assembled, it can be phosphorylated, ***225** glycosylated, acetylated, ubiquitinated, farnesylated, sulphated, linked to other molecules, and modified in a variety of ways that make the protein fully functional or, alternatively, change its function.[16]

The genome achieves and promotes diversity between cells and individual organisms using multiple mechanisms. First, individual cells differentially express the genes within their genome.[17] In other words, although every cell of an organism has the same genome, a cell expresses a different set of genes depending on its function.[18] While a small subset of genes, known as housekeeping genes, is expressed in each cell, most of the genes expressed are strictly related to its cellular functions.[19] Second, the transcription of a gene can produce variants of its full-length protein that differ in size and function without requiring any alterations in the genomic sequence.[20] Differential splicing of the mature mRNA transcript results in these functionally unique, and sometime disparate, protein variants.[21] For example, the protein Fas induces cell death in its

full-length form, functioning as a critical growth regulator of certain pre-cancer and cancer cells.[22] The splice variant of Fas, on the other hand, acts as an inhibitor to Fas-mediated cell death, thereby promoting cell growth.[23] Third, differential gene expression results from exposure to various environmental stimuli.[24] Changes in hormones, growth stimuli, or stressful insults elicit gene expression variations and permit essential responsiveness to the environment.[25] Fourth, differential gene expression lies in random changes within the gene sequence itself.[26] Mutations or changes in the gene's DNA sequence occur spontaneously or in response to an environmental mutagen.[27]

***226** Genetic sequences form the genotype of an individual organism. Alleles are different forms of the same gene that affect the physical expression of that gene due to an alteration in its function or expression.[28] Polymorphisms can result from as little as a single nucleotide change (loss, deletion, or change) in the gene.[29] Such changes are known as single nucleotide polymorphisms (SNPs), and some are linked to a person's susceptibility to certain diseases.[30]

The simplicity of the genetic code lends itself to many immediate applications in medicine, while its complexity and environmental responsiveness simultaneously make the application of such knowledge unpredictable and difficult to uniformly implement. A few applications of the knowledge gained from the Human Genome Project illustrate this paradox with which we now struggle.

B. Some Medically Relevant Uses of Genes

The Human Genome Project successfully identified the sequence of the genome. As a result, we will soon be able to identify all human genes by their DNA sequences. Although a function has been identified for less than 50% of genes,[31] those genes identified offer opportunities for genetic intervention that include medical therapy (gene therapy), diagnostic screening for diseases (genetic testing), and large-scale production of medically-relevant purified proteins.[32] Although one gene may be used for gene therapy, genetic testing, and protein production, each use has distinct and sometimes non-overlapping requirements for development into a reliable and commercially viable product.

1. Gene Therapy

Gene therapy constitutes a disease treatment where a functional gene replaces a malfunctioning gene. Gene therapy substitutes for the commonly prescribed medication or lifestyle change, while potentially offering a complete and permanent cure. Moreover, gene therapy renders once untreatable diseases (e.g., immunodeficiencies) and intractable diseases (e.g., cancer) within the reach of medicine.[33] The ***227** treatment of infants with severe combined immunodeficiency (SCID)-XI disease illustrates the potency of genetic medicine.[34] In a clinical trial, infants born lacking a functional copy of a gene essential for a competent immune system received the missing gene using viral gene transfer technology.[35] The successful gene transfer transformed the previously inoperative immune system into a fully functional one, granting normal life to these sickly children.[36] The media and scientists heralded the trial as the "first time gene therapy has unequivocally succeeded."[37]

The simplicity and power of gene therapy belies the complexities and difficulties in achieving its viability as a medical option. For example, a candidate gene for gene therapy must first be identified as critical in the disease process.[38] Next, the candidate gene requires isolation and functional characterization.[39] The development of effective cellular targeting, delivery, and expression strategies follows for the candidate gene.[40] Finally, the candidate gene must be safe and effective as a medical option in the target patient populations.

Naturally, the best candidate diseases for gene therapy are monogenic diseases (i.e., caused by a single gene). In such diseases, a mutation in a single gene is necessary and sufficient to cause the disease.[41] About 1,500 monogenic diseases have been identified, including cystic fibrosis, Tay Sachs, hemophilia, and SCID.[42] Most diseases, however, are polygenic, meaning more than one gene contributes to its clinical symptoms.[43] Other factors such as metabolism, stress, and the environment influence the induction of the disease as well as its severity, adding an additional and sometimes substantial layer of complexity to gene therapy.[44] Taken together, ***228** the development of an effective gene therapy candidate requires a significant investment of resources, both economic and intellectual, at every stage of development.

2. Diagnostic Genetic Testing

The ability to pre-screen individuals for genetic predispositions to specific diseases is the second potent use of genetic sequences and one of the more immediate applications of the sequencing information gained from the Human Genome

Project.[45] Genetic diagnostic testing includes diagnosing a disease; providing prognostic information; permitting early intervention in asymptomatic, high-risk individuals; predicting the future risk of disease; and designing patient-specific therapeutic regimens.[46] Several hundred genetic tests are already in clinical use with a significant increase anticipated in the next decade.[47] The proliferation of such tests will undoubtedly aid physicians in diagnosing patients and in practicing more effective preventive medicine. Although there are a finite number of genes, there will presumably be a much larger number of commercially viable diagnostic genetic tests helpful to physicians.

3. Purified Protein Production

The availability of a full genomic sequence also provides for additional opportunities to identify important proteins and produce them on a large scale at a high purity.[48] The availability of purified, biologically functional proteins permits directed therapy for diseases where gene therapy is not available or is contra-indicated in the disease.[49] Similar to other medical options, identification of relevant diagnostic indicia, effective therapeutic parameters, and remedies for toxic side effects requires intensive research efforts and significant resource allocation.[50] The FDA dictates multiple clinical trials and minimal safety and efficacy standards ***229** while maintaining a measurable risk that an approved therapeutic agent may be pulled from the market if unforeseen side effects are found.[51]

In summary, the genome offers a vast and complex set of powerful information related to human health and disease. Most intriguingly, the Human Genome Project revealed the presence of a relatively small number of genes in the genome--a mere 30,000. Of those 30,000 genes, an estimated 10% are thought to correspond to potential drug targets related to diseases of socio-economic importance.[52] In other words, a relatively small number of genes hold a vast wealth of information and potential scientific breakthroughs. Here, the patent system exerts its incisive influence. The holder of a gene patent controls the making and using of that gene and, by proxy, may control related medical discoveries and uses. It is here the gene patent debate begins.

II. The Present Contours of a Gene Patent

The standard for patenting a gene follows the same general contours as any other invention. The Patent and Trademark Office (PTO) will award a patent if the invention is patentable subject matter,[53] useful,[54] novel,[55] nonobvious,[56] and adequately enabled and described[57] in the patent application. To date, gene patents have no unique novelty or priority requirements.[58] However, the unique properties of genes and genetic material do color the doctrinal interpretations by the courts and the PTO.

*230 A. Genes as Patentable Subject Matter

Patentable subject matter is defined in the Patent Act of 1952 as a "process, machine, manufacture, or composition of matter."[59] Courts have traditionally held that these categories do not encompass products of nature.[60] However, in considering the validity of a patent for genetically modified bacteria, the Supreme Court recognized the patentability of "nonnaturally occurring" living things under 35 U.S.C. § 101 of the Patent Act.[61] Under this reading, genetically modified microorganisms as well as purified natural proteins were patentable.[62] This relaxation of the prohibition against patenting products of nature eventually led the Federal Circuit to recognize purified DNA sequences as patentable subject matter.[63] The court has disregarded arguments that DNA should be beyond the scope of patentable subject matter because it is the prime molecule of life,[64] and held that the highly purified genetic material was in a nonnatural state and, therefore, was not in a form found in nature.[65] According to the Federal Circuit, the nonnatural state was determinative of patentability under the statute.[66] This means that any gene (and potentially any genetic sequence less than a complete gene) in a nonnatural state is patentable.

B. Written Description and Enablement Requirements

Since the written description requirement is heavily fact-specific, the courts have tailored specific requirements for different classes of inventions. In most cases, an inventor can file a patent application before the actual reduction to practice by relying on the filing of the patent application as a constructive reduction to practice.[67] This is not the case for DNA sequences because the Federal Circuit ***231** treats DNA sequences similarly to other naturally occurring chemicals and requires a higher threshold for patent applications claiming DNA sequences.[68] The Federal Circuit has held that an inventor generally cannot sufficiently distinguish a gene's DNA sequence from other DNA sequences until it is isolated.[69] This standard of

simultaneous conception and reduction to practice prevents the patenting of the idea of the DNA sequence or compound if the actual sequence is not known.[70] Therefore, an inventor must possess and disclose the complete sequence of a gene (or cDNA) "by means of the recitation of the sequence of nucleotides"[71] that make up the claimed gene or cDNA to satisfy the written description requirement.

The claims of a patent application must be enabled by its specification.[72] In other words, the specification must teach a person of ordinary skill in the art how to make and use the invention without undue experimentation.[73] The Federal Circuit has given some guidance in the fact-intensive analysis required to determine whether a specification requires undue experimentation by setting out eight factors to be considered:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictably of the art, and (8) the breadth of the claims.[74]

In practice, the stringency of the enablement requirement attempts to balance the unpredictability of the life sciences against the desire not to limit an inventor solely to the actual embodiments of his invention.[75] For example, a patent claiming all possible DNA sequences for functional substitutes of a naturally occurring protein has been found invalid for lack of enablement.[76] The patentee defined substitutes as a protein with the biological properties of the identified protein but encoded by a distinct DNA sequence.[77] Citing the unpredictability of the art, the ***232** court held that a gene patent did not enable all possible biologically active variants of the gene sequence unless the inventor could reliably predict the effect of such variations of the biological activity.[78] Therefore, the inventor was not necessarily limited to the embodiments disclosed in the specification but instead was limited to those whose biological activity was ascertainable with some accuracy or without undue experimentation.

The current judicial approach to the written description and enablement requirements for gene sequences (and other biotechnology-related inventions) seeks to limit overly broad patents and prevent unfair results while still rewarding an inventor for his invention.[79] By using these heightened disclosure requirements to limit the patentees to their actual inventions, the court seeks to strengthen one of the underlying policies of the Patent Act--the incentive to innovate.[80]

C. Utility Requirement

Utility requirement guidelines suggest that this criterion for patentability is also heightened for DNA sequences.[81] Traditionally, the requirement for evidence of any practial utility has provided only a minimal bar to patentability.[82] As a result, the demonstration that a DNA sequence could act as a probe for itself was a sufficient showing of utility.[83] In response to widespread criticism of this standard as "meaningless," the PTO issued new utility guidelines requiring a "well-established utility."[84] A well-established utility is one appreciated by a person skilled in the art at the time the application is filed and has a "specific, substantial, and credible" utility.[85] The PTO relies on the standard set forth by the Supreme Court in Brenner v. Manson,[86] requiring the disclosure of at least one available practical benefit to the public.[87] Although it is difficult to know the exact contours of a "specific, substantial, and credible" utility at this time, it seems likely that such a requirement will prevent the patenting of DNA sequences without more than speculative or negligible utility.

*233 D. Nonobviousness Requirement

Section 103 of the Patent Act defines nonobviousness as when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains."[88] Nonobviousness is a fact-intensive determination where potential success in experimentation and new properties of the invention carry significant weight for biotechnology. An invention in biotechnology is obvious if the prior art provides motivation for the invention and enables one of skill in the art to invent with a "reasonable expectation of success."[89] The predictability of success is a critical factor in the court's obviousness determination in light of the unpredictable nature of biological science.[90] Furthermore, even if the prior art provides the motivation for success and a "reasonable expectation of success," the exhibition of "unexpected properties" will render an invention nonobvious.[91] Examples of unexpected properties are superior purity, specific activity, and unexpected yield.

E. The Boundaries of a Gene Patent

1. Extent of Protection

A patent is granted for twenty years from the filing date of the patent application.[92] During this time, the patentee has the right to exclude all others from making, using, selling, or offering to sell the patented invention in the United States and to exclude all others from importing the patented invention into the United States.[93] However, a patent is not an affirmative right; it does not give its owner the right to make, use, sell, or offer to sell the invention.

The patent claims, not the disclosure in the specification, define the invention.[94] When considering any biologically active molecule, a patent on the molecule itself generally confers the broadest protection to the patentee because the claimed molecule will fall within the scope of the patent regardless of what process is used to make the product. A process patent, on the other hand, provides more limited protection because of the narrowing effect of the process limitations. For example, if a patentee has a product patent on protein X, he can exclude all others ***234** from making protein X. The patentee can also exclude all others from any and all other methods of making protein X, even if only a single method is disclosed in the specification.[95] A process patent, on the other hand, limits the patentee's monopoly to protein X made only by the disclosed method. Another inventor can "invent" a new method of making protein X and operate under this method to compete with the patentee without fear of infringement.

2. Use of a Gene Patent by Third Parties under Current Law

A patent claiming a gene as a composition of matter provides a far-reaching monopoly on the gene. The gene patentee can control any use of the patented gene whether in diagnostic testing kits, gene therapy vectors, or expression vectors for protein production. In other words, the patentee's right to exclude permits domination of related and subsequent inventions using the patented gene. For example, an inventor other than the patentee may patent a gene therapy vector, but may be blocked from operating under the gene therapy patent without a license from the patentee holding the gene patent.

Dominating gene patents provide their patentees with an enviable position in licensing negotiations. For the economically rational patentee and potential licensee, the gene patent permits effective negotiations for reasonable royalties that are in the best economic interest of both parties (e.g., the gene patentee and the gene therapy patentee) so they can recover the investment in their respective inventions.[96] The parties keep their transaction costs low by avoiding litigation and, presumably, make rational valuations of each other's inventions to make the bargain and license the invention.[97] However, if bargaining breaks down because of mistakenly high valuation or an irrational moral claim based on pride or spite, the blocking patent provides opportunity for "hold-ups."[98] For example, the gene patentee's refusal to grant a license on a gene used in a new method for purified protein production restricts the protein production patentee's freedom to operate under his patent without fear of infringement litigation. Due to the unique interdependence of a gene with upstream and downstream biological events driven by other genes and gene products, fair and efficient licensing of gene product patents becomes a critical feature in an effective patent system.

***235** The patent owner can license all of his rights or any portion of his rights under the patent to one or more parties.[99] A patentee is not required to give a license to anyone. A patentee can grant licenses that are restricted by territory, limiting the licensee to a particular geographic region.[100] A patentee can grant an exclusive license to an individual or or entity or nonexclusive licenses to multiple entities. Licenses restricting an invention's use limit the licensee to one of a myriad of potential uses.[101] For example, a license limiting the use of a gene patent to a specific genetic diagnostic test kit made by the licensee would not permit the licensee to use the gene in any other genetic diagnostic kit or other use. If a licensee violates any of the license restrictions, his activities constitute infringement of the patent.[102] Importantly for the analysis of gene patent policy, a patentee can license his patent for any consideration he chooses, including future patent rights or automatic licensing of future inventions.[103] According to the Supreme Court, such a "grantback" of rights serves patent law's underlying policy as long as the actions are not anticompetitive.[104]

One narrow exception to a patentee's absolute monopoly is experimental use.[105] An unlicensed third party can use or make the invention under the experimental use exception if the use is for strictly philosophical purposes without any commercial use.[106] Therefore, under the current experimental use exception, a university researcher would be able to use a patented gene in his research as long as the research did not result in any viable commercial use.

During the patent term, the patentee's rights can also be constrained if there is a finding of patent misuse. If a patentee has impermissibly broadened the physical or temporal scope of the patent with an anticompetitive effect, the patent can be rendered unenforceable because of patent misuse.[107] Based on the underlying patent policy that an inventor is awarded a patent for his invention and nothing more, patent misuse inquiries center on the patentee's conduct and its effect on the market ***236** of substitutes for the patented product. A finding of patent misuse, however, does not render a patent invalid.[108] Once misuse is cured by ceasing the prohibited conduct, the patent is again enforceable.[109]

A gene patent requires disclosure of a new and complete DNA sequence, a finding of nonobviousness to one skilled in the art, and utility that is specific, substantial, and credible. Such a patent is broad and powerful, permitting the patentee to control all manufacture and use of the gene and any derived protein products for the twenty-year term. Since no gene operates in isolation, a single patentee effectively controls any and all upstream and downstream commercialization efforts.

III. Current Viewpoints on Gene Patents

The monopoly given to an inventor in a patent is in exchange for the disclosure of the invention in the specification and claims of the patent. In this way, the public benefits from the knowledge of the patented advance by allocation of intellectual and economic resources in an efficient manner by (a) allowing the inventor to recoup his investment and reap the rewards of his success, encouraging others to disclose their inventions through patents, (b) encouraging competitors to "invent around" the patented invention, avoiding wasteful duplication of efforts, and (c) insuring the eventual dedication of invention to the public with the expiration of the patent.[110] With a traditionally high barrier against the patenting of ideas and phenomena of nature, the Patent Act seeks to provide incentive to invent and innovate while protecting discoveries of the core elements of nature.[111] In a seeming contradiction, genes are products of nature and yet have the full patent protection of an invention, such as a typewriter or a light bulb. The rationale supporting the protection of genes and DNA sequences will be discussed in this section as well as the counterargument that such sequences should be outside of the scope of the Patent Act.

A. Strong Patent Protection Strengthens and Stimulates Scientific Progress and Innovation

Economic analysis of research and development (R&D) investment requirements and commercial success among biotechnology companies drives the debate ***237** over gene patents in favor of strong and broad gene patent protection.[112] The biotechnology industry has tripled in size since 1992.[113] In 1999, the biotechnology industry generated 150,800 jobs directly and 286,600 jobs indirectly as well as revenues totaling $20 billion directly and $27 billion indirectly.[114] Biotechnology generated $10 billion in tax revenues in 1999 alone.[115] In 2000, venture capitalists invested approximately $353.5 billion in biotechnology industry.[116] In the United States, there are 1,457 biotechnology companies, 342 of which are publicly held.[117] Revenues now stand at $22.3 billion in 2000 and roughly 9,000 patents are granted per year.[118] Biotechnology, particularly in light of the potential wielded by the Human Genome Project, has emerged as a major player in big business with inevitable ties to the pharmaceutical industry. Therefore, according to gene patent advocates, basic business economics supports strong patent protection as an incentive to promote continuing progress in the biotechnology industry.[119]

1. Economic Theories Supporting Biotechnology Patents

The scope of a patent's claims determines its economic strength.[120] Four economic theories provide alternative explanations of the role of patents in promoting technological progress, each relying on a different necessary scope for the claims of a patent.[121]

***238** First, the inventive theory rests on the premise that the incentive-to-invent is derived from an inventor knowing that he will be compensated for his investment in developing and perfecting his invention.[122] In other words, if an inventor fears easy appropriation of his invention by a competitor, he will be less likely to bear the initial economic burden of development.[123] Such freeriding by a competitor denies the inventor the desired compensation for his economic and intellectual investment.[124] As a result, socially beneficial inventions may be significantly delayed or completely thwarted.[125] Therefore, under this theory, the scope of patent claims should be broad to both insulate the patentee from freeriders and permit sufficient recovery of his investment costs.[126]

Second, the disclosure theory views the patent system as encouraging disclosure of an invention while discouraging reliance

on trade secrets to reduce competition.[127] Since inventions generally build on the available knowledge base, secrecy inhibits any immediate public benefit from that knowledge.[128] The public is also deprived of potentially wider distribution, alternative uses, and market competition from substitutes.[129] Furthermore, the lack of disclosure may also result in inefficient allocation of resources as multiple inventors invest their time and money into the same invention.[130] The scope of patent claims under the disclosure theory would also be broad.[131] Broad patent protection of the invention and any variations sufficiently disclosed would further the public benefit of access to the knowledge while simultaneously encouraging maximum disclosure in individual patents.[132]

Third, the innovation theory recognizes the inventor's initial investment in the discovery as significantly upstream of commercial exploitation.[133] Innovation represents more than the initial discovery or invention.[134] Innovation also includes ***239** any further research and development necessary for commercialization.[135] This theory represents an economic belief that the patent monopoly is superior to competition in promoting commercially exploited inventions.[136] When analyzing a patent's scope in light of the innovation theory, the innovation costs become part of the analysis for the determination of patent scope.[137] For example, a patent that has few innovation costs would naturally have a narrower claim scope while a so-called pioneer patent[138] (disclosing a substantial step forward) would have a correspondingly broader claim scope because of high innovation costs. Under this theory, the scope of the patent claims would be determined on an invention-by-invention basis, with a possible range of narrow to very broad protection.

Fourth, the prospect theory values patents as an efficiency mechanism regulating the development of the patented invention.[139] The patent monopoly creates an optimally efficient allocation of resources by permitting the coordination of research and development efforts downstream of the patent.[140] In this way, according to the theory's proponents, invention development progresses efficiently, reducing wasteful resource investment in duplicative improvements or variations.[141] Advocates of the prospect theory of patent law support broad protection that is not limited to embodiments in the patent and that extends to any and all subsequent versions or improvements.[142] Such broad patent protection assumes that the patentee's control of development will ultimately be more efficient than having multiple inventors investing their individual resources. The scope of patent claims is the broadest under this theory of patent protection.

2. Stimulation of Innovation and Progress

Little direct evidence supports strong patent protection as a driving force in the development and commercialization of useful applications in biotechnology. Biotechnology industrialists forcefully maintain that strong patent protection is essential to protect risky investments in biology-based research because of the unusually high failure rate of products. According to Randal Scott, president and chief scientific officer of Incyte Genomics, patent protection provides the necessary incentive ***240** to invent and disclose genetic inventions.[143] "[M]assive investment in genomic research is essential to capital formation" and gives investors the necessary assurance that they will profit from such investments.[144] Moreover, patent protection for genes "encourage[s] the broad dissemination of genomic information" because patents encourage broad distribution.[145] Scott further asserts that gene patenting fulfills the constitutional purpose of promoting the progress of science and useful arts by encouraging innovation.[146] Relying primarily on a tripartite approach to patent theory, biotechnology industrialists defend their right to gene patents in terms of invention, disclosure, and innovation critical for the necessary investment of economic resources and the resulting efficiency of a monopolistic approach to the genome.[147]

Biotechnology industrialists strenuously defend the patentability of genes and resist industry-specific intervention by Congress. According to those in biotechnology, gene patents represent real invention and, therefore, should be treated as any other technology within the current patent system.[148] Biotechnology is likened to information technologies as a key driver of economic growth and a direct beneficiary of the patent system. Accordingly, any adaptation should be left to the courts and the market while Congress or the PTO should be "extremely circumspect in applying different legal standards to gene patents in a misguided attempt to address problems that are at this point only theoretical, and are in fact highly unlikely to occur."[149] Patent protection, the biotechnology industry argues, does not cause a lack of product competition. Instead, gene patents promote efficiency in greater numbers of safer, cheaper, and more effective drugs reaching the consumer.[150] "Using rapid, accurate technologies, it will be possible to test drugs for toxicity and effectiveness against known classes of genes, thereby eliminating many costly drug failures late in the drug development cycle."[151] According to the Biotechnology Industry Organization (BIO) and its members, any biotechnology-specific alterations in patent requirements or patent licensing will not only upset the stability of the patent system, but also the successful partnership between the private and public ***241** sector-- a partnership that ultimately benefits the public through dramatic improvements in medical diagnosis and treatment.[152]

B. Arguments Against Gene Patents

On the other side of the gene patent debate are those who decry the patenting of genes as permitting a monopoly over products of nature that is contrary to the constitutional intent underlying the Patent Act. For example, the American College of Medical Genetics takes a definitive position, stating that "[g]enes and their mutations are naturally occurring substances that should not be patented."[153] Others argue that traditional economic analysis does not support the application of the current patent system to genes.[154] Francis Collins, director of the Human Genome Project, has expressed concern that putting "toll booths on basic science" will stifle the very progress gene patents should encourage.[155] The debate continues to intensify, as the number of total genes in the human genome is approximately 35,000 to 45,000,[156] while greater than 28,000 gene patents have already been filed with the PTO by a handful of biotechnology companies.[157]

1. Interpretation of 35 U.S.C. § 101

Prior to the decision in Diamond v. Chakrabarty in 1980, products of nature were expressly unpatentable.[158] Again and again, the Supreme Court denied patentable subject matter status to phenomena of nature, mental processes, and abstract intellectual concepts.[159] The Court expressed concern that a patent on a product of ***242** nature would prohibit all other persons from using that product.[160] Justice Douglas reiterated this concern in Funk Brothers Seed Co. v. Kalo Inoculant Co.[161] The patent at issue claimed a mixture of three types of naturally occurring bacteria that, in combination, formed a superior growth supplement allowing for the growth of previously incompatible leguminous plants in the same soil tract.[162] Douglas concluded that:

> [P]atents cannot issue for the discovery of the phenomena of nature. The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none.[163]

This seemingly absolute prohibition against patenting newly discovered products of nature has been eroded only recently. In reinterpreting its position on the patenting of natural products, the courts have relied on one of two theories. The first theory asserts that a purified product differs in form from the natural product; thus, it is not a product of nature per se.[164] The second theory asserts that all inventions are ultimately products of nature.[165] Therefore, despite a gene's status as a product of nature, it is patentable subject matter in a purified form that differs from the natural gene.[166]

2. Difficulty in Applying Traditional Economic Theories to Gene Patents

Basic science research in academic institutions forms the interface between biotechnology and the public sector. The basic science research of university scientists largely drives technological advances in biotechnology, making biotechnology a "science-based" technology.[167] For example, publicly funded basic science research comprises 71.6% of the scientific references in biotechnology patents, while university patents historically have accounted for one-tenth to one-fifth of patents ***243** granted on biotechnology inventions.[168] In fact, in the 1990s, the vast majority of all biotechnology companies had a university research partner.[169] Therefore, analysts suggest that economic analysis of biotechnology must account for its distinctive features resulting from this interface with and dependency on basic science researchers.

The critical differences lie in the motivating incentives for the basic science researchers to invent. Peer recognition and personal contribution provide the strongest motivation for basic researcher scientists to invent, disclose, and innovate.[170] The career path of a basic science researcher begins with a long, difficult, and highly competitive training period where access to personal wealth is shunned in favor of highly prized mentors in prestigious laboratories.[171] The researcher then competes to obtain an independent research position where he continues to compete for laboratory funding and publication opportunities, again with little regard for personal compensation.[172] "[R]eputational rewards for publication and priority" define individual achievement.[173] In other words, a scientist invents with an eye towards making a breakthrough discovery that will be both remembered and recognized by his peers. Although some economic incentive exists in the form of increased research funding, the primary drive to invent and disclose is without thought of investment costs or efficiency concerns.[174]

The absence of the strong monetary incentives assumed in economic analyses challenges the function of a broad patent system encompassing basic science research as contrary and potentially stifling to scientific progress.[175] First, the norm in scientific progress, particularly in the life sciences, frequently promotes the investment of significant research resources on answering a single narrow question.[176] For example, the identification of a new gene that suppresses the growth of colon cancer will result in numerous scientists investing their research resources into investigating that gene in colon cancer, other

cancers, and biologically related phenomena. Such efforts simultaneously scrutinize the original research results for ***244** validity and scientific significance. In other words, does this original research represent a significant step forward in the understanding of the anti-colon cancer gene itself and/or processes involved in cancer development? This well-worn approach has been criticized as inefficient and wasteful of valuable research resources and intellectual capital.[177] Yet, within the scientific community, the validation and extension of a scientific finding by other researchers is essential in searching for the "scientific truth" among various research models and approaches.[178] In the absence of such validation, the scientific finding is viewed with skepticism.[179] A strong patent system discourages such validation and extension by multiple groups of researchers and can potentially slow or stifle progress during the patent term.

Second, broad patenting of basic genetic information endangers prompt disclosure among scientists.[180] The scientific norm of disclosure springs from the communality of the scientific community, wherein access to new discoveries is an obligation to ensure that all members of the scientific community have access to the new knowledge to learn from and build on in future work.[181] Patenting necessarily mandates delays in disclosure during the examination process, therefore delaying access and use of the research by the scientific community.[182] With the current eighteen month publication date for pending patent applications,[183] such a delay may be viewed as insignificant. However, with the availability of DNA arrays and other high-throughput technologies, even eighteen months could represent a significant delay in the rapid development of scientific knowledge.

Finally, negotiating patent licenses and valuing the risk of reach-through royalty or invention right agreements result in high transaction costs for basic science research and will quickly interfere with the norms of research. Researchers usually rely exclusively on grants awarded by the National Institutes of Health (NIH) and other public funding sources to support the laboratory, its staff, students, and post-doctoral fellows, as well as the researcher herself. Therefore, the typical researcher has a limited budget woefully insufficient if a license is required for many of the genes necessary for continuing scientific development. Furthermore, the ability to engage in small pilot projects to determine the feasibility of a hypothesis or new research direction ceases without access to the necessary reagents because even a single license is likely to have a prohibitively high transaction cost. Recognizing this potential threat, the NIH has pressured biotechnology companies for free use of ***245** inventions and actively condemns reach-through royalty or product rights, unreasonable restraints on publication and academic freedom, and improper valuation of tools.[184] In an industry dependent on university-based scientific research, such curbs on scientific freedom would undoubtedly suppress continued scientific progress and potentially strangle the recent growth in biotechnology.

IV. The Significance of Gene Patents to the Public and Basic Science Researchers

The role of patent protection for gene-based research has been seriously questioned from many sectors of society in the United States and abroad. The trend in reach-through patent claims and reach-through licenses has elicited concern from the Human Genome Organisation (HUGO) that future research and development will be negatively impacted in such a way that "could, eventually, discredit the entire patent system as an invaluable incentive to invent, innovate and invest in new technologies."[185] As the public and the scientific community struggle to absorb the flood of information regarding the human genome, criticism flares and concern rises as tangible, thoughtful policy decisions still lag hopelessly behind.

The first reported lawsuit alleging that a gene patent hinders research provides a somewhat ominous view of its potential downstream effects.[186] In this case, the parents of children with Canavan disease, a single gene disorder, solicited the help of a researcher to develop a prenatal genetic test.[187] Using genetic material from the families, the researcher successfully developed a diagnostic genetic test and patented the test.[188] Thereafter, the patentee began charging the families for testing as well as actively enforcing his rights by limiting other research efforts.[189] The families brought suit, alleging the patentee used resources dedicated to the public (i.e., by using publicly funded research) to obtain a patent, charge royalties, and limit testing availability.[190] While not yet resolved, this case highlights the unique ***246** nature of genes as well as the peculiar intersection of gene patents with important and fundamental public policy issues.

Basic science researchers also condemn the "gold rush" on the genome as "divert[ing] attention and resources away from the real causes of ill-health and . . . stigmatiz[ing] the victims [those with genetic mutations]."[191] Since genetic diseases attributable to a single gene account for less than 2% of all diseases, scientists worry that the pursuit of gene patents drain valuable resources from organism-based research.[192] Active protest from scientists has forced some biotechnology companies to agree to free non-commercial use,[193] while others have resorted to litigation.[194]

Neither a loss of public faith in the patent system nor a diminution in the historical surge in scientific knowledge is necessarily an inevitable outcome during these critical years. It is true that the Federal Circuit will likely craft a more workable framework that fully appreciates and balances the unique nature of genes and the contributions of the inventors and basic science researchers. However, the question is whether there is time to wait for the courts to resolve the ongoing debate as more gene patents issue and basic science research grapples with increasing tolls on their research.

V. Possible Approaches to Gene Patenting: Strengths and Weaknesses

In this section, approaches to gene patents in the context of the various economic, scientific, and public concerns are discussed using the three medically relevant uses of genetic material discussed in section II--gene therapy, genetic diagnostic tests, and purified protein production--as guides to the nuances of the various approaches. Such an examination readily reveals some of the strengths and weaknesses of each approach and highlights the critical nature of the debate in the immediate future and the necessity for action now rather than later.

A. No Protection for Any Naturally Occurring Gene Sequence

In the complete absence of gene patents, all naturally occurring genes (as well as other gene sequences such as cDNA) would be in the public domain, as well as all alleles, splice variants, and naturally occurring mutations within the human genome. ***247** As with other scientific discoveries of natural phenomena, genes and the encoded information would be freely available to basic science researchers as well as to biotechnology researchers. Inventions produced by man using genetic material, on the other hand, would still be eligible for patent protection.

For example, the creation of a DNA sequence encoding a protein consisting of a single protein domain with a particular binding specificity from gene A and a second protein domain with a particular enzymatic activity from gene B is still patentable subject matter under this scheme. The A-B protein is not naturally occurring and represents true invention by its inventor because he used the tools (genes) that nature has provided. The inventor could not extend his patent protection to the portions of gene A and B in the naturally occurring gene or its variants. Rather, genes A and B and their respective independent functions would become part of prior art examined for patentability of the A-B gene. If the A-B gene meets the statutory requirements for patentability, the resulting broad patent protection of the A-B gene provides the incentive to invent and innovate while maintaining the unfettered access to the A and B genes.

The definition of a naturally occurring gene determines patentability in this scheme. Presumably, the naturally occurring gene is one identified in a genome. Patentability of such a gene would not be obtained through the introduction or identification of a single nucleotide change not affecting the gene (or its protein product's) function because it would be obvious in light of the prior art of the gene in the public domain. One counterargument is that random changes in nucleotides are anticipated within the genome. Because a gene's activity can be dramatically altered by as little as a single nucleotide change,[195] at what point does a gene deviate sufficiently so it no longer qualifies as naturally occurring gene? And what of the artificially introduced single nucleotide change that dramatically alters function and is as yet unobserved in any genomic database? Must the inventor prove that it is absolutely not found in any human genome? It can be argued that such definitive proof would be unavailable or inconclusive. Yet, a workable definition of a naturally occurring gene is possible and can credibly rely on accepted notions regarding conservative substitutions.

Genetic diagnostic tests also remain patentable subject matter under this scheme as inventions made by man, despite an absolute prohibition against patenting naturally occurring genes. With such genes in the pubic domain, innovation should increase through the pressures of free market competition by providing incentives for biotechnology companies to invent more rapid, efficient, and inexpensive diagnostic tests to compete in the diagnostic test marketplace. Therefore, the diagnostic test patents create no barrier to basic research efforts on the target genes while still permitting the patentee to be compensated for his invention and innovation in the presence of such a prohibition.

***248** The essential tool of gene therapy, the vector containing the desired gene, would also remain patentable subject matter under an analysis of whether the claimed DNA sequence occurs naturally. In other words, a patent claiming a gene therapy vector would not be hindered by the desired gene being in the public domain. For example, a gene therapy vector is created using gene C in a retroviral vector for the treatment of skin cancer. The retroviral vector is encoded by a DNA sequence containing all of the necessary genes for the virus to replicate, form a viral capsid, and initiate expression and insertion of

gene C into the target cell's genome. This conglomerate of viral gene sequences and gene C sequences are not naturally occurring and should be patentable. Again, such a patent would not hinder any other inventor from the use of gene C in his research or development except in the area of retroviral gene therapy vectors, while permitting the inventor of the gene C gene therapy vector to be compensated for his invention and subsequent innovation in taking the vector into the marketplace.

A strict prohibition against patenting naturally occurring genes and genetic sequences requires a clear definition of a naturally occurring gene or genetic sequence. The greatest difficulty in a strict prohibition lies in this definition. Such a prohibition provides access to genes and promotes basic science research. If the definition of a naturally occurring gene was sufficiently narrow, the prohibition would discourage biotechnology from investing in gene-based research and commercial development. While the gene itself would remain unpatentable, any improvement or manipulation remains patentable subject matter, which would significantly reduce the incentives for biotechnology industry.

B. Protection under Current Patent Requirements

Genes are currently patentable if the sequence is new, nonobvious, fully disclosed and enabled, and has a specific, substantial, and credible utility.[196] Gene patents are usually broad product patents. According to those in biotechnology, this broad patent protection has been and continues to be essential to the continued growth of the industry.[197] Meanwhile, others cite the problems of blocking patents, stacking patents and royalties, litigation costs, and long-term dampening effects on basic science research.

Gene patents may represent the ultimate in blocking patents. For example, if inventor X has a patent on gene A, then protein production using gene A, diagnostic tests detecting gene A,[198] and a gene therapy vector containing gene A all come within the scope of X's gene A patent. Additional inventors may also patent such ***249** uses of A. Inventor A can patent protein A, inventor B can patent a diagnostic test for gene A, and inventor C can patent a retroviral gene therapy vector with gene A. Inventor X would hold a blocking patent against inventors A, B, and C. Because X has the right to exclude all others from making, using, selling, or offering to sell his product, each subsequent inventor will have to acquire a license under X's patent in order to operate under his own patent. Inventor X can legally and effectively control all upstream and downstream uses of gene A simply because of the fundamental nature of a gene in biological research. Genes are ultimately the basis of all cellular function, controlling and participating in all aspects of health and disease and in all research in those areas.

Biotechnology industrialists are quick to diffuse any misgivings regarding the fundamental nature of genomics. Analogizing genes to computer programs and microprocessors, they assert that the biotechnology industry will be able to develop a cross-licensing scheme that will protect their investments while delivering major advancements in science and medicine to the public just as the information industry did.[199]

Gene patents may also provide a worst-case scenario for cross-licensing because of stacking patents. Stacking patents occur when different inventors own overlapping sequences or technologies.[200] For example, it is currently possible for patents to issue for a full-length sequence of gene A, the sequence of gene A including a disease-related polymorphism, a splice variant of gene A, and protein A (that gene A encodes) simultaneously and to different inventors. Again, any one of these patents may be used as blocking patent against the others. It also creates a stacking royalty problem for all of the patent owners.[201] Negotiating licenses and paying royalties to multiple parties after a considerable investment in one's own patentable invention can quickly create prohibitive transaction costs for all but the largest biotechnology companies.

This is further complicated by the potential ownership of all of the 30,000 genes in the human genome by a handful of companies.[202] These companies may have equivalent bargaining power permitting beneficial cross-licensing agreements among themselves. It is unclear where that leaves the remaining biotechnology companies and basic science researchers. Genes are essentially a scarce and limited resource that is absolutely required for basic science research. As a result, limited and exclusive ownership could deter innovation by creating an anticommons effect, where genetic information is underutilized because of high transaction costs, strategic ***250** behavior, and overvaluation.[203] Therefore, strong patent protection for genes will potentially delay the efficient use of genes and genetic information in all areas of life science research, denying the public the benefit of the knowledge. It is also reasonable to assume that no one company has the resources to efficiently research and develop approaches to a multitude of diseases. If a company cannot fully develop a patented invention, the public benefit is not ultimately served by allowing broad patent monopolies on genes.

Furthermore, extensive use of patents to negotiate rights to downstream research may result in inefficiency because of

ownership by a few. The ground for hold-ups could become increasingly fertile once all genes are patented. Publicly funded basic science researchers are increasingly resistant to paying tolls at every turn to continue their research.[204] The lack of an equal bargaining position, the inability to absorb transaction costs associated with licensing negotiations, and the bias against ceding control of future research to third parties creates disincentives for science researchers to do basic research.

Finally, reliance on the courts to apply patent law principles to a relatively new patentable subject matter will be expensive, time consuming, and potentially incomplete. An estimated $100,000 to $500,000 is required to maintain one patent for its twenty-year term.[205] Active enforcement of patent rights typically costs $1.6 million per contested patent.[206] Moreover, the first two or more years of the patent term can be lost to its prosecution and issuance.[207] Additionally, the courts may not have the opportunity to address the critical issues at hand for years to come, leaving the current patent system untouched for the majority of these critical initial years following the availability of the human genomic sequence.

In summary, the current patent system strongly favors the few biotechnology firms that currently hold patents (or have submitted patent applications) for the gene sequences of the human genome. The broad patent protection granted threatens to create significant disincentives for basic science researchers and smaller biotechnology companies to perform genetic research. Furthermore, broad patent protection promotes the inefficient use of a fundamental scientific tool.

***251 C. The Possibilities of a Distinct Regime for Gene Patents**

1. Shorter Patent Term

A first and simple reform would be a change in the patent term. A shorter patent term would immediately increase access to newly discovered genes by accelerating the time when those genes are dedicated to the public domain. This would be implemented easily and immediately by legislative amendment. Faster access potentially diminishes the disincentives to basic science researchers by limiting the duration of royalty payments and licensing negotiations. Furthermore, the unique status of genes as a fundamental element of all life science research allows the biotechnology industry to receive economic awards through licensing agreements during the shorter patent term. The immediate and principal market for gene sequences is the basic science researcher and smaller biotechnology firm. No further research and development costs are required to deliver the product to this market once the gene is patented. With the development of bioinformatics technology, biotechnology companies have been able to use the genetic database to accelerate the drug discovery process by three-fold or more.[208] The significantly shorter development time will make a patent profitable much earlier and would allow the biotechnology company to economically benefit from its research and development investment.

Biotechnology industrialists, on the other hand, argue that a shortening of the patent term would create a significant disincentive for invention and innovation. In the short term, many biotechnology companies stand to lose significant royalty payments on past R&D investments leading to gene patents. In the long term, biotechnology companies continue to provide value to the public by developing and marketing new gene-based products as well as significantly contributing to the national economy. The biotechnology industry argues that diminution in patent term ultimately hurts the patient in reducing his choices of medical therapies. In fact, the Biotechnology Industry Organization (BIO) has recently sought to increase the patent term in certain situations, asserting that no other industry is more sensitive to the length of the patent term than biotechnology.[209] According to BIO, biotechnology companies rely on patents for company valuation and generation of equity capital.[210] Research is funded primarily from equity capital rather than from product sales revenues as in other industries.[211] Without adequate patent protection, ***252** sufficient capital cannot be generated due to the substantial risk inherent in biotechnology research. This could jeopardize gene-based product development as well as its continued contribution to the market.[212] In sum, shortening the patent term would likely meet strong resistance from BIO and others in biotechnology.

2. Renewable Patent Term upon Agency Review

A second potential reform is the use of a renewable patent term after a review by a designated agency. At a predetermined point, presumably at year ten of the patent term, a patentee's right to the second half of the term would be determined by an agency using mandated criteria regarding the patentee's use of the patent during the first half of the patent term. In other words, if a patentee has asserted his patent rights in ways that have thwarted research efforts in that field, the patentee would have to cure his conduct or would have the patent terminated at year ten. If, on the other hand, the patentee has diligently utilized his patent without impeding research in the same field, the additional ten years would be granted.

Reviews of this nature maximize flexibility in valuation of a gene patent relative to scientific progress and increase patentee accountability. Under such a review scheme, a gene patent that is dominating a particularly active area of research would be most heavily scrutinized. Patentee actions in licensing the gene and the impact of reach-through license agreements would likely be determinative in granting the second half of the term. Evidence of licensing for reasonable royalty rates would strongly favor the patentee even if the patent dominated a particularly active research area. In contrast, blocking access through unreasonable royalty rates, hold-ups, or oppressive reach-through licensing agreements would result in termination of patent protection, even if the patent represents only one of many tools in the research area.

The most significant limitations of this reform are implementation and introduction of uncertain patent terms. Successful implementation requires the establishment of a new agency by Congress with sufficient funding and adequately skilled staffing to merit the agency's authority in patent examination. In the face of the current economic downturn, this is a remote possibility at best. Moreover, this reform would introduce uncertainty as to the length of the patent term. An uncertain patent term may prove to be a greater disincentive to investment by biotechnology investors than would a simple reduction of patent term by adding an additional high risk factor to an already risky investment.

***253** 3. Fair Use Exception

A fair use exception would permit the use of a patented gene by third parties in the absence of a license without fear of an infringement action.[213] The fair use exception originates in copyright law and has been suggested as a needed construct in patent law to promote an appropriate balance between encouraging innovation and maintaining progress through a viable public domain.[214] A fair use exception for gene patents would excuse infringement in circumstances where market failures (hold ups) render the exclusionary patent rights overbroad and would prevent socially efficient and desirable uses of the patented gene. In other words, market failures are circumstances where the patentee refuses to license the patented gene out of a desire unrelated to the goals of patent law.[215] Using such an exception to limit a patentee's actions could potentially avoid the development of an anticommons for genes.[216]

Any implementation of a fair use exception would require legislative action and subsequent development of the exception's contours by the courts. Maureen O'Rourke has suggested a five-factor framework for a fair use analysis.[217] The first factor is "the nature of the advance represented by the infringing work."[218] The more significant the advance, the more likely availability benefits public welfare.[219] The second factor is "the purpose of the infringing work."[220] As in copyright, a commercial use cuts strongly against a finding of fair use unless the benefit to public welfare is high.[221] A non-commercial use, on the other hand, cuts in favor of fair use. The third factor is "the nature and strength of the market failure that frustrates licensing."[222] If the impact on innovation is significant because of network ***254** effects or high transaction costs, this factor will favor permitting the use as fair.[223] Although a patentee's right to refuse to license should usually be respected, this factor considers the reasonableness of that refusal in light of all of the circumstances.[224] The fourth factor is "the impact of the use on incentives and social welfare."[225] If widespread use of the patented invention would significantly affect the market for that invention without a significant effect on the public benefit, this factor weighs against a finding of fair use.[226] If, on the other hand, the public benefit of the use is high, negative effects on the patentee's royalties on balance will not prevent a finding of fair use.[227] According to O'Rourke, this is the most important factor.[228] The fifth factor is "the nature of the patented work."[229] Is the advance a small advance over the prior art or is it a major advance? Although a patent that constitutes a major advance would traditionally have a narrow fair use exception, "there may be a direct relationship between the degree of inventiveness of the first innovation and the need for follow-on inventors to infringe the patent in adding to the store of knowledge."[230] This would seem to be particularly true in the case of gene patents where any inventor seeking to add to the knowledge about a patented gene's function or role in disease requires the use of that gene. Overall, the determination of an infringing use as fair is fact-intensive and usually would be decided in the courts.

While a fair use exception would permit access to a patented gene when the public benefit is significant, it is likely to be decided through expensive and time-consuming litigation. Basic science researchers would have the strongest case for the fair use of a patented gene but would rarely have the necessary time or money to litigate for that use. Moreover, a finding of fair use does not necessarily mandate a royalty-free fair use but leaves that determination to the court.[231] A reasonable royalty still may be beyond the economic means of the basic science researcher. On the other hand, biotechnology industrialists would likely vigorously oppose any diminution of potential royalty payments and control of downstream research efforts as reducing the valuation of their patent portfolio, which would weakening investment opportunities. The uncertainty of whether a use is fair and what a reasonable ***255** royalty would be is a high risk for both the basic science researcher and the biotechnology industrialist.

4. Stringent Licensing Control

Strict guidelines governing licensing would likely eliminate high transaction costs, overvaluation, and reduced access to genes. The immediate concerns of toll booths on basic science could be assuaged if licensing were standardized and offered at a reasonable royalty rate. Industry-wide licensing guidelines could ensure access while protecting the patentee's rights to royalties on his gene patent. For example, a two-tiered system with a lower rate for basic science researchers and a higher rate for biotechnology companies recognizes and facilitates the difference in economic resources inherent in each group. Another system might have three royalty rates: a higher rate for the small biotechnology company, an intermediate rate for the basic scientist who may be developing a patentable invention, and a lower rate for the basic scientist who has a strict research use without immediate commercial opportunities. Such a system would guarantee access at a known rate for researchers and potentially allow them to develop the budget necessary for such fees.

Implementation would likely prove somewhat problematic. Presumably, a uniform licensing scheme requires the establishment of an agency that has the power to determine a reasonable royalty and enforce the licensing regulations. Whether formed within the biotechnology industry or by Congress, sufficient funding and skilled staffing are immediate requirements. An additional difficulty is the valuation of a gene patent. The value of a gene tends to increase in direct proportion to the number of investigators working on the gene and the information known about the gene's function in health and disease. Therefore, the value of a gene is often subjective and may be difficult to ascertain with certainty from gene to gene. Finally, BIO has stated emphatically that it is opposed to any form of licensing control whatsoever.[232]

5. Stricter Limitations on the Boundary of a Gene Patent

A narrow interpretation of a gene patent provides greater access and increased incentives to innovate using the gene while decreasing transaction costs and eliminating valuation problems. Such an interpretation increases access by limiting the patentee to the use of the gene described in the patent application. This would not necessarily limit an inventor to the actual embodiments provided in the specification; instead it would narrow the scope of the patent claims to what could be reasonably enabled by the specification. In other words, if an application describes a gene that inhibits the growth of tumor cells and the embodiment demonstrates this activity, the inventor would be limited to claiming the gene in the context of this use. The inventor would be precluded from claiming the use of that gene in other ***256** diseases where abnormal cellular growth may occur (e.g., autoimmune disorders) unless he also provided an embodiment addressing the other diseases. This would serve two distinct functions. First, the incentive to invent would be focused on the disease most likely to be profitable for that inventor. Since it is quite unusual that a researcher, whether a basic scientist or a biotechnology industrialist, would be active in areas as distinct as cancer and autoimmunity, a strict interpretation encourages efficient allocation of resources. For those researchers with the resources to adequately address the gene in both diseases, broader patent protection would still be available through the inclusion of additional disclosure while discouraging researchers with limited resources from having protection in an area that he cannot exploit. Second, the incentive to innovate increases without simultaneously decreasing access to the patented gene. For genes that are downstream and critical participants in distinct cell types, such narrow patent protection enhances the incentives of basic science researchers to continue in the successful validation and extension science model. Biotechnology industrialists, on the other hand, maintain monopolistic control over the gene product in the use they have defined.

Implementation of a more restrictive patent protection regime for gene patents is straightforward and relatively inexpensive. First, tougher utility guidelines from the PTO raise the bar for patentability of gene product patents. In cases where an inventor seeks broad claims for a few or limited embodiments, the patent claims would be rejected and subject to amendment during prosecution. Second, narrow claim construction at the judicial level sends a clear signal regarding the strength of product patents for infringement suits as well as licensing negotiations. Therefore, even if a patent had issued with broad claims, the scope of protection would be limited to those embodiments disclosed in and reasonably drawn from the specification.

The clear advantage of restricting the scope of a product patent claiming a gene is the access of greater numbers of inventors and basic science researchers to the gene. The difficulty in this regime is the determination of how far the scope of protection should extend beyond the disclosed embodiments. For example, if a gene is shown to inhibit the growth of prostate cancer, should patent protection extend to use in all forms of prostate cancer, other related forms of cancer, or all cancers? If a patent's scope stopped short of protecting the gene's use in all cancers, how many embodiments would be required to claim its use in all cancer? Would it necessarily depend on the state of the scientific knowledge at the time of filing? With the pace of new information growing exponentially regarding genes and gene function, such ambiguity may in fact be necessary if the

stifling effect of patent monopolies is to be minimized. Again, the biotechnology industrialists will likely be unsupportive because such a regime would lessen the absolute value of any one gene patent.

6. A Combined Approach

In view of the singular importance of genes to scientific research and continued medical progress, it is essential to implement specific limitations on gene patents ***257** in a manner that does not simultaneously drive biotechnology from the field. It cannot be ignored that through the mutual participation of biotechnology and basic science researchers that the human genome is available. Nor is it trivial the vast resources that biotechnology brings to bear on previously intransigent stumbling blocks in research and in medicine. Proper management of gene patents requires an accounting of the distinct economic incentives, the underlying policy concerns for continued scientific and medical progress, and the unique, and often interdependent, contributions of basic research scientists and biotechnology.[233]

A tripartite approach to gene patenting that implements a combination of fair use, licensing control, and narrow patent scope reforms discussed above retains the necessary economic incentives for biotechnology while encouraging continued scientific research and progress. The most effective method of implementing such significant reform is through legislative action. Piecemeal implementation by the Federal Circuit, the PTO, or the biotechnology industry itself (in a self-regulatory licensing situation) is likely to be slow and of questionable effectiveness because of the urgency in maintaining the availability of genes for research. Therefore, a decisive move by Congress is essential to maintaining the exciting and growing momentum in biotechnology and basic science research.

Each potential reform has its difficulties. These difficulties reside largely in the subject matter itself. Only 30,000 genes control the functions of a cell and, ultimately, all manifestations of health and disease. Genes, unlike other inventions, cannot be "invented around." If a particular gene is at the critical juncture in a disease process, another gene cannot be created to imitate that gene, and it is highly unlikely that a second gene in the cell will have the identical function. Furthermore, little is still known about many of the individual genes. Although computer technology has enhanced the ability to sequence DNA and even determine levels of mRNA expression, long-term experimentation in animal models and patient populations is still necessary to determine a gene's true role in health or disease. The need for continued, aggressive research efforts from a maximum number of researchers is paramount if DNA sequencing information is to be meaningful in our daily lives. The potential reforms discussed in this article simply represent a starting point. In all likelihood, the most effective and efficient reform will be a combination of restricting the scope of a gene patent, introducing a fair use defense, and instituting some form of regulation of licensing control. Coordinated action from ***258** the legislature, the PTO, and the courts will be required to make these reforms expediently. As we stand on the brink of truly amazing advances in science and medicine, we simply cannot afford to hope everything will work out for the best. Congress and the PTO must act.

Conclusion

Human genes are a rich frontier for both scientific advancement and a young biotechnology industry. Gene patents stand at the crossroads between research and biotechnology with distinct incentives, economic realities, and ultimate goals. With these distinctions in mind, a reexamination of gene patents and consideration of modifications to the current system must be contemplated thoughtfully and thoroughly. Most importantly, if changes are to be made, now is the time. The social benefit of this wealth of new scientific knowledge must be balanced against the urge to own the genome for the sake of science, biotechnology, and, most importantly, the individual that medical progress will save.

Footnotes

[a1] Associate, Morrison & Foerster, L.L.P., San Diego, California; J.D., 2002, University of Texas School of Law; Ph.D., Microbiology & Immunology, 1993, Thomas Jefferson University. The author thanks Jane Cohen for her many helpful insights and guidance with this article and Bill Dow, Karen Dow, and Laurie Owen for their comments and suggestions.

[1] U.S. Const. art. I, § 8, cl. 8.

[2] James D. Watson et al., Recombinant DNA: A Short Course 1-2 (1983).

[3] Harvey Lodish et al., Molecular Cell Biology 102 (3d ed. 1995).

[4] Watson, supra note 2, at 11-12.

[5] See id. at 12, 38.

[6] Lodish, supra note 3, at 12.

[7] Sunil Maulik & Salil D. Patel, Molecular Biotechnology: Therapeutic Applications and Strategies 1 (1997).

[8] The Science Behind the Genome Project: Basic Genetics, Genome Draft Sequence, and Post-Genome Science, Human Genome Project Information, at http:// www.ornl.gov/hgmis/project/info.html (last visited Dec. 22, 2002).

[9] Watson, supra note 2, at 133.

[10] Id.

[11] Lodish, supra note 3, at 119.

[12] Id. at 119-22.

[13] Id. at 234-36. The instability of mRNA makes DNA a more suitable research tool.

[14] Id.

[15] Id. at 119-22.

[16] Stanley Fields, Proteomics in Genomeland, 291 Science 1221 (Feb. 16, 2001).

[17] Lodish, supra note 3, at 426-28.

[18] Id.

[19] Benjamin Lewin, Genes VI 1225 (1997).

[20] Lodish, supra note 3, at 309-10.

[21] Id.

[22] See, e.g., Laurie L. Hill et al., Fas Ligand: A Sensor for DNA Damage Critical in Skin Cancer Etiology, 285 Science 898 (Aug. 6, 1999) (finding that the absence of Fas in the skin prevented the elimination of cells that accumulated signature mutations indicating an increased incidence of skin cancer in mice).

[23] See Laurie B. Owen-Schaub et al., Soluble Fas/APO-1 in tumor cells: a potential regulator of apoptosis, 94 Cancer Letters 1 (1995) (hypothesizing that the production of soluble Fas inhibits Fas ligand-mediated apoptosis in cancer cells increasing the aggressiveness of the tumor).

[24] Lodish, supra note 3, at 457-62.

[25] Id.

[26] Id. at 267-69.

[27] Id.

[28] Id. at 266.

[29] Id. at 280.

[30] Id. at 269, 280.

[31] The Science Behind the Human Genome Project: Basic Genetics, Genome Draft Sequence, and Post-Genome Science, supra note 9.

[32] Other uses for genes certainly exist (such as DNA fingerprinting in criminal investigations), but they are beyond the scope of this paper. I have selected the three medically relevant uses for illustrative purposes only, not to indicate their importance over other potential uses.

[33] Maulik & Patel, supra note 7, at 37. See, e.g., Marina Cavazzana-Calvo et al., Gene Therapy of Human Severe Combined Immunodeficiency (SCID)-X1 Disease, 288 Science 669 (April 28, 2000) (reporting the successful gene transfer in infants with an incurable and usually fatal immunodeficiency disease); Jack A. Roth et al., Retrovirus-mediated wild-type p53 gene transfer to tumor of patients with lung cancer, 2 Nature Medicine 985 (Sept. 1996) (reporting the successful transfer of a tumor suppressor gene into the tumors of nine terminal patients with non-small cell lung cancer that resulted in tumor regression in three patients and tumor stabilization in three others).

[34] Cavazzana-Calvo, supra note 33, at 669.

[35] Id.

[36] Id. at 670-71.

[37] Gina Kolata, Scientists Report the First Success of Gene Therapy, N.Y. Times, Apr. 28, 2000, at A1.

[38] Maulik & Patel, supra note 7, at 4, 8.

[39] Id.

[40] Id. at 37.

[41] Leena Peltonen & Victor A. McKusick, Dissecting Human Disease in the Postgenomic Era, 291 Science 1224, 1227 (Feb. 16, 2001).

[42] Katrina M. Dipple & Edward R.B. McCabe, Modifier Genes Convert "Simple" Mendelian Disorders to Complex Traits, 71 Molecular Genetics and Metabolism 43 (Sept. 2000).

[43] Peltonen & McKusick, supra note 41.

[44] Elliott Sober, The Meaning of Genetic Causation, in From Chance to Choice: Genetics and Justice 1 (Allen Buchanan et al. eds., 2000) (explaining the genetic control of a particular trait may be modified by environmental influences). See, e.g., Maria Anderson, Crohn's: An Autoimmune or Bacterial-Related Disease?, The Scientist, Aug. 20, 2001, at 22 (arguing that Crohn's disease, an autoimmune disease, requires the presence of the mutant NOD2 gene and the exposure to a group of bacteria for the onset of disease in approximately 15% of this patient population).

[45] Medicine and the New Genetics: Human Genome Project Information, at http://www.ornl.gov/hgmis/medicine/medicine.html (last visited on Dec. 22, 2002). See, e.g., Denise K. Casey, What Can the New Gene Tests Tell Us? 36 Judges' J. 14 (Summer 1997).

[46] Id.

[47] Id.

[48] See, e.g., Lodish, supra note 3, at 252-54.

[49] Id. at 256, Maulik & Patel, supra note 7, at xiii-xviii.

[50] See, e.g., Andrew Pollack, Biotech and the F.D.A.: Blame Game, N.Y. Times, Dec. 16, 2002, at C19 (noting the reduced number of drug approvals with the greater attention to adverse side effects); Peg Brickley & Paula Park, FDA Actions, Economy Affect Biotech Industry, The Scientist, July 9, 2001, at 28 (discussing the negative effects of long approval times on the success of biotechnology firms).

[51] Human Gene Therapy and the Role of the Food and Drug Administration, U.S. Food and Drug Administration (Sept. 2000) (noting the strict testing requirements for a biologic therapeutic to reach the market, at http:// www.fda.gov/cber/infosheets/genezn.html (last visited on Dec. 22, 2002). See, e.g., Larry Thompson, Human Gene Therapy: Harsh Lessons, High Hopes, FDA Consumer, Sept.-Oct. 2000, at 21-22 (noting the strict time requirements for reporting adverse effects or deaths in a gene therapy trial and the resulting immediate alteration or cessation of the trial).

[52] Jean-Michel Claverie, What If There Are Only 30,000 Human Genes?, 291 Science 1255, 1256 (Feb. 16, 2001).

[53] 35 U.S.C. § 101 (1994).

[54] Id.

[55] 35 U.S.C. § 102 (1994).

[56] 35 U.S.C. § 103 (1994).

[57] 35 U.S.C. § 112 (1994).

[58] See3 Donald S. Chisum, Chisum on Patents § 7.04 (2002) (the filing date is the prima facie date of invention for determining novelty with the possibility of the inventor being able to provide evidence of an earlier date of invention by documenting conception and reduction to practice in the case of a priority dispute).

[59] 35 U.S.C. § 101 (1994).

[60] Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130, 76 U.S.P.Q. (BNA) 280, 281 (1948) (invalidating a patent for a mixed bacterial cell culture because the invention was "no more than a discovery of some of the handiwork of nature"); Diamond v. Chakrabarty, 447 U.S. 303, 309, 206 U.S.P.Q. (BNA) 193, 197 (1980) (affirming that "laws of nature, physical phenomena, and abstract ideas" are unpatentable).

[61] Chakrabarty, 447 U.S. at 309, 206 U.S.P.Q. (BNA) at 197.

[62] See, e.g., Parke-Davis & Co. v. H.K. Mulford & Co., 189 F. 95, 103 (C.C.S.D.N.Y. 1911) (upholding the validity of a patent claiming purified adrenaline).

[63] Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1218 (Fed. Cir. 1991).

[64] Id.

[65] Id.

[66] In other words, cDNA is distinct from its naturally occurring counterpart, the gene in the chromosome, in two significant ways: (1) no intronic sequences are present in cDNA and (2) cDNA is no longer under the control of its native sequences (e.g., promoters). Lewin, supra note 19, at 170-71; Lodish, supra note 3, at 234-36.

[67] Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376, 231 U.S.P.Q. (BNA) 81, 87 (Fed. Cir. 1986). However, an inventor must maintain due diligence in working to reduce to practice to maintain the priority of his invention.

[68] Amgen, 927 F.2d at 1206, 18 U.S.P.Q.2d (BNA) at 1021 (reasoning that DNA is simply a complex chemical structure).

[69] Id.

[70] Fiers v. Revel, 984 F.2d 1164, 1169, 25 U.S.P.Q.2d (BNA) 1601, 1604 (Fed. Cir. 1993).

[71] Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1569, 43 U.S.P.Q.2d (BNA) 1398, 1406 (Fed. Cir. 1997).

[72] 35 U.S.C. § 112 (1994).

[73] Id.

[74] In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d (BNA) 1400, 1404 (Fed. Cir. 1988).

[75] Margaret Sampson, Comment, The Evolution of the Enablement and Written Description Requirements Under 35 U.S.C. § 112 in the Area of Biotechnology, 15 Berkeley Tech. L.J. 1233, 1239-40 (2000).

[76] Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212-14, 18 U.S.P.Q.2d (BNA) 1016, 1026-27 (Fed. Cir. 1981).

[77] Id. at 1212-13, 18 U.S.P.Q.2d at 1026.

[78] Id. at 1214, 18 U.S.P.Q.2d at 1027-28.

[79] Sampson, supra note 75, at 1272.

[80] Id. at 1250.

[81] Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

[82] See, e.g., Raytheon Co. v. Roper Corp., 724 F.2d 951, 958, 220 U.S.P.Q. (BNA) 592, 598 (Fed. Cir. 1983) (interpreting the utility requirement under 35 U.S.C. § 101 as being met "[w]hen a properly claimed invention meets at least one stated objective").

[83] Id.

[84] Utility Examination Guidelines, 66 Fed. Reg. at 1098.

[85] Id.

[86] 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[87] Utility Examination Guidelines, 66 Fed. Reg. at 1094 cmt. 9.

[88] 35 U.S.C. § 103(a) (1994).

[89] See In re Vaeck, 947 F.2d 488, 494-95, 20 U.S.P.Q.2d (BNA) 1438, 1443-44 (Fed. Cir. 1991).

[90] See In re O'Farrell, 853 F.2d 894, 903-04, 7 U.S.P.Q.2d (BNA) 1673, 1681 (Fed. Cir. 1988).

[91] In re Vaeck, 947 F.2d at 494, 20 U.S.P.Q.2d (BNA) at 1443-44.

[92] 35 U.S.C. § 154(a)(2) (1994).

[93] 35 U.S.C. § 271(a) (1994).

[94] In re Hiniker Co., 150 F.3d 1362, 1369, 47 U.S.P.Q.2d (BNA) 1523, 1529 (Fed. Cir. 1998) ("[T]he name of the game is the claim.").

[95] Currently, under the doctrine of equivalents, if another product performs substantially the same function in substantially the same way to yield substantially the same result, it will be considered within the scope of the patent claims and thus an infringing product. The outer reach of such claim interpretation is presumptively limited by prosecution history estoppel if a claim is narrowed to satisfy a patentability requirement. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co, Ltd., 122 S.Ct. 1831, 1835, 62 U.S.P.Q.2d (BNA) 1705, 1711 (2002).

[96] Robert Merges, Intellectual Property Rights and Bargaining Breakdown: The Case of Blocking Patents, 62 Tenn. L. Rev. 75, 78-79 (1994).

[97] See id. at 78.

[98] Id. at 89-91.

[99] Waterman v. Mackenzie, 138 U.S. 252, 255-56 (1891).

[100] Adams v. Burke, 84 U.S. 453, 456-57 (1873).

[101] Sanofi v. Med-Tech Veterinarian Prods., Inc., 565 F. Supp. 931, 936-37, 220 U.S.P.Q. (BNA) 416, 419-20 (D.N.J. 1983).

[102] 35 U.S.C. § 271 (1994).

[103] Transparent-Wrap Mach. Corp. v. Stokes & Smith Co., 329 U.S. 637, 642-43, 72 U.S.P.Q. (BNA) 148, 152 (1947).

[104] Id.

[105] Rebecca S. Eisenberg, Patents and the Progress of Science: Exclusive Rights and Experimental Use, 56 U. Chi. L. Rev. 1017, 1018-19 (1989) (discussing the limitation of experimental use of a patented invention to those uses without commercial use).

[106] Id.

[107] Windsurfing Int'l v. AMF, Inc., 782 F.2d 995, 1001, 228 U.S.P.Q. (BNA) 562, 566-67 (Fed. Cir. 1986).

[108] Id.

[109] See, 6 Donald S. Chisum, Chisum on Patents § 19.04[4] (2002).

[110] See, e.g., Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 145, 489 U.S.P.Q.2d (BNA) 1847, 1850 (1989).

[111] See, e.g., Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 132, 76 U.S.P.Q. (BNA) 280, 281 (1948).

[112] For the purposes of this analysis, the biotechnology industry and its economic and policy positions are discussed generally and not from the strict perspective of the biotechnology company with gene patents as its platform.

[113] Biotechnology Industry Organization, Biotechnology Industry Statistics: Some Facts About Biotechnology, at http://www.bio.org/er/statistics.asp (last visited Dec. 22, 2002).

[114] Ernst & Young, The Economic Contributions of the Biotechnology Industry to the U.S. Economy, Biotechnology Industry Organization (May 2000), available at http://www.bio.org/news/ernstyoung.pdf (last visited Dec. 22, 2002).

[115] Id. at 6.

[116] Supra note 113.

[117] Id.

[118] Id.

[119] See Gene Patents and Other Genomic Inventions: Hearing Before the Subcomm. on Courts and Intellectual Property of the House Comm. of the Judiciary, 106th Cong. 44-63 (2000) [hereinafter Hearing on Gene Patents] (statements of Dr. Randal W. Scott, President and Chief Scientific Officer, Incyte Genomics, and Dennis J. Henner, Ph.D., Senior Vice President, Research, Genentch, Inc.).

[120] Robert P. Merges & Richard R. Nelson, On the Complex Economics of Patent Scope, 90 Colum. L. Rev. 839 (1990).

[121] Yusing Ko, Note, An Economic Analysis of Biotechnology Patent Protection, 102 Yale L.J. 777, 791-804 (1992). See also Michael S. Greenfield, Note, Recombinant DNA Technology: A Science Struggling with Patent Law, 44 Stan. L. Rev. 1051, 1058-59 (1992) (discussing the reliance on the incentive and disclosure theories for patent law).

[122] Ko, supra note 121, at 791.

[123] Greenfield, supra note 121, at 1058.

[124] Ko, supra note 121, at 792.

[125] Id.

[126] Id. at 793.

[127] See id. at 795.

[128] See Greenfield, supra note 121, at 1059.

[129] Ko, supra note 121, at 795.

[130] See id. at 795-96.

[131] See id. at 796.

[132] Id.

[133] Id. at 799.

[134] Id.

[135] Ko, supra note 121, at 799.

[136] Id. at 800.

[137] Id.

[138] The Supreme Court has defined the pioneer patent as "a patent covering a function never before performed, a wholly novel device, or one of such novelty and importance as to mark a distinct step in the progress of the art, as distinguished from a mere improvement or perfection of what has gone before." Westinghouse v. Boyden Power Brake Co., 170 U.S. 537, 561-62 (1898).

[139] Ko, supra note 121, at 800-01.

[140] See id. at 801.

[141] Id.

[142] Id.

[143] Hearing on Gene Patents, supra note 119, at 54 (statement of Randal Scott).

[144] Id. at 51.

[145] Id.

[146] Id. at 51-52.

147 Id.

148 Id. at 52-53.

149 Hearing on Gene Patents, supra note 119, at 53-54 (statement of Randal Scott).

150 Hearing on Gene Patents, supra note 119, at 56 (statement of Dennis Henner).

151 Hearing on Gene Patents, supra note 119, at 51 (statement of Randal Scott).

152 See Hearing on Gene Patents, supra note 119, at 44-55 (statement of Randal Scott); Biotechnology Industry Organization, Importance of Intellectual Property,at http://www.bio.org/ip/background.asp (last visited Dec. 22, 2002); Biotechnology Industry Organization, Technology Transfer, at http://www.bio.org/issues/ip/licensing.asp (last visited Dec. 22, 2002).

153 American College of Medical Genetics, Position Statement on Gene Patents and Accessibility of Gene Testing, 1 Genetics in Medicine 237 (1999).

154 John M. Golden, Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System, 50 Emory L.J. 101, 165-67 (2001); Merges & Nelson, supra note 120, at 904-10.

155 Ken Garber, Homestead 2000: The Genome, Signals Magazine, (Mar. 3, 2000), at http:// www.signalsmag.com/signalsmag.nsf/0/FD168FB6C42ACF6E882568950015E2D0 (last visited Dec. 22, 2002).

156 Claverie, supra note 52, at 1256; David Malakoff, Will a Smaller Genome Complicate the Patent Chase?, 291 Science 1194 (Feb. 16, 2001).

157 Garber, supra note 155. It is not currently known whether the gene patent applications actually claim 28,000 of the 30,000 identified genes.

158 Chakrabarty, 447 U.S. at 310-14, 206 U.S.P.Q. at 197-99.

159 Gottschalk v. Benson, 409 U.S. 63, 67, 175 U.S.P.Q. (BNA) 673, 675 (1972) ("Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are basic tools of scientific and technological work."). See also LeRoy v. Tatham, 55 U.S. 156, 176 (1852), rev'd on other grounds, 63 U.S. 132 (1859) (holding that a lead pipe would not become patentable subject matter if the patentee relied solely on the naturally occurring lead); Am. Fruit Growers v. Brogdex Co., 283 U.S. 1, 11 (1931) (holding that an orange injected with borax in an amount sufficient to render the fruit resistant to mold did not make the orange new or patentable).

160 Leroy, 55 U.S. at 176.

161 333 U.S. 127, 76 U.S.P.Q. (BNA) 280 (1948).

162 Id. at 129-30, 76 U.S.P.Q. (BNA) at 281.

[163] Id. at 130, 76 U.S.P.Q. (BNA) at 281 (citation omitted).

[164] See, e.g., Merck & Co. v. Olin Mathieson Chem. Corp., 253 F.2d 156, 164, 116 U.S.P.Q. (BNA) 484, 488-89 (4th Cir. 1958) (holding that purified vitamin B_{12} was patentable because the purified form "did not exist in nature in the form in which patentees produced it.").

[165] Funk Bros., 333 U.S. at 135, 76 U.S.P.Q. at 283 (Frankfurter, J., concurring).

[166] Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206, 18 U.S.P.Q.2d (BNA) 1016, 1021 (Fed. Cir. 1981).

[167] Golden, supra note 154, at 117; Merges & Nelson, supra note 120, at 880.

[168] Golden, supra note 155, at 117.

[169] Id. at 119. In the mid-1990s, 70.5% of biotechnology companies in the U.S. had a university research partner.

[170] Id. at 144-52.

[171] Id. at 147-49.

[172] Id. at 149-52.

[173] Id. at 156.

[174] Golden, supra note 154 at 144-52.

[175] Merges & Nelson, supra note 120, at 839.

[176] Merges & Nelson, supra note 120, at 883; Fields, supra note 17, at 1222 (In support of the need for access to genetic information from the Human Genome Project, "[t]he likelihood of new approaches increases in proportion to the number of investigators participating in the field.").

[177] Eisenberg, supra note 105, at 1049-52.

[178] Id.

[179] Id. at 1048-53.

[180] Golden, supra note 154, at 174.

[181] Eisenberg, supra note 105, at 1046-47.

[182] Golden, supra note 154, at 174-75.

[183] 35 U.S.C. § 154 (1994).

[184] Eliot Marshal, A Deluge of Patents Creates Legal Hassles for Research, 288 Science 255, 257 (Apr. 14, 2000).

[185] Human Genome Organisation, HUGO Statement on Patenting of DNA Sequences - In Particular Response to the European Biotechnology Directive (Apr. 2000), available at http://www.gene.ucl.ac.uk/hugo/patent2000.html (last visited Dec. 22, 2002).

[186] Bioresearch Online, Gene Patenting Run Amok? Lawsuit alleges patent hinders research (Nov. 21, 2000), at http:// www.bioresearchonline.com/content/news/article.asp?DocID=[D729C405-BF95-11D4-8C7F-009027DE0829]&Bucket=&Featured=&VNETCOOKIE=NO (last viewed Dec. 21, 2002). Children with Canavan disease suffer myelin sheath destruction with the first symptoms appearing between 3 and 6 months as impaired walking, talking, and eating. Seizures, severe feeding problems, retardation, and blindness follow until the child eventually dies between the ages of 10 and 15.

[187] Id.

[188] Id.

[189] Id.

[190] Id.

[191] Mae-Wan Ho, Human Genome - The Biggest Sellout in Human History, Institute of Science in Society, at http://www.i-sis.org.uk/humangenome.php (last visited Dec. 22, 2002).

[192] Id.

[193] Golden, supra note 154, at 175-76 (describing the events eliciting the free access to the Onco-Mouse).

[194] Genetic Face-Off: Scientists, Corporation Feud Over Gene Patent, ABC News Online (Feb. 28, 2001) (reporting the filing of a lawsuit by a group of university scientists against a biotechnology patent involving a gene patent claiming a human HIV-viral receptor), at http:// www.abcnews.com/sections/living/DailyNews/genepatent000228.html (last visited Oct. 19, 2001).

[195] Lodish, supra note 3, at 267-69.

[196] See supra notes 85-89 and accompanying text.

[197] Hearing on Gene Patents, supra note 119, at 52 (statement of Randal Scott).

[198] For example, diagnostic tests require the use of gene A to develop the test, and some sequences may be included as a positive control in the tests. Both are uses of gene A that are within the scope of a product patent on gene A.

[199] See Hearing on Gene Patents, supra note 119, at 45-46 (statement of Randal Scott).

[200] Garber, supra note 155.

[201] Id.

[202] At least 28,000 patents on full genes have been filed by six companies: Incyte Pharmaceuticals, Human Genome Sciences, Hyseq, Celera Genomics, Genset, and Millennium Pharmaceuticals. See Garber, supra note 155.

[203] Michael A. Heller & Rebecca S. Eisenberg, Can Patents Deter Innovation? The Anticommons in Biomedical Research, 280 Science 698 (May 1, 1998).

[204] See Garber, supra note 155.

[205] Malakoff, supra note 156, at 1194.

[206] Id.

[207] This results because the 20 year patent term is measured from the date of filing rather than the date of issuance. 35 U.S.C. § 154 (a)(2) (1994).

[208] Hearing on Gene Patents, supra note 119, at 50 (statement of Randal Scott).

[209] Patent Reform and the Patent and Trademark Office Reauthorization for Fiscal Year 2000: Hearing Before the Subcomm. on Courts and Intellectual Property on the House Comm. On the Judiciary, 106th Cong. 72-75 (1999) (statement of Charles E. Ludlam, Vice President for Governmental Relations, Biotechnology Industry Organization) http://www.bio.org/laws/tstm032599.html (seeking to extend the patent term in cases where the PTO has not processed an application efficiently despite diligence by the patent applicant).

[210] Id.

[211] Id.

[212] Id.

[213] The Federal Circuit has recently narrowed the experimental use defense available for patentees significantly. In an infringement action where the defendant was a research institution, the court held that the experimental use defense was not available "so long as the act [of alleged patent infringement] is in furtherance of the alleged infringer's legitimate business and is not solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry." Madey v. Duke Univ., 307 F.3d 1351, 1362, 64 U.S.P.Q.2d (BNA) 1737, 1746 (Fed. Cir. 2002). According to the court, whether the purpose of the act was for commercial gain was not determinative, rendering the fair use exception an empty one for virtually any patentee.

[214] Maureen A. O'Rourke, Toward a Doctrine of Fair Use in Patent Law, 100 Colum. L. Rev. 1177 (2000).

[215] Id. at 1179.

[216] Id.

[217] Id. at 1205-09.

[218] Id. at 1206.

[219] Id.

[220] O'Rourke, at 1206.

[221] Id.

[222] Id.

[223] Id.

[224] Id. at 1207.

[225] Id.

[226] O'Rourke, at 107-08.

[227] Id.

[228] Id. at 1208.

[229] Id.

[230] Id.

[231] Id. at 1209.

[232] Biotechnology Industry Organization, Technology Transfer, supra note 153.

[233] The House of Representative has recently considered a bill to "provide for noninfringing uses of patents on genetic sequence information for purposes of research and genetic diagnostic testing, and to require public disclosure of such information in certain patent applications." H.R. 3967, 107th Cong. (2002). This bill seeks to remove liability from researchers using patented genetic sequences in their work through the amendment of 35 U.S.C. § 271. In the accompanying bill authorizing a Congressional study, its authors note the importance of genomic research, the critical nature of federal policies in this area, and the lack of adequate understanding of the impact of such policies on innovation. H.R. 3966, 107th Cong. (2002). While the importance of these issues are recognized by some members of Congress, neither of these bills have been acted on to date.

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