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Gene Concepts, Gene Talk, and Gene Patents

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"Three billion bases of sequence can be put on a single compact disk (CD), and one will be able to pull a CD out of one's pocket and say, 'Here is a human being; it's me!'"

—Walter Gilbert in *Vision of the Grail*[1]

"It's been a growing conviction of mine that biologists have a whole other way of talking to each other in the lab than they do to the public."

—Evelyn Fox Keller[2]

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1. Walter Gilbert, *Vision of the Grail*, *in* THE CODE OF CODES 96 *Daniel J. Kevles and Leroy Hood eds., 1992).

2. Andrew Brown, *Fox Among the Lab Rats*, THE GUARDIAN, Nov. 4, 2000, *available at* 6, http://www.guardian.co.uk/books/2000/nov/04/books.guardianreview6 (quoting Evelyn Fox Keller).

Since the existence of a discrete unit of heredity was first proposed by Gregor Mendel, scientific concepts of the "gene" have undergone rapid evolution. Beyond obvious epistemic and operational importance to the scientific community, changing gene concepts have exerted strong effects on institutions such as medicine, the biotechnology industry, politics, and the law. A particularly rich example of this is the interplay between gene concepts and patent law. Over the last century, biology has elaborated gene concepts that variously emphasized genes as discretely material, genes as information, and genes as extremely complex. By contrast, patent law has steadily adhered to a simpler, more stable concept of the gene since the advent of gene patents in the late 1970s. In fact, while the biology community[3] has increasingly engaged in vigorous internal debate regarding the gene's complexity and uncertainty, it has tended simultaneously to emphasize the simplicity and certainty of the gene to constituencies outside the biology community, most notably the United States Patent and Trademark Office (USPTO) and the Federal courts. Rather than allow gene concepts to become contested by constituencies outside biology, the biology community appears to have used its authority to maintain a portrayal of the gene that facilitates the appropriation of rents from genes through the patent system. This use of "gene talk" has undergirded the growth of biotechnology into a powerful industry that has economically rewarded investors, academic institutions, and biologists. Not only may gene talk have facilitated the patenting of genes, but the prominence of gene patents describing a relatively simpler gene concept may have

3. "Biology community" is used hereafter to describe the professional biologists, whether in academia, biotechnology, or the government.

fed back into biological science to promote a simpler, and more patentable, concept of the gene even among members of the biology community.

I. INTRODUCTION

The concept of the "gene" has undergone tremendous transformation over the course of the last century. It began its life as a hypothetical mechanism for transferring characters[4] from one generation to the next. A flurry of experimentation by Morgan and other early "classical" geneticists, whose results revealed a satisfying predictability to the inheritance of characters, caused the inchoate and hypothetical gene to coalesce into a unit possessing substantiality and materiality.[5] The materiality of the gene was grounded even more firmly by the discovery that genes were made of a specific chemical, that is, deoxyribonucleic acid ("DNA"). The discovery of the double-helical structure of DNA by James Watson and Francis Crick, along with the implications of the double helix structure for the existence of a "genetic code," represented the high-water mark of the material gene.[6]

The breaking of the genetic code suggested a new characteristic of the gene: information. Genes were portrayed as carrying information encoded by their constituent nucleotides.[7] In fact, the characterization of the operon[8] by Jacob and Monod suggested that the information carried by genes was not simply information, but programmatic in nature.[9] Similar to computer software, the information encoded by a gene was viewed as operating like an algorithm, instructing the chemical machinery of the cell to make structures and perform functions in particular orders with specific effects.

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4. The term "character" is herein used in its taxonomic sense to denote any characteristic or feature of an organism, including those characteristics or features related to morphology, physiology, and behavior.

5. *See* discussion *infra* Part II.B.

6. *See* discussion *infra* Part II.C.

7. *See* discussion *infra* Part II.D.

8. BENJAMIN LEWIN, GENES IX 858 (2008) ("An operon is a unit of bacterial gene expression and regulation, including structural genes and control elements in DNA recognized by regulator gene product(s)."); EVELYN FOX KELLER, THE CENTURY OF THE GENE 57 (2000) (The word "operon" denotes "a linked cluster of regulatory elements and structural genes whose expression is coordinated by the product of a regulator gene situated elsewhere in the genome.")

9. *See* discussion *infra* Part II.E.

Methods of determining the specific nucleotides located on particular genes developed substantially in the 1970s with the invention of relatively rapid DNA sequencing technologies.[10] The ability to sequence genes rapidly created a flood of DNA sequence data. Meanwhile, recombinant DNA technology allowed genes and gene fragments to be excised from one location in a genome, and then spliced into a different genomic location, either in the same or a different individual organism, or even in a different type of organism.[11] Gene concepts emphasizing particulate materiality, information content, or encoded algorithmic programs, coupled with DNA sequencing and recombinant DNA technologies, facilitated a view among biologists, and others, that one could "invent" DNA-based innovations just as one could write software to run on a computer.[12] Newly-sequenced genes, as long as they had been isolated and purified, could now be conceived of as inventions ripe for patent protection.[13] After the landmark decision in *Diamond v. Chakrabarty*, the United States Patent and Trademark Office (USPTO) began regularly to issue patents claiming sequenced genes.[14]

Just prior to the issuance of the first gene patent in 1981, the simple linearity of the prevailing gene concept was fatally challenged by the discovery that eukaryotic polypeptides tended to be encoded by physically separate and noncontiguous stretches of DNA. Many genes, rather than consisting of simple, contiguous linear arrays of nucleotides, like beads strung together on a necklace, more accurately resembled fragments of beads ("exons") dispersed throughout a necklace, and separated by non-gene-related sequences of nucleotides ("introns").[15] However, to a large degree, biologists do not acknowledge the growing complexity of the gene concept when claiming genes in patents (hereinafter "gene patents"). USPTO regulations and judicial opinions, as they relate to gene patents, do not reflect this complexity either.[16] In fact, neither gene patents nor judicial opinions considering gene patents tend even to consider gene concepts or definitions.

Meanwhile, debates about what a "gene" really is have

10. *See* discussion *infra* Part II.F.
11. *See* discussion *infra* Part II.C.
12. *See* discussion *infra* Part II.F.
13. *See* discussion *infra* Part III.B.
14. *See* discussion *infra* Part III.B.
15. *See* discussion *infra* Part II.F.
16. *See* discussion *infra* Part III.B.

raged within the biology community. Since the first gene patents issued early in the 1980s, the gene concept has decayed towards incoherence. Evidence that genes may not only possess introns and exons, but that they sometimes overlap each other, encode products in multiple reading frames, and even encode products in both directions, has led many biologists, including some very prominent in the field, to conclude that the very idea of a "gene" is no longer useful.[17] In the meantime, patenting genes has become routine for geneticists in both industry and academia. Encouraged by the Bayh-Dole Act, universities have become fertile sources of gene patents, and have thereby earned vast sums of money from licensing these gene patents to the biotechnology industry. The biotechnology industry itself, much of whose market value is undergirded by gene patents rather than actual commercial products, has also contributed to the flood of gene patent applications.[18]

Growing incoherence in the biological understanding of what a gene might be, and of what gene concept can best reflect the empirical evidence, would seem to threaten the continued availability of patents claiming genes. After all, the disclosure requirements of patent law preclude the patenting of any invention that cannot be adequately and accurately described.[19] Yet, gene patents tend to include minimal disclosure defining what genes are or describing claimed genes beyond recitation of their DNA sequences and putative utilities.[20] Gene patents certainly do not teach the controversy surrounding gene concepts. This raises the question of whether patent applications that claim genes or gene-related inventions, but whose specifications oversimplify or simply ignore gene definitions, should issue as patents.

This article argues that the rhetorical portrayal of genes as relatively simple and predictable entities can explain, at least in part, the failure of gene patents or judicial opinions about gene patents to reflect the controversy and complexity of the biological understanding of genes. Evelyn Fox Keller coined the phrase "gene talk" to describe the rhetorical practices of conversing about genes both among biologists and between biologists and non-biologists. Gene talk may be employed in re-

17. *See* discussion *infra* Part III.C.
18. *See* discussion *infra* Part VI.A.
19. 35 U.S.C. §112, para 1 (2008).
20. *See* discussion *infra* Part II.B.

sponse to cultural, institutional, and economic imperatives that create strong incentives to justify property (that is, patent) rights in genes.[21] Gene talk provides a useful shorthand for discussing a scientific concept whose meaning inspires tremendous disagreement among biologists; by using the word "gene" loosely and contextually as a conceptual placeholder, biologists have been able to elucidate much about genetics. However, the biology community has also used gene talk successfully to foster enthusiasm, respect, and trust outside the biology community for the power and potential of genes without communicating the prodigious scientific uncertainty that surrounds the structure, function, and even the existence of genes. Gene talk in the context of gene patents could even influence gene concepts internal to the biology community.

II. HISTORY OF THE GENE CONCEPT

A. UNIT OF HEREDITY

The *Origin of Species by Means of Natural Selection* revolutionized biology by suggesting not only that lineages of organisms change their characters over time (that is, they evolve) but by offering a causal mechanism for these changes (that is, natural selection).[22] Nevertheless, Darwin left a significant question unanswered: what hereditary unit is associated with the characters of organisms? Although he did suggest that a "gemmule" might be a unit of "pangenesis," Darwin left to others the task of elaborating a coherent concept of a unit of heredity. Darwin never even knew the word "gene" because it was not coined until more than twenty years after his 1882 death.

It took Gregor Mendel, an Augustinian monk who worked contemporaneously with Darwin, to elucidate the fundamental system of genetic inheritance. Mendel imagined a unit of heredity that he called the "*Elemente*."[23] Though his discoveries would later form one of the bases of modern genetics, the contrast between the public reception of Mendel's ideas and Darwin's is remarkable: *On the Origin of Species by Means of Natural Selection* attracted immediate international attention, while Mendel's research remained obscure until translated

21. *See* EVELYN FOX KELLER, THE CENTURY OF THE GENE 10 (2000).

22. *See generally* CHARLES DARWIN, ON THE ORIGIN OF SPECIES BY MEANS OF NATURAL SELECTION (1859).

23. *See* KELLER, *supra* note 21, at 19.

from the original German and published in English in 1901.[24] Soon after this rediscovery of Mendel's research, Wilhelm Johannsen provided a name for the fundamental unit of heredity, the "gene," a term he derived from the last syllable of Hugo de Vries's "pangens."[25]

Biologists quickly adopted the concept of the "gene" as the unit of heredity, in part because it offered a solution to the problem of how many observable traits appeared to pass from generation to generation unchanged. "[T]he problem of trait stability was answered by assuming the existence of an inherently stable, potentially immortal, unit that could be transferred intact through the generations."[26] This unit was the gene.

B. GENE AS PARTICLE

Long before Mendel's research became widely known, and before the term "gene" had been coined, August Weismann had predicted several characteristics of the unit of heredity. As Keller explained:

> Whatever the mechanism by which a single cell reproduces the traits of the parent, Weismann assumed the existence of particulate, self-reproducing elements that "determine" the properties of an organism; appropriately enough, he called these elements determinants. This assumption was hardly unique to Weismann—in fact, Darwin himself had hypothesized the existence of some such elements (his gemmules).[27]

According to Weismann, determinants (that is, genes) were not inchoate, but, rather, possessed discrete materiality. Specifically, his determinants were of "a definite chemical, and above all, molecular composition."[28] A contemporary, Hugo de Vries echoed Weismann's materiality hypothesis, explaining that "[j]ust as physics and chemistry go back to molecules and atoms, the biological sciences have to penetrate to these units in order to explain, by their combinations, the phenomena of

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24. *See generally* Gregor Mendel, *Experiments in Plant Hybridisation*, 26 J. ROYAL HORTICULTURAL SOC'Y 1 (1901) (proving that certain pairs of differentiating characters, the germ-cells of a hybrid, or cross-bred, are *pure*, being carriers and transmitters of either the one character or the other, not both).

25. KELLER, *supra* note 21, at 1–2.

26. *Id.* at 14.

27. KELLER, *supra* note 21, at 16.

28. August Weismann, *The Continuity of the Germ-Plasm as the Foundation of a Theory of Heredity*, *in* ESSAYS UPON HEREDITY AND KINDRED BIOLOGICAL PROBLEMS 161, 168 (Edward B. Poulton et al. eds., 1889).

the living world."[29]

Thomas Hunt Morgan was the first great experimental geneticist since Mendel. In his "Fly Room" at Columbia University, Morgan established the fruit fly, *Drosophila melanogaster*, as the experimental organism of choice for studying genetics, and empirically that genes were located on chromosomes.[30] By the time Morgan became the first geneticist to receive the Nobel Prize in Medicine, in 1933, in part due to the work of his laboratory and alumni thereof, the majority of other geneticists had come to believe that "genes . . . [were] incontrovertibly real, material entities—the biological analogue of the molecules and atoms of physical science . . . ."[31] Morgan suggested in his 1926 book, *The Theory of the Gene*, that genes on chromosomes were "like beads on a string."[32] Morgan's analogy to jewelry assumed significant influence over time, and "genes became generally viewed as discrete, stable, independently segregating units of inheritance lined up along a chromosome."[33]

C. GENE AS SEQUENCE

By the 1940s, the particulate theory of genes as discrete, physical structures on chromosomes had been widely accepted among geneticists. The gene's structure and function was also assumed to be linked to the genes' causal effects:

> Throughout the history of both classical and early molecular genetics, the gene was generally assumed to be not only a fixed and unitary locus of structure and function but also a locus of causal agency. T.H. Morgan, for example, regarded the idea that genes are the causal agents of development as so basic and so self-evident that an understanding of heredity did not require its elaboration.[34]

However, lacking specific knowledge of gene structure, geneticists were limited in understanding both gene function and causal agency.

In 1943, Avery, McLeod, and McCarty identified "DNA as the carrier of biological specificity in bacteria."[35] They proposed

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29. HUGO DE VRIES, INTRACELLULAR PANGENESIS 13 (C. Stuart Gager trans., The Open Court Publishing Co. 1910) (1889).

30. *See* JAMES D. WATSON ET AL., MOLECULAR BIOLOGY OF THE GENE 12–13 (Beth Wilbur et al. eds., 6th ed. 2008).

31. KELLER, *supra* note 21, at 2.

32. THOMAS HUNT MORGAN, THE THEORY OF THE GENE 24 (1926).

33. Leonie Moyle, *Most Ingenious: Troubles and Triumphs of the Century of Genes*, 17 BIOLOGY AND PHIL. 715, 715–16 (2002).

34. KELLER, *supra* note 21, at 46.

35. *Id.* at 3.

that DNA "must be regarded not merely as structurally important but as functionally active in determining the biochemical activities and specific characteristics of pneumococcal cells."[36] Their conclusions were confirmed by Hershey and Chase in their 1952 "blender" experiment, which used radiolabeled amino acids and nucleotides to detect whether proteins or nucleic acids were the carriers of heredity.[37]

One year later, one of the greatest scientific advances in genetics allowed gene structure, function, and causal agency to be linked together intimately: elucidation of the double-helical structure of DNA. "[I]t was the triumphal announcement by James D. Watson and Francis Crick in 1953 which convinced biologists not only that genes are real molecules but also that they are constituted of nothing more mysterious than deoxyribonucleic acid."[38] As Keller relates,

> [n]ot only did that structure provide a mechanism for the gene's remarkable capacity for self-replication—a mechanism that was stunning in its very simplicity—but also, and at the same time, it provided an (equally simple) explanation for the stability of the gene—for the ostensibly miraculous fidelity with which it could be copied over so many generations. Complementary base-pairing could, at one fell swoop, do the work of both replication and conservation. . . . [A]n actual chemical substance—one already known to be a basic constituent of chromosomes—had been shown to have the necessary defining properties. Even before a mechanism was worked out by which the sequence of nucleotides in a DNA molecule could be translated into a sequence of amino acids in a protein molecule, confidence was widespread that the material basis of genetics had finally been established.[39]

Watson and Crick demonstrated that:

> In the double helix, the two DNA chains are held together by hydrogen bonds . . . between pairs of bases on the opposing strands . . . . This base pairing is very specific: the purine adenine only base-pairs to the pyrimidine thymine, whereas the purine guanine only base-pairs to the pyrimidine cytosine. In double-helical DNA, the number of A residues must be equal to the number of T residues, whereas the number of G and C residues must likewise be equal . . . . As a result, the sequence of the bases of the two chains of a given double helix have a complementary relationship, and the sequence of any DNA

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36. Oswald T. Avery et al., *Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types*, 79 J. EXPERIMENTAL MED. 137, 155 (1944).

37. A. D. Hershey and Martha Chase, *Independent Functions of Viral Proteins and Nucleic Acid in Growth of Bacteriophage*, 36 J. GEN. PHYSIOLOGY 39 (1952).

38. KELLER, *supra* note 21, at 3.

39. *Id.* at 23–25.

strand exactly defines that of its partner strand.[40]

Studying the rII gene of the T4 bacteriophage, Seymour Benzer went beyond the discoveries of Watson and Crick, and "provided the crucial genetic evidence for the linearity of the internal structure of genes."[41]

Thus, the general materiality of the gene was complemented by the additional conception of the gene as composed of a linear molecule comprised of a specific sequence of four deoxyribonucleotides. In the less than fifty years that had passed since the word "gene" had been coined, the gene concept now included molecular materiality and a highly specific structure. This definitively physical concept allowed "the gene to become the foundational concept capable of unifying all of biology."[42]

Since the 1970s, it has been possible to determine the precise ordered sequence of nucleotides in a particular stretch of deoxyribonucleic acid of any type of organism, from eubacteria and archaea to plants and animals. Recombinant DNA technology, by providing biologists with the ability to cut apart a DNA sequence at a specified locus, facilitated early sequencing efforts.[43] However, it was a pair of new sequencing techniques in the 1970's that allowed DNA sequencing to commence on a grand scale. Almost simultaneously, two research groups developed methods by which one could determine the precise nucleotide sequence of a fragment of DNA nucleotide base-pair by nucleotide base-pair. Both methods shared the same general approach:

> The underlying principle of DNA sequencing is based on the separation, by size, of nested sets of DNA molecules. Each of the DNA molecules starts at a common 5' end, and terminates at one of several alternative 3' endpoints. Members of any given set have a particular type of base at their 3' ends. Thus, for one set, the molecules all end with a G, for another a C, for a third an A, and for the final set a T. Molecules within a given set (e.g., the G set) vary in length depending on where the particular G at their 3' end lies in the sequence. Each fragment from this set therefore indicates where there is a G in the DNA molecule from which they were generated.[44]

One group, led by Walter Gilbert and Allan Maxam, invented a method of DNA sequencing later named "Maxam-

40. WATSON ET AL., *supra* note 30, at 22.
41. KELLER, *supra* note 21, at 52.
42. *Id.* at 3.
43. GRIFFITHS ET AL., INTRODUCTION TO GENETIC ANALYSIS 343-60 (2005).
44. WATSON ET AL., *supra* note 30, at 753.

Gilbert sequencing."[45] Maxam-Gilbert sequencing is based on radioactively labeling DNA molecules at their 5' termini and then subjecting them "to four different regimens of chemical treatment that cause them to break preferentially at Gs, Cs, Ts, or As."[46] The other group, led by Frederick Sanger, developed the "chain-termination" method.[47] In chain-termination sequencing, DNA polymerase is used to make a new copy of DNA from an existing DNA template, and modified 2'-,3'- dideoxynucleotides (ddNTPs) are incorporated into the new copy of DNA by DNA polymerase, preventing further elongation of the strand.[48]

Gilbert and Sanger won the 1980 Nobel Prize in Chemistry "for their contributions concerning the determination of base sequences in nucleic acids."[49] Their methods of relatively rapid DNA sequencing spurred a rapid increase in the determination of the specific DNA sequences of many organisms, including humans. Rapid advancements in PCR, automated sequencers, and bioinformatics would later turn this rise into a flood, ultimately leading to the sequencing of entire genomes.[50]

D. GENE AS INFORMATION

As the material gene concept reached its apotheosis with the elucidation of the double helical structure of DNA, a quite different concept of the gene—as information—was simultaneously growing in importance among biologists. Early in the Twentieth Century, Archibald Garrod had proposed that "genes work by controlling the synthesis of specific enzymes."[51] In the early 1940s, George Beadle and Edward Tatum "used the fungus *Neurospora* as a probe into the gene. Linking biochemical methods with the techniques of Mendelian genetics, the two researchers demonstrated that one gene controlled a single chemical reaction, which in turn was regulated by a specific en-

45. *See* Allan M. Maxam and Walter Gilbert, *A New Method for Sequencing DNA*, 74 PROC. NAT'L ACAD. SCI. U.S. 560 (1977).

46. WATSON ET AL., *supra* note 30, at 754.

47. *See* F. Sanger et al., *DNA Sequencing with Chain-Terminating Inhibitors*, 74 PROC. NAT'L ACAD. SCI. U.S. 5463 (1977).

48. WATSON ET AL., *supra* note 30, at 754.

49. *See* Bo G. Malmstrom, Professor, Royal Academy of Sciences (1980), *in* NOBEL LECTURES: CHEMISTRY 377-432 (1980).

50. *See, e.g.*, J. Craig Venter et al., *The Sequence of the Human Genome*, 291 SCIENCE 1304 (2001); E. S. Lander et al., *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860 (2001).

51. WATSON ET AL., *supra* note 30, at 19.

zyme . . . ."[52]

By specifically linking the action of a single gene to the action of a single enzyme, Beadle and Tatum confirmed Garrod's "One Gene-One Enzyme Hypothesis."[53] Since all of the enzymes known at that time were proteins, "the key problem was the way genes participate in the synthesis of proteins."[54] Although there were numerous possible explanations for this phenomenon, "[f]rom the very start of serious speculation, the simplest hypothesis was that genetic information within genes determines the order of the 20 different amino acids within the polypeptide chains of proteins."[55]

Soon after their discovery of the double helical structure of DNA, Watson and Crick were able to make informational inferences from the double helix. As Keller relates:

> Watson and Crick published a second paper—on "Genetical Implications of the Structure of Deoxyribonucleic Acid"—whose main point was to argue that the structure of DNA show us [the mechanism by which DNA duplicates itself] . . . . Within such a framework, the one gene-one enzyme hypothesis took on a new kind of sense. Now it could be understood as suggesting a direct correspondence between the sequence of nucleotides in a gene and the sequence of amino acids in a protein . . . .[56]

The information encoded by the sequence of deoxyribonucleotides in a strand of DNA could be used to specify the synthesis of a corresponding sequence of amino acids, yielding a protein.

In 1957, Francis Crick proposed the "sequence hypothesis."[57] "In its simplest form [Crick's hypothesis] assumes that the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and that this sequence is a (simple) code for the amino acid sequence of a particular protein."[58] Although many additional details about protein synthesis are now known, this basic principle of information transfer from gene to protein is still considered sound.

Despite elucidation of the general mechanism by which genetic information translated into protein synthesis, the precise

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52. LILY E. KAY, WHO WROTE THE BOOK OF LIFE 52 (2000).
53. *Id.*
54. WATSON ET AL., *supra* note 30, at 19.
55. *Id.*
56. KELLER, *supra* note 21, at 51–52.
57. *Id.* at 52.
58. F. H. C. Crick, *On Protein Synthesis*, 12 SYMP. SOC'Y FOR EXPERIMENTAL BIOLOGY 138, 152 (1958).

code remained unknown. In the first definitive demonstration that information from nucleic acids corresponds specifically to protein sequence, Marshall Nirenberg and Heinrich Matthaei "observed in 1961 that the addition of the synthetic polynucleotide poly U (UUUUU . . .) to a cell-free system capable of making proteins leads to the synthesis of polypeptide chains containing only the amino acid phenylalanine. The nucleotide groups UUU thus must specify phenylalanine."[59]

Over the next six years, Nirenberg, Matthaei, and other biologists raced to unravel all of the "words" in the "[genetic] code."[60] Accelerated by "fierce competition" among numerous research groups, "[b]y 1967 the [genetic] code was essentially completed; its momentous significance captured by the many scientific writings and media coverage which announced an impending revolution in biology, both its epic promises and its perils."[61]

The influence of the "information gene concept" has retained its salience right up until the present time. In addition to the widespread understanding of genes as material particles, "[t]he human genome is now generally viewed as an information system and, more specifically, as a 'Book of Life' written in the language of DNA, or DNA code, to be read and edited."[62]

E. GENE AS PROGRAM

In an extension of the "information gene concept," some biologists have suggested that genes are like programs that encode instructions that the cell must carry out. Even before the genetic code had been cracked, Francis Crick remarked that "DNA makes RNA, RNA makes protein, and proteins make us."[63] François Jacob and Jacques Monod proposed that "the genome contains not only a series of blue-prints, but a coordinated program of protein synthesis and the means of controlling its execution."[64] In late 1950s, Jacob and Monod had discovered that some genes encoded products that regulated the actions of other genes.[65] They proposed the "operon model"

59. WATSON ET AL., *supra* note 30, at 37.

60. KAY, *supra* note 52, at 330.

61. *Id.*

62. *Id.* at 1.

63. KELLER, *supra* note 21, at 54.

64. François Jacob & Jacques Monod, *Genetic Regulatory Mechanisms in the Synthesis of Proteins*, 3 J. MOLECULAR BIOLOGY 318, 354 (1961).

65. WATSON ET AL., *supra* note 30, at 561.

to represent how such gene regulation might occur.[66] The operon model spurred acceptance of the genetic program gene concept by providing a specific example of such a genetic program.

In his 1965 book, *The Molecular Biology of Development*, James Bonner envisioned a comprehensive "genetic program" to explain how genes built and maintained organisms.[67] In this book, Bonner described a "master programme constituted in turn of a set of subprogrammes or subroutines."[68] He subdivided the subroutine even further into "a list of cellular instructions or commands."[69]

Despite obvious similarities between computer programs and genetic programs, the latter do appear to possess important differences from the former. In light of these differences,

> computers cannot take sole credit for the notion of a genetic program. Compelling as the analogy may be, equating the genetic material of an egg with the magnetic tape of a computer does not imply that that material encodes a program; it might, for example, just as well be thought of as encoding data to be processed by a program located elsewhere in the cell.[70]

However, the program gene concept has been influential in suggesting that, just like computer software, a genetic program can confer qualities of consistency and predictability on an organism.[71] Furthermore, if genes can be conceived of as genetic programs, then one may be able to "reprogram" organisms by modifying their genes.

F. THE GENE CONCEPT UNRAVELS

The operon model proposed by Jacob and Monod significantly complicated the understanding of what genes are. No longer did genes merely encode enzymes. They also encoded regulatory products. These products include "repressors," "operators," "promoters," "terminators," "leaders," and "activators," each playing specific roles in the regulation of gene expression.[72] This represented a dire threat to the "One Gene-One

66. LEWIN, *supra* note 8.

67. *See* JAMES BONNER, THE MOLECULAR BIOLOGY OF DEVELOPMENT 6 (1965).

68. *Id.* at 134.

69. KELLER, *supra* note 21, at 85–86.

70. *Id.* at 81.

71. As discussed below, organisms, in fact, tend to exhibit much less consistency and predictability than the analogy with computer software would suggest.

72. WATSON ET AL., *supra* note 30, at 394–97, 547–49.

Enzyme Hypothesis."

The DNA sequencing technologies developed in the 1970s revealed eukaryotic genes to be radically different in structure than had been assumed. Until the 1970s, most of the genes with known specific nucleotide sequences were derived from eubacteria or their viruses. For most of these organisms, "the coding sequence is contiguous: the codon for one amino acid is immediately adjacent to the codon for the next amino acid in the polypeptide chain."[73] However, the accumulation of DNA sequences from eukaryotic organisms demonstrated that eukaryotic genes almost always had more complex structures.[74]

By the late 1970s, Richard Roberts and Philip Sharp had disproven the hypothesis that all genes were linear and continuous by demonstrating that quiescent, "nonexpressed" portions of DNA (that is, "introns") were situated in the midst of active, "expressed" portions of DNA (that is, "exons") coding for polypeptides.[75] In other words, "[m]any of the genes that code for proteins in higher organisms turn out not to be continuous but fragmented . . . ."[76] Because of "this alternating pattern of exons and introns, genes bearing noncoding interruptions are often said to be 'in pieces' or 'split'."[77] Thus, genes in eukaryotes depart significantly from earlier gene concepts that envisioned simple, linear contiguity. Rather, "[t]he highly interrupted structure of eukaryotic genes suggests a picture of the eukaryotic genome as a sea of introns (mostly but not exclusively unique in sequence), in which islands of exons (sometimes very short) are strung out in individual archipelagoes that represent genes."[78]

The existence of introns and exons destroyed the universal applicability of the One Gene-One Enzyme Hypothesis. If genes are not linear and contiguous in sequence structure, but instead fragmented,

> there is no strict one-to-one correspondence between the sequence of a gene and that of a protein it gives rise to. Thus the original RNA transcript directly transcribed from the gene (the messenger RNA, or mRNA) must be processed to remove these junk sequences before pro-

73. *Id.* at 415.
74. *See id.*
75. KELLER, *supra* note 21, at 59.
76. *Id.*
77. WATSON ET AL., *supra* note 30, at 415.
78. LEWIN, *supra* note 8, at 47.

tein synthesis can begin.[79]

On average, a eukaryotic gene is split into four exons by three introns.[80] There exists great variability in the number of introns a gene may have, "from one in the case of most intron-containing yeast genes (and a few human genes), to 50 in the case of the chicken *proα2* collagen gene, to as many as 363 in the case of the *Titin* gene of humans."[81]

Even genes divided by introns tend to be "transcribed into a single RNA copy of the entire gene."[82] Because "the protein-synthesizing machinery of the cell . . . is equipped only to translate mRNAs containing a contiguous stretch of codons,"[83] the introns present in the initially transcribed "pre-mRNA" are further processed by "RNA splicing."[84] The resulting mRNA is then ready to be translated into a polypeptide.[85] However, even this scenario may be complicated further by "alternative splicing," wherein "mRNAs containing different selections of exons can be generated from a given pre-mRNA."[86] Through alternative splicing, "a gene can give rise to more than one polypeptide product," each of which alternative polypeptides are called "isoforms."[87] Isoforms are the rule rather than the exception: "[i]t is estimated that up to 75% of the genes in the human genome are spliced in alternative ways to generate more than one isoform."[88] Furthermore, the numbers of possible isoforms from each individual gene can be staggering, ranging

> from two to hundreds or even thousands. For example, the *Slo* gene from rat, which encodes a potassium channel expressed in neurons, has the potential to encode 500 alternative versions of that product. And . . . one particular *Drosophila* gene can encode as many as 38,000 possible products as a result of alternative splicing."[89]

Alternative splicing suggests a One Gene-Multiple Enzyme Hypothesis.

There is even more complexity in genes beyond alternative splicing. Genes may also overlap one another. This may occur

79. KELLER, *supra* note 21, at 60.
80. WATSON ET AL., *supra* note 30, at 415.
81. *Id.* at 415–16.
82. *Id.* at 416.
83. *Id.* at 417.
84. *See id.*
85. *See id.*
86. *Id.*
87. *Id.*
88. *Id.*
89. *Id.*

when "[t]he first half (or second half) of a gene is used independently to specify a protein that represents the first (or second) half of the protein specified by the full gene."[90] Genes may also

> overlap in a more subtle manner when the same sequence of DNA is shared between two *nonhomologous* proteins. This situation arises when the same sequence of DNA is translated in more than one reading frame. In cellular genes, a DNA sequence usually is read in only one of the three potential reading frames. In some viral and mitochondrial genes, however, there is an overlap between two adjacent genes that are read in different reading frames.[91]

Genes have been discovered contained within larger genes,[92] "nestled within the non-protein coding intron of another [gene],"[93] and in "countless other weird arrangements."[94] Recent studies of "all the transcripts from ten chromosomes across eight human cell lines" have yielded a view of genes and their products characterized by "mind-boggling complexity."

> Instead of discrete genes dutifully mass-producing identical RNA transcripts, a teeming mass of transcription converts many segments of the genome into multiple RNA ribbons of differing lengths. These ribbons can be generated from both strands of DNA, rather than just one as was conventionally thought. Some of these transcripts come from regions of DNA previously identified as holding protein-coding genes. But many do not.[95]

In light of the evidence, a One Gene-Multiple Enzymes Hypothesis might be inadequate to describe what a gene is. Given the complexity discussed above, Benjamin Lewin, of Harvard University, has suggested an inversion of the Hypothesis' usual order; rather than One Gene-One Enzyme, he suggests One Enzyme-One Gene.[96]

One of the leading genetics textbooks , *GENES IX*, by Benjamin Lewin summarizes the complexities that increasingly call into question existing gene concepts in understated and somewhat enigmatic fashion: "[t]he concept of the gene has evolved significantly in the past several years. The question of what's in a name is especially appropriate for the gene."[97] The

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90. LEWIN, *supra* note 8, at 45.

91. *Id.*

92. *See* Helen Pearson, *What is a Gene?*, 441 NATURE 399 (2006).

93. *Id.* at 401.

94. *Id.* at 399.

95. *Id.*

96. LEWIN, *supra* note 8, at 53 (using the most general term "polypeptide" instead of "enzyme": "Instead of saying 'one gene-one polypeptide,' we may describe the relationship as 'one polypeptide-one gene.'").

97. *Id.*

name that has dominated discussions of units of heredity for a century—"gene"—has achieved vast influence both within biology and in wider society. Yet, the scientific usefulness of the word "gene" is now in doubt among those most familiar with the evidence increasingly undermining the accuracy of gene concepts. Almost one-hundred years ago, the man who coined the term "gene," Wilhelm Johannsen, justified his neologism by expressing his anxieties about previous descriptions of hereditary units: "[i]t is a well established fact that language is not only our servant, when we wish to express—or even to conceal—our thoughts, but that it may also be our master, overpowering us by means of the notions attached to the current words." [98]

After a century, Johannsen's "very applicable little word"[99] may have graduated from servant to master and may now be "overpowering us by means of the notions attached to [it]."[100] One of the world's preeminent geneticists, William Gelbart, has written that the gene might be "[a] concept past its time . . . . [U]nlike chromosomes, genes are not physical objects but are merely concepts that have acquired a great deal of baggage over the past decades.[101] Though important in the development of genetics "we may well have come to the point where the use of the term 'gene' . . . might in fact be a hindrance to our understanding."[102]

Though the scientific justification of the "gene" has begun to wane, the power of what Keller terms "gene talk" has remained strong. For the purposes of this article, "gene talk" refers to the verbal invocation of the word "gene" or its attendant concepts. As Keller has suggested, gene talk has played key roles in the rise of biotechnology and the biotechnology industry.[103] And, one of the ways in which gene talk has been highly successful has been to secure property rights in genes through the patent system despite declining scientific certainty about what exactly a gene is.

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98. W. Johannsen, *The Genotype Conception of Heredity*, 45 THE AM. NATURALIST 129, 132 (1911).

99. *Id.*

100. *Id.*

101. William M. Gelbart, *Databases in Genomic Research*, 282 SCIENCE 659, 660 (1998).

102. *Id.*

103. KELLER, *supra* note 21, at 10.

III. GENE PATENTS

A. RECOMBINANT DNA

In 1972, Dr. Ananda M. Chakrabarty, a staff biologist at General Electric Company, filed U.S. patent application serial number 05/260,563.[104] This patent application claimed, among other inventions, a "bacterium from the genus Pseudomonas containing therein at least two stable energy-generating plasmids . . . ."[105] In the wake of the watershed 1980 Supreme Court decision in *Diamond v. Chakrabarty*, allowing the patenting of recombinant eubacteria,[106] this patent application issued as United States Patent No. 4,259,444 ('444 patent).[107] The '444 patent, which involves non-genomic "plasmids" containing desired genes, [108] represents a key moment in the evolution of patentable subject matter.

Stanley Cohen and Herbert Boyer, molecular biologists at Stanford University and the University of California San Francisco ("UCSF"), respectively, spent 1973 and 1974 developing a method for transferring DNA from one type of organism into the cells of a distinctly different type of organism.[109] This marked the birth of the "recombinant DNA" revolution in biology.[110] In November of 1974, Stanford University and UCSF filed parent patent application 520,691 that ultimately matured into patent application 06/001,021, claiming recombinant DNA methods invented by Cohen and Boyer, and issued in 1980 by the USPTO as U.S. Patent Number 4,237,224 ('224 patent);[111] the '224 patent claimed only recombinant DNA methods, not DNA molecules or recombinant organisms themselves.[112] By 1977, the human gene, somatostatin, had been expressed within the eubacterium, *Escherichia coli*.[113] Recom-

104. U.S Patent No. 4,259,444 (filed June 7, 1972).

105. *Id.* at col.16 l.23–25.

106. *See* Diamond v. Chakrabarty, 447 U.S. 303, 318 (1980).

107. '444 Patent.

108. *See id.*

109. Sally Smith Hughes, *Making Dollars Out of DNA: The First Major Patent in Biotechnology and the Commercialization of Molecular Biology*, 92 ISIS 541, 541 (2001).

110. *Id.* at 542.

111. *Id.*

112. U.S. Patent No. 4,237,224 col. 17 l.4–31(filed Jan. 4, 1979). Note that all fourteen claims begin with the words "A method."

113. *See* Keiichi Itakura et al., *Expression in* Escherischia coli *of a Chemically Synthesized Gene for the Hormone Somatostatin*, 198 SCIENCE 1056,

binant DNA technology offered "a simple method for isolating and amplifying any gene or DNA segment and moving it with controlled precision, allowing analysis of gene structure and function in simple and complex organisms."[114] When coupled with the relatively rapid DNA sequencing methods developed in the mid-1970s, modern biotechnology had been born.[115]

B. PATENTS ON GENES

As the 1970's dawned, biologists, and the institutions that employed them, began securing significant numbers of patents claiming the complex organic molecules of life. In 1971, U.S. Patent Numbers 3,607,370[116] and 3,619,206[117] issued, claiming "polypeptide" and "protein" *per se*, respectively. Earlier, patents had issued claiming methods involving polypeptides and proteins. In 1972, the first claim to a "peptide" *per se* appeared in U.S. Patent Number 3,645,689.[118] By 1973, "DNA" had been included as an element of a patented claim.[119]

The term "gene" first appeared as a claim element in U.S. Patent No. 3,710,511.[120] By 1978, U.S. Patent Number 4,116,770 had issued, and its claims 10, 11, and 12 were directed to phenotypic traits expressed by specific "genes."[121] Finally, in 1982 U.S. Patent No. 4,363,877 ("the '877 patent") issued, and included independent claims 1 and 4, which were directed to "recombinant DNA transfer vector[s]" comprising specified nucleotide sequences of codons for "human chorionic somatomammotropin" and "the growth hormone of an animal species," respectively.[122] This was the first "gene" patent, claim-

1056–63 (1977).

114. Hughes, *supra* note 109, at 541.

115. *See* discussion *supra* Part II.F.

116. Entitled "Pressure-Sensitive Adhesive Tape Comprising Gluten Hydrolypate Derivatives."

117. Entitled "Modified Proteins."

118. *See* U.S. Patent No. 3,645,689 (filed Apr. 9, 1970) (Entitled "Method and Apparatus for Analyzing Proteins").

119. *See* U.S. Patent No. 3,755,086 (filed Feb. 9, 1971) (Entitled "Diagnostic Method Utilizing Synthetic Deoxyrilionucleotide Oligomer Template").

120. *See* U.S. Patent No. 3,710,511 (filed Apr. 21 1971) (Entitled "Procedures for Use of Genic Male Sterility in Production of Commercial Hybrid Maize").

121. *See* U.S. Patent No. 4,116,770 (filed Feb. 27, 1975).

122. *See* U.S. Patent No. 4,363,877 (filed Apr. 19, 1978) (Entitled "Recombinant DNA Transfer Vectors").

ing genes *per se*.[123] Although the claims of the '877 patent did not specifically recite the word "gene," the specification's "SUMMARY OF INVENTION" did identify "genes coding for RGH, the major portion of HCS and the major portion of HGH, respectively."[124] Oddly, this first gene patent largely failed to define a gene. The closest the '877 patent's specification gets to such a definition is the following passage: "isolating the mRNA which contains the nucleotide sequence coding for the amino acid sequence of a particular protein is equivalent to the isolation of the same sequence, or *gene*, from the DNA itself."[125] In other words, the '877 patent equates a gene with the nucleotide sequence of an mRNA transcript; by implication, a gene is simply a nucleotide sequence that produces an mRNA.

Patents and patent applications claiming genes both increased rapidly after the *Diamond v. Chakrabarty* decision in 1980. Figure 1 shows annual patent application filings with "gene" in at least one claim during the period from 1971 to 2007. Such filings rose from just above zero in 1977 to more than 100 in 1984, more than 500 in 1993, almost 1000 in 1994, to a peak of over 1600 filed in 1995 alone. While filings remained at least—or extremely close to—1000 per year from 1994 until 2002, thereafter filings of such patent applications declined rapidly to well below 500 through 2007.[126] By way of comparison, Figure 1 also shows that annual patent filings with "DNA" or "nucleotide sequence" in at least one claim follow the same trajectory as do those with "gene."

123. Leslie Gladstone Restaino & Theresa Takeuchi, *Gene Patents and Global Competition Issues*, 26 GENETIC ENGINEERING AND BIOTECHNOLOGY NEWS 10, 10 (2006).

124. '877 Patent, at col.8 l.7–9.

125. *Id.* at col.5 l.35–40 (emphasis added).

126. These data includes a lag-time of approximately 18 months, reflecting the rolling publication window of 18 months from earliest priority date.

Figure 1. Claim Language in Patent Applications

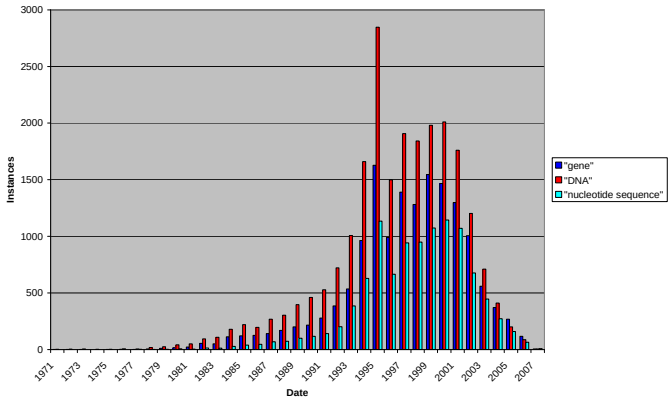
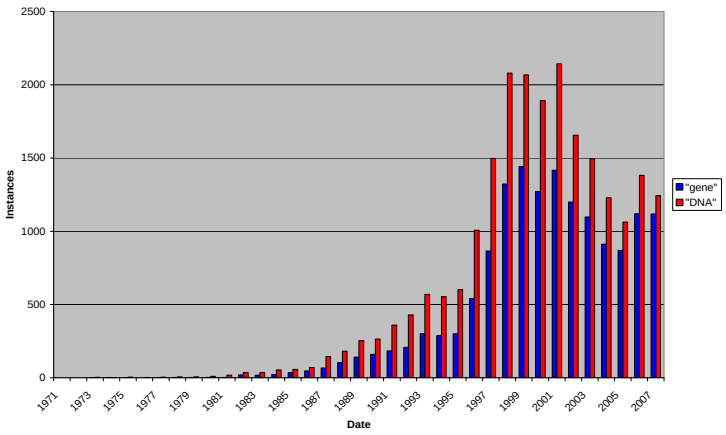


Figure 2 shows annual patent issuances with "gene" in at least one claim during the period from 1971 to 2007. Such filings rose from just above zero in 1981 to more than 100 in 1988, more than 500 in 1996, more than 1300 in 1998, to a peak of almost 1500 in 1999. From 1998 to 2007, patent issuances have remained above 1000 per year in all but two years, and there has been only a relatively gradual decline in issuances from the peak year of 1999. By way of comparison, Figure 2 also shows that annual issuances of patents with "DNA" in at least one claim follow the same trajectory as do those with "gene."

Figure 2. Claim Language in Issued Patents



C. GENES IN PATENTS

Neither patents nor patent litigation tend to spend much

effort attempting to define what a gene is.[127] Although many thousands of patent applications have employed the words "gene" or "genes" within their claims, and a significant fraction of these patent applications have issued as United States patents, seldom do patent applicants trouble themselves with defining these terms in their specifications. For example, of the more than 15,000 issued U.S. patents that include the term "gene" in their claims, only sixteen include the phrase "a gene is defined as," only seventeen include the phrase "genes are defined as," only ten include the phrase "definition of a gene," and only four include the phrase "definition of genes."[128]

Similarly, of a group of fifteen federal court opinions that discuss gene definitions,[129] only two, *Amgen, Incorporated v. Chugai Pharmaceutical Company*, [130] and *Carnegie Mellon University v. Hoffman-La Roche Incorporated*,[131] actually provide a definition of a gene.[132] However, the *Amgen* definition

127. A review of the first 500 search results of patents in "Google Patent Search" reveals that only about 20% of the resulting patents attempt to define "gene." Almost all of these definitions are highly simplistic in nature, and none of them seriously reflects the scientific complexity that has surrounded genes over the last several decades.

128. These results are based on searches of these exact phrases in the Google Patent Search database of all "Issued Patents" on April 9, 2008.

129. Monsanto Co. v. Bayer Bioscience N.V., 514 F.3d 1229, 1232 (Fed. Cir. 2008); Mycogen Plant Sci., Inc. v. Monsanto Co., 91 Fed. Appx. 666, 667 (Fed. Cir. 2004); Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F.3d 1094, 1105 (Fed. Cir. 2003); Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316 (Fed. Cir. 2002); Mycogen Plant Sci., Inc. v. Monsanto Co., 252 F.3d 1306, 1319 (Fed. Cir. 2001), *vacated*, 535 U.S. 1109 (2002); Hitzeman v. Rutter, 243 F.3d 1345, 1357 (Fed. Cir. 2001); *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991); *In re* Merat, 519 F.2d 1390, 1392 (C.C.P.A. 1975); Carnegie Mellon Univ. v. Hoffman-La Roche, Inc., No. C 95-3524 SI, No. C 01-0415 SI, 2007 U.S. Dist. LEXIS 20386, at *8 (N.D. Cal. Mar. 22, 2007); Carnegie Mellon Univ. v. Hoffman La Roche, Inc., 148 F. Supp. 2d 1004, 1013 (N.D. Cal. 2001), *aff'd*, 541 F.3d 1115 (Fed. Cir. 2008); E.I. Du Pont de Nemours & Co. v. Okuley, No. C2-97-1205, 2000 U.S. Dist. LEXIS 21385, at *57 (S.D. Ohio Dec. 21, 2000), *aff'd*, 344 F.3d 578 (6th Cir. 2003); Trs. of Columbia Univ. v. Roche Diagnostics GmbH, 126 F. Supp. 2d 16, 21 (D. Mass. 2000); Monsanto Co. v. Mycogen Plant Sci., Inc., 61 F. Supp. 2d 133, 155 (D. Del. 1999); Genentech, Inc. v. Boehringer Mannheim GmbH, 989 F. Supp. 359, 364-65 (D. Mass. 1997). These opinions were the result of a search ("gene" w/3 defin!) of the LexisNexis® "Federal Court Cases, Combined" database.

130. *Amgen*, *927* F.2d at 1206.

131. *Carnegie Mellon*, 2007 U.S. Dist. LEXIS 20386, at *8.

132. Note that *Carnegie Mellon*, 148 F. Supp. 2d at 1013, simply cites *Amgen* for how *not* to define a gene.

("A gene is a chemical compound, albeit a complex one.")[133] is so general as to approach the tautological, and the *Carnegie Mellon University* definition ("A gene may be defined as a region of DNA that contains information that a cell uses to make a particular protein.")[134] is scientifically inaccurate (*e.g.*, because it ignores introns), vague, and uninformative.

In 2006, an article provocatively entitled *What is a Gene?,* was published in *Nature*,[135] a journal many—perhaps even most—scientists would acknowledge as the most prestigious and influential scientific journal in the world. In this article, Helen Pearson describes widespread disagreement and confusion among biologists about the meaning of the word "gene."[136] She quotes William Gelbart, a famous and well-published geneticist at Harvard University, as saying, "I find it sometimes very difficult to tell what someone means when they talk about genes because we don't share the same definition."[137] Despite the fact that *What is a Gene?* was published in such a prominent journal, and has undoubtedly been read by many geneticists, this article about the uncertainty surrounding gene concepts has been cited only a single time by a U.S. patent or patent application.[138] This application cites to *What is a Gene?* and states that "[w]hile the definition of a 'gene' is an increasingly complex issue, what is of immediate interest for drug discovery and development is a catalogue of those genes that encode functional, expressed proteins."[139] In other words, despite difficulties in describing what a gene actually is, the overriding priority for "drug discovery and development"[140] should be to "catalogue"[141] the useful products of genes rather than the genes that encode those useful products. This patent application may reflect a larger manifesto of biotechnology: it is more important to locate potentially useful products of genes than to know the characteristics of the genes that encode them. Applied

133. *Amgen*, 927 F.2d at 1206.

134. *Carnegie Mellon*, 2007 U.S. Dist. LEXIS 20386, at *8.

135. Pearson, *supra* note 92.

136. *Id.* at 399.

137. *Id.* at 401.

138. U.S. Patent Application Publication Number US 2007/0166765 A1, at [0358] (filed Jan. 7, 2007) (the publication for U.S. Patent Application Serial Number 11/653,771 ("'771 application")).

139. *Id.* (internal citation omitted).

140. *Id.*

141. *Id.*

to gene patents, this manifesto would emphasize the description of gene function over the description of gene structure. Patent law, however, requires description of structure,[142] and disallows "functional claiming" of biotechnological inventions.[143]

IV. GENE TALK

A. THE BIOTECHNOLOGY INDUSTRY

The biotechnology industry[144] is substantially based on gene—and gene-based— inventions. The products of that industry are made possible by technologies that allow genes to be located within the genome, sequenced deoxyribonucleotide by deoxyribonucleotide, isolated out of their original genomic loci and spliced into brand new loci, and expressed more or less than usual. The biotechnology industry relies on the availability of patent protection to appropriate the economic value of genes. Patents and patent applications allow biotechnology companies to attract investments and other sources of funding and to protect their own immense investments in discovering, developing, securing regulatory approval, and successfully marketing their products. Consequently, the biotechnology industry also has strong incentives to maintain the patentability of gene inventions. As Sheila Jasanoff has described in her book, *Designs on Nature*,

> [e]specially in the United States, patents played a foundational role in the development of the biotechnology industry at several levels. First, the extension of patents to the life sciences created new classes of property rights in things that were previously outside the realm of what could be owned, or even thought of as subject to ownership claims. As a result, these objects became commodities that could have value, be exchanged, circulate in markets, and foster productivity. Second, much of the early development of biotechnology occurred before there were any marketable products, and patents were the only evidence for eager venture capitalists that there might be something

142. Medical Instrumentation and Diagnostics Corp. v. Elekta AB, 344 F.3d 1205, 1211 (Fed. Cir. 2003) ("If the specification is not clear as to the structure that the patentee intends to correspond to the claimed function, then the patentee has not paid that price [the quid pro quo of disclosing structure corresponding to function] but is rather attempting to claim in functional terms unbounded by any reference to structure in the specification. Such is impermissible under the [Patent] statute.")

143. *See*, *e.g.,* University of Rochester v. G. D. Searle, Inc., 249 F. Supp. 2d 216–236 (W.D.N.Y. 2003).

144. Herein, the biotechnology industry is assumed also to include pharmaceutical companies significantly dependent on biotechnologies.

> of future value to justify present investment. Third, patents provided some assurance to jittery investors that they would not be mired in endless legal wrangling if commercially useful products ever came on line. Fourth, patents proved to be a way of sorting out the competing claims to participants in an increasingly complex web of invention that linked together the disparate interests of patients, research subjects, farmers, academic researchers, universities, start-up firms, government, and industry.[145]

The patent system offers federal legal protection for gene inventions, offering powerful rights to exclude others from making, using, offering to sell, or selling patented genes within the United States, or importing patented genes into the United States.[146]

Patent protection for genes and their products is a keystone asset of pharmaceutical and biotechnology companies, as well as a valuable source of revenue for universities and government research institutes. In fact, some have argued that the main product of the biotechnology industry, which, as a whole, has yet to turn a profit, is not genes *per se*, or their uses or products, but patents claiming genes or the uses or products thereof.[147] Availability of patent protection for genes has generally been assumed to promote innovation in biotechnology,[148] spurring the discovery and elucidation of relatively more new genes, while simultaneously limiting others' access to those same new genes.[149]

B. THE RISE OF GENE TALK

Given the importance of genes to the biotechnology indus-

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145. SHEILA JASANOFF, DESIGNS ON NATURE: SCIENCE AND DEMOCRACY IN EUROPE AND THE UNITED STATES 203–04 (2005) (internal citations omitted).

146. 35 U.S.C. § 271(a) (2006).

147. *See, e.g.*, John M. Golden, *Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System*, 50 EMORY L.J. 101, 105-06 (2001).

148. In their recent study of the role that the patent system plays in spurring innovation, James Bessen and Michael J. Meurer suggest the patent system may indeed promote innovation in the pharmaceutical/biotechnology industry. JAMES BESSEN & MICHAEL J. MEURER, PATENT FAILURE—HOW JUDGES, BUREAUCRATS, AND LAWYERS PUT INNOVATORS AT RISK 85–88 (2008). As Bessen and Meurer have stated, "The evidence certainly is consistent with the notion that patents encourage American pharmaceutical R & D." James Bessen & Michael J. Meurer, *Do Patents Stimulate R & D Investment and Promote Growth*?, PATENTLY-O BLOG (Mar. 13, 2008, 4:17 AM), http://www.patentlyo.com/patent/2008/03/do-patents-stim.html.

149. Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 699 (1998).

try, threats to the coherence or accuracy of gene concepts, if they were to undermine the prospect of receiving gene patents, could threaten the biotechnology industry itself. Until recently, the widespread perception of such threats has appeared to be minimal. According to Keller,

> [f]or almost fifty years, we lulled ourselves into believing that, in discovering the molecular basis of genetic information, we had found the "secret of life"; we were confident that if we could only decode the message in DNA's sequence of nucleotides, we would understand the "program" that makes an organism what it is. And we marveled at how simple the answer seemed to be.[150]

As Francis Crick so succinctly put it, "DNA makes RNA, RNA makes protein, and proteins make us."[151]

In fact, genes have been a scientific and cultural success story to rival any in the history of science. As Keller suggests,

> [t]oday, the prominence of genes in both the general media and the scientific press suggests that in this new science of genomics, twentieth-century genetics has achieved its apotheosis. Yet, the very successes that have so stirred our imagination have also radically undermined their core driving concept, the concept of the gene.[152]

Keller considers the gene to be a scientific concept whose days of influence may be numbered, because

> even though the message has yet to reach the popular press, to an increasingly large number of workers at the forefront of contemporary research, it seems evident that the primacy of the gene as the core explanatory concept of biological structure and function is more a feature of the twentieth century than it will be of the twenty-first. What will take its place? Indeed, we might ask, will biology ever again be able to offer an explanatory framework of comparable simplicity and allure?[153]

However, Keller has identified several important roles that gene talk serves in maintaining belief in the fiction of the "gene" even in the face of mounting scientific evidence to the contrary:

> Paramount among these is the convenience of gene talk as an operational shorthand for scientists working in specific experimental contexts. Furthermore, gene talk identifies concrete levers or handles for effecting specific kinds of change. And finally, gene talk is an undeniably powerful tool of persuasion, useful not only in promoting research agendas and securing funding but also (perhaps especially) in marketing the products of a rapidly expanding biotech industry.[154]

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150. KELLER, *supra* note 21, at 7.
151. *Id.* at 54.
152. *Id.* at 5.
153. *Id.* at 9.
154. *Id.* at 10.

C. GENE TALK AND GENE PATENTS

Gene talk by the biology community to constituencies outside that community rarely addresses the complexities and uncertainties surrounding genes. One explanation for such omission is the perceived need to simplify complex scientific concepts to communicate effectively to constituencies lacking scientific knowledge and training. The lack of consensus within the biology community regarding gene concepts may constrain what information can accurately and effectively be communicated. An alternative explanation is that the biologists circumscribe their disagreements about gene concepts to occur only within their own community, while they maintain a normative silence on those same disagreements when addressing outside constituencies, to protect their access to valuable gene patents. In other words, the biology community tells a story of complexity internally, whereas it tells a different, much simpler, story externally. Such epistemic compartmentalization would help the biology community to achieve two important goals simultaneously: (1) relatively free internal scientific enquiry about genes to foster scientific advances and (2) minimization of external leakage of internal scientific disputes to protect continued access to potentially valuable gene patents. In fact, goal (2), by proprietizing and monetizing the fruits of goal (1) might be viewed by at least some in the biology community as one method of promoting goal (1).

Keller's research supports the notion that those with strong incentives to sustain the concept of the "gene" may engage in gene talk with the aim of sustaining the vitality of what many geneticists now consider a moribund idea:

> Throughout the many variations and transformations that we have seen in the concept of the gene over the course of its lifetime, it had always been possible in the past to contain whatever definitional difficulties had plagued that concept; one might even say that it had been functional, both experimentally and professionally, to keep its internal incoherence under wraps.[155]

In fact, Keller has expressly questioned whether the biology community has attempted to obscure the failure of the gene concept from constituencies outside biology community. As she has stated, "It's been a growing conviction of mine that biologists have a whole other way of talking to each other in the lab than they do to the public."[156]

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155. *Id.* at 69–70.

156. Brown, *supra* note 2.

How the biology community portrays genes to the public may have profound effects on what society believes about genes. To understand how scientific concepts or technologies affect societies, Jasanoff has stressed the importance of also "ask[ing] how societies produce authoritative knowledge and functioning technological artifacts."[157] By considering the latter question,

> it has been possible to demonstrate that the products of the sciences, both cognitive and material, embody beliefs not only about how the world *is*, but also how it *ought* to be. . . . The apparent firmness of the devices with which we make sense of our existence . . . is maintained through more or less purposive action by identifiable actors. Accordingly, to understand how . . . natural entities such as "the gene" function in the world, one has to ask how diverse actors use and understand the concept, how it is articulated through formal and informal practices, where and by whom it is contested, and how it reasserts itself in the face of challenges to its integrity or meaning.[158]

Gene talk fits well into this conceptual framework.

Biology is a branch of science devoted to studying especially complex structures and processes. Perhaps due in part to this complexity, the biology community has achieved considerable success in preventing the gene concept from becoming externally contested. While gene concepts are vigorously contested *within* the biology community, [159] the bar for legitimacy and authority in this debate is exceedingly high: doctoral degrees, professorships, publication in peer reviewed journals, memberships in exclusive learned societies, and perhaps even gene patent inventorship are required. Indeed, this high entry barrier largely excludes those with lesser credentials from access to these internal gene debates. Members of the biology community already in possession of such credentials tend to command a privileged position in external discourse about genes. Their opinions about genes tend to be considered more authoritative by constituencies beyond the biology community than are opinions expressed by less credentialed actors outside that community. Although the biology community understands that there remain great uncertainties regarding gene concepts, the value its members place on the prospect of receiving gene patents, and the monetary rewards that may accompany them, may create significant disincentives to expressing to those outside the biology community—including the USPTO—how com-

157. JASANOFF, *supra* note 145, at 19.

158. *Id.*

159. *See, e.g.*, Pearson, *supra* note 92 at 399–401.

plex, complicated, and uncertain gene concepts actually are. Consequently, the biology community contests gene concepts internally, while simultaneously portraying the gene to other constituencies—including the USPTO—as relatively predictable and straightforward. Thus, adapting the Jasanoff rubric, the biology community may be able to maintain "the apparent firmness of the [gene] device[]" by its "purposive action" of promoting a simple and predictable gene to outside constituencies,[160] in particular the USPTO.

Significant incentives exist for a patent applicant not to acknowledge uncertainty or incoherence in the gene concept because such acknowledgment risks lowering the probability that the USPTO will grant the applicant's patent, or exposing the patent later to invalidity challenges in litigation. Widespread acknowledgment of this uncertainty or incoherence would have the potential to undermine the market value of the biotechnology industry, as well as to impoverish other beneficiaries of gene patents, such as investors, universities, and patent attorneys and agents. Patent applicants have an affirmative obligation to disclose certain information to the USPTO.[161] Such "[i]nformation must be disclosed [by a patent applicant] when it is material to patentability [of a patent application]."[162] The reluctance to admit uncertainties in gene concepts certainly violates the spirit of this affirmative obligation of disclosure; and, depending upon the context, it could also violate the letter of this obligation. If a patent applicant claiming a gene or gene-related invention were aware of a prior art reference whose teaching cast into doubt the validity of the claimed invention or the sufficiency of the disclosure supporting the claimed invention, the patent applicant would be obligated to provide that prior art reference to the USPTO even if this lowered the probability of the claim ever issuing. Much prior art exists detailing the many uncertainties that surround genes, gene structures, and gene functions.[163] Yet, such prior art is rarely included in the patent specifications of gene patents. Even in litigation, gene patents rarely fact the issue of gene concepts in more than

160. JASANOFF, *supra* note 145, at 19.

161. 37 C.F.R. §1.56 (2008).

162. Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1257 (Fed. Cir. 1997).

163. *See, e.g.*, Pearson, *supra* note 92, at 399–401 (citing studies and the general consensus within the biology community that our understanding of 'gene' is not completely accurate).

a cursory manner, despite the fact that uncertainty about gene concepts may have the potential to cast doubt on the validity of many gene patents. Gene concepts rarely arise in patent litigation, which may be evidence that gene talk has successfully influenced even the judicial process.[164]

Jasanoff has suggested that the economic success, and even existence, of the biotechnology industry is undergirded by the availability of gene patents."[165] In her view, the patent system serves a variety of functions as it mediates between "inventors" of genes (and other biotechnological inventions) and markets capable of imbuing genes with economic value.[166] Patents play many valuable roles in support of the biotechnology industry, and confer considerable economic value on the beneficiaries of gene, and gene-based, inventions. Consequently, it would be rational for beneficiaries of the patent system to support the continuing availability of patent protection for gene, and gene-based, inventions by engaging in gene talk.

The acceptance by the patent system of a gene concept that is inaccurately simplified and predictable might even influence gene concepts in the reverse direction as well. The "patent gene concept" might influence biologists to describe, and even think about, genes in a manner consistent with patent availability. The prospect of a patent-derived windfall is ever-present among biologists, especially those involved in medical research. Although there may be other rewards for pursuing biology, such as Mertonian norms of free enquiry and free exchange of ideas, prestige, intellectual challenge, and a sense of importance to society, the possibility of winning the patent-lottery by patenting a lucrative gene may be a significant incentive not to undermine the patentability of genes, even at the expense of debate within the biology community. The biology community may thus possess an incentive to privilege a simple and uncomplicated gene concept not only to the outside world, but also within its own intellectual community, instead of promoting debate about competing gene concepts, or what, if anything, a gene actually is. In short, the "patent gene concept" may also influence how biologists portray and conceive of genes, encouraging them, for example, to emphasize the certainty of knowledge about the gene over the uncertainty.

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164. *See supra* note 129 and related discussion.

165. JASANOFF, *supra* note 145, at 203–04.

166. *Id.*

Biologists and the biotechnology industry may have good reason to avoid publicly trumpeting the failure of the gene concept in public. Although the USPTO does consider genes *per se*—at least when isolated or purified—to be patentable subject matter, it has excluded fragments of genes from patentability.[167] In the early 1990s, the USPTO began to reject patent applications claiming expressed sequence tags ("ESTs").[168]

As defined by the Court of Appeals for the Federal Circuit, "[a]n EST is a short nucleotide sequence that represents a fragment of a cDNA clone."[169] In *In re Fisher*, the Court rejected the patentability of such gene fragments as lacking utility (and enablement) "because Fisher does not identify the function for the underlying protein-encoding genes."[170] If claims to ESTs tend to lack utility and enablement, then so might claims to genes composed of multiple gene fragments. Gene talk can contribute to the solution to this problem by avoiding discussion of the complexities of gene structure, and focusing, instead, on a simple and comfortable, though inaccurate, gene definition.

An influential gene patent case, *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991), may provide additional incentive for biologists and those in the biotechnology industry to engage in protective gene talk. *Amgen* mandates a significant level of detailed knowledge about a gene before a patent claiming the gene can be granted:

> A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to

167. *In re* Fisher, 421 F.3d 1365, 1373 (Fed. Cir. 2005).

168. *See* Leslie Roberts, *Gene Patents: Rumors Fly over Rejection of NIH Claim*, 257 SCIENCE 1855, 1855 (1992) (noting that the USPTO rejected NIH's EST application in an office action dated August 20, 1992).

169. *In re* Fisher, 421 F.3d at 1367.

170. *Id* at 1376.

practice has occurred, *i.e.*, until after the gene has been isolated.[171]

Without gene talk, the standard of description mandated by *Amgen* might be insurmountable for many gene patent applicants. In light of the current understanding of how difficult it is to define a eukaryotic gene, the standard articulated by the court may be unreachable. Patent applicants might be able to isolate mRNA molecules and then reverse transcribe them into cDNAs. However, successfully envisioning "the detailed constitution of a gene" has the potential to become an ever more difficult challenge if gene concepts continue to decay and degrade. Again, gene talk may provide a degree of prophylaxis.

For example, as a consequence of how genes tend to be claimed in patents, the perception may already have grown among biologists that "genes" are synonymous with nucleic acid sequences. The patenting of gene-associated DNA sequences may have altered the perception among both biologists and the public regarding what is, and is not, a gene. Gene talk may even create an incentive among biologists for duplicity; it may encourage them to depict genes inconsistently in scientific publications and patent applications. Differing portrayals of the same gene in related publications and patent applications might encourage patent examiners to doubt the sincerity of gene definitions in patent applications. In addition, such behavior might qualify as inequitable conduct, rendering relevant patents unenforceable.[172]

Not every aspect of genes has been beyond public contention. Indeed, the biology community appears to have failed to persuade the public that patenting genes is socially valuable; in this sense, the gene concept promoted by the biology community has failed to become a generally authoritative view among constituencies outside the biology community. As Jasanoff describes,

> [t]he political controversies surrounding the patenting of DNA sequences in the United States raises [sic] an interesting puzzle. Why did concern surface with regard to these products when equally significant enlargements in the scope of patentability—from nonliving to living matter and from lower to higher organisms—had garnered nothing but praise from U.S. scientists? We must conclude that this

171. *Amgen*, 927 F.2d at 1206 (citation omitted).

172. Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1256 (Fed. Cir. 1997) ("Inequitable conduct resides in the failure to disclose material information with an intent to deceive or mislead the PTO.") (citing J.P. Stevens & Co. v. Lex Tex, Ltd., 747 F.2d 1553, 1559–60 (Fed. Cir. 1984)).

> step more than any previous one created competitive divisions within the very heart of biotechnological research and development.[173]

Yet, even where the gene patent issue has become contentious, it has been concerns over ethics, morality, and free access to genes for research purposes—not any perceived ambiguities or complexities of the gene concept—that have animated the debate. For example, in the vigorous debate surrounding proposed H.R. 977 ("A bill to amend title 35, United States Code, to prohibit the patenting of human genetic material"), little support exists in the legislative history for the proposition that genes should be unpatentable because the gene concept is inaccurate.[174] Despite the influence public acknowledgement of uncertainties surrounding the gene concept might have had on the debate, it is possible that gene talk successfully influenced members of the biology community not to share their internal controversies and debates with outside constituencies that could have interfered with the prospect of receiving valuable gene patents.

V. CONCLUSION

The concept of the gene has evolved rapidly over the last one-hundred years. At various times, gene concepts have emphasized materiality, agency, reproductive capacity, and the ability to direct cells and organisms.[175] In the words of Erwin Schrodinger, the gene is "lawcode and executive power—architect's plan and builder's craft—in one."[176]

Methods of isolating, manipulating, sequencing, and controlling genes formed the foundations of the biotechnology in-

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173. JASANOFF, *supra* note 145, at 224.

174. Genomic Research and Accessibility Act, H.R. 977, 110th Cong. (2007)*; see, e.g.*, *Legislation to Prohibit Human Genetic Patents Proposed in U.S.*, PHG FOUND., Feb. 12, 2005, http://www.phgfoundation.org/news/3148 (pointing out concern that gene patents hinder scientific research); *Bill Seeks to Ban Gene Patents* (National Public Radio radio broadcast Mar. 2, 2007), *available at* www.npr.org/templates/story/story.php?storyId=7689495 (discussing the implications of gene patenting with Stanford Law Professor Robin Feldman, but not discussing potential problems with the gene concept); Sheppard Mullin, *Bill to Prohibit Patents on Nucleic Acid Sequences Presented to U.S. House of Representatives*, INTELLECTUAL PROPERTY LAW BLOG (June 21, 2007), http://www.intellectualpropertylawblog.com/archives/patents-bill-to-prohibit-patents-on-nucleic-acid-sequences-presented-to-us-house-of-representatives.html (discussing motivating factors behind bill, but not mentioning insufficiencies in gene concept.

175. KELLER, *supra* note 21, at 47 (citations omitted).

176. *Id.*

dustry. Gene patents contributed to the growth of the biotechnology industry into a huge and valuable component of the modern economy.

However, the concept of the gene has increasingly been in jeopardy since at least the discovery of introns in the late 1970s. Regardless of the complexity, predictability, definability, or even the actual existence of the gene, gene talk has been, and remains, a powerful form of persuasion. The biology community has relied on vigorous internal debates about gene concepts continually to push back the frontiers of genetics, while the same community has simultaneously used gene talk authoritatively to portray the gene to external constituencies as uncontroversial and relatively simple. Patent applicants, who are typically members of the biology community, also appear to have employed gene talk to assist them in securing patent rights in their gene, or gene-based, inventions.

Gene talk about the particulate materiality and simple predictability of genes may even have subverted the view that members of the biology community have of genes by creating an incentive for patent applicants to view the process of patenting genes—a process rich in institutional and governmental legitimacy—as making the object of a patent—the gene—more substantial and real. Based on the failure of structural concepts of the gene, functional claiming of genes might seem a more fruitful strategy for applicants seeking to patent genes. However, the success of gene talk may have retarded this development.

Gene talk may be a powerful mode of communication and persuasion. It appears to have maintained the view of genes as simple and predictable enough to be patentable long after the biology community broadly lost faith in a single, objective, and relatively uncomplicated gene concept. Thus, gene talk has preserved the prospect of gene patents and their attendant monetary rewards. Given the powerful results of, and the vast authority achieved by, gene talk, it may take much longer to fade in influence than the concept of the gene itself.