Revisiting Isolation as Invention: The Obviousness of Isolated Natural Genes and a New Test for Naturalness

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I. INTRODUCTION

The United States Patent and Trademark Office (PTO) is presently being sued for its practice of issuing patents on isolated but otherwise-natural genes.[2] In this essay I challenge such patents on two distinct but related grounds: obviousness and naturalness. The Supreme Court has held all "human-made inventions" – biological or otherwise – to be patentable, in contrast to "products of nature" which are not.[3] Hence, patentability is well-settled for truly modified genes or engineered organisms, but it is less clear when a substance exists in nature – albeit encumbered by other comingled matter obstructing its access or use. The PTO contends that "isolated and purified" genes are patentable subject matter (not just the means of isolation, or subsequent uses).[4] However, genes do become isolated and purified in the natural course of cells synthesizing proteins via transient structures which are readily extractable and substantially identical to their artificially-reconstituted (and patented) counterparts. Although precedent on the product-of-nature doctrine admittedly makes it an easy barrier to overcome, such precedent uses an inadequate test for naturalness. Additionally, in general when courts have regarded mere isolation as invention, they seem to have implicitly misattributed the ingenuity of certain *methods and processes* to the underlying objects thereof.

I submit that an isolated gene is an obvious variation of – and a distinct element within – a product of nature. The obviousness argument is based on relevant caselaw being applied to a composite of pertinent biological facts. As explained later, the significance of "distinct-element" status requires revising the current approach to the product-of-nature doctrine in a way that I contend would more fully apply its purpose and substance. Either rationale would restrict patents on natural genes to truly modified forms thereof (beyond isolation), and tools and methods for excising, synthesizing, or using them. While policy and economic arguments abound on both sides of this issue, I do not suggest that gene patents are inherently unethical or bad policy[5] – but rather that they do not satisfy certain legal requirements, as properly understood. Nor do I relegate

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[2] Ass'n for Molecular Pathology, et al. v. U.S. Patent & Trademark Office, et al., 09-cv-04515 (S.D.N.Y., filed 2009).

[3] Diamond v. Chakrabarty, 447 U.S. 303, 313 (1980). This case involved a human-modified organism, an attribute explicitly relied upon for permitting the patent.

[4] U.S. Patent & Trademark Office, Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001).

[5] Such views are emphasized by DAVID KOEPSELL, WHO OWNS YOU? THE CORPORATE GOLD RUSH TO PATENT YOUR GENES (2009).

genes to mere abstract data or diminish their physical nature,[6] even while relying on the reality that information storage and transfer are their core functions.

II. PATENT SCOPE

U.S. law deems patentable subject matter to include new articles of manufacture, compositions of matter, machines, processes, or otherwise-eligible changes to these.[7] As noted, products of nature have long been excluded – along with natural principles and phenomena, and abstract (unapplied) theories and formulas.[8] Hence, there should always be a distinction between *new* and newly-identified, newly-located, or newly-understood. An eligible invention or discovery[9] must also be useful, novel, and non-obvious (to a "person of ordinary skill in the art").[10] Applicants must describe and disclose an invention sufficiently to enable a person of ordinary skill in the art to exploit it.[11] When a product or process is eligible but incorporates other patented concepts, it may still be patented, but may not be used without a license from the first patentee.

A patent on an item (product) potentially confers a broader monopoly than a patent on any process for acquiring or utilizing an item. While either must initially show at least one practical use, a patent on the item itself then monopolizes all right to any use[12] of that item whatsoever – even future uses yet unknown. This is eminently legal and fair for an item that never existed before, as the patent system was designed to impart monopolies coextensive with inventors' contributions. It is also reasonable for new means of obtaining or using existing items. But an item itself is hardly inventive when an applicant only reduces to practice something that nature has already conceived, produced, and *even isolated* – just not in a *way* that is as useful as when almost the same result is obtained in a non-natural way.

III. GENES IN CONTEXT

An overview of the relevant biology provides a useful background for such a fact-sensitive obviousness inquiry.[13] DNA is a long double-stranded series of paired bases, with each strand being assembled on a sugar-phosphate backbone and oriented in opposite directions (denoted 5' to 3' and 3' to 5'). The four recurring bases are abbreviated A, G, C, and T, and their sequences and placement constitute the principal source of biological information. For example, a 6-base-long section in one strand could read 5'-GCAGTT-3'. Wherever A or T appears on one strand, the complementary base appears at that point along the opposite strand; likewise for G and C. Hence, along the

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[6] For this kind of argument, see Debra Greenfield, *Intangible or Embodied Information: The Non-Statutory Nature of Human Genetic Material*, 25 SANTA CLARA COMPUTER & HIGH TECH. L.J. 467 (2009).
[7] 35 U.S.C. § 101 (2008).
[8] *See Chakrabarty*, 447 U.S. at 309.
[9] Use of this term need not affect the standards, as inventive applications are often said to be "discovered."
[10] *See* 35 U.S.C. §§ 101-103 (2008).
[11] *See id*. § 112.
[12] *See id*. § 154(a)(1).
[13] For a general overview covering many other related topics as well, see LAWRENCE E. HUNTER, THE PROCESSES OF LIFE: AN INTRODUCTION TO MOLECULAR BIOLOGY (2009).

strand opposite the example given would read 3'-CGTCAA-5'. The human genome totals roughly three billion base-pairs[14] which reside in cell nuclei in complex, dynamic patterns. Diploid organisms (such as humans) receive two of the entire genome – and thus of each gene – with each occurrence of each gene being a copy of one of each respective parent's occurrence of that gene.

A gene is a segment of DNA that encodes for a particular protein; proteins are the vast category of macromolecule collectively responsible for most of the structure and function of cells – and thus ultimately many characteristics of the organism.[15] Whenever a cell decodes a gene to create its corresponding protein, that gene is said to be expressed. Different variations of a given gene among individuals are called alleles; when one or both inherited alleles of a given gene deviate from the "normal" (wild-type) sequence, that gene's expression can be hindered or altered. For example, a person with blue eyes lacks a wild-type allele for the gene causing brown eye color (for either inherited gene). Not every gene gets expressed in every type of cell, or to the same degree or under the same conditions; expression is continuously and dynamically regulated through a vastly complex interactive feedback system only partly understood. For reasons still being elucidated, genes comprise but a small fraction of human DNA. Most DNA is found *between* genes (intergenic regions), and in unexpressed segments *within* genes (introns) between the parts directly coding (exons) for the corresponding protein.

So how do genes become expressed as proteins? A gene is first copied from DNA into a strand of mRNA – another nucleic acid similar to DNA except that (1) it's much shorter, as it's only copying one gene, (2) it's single-stranded, made to be complementary to one of the DNA strands (template strand) and thus similar to the other strand (coding strand), (3) it uses a different sugar for its structural backbone, and (4) it substitutes a new base – U – wherever DNA would use T. None of this keeps mRNA from faithfully mirroring all relevant content, and hence this step is termed "transcription." The next step is for the mRNA to leave the nucleus and travel within the cell to a ribosome. In a process termed "translation," the ribosome converts the mRNA's sequence of bases into a sequence of amino acids, which in turn assembles into a protein.[16] Because there are twenty different amino acids incorporated into nascent protein molecules, the informational equivalence between base and amino acid sequences is looser than the strict one-to-one correspondence between nucleic acids.

After transcription but before translation, it is crucial to note that the cell selectively "splices" the RNA to remove unused segments – that is, it cuts out the introns and joins together the exons.[17] Hence, individual genes naturally become "isolated and purified" from their own introns as well as intergenic regions and entangled proteins – albeit as mRNA, which can then be extracted from the cell for further study and use.[18]

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[14] J. Craig Venter et al., *The Sequence of the Human Genome*, 291 SCIENCE 1304 (2001).
[15] *See generally* ANTHONY J. F. GRIFFITHS ET AL., AN INTRODUCTION TO GENETIC ANALYSIS (7th ed. 2000), *available at* http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=iga.section.60.
[16] Proteins, ESTs, and other biological materials are not addressed here.
[17] A gene notably could be spliced multiple ways to code for different proteins (alternative splicing).
[18] *See supra* note 4 and accompanying text.

IV. ISOLATED GENES: RECONSTITUTED, NOT INVENTED

Genes isolated *in vitro* are typically converted to a more workable form, such as (at first) single-stranded "complementary DNA" (cDNA), a common basis of patent applications. These cDNA versions are made by reverse-transcribing extracted mRNA, often for multiple genes simultaneously before later separating them (after cloning via host-cell culture) via established screening methods. Things facilitating all such steps can indeed be novel and inventive, as can new uses for the genes, but *the cDNA and its sequence differ only trivially from the natural mRNA which is readily isolated and screened*. While there may indeed be painstaking experimental or computational efforts involved with acquiring beneficial understandings of these natural products, the current patent system simply does not reward all intelligent or laborious accomplishments.

I suggest that three colorable grounds exist for invalidating gene patents, and are as follows (in order of increasing strength):[19]

1. Lack of *novelty*, owing to the informational – and ultimately functional – equivalence between extracted mRNA and reverse-transcribed cDNA. However, this seems plausible only by focusing exclusively on genes' status as *information* – as the cDNA structures and literal sequences are technically new. But it should be noted that some gene sequences actually exist in spliced, cDNA form – called retrotransposons – albeit within the intergenic regions of cell DNA.

2. The *product of nature* doctrine, based largely on the same purported equivalences between cDNA and natural DNA/mRNA.[20] Judge Learned Hand's early and since well-accepted test for pre-existing but newly-isolated substances to overcome this doctrine was merely to show material difference "in kind" from the pre-isolated state, as measured solely by the achievement of "new utility."[21] But as subsequently argued, that test alone – when applied not just to methods but to substances – is at best only weakly probative of naturalness. This superficial inquiry seems to conflate the respective analyses of methods and products, albeit perhaps understandably in cases where human ingenuity gives profound new significance to long-existent items. But the distinction must nonetheless be meticulously policed, as rapid advancements can vastly accelerate the consequences of misidentifying means and ends (and which of each are human-made). Below I propose an additional test in determining what constitutes a "product of nature," which if adopted would cause this doctrine to preclude gene patents.

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[19] Utility is not challenged here.

[20] *See* Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 132 (1948) (holding trivial variations upon natural phenomena unpatentable, although it is unclear whether obviousness was an implicit factor). Its applicability to genes is argued by John M. Conley & Roberte Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as Barrier to Biotechnology Patents (Part II)*, 85 J. PAT. & TRADEMARK OFF. SOC'Y (2003).

[21] *See* Parke-Davis & Co. v. H.K. Mulford & Co., 189 F. 95 (C.C.S.D.N.Y. 1911); Merck & Co., Inc. v Olin Mathieson Chem. Corp., 253 F.2d. 156, 164 (4th Cir. 1958). For an analysis contending that Judge Hand had likely misapplied extant precedent, see Richard Seth Gipstein, *The Isolation and Purification Exception to the General Unpatentability of Products of Nature*, 4 COLUM. SCI. & TECH. L. REV. 2 (2003).

3. *Obviousness* of the cDNA produced (and its sequence) *compared to the natural states, in light of contemporaneously available methods coupled with relevant phenomena* like transcription, splicing, mRNA, and nucleic acids. Crucially, the Supreme Court had effectively held non-obviousness to be an inherent requirement of inventorship long before Congress ever codified it.[22] And recently, the Court unanimously reasserted that this inquiry must reflect all relevant facts and circumstances – even "ordinary creativity" and "common sense."[23] Since then, the Federal Circuit has affirmed the importance of chemical structural similarity in relevant obviousness inquiries,[24] as well as whether a sequence is "obvious to try."[25] Finding or characterizing a given gene may be nontrivial, but that should not be rewarded under pretense that the product *itself* is innovative.

V. TOWARD A MORE COMPLETE EVALUATION OF PRODUCT NATURALNESS

More generally, when if ever should "isolating" be deemed inventing? Beyond the noted "difference in kind" test which looks only for "new utility," I further propose that any otherwise-unaltered *distinct element* extracted or reconstituted from a product of nature likewise be deemed a product of nature. By "distinct element" I mean any part whose defining qualities are identifiable solely on the basis of passive, non-causal observation – however challenging such observation might prove to be. In essence, the characteristics motivating its separation/extraction existed prior to (and independently of) it.

As a blatant example, a widget whittled out of a log could clearly be a patentable invention. Although the change is purely subtractive, the selection of which material should and should not remain is substantially attributable to human ingenuity. By contrast, a log's bark is natural – even if stripped off, and even if stripped by novel means or for a novel use – because purely observable, pre-existing features are responsible for its unique identity.[26] With respect to genes, once given adequate *observational* capacity and manipulative *methods* to explore the biological principles described above, the same phenomena rendering their artificially-isolated state *obvious* are also largely responsible for their objective *distinctness*.

As another critique of the isolation-as-invention paradigm, consider that it could require inquiries into certain derivative issues such as how long an isolation must be sustained. For example, natural mRNA occurs dynamically and transiently; when extracted at first it is essentially a frozen "snapshot" of all the mRNA molecules in a cell at a given time. So before this (and subsequent screening) is performed, can we say the gene existed in its isolated state when it would have been so fleeting? Yes, but it shifts

[22] *See* Hotchkiss v. Greenwood, 52 U.S. 248 (1850).
[23] *See* KSR Internat'l Co. v. Teleflex Inc., 550 U.S. 398 (2007).
[24] Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1356-57 (Fed. Cir. 2008).
[25] *See In re* Kubin, 561 F.3d 1351 (Fed. Cir. 2009) (holding that a known protein plus established biotechnology methods rendered the encoding gene obvious).
[26] Michelangelo famously said of his sculptures that they were "locked inside" raw stone and all he had to do was "remove the excess," but despite such humility this distinction – unlike cDNA – did involve human agency.

the focus from purification to prolongation of purification – all the more glaringly a *process* issue. By Judge Hand's incomplete standard, the mere fact that longer or more stable isolation presents "new utility" would seem to compel recognition of it as a *new substance*. No one could deny that briefly-isolated and permanently-isolated items can be "different in kind," particularly when the difference makes new uses possible. But just as with the contrast between pre-isolated and post-isolated elements, any new utility is properly attributed to the methods, processes, and tools for achieving and exploiting such states.

VI. CONCLUSION

The question of whether isolated but otherwise-unaltered genes deserve patent protection presents a dual-slippery-slope dilemma: the sweeping "distinct element" bar proposed above may admittedly hold mistaken some historical patents on newly-isolated items, but a bare "difference in kind" or "new utility" standard could conceivably justify patenting even a (non-synthetic) chemical element. I submit that the former is a more complete conception of the doctrine, which would deny patents on the genes in question because no human ingenuity is specifically involved in determining their material composition or informational content. The current patent system contemplates that grants be coextensive with what is contributed; that certainly includes genetically-engineered organisms and human-altered genes, as well as tools and methods for working with or applying natural genes, but not genes whose defining qualities existed apart from any human conception.

It can well be the case that the same observable phenomena causing a given component of a naturally-occurring item to be objectively distinct will likewise contribute to making the isolated state of said component obvious. Such is true with natural genes, for which observable phenomena combined with naturally-occurring substances and available analytical methods render their structure and content obvious – especially under the rather rigorous obviousness standards that the Supreme Court and Federal Circuit are reasserting.