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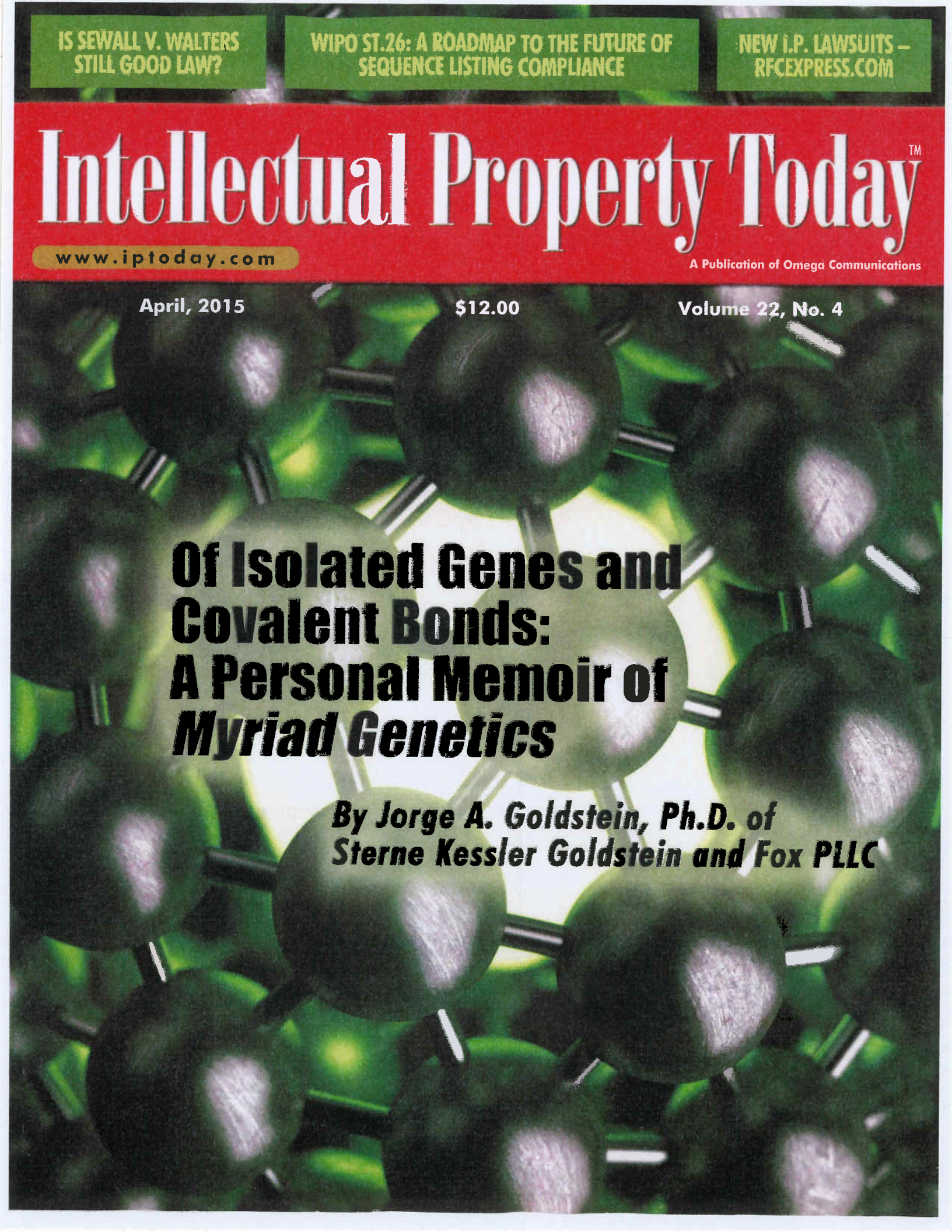
Intellectual Property Today™

www.iptoday.com

A Publication of Omega Communications

April, 2015 $12.00 Volume 22, No. 4



Of Isolated Genes and Covalent Bonds: A Personal Memoir of *Myriad Genetics*

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In 1973, as a young graduate student in organic chemistry at Harvard, influenced by my advisor Frank Westheimer's prescient view that "the future belongs to biology," I took James Watson's introductory course in genetics. Three times a week I left my lab and walked over to the Bio Labs, its entrance flanked by Bessie and Victoria, the two massive rhino sculptures that have stood guard since the 1930s, a time when biology was about big animals and plants, not their genomes and proteomes.

Watson, who twelve years earlier had won the Nobel Prize for his discovery, together with Francis Crick, Rosalind Franklin and others, of the double helix structure of DNA, duly held forth on the biological roles of genes, promoters, and operons. While I was very impressed by my celebrity professor, the class bored me to tears. I was an organic chemist. I didn't think of DNA or RNA as organic chemicals that could be readily manipulated in the lab by making and breaking covalent bonds, the way you could modify a steroid or a prostaglandin molecule. These DNAs and RNAs were information storage elements, and the closest they got to organic chemistry was their polymeric nature, a fact that did not impress me much.

Little did I know that the tension between the views of DNAs as information storage or as organic molecules would be played out dramatically one morning forty years later in the courtroom of the U.S. Supreme Court, with Dr. Watson sitting in the front row of the public gallery and I sitting a few seats beyond him. The case before the court that day was *Association for Molecular Pathology v Myriad Genetics*,[1] and the issue was whether isolated BRCA1 and BRCA2 genes claimed by sequence were patentable subject matter, or whether the mere fact of breaking covalent bonds was not enough to distinguish such isolated gene fragments from their natural counterparts, which were fully integrated into the genome.[2]

The justices and the advocates were discussing patent law, although, listening to the arguments, I easily imagined being back in the Bio Labs in Dr. Watson's class four decades earlier. I had not seen Dr. Watson again since I took his course. He had left Harvard three years later to head the Cold Spring Harbor Lab. I left that same year, a PhD in organic chemistry in my resume, and, after a short stint as a post-doc doing research on enzymes, went to law school and became a biotechnology patent attorney. It was as a patent attorney that I started thinking of isolated DNAs as organic chemical molecules. In this manner I could obtain patents for my clients, who had isolated important genes and wanted to protect and commercialize their use.

For decades, all of us biotech lawyers were convinced that breaking the bonds that held a gene covalently attached to the chromosome turned the fragment into a material that was artificial enough to make it eligible for patents. The US Patent and Trademark Office thought so too and, in the period from the late 1970s, when the modern biotech revolution started, to the early 2010's, when AMP challenged the practice for the first time, it issued thousands of patents on isolated genes. The courts also went along. They routinely evaluated patents on isolated genes, finding fault with them only if they lacked novelty, or non-obviousness, or clarity, or enablement, or written description. The courts never considered that breaking covalent bonds and excising a gene fragment from the chromosome were not enough to make them eligible for patents, or that these were minor steps with no legal significance. I represented many patent challengers who attacked isolated gene patents based on every possible ground of invalidity, except that I never argued that they were natural materials and therefore not eligible. The main reason, of course, was that my clients also held patents on other isolated genes, and they did not fancy rocking the boat of eligibility, lest their own patents fell off.

I confidently wrote or helped obtain patents on many isolated genes, such as those for Huntington's Disease[3] (isolated by Dr. James Gusella), cystic fibrosis[4] (isolated by Drs. Lap-Chee Tsui, Francis Collins, and others) and Parkinson's Disease[5] (isolated by Dr. Nobuyoshi Shimizu). We all thought as organic chemists in those days. DNA molecules were chemicals that could be manipulated. The resulting fragments were chemically different than the identical sequences embedded in long polymers of DNA in nature, and such chemical difference was enough to make the isolated materials eligible for patents. Our biggest champion was Judge Alan Lourie of the U.S. Court of Appeals for the Federal Circuit. A Harvard undergrad, he had received a PhD in organic chemistry from Penn, had been a chemist at Monsanto, then a patent agent at Wyeth, and an in-house patent counsel at Smith Kline Beecham, before he became a federal judge in 1990. He was the ultimate scientist–lawyer. He understood chemistry and his decisions were exemplary for the clarity of his scientific reasoning.

When the patent eligibility of Myriad's BRCA1 and BRCA 2 isolated genes was first challenged by AMP in 2010, Judge Robert Sweet of the Southern District of New York, to my shock (and that of most of my peers in the profession), ruled that AMP was correct and that such isolated genes were not eligible for patents.[6] To our collective astonishment, Judge Sweet said that, as a matter of law, breaking bonds does not make any difference. With a fair amount of snobbishness I remember thinking, He does not understand chemistry; just wait until Judge Lourie sets him straight. And Lourie did not disappoint. In 2012, on appeal from Judge Sweet's holding, the Court of Appeals, in a split 2-1 decision written by Judge Lourie, provided a master class in organic chemistry.[7] Lourie made the existence of covalent bonds the scientific centerpiece of his legal reasoning:

> Isolated DNA has been cleaved (i.e., had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule.
>
> *** BRCA1 and BRCA2 in their isolated states are different molecules from DNA that exists in the body; isolated DNA results from human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA, imparting on that

isolated DNA a distinctive chemical identity as compared to native DNA.

*** In this case, the claimed isolated DNA molecules do not exist in nature within a physical mixture to be purified. They have to be chemically cleaved from their native chemical combination with other genetic materials. In other words, in nature, the claimed isolated DNAs are covalently bonded to such other materials. Thus, when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity that is obtained by human intervention.[8]

When Judge Bryson dissented in part from Lourie's opinion, Judge Lourie, no doubt recalling the organic chemistry he had learned at Harvard (probably from Frank Westheimer, my own advisor) responded with more chemistry:

The dissent disparages the significance of a "chemical bond," presumably meaning a covalent bond, in distinguishing structurally between one molecular species and another. But a covalent bond is the defining boundary between one molecule and another...[9]

I loved it. DNA was a chemical, and covalently unmoored pieces of it were not products of nature. They were man-made and patent-eligible. The covalent bond stood supreme. Judge Lourie understood it and explained it for the ages.

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Except the ages did not last more than a year. The case was immediately appealed to the Supreme Court and, in 2013, the morning of the oral hearing, I found myself in the courtroom sitting half a bench away from my old genetics professor. Coincidentally I was also sitting next to a distinguished older gentleman whom I did not recognize. Since we were bound to wait another hour or so before the start of the proceedings, I decided to introduce myself and start a conversation.

"Good morning," he smiled. "Very nice to meet you. I am Judge Robert Sweet, of the Federal District Court in New York." Oh my god! I thought. I am sitting next to the very Judge who wrote the 2010 opinion in favor of AMP, holding that isolated genes are not eligible for patents! I better not tell him that I thought he knew no chemistry. "I flew down from New York bright and early this morning," he continued. His excitement was contagious.

"Do you think that you will be redeemed today?" I asked.

"Sure hope so. I knew that we would be here one day, and I wrote my opinion with that in mind. I wouldn't want to miss this day for anything in the world."

By then, almost 50 parties (in addition to the two principals in the case) had filed *amici* briefs, as friends of the court. Among them were many law professors, scientists, lawyers, public interest advocates, and professional associations backing one side or the other. The academicians expounded on the dual nature of DNA: It is both a molecule *and* a storage information unit, they said, and this has generated confusion in the case. One of them even pronounced rather glibly that the whole problem was that Judge Lourie had confused science with law; there is nothing legally special about breaking covalent bonds.[10] I had also read Dr. Watson's *amicus* brief, who focused on the unique nature of DNA. As in 1973, he was fully on the side of function and information, and minimized the view of DNA as a chemical entity:

[T]he opinions by the appeals court miss the fundamentally unique nature of the human gene. Simply put, no other molecule can store the information necessary to create and propagate human life the way human DNA does. It is a chemical entity, but DNA's importance flows from its ability to encode and transmit the instructions for creating a human being. *** [H]uman genes are much more than chemical compounds. ***A human gene's patentability cannot depend simply on whether a covalent bond is broken during purification.[11]

Reluctantly, by the morning of the hearing I had already come around to believe that the Supreme Court would reverse the Court of Appeals, rule against Myriad Genetics, and hold that isolated genes were not eligible for patents. A few months earlier I had given a lecture on the case at the University of Pennsylvania law school. In preparing for the lecture I read most of the 50 or so *amici* briefs. I also was keenly aware that, in recent years, the Supreme Court had been on a streak, predictably reversing the Court of Appeals in patent cases. So, I told the Penn Law class that if I were on the Supreme Court I would hold, along the lines of my hero Judge Lourie, that isolated genes are chemical compounds and patent-eligible. However (in hedging my bet) I also predicted that the Court would reverse. It was a win-win for me, and the students laughed along.

Half of me was right, of course. The Supreme Court held that the mere breaking of covalent bonds is not enough for isolated genes to be legally "man-made."[12] My opinion that the case should have gone the other way is irrelevant. This is now the law of the land.

When I took Dr. Watson's course 40 years earlier I had complained that genetics was insufficiently chemical, yet that was the very point that convinced the Supreme Court. To them, as for Dr. Watson, DNA was storage for biological information. My advisor Westheimer had also been right: the future (even the legal future) did belong to biology. Judge Sweet had been redeemed. And sadly, my hero Judge Lourie had been wrong. The Supreme Court told him - told all of us – that we shouldn't confuse chemical novelty with patent eligibility; they are two different legal concepts. An isolated gene fragment, while a novel chemical compound, is not necessarily eligible. This is now a fundamental lesson in patent law.

I too had forgotten that my background as a scientist, while helpful to inform and educate my views, should not necessarily control when venturing the outcome of legal debates. As I always tell my associates and students, the law is part logical reasoning and part public policy – and too much emphasis on one or the other risks leading you astray.

And what about all of those dozens of patents on isolated genes that I had written and so successfully defended in years past? I am reminded of an apocryphal story about Abraham Lincoln as a practicing lawyer in the courts of Illinois in the 19th Century. Lore has it that one morning, Lincoln argued a contract case before the State Supreme Court and, before the court broke for lunch, won a decision for his client. In the afternoon, in arguing a different case, this time for the other side of a similar contract dispute, he took an opposite position than the one that had proven successful in the morning. The Judges were taken aback.

"But Mr. Lincoln," one judge said. "This morning you argued the exact opposite."

"Yes, your Honor," responded Honest Abe. "But this morning I was wrong."

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Undeterred by their Supreme Court loss, Myriad Genetics went back to federal court a few months later, this time in Salt Lake City, and sued seven companies for patent infringement, based on almost twenty patents that had not been clearly vanquished by the 2013 decision.[13] By then, however, the tide had turned. I was on the other side of their renewed battle, as the attorney for one of the seven companies. I joined in the attack of Myriad Genetics' patents as no longer eligible. Isolated gene fragments, in whatever guise, were nothing but products of nature, I argued, echoing Dr. Watson. Federal Judge Robert Shelby agreed, and the Court of Appeals affirmed his decision that Myriad's remaining patents would not likely survive our collective challenges.[14] Myriad then settled with all seven companies, and the isolated gene battles ended at last. IPT

ENDNOTES

1. *Ass'n for Molecular Pathology v Myriad*, 133 S. Ct. 2107 – Supreme Court 2013.
2. Neither I nor my firm played any role as lawyers for any party or *amici* in the case.
3. U.S. Patent 5,686,288
4. U.S. Patent 6,984,487
5. U.S. Patent 6,716,621
6. *Ass'n for Molecular Pathology v USPTO*, 702 F.Supp.2d 181-Dist. Court, SD New York, 2010
7. *Ass'n for Molecular Pathology v USPTO*, 689 F.3d 1303 – Court of Appeals, Federal Circuit, 2012
8. *Id.*, at pp. 1328-1329
9. *Id.*, at p. 1329
10. *Amici Curiae* Brief for Academics in Law, Medicine, Health Policy and Clinical Genetics in Support of Neither Party, October 26, 2012.
11. Brief of James D Watson, Ph.D. as *Amicus Curiae* in Support of Neither Party, January 31, 2013, p.12
12. See Note 1.
13. *In Re: BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation* 2:14-md-02510-RJS
14. *In Re BRCA1-and BRCA2-Based Hereditary Cancer Test Patent Litigation*, No. 2014-1361 (Fed. Cir. Dec. 17, 2014) (Judge Lourie was not part of the panel that decided this case.)