On Slicing an Obvious Salami Thinly

science, patent case law, and the fate of the early biotech sector in the making of EPO

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ABSTRACT This essay reconstructs in previously unavailable detail the 1980s race to clone and market what would be biotechnology's most important product to date, erythropoietin or EPO. The scientific contest continued into the U.S. courts, which were charged with deciding competing patent claims to the natural substance as a drug. Through case law in the new domain of recombinant DNA, the courts imposed a de facto policy that shaped the business and scientific environment of small biotechnology firms so as to narrow research efforts and assimilate the sector to the established pharmaceutical industry. However, alternative dispensations in patent law were possible at the time, and the public's interest might have been better served.

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There was a time, in the late 1970s and 1980s, when great feats were expected of recombinant DNA biotechnology, some verging on the miraculous. According to both business enthusiasts and sober analysts like the U.S. Congressional Office of Technology Assessment, the new techniques of gene splicing would not only lift the drug industry out of its deep scientific and economic rut (characterized by long-declining introduction rates of genuinely novel medicines), but rejuvenate the American manufacturing sector (Chase 1979; *Chemical Week* 1987; OTA 1984). Once freed by policy interventions to promote academic-industry collaboration, such as the 1980 Bayh-Dole Act, life-saving drugs locked up in ivory towers would revolutionize medicine. Universities and university biologists also expected to benefit, through generous funding from the private sector that would fuel important new science (Etzkowitz 1983; Kenney 1986; Mowery et al. 2001; Popp Berman 2012). The quick resolution of regulatory debate over recombinant DNA safety was driven largely by the overlapping interests of academic institutions and government in realizing such potential benefits (Gottweiss 1998; Krimsky 1984; Wright 1994). And the idea that fundamental research in the biological sciences could be commercially rewarding was encouraged by the U.S. patent system, for example through the broad and fundamental Cohen-Boyer gene-splicing method patent awarded to Stanford in 1980—the first from a backlog of 100 applications on recombinant inventions that had accumulated while the Patent Office awaited the Supreme Court's Chakrabarty decision establishing the patentability of genetically engineered organisms (Hughes 2001; Kevles 1994; *Wall Street Journal* 1980).

On the heels of Genentech's legendary stock float in October that same year, investment flooded into biotechnology (Hughes 2011; Teitelman 1989). The handful of existing firms, like Cetus and Biogen, were quickly joined by a crowd of newcomers. Some, like the Stanford spinoff DNAX, seem to have been conceived and sold to investors as "think tanks," where top scientists would pursue cutting-edge basic molecular biology, and whose only products would be knowledge and patented, licensable techniques (*Business Week* 1984; Kornberg 1995). Others concentrated on the race to clone the low-hanging fruit—well-characterized natural proteins with potentially useful physiological activity—that would become the first-generation recombinant drugs. Nearly all the firms boasted a quasi-academic atmosphere to the young molecular biologists they vied to recruit, a place where they could pursue the same curiosity-driven projects as they would on the academic career path, but with better resources and no teaching demands (Hughes 2011; Rasmussen, n.d.).

This essay is about these early halcyon days of biotechnology, when there seemed no necessary clash between the demands of fundamental life science and those of commerce. It is therefore about what Swanson (2007) calls the foundational "mythology" of biotech, a characterization I embrace on the understanding that this notion— that important basic life science could be pursued profitably, and in small independent biotech firms—was a belief that informed not

only the career decisions of scientists, but also the business decisions of managers in their firms and the investment decisions of their backers. So like many myths, this one was to some extent self-fulfilling: true, so long as the basic beliefs were widely shared. Here I will reconstruct the early 1980s race to clone and commercialize what would later become the biotechnology sector's biggest product: erythropoietin or "EPO," the red blood cell–boosting hormone. I then follow that cloning contest into the courts, which I treat as an arena where different interest groups and factions vie to establish what society's rules should be, in order to assess the policy implicit in the courts' decisions and also its consequences (Jasanoff 1997, 2005).

Much existing scholarship addresses the way in which U.S. lawmakers and courts acted in concert with scientists to encourage the patenting and commercialization of academic biology in the years around 1980 (Jasanoff 1997; Kevles, 1994; Wright 1994). Here I explore the particular kinds of commercial life-science research encouraged by the U.S. federal courts through their interpretation of patent law. In brief, I argue that in the EPO litigation, the courts established case law that acted as an unheralded but powerful policy instrument to close the mythic golden age of privately funded basic biology, by incentivizing comparatively uninnovative, incremental, or "salami-slicing" research. Speaking metaphorically, this is a tale about how judges ended the blue-sky era and the garden of scientific delights that characterized early science-driven biotech firms, and replaced them with the fluorescent lights and cubicles of big pharma.

PITFALLS OF THE SECRET SEQUENCE

Genetics Institute was certainly one of the paradigmatic blue-sky firms of early biotech. In 1980, Harvard's President Derek Bok, annoyed by the way Nobelist Wally Gilbert had started the Biogen firm under Harvard's roof without financially involving the university, decided he wanted his own company. Bok arranged for financing from Harvard's endowment managers and asked the as yet commercially unsigned, star molecular biologist Mark Ptashne to organize the science, but Harvard's professoriat balked and scotched the plan. However, the scheme took on a life of its own. Ptashne had lured his one-time postdoctoral fellow and cloning wunderkind Tom Maniatis back from Caltech to a Harvard professorship, and alternate financing was easily found in the Rockefeller family investment managers. In early 1981, the firm began hiring young scientists from the best labs to do the actual work (Hilts 1980; Sanger 1982).[1]

Another major player was a firm across the continent, organized by venture capitalists hoping to retrace the Genentech road to riches. Although Applied Molecular Genetics—soon, Amgen—would not have its own facilities until late 1981, by January that year the firm was already working on cloning EPO. Cal-

[1] Author interview with Tom Maniatis, Nov. 2010.

tech Professor Leroy Hood, an early recruit to the scientific board, had obtained a small but pure sample of the rare red blood cell–stimulating hormone prepared by the leading American EPO expert, biochemist Eugene Goldwasser of the University of Chicago. Goldwasser had thrown his lot in with Amgen as a special consultant and began attending scientific board meetings in the third quarter of 1980, shortly after rejecting overtures from Biogen. At the time, Hood was putting the finishing touches on an instrument he was developing with the Applied Biosystems firm, the gas-phase protein micro-sequencer or sequenator, which could determine the amino acid sequence of heretofore impossibly small samples of protein (Goldwasser 1996; Hewick et al. 1981; Miyake, Kung, and Goldwasser 1977; Rasmussen, n.d; Rathmann 1991).

Around the end of December 1980, Rodney Hewick, a protein chemist from England collaborating with Hood in the sequenator project, fed a tiny sample of Goldwasser's EPO protein into the machine. To everyone's surprise, he obtained a reading on the first 26 amino acids. As Hewick later recalled in court, the reaction was "helter skelter; there were people running around and a lot of different people that I hadn't seen before. And, basically, the raw data that I generated was taken away from me." These were given, along with the rest of Goldwasser's sample, to Carlton Paul, a protein chemist who was Amgen's first scientist employee, working in rented Caltech lab space. Hewick had been unaware of EPO's potential value, but the helter-skelter reaction was telling, so he wrote down his sequence before surrendering his lab notebooks. Further reactions would have encouraged him to keep it close to his chest. David Golde, a UCLA hematologist collaborating with Genentech at the time, joked to another scientist: "He is the guy that got amino acid sequence; shall we inject him with something" to make him talk?[2]

Erythropoietin was an attractive target for cloning and commercial drug development because it was a known protein that had been studied fairly extensively biologically, although its biochemical characterization was incomplete. It was a low-hanging fruit with obvious promise as a potential drug, but it also offered intellectual problems whose solution would bring scientific credit. Since the turn of the 20th century, physiological experiments had suggested that a hormone might be responsible for animals' blood-making response to high altitudes. In the 1950s, Yale physiologists proved the hormone's existence: something in blood plasma from anemic rabbits raised red blood cell counts in nor-

[2]Author interview with Daniel Vapnek, Jan. 2012; Deposition of Carlton Paul, 18 May 1989, designated Deposition Transcripts and Summaries; Testimony of Rodney Hewick, 23 Aug. 1989, Transcripts vol. 11, pp. 30–32; sequence entry in Hewick Lab notebook of March 1984, p. 20, Plaintiff's Exhibit 588, attached to Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law, vol. 7, XI–2; all in records of Amgen v Chugai and Genetics Institute, C.A. No. 87-2617-Y (Mass. Dist.) and associated countersuits and appeals, Accession AAC1-10743596, NARA Federal Records Storage Facility, Waltham, Massachusetts (hereafter, Amgen v Chugai files).

mal rabbits (Erslev 1993). In the Chicago laboratory of Leon Jacobson, who studied radiation sickness and recovery with funding from the Atomic Energy Commission and the NIH, the circulating hormone was traced to the kidney, and Jacobson's student Goldwasser made the pursuit of this hormone ("erythropoietin," meaning "creator of red blood cells") the focus of his career. The biochemist had partly purified and crudely characterized the hormone from sheep blood by about 1970, and then in the early 1970s extended this work with human erythropoietin obtained from the urine of anemic patients, collected on a large scale by Japanese collaborators (Jacobson et al. 1957; Goldwasser 1996; Goldwasser and Kung 1971; Miyake, Kung, and Goldwasser 1977).

The NIH then began sourcing large quantities of anemic human urine from these Japanese researchers, which was purified in Goldwasser's lab both for his own and other NIH-supported biochemical research, and also for biological and clinical work on the hormone, including small-scale clinical trials with anemic patients (Goldwasser 1996; Rasmussen, n.d.). Thus in the late 1970s, erythropoietin was already well on its way to becoming a drug, the chief obstacle being its mode of production: the cost, limited purity, and very limited supply of the hormone from human urine. As we will later see, it was widely assumed that whoever cloned the EPO gene first, and used that human DNA to produce EPO protein from engineered cells, would gain a monopoly on a highly saleable drug. This expectation attracted investment.

In April 1981, Hewick brought his knowledge of EPO to Genetics Institute in Boston, and a year later efforts to clone the gene based on that 26-residue sequence commenced, just as they had at Amgen a little earlier. The method both firms would use was newly introduced by Keiichi Itakura and associates at the City of Hope Medical Center near Los Angeles. When the DNA sequence encoding a protein was entirely unknown, and it also was not possible to obtain messenger RNA known to encode the protein, one could not use such unique DNA or RNA as a "probe"—to hybridize with and thus identify matching sequence in a so-called "library" of diverse, isolated gene fragments made either from cloned chromosome fragments or from cDNA (reverse-transcribed mRNA). However, the City of Hope group had shown that with some partial amino acid sequences from the protein in hand, strings of synthetic DNA encoding that sequence could be constructed and used as a probe to retrieve the gene from a library. This was a difficult feat because of the many-to-one relationship between triplets of DNA sequence and most amino acids. The greater the number of possible DNA sequences specifying a particular segment of protein sequence, the higher is that segment's "degeneracy" and the more problematic its use as a basis for synthetic probe. For example, a probe set based on a sequence of three twofold degenerate amino acids would have to include eight (2 X 2 X 2) different synthetic nine-base nucleotide oligomers, or nonamers, to cover all possibilities. Replacing one of those twofold degenerate amino acids

with sixfold-degenerate leucine, arginine, or serine brings the required number of different oligonucleotides in the set to 24 (6 X 2 X 2) nonamers. Furthermore, nine bases was too short: Itakura's team had demonstrated the technique by cloning a low-abundance cDNA that used two synthetic DNA probe sets, the larger one consisting of 24 15-mers (Suggs et al. 1981). Nobody had yet used the synthetic probe technique to find clones in a genomic library, which at the time meant identifying one out of 1 million lambda viruses carrying random pieces of the human genome (Lawn et al. 1978; Maniatis, Fritsch, and Sambrook 1982; Maniatis et al. 1978).

So when Fu Kuen Lin became roughly Amgen's seventh scientist in the fourth quarter of 1981, and shortly after took on the project of cloning EPO, he was not alone in that ambition. Despite Paul's efforts, the firm still had nothing more than Hewick's sequence of 26 amino acids, only one-eighth of the protein. As a basis for probe design, the Hewick sequence presented a daunting challenge. It contained no fewer than eight of the dreaded sixfold-degenerate amino acids, and no undegenerate tryptophans or methionines. Further, it contained errors at positions 7—suspected by Hewick—and also 24. Lin avoided the first section, thanks presumably to awareness of Hewick's (or Paul's) doubts. His first probe set was a single long 20-mer spanning amino acids 20 to 26. There were 48 different 20-mers in this first probe set, only a quarter of the "fully degenerate" set of 192 needed to fully cover all possible combinations. He soon ordered more probe sets, but they were not fully degenerate either, with one exception. This January 1982 effort with a fully degenerate (32-member) 14-mer probe set, from the five amino acid stretch in positions 18 to 22, must have discouraged him with its very high background noise. For the rest of 1982, Lin's approach was to order probes containing small subsets from segments spanning amino acids 20 to 26, varying the conditions of hybridization so that his "guessmers" would still stick to the EPO gene even if slightly mismatched (Table 1). Given that five of the six probe sets used by Lin between September 1981 and July 1982 embraced the erroneous amino acid 24, there is no surprise that none of the clones he recovered turned out to be EPO. By the end of 1982 Amgen CEO George Rathmann and research director Daniel Vapnek rated the EPO project as a "disappointment" and "dead"—unfruitful compared with projects started much later.[3]

By this stage, teams at both Genentech and Biogen also had made indepen-

[3]Lin to Caruthers, 24 Sept. 1981, Defendants' Exhibit 626; Lin Probe chart, Defendants' Exhibit 750; Rathmann meeting notes of Dec. 1982, Defendants' Exhibit 225, all attached to Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law; Lin testimony, 11 Aug. 1989, Transcripts vol. 4, pp. 58–59; Lin testimony, 14 Aug. 1989, vol. 5, pp. 102, 110–13; Lin testimony, 15 Aug. 1989, Transcripts vol. 6, pp. 34, 128–29; Lin testimony of 16 Aug. 1989, Transcripts vol. 7, pp. 12, 17, 67; all in Amgen v Chugai files.

TABLE 1 DATES AND CHARACTERISTICS OF SYNTHETIC DNA PROBE SETS ORDERED BY AMGEN (LIN) AND GENETICS INSTITUTE (FRITSCH) SCIENTISTS

Scientist	*Date ordered*	*Epo AA positions*	*Size*	*Oligomers/ full set*	*Fully degenerate?*
Lin	Sep-81	20-26	20mer	48/192	no
Lin	Jan-82	18-22	14mer	32/32	yes
Lin	Feb-82	20-26	20mer	48/192	no
Lin	Feb-82	20-26	20mer	16/192	no
Lin	Mar-82	20-26	20mer	8/192	no
Lin	Jul-82	20-26	20mer	1/192	no
Lin	Jul-82	19-25	20mer	4/256	no
Fritsch	Sep-82	18-24	19mer	256/256	yes
Fritsch	Sep-82	22-26	14mer	48/48	yes
Fritsch	Sep-82	18-22	14mer	32/32	yes
Lin	Apr-83*	62-67	17mer	64/64	yes
Lin	Sep-83	86-91	17mer	128/128	yes
Lin	Sep-83	46-52	20mer	128/128	yes
Lin	Sep-83	18-23	17mer	128/128	yes
Fritsch	Apr-84	144-150	14mer	96/96	yes
Fritsch	Apr-84	46-52	17mer	32/32	yes
Fritsch	Apr-84	46-52	17mer	128/128	yes

*Lin's April 1983 probe set was never used for screening due to low specificity; all others were used within one month of synthesis request.

dent, concerted efforts to clone EPO by other means. Biogen scientists began trying to clone EPO in the second half of 1981 using what can be called the competition strategy. Here, mRNA is obtained from a tissue expressing EPO and also mRNA from the same tissue not expressing it. At its Geneva labs, Biogen used kidneys from healthy rats and rats made anemic with chemical treatment, while in a parallel cloning effort at the Boston lab, the firm used baboons as kidney mRNA sources. The healthy animals' mRNA was used to subtract away the irrelevant sequences from the anemic mRNA "competitively," for instance by immobilizing double-stranded cDNA prepared from healthy mRNA on a surface and allowing cDNA made from anemic mRNA to hybridize, thus leaving in solution those sequences expressed specifically in anemia. After such an enrichment procedure, cDNA clones made from the anemia-specific message had to be screened to determine whether they were EPO. Biogen scientists at first employed bioassay for this purpose. Pools of anemic cDNA clones were immobilized on filters and allowed to hybridize with mRNA prepared from anemic kidney. Then retained RNA was translated into protein in a cell-free system, and the translation product subjected to a bioassay such as rat bone marrow proliferation. If any pool of clones tested positive for EPO activity, the pool was subdivided and reassayed until the one clone specifically retaining EPO mRNA was

identified. Over about a year during 1981 to 1982, Biogen scientists found no EPO clones by this laborious screening procedure.[4]

Meanwhile, at Genentech Axel Ullrich, one of the University of California postdoctoral scientists who cloned insulin into an unapproved vector (Hall 1987), was employing another approach that did not depend on knowing the EPO gene's or protein's sequence: "differential screening." In this strategy, a large set of cDNA clones would be made from EPO-expressing cells; in Genentech's case, these were came from anemic mouse kidneys. To identify clones of the genes expressed strictly in anemic kidney—which, again, would include EPO—radioactive mRNA was prepared from both anemic and normal kidneys. These two preparations were used as probes with duplicate filter papers bearing spots representing transformed bacteria; clones carrying anemia-specific genes would hybridize only with the anemia RNA probe, but not the normal RNA (Maniatis, Fritsch, and Sambrook 1982). Essentially this same procedure was used simultaneously in Genentech by David Goeddell, as part of his successful screening strategy for cloning interferons (Goeddel et al. 1980). (It is unclear how the Genentech team intended to identify the EPO gene among their anemia-specific clones; perhaps by bioassay in cultured bone marrow.) Ullrich commenced his work in mid-1981 and continued until the end of 1982, when a false rumor that Amgen had succeeded in cloning EPO convinced Genentech to drop the project.[5]

Despite hearing the same rumor, Biogen pressed on, ultimately devoting four years, $6 million, and half a dozen PhD scientists (each aided by several technicians) to the EPO cloning project at both their Geneva and Boston facilities. A second push for Biogen began with what seemed a lucky break in December 1981, when at a hematology conference Goldwasser showed a slide displaying Hewick's sequence from the EPO protein. Before he changed slides, two Biogen-affiliated scientists in the audience hastily scribbled it down from either end, not quite meeting in the middle. Biogen used the sequence as a basis for probe design, just like Amgen and Genetics Institute. On hearing of Goldwasser's talk and suspecting such consequences, Amgen's chief executive Rathmann scolded the Chicago professor for his "fundamental mistake in collaboration," but Goldwasser's open scientific communication may ultimately have benefited Amgen, since it shared the pitfalls of the Hewick sequence with the firm's rivals. When Biogen scientists failed to retrieve any EPO clones by screening with large synthetic probe sets based on that sequence, for the same reasons the others failed,

[4] Author interview with Julian Davies, Oct. 2011; Testimony of Dr Julian Davies, 17 Aug. 1989, Transcripts vol. 8, pp. 18–44, Amgen v Chugai files.

[5] Testimony of Dr. Axel Ullrich, 16 Aug. 1989, Transcripts vol. 7, pp. 12, 17, 67; Eugene Goldwasser, deposition transcript (with summaries) from ITC hearings, 17 June 1988, pp. 59–61, 217–18; both in Amgen v Chugai files.

the firm was forced to attempt its own large-scale purification of EPO from urine. When that too failed, in late 1983 Biogen purchased a large quantity of partly purified urinary EPO at great expense from Green Cross, one of the largest producers of blood products in Japan. In the end, they wound up cloning a different urinary protein.[6] More and better EPO protein to sequence was the decisive factor in this cloning race, as we shall soon see.

Meanwhile, at Genetics Institute the EPO cloning effort did not begin in earnest until the third quarter of 1982, once Maniatis's old post-doc Ed Fritsch—co-inventor of the Maniatis genomic library he and Lin were both screening for EPO—joined the firm and talked to Hewick. The first synthetic probes Fritsch ordered were three fully redundant sets from the Hewick sequence, all from the segment between amino acids 18 and 26 (see Table 1). In October, Fritsch screened his genomic phage library with two of the probe sets, becoming the first among the competitors to use two large fully redundant probe sets, one of 256 19-mers from amino acid positions 18 to 24, and the other of 48 14-mers from positions 22 to 26. None of the clones that hybridized with both probes turned out to be the EPO gene—unsurprisingly, because of the same error at position 24 in the Hewick sequence that bedevilled Lin. Fritsch had no better luck in January 1983 with a third probe set of 32 14-mers, even though they came from error-free positions 18 to 22, because he had to determine which of the clones testing positive were EPO by a second hybridization with one of the other two erroneous probes. In late 1982, Genetics Institute approached Takaji Miyake, Goldwasser's onetime collaborator and a skilled producer of urinary EPO, for a quantity of pure protein in order to get additional sequence for probe construction, but management decided that the price was too high.[7] So by early 1983, Genetics Institute was as stumped as the Biogen and Amgen teams using essentially the same approach.

Back to the Source

Amgen research managers decided that to resuscitate the "dead" project, they had to pry more EPO protein from Goldwasser so they could design probe from elsewhere in the protein. In December 1982, product development chief Nowell Stebbing wrote the Chicago professor a stern letter. Stebbing reminded him that Amgen expected that the $30,000 given annually to his lab would "provide

[6]Davies interview; Goldwasser ITC Deposition, pp. 14 and 16; Davies testimony, vol. 8, pp. 21–44; Testimony of Dr. Richard Flavell, 27 Sept. 1989, Transcripts vol. 27, pp. 16–18, 96–97, in Amgen v Chugai files.

[7]Author interview with Edward Fritsch, May 2011; Fritsch probe chart, Defendants' Exhibit 886, attached to Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law, II-35. Testimony of Edward Fritsch, 26 Sept. 1989, Transcripts vol. 26, pp. 34–35; both in Amgen v Chugai files.

reagents which are critical to our program," especially "purified EPO." While Goldwasser had good reason to be stingy, in that he needed his limited supply of pure EPO for his own biochemical studies on the protein (as Amgen understood), Goldwasser had not been totally unforthcoming.[8] In April 1982, he sent some pure EPO, but Paul got nothing from it. In June, Goldwasser sent another batch, previously digested into 15 fragments with the enzyme trypsin (a standard method) and isolated in his Chicago lab. Paul again was unable to obtain usable, uninterrupted protein sequence from the first four fragments that he attempted. Then in early December, Paul at last obtained a sequence of six continuous amino acids from another of the June fragments, covering positions 77 to 82, but it was far too degenerate to use. Since it contained two of the dreaded leucines and three fourfold-degenerate amino acids, a set of 4,608 different 18-base oligonucleotides would have to be synthesized to cover all possible sequences encoding it. After Stebbing's letter, frustration continued at Amgen. In February 1983, Goldwasser sent another batch of EPO fragments, and these were sequenced by Por Lai, Amgen's new protein chemist. In April, Lin ordered his first set of synthetic probes based on protein sequence from one of these fragments, a fully degenerate set of 64 17-mers covering positions 62 to 67 (Table 1). But this time Lin tested the probe set first, checking if it would hybridize preferentially with any band on a gel separating anemic monkey kidney mRNA by size (a "Northern blot"). In May it failed this test and was not used for screening.[9]

So Amgen wanted still more high-purity EPO. In July or August 1983, a delegation of Amgen scientists visited Chicago and discovered that Goldwasser had a bigger supply than he had protested. Somehow "loosened up," Goldwasser soon sent a larger batch, and by September Lin had already requested a synthetic probe based on fresh sequence information, a fully degenerate set of 128 20-mers covering amino acids 46 to 52. Two weeks later, Lin requested another new fully degenerate probe set, 128 17-mers covering amino acids 86 to 91, based on another fragment of the fresh sample. This probe passed the monkey Northern test for specificity. By the second week of October, Lin had screened his genomic library and recovered 24 clones that hybridized strongly with both probe sets, and by the end of the month chose four clones for DNA sequencing. In early November, DNA sequence from two of the genomic clones was found to

[8]Stebbing to Goldwasser, 2 Dec. 1982, Defendants' Exhibit 407, attached to Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law, II-91; Amgen v Chugai files. Sally Hughes interview with George Rathmann, Oct. 2003, pp. 64–65, available at Regional Oral History collection of the University of California, Bancroft Library, Berkeley (http://bancroft. berkeley.edu/ROHO/projects/biosci/oh_list.html).

[9]Lin Probe chart; Testimony of FK Lin, 11 Aug. 1989, Transcripts vol. 4, pp. 58–59; 14 Aug. 14 1989, Transcripts vol. 5, pp. 111–21; and 15 Aug. 151989, Transcripts vol. 6, pp. 24–25, 34; FK Lin, Request form for oligonucleotides, 26 April 1983, Defendants' Exhibit 629–39, attached to Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law, II-92; all in Amgen v Chugai files.

agree with protein sequences from EPO. On December 13, 1983, Amgen filed a U.S. patent on DNA encoding EPO in Lin's name, and soon after it issued a vaguely worded announcement of its cloning success. So less than two months after Goldwasser's new and more generous protein shipment, Amgen had their genomic EPO clones. It is hard to dispute that Goldwasser's contribution was what made Amgen the winner. Indeed, between 1981 and 1983, Amgen consumed 5–10% of the U.S. supply of high-purity EPO, which all passed through Goldwasser's lab—and technically belonged to the NIH. (There was no very strict accounting scheme, however, matching the amount of purified EPO prepared by Goldwasser for the NIH to the quantities distributed by the NIH panel that determined which researchers should have access to it).[10]

While Amgen hastily moved their cloned genomic sequence into hamster cells for scaled-up production, rather than wait to clone a human cDNA, Genetics Institute returned to the pursuit of EPO with funding from Japanese drugmaker Chugai. The Amgen announcement was too vague to assess its veracity, Genetics Institute convinced Chugai, and furthermore it was not followed closely by a publication in *Science* or *Nature* proving the accomplishment in the quasi-academic style pioneered by Genentech (Hughes 2011). Besides, Chugai considered a legal "war" warranted by the "mountain of treasure" (as one Japanese executive put it, a year later) that would go to the firm that marketed EPO as a drug. This time Genetics Institute struck a bargain with Miyake to supply some pure EPO, the first batch of which arrived in April 1984. Though there would be three more batches by November, the sequence Hewick got from Miyake's first shipment sufficed for the cloners. Fully degenerate probe sets 17 nucleotide bases long were made from the protein sequence spanning positions 46 to 52, and 14 nucleotides long from positions 144 to 150; this first set came from one of the same tryptic fragments that Lin successfully had used. By the end of May 1984, Fritsch's team had retrieved human genomic clones, and after confirming that the cloned DNA matched EPO protein sequence, in July the team found clones in a cDNA library Fritsch had made from human fetal liver.

10 Vapnek interview; Hughes interview with Rathmann, pp. 64–65 (quotes). Lin Probe chart; Lin testimony, vol. 4, p. 55; D Alegretti, EPO Timetable, 27 July 1989, Plaintiff's Exhibit 832, with Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law (loose); all in Amgen v Chugai files. On Amgen's announcement: Fritsch interview; also the reactions of Genetics Institute and Chugai management at this time confirm that there must have been some such announcement, e.g., M. C. Yang to R. Sadahiro, 16 Jan. 1984, Plaintiff's Exhibit 683, Plaintiff's Appendix to Proposed Findings of Fact and Conclusions of Law IX-2, Amgen v Chugai files. FK Lin, DNA sequences encoding erythropoietin, US Patent 4,703,008, issued 27 Oct. 1987 on application of 30 Nov. 1984 (continuing application of Dec. 1983). On Amgen's share of the U.S. purified EPO supply, Testimony of Thomas Wall, 19 Oct. 1989, Transcripts vol. 37, pp. 43–47, 52, 60–62; Erythropoietin distribution data June 1978–present (NIH), 22 Dec. 1983, Plaintiff's Exhibit 344, attached to Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law Appendix with attached documents, vol. 3, II-98; both in Amgen v Chugai files.

By October or November, Genetics Institute scientists had integrated a human cDNA into hamster cells and started moving toward production. By mid-December, Genetics Institute had filed patents on EPO made by cloned human cDNA in the United States, Europe, and Japan, and Fritsch sent a report of the success to *Nature* which was published in late February 1985 (Jacobs et al. 1985). Genetics Institute also filed another patent. Using the new method of reverse-phase high-performance liquid chromatography (RP-HPLC), Hewick found that the Miyake-Goldwasser EPO that everyone regarded as ultra-high purity was actually half impurities. Hewick claimed, and received, not only a patent on using RP-HPLC to purify EPO, but also on the purified protein, which must have been a nasty surprise to Genetics Institute's competition.[11]

War of Lawyers

If war is politics by other means, to paraphrase Clausewitz, then the legal "war" over the EPO "mountain of treasure" extended the cloning races to the courtroom and became science policy by other means. Doubtless due partly to uncertainty over how the courts would decide, there were by 1986 many claimants positioned to move the protein toward the marketplace as a medicine. Apart from Genetics Institute and Amgen, Biogen finally cloned EPO independently, and so too did University of Washington biologist Jerry Powell, somehow succeeding in obtaining genomic clones with the synthetic probe method using only the Hewick sequence. Powell was collaborating with the Seattle firm Elanex in its further development (Chahine 1998; Powell et al. 1986). Moreover, California Biotech and Integrated Genetics of Massachusetts each had cloned EPO with help from Genetics Institute's publication disclosing the gene sequences, and both were moving the product toward production in partnership with larger firms. In October 1987, on the day that the U.S. Patent Office

11 See Lin patent 4,703,008, especially Examples 7, 10. D Vapnek, minutes of EPO meeting of 27 March 1984, dated 4 April 1984, Affidavits Submitted on Behalf of Defendants Memorandum in Opposition to Plaintiff's Motion for Preliminary Injunction, filed 11 Feb.1989, Exhibits; J. Browne, 28 Nov. MC EPO PDT meeting minutes, dated 30 Nov. 1984, Defendants' Exhibit 349, Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law, Appendix IV-22; Defendants Summary, ITC Deposition of Jeffrey Browne, 20 May 1988 (admitted as evidence 18 Oct. 1989), Designated Transcripts and Summaries; M. C. Yang to Takaji Miyake, 6 Feb. 1984, attached to Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law, Appendices, II-58; Testimony of Gabriel Schmergel, 16 Oct. 1989, Transcripts vol. 36, pp. 35–36 (quoting translation of Aug. 1985 document, Plaintiff's Exhibit 335); Testimony of Rodney Hewick, 23 Aug. 1989, Transcripts vol. 11, pp. 39–40, and 19 Sept.1989, Transcripts vol. 21, pp. 53–55; Testimony of Edward Fritsch, 26 Sept. 1989, Transcripts vol. 26, pp. 104–6; all in Amgen v Chugai files. E. Fritsch, K. Jacobs, and R. M. Hewick, Method for production of erythropoietin, European Patent 0411678B2, filed 3 Dec. 1985; R. Hewick and J. Seehra, Method for the purification of erythropoietin and erythropoietin compositions, US Patent 4,677,195, granted 30 June 1987 on an application of 11 Jan. 1985.

granted Lin's patent on the genomic DNA sequence, Amgen declared war, filing infringement suits against Genetics Institute, Chugai, and Integrated Genetics. (Amgen did this despite pressure from Johnson & Johnson to cross-license with Genetics Institute. The large drug firm had licensed EPO from Amgen for uses other than kidney disease and now feared the invalidation of their shared Lin patent.)[12] Two days later, Genetics Institute filed a countersuit against Amgen for infringing Hewick's patent on the pure EPO protein, which had been granted in June (*New York Times* 1987; Stipp and Harris 1987).

The question at issue was, essentially, how much to reward the first to clone a gene, and on precisely what grounds. Many aspects of patent law were involved. One was subject matter: the dividing line between scientific discovery and patentable invention was unclear when it came to naturally occurring DNA sequences and proteins, although there was good reason in the 1970s to suppose that the courts—especially in the United States—would be generous to cloners. In a body of case law largely built up around the pharmaceutical industry's commercialization of hormones in the early 20th century, naturally occurring substances as isolated and purified could be patented if they were useful in ways that their natural source was not (Harkness 2011; Moxon 1971). But there were many other issues at stake beyond this "product of nature" matter, such as defining the date of an invention and also the significance of inequitable conduct. (These lines were pursued by Genetics Institute, who demonstrated that Fritsch was the first both to design and to screen with dual large fully degenerate probe sets, and contended that Amgen's decisive expropriation of NIH EPO from Goldwasser was inequitable.) Most important for present purposes was the issue of obviousness: a patentable invention must not be obvious to someone skilled in the relevant art. Nobody knew where the courts would draw the obviousness line, nor what scope would be afforded to first comers with patents on isolated natural genes.

A common expectation among the lawyers and managers of biotech firms was that the courts would affirm standards of novelty and non-obviousness, together with patent breadth, such that whoever first cloned a natural gene and used it to produce a protein drug would obtain defensible rights sufficient at least for a monopoly on first-generation, unmodified protein drug products. But clearly this expectation was not universal, as the actions of California Biotech and Integrated Genetics illustrate, for these firms could only have marketed EPO

[12]A. K. Beck, R. M. Withy, J. R. Zabrecki, and M. C. Masiello, Cell encoding recombinant human erythropoietin, US Patent 4,954,437, issued 4 Sept.4, 1990, on application of 15 Sept. 1986; J. Powell, Human erythropoietin gene: High level expression in stably transfected mammalian cells, US Patent 5,688,679, issued 18 Nov. 1997, on application of 6 Oct. 1993, continuing abandoned application of June 1986; Jack Bowman to George Rathmann, 26 Feb. 1988; Defendants' Exhibit 818, attached to Defendants' Joint Appendices to Proposed Findings of Fact and Conclusions of Law, Appendix, vol. 3 XVII-6, Amgen v Chugai files.

if the patent rights of the initial cloners (whose published sequences they openly used) had been more narrowly circumscribed by the courts, for example to cover only the specific DNA constructs used to express the natural genetic sequences. Furthermore, the common expectation had just been destabilized by a British High Court's ruling in the important Wellcome–Genentech case. In this case, Genentech had been denied a patent monopoly on another first-generation protein drug, tissue plasminogen activator, because the firm had used only routine methods to obtain a known end—the gene and its product, the natural protein (*Biotechnology Law Report* 1987). Adding to the unpredictability surrounding such legal issues in the new domain of recombinant DNA drugs, in order to strengthen patent protection and make it more uniform, an entirely new American court was established in 1983 to hear patent litigation appeals, the Court of Appeals for the Federal Circuit (CAFC; *Washington Post* 1985). No wonder that, even after Amgen announced cloning the human EPO gene in 1983 (and did not publish the work in a journal), competitors had continued their own efforts.

The legal battles for EPO were lengthy, expensive, and remarkable for the wide range of arenas they occupied, but for reasons of space I will focus on the U.S. Federal courts hearing the infringement cases. In January 1989, to expedite a full decision on the validity and coverage of both Genetics Institute's and Amgen's patents over EPO, the two companies agreed to a trial before a magistrate in the Massachusetts Federal District court (Rundle 1989). In December that year, the Boston magistrate, Patti Saris, decided on the multiple questions at issue. Saris called her decision "close," unsurprising given the distinction of the opposing firms' principal scientists and expert witnesses, and also on the closeness of the cloning race. For example, Amgen cloned the genomic human EPO sequence first, but Genetics Institute evidently cloned the human cDNA sequence first—the parts of the gene actually expressed as protein and the preferred form for producing the EPO protein in engineered cells. Also, as noted above, neither side invented the basic method of cloning natural genes from a library using degenerate synthetic probe sets, and it was Genetics Institute who could show both that Fritsch had first planned to use dual large probe sets to screen a genomic library and that he had been the first actually to attempt it.

On the product of nature issue, Saris's decision took the standard line that Lin's patent applied to the isolated EPO gene (that, is the sequences isolated from the genome, including those also found in cDNA), not the gene as it exists in the body. On the issue of scope, Saris upheld most claims of Amgen's Lin patent, but excluded ambit claims to every possible (unspecified) DNA sequence encoding a protein with erythrocyte-stimulating activity. Another thorny issue she decided on was date of conception, ruling that the fact that Fritsch could show he was the first to plan and to use two large fully degenerate probe sets did not entitle him to the invention. On the particularly close question of obviousness, Saris rejected Genetics Institute's argument that Lin was not entitled to a patent because his method was well known, following Ullrich's testimony in

favor of the Amgen position (and for which they could cite Maniatis himself as an authority): "although cloning seems straightforward on paper, it is more difficult to put into practice" because small variations in standard procedures can make all the difference.[13] Thus, judged Saris, it was "obvious to try" screening with synthetic oligonucleotide probe sets, as Lin and Fritsch and Biogen's scientists and others all tried, but in 1982–83 nobody had successfully cloned a gene from a genomic library using *two* sets of fully redundant synthetic probes as large as those ultimately used by Lin (128 different probes in each set). So there was no obvious assurance of success in this way of overcoming the difficulties besetting the cloners (Bernstein 1989).[14] As legal scholar Philippe Ducor has observed, the meticulousness with which Saris—and subsequently the CAFC—treated the prior art of probing reflects the strenuous efforts of the courts to justify, within laws written to reward not just perspiration but inspiration too, patent rewards for the practitioners of an increasingly routine industry of isolating natural genes to make protein drugs.

This problem has since faded in the realm of drugs, as genetic engineering firms have moved to second- and third-generation protein drugs, which contain sequences and properties not found in natural, first-generation proteins. However, it has recently come to a crisis in diagnostic testing with natural gene variants, which cannot be improved upon for diagnostic purposes. In the 2013 *Myriad* case, the U.S. Supreme Court, at the urging both of the executive branch and most life scientists, seems finally to have taken steps to remedy that situation—not on grounds of obviousness, but by ruling natural gene sequences per se to be unpatentable subject matter (Cook-Deegan 2012; Harkness 2011; Kevles 2012; Liptak 2013).

Saris's decision was symmetrical in supporting most of Genetics Institute's patent on purified EPO. Again, it was a close question of whether Hewick's innovation, using RP-HPLC to purify EPO, was obvious. As with the Lin patent on the cloned EPO gene, Saris gave the benefit of the doubt to the patenting biotechnologist. It was obvious in 1983 to apply RP-HPLC to separate and purify glycoproteins, and even to purify EPO from urine, but "it was not obvious to apply RP-HPLC to EPO prepared by the [Miyake-Goldwasser] procedures because . . . the scientific community believed that material to be pure already."[15] As the *New York Times* reported on the implications of the decision, because Amgen had so far been unwilling to consider cross-licensing or other

[13]Ullrich testimony of 16 Aug. 1989, Transcripts vol. 7, p. 15.

[14]Memorandum and Order, Amgen Inc. v Chugai Pharmaceutical Co. Ltd. and Genetics Institute, Inc. C.A. No. 87-2617-Y, U.S. District Court, Massachusetts District, 11 Dec. 1989, as reproduced in *Biotechnology Law Report* 9:25–71.

[15]Memorandum and Order, Amgen Inc. v Chugai Pharmaceutical Co. Ltd. and Genetics Institute, Inc. C.A. No. 87-2617-Y, U.S. District Court, Massachusetts District, 11 Dec. 1989, as reproduced in *Biotechnology Law Report* 9:25–71.

negotiated solutions, they might expect reprisals for the legal tribulations they had imposed on Genetics Institute. Or as Genetics Institute attorney Bruce Eisen put it: "They set the ground rules—winner take all—and if they lose, they've got to be big boys about it" (Andrews 1989).

The struggle moved on to the U.S. Congress, where for a year EPO played a key role in fierce debates over whether the Orphan Drug Act was a lifesaving boon to patients or corporate welfare. By this time the drug had been approved for the anemia often seen in advanced kidney failure, and it was certainly beneficial to the estimated 25% of America's 80,000 to 100,000 dialysis patients who required frequent transfusions (which can lead to iron poisoning), although a large proportion of sales were already coming from other, unapproved uses (Anderson and van Atta 1990; *FDC Reports* 1990; Gladwell 1990; *New York Times* 1989; Rasmussen, n.d.). Meanwhile, the CAFC heard the appeals of Saris's decision upholding both Lin and Hewick patents. In March 1991, Judge Alan Lourie issued the court's decision. Newly appointed to the CAFC by President George Bush, himself a director of the Lilly Drug firm, Lourie had in his youth been a chemist at Monsanto and Wyeth Pharmaceuticals, and later chief counsel for Smith, Kline and French. It would be fair to assume that this judge brought the wisdom of the established drug industry to bear. Lourie entirely upheld Saris's opinion supporting Amgen's EPO DNA patent, agreeing that the claims covering Lin's genomic clone also covered the sequence found in Genetics Institute's cDNA clone that encoded natural EPO, and also confirming her rejection of sweeping claims to unspecified DNA sequences encoding any protein with EPO activity (which might have blocked further development of this type of drug). Thus, as to scope, Lourie suggested that future patents could be sustained on EPO variants with improved properties, a suggestion he would underscore in subsequent decisions (see below). As to conception of recombinant DNA inventions, Lourie made another particular point in upholding Saris's rejection of Genetics Institute's argument that Fritsch's earlier plans and efforts to use two large fully degenerate probe sets made any invention his. Citing an expert witness, he noted that "You have to clone it first to get the sequence"—that is, the invention occurred only when the probing idea was reduced to practice, when Lin actually cloned EPO this way and determined the DNA sequence.[16] Or, as the implications of this reasoning were informally taken to heart in the biotech world: "You haven't got it until you've cloned it" (Lentz 1993; Warburg 1993).[17]

The important precedent set by this part of the decision makes common sense as policy: scientists and investors would be discouraged from trying to

[16]Decision of Judge Lourie, U.S. Court of Appeals, Federal Circuit, 5 March 1991, in Amgen, Inc., Plaintiff/Cross-Appellant, v Chugai Pharmaceutical Co., Ltd., and Genetics Institute, Inc., Defendants-Appellants, Nos. 90-1273, 90-1275; 927 F.2d 1200, 59 USLW 2575, 18 U.S.P.Q.2d 1016. Alan Lourie, http://judgepedia.org/index.php/Alan_Lourie.

[17]Fritsch interview.

clone something new, if anyone might later take the spoils by showing they had once thought of doing the same thing. However, common sense can't be said to support the way the CAFC favored Amgen's isolated DNA patent over Genetics Institute's purified protein patent. The court could have interpreted the law so as to offer a criterion for deciding which patents on purified natural biochemicals should be valid, such as whether the more purified preparation has some new medical utility beyond previously available preparations. Such a criterion might have helped guide biotechnology research away from work aiming only to gain patent leverage on natural entities (Greenfield 1992). Instead, it quibbled with the lower court's construal of an uncertain point in the Hewick patent, which had been treated by Saris so as to give benefit of the doubt to the patent holder, as is the rule. To be precise, Lourie decided that there was no convincing evidence that Hewick's patent showed how to purify EPO protein with a certain minimum specific activity measured in vivo, when the patent did not specify in vivo or in vitro. This "shocker" of a decision—according to legal and business analysts at the time, who had seen nothing wrong with Genetics Institute's patent, and expected compulsory cross-licensing—sent Genetics Institute stock into a tumble. The little firm was snapped up by a big drug company, and the heady days of cutting-edge science there quickly ended (Ratner 1991; Rundle and Stipp 1991; Thayer 1991). This part of Lourie's decision may have reflected a common prejudice favoring DNA over protein, or a genuine mistake in understanding factual evidence (likely both, in my view).[18] Or perhaps it was simply a desperate effort to find any grounds on which to hand all the spoils unambiguously to one or another patent holder, and thus signal that biotechnology drug research offered big jackpots. It certainly had this last effect.

Most important, on the question of obviousness, Lourie in his *Amgen* ruling—and in a series of decisions in which he participated around the same time (*Bell*, *Duell*, and *Wellcome*)—made the following clear to the world of biotechnology law: firms could expect an enforceable patent monopoly on any natural protein that they succeeded in cloning first, no matter how straightforward the methods and path to success. Here the CAFC was pushing back against the Patent Office, which in the 1990s was trying to raise the bar on the grounds of nonobviousness by denying patents on genes for previously known, naturally occurring proteins cloned by well-known standard methods. The CAFC's logic may have made a "fetish of unpredictability" as the antidote to obviousness, legal crit-

[18]Genetics Institute and Chugai argued to my mind convincingly that in rejecting the Hewick patent on enablement grounds Judge Lourie confused the specific activities of Miyake Shipment 3 before Hewick's application of RP-HPLC with its activity after, and further ignored both the success of expert witness Kung in obtaining EPO with in vitro specific activity greater than 170,000, and Goldwasser's own testimony that RP-HPLC-purified EPO with activity greater than 80,000 showed in his own hands virtually identical in vitro and in vivo activity measures. Defendant-Appellants' Joint Petition for Rehearing and Joint Suggestion for Rehearing *in banc*, CAFC Appeal Nos. 90-1273, -1275, 19 March 1991, pp. 4–8 et passim (document gift of Bruce Eisen).

ics observed at the time, but (in line with this court's raison d'etre) it was geared to reward those who "elect to invest the time and money" to prove a cloning strategy would actually work with a monopoly over a drug product (Rowland and Field 1995). But how appropriate a reward?

The lower the bar on obviousness, the less the patent system encourages innovation, its chief purpose. In the extreme, no new drug development methodology might be introduced, and biotechnology might grind to a stop after making the first generation of products from well-known natural proteins. Alternative dispensations in patent law to manage this problem were possible. For example, one alternative may be found in an emphasis on innovation in methods and processes, where greater inventiveness would justify broader claims to products of the processes. This was the direction in which the British High Court had actually gestured (briefly) in its aforementioned decision allowing Genetics Institute and partner Wellcome to market recombinant tissue plasminogen activator in competition with Genentech: only more fundamental advances in cloning method would justify a patent broad enough to cover all forms of a natural gene product (*Biotechnology Law Report* 1987; Sherman 1990). (Of course, such an emphasis on method and process innovation in patent scope might have brought its own problems; the point here is simply that the law offered more than one possible approach.) But the answer chosen by the CAFC, in taking obviousness off the table, can be found in the intermediate scope of patent protection afforded to the proteins and analogs actually produced by biotech firms, providing strong monopolies on natural first-generation products, but leaving open further variants not explicitly disclosed. Amgen took this message to heart, developing a second-generation EPO product with a slightly altered protein sequence extending its duration of action, called Aranesp, which it marketed in competition with its partner in marketing the first-generation product, Johnson & Johnson (Rundle and Henseley 2001). Looking at the new case law in 1995, one general counsel for a biotechnology firm described the implications thus: "Judge Lourie seems to creating a doctrine for 'gene jockey' cases which permits one to slice the salami thinly," allowing patent protection for almost every new biopharmaceutical meeting very low standards of novelty and non-obviousness, but at the same time offering defensible patents on very slightly altered products (Bent and Sandercock 1995).

This, of course, was precisely the intellectual property regime that the big U.S. pharmaceutical firms were accustomed to. It was one that since the 1950s has been critiqued for directing more resources to marketing than research, and the bulk of research effort into trivially different, medically redundant or "me-too" drugs (Hilts 2003; Lasagna 1989; Tobbell 2012). The established regime's rewards for trivially different new drugs incentivized correspondingly trivial, thinly sliced innovation. By the same token, it disincentivized the academic-style fundamental research, aimed at broad, basic, and particularly method patents (epitomized by the Stanford Cohen–Boyer patents), such as many early biotech firms boasted.

Apart from the fact that, at the time, some lawyers in biotechnology perceived the implications thus, what evidence can be offered that in fact the CAFC's decisions regarding obviousness and scope had the anticipated salami-slicing effects? According to one prominent and comprehensive economic analysis, the collective business performance of biotechnology firms in the late 1980s through the early 2000s just equaled that of traditional drug firms (Pisano 2006). Another influential analysis of biotechnology's productivity, measured in terms of drug innovation rather than sales, found that overall new drug submissions for regulatory approval have not increased since biotech firms started producing them, and that a biotech-influenced rise in new drug patents has only kept up with generally skyrocketing research expenses in the flagging pharmaceutical sector (Hopkins et al. 2007). So the business performance of biotech firms has very closely mirrored that of the broader pharmaceutical sector. Talk of molecular biology visiting creative destruction on the drug industry is now rare. But all this is exactly what one expects if, as I have argued here, biotech was quickly forced by American legal (as well as financial and regulatory) institutions to become simply an ordinary part of the established pharmaceutical industry.

The behavior of the finance community similarly fits with a view that the CAFC set an implicit science policy that ended the mythic age of fundamental science in small biotech firms. On the heels of the court decisions alluded to here, in 1994 a macroeconomically driven finance crunch produced a large-scale shakeout in the biotech sector that especially hurt science-driven firms of the Genetics Institute type. Those that survived were more narrowly product-focused (Rundle 1994). Thus in the 1990s the biotechnology that had promised to revolutionize drug development, dragging the American pharmaceutical industry out of its me-too rut and bringing a new wave of therapeutic breakthroughs, was instead rapidly channeled into the familiar pattern by the legal system. The direction in which these decisions pointed, towards second- and third-generation products that offered novel properties not found in the natural proteins that were the first-generation recombinant drugs, promoted some competition, albeit of an oligopolistic tenor.

CONCLUSION

In effect, I have argued here, the American courts derived science policy from big pharma and imposed it on the small biotechs. These events might well be characterized as another case of what legal historian Graham Dutfield (2009) has called the "interpretive capture" of patent law by its chief users, the major firms that file the bulk of the patents and their lawyers, to serve their shifting short-term demands, rather than the long-term needs of a productive pharmaceutical industry and of medicine. Certainly, the CAFC's extension of the thinly sliced, product-focused tradition of 20th-century American patent law in pharmaceuticals cannot be regarded as necessary for a successful drug industry, as a mo-

ment's reflection on history will prove. After all, before the Second World War, German and Swiss drug firms dominated the world, outperforming all others while based in legal regimes that did not grant patent protection to *products* at all (Dutfield 2009; also see Gaudillière 2008). Similar critiques have been made of innovation policy as implemented recently by the U.S. patent system across many industries (Jaffe and Lerner 2011).

A comparison with parallel events in Europe reinforces the impression that the CAFC's dispensations could have served the American public much better, at least in the EPO case. Since European patent law has traditionally been less generous to claimants on natural biological entities than U.S. law, it comes as no surprise that Genetics Institute's patent on the pure natural erythropoietin protein did not stand. While Amgen's patent on the natural EPO DNA sequence did not fall in Europe, its scope was more restricted, for instance not to cover all EPO-encoding DNA, but only the human genomic DNA and monkey cDNA that the firm demonstrably cloned first and specified in its patent. Genetics Institute's patent claims to human EPO cDNA survived challenge in the European Patent Office and many jurisdictions, and the rights were acquired by Roche. And the Powell patents underpinning the Elanex EPO also survived to a degree, as they did not in the United States; these rights were later bought by Baxter. From the mid-1990s onwards, Europeans therefore had greater access to different but clinically equivalent first-generation erythropoietins from competing makers: Amgen's Epogen product sold by Johnson & Johnson under the name Eprex; the product based on Genetics Institute's patent, from its partner Boehringer Mannheim and then Roche, best known as NeoRecormon; and the product that Elanex named Epomax (Chahine 1998; Dove 2001; Firn 2001; Maebius and Sandercock 1995). As one would expect in a more competitive market, prices paid by Europeans were lower.

The supposed health benefits of new drugs are routinely invoked as justification for the high prices Americans pay, and likewise for the way the American patent system richly incentivizes their commercial development. "Greed is good for patients," one analyst today puts the view, and "saves lives one gene patent at a time" (Buck 2013). More carefully considered opinion on all sides must concede that outcomes in drug development, good and bad, depend on more than just the patent system and the level of "greed" or profit motivation it excites. Still, in case anyone might be tempted to seek a post hoc rationale along these lines for the CAFC's implicit policy, a final word is warranted concerning the actual health consequences of the EPO monopoly provided by the court's decisions (in fact a duopoly, through licensing). Not only did European patients benefit from the lower EPO prices associated with the competition allowed by narrower patent protection there, because the money saved could be used elsewhere in health care, but, perhaps counterintuitively, they ultimately consumed less of the drug and directly benefited as a result. This occurred because the same national health insurance systems that negotiate reasonable drug prices also restrain

"greed" by regulating drug marketing more strictly and by guiding prescribing. Particularly for anemias caused by some cancers and most cancer chemotherapy, a market larger by an order of magnitude than advanced kidney disease, European patients received EPO less frequently than transfusions, and they were given less EPO when they did receive the drug. In contrast, American use of the drug exploded in the late 1990s and especially after Amgen launched Aranesp in 2001, driven by an extravagant marketing battle with erstwhile partner Johnson & Johnson. This contest was enabled by monopoly-assured higher drug prices (which paid for "rebates" to prescribing physicians as large as $1200 per prescription), and also laxer regulation in the United States (permitting, for instance, television ads telling cancer patients that their "fatigue" was treatable, rather than their anemia; Napoli 2007; Newman 2000). Between 2001 and 2006, annual worldwide erythropoietin sales doubled to a peak of around $13 billion, three-quarters of which came from the United States, where Amgen's two EPO products were the fourth and sixth bestselling prescription drugs. In that same interval, medical usage of erythropoiesis-stimulating agents (prescribing of all first-generation EPO brands and second-generation Aranesp) increased 51% in Europe, as compared with 340% in the United States (Greb and Van Arnum 2007; Melnikova 2006; Repetto, Moeremans, and Annemans 2006; Steinbrook 2007). But eventually, mounting evidence that American cancer patients given EPO were dying at a roughly 10% higher rate than their European counterparts—because the hormone stimulates many cancers, and because at high doses it may cause lethal thromboembolisms—led to a sharp decline in the use of these drugs in the United States (Bennett et al. 2008, 2010; Bohlius et al. 2009). This deadly overuse of EPO in the United States obviously owes much to the drug's enormous profitability—that is, partly to the patent decisions of the U.S. courts. Even if high profitability does not always lead to drug overuse, the EPO case shows that over-reward for pharmaceuticals development can have consequences beyond economic waste.

To sum up, in the case of biotech's most important product, the American patent system's protection for the cloned sequences encoding naturally occurring proteins—the first-generation recombinant drugs—did not benefit American patients, many thousands of whose lives were shortened, any more than it benefited the science-driven biotech firms or revolutionized the drug industry. As I have argued here, these suboptimal outcomes were no accident, but the result of a de facto policy imposed by American court decisions, unconsciously or not, to assimilate biotechnology to the established, dysfunctional pharmaceutical sector. If the patent system is to serve the public better, the time has surely come to seek policy lessons in the failings as well as the triumphs of biotechnology drug development in the United States. I hope policy scholars will take heed of the example presented here.

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