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2003

### Reaching Through the Genome

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#### Publication Information & Recommended Citation

Eisenberg, Rebecca S. "Reaching Through the Genome." In *Science & Cents: Exploring the Economics of Biotechnology: Proceedings of a Conference Sponsored by the Federal Reserve Bank of Dallas, April 19, 2002*, edited by J. F. Duca and M. K. Yükel, 105-15. Dallas, Tex.: Federal Reserve Bank of Dallas, 2003.

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# *Reaching Through the Genome*

Rebecca S. Eisenberg

**T**he past two decades have been a period of rapid evolution in the science of biotechnology and therefore in patent strategies, if not in patent law itself. Patent law takes a long time to catch up with science, and commentators take a long time to catch up with the law, but patent lawyers don't have that luxury. They have to keep ahead of the game, figuring out claiming strategies that allow their clients to capture the value of future discoveries. I want to discuss some of these strategies today.

The patenting of DNA sequences is hardly a new thing, but rather an established practice that goes back at least two decades. It began with little fanfare and little controversy, in contrast to other first encounters of the patent system with new categories of invention in biotechnology and other fields. Considerably more public controversy accompanied the allowance of patents on microorganisms, animals, computer software, and business methods. The issuance of patents in each of these areas provoked immediate opposition, along with critical media commentary and congressional hearings.

In recent years we've seen similar attention focused on the practice of patenting genes, but nothing like that happened when people first started patenting genes in the early 1980s. At the time, public outcry over biotechnology patents was focused on living organisms rather than genes. We didn't see any significant controversy over patenting DNA sequences until the advent of high-throughput DNA sequencing in the early 1990s, when genomics started to look more like information technology than like chemistry. By this point, patenting genes was such a well-established practice that questions about whether DNA should be patentable seemed quaint and out of touch.

Even in the early 1980s, when the courts were still wary of protecting information technology,<sup>1</sup> they viewed DNA as a molecule, a chemical, a composition of matter, rather than as information.<sup>2</sup> Perhaps if the Patent and Trade-

mark Office (PTO) and courts had coded DNA as a storage medium for information, a metaphor that is more common in popular understandings today, the outcome would have been different. Instead, paradoxically, for a while it was far easier to patent *nature's* information technology than it was to patent *human-made*, electronic information technology.

Why was the patenting of genes so uncontroversial in the early days, and why has it become so controversial since then? In the early days, patenting genes looked like patenting drugs. Now it looks more like patenting scientific information. We have a clear story about why we should issue patents on drugs. It is less clear whether we want to issue patents on scientific information.

In fact, it was the scientific community, and not the usual antibiotech suspects, that first provoked public controversy over the patenting of DNA sequences. The focus of the controversy was the filing of patent applications by the National Institutes of Health in the early '90s on the first random gene fragments (expressed sequence tags, or ESTs) coming out of the laboratory of Dr. Craig Venter while he was at NIH.<sup>3</sup> But until the era of high-throughput DNA sequencing, the scientific community did not complain about patenting DNA.

The first generation of DNA sequence patents was directed toward genes encoding proteins of interest. They typically claimed:

1. An isolated and purified DNA sequence.
2. A recombinant vector that includes the DNA sequence.
3. A transformed host cell that includes the vector.

These claims all covered tangible materials used to make pharmaceutical products. The effect was similar to a patent on a drug, although the gene patent was directed to the recombinant materials used in production of the protein rather than to the protein product itself. The PTO and the courts treated these patents the same way they treated patents on new chemical compounds. The analogy may never have been perfect, but it worked, in the sense that it provided commercially effective patent protection that motivated investment in the development of new products.

This was important because in the biopharmaceutical industry the patent system does real work. In some industries, firms report that patents aren't really very important to their investment decisions, that other things matter more in determining the profitability of innovation, such as being first to market, that patents are just trading currency to get other patent holders to leave you alone.

That is not what one hears in the pharmaceutical industry. Empirical evidence indicates that this is a field where patents really matter.<sup>4</sup> Why? The standard account from the pharmaceutical industry is that new drugs cost a fortune to develop, and there are many costly failures for each successful product. If generic firms could compete and drive down prices on the successful products

without incurring all the development costs on the full range of successful and unsuccessful candidates, they would drive them out of business.

Early biotechnology firms saw themselves as “high-tech” pharmaceutical firms developing therapeutic protein products rather than small molecule drugs. They, too, wanted patents that would prevent free riders from destroying their profits. Patents on genes promised to provide that protection and allowed these new firms to raise capital and sometimes to get pharmaceutical firms to collaborate with them.

But in recent years the biotechnology and genomics industries have become much more diverse in their research and business strategies. As the Human Genome Project has generated vast quantities of DNA sequence information, with biological significance yet to be determined, many firms have emerged in a market niche that requires appropriating the value of information resources for use in future research and product development. Research that builds upon today’s bioinformatics platforms can contribute to the development of products that are several steps removed from the genomic information base that helped researchers on the path to discovery. It’s not obvious how to use patents to capture the value that upstream research platform technologies contribute to these discoveries. Firms are seeking strategies for reaching into the revenues from end product sales, especially drug sales. The introduction of new pharmaceutical products is typically the point at which bioscience starts to yield real money.

Needless to say, the pharmaceutical industry is viewing these strategies with concern. The industry has long relied on patents on drugs to make drug development profitable, but patents on drugs are not the only patents that accompany new drugs on the road to market these days. Patents on the prior “upstream” inventions that explain disease pathways and mechanisms and identify potential drug targets impose costs on drug development. They are like so many siphons at the feeding trough of new drugs, draining away profits in a lot of different directions.

From a strategic perspective, the issue for upstream firms is how to use intellectual property rights in advances that facilitate future research to capture a share of the commercial value of the future discoveries that they facilitate, and the issue for downstream drug developers is how to resist these strategies. From a public policy perspective, we can recast the issue as how to allocate intellectual property claims along the complex course of cumulative innovation in biomedical research.

When researchers identify the disease relevance of a gene or set of genes, perhaps identifying a new drug target, can or should they be able to get patent claims that dominate future products that bind that target?

Various strategies are available for achieving that goal. Each of these strategies depends for its viability upon legal rules that might be interpreted or fine-

tuned to promote, permit, inhibit, or forbid these strategies, depending on how we feel about them as a normative matter.

One approach is called “reach-through licensing.” This is primarily a contract strategy, although often the contract involves a license to use a patented research platform technology or material. The basic idea is that the patent-holder restricts access to a patented research-enabling technology to users that agree, as a term in the license, to share a piece of the action in future products. Sometimes the piece of the action takes the form of a royalty on future product sales, and sometimes it takes the form of a license to use future inventions made in the course of the research. Many institutions resist these strategies, but some agree to them.<sup>5</sup>

Pharmaceutical firms will go to great lengths to avoid incurring reach-through royalty obligations, such as inventing around a patent or even going offshore to conduct drug screens. They will not sign a reach-through license agreement unless they absolutely have to. Universities are rarely targeted for reach-through royalties because they are unlikely to develop and sell products on which royalties might be collected. But firms often seek grant-backs of licenses to future inventions made in the course of university-based research as a license term when they provide research tools to universities. For their part, universities resist agreeing to grant-backs whenever possible. They view these provisions as compromising their stewardship over future discoveries and believe that firms should provide them with free access to research tools so that they can advance the frontiers of knowledge.

Both pharmaceutical firms and universities believe that reach-through rights overvalue the past contribution of tool providers relative to the work that remains to be done by themselves as tool users in order to advance the course of cumulative innovation. But for some institutions, particularly biotechnology firms, reach-through license terms make sense. Not only do they ask others to agree to pay them reach-through royalties, but they sometimes agree to pay them themselves.

The diverse institutions comprising the biopharmaceutical research community do not easily arrive at agreement on reach-through rights. They consume a lot of transaction costs in haggling about them, and if the haggling takes place far enough upstream, when the profitable end point of the research looks speculative and far away, they might conclude it's just not worth the costs of getting to yes. This risk enhances the attractiveness of reach-through strategies that don't require *ex ante* agreements. Two such strategies have been getting attention: reach-through remedies and reach-through claiming.

A reach-through remedy is a damage award for infringement that is measured as a reach-through royalty on sales of products developed through unlicensed use of a research tool. Janice Mueller has recently proposed such a remedy as a modified “research exemption” from infringement liability.<sup>6</sup> Under this pro-

posals, researchers who use a patented tool to develop a commercial product don't need to get permission in advance, provided they give notice, but if their research yields a product, they will be liable for reach-through royalties on that product. If reach-through royalties become common in license agreements for research tools, then they would arguably be an appropriate damage remedy under current law, on the theory that they approximate the value to which a willing licensor and licensee would have agreed. But in the present environment, with many would-be licensees putting up strong resistance to reach-through royalties, such a remedy seems to substitute a court's evaluation of fair license terms for that of the market.

Another strategy is called "reach-through claiming," which means issuing patents that are broad enough to cover future discoveries enabled by prior inventions. This strategy depends less on contract and more on patents. If the claims of a patent cover future products, the owner does not need to get the user to agree in advance to pay royalties on future product sales but can wait until the user has a product ready to bring to market before sitting down to bargain. Users that avoid patent owners at the research stage will still have to deal with them later, perhaps from a weaker bargaining position.

Patent claims that reach beyond the technological accomplishments of the patent holder are by no means unprecedented. It is common for pioneering inventions that open up new fields (in which there is little prior art) to receive broad patents that dominate future advances, including products that require significant further R&D. An example of an early advance in the biotechnology field that received broad reach-through claims is the Cohen-Boyer gene-splicing technique patented by Stanford University. The patent claims covered not only the enabling technology, subsequently put to use in many different academic and industrial laboratories across a broad range of R&D problems, but also any recombinant organisms created through use of the technology. The claims to recombinant organisms reached through the disclosed technology to cover later-developed starting materials used in recombinant production of proteins, giving the patent owner a dominant claim over a whole generation of biotechnology products.

But the history of patent law also includes many examples where the courts have held that a broad claim on a pioneering invention simply proves too much, including claims from such pioneering inventors as Morse and Edison.

Today the courts and the PTO seem to be viewing reach-through claims in genomics with some skepticism, but that doesn't stop inventors from continuing to pursue such claims, and some of them may be succeeding.

A stylized example illustrates how these reach-through claims work. Suppose a firm has identified a novel gene encoding a receptor, and based on similarities to previously characterized genes, it appears to be a new member of a known receptor family. Suppose further that based on what is known about

other members of this family of receptors, the inventor plausibly speculates that this new receptor might be a drug target. Let's suppose the applicant wants to patent:

1. The receptor itself, as an isolated and purified composition of matter.
2. A method of identifying a ligand that binds the receptor through screening procedures described in the specification.
3. Ligands identified by the screening method.

Is the applicant entitled to any of those claims? The applicant's best hope is for the first two claims—the claims to the isolated and purified receptor and the drug-screening method. The biggest obstacle to obtaining these claims is the requirement of utility (or industrial applicability, as it is known outside the United States). In order to get a patent, the inventor must have a useful invention and must disclose how to use it. All the claims will fail unless the application discloses a specific and substantial use for the receptor protein.<sup>7</sup>

Disclosure of a specific and substantial utility will be enough to permit the inventor to claim the isolated and purified receptor and the screening method to identify agonists. But it won't permit him to reach through to claim the as-yet-unidentified ligands. The primary obstacle to obtaining these reach-through claims is the *disclosure requirements* of the patent laws. To patent an invention, the inventor must provide a written description that is sufficient to enable a person of ordinary skill in the relevant field to make and use it without undue experimentation.<sup>8</sup> For product claims to meet this standard, one must supply information about the structure of products covered by the claim, and not just their function.<sup>9</sup> The hypothetical claims to ligands that bind the receptor fail to meet this standard because all the applicant has disclosed is the function of the molecules covered by the claim, without saying anything about their structure. The Federal Circuit has been particularly tough in applying the written description requirement to biotechnology inventions,<sup>10</sup> in contrast to its relatively light touch on the utility<sup>11</sup> and nonobviousness<sup>12</sup> standards.

Nonetheless, technology has advanced in ways that give some firms a strategy for addressing this written description problem. Researchers studying new proteins can sometimes crystallize the protein and determine its three-dimensional structure using X-ray crystallography. They can then obtain Cartesian coordinates permitting visualization of the target on a computer screen, creating a 3-D model of the target for use in designing ligands. Some patent claims have been issued for methods of identifying candidate inhibitor compounds that involve introducing crystal coordinates for a drug target into a computer program and superimposing models of inhibitor test compounds to identify those that fit spatially into an active site of the target.<sup>13</sup>

Might such an inventor also claim compounds identified through this computer visualization technique? Perhaps. Although the written description require-

ment is a potential problem, one might argue that the requirement is satisfied if the crystal coordinates provide enough structural information linked to the function of binding the target to permit visualization of the molecules falling within the scope of the claim. In other words, the applicant is not just claiming any molecules that do the job but actually describing what such molecules would look like.

Of course, the speculation might be wrong. Perhaps the shape of the receptor in the environment in which it interacts (or not) with the rationally designed compound is quite different than the shape found for the crystallized protein. Or perhaps a prior art compound will turn out to fall within the scope of the claims, rendering them invalid. A broad claim to a genus of compounds fails to meet the novelty standard if even a single member of the genus was disclosed in the prior art, even if the properties of the prior art compound that make it fall within the scope of the claim were merely inherent and not disclosed. Broad claims make big targets.

So while there are a lot of open questions yet to be resolved, there may be some claiming strategies that allow upstream inventors to get reach-through claims that will dominate future pharmaceutical products on the basis of preliminary genomics and bioinformatics work.

How should we be thinking about these reach-through practices as a normative matter? Should the law permit or promote practices that allow early-stage inventors to reach through to capture a share of the value of future discoveries? Should it discourage or prohibit these practices?

Critics argue that reach-through rights over-reward those who rest on their laurels at the expense of those who carry research forward. Moreover, mechanisms that permit leveraging of patents on early discoveries into control of future inventions raise potential antitrust concerns. To the extent that reach-through rights continuously augment the number of rights-holders at the bargaining table as cumulative research proceeds, they magnify risks of bargaining failures in a potential "tragedy of the anticommons."<sup>14</sup>

On the other hand, reach-through rights may be a valuable way to permit early innovators to capture the value that their discoveries contribute to subsequent research. Otherwise the stand-alone value of early innovations may be too low, undermotivating the initial investment that is necessary to identify and enable socially valuable research paths. A reach-through remedy may be a solution to the anticommons problem, permitting research to proceed without need for constant negotiations over access to each proprietary input.

How one weighs these competing concerns depends upon how one views the relative need for incentives at different points in the course of cumulative innovation. If one worries more about the adequacy of incentives for early-stage innovation and less about the adequacy of incentives for later-stage innovation, then reach-through strategies make a lot of sense. On the other hand, if one



worries more about the adequacy of incentives for downstream research and product development, then reach-through strategies are cause for concern. Judicial opinions about patent law reflect both of these perspectives.

Patent law sometimes rewards pioneers in a field with broad claims (and a broad range of equivalents), while giving only narrower claims to those who make follow-on improvements, even though the improvements may have more stand-alone commercial value than the primitive versions of the invention developed by the pioneer. Suzanne Scotchmer has argued<sup>15</sup> cogently that upstream research is both riskier and less likely to have a high stand-alone value than downstream research, which by definition is closer to market. She therefore argues for giving broad rights to early innovators that allow them to force subsequent improvers to deal with them. Giving a broad patent to the pioneer who invents, say, a primitive sewing machine allows her to capture some of the follow-on value created by those who tweak the invention and make it more user-friendly.

But one gets a very different picture of the relative contributions of early and subsequent innovators from observing biotechnology and genomics research. Of course, in biotechnology, as in other fields, there have been path-breaking, pioneering discoveries that paved the way for lesser discoveries that were more financially viable. But many of these discoveries were paid for by NIH, raising questions about the need for strong patents to motivate and reward the work that generates that sort of basic research. In recent years some private firms have tried to figure out business models for generating biomedical research information to provide a platform for downstream discovery, especially in genomics, but often by the time private firms see such an opportunity, the so-called upstream research has become relatively mechanical. For example, when Celera decided they could take on the publicly funded Human Genome Project and complete their own version of the human genome sequence,<sup>16</sup> much of the pathbreaking work had been done already. Although much work remained, there was little question but that the job could be done. In this setting, the “upstream” work of sequencing the genome looks relatively routine, riskless, and uncreative compared with the “downstream” work of figuring out what it all means and how to use the information to develop new diagnostic and therapeutic products.

More generally, in the biomedical field, upstream research is relatively cheap and heavily subsidized with public funding. Downstream research is relatively costly and risky and relies primarily on private funding. This configuration of risk and cost argues for focusing on motivating and rewarding downstream research more than upstream research.

But other factors would support the opposite intuition. The biotechnology industry, already in its third decade, has mostly been unprofitable, while the pharmaceutical industry over the same time period has been extremely prof-

itable. Maybe this is partly because the pharmaceutical firms are smarter about business than the biotechnology firms, but perhaps this gross disparity in the bottom lines reflects in part a failure of the biotechnology industry to capture the social value that they have contributed to the pharmaceutical industry. If that is indeed what is going on, that cautions against disabling biotechnology firms from using legal strategies to get their fair share.

Persistent bargaining failures in the biomedical research community over the terms of access to research tools also caution against precluding reach-through strategies. Universities, biotechnology firms, and pharmaceutical firms describe these problems in different ways, each pointing the finger at the others, but they all report difficulties in agreeing about what is fair and reasonable when one institution provides another with resources that might facilitate future discoveries. In this environment it makes little sense for the law to foreclose options that might help the parties get to yes. Reach-through provisions can help with two big problems in the licensing of research tools: valuation and financing. If the parties cannot use reach-through provisions, they need to use pay-as-you-go terms for access to research tools. This suits the pharmaceutical industry just fine, because they have plenty of cash and would rather pay a relatively small amount upfront than agree to share profits later. But reach-through terms are more attractive to biotechnology firms that otherwise would be unable to pay enough to compete with the pharmaceutical industry to get access to research tools. In effect, reach-through agreements allow upstream and downstream biotechnology firms and universities to form joint ventures, sharing risks without draining cash at the research stage.

Reach-through grant-back licenses—i.e., precommitments to license future discoveries back to the provider of an upstream research platform—are more troubling but may also be a valuable contract option. What makes these provisions troubling is that they allow early innovators to exercise continuing control over future research and perhaps to suppress new innovation. On the other hand, such provisions may be a necessary defensive maneuver to permit early sharing of research tools without having to worry about facilitating domination by a competitor. Reach-through licenses can have a “copyleft” aspect to them, disabling subsequent innovators who have benefited from access to a predecessor’s research platform from monopolizing their own subsequent inventions.

Given that these provisions have the potential to enhance efficiency and promote exchanges that are currently vexed by bargaining problems, it seems unwise to preclude the use of reach-through provisions as terms in voluntary agreements as a matter of law.

On the other hand, the case for reach-through royalties as a remedy for patent infringement is far weaker. Such a remedy (which amounts to a compulsory license in exchange for court-ordered payment of reach-through royalties) has the advantage of permitting research to proceed without compelling

researchers to get licenses in advance, when the transaction costs may loom large relative to the expected value of research that is far removed from commercial payoffs. But they present a danger that a court-ordered remedy will be too high or too low. The standard worry about compulsory licenses is that the court-ordered remedy will be too low. In this setting there is also a risk that a royalty rate determined *ex post*, when the research has proven successful and valuable, will be significantly higher than an *ex ante* valuation arrived at between the parties. If reach-through royalties become common in licenses, the terms of actual reach-through licenses negotiated *ex ante* will provide a benchmark to guard against overvaluation *ex post*. The law should follow, not lead, actual contracting practices and award reach-through royalties if and when they become common as a license term for research tools.

Reach-through claims raise all the problems of reach-through remedies and more. Approved by the PTO in the course of *ex parte* patent prosecution, patent claims are not tied even to a hypothetical agreement between prior and subsequent innovators. Patent examiners who speak only to patent applicants without hearing from future innovators may overvalue the importance of the applicant's invention relative to potential future discoveries. Multiple overlapping claims, already common even with the PTO viewing reach-through claims skeptically, will become much more common if reach-through claiming strategies become more commonplace, giving multiple owners hold-up rights over future products.

Patent law has a tradition of limiting patent protection to actual accomplishments and future variations that can be achieved through work that is routine and predictable. This is a sensible limitation that appropriately guides patent examiners away from acceding to unreasonable requests for patent claims that dominate future research that is itself fraught with risk and uncertainty.

There are good reasons for permitting prior innovators to use their intellectual property to capture a fair share of the value that their discoveries contribute to subsequent downstream innovation, but we can be more comfortable with strategies that are negotiated in the market for licenses than with those that are negotiated in the course of patent prosecution.

## NOTES

- <sup>1</sup> See generally *Diamond v. Diehr*, 450 U.S. 175 (1981).
- <sup>2</sup> See, e.g., *Amgen v. Chugai Pharmaceuticals*, 927 F.2d 1200 (Fed. Cir. 1991). ("A gene is a chemical compound, albeit a complex one.")
- <sup>3</sup> For a history of this controversy, see Robert Cook-Deegan (1994), *The Gene Wars: Science, Politics, and the Human Genome* (W.W. Norton).
- <sup>4</sup> W. M. Cohen et al. (2000), "Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)," National Bureau of Economic Research Work-

ing Paper Series, no. 7552 (concluding on basis of survey results that "patents are used in substantially different ways across different technologies" and indicating that patent incentives are particularly important in motivating R&D in the pharmaceutical industry).

- <sup>5</sup> See Rebecca S. Eisenberg (2001), "Bargaining Over the Transfer of Proprietary Research Tools: Is This Market Failing or Emerging?" in *Expanding the Bounds of Intellectual Property: Innovation Policy for the Knowledge Society*, ed. R. Dreyfuss, H. First, and D. Zimmerman (Oxford University Press), 209.
- <sup>6</sup> Janice Mueller, "No 'Dilettante Affair': Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools," 76 Wash. L. Rev. 1 (2001). See also Jorge A. Goldstein (2001), "Patenting the Tools of Drug Discovery," *Drug Discovery World*, Summer, 9–18; James Gregory Cullem (1999), "Panning for Biotechnology Gold: Reach-Through Royalty Damage Awards for Infringing Uses of Molecular Sieves," *IDEA* 39 (4): 553.
- <sup>7</sup> 35 U.S.C. §§ 101, 112. See U.S. Patent and Trademark Office, Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).
- <sup>8</sup> 35 U.S.C. § 112.
- <sup>9</sup> See U.S. Patent and Trademark Office, Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001).
- <sup>10</sup> E.g., *Enzo Biochem. v. Gen-Probe*, 2002 U.S. App. LEXIS 5642 (Fed. Cir. April 2, 2002); *University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997).
- <sup>11</sup> E.g., *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).
- <sup>12</sup> E.g., *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).
- <sup>13</sup> U.S. Patent 6,083,711.
- <sup>14</sup> M. Heller and R. Eisenberg (1998), "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *Science*, May 1, 698–701.
- <sup>15</sup> See Suzanne Scotchmer (1991), "Standing on the Shoulders of Giants: Cumulative Research and the Patent Law," *Journal of Economic Perspectives* 5 (Winter): 29–41; Jerry R. Green and Suzanne Scotchmer (1995), "On the Division of Profit in Sequential Innovation," *RAND Journal of Economics* 26 (Spring): 20–33.
- <sup>16</sup> J. Craig Venter et al. (1998), "Shotgun Sequencing of the Human Genome," *Science*, June 5, 1540.