Protecting rights to early-stage technology

Michael J Shuster, Henry Su & Sasha Blaug

Does the recent court decision invalidating the University of Rochester's 'method of treatment' patent herald a shift in policy indicating that such patents require successful testing of lead compounds?

The birth of the biotechnology industry in the mid-1970s along with the enactment of legislation such as the Bayh-Dole Act in the 1980s coincided with an increase in the United States in the patent holdings and subsequent licensing activities of public institutions and universities. Though a causal relationship to this increase still is open to debate[1], the legislation marked the beginning of a new policy to "use the patent system to promote the use of inventions arising from federally supported research or development"[2]. In response, universities, other publicly funded institutions and government laboratories set up technology transfer offices to oversee the patenting and licensing of inventions funded with tax dollars.

The licensing of federally funded inventions to the private sector has created enormous economic and social benefits, such as the creation and commercialization of innovative products, job generation and the inflow of licensing revenue to the universities. From the 1960s to 1980, US university research generated approximately 100 to 250 patents annually[3]. This number has steadily increased. Since 1998, over 3,000 patents have issued annually over university inventions, many covering biotechnology and biomedical-related inventions subsequently licensed to the private sector. Total revenue generated from these types of technology transfer deals has grown from about $30 million in 1986 to about $1.26 billion in 2000 (ref. 4) and now approaches almost 10% of the support provided by the National Institutes of Health (compared to less than 1% in 1986)[5].

Because of its reliance on basic research discoveries and intellectual capital, the biotechnology industry always has been closely associated with universities and public health institutions. Given their focus on basic research, these institutions generally are not equipped to commercialize technology. Instead, early-stage technologies developed at universities, public health institutions and niche biotechnology companies often are licensed to biopharmaceutical companies for further development. These early-stage technologies may include target identification, pathway analysis, platform technology development and even generation of putative biotherapeutic compound leads. According to this model, the path to commercialization involves transfer of early-stage technology to a different entity that further develops the technology with the ultimate goal of bringing a product to market.

How should patent protection be allocated to reward the relative contributions of early- and later-stage developers whose combined efforts are required to translate basic research discoveries into actual products? The scope of a patent is defined by 'claims' that appear at the end of the patent document. To capture downstream profits, early-stage developers historically have filed patent applications with broad claims designed to cover conceivable future uses of their discoveries. For example, a basic researcher who discovers a new gene, mutation or gene product (protein) will usually associate her discovery with a disease state. A patent application for this discovery would describe the nucleic acid sequence or protein, along with its deduced or proved function. The requirement to associate the sequence or protein with a function arises under the utility element of US patent laws. Claims covering the isolated or purified nucleic acid or polypeptide would be included in the application. These are referred to as 'composition of matter' claims. Because the claims define the scope of the patent's exclusionary right, a composition of matter claim would effectively block someone from using the nucleic acid or polypeptide as a drug discovery tool.

The patent application also might describe an assay using the nucleic acid or protein to screen for agents that modulate function. Claims would be drafted to cover the assay. This strategy can provide valuable protection in addition to the composition of matter claims. Consider, for example, a scenario in which the nucleotide sequence or protein is already known, but the function is newly discovered. Claims to the composition of matter would be barred, but an assay based on measuring the newly discovered function may well be patentable. Assay claims would prevent others from measuring the newly discovered function to screen for drug leads.

Once the target has been identified and an assay developed, the assay can be used to find lead compounds that are expected to result in therapeutic benefit. It therefore also is common for patent applications directed to newly discovered or newly validated targets to include 'method of treatment' claims. A representative claim might read: "A method of treating an individual having condition X, comprising administering an effective amount of an agonist/antagonist of target Y." Like the assay claim, this also may be supported by the association between the target and a disease state. Alternatively, if the patent application describes an actual screening experiment, the claim may be supported by the identification of a compound that modulates target function.

The case

On March 5, 2003, a US district court judge invalidated a patent assigned to the University

M.S. is at Fenwick & West LLP, 275 Battery Street, San Francisco, CA 94111, USA (mshuster@fenwick.com), H.S. and S.B. are at Fenwick & West LLP, Silicon Valley Center, 801 California Street, Mountain View, CA 94041, USA (hsu@fenwick.com, sblaug@fenwick.com).

of Rochester with method of treatment claims directed to nonsteroidal anti-inflammatory drugs (NSAIDs) that selectively inhibit Cox-2 but not Cox-1 (ref. 6) and dismissed the university's lawsuit against Pfizer, Searle, Monsanto and Pharmacia[7]. The university sought royalty payments from manufacturers of the blockbuster arthritis drug Celebrex. The case has garnered attention not only because the university purportedly sought royalty payments from Pfizer on the order of 10% on $3 billion annual sales of Celebrex (had it been successful, the university would likely have asserted its patent against Merck's Cox-2 inhibitor Vioxx, seeking royalties on its $2.5 billion annual sales), but also because of its broader implications for obtaining patent protection on early-stage technology.

The University of Rochester's asserted patent (No. 6,048,850, or 'the '850 patent') was based on Donald Young, Michael O'Banion and Virginia Winn's work suggesting that differential regulation of cyclooxygenase (Cox) gene family members is central to understanding and treating various inflammatory disorders. Young *et al.* proposed that anti-inflammatory drugs should differentially target Cox-2 and not Cox-1. Given differences in the expression patterns, they reasoned that selective targeting of Cox-2 would effectively treat inflammatory pain while minimizing the often dose-limiting Cox-1-associated gastrointestinal side effects accompanying NSAID therapy.

The '850 patent specification disclosed the mouse and human nucleotide sequences for Cox-2 and Cox-1, described actual experiments transfecting, expressing and quantifying expression and activity in a human cell culture system, and asserted that the transfected cells could be used for diagnostics, gene therapies and drug screening assays[8]. The specification also described results from actual 'screening assay' experiments testing the effects of four well-known NSAIDs (acetaminophen, ibuprofen, naproxen and indomethacin) on Cox-2 and Cox-1 activity. Though none of these compounds demonstrated preferential Cox-2 inhibition, the results provided proof of principle that the assay could be used to identify selective Cox-2 inhibitors.

The specification also included a list of possible classes of compounds that could be identified in the screening assay, that is, "antisense, ribozyme, triple helix, antibody and polypeptide molecules and small inorganic molecules" along with extensive 'boilerplate' disclosure generically directed to topics such as "pharmaceutical formulations and routes of administration," "effective dosage" and "composition and formulation." These latter sections presumably were included to address the enablement and written description requirements for patentability, yet contained no description of actual work carried out along the lines of the heading topics. Instead these sections merely described information and techniques well known to one skilled in the pharmaceutical arts. The '850 patent then concluded with method of treatment claims that, if valid, would have been infringed each time someone swallowed a Celebrex tablet, leaving Pfizer with liability for inducing infringement of the method of treatment claim.

The decision

The district court granted summary judgment of invalidity for failure to comply with the written description requirement. It held that the inventors had not identified even one compound that would be suitable for use in practicing the claimed treatment method. In this regard, the inventors' disclosure was no different from those held insufficient in earlier-decided cases such as *The University of California v. Eli Lilly*[9], *Amgen v. Chugai*[10], and *Fiers v. Revel*[11]. A description of the needed compound only by its desired biological function or activity does not satisfy the written description requirement because it does not show that the inventors were actually in possession of a compound that could be used to practice the invention. Quoting from *Fiers v. Revel*, Judge Larimer reiterated that "an inadequate patent description that merely identifies a plan to accomplish an intended result 'is an attempt to preempt the future before it has arrived.' Such a patent fails to comply with the requirements of the federal statutes concerning issuance of patents and therefore must be held invalid"[7].

The district court rejected the inventors' attempt to distinguish their situation from Federal Circuit precedent on the ground that the latter cases all pertain to nucleic acid sequences. The written description requirement mandates that an inventor include enough detail about his or her invention, whether it is a nucleic acid or some other chemical compound, so that one skilled in the art will understand what is being claimed and recognize that the inventor has invented what is claimed. The fact that the claimed invention is a method and not merely a compound also does not change the invalidity analysis. Judge Larimer reasoned that the claimed method is essentially the use of a compound that the inventors were unable to identify or isolate: "Virtually any compound claim could be transformed into a method claim, however, simply by means of wording the claim in terms of a method of using a compound"[7].

The *Rochester* court also held on summary judgment that the patent was invalid for failure to comply with the enablement requirement; specifically, one skilled in the art would have to engage in undue experimentation—a trial and error process of screening compounds—with no guarantee of success in order to have a chance at identifying a compound that would be suitable for use with the claimed method. The court determined that the patent does not contain sufficient detail to enable someone to understand and carry out the invention and that it does not guide someone on how to select a particular compound or to narrow the range of possible compounds without undue experimentation. In essence, the court said, the disclosure fails to meet the enablement requirement because it describes a starting point for further research, not its successful conclusion[7].

The district court's decision in the *Rochester* case is now under review by the US Court of Appeals for the Federal Circuit.

Discussion

While the last word on the *Rochester* decision has yet to be written, current trends in biotechnology patent law suggest that the Federal Circuit may likely affirm the district court's decision. In what appears to be an attempt to craft policy allocating patent protection to those who actually carry out and describe experiments that fall within the scope of the patent claims, the Federal Circuit may be establishing a *de facto* 'actual reduction to practice' standard for biotechnology-based inventions. The *Rochester* case can be seen as an example of the district court following this lead.

Actual reduction to practice involves achieving an actual result or making a compound or apparatus that falls within the scope of the claims. In contrast, the patent laws provide that patents may be granted based on 'constructive reduction to practice,' which means that an inventor has prepared and filed a patent application complying with the written description, enablement and best mode requirements even though the invention itself may not have been in a form or state suitable for actual practice[12]. In decisions such as *Fiers, Amgen, Eli Lilly*, and now *Rochester*, courts have relied on the written description or enablement requirements to invalidate claims to subject matter not actually reduced to practice.

In such cases, the patentee resorts to claiming through functional language, that is, a ref-

erence to something by what it does, rather than to what it is structurally or chemically, because the specific structure of the sought-after molecule remains unknown at the time the patent application is filed. The Federal Circuit points out that functional claim language results in a claim whose scope is limited by the desired objective, not by the successful conclusion of research that defines the compositions that accomplish the objective. Allowing claims using functional language without evidence of actual reduction to practice thus results in the grant of patent rights to someone who conceived of a problem, but not its solution[7].

Given this trend, how can an early-stage technology developer adapt to secure maximum patent protection based on the work actually carried out? Obviously, if at all possible, patent filings should be delayed until there is actual reduction to practice of the claimed subject matter. Next, the US Patent and Trademark Office's (USPTO) written description guidelines make clear that functional characteristics may satisfy the written description requirement when coupled with a known or disclosed correlation between function and structure. Generic method of treatment claims not limited to a particular chemical entity might be supported (even without actual reduction to practice) based on the well-known correlation between a target nucleotide sequence (once actually reduced to practice) and the structure of antisense molecules and ribozymes that could be designed to inhibit protein expression or on the well-established ability to generate antibodies (preferably humanized) that can inhibit ligand binding or enzymatic activity[13].

In addition, inventors should recognize the value of assay claims. The risk that such claims will be invalidated on the basis of written description is minimized by including actual working examples (like those provided in the *Rochester* patent application), although an application that describes how to set up the assay using techniques well known to those of ordinary skill also should support such claims. These claims may be more difficult to assert since companies often hold as trade secrets their drug discovery methods.

With regard to the enablement requirement, a few observations are in order. It seems difficult to understand how making approximately 150 hybridomas and screening them to identify those secreting desired antibodies is considered by the courts to be "routine experimentation"[14], yet evidence in the *Rochester* case showing that Pfizer developed Celebrex by screening 600 compounds over an eight-month period[7] somehow was insufficient to rebut the enablement challenge to the University of Rochester's patent. One possible explanation is that the result is policy driven. The court may have felt that it was unfair, given the court's perception of the relative contributions of the University of Rochester and Pfizer to require Pfizer to pay a substantial royalty on its blockbuster sales of Celebrex. Another possibility is that the current scientific realities of high-throughput screening and structure-based design have not been adequately explained to the legal decision makers (judges and juries).

Conclusions

Federal Circuit decisions such as *Fiers, Amgen, Lilly,* and if affirmed, *Rochester*, appear to have established a *de facto* actual reduction to practice standard that risks lessening the real or perceived value and strength of intellectual property for early-stage biotechnology. How this affects the ability of institutions to fully protect early-stage technology and maximize return on research investment remains to be seen. The *Rochester* case raises many issues germane to modern drug discovery paradigms and points to a need for the courts to adapt to changing scientific norms. Unlike what was found in *Rochester*, will the courts eventually find that high-throughput drug screening processes are routine in the pharmaceutical arts? If so, shouldn't early-stage work on target identification support broad claims to methods of treatment? Assuming that target identification becomes the bottleneck in drug discovery, how will the patent system equitably allocate rewards to early-stage innovators and to those who underwrite the development and clinical testing of compounds? Can this be done without further escalating drug costs as layers of patent royalties stack on these products?

What is known is that the ability of universities to patent and license their technology creates measurable value. In 2000, academic discoveries resulted in the creation of over 400 startup companies and 300 new commercial products[15]. Though not all biotechnology related, these statistics attest to the significant economic and public health contributions resulting from universities' technology transfer activities. Courts should keep these contributions in mind when deciding the appropriate scope of protection to be accorded to early-stage innovators.

1. Mowery, D.C. *et al.* The growth of patenting and licensing by US universities: an assessment of the effects of the Bayh-Dole Act of 1980. *Research Policy* **30**, 99–119 (2001).
2. 35 USC, section 200.
3. USPTO data (http://www.uspto.gov/web/offices/ac/ido/oeip/taf/univ/univ_toc.htm).
4. GAO. R&D funding foreign sponsorship of US university research (http://archive.gao.gov/d34t11/135368.pdf), 33 (1988).
5. NIH data (http://grants1.nih.gov/grants/award/research/currcons5002.htm).
6. US Pat. No. 6,048,850 Claim 1 reads "A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment."
7. *Univ. of Rochester v. G.D. Searle & Co., Inc.*, No. 00-CV-6161L, 2003 US Dist. LEXIS 3030 (WDNY Mar. 5, 2003).
8. The University of Rochester received a separate patent, US Pat. No. 5,837,479, issued from a related application directed to screening assays.
9. 119 F.3d 1559, 43 USPQ2d (BNA) 1398 (Fed. Cir. 1997), *cert. denied* 523 U.S. 1089 (1998).
10. 927 F.2d 1200, 18 USPQ2d (BNA) 1016 (Fed. Cir. 1991).
11. 984 F.2d 1164, 25 USPQ2d (BNA) 1601 (Fed. Cir. 1993).
12. *Manual of Patent Examining Procedure*, edn. 8, section 2138.05, (Aug. 2001).
13. *Synopsis of Application of Written Description Guidelines* available at http://www.uspto.gov/web/menu/written.pdf.
14. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (BNA) 81 (Fed. Cir 1986), *cert. denied*, 480 U.S. 947 (1987).
15. Association of University Technology Managers survey (2000).