Navigating the future(s) of biotech intellectual property

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What changes, if any, can we expect in the system currently used to protect biotech inventions?

In the fifteenth century, Prince Henry of Portugal financed a school of navigation and mapmaking, which led to new and lucrative expeditions to Africa and the Indies. His investment helped usher in the great age of exploration, trade and innovation. Although it would not have been possible without both the maps and the newly designed ships, the maps in many respects held the real value. Indeed, the maps were treated as state secrets and closely guarded. Eventually the crown was forced to share the bounty of the seas with the private merchants and entrepreneurial explorers who organized the voyages, in part because the high seas could not be cordoned off like land, but moreover because rulers came to realize that the maps were only as valuable as the journeys that they made possible.

Today, the same interplay between science and commerce challenges the biotech industry. And what Henry the Navigator's closely guarded maps were for the age of discovery, patents are for biotech: the fundamental and defining business asset of the industry, and something to keep secure. Yet the role of intellectual property (IP) in biotech promises to become more, not less, complicated over the next decade, as the sector faces the need both to protect innovations and to open them up.

For patent holders—and the governments that provide a large portion of the funding needed to produce the inventions upon which patents are based—managing this IP wisely is no small challenge. In particular, one of the vexing problems going forward will be reconciling the needs of the biotech industry and its financial backers with the needs of government grant-makers and academic researchers. Likewise, although it is hardly a threat now, it is very possible that the biotech industry will be forced to make concessions to open-source research groups like BIOS (Biological Innovation for Open Society), which is headed up by the very determined Richard Jefferson, whose cause is rapidly gaining supporters.

Save for price controls and generic competition, the biotech industry's commercial fate will be dictated mainly by patents. The overarching question on every patent attorney's mind at every biotech company in the world is whether the patent systems in the two most important markets—the US and Europe—will over the next ten years remain intact, or be tweaked or overhauled? In all likelihood, the patent systems will stay largely as they are—and that means much needed reforms will sadly flounder. However, pressure is building to do something to assuage concerns that patents are stifling, not stimulating, innovation. There is a growing sentiment that IP rights are at least indirectly denying the public some of the biomedical and agricultural benefits that critics like Jefferson feel the public rightly deserves, as part of the social contract for which the patent system was established in the first place.

Whose patent is it anyway?

Over the past decade, the concern of the nonprofit sector is that industry has been amassing so many patents that the system, designed to provide incentives, risks inhibiting follow-on innovation. For example, as much as 20% of the human genome is claimed by patents, of which about two-thirds are owned by private firms[1]. More problematic is that the validity of the patents themselves is open to question. By one measure, over two-thirds of the DNA-related

How will biotech copmanies chart their course through the world of IP in coming years?

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patents make claims that are legally problematic because they are overbroad or improperly disclosed or because they overlap other patent claims[2]. Many in the industry and in academe believe that human genome–related patents will become increasingly important to biomedical innovation over the next ten years, perhaps even surpassing the scientific and commercial importance of the industry's first-generation patents like those covering PCR and recombinant DNA.

At the same time, the need to license numerous patents has given rise to concerns that this may create a 'patent thicket' that thwarts the development of a final product or procedure. Some even worry that the multitude of patents may lead to an 'anticommons,' whereby the granting of so many property rights actually leads to the underuse of the inventions (in contrast to the classic 'tragedy of the commons,' in which property rights are invoked to prevent a resource's overuse)[3]. Although a study commissioned by the US National Academies of Science argued that such concerns are overstated, the study's authors based their conclusions in part on the tendency of researchers to ignore or infringe patents—an ironic basis on which to justify public policy[4].

Furthermore, the governmental and nonprofit sector is wary of what it sees as the commercialization of academe. Around the world, many countries from Germany to Japan have implemented policies similar to the US's 1980 Bayh-Dole Act, which encourages universities to patent their inventions as a way to better bring them into the marketplace. Yet in a number of high-profile cases—such as Columbia University's recent attempts to claim new patents on gene-splicing technology invented in the 1970s by Richard Axel—the act has been criticized for distorting the noncommercial ethos of academia. Studies show that commercial ties often delay university research and make sharing material more difficult[5,6]. The US institutions that hold the most DNA patents are evolving their practices towards less exclusive licensing[7]. Still, as the number of patents increases, so may the problems. In 2004, US universities filed over 10,500 new patent applications and earned around $1.4 billion from IP licensing[8].

The global biotech industry needs to understand that the United States is not the only place where calls for change in the way biomedical innovations are patented can be heard. Likewise, it is unclear whether the global biotech industry appreciates the caliber of critics that are lining up against patents that are overly broad or inhibit biotech research—even if, on the surface, more investments in biotech are taking place.

In the United Kingdom, for example, a publicly traded firm called IP2IPO (Intellectual Property to Initial Public Offering) has invested millions of dollars in numerous universities in the country in return for a percentage of the schools' technology-licensing revenue and stakes in spin-out companies. Its first deal in 2000, an investment of £20 ($35.7) million in the University of Oxford's chemistry department, gives the firm an equity stake in the schools' technology until 2015. Sir John Sulston, the former director of the Sanger Institute in the UK, which sequenced one-third of the human genome, worries that such agreements undermine the integrity of universities, because there will be considerable pressure to patent technologies that might otherwise have been placed in the public domain for society's free use—which, after all, is the historic mission of academia.

There is currently no legal equivalent that can act alongside the patent system for protecting inventions to ensure that they are opened up—indeed, it is tricky to see how it might be put into practice.

Jefferson versus Jefferson

Nearly every country has a patent office. But few are under more pressure and scrutiny than the US Patent and Trademark Office (USPTO). Although the USPTO was established in 1790 by Congress, it was Thomas Jefferson who played a key role in its creation. Thomas Jefferson served as the USPTO's first patent examiner (even though he was extremely wary of granting them). Today, one of the most vocal critics of Jefferson's patent system is one Richard Jefferson, who runs BIOS. The modern Jefferson's chief complaint is that the IP system around the world is unfair and unwise. As such, he is fomenting a backlash against biotech patenting.

Thanks in part to his efforts, many discussions about giving academics and government researchers more access to patented biomedical discoveries, and activities to promote this idea, are cropping up. The initiatives take their inspiration from the open-source movement for software development, in which programming code is shared, not kept closed. Collaborations are starting to form, fueled in part by the Internet, which lowers searching and transaction costs, so people can more easily contribute their time and expertise, along with research tools like software or databases. Even if such collaborations don't work for higher-end research in a wet lab, their formation represents an important trend in the life sciences that industry needs to take note of.

Jefferson's BIOS initiative, organized by the Australian nonprofit research organization CAMBIA, has taken the unprecedented step of making technologies—including one that bypasses the preeminent *Agrobacterium tumefaciens* transformation process for transferring genes into plants—available under an open-source license. This lets researchers freely use the technique under the condition that others openly share any improvements. Although a buzzing community of researchers has yet to form around the innovation, it represents an early example of how a new model of biotech research could take hold, one that uses IP to enable openness and sharing, rather than simply enforce proprietary control.

In the information-technology sector, open-source practices have challenged the most important companies such as Microsoft, by making lower-level tools, such as operating systems, into commodities, so that innovation can take place at higher levels closer to the customers' needs, such as in applications. The same may happen in biotech for underlying research tools, bioinformatics software and access to data. Meanwhile, the information technology world has established other ways to overcome strict IP laws by harnessing aspects of the system itself—a jujitsu maneuver of law, whereby the opponents strength is used against him. In this instance, the strategy is to dilute the power of stringent copyright laws (that blindly assign 'all rights reserved' to any work), through a special licensing system from an international organization called Creative Commons. The licenses let the creators themselves choose what rules apply to their works.

Sulston of the Sanger Institute believes that devising a similar approach for biotech research would facilitate sharing, as opposed to the patent system's sole focus as a negative right to exclude others from practicing the invention. There is currently no legal equivalent that can act alongside the patent system for protecting inventions to ensure that they are opened up—indeed, it is tricky to see how it might be put into practice. Yet an offshoot of Creative Commons called Science Commons has formed to try to devise just such a mechanism.

Working around the lack of work-arounds

The open-source approach is just one of a number of ways that the IP system can be made more accommodating to different models of how science is performed. There are a myriad of ideas floating around for how to

tweak or overhaul the patent system, but few stand a chance of being implemented any time soon. For instance, there are calls to dramatically strengthen the USPTO's standard that an invention be 'nonobvious', considering that what may have seemed quite clever when biotech-related patents were first granted two decades ago may be quite ordinary, yet is now treated by patent office out of custom as nonobvious for the sake of granting the patent. Thus, the standards for granting a patent should change as the technology improves. However, although courts have toyed with the issue, generalizing this sort of rule puts the USPTO in the uncomfortable position of having to second-guess technology trends, and so it is not likely to happen.

However, there is one reform where the public-sector, academia and industry ought to be able to find common ground. It is establishing a research exemption from infringement on gene-related patents. The logic behind it is this: genomic materials are inherently unique, but unlike other technologies, they do not offer any possibility of a so-called 'work-around', whereby an alternative technical approach can yield the same benefit. This is because when it comes to genomics IP, comprising, for example, genes detecting disease susceptibility or encoding therapeutic proteins, substitutes are by nature not possible.

The consequences of such patents are that any work done in a particular area—be it to develop a commercial therapy or simply to perform follow-on research to understand a technology better—needs the approval of the patent holder. The entire domain could well be foreclosed to subsequent research and development. For example, the *BRCA1* and *BRCA2* genes underlying hereditary breast cancer, identified in part by a researcher at the University of Utah in 1994, were licensed exclusively to Myriad Genetics, which has a monopoly on testing and even went as far as to block a University of Pennsylvania researcher from using the technology by threatening to sue for patent infringement[9].

However, a sort of market failure exists, because the impossibility of a work-around was never anticipated in patent law. One of the ingenious features of the patent system is that it not only promotes innovation by handing out a temporary exclusive right to the inventor and requiring disclosure to the public, but it also encourages inventors to find alternative ways to do the same thing. Such copycat activity in some ways seems wasteful (and it might be; it is often more sensible to license the patent). However, a diversity of similar, but not exact, approaches actually represents the hallmark innovation; it generates the competition and subsequent 'creative destruction' that is the cornerstone of capitalism.

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Sensing a problem in this regard, the USPTO in 2001 implemented policies to apply stricter standards on what is eligible for a patent. Guidelines by the US National Institutes of Health issued in 1999 and updated in 2005 recommend that patented genomic materials be licensed on a nonexclusive basis[10,11]. A report by the National Research Council of the US National Academies of Science in November 2005 echoes the position, and adds that research 'on' genomic materials (as opposed to 'with' the materials) be exempt from infringement[9]. Independent test verifications should receive a statutory exemption from infringement, the report baldly states.

It is clear that the lack of a potential for a work-around represents an enormous vulnerability in how the patent system operates for biotech research, which can easily create huge concerns for society. Providing for a research exemption is in everyone's interests—and is a low-impact solution to a high-impact problem.

You have the right to remain frustrated

When *Nature Biotechnology* was launched a decade ago, it felt the need to publish "A Benchside Guide to Patents and Patenting" in its inaugural issue, as well as a legal analysis of inventors' rights[12,13]. The choice of articles was emblematic of the commercial changes in the sector, and the growing importance of IP. Likewise, over the next ten years, the open-source activities may come to be seen as a marketplace solution to a marketplace problem.

Support for open-source practices comes amid a deeper shift in how innovation happens. Although the private-sector is now shouldering more basic research, there is a growing preference among venture capitalists and acquisitive pharmaceutical firms for biotech companies with products that have some clinical validation, as a safeguard that they're picking a winner. The implication is that biotech companies won't be given the capital or time to do early-stage or risky research. And that, ironically, leaves a big opening that academia can fill because it can rely on the public purse, follow blue-sky inclinations and enjoy longer time-horizons. The risk to the biotech industry that will arise, if academia does move aggressively to fill this gap, is that the public and nonprofit sector will put greater pressure for bigger changes in the patent system. It is unclear whether academe has the political clout to change much, but the biotech industry ignores their gripes at its own risk.

What is certain is that the rapport between the public and private sectors in biotech is in flux, and if history is any guide, the long-term trends favor both greater commercialization and more openness. Indeed, the experience of Henry the Navigator served as an appropriate precursor to today. Where private ships once plied the waters in search of riches, now the cofounder of Celera Genomics, J. Craig Venter, is looking to identify new forms of micro-organisms from his 95-foot sloop *Sorcerer II*. In the Middle Ages, cartographers identified unchartered areas by simply writing "*hic sunt dracones*." The fear of sea monsters was meant to ward off explorers. But such attempts to stall pioneers, then as now, never work for long.

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