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Models of Technology Transfer for Genome-Editing Technologies

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Abstract

Many of the fundamental inventions of genome editing, including meganucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR, were first made at universities and patented to encourage commercial development. This gave rise to a diversity of technology transfer models but also conflicts among them. Against a broader historical and policy backdrop of university patenting and special challenges concerning research tools, we review the patent estates of genome editing and the diversity of technology transfer models employed to commercialize them, including deposit in the public domain, open access contracts, material transfer agreements, nonexclusive and exclusive licenses, surrogate licenses, and aggregated licenses. Advantages are found in this diversity, allowing experimentation and competition that we characterize as a federalism model of technology transfer. A notable feature of genome editing has been the rise and success of third-party licensing intermediaries. At the same time, the rapid pace of development of genome-editing technology is likely to erode the importance of patent estates and licensing regimes and may mitigate the effect of overly broad patents, giving rise to new substitutes to effectuate commercialization.

INTRODUCTION

Genome editing is one of the most revolutionary breakthroughs in biotechnology: a versatile set of techniques that are equal parts research tool, technology platform, and molecular therapy (9). As the name suggests, the technology allows researchers to edit the genome of a living cell at any specific location within the larger genome by precisely cleaving the DNA at that location and exploiting the cell's natural DNA repair mechanisms to delete or insert DNA at the cleavage site (27, 42, 67). Researchers have also expanded the uses of genome-editing systems to edit RNA, regulate gene expression, and change single nucleotides (30, 44, 106). While genome editing, broadly speaking, encompasses several technologies, the precision, ease, and flexibility of one recently developed technique, CRISPR (an abbreviation for "clustered regularly interspaced short palindromic repeats"), have led one of its progenitors to describe it as the "Holy Grail of genome editing" (43).

Many of these genome-editing technologies were originally developed at universities with an eye toward multiple possible uses, including use as a research tool; use in industrial biotechnology; use in livestock or crops; and, especially, use in human therapies (28, 34). This has made technology transfer for genome editing a complex affair, with universities and research institutions employing a panoply of strategies for commercializing genome editing. Some of these strategies include material transfer agreements (MTAs), controlling access to important data and methods, and the use of nonprofit, third-party intermediaries (18, 68, 117). And, as is to be expected, they also include the formal acquisition and licensing of traditional intellectual property (IP) rights—particularly patents (34, 85).

Many genome-editing inventions have been and are continuing to be patented (34, 85). These include not only the first genome-editing tools, meganucleases, which were elucidated in the 1990s and 2000s (26), but also zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR, not to mention vectors for all of the above (10, 18, 26, 115, 121). Patent landscapes for these technologies are global and varied, held by researchers hailing from many different types of research institutions and companies around the world (34, 85). The range of technologies and, consequently, the future patent landscapes in this area are expected to continue to diversify (119).

Across this array of genome-editing technologies, patents have been involved in several disputes, including among academic research institutions. Patents over meganucleases originally licensed from Duke University and the Pasteur Institute were disputed for years (77). Academic institutions' licensing practices for ZFNs sparked controversy (18, 117). And several of the core patents over CRISPR/Cas9 have been involved in a dispute between the Broad Institute and the University of California, Berkeley (119). As a consequence, a policy debate has grown regarding best practices for licensing genome-editing technologies (28, 34, 39, 68).

This is, of course, not the first time that revolutionary biotechnologies have experienced friction surrounding their patent-licensing practices. The Bayh–Dole Act—the 1980 law that streamlined rules for institutions to take title to patents on inventions resulting from federally funded research—was enacted contemporaneously with the rise of research on recombinant DNA (120). This law greatly expanded university technology transfer, giving rise to offices dedicated to the practice at many universities that did not have them before. It also led to the intensification of the practice at those universities that were already actively engaged in licensing their technologies (36). In subsequent years, the rapid development of biotechnology and increased sophistication of technology transfer offices led to several controversies surrounding research institutions' patent-licensing practices (47, 101). While many of these controversies have since subsided, if not been entirely resolved, this has not led to research institutions adopting and adhering to a single standard of best practices.

To the contrary: As molecular biology has developed and grown more complex, so too has the diversity of approaches to technology transfer. Today, many technology transfer and patent-licensing strategies are available and being used for genome editing, including surrogate licensing, which entails the employment of a for-profit surrogate to sublicense a technology on behalf of a university (28); direct and indirect exclusive licenses to other commercially minded entities (77); direct nonexclusive licenses doled out to multiple parties (102, 136); open licenses and research MTAs, which are available to all comers who meet certain criteria, such as nonprofit status or noncommercial research and development (69); auctions of licenses (84); and IP-free models, where the originating researchers essentially dedicate all of their work to the public domain (105). Importantly, not all of these models are mutually exclusive. Depending on the specific genome-editing technology and application, research institutions may—and do—pick and choose among these models in an effort to best transfer that technology to market applications (28). This makes sense: Given the breadth of genome editing, one size does not fit all. Yet the choice of technology transfer models used by research institutions has a lasting impact on how the technology is developed and utilized.

This diversity in technology transfer models for genome editing has several implications for the future of biotechnology licensing practices. First, there is an imperfect trade-off between the virtues and vices of a multifaceted approach to licensing: It allows institutions to experiment with and tailor competing models, which variously narrows or expands the scope of exclusivity for each application. We characterize this below as a federalism model of technology transfer. Second, it shows how rapidly developing areas of biotechnology, such as genome editing, may outpace licensing practices, with new applications of CRISPR outside the scope of legacy patent estates being a prime example (119). And third, it suggests the future significance of some licensing practices without perfect historical antecedents—such as nonprofit, third-party intermediaries (69). This article explores the history of these developments in technology transfer, reviews the landscape of patent estates for genome editing, describes the current licensing models and technology transfer approaches as applied to genome-editing technologies, and discusses the implications of these models before suggesting areas for future research.

TECHNOLOGY TRANSFER MODELS THROUGHOUT HISTORY

Technology Transfer Models Before Bayh–Dole

Historically, the patenting of inventions made at universities was influenced at least as much by the norms of science as by formal public policy (75). While the frontiers of science have often stretched well beyond the scope of patentable subject matter, in both the United States and Europe, professors doing research within patentable subject matters would occasionally apply for patents as individuals. For example, William Thomson (known more famously as Lord Kelvin), a professor, dean, and then chancellor at the University of Glasgow from 1846 through 1907, patented more than 70 inventions covering a wide range of instruments and measurement devices in his own name (132). In other cases, professors working in close collaboration with industry partners often followed the norms of industry consultancy or internships and directly assigned inventions to their industry partners. Fritz Haber, a professor of physical chemistry at the Karlsruhe Institute of Technology, patented his 1909 invention of a high-pressure, scalable nitrogen fixation technique to produce ammonia and then assigned it to BASF (54), where he was collaborating with Carl Bosch, resulting in the enormously impactful Haber–Bosch process that remains the mainstay of fertilizer production to this day (124). In German-speaking and Scandinavian countries, public policies emerged by the mid-twentieth century to enshrine the so-called professor's exemption—deviating from standard laws of employees being "hired to invent"—such that that professors were not obligated to assign patent rights to their university employers (72).

The modern proliferation of university patenting and licensing is often considered to begin, at least in the United States, with the 1980 Bayh–Dole Act and the lesser-known but also important Stevenson–Wydler Act, both of which streamlined rules allowing research institutions to take assignment of patents on inventions created with federal research funds (36). Yet the main models of university technology transfer emerged long before 1980 (91, 92, 101, 120). The practice arguably derived from the pragmatic norms and decentralized governance structures of the land-grant university system in the United States, where results of research were more likely to be useful in commercial applications, to fulfill regional economic development objectives, and to fall within the legal scope of patentable subject matter (112).

In the first decades of the twentieth century, several pioneering US land-grant university inventors influenced the development of three basic approaches to university patent management, which were taken up at leading universities by the 1930s and still largely define the organizational structures of university technology transfer today (126). The first arrangement was the Research Corporation, established in 1912 as a licensing organization to manage patents on the "cleantech" electrostatic precipitation inventions made by Frederick Cottrell at the University of California, the first of which was filed in 1906 (29). The Research Corporation was an independent entity that managed patents as a service and later expanded to manage inventions arising beyond the University of California, effectively establishing its business model as a third-party technology licensing agency. By the 1970s, it was serving hundreds of research universities (91).

The second arrangement was the internal management of patents by the university administration—often in the office of the university general counsel—as was done at the University of California for the 1915 invention by T. Brailsford Robertson of tethelin, a pharmaceutical pituitary extract (111). This model was replicated at the University of Minnesota for the 1916 invention by Edward Kendall of a pharmaceutical thyroid extract at the Mayo Clinic (71, 142).

The third arrangement—a sort of compromise between the previous two models—was a university-affiliated research foundation, beginning with the Wisconsin Alumni Research Foundation (WARF), founded in 1925 by several wealthy alumni of the University of Wisconsin to manage the invention by professor Harry Steenbock of vitamin D fortification of foods through irradiation (2, 127). Most significantly, these developments established the principle that an invention could be patented and assigned to the academic institution as a credible, if controversial, practice within the scientific community (103).

Technology Transfer from Cohen–Boyer to Bayh–Dole

During the decade prior to the Bayh–Dole Act, Stanley N. Cohen and Herbert W. Boyer of Stanford University and the University of California, San Francisco (UCSF), respectively, filed for patents on their breakthrough in the use of restriction enzymes to genetically engineer bacteria. The Cohen–Boyer invention has perhaps been the single piece of technology most responsible for establishing precedent concerning the licensing of biotechnology research tools by academic institutions (63). That precedent, a licensing program developed by Niels Reimers at Stanford University, centered on broad and nonexclusive licensing, recognizing the political sensitivities of the universities seeking patent protection over, essentially, techniques for doing research (110). Over the life of the technology's licensing program, the Cohen–Boyer patents were licensed to more than 450 companies, enabled more than 2,400 new products with more than $35 billion in product sales, and brought more than $250 million in royalties to Stanford and UCSF (40).

Only 10 days after the first of the Cohen–Boyer patents were issued by the US Patent and Trademark Office, President Jimmy Carter signed the Bayh–Dole Act into law, uniformly allowing inventions created with federal funding to be assigned to the universities where they were created

(120). The act's objective was to encourage commercial development of the results of federally funded research—not, as has become a common misconception, to simply allow universities to collect royalty income based on their researchers' successes (36).

The actual changes in federal policy that the Bayh–Dole Act introduced were relatively minor—essentially, a harmonization of federal agencies' rules for federal contractors to patent inventions made while working under a federal contract, and a clarification that universities, as contractors, could take title to inventions that occurred under federal research grants (101). But the legislation effected a paradigmatic if not cultural shift among research institutions, spawning a wave of technology transfer offices at hundreds of universities in the United States (104).

Whether this shift was the result of Bayh–Dole or other factors is, even today, not entirely clear (91). The expectations set by the Cohen–Boyer royalties and similar successes by a handful of other major university inventions may have influenced university administrators who saw that patent royalties could become a significant source of discretionary revenue. And this attraction persists even though the preponderance of evidence continues to suggest that only a very small number of exceptional inventions yield such returns (114). Today, most universities' patent portfolios do not earn positive net returns from licensing in the long run (16). Whether technology transfer will come to be seen as a service for faculty—even if not profitable—or as a mechanism to encourage more engaged research remains to be seen. But efforts in the area have led to robust experimentation, some of which has resulted in missteps and course corrections along the way.

TECHNOLOGY TRANSFER MODELS FOR RESEARCH TOOLS: CASES AND CONTROVERSIES

While the Bayh–Dole Act focused on using patents to move university research into commerce, the increased tendency of patenting research tools presented several challenges. By their very nature, research tools, such as methods, biological materials, reagents, equipment, software, and databases, are often developed in academic laboratories in response to the needs of ongoing research. Their value lies in reducing the costs or increasing the feasibility of future research and innovation in both academia and industry (100).

The patenting of research tools consequently presents two main complications. First, a given invention can have a dual nature, being useful both upstream as a research tool and downstream as a component of a commercial product or process. For its upstream uses, it is socially optimal for a technology to be made broadly and widely available—at merely the marginal cost of production and distribution of the tool—since proprietary or strategic withholding of research tools can slow innovation rates or distort the direction of research and development across the entire economy (140). For downstream commercial applications, exclusivity in the marketplace or royalties from other users can be crucial in ensuring that returns can cover the fixed investments required. Yet the extent and nature of these possible downstream applications may be highly speculative and uncertain at the time of the invention in an academic setting, complicating licensing practices (96). This gives rise to the challenge of managing the IP to allow for relative nonexclusivity for upstream uses, while also allowing for eventual exclusivity for downstream uses—if and when needed to incentivize product development.

The second complication, especially in new fields of technology, arises from patents covering research tools that often end up being excessive in scope—both broader than what was invented and broader than needed to further develop the technology through licensing. Some of this breadth stems from patent law doctrines and economic incentives that encourage applicants to claim the full scope of a new tool they have created in the early days of a new technology, even while patent examiners have only limited prior art to assess such applications. The messy dual

nature of research tools and the problem of overly broad claims have been particularly salient for biotechnologies, which have long posed challenges for both patent law and university technology transfer policy. The realization of commercial opportunities created by new research tools has—aside from the broad, nonexclusive licensing practices demonstrated in the Cohen–Boyer case—depended on three different regimes in varying combinations: exclusive licensing, MTAs, and IP-free or public-domain models. Examples of each of these models—and their controversies—have informed the emergence of normative values concerning technology transfer practices among research institutions. We review cases from each of these models below.

Exclusive Licenses

Individual genes—their sequences and functions—are a canonical example of a dual-nature biotechnology research tool, both a means to further research and an integral component of commercial products. Genes have been the subject of patents and exclusive licenses under the auspices of government-sponsored research (120). As they began to proliferate in the 1990s with improvements in sequencing, exclusively licensed gene patents were viewed as counterproductive to the very research being promoted by the government (37, 45, 61).

One set of such patents, pertaining to the genes *BRCA1* and *BRCA2*, originated at the University of Utah and were licensed exclusively to Myriad Genetics, which managed them in a manner that caused significant controversy (120). The patents were eventually challenged by a coalition of other researchers and patient advocacy organizations in a case that wound its way to the US Supreme Court. In its 2013 decision, *Association for Molecular Pathology v. Myriad Genetics* (6), the Supreme Court disallowed composition-of-matter claims to isolated DNA molecules that had naturally occurring sequences. The opinion homed in on "the considerable danger that the grant of patents would 'tie up' the use of such tools and thereby 'inhibit future innovation premised upon them'" (6, p. 589). An empirical analysis looked at how many US patents had claims of the sort that were invalidated by the *Myriad* decision and found that academic and government assignees accounted for fully a third of such patents, with the University of California, the University of Washington, Johns Hopkins University, the University of Texas, and the US National Institutes of Health (NIH) among the top assignees of such research-tool gene patents (48).

The patents on methods for deriving human embryonic stem cells and the resulting cell lines, which were granted in 1998 to the University of Wisconsin and WARF (131), posed a more complex set of challenges (139). Federal funding for embryonic stem cell research had been long contested due to its reliance on the destruction of fertilized human embryos. Thus, it was largely a private firm, Geron, that sponsored the research leading to the invention. WARF granted an exclusive commercial license to Geron for therapeutic applications of human embryonic stem cells. Then, after federal funding was further curtailed under the Bush administration in 2000, a few state-level initiatives were set up to finance stem cell research, the most significant being the California Institute of Regenerative Medicine (CIRM). In a resource-poor environment, WARF sought to require commercial licenses from companies, even when the companies sponsored stem cell research at academic and nonprofit institutions. Under this approach, WARF sought to establish a royalty-bearing license from CIRM for CIRM-funded research at California universities and research institutions. And, beginning in 2006, WARF also sought royalties for the derivation and use of induced pluripotent stem cell lines, which emerged as a competing technology from discoveries at the University of Kyoto, the Massachusetts Institute of Technology (MIT), and elsewhere. After pressure and criticism mounted, including a reexamination of the underlying patents in 2006, WARF relaxed these positions (53). Still, it was WARF's original sponsor and exclusive licensee, Geron, that in 2009 initiated first-in-human phase 1 clinical trials of a therapy

based on human embryonic stem cells (20). Some of the original patents have since expired; given the paucity of approved human stem cell therapies, it is unclear whether the cost of such licenses ultimately hindered the technology's potential or other technical, regulatory, or ethical factors are what held it back.

In some extreme cases—and contrary to the objectives of the Bayh–Dole Act—universities have sought to assert research-tool patents to collect royalties on already-developed drugs without actually facilitating the development of those drugs. In one instance, the University of Rochester obtained, in 2000, a patent covering methods to assay drug candidates that inhibit the *COX2* inflammation pathway. The university then sued the pharmaceutical company G.D. Searle, which had launched a *COX2* inhibitor, Celebrex, two years earlier in 1998 (35). During the litigation, no licensee of the university's invention who had been harmed by competition from Searle was disclosed, nor had Searle needed the protection of the Rochester patent as an incentive or asset to develop Celebrex. Rochester lost its case in 2003, and the patent was declared invalid (133). In a similar instance, MIT licensed its NF-κB-inhibition screening patent exclusively to Ariad Pharmaceuticals, which—with no product even under clinical trials at the time—then proceeded to sue Eli Lilly and Company, the developer of two NF-κB-inhibitor drugs, Xigris and Evista (41, 107). Ariad and MIT lost their case on validity grounds, including a complex statutory dispute (3). But again, there was no evidence that MIT's exclusive licensing regime furthered the development of any particular product. Debates about universities' enforcement of their patents against commercial developers have become part of a larger debate about patent enforcement by nonpracticing entities or so-called patent trolls (8, 76).

Of course, universities are not the only source of research tools. Commercial companies can be quite aggressive with patents on research tools they come to control, frequently pursuing a winner-takes-all strategy. One of the most infamous cases concerned Monsanto's use of patents covering *Agrobacterium*-mediated transformation of plants—a widely used research tool in crop research—to assert broad dominance in the commercial development of genetically modified crops (99). *Agrobacterium* is a complex technology, with variants for its use in different plant species (99). But the core inventions resulted in a three-way patent dispute between Washington University in St. Louis, the Max Planck Society for the Advancement of Science, and Monsanto (21). Monsanto's acquisition of additional *Agrobacterium*-related patents through exclusive in-licensing and the purchase of smaller agricultural biotechnology companies, such as Agracetus, Asgrow, Calgene, and DeKalb, followed a strategy of combining protections over research tools, trait genes, and elite breeding lines (49, 66). After this consolidation, Monsanto engaged in aggressive enforcement against farmers (93) and declined to out-license the core research tools for use in crop species or markets that it was not pursuing (50).

Complexity arising from multiple exclusive licenses—from different academic institutions—has also proven problematic. This was the case with RNA interference (RNAi) technology, a tool for suppressing gene expression that has enabled an entirely new class of therapeutics (56) and crop traits (24). Beginning in 1998, key patents were filed by the Carnegie Institute of Washington, the University of Massachusetts, MIT, the Whitehead Institute for Biomedical Research, and the Max Planck Society (116). Overlapping ownership and licensing responsibilities were negotiated in two interinstitutional agreements in 2001 and 2003. In between, one of the technology's lead inventors founded Alnylam Pharmaceuticals and took exclusive licenses to several of the core RNAi inventions, with a strategy to aggregate and build on them for the development of human therapeutics. In 2009, however, conflict over ownership and the management of these licenses erupted in a lawsuit between the Max Planck Society, on one hand, and the Whitehead Institute, MIT, and the University of Massachusetts, on the other (87). Alnylam joined the side of the Max Planck Society, but the case was settled out of court, with the four academic institutions agreeing to

common ownership and to exclusively licensing the patents in question to Alnylam (135). Alnylam remains, to date, the only company successful in developing a therapeutic product licensed from these original RNAi research-tool patents (57, 79).

Material Transfer Agreements

The advance of the life sciences has long involved the exchange of physical biological materials, including whole organisms, reproductive materials (seed, sperm, and eggs), tissue samples, cell lines, plasmids carrying key segments of DNA, and other components that embody the complex biological systems being studied. Traditionally, academic laboratories, upon request from other researchers, share these materials by shipping them to the requesting laboratory, and many view such sharing as an inherent public service of the scientific community (15).

Over time, a range of banks, repositories, and biological resource centers emerged to help curate biological materials and fulfill such requests (109). The oldest still in existence may be the seed banks of the US Department of Agriculture, some of which date back to 1897 (113). Cells and tissues have similarly been deposited and disseminated by the American Type Culture Collection since 1925 for scientific research purposes—and, due to a feature of patent law, as support for patent filings (37 C.F.R. § 1.802). In fact, 47 similar depositories worldwide are currently recognized under the Budapest Treaty for microorganisms and other biological materials (144). The Jackson Laboratory has, since it was established in 1929, specialized in mice as a model research organism and has served as a leading animal repository for dissemination of laboratory mice (88). And the Developmental Studies Hybridoma Bank was founded in 1986 at the University of Iowa as a repository to curate and disseminate the hybridomas that produce monoclonal antibodies (32). Such biological resource centers have long served as a means of preserving, curating, and distributing research tools.

As academic institutions began to patent such research tools, the use of MTAs—essentially, contracts—arose as a mechanism to formalize the legal terms of direct exchange of biological research tools between institutions (15). To facilitate the management of these agreements, differentiate them from commercial technology transfers, and minimize transaction costs, the NIH developed and published the Universal Biological Material Transfer Agreement (UBMTA) in 1995. The UBMTA, perhaps more than any other legal innovation, helped streamline the exchange of research tools among research institutions funded by the NIH (38, 95). Among its many provisions, the UBMTA stipulates general rules about how materials can be used, including the rule that use be limited to nonprofit research institutions. The UBMTA limits how and when materials can be transferred on to third parties and caps fees at the costs of providing the materials to the recipient (15).

As the number of exchanges continued to proliferate, particularly for DNA plasmids, the fulfillment of requests and the management of MTAs became a time-consuming and expensive proposition for research laboratories focused on doing many things other than supplying plasmids. In 2004, researchers at MIT and Harvard established Addgene, an independent nonprofit repository for DNA plasmids designed to solve this problem (59). It now ships well over 100,000 plasmids each year to researchers all over the world, with each shipment accompanied by a standardized, take-it-or-leave-it, electronic version of the UBMTA (69). In this sense, Addgene operates as a centralized materials transfer, product curation, quality assurance, and shipping organization. In addition to nonprofit repositories, as biological research has advanced, a range of commercial collections, private collections, and commercial biobanks—including associated bioinformatic and clinical or field data—have grown as well, competing in an increasingly market-like exchange of materials and data between laboratories with ever-greater legal encumbrances (143).

IP-Free Models

Although universities and science-funding agencies have sought to maintain the distinction between the dissemination of research tools for scientific pursuit and the commercial development of product and process innovations, cases of research tools wholly unencumbered by patents are increasingly rare. One prominent example, however, is that of the hybridoma technique for making antibodies, pioneered by Georges Köhler and César Milstein. About the same time that Cohen and Boyer were patenting their technique for genetically engineering bacteria, Köhler and Milstein, at the Medical Research Council Laboratory of Molecular Biology in Cambridge, United Kingdom, developed the hybridoma technique for producing antibodies, first published in 1975 (74). (They received a Nobel Prize for their work in 1984; notably, Cohen and Boyer never received Nobel recognition for their invention, although Paul Berg was recognized in 1989 for his work leading to the field of recombinant DNA.) The National Research Development Corporation, which at the time handled patenting of results from research supported by the British government, declined to patent the hybridoma technique (80). As a result, the methods, together with the cell lines necessary for the technique, were made readily available and diffused quickly throughout the scientific community, some contemporaneous patents from others in the field notwithstanding (130). A retrospective of this case concluded that the absence of patents on hybridoma cell lines had a positive effect on research, both advancing the field of immunology and giving rise to one of the earliest profitable sectors of the biotechnology industry: diagnostic and therapeutic monoclonal antibodies (81).

The Emergence of Technology Transfer Norms

In response to the challenges of making complex decisions about the patenting and licensing of research tools, funding agencies and technology transfer professionals began crafting formal guidelines for technology transfer practice. In 1999, the NIH published its sharing policy for research tools as "Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources" (96); in 2005, the NIH published the final draft of its "Best Practices for the Licensing of Genomic Inventions" (97). And shortly thereafter, in 2007, the leadership of several university technology transfer offices convened to draw up a set of guidelines titled "Nine Points to Consider in Licensing University Technology," which dealt almost entirely with the challenges of licensing technologies with research-tool characteristics. These guidelines were subsequently endorsed by the board of the Association of University Technology Managers and more than 100 universities and research institutions (7). These documents draw lessons from the history of technology transfer for research tools and argue that each technology is unique in content and context and that simple, absolute rules are therefore insufficient for assuring optimal outcomes in all cases (7, 96, 97). Even when an invention is useful only as a research tool, there are multiple possibilities for how the technology could be developed and, as a consequence, managed. When an invention is useful both as a research tool and as a component of a downstream commercial product or process, these challenges are multiplied. The remainder of this article explores the extent to which these lessons of history have been applied in the commercialization of genome-editing technologies.

GENOME-EDITING TECHNOLOGIES AND THEIR PATENT ESTATES

Genome-editing technologies first emerged in the late 1990s against this historical backdrop; to date, they include meganucleases, ZFNs, TALENs, and CRISPR. While CRISPR has arguably attracted the greatest public and scientific attention, the approaches that preceded it were also

significant breakthroughs and were deployed for both research and therapeutic uses. To a large extent, these genome-editing technologies were originally developed at universities and public research institutions, which then patented and licensed them to industry. While we identify them here as separate technologies, they utilize and build upon similar strategies of targeting restriction endonucleases and are thus closely related to one another (83). University researchers have also been responsible for creating—and patenting—vector technologies needed to transport these various molecular genome-editing systems into living cells (121). We briefly review these technologies and their foundational patent estates.

Meganucleases

Meganucleases are naturally occurring large nucleases that possess a large DNA-binding domain—sometimes spanning as many as 40 base pairs (128, 137). The size of these DNA-binding segments means that any genomic sequence complement is likely to occur only once in a given genome (23). In this sense, meganucleases are thought of as single-cut enzymes with minimal risk of off-target cleavage (137). In the wild, there are hundreds of meganucleases, from a variety of bacterial species (128). Given their specificity, however, they cannot be readily engineered to specific genomic sequences; their utility lies in their diversity and the ability to select from the wide variety of naturally occurring options (128).

Meganucleases were the subject of a variety of patent applications when first discovered (26). Duke University licensed its 2005 meganuclease inventions (125) exclusively to a faculty startup, Precision BioSciences. A rival company, Cellectis, a 1999 startup from the Pasteur Institute, also aimed to commercialize meganucleases, licensing patents from the Pasteur Institute and Pierre and Marie Curie University (33). Cellectis continued to developed its meganuclease technology in-house (4, 5). A patent dispute arose between Precision BioSciences and Cellectis in 2008 (18) that was not resolved until 2014, when several of the original meganuclease patents were invalidated and a cross-licensing agreement between the rivals was reached (77). With the advent of ZFNs and TALENs, interest in meganucleases waned (94), a possible contributing factor leading to the settlement.

Zinc Finger Nucleases

ZFNs are recombinant proteins, hybrids of zinc finger proteins—a broad class of transcription factors utilizing zinc in their catalysis—and a restriction enzyme, typically Fok1 (134). Each zinc finger protein used in ZFN engineering can recognize a different triplet nucleic acid sequence (134). These proteins can then be linked together, allowing engineers to target relatively long stretches of DNA—long enough, in many instances, to be unique to a specific site in the genome (134). This system can be further designed to insert and modify DNA around the cleavage site (134). ZFNs are not entirely modular, however, because there are often interacting effects among individual zinc finger proteins that diminish their effectiveness and specificity (82, 137). Knowledge of which combinations of zinc finger proteins can bind to which sequences—termed the zinc finger rule set—has therefore been valuable in developing operable, recombinant ZFNs that are unique to a single genomic site (117).

Like other genomic engineering technologies, ZFNs were developed first in academic laboratories, notably at MIT, Johns Hopkins, the California Institute of Technology, and Harvard (19). While different aspects of the ZFN system were patented by universities, one company, Sangamo Biosciences, sought and successfully negotiated exclusive or field-specific exclusive patent licenses to a large portion of the originating research institutions' IP to commercially develop human therapies using ZFNs (19). These licenses added to Sangamo's already large patent portfolio

covering other aspects of the ZFN technology as well as a proprietary rule set (117). This amounted Sangamo having "consolidated the majority of this patent estate" and exercising "monopoly control over an important and versatile research platform" (19, p. 140). Sangamo is now widely considered to have built an IP fortress in the area, including patents covering the design, selection, and optimization of ZFNs (19). A ClinicalTrials.gov search shows that the company has initiated several clinical trials of ZFN-based therapies—for treating HIV as of 2009, hemophilia and mucopolysaccharidosis as of 2016, and beta thalassemia as of 2019. Moreover, Sangamo is the only company to have initiated clinical trials of ZFN-based therapies, even though the technology has existed for more than 20 years.

Transcription Activator-Like Effector Nucleases

TALENs are another class of nucleases useful for genome engineering. TALENs are fusion proteins consisting of two components: a DNA-binding domain, known as a TAL effector DNA-binding domain, and a nuclease (25, 78). TAL effectors—proteins from the plant-infecting bacterial genus *Xanthomonas*—have largely conserved amino acid sequences (12), with high variability around two amino acids at positions 12 and 13 (12, 90, 115). These amino acids can be altered to bind to a variety of DNA sequences in what has been described as "a simple cipher" (90). TALENs can then be linked together modularly—more easily than ZFNs—to recognize and cleave a specific site in a genome (137). With the addition of exogenous DNA, engineers can then rely on endogenous cellular repair mechanisms to edit the genome (137).

TALENs were originally developed by researchers at Iowa State University, the University of Minnesota, and Martin Luther University of Halle-Wittenberg in Germany (12, 25, 78, 90, 115). Like their sister genome-editing technologies, fundamental uses of TALENs were patented by these institutions (13, 138). The patents issued to Iowa State and the University of Minnesota were licensed exclusively to Cellectis and its US subsidiary, Calyxt, a startup founded by the inventors at Iowa State and the University of Minnesota (115). The patents granted to Martin Luther University were licensed (in agriculture, at least) exclusively to a US nonprofit organization, the 2Blades Foundation (115). The foundation has been dedicated to widely dispersing TALENs for agricultural applications, centered largely on its long-standing sublicensing efforts for agricultural commercial applications, included licenses to Calyxt (115). To date, Cellectis and Calyxt have maintained arguably the preeminent patent position for TALENs, for both agriculture and human therapeutics (10, 26, 115).

CRISPR

CRISPR is the newest genome-editing technology and has a wide variety of applications, from precise genome editing to sensitive detection of specific nucleic acid sequences for diagnostic purposes (9, 46, 62). Its most heralded application, though, is likely genome editing for therapeutic purposes. This system's most basic form requires only two components: a type II CRISPR nuclease (with Cas9 being the most well understood) and a single guide RNA—a short piece of RNA that both activates the CRISPR nuclease and directs the enzyme to a complementary portion of the DNA in the genome to cleave (27, 42, 67).

The patent estate for CRISPR/Cas9 has been controlled primarily by two research institutions: the Broad Institute, stemming from work done by Feng Zhang, and the University of California, stemming from work done by Jennifer Doudna and Emmanuelle Charpentier (affiliated with the University of Umeå, in Sweden, at the time of her contribution) (28, 34). In addition, Virginijus Šikšnys (Vilnius University, Lithuania) was a substantial contributor to the core technology and filed some of the earliest patents on CRISPR/Cas9 (123). A complex set of licenses, sublicenses,

and cross-licenses as well as surrogate licensing companies—some of which have begun clinical trials—define the patent landscape of CRISPR/Cas9 (28). The situation has been made yet more complicated by an ongoing dispute over the scope of the foundational patents and thus the technology's ownership in both the United States and Europe (39, 119).

Since the foundational patents were filed, several other entities have also obtained patent protection on various aspects of CRISPR, including the research-tool companies Sigma-Aldrich and ToolGen (22, 73). The landscape of patents and patent applications—from both universities and the private sector—has continued to increase throughout the world as the applications of CRISPR have continued to diversify (34).

Genome-Editing Vectors

Genome editing's promise cannot be realized without vectors to insert the genome-editing machinery into and express it within living cells (60, 141, 145). There are an almost endless variety of genome-editing vectors, including physical insertion mechanisms, viral vectors, and even synthetic nanoparticles (121). Recent successes in human gene therapy have demonstrated the importance of improvements in vector technology. Spark Therapeutics (now owned by Hoffmann–La Roche), for example, developed an adeno-associated virus vector for ocular delivery of an episome coding for RPE65, the absence of which causes degenerative blindness in childhood. Spark's product, Luxturna, was recently approved by the US Food and Drug Administration after a long history of failures for other viral vectors (108).

The diversity of vectors for genome editing is characterized by a significant patent landscape, including methods of using and manufacturing them (34, 121). Some—such as ex vivo T cell modifications—were developed by universities and subsequently licensed to commercial developers (121). Others—such as Spark's adeno-associated virus technology—were developed mainly in the private sector (108). In addition, patents concerning vectors' use and manufacturing are also held by a range of parties, complicating development and licensing (121). These patents do not pertain to genome editing per se; however, given that they are necessary to develop many genome-editing products, they represent a strategically important area within the overall IP landscape.

CURRENT TECHNOLOGY TRANSFER MODELS FOR GENOME EDITING

A range of models have been employed to manage the transfer of genome-editing technologies from research institutions to subsequent users. These include IP-free models that place such technologies in the public domain; open access models supported by MTAs; nonexclusive IP licenses for downstream tool or kit uses; nonexclusive licenses for products, the distribution of which is humanitarian in nature; aggregated nonexclusive licenses; field-of-use licenses; and exclusive licenses to surrogates. We also discuss IP licenses through auctions and clearinghouses—models that have received significant scholarly interest but little purchase among IP holders (65, 84).

Despite the diversity in models, several key factors broadly characterize the relative degree of restriction or openness. First, the number of rights holders over mutually interdependent or complementary parts of a given genome-editing technology determines how fractured the technology patent estate is for that technology. Consequently, this factor can be used to assess how endemic the problem of the anticommons is for that technology—that is, how much aggregation of separate permissions is necessary for a user to arrive at reasonable freedom to operate, and at what cost (58). While claims of anticommons in biomedical research have produced more smoke than fire, the fractured patent estates for genome-editing technologies should nonetheless instill caution.

Second, exclusivity is a spectrum, not a binary choice. The number of users who are ultimately licensed defines the extent to which a licensing model is exclusive or nonexclusive: More users with licenses means that those tools are less exclusive; conversely, fewer users with licenses means that the tools are more exclusive.

Third, segmentation is a function of not merely how many users have access to a genome-editing research tool, but also which uses are permissible for each user. Delimitations of the terms of a license to a specific type of use, a specific market, or even a specific target, such as a single gene or therapeutic, create the segmentation or differentiation of a licensing model. In this sense, licensing can be quite exclusive for some uses of a patent but quite nonexclusive for other uses (28).

Finally, licensing models can be further characterized by their degree of directness. Licenses can span a range from direct, to mediated, to indirect. The nature of these transactions is ultimately a result of the extent to which the original assignee has entrusted or outsourced to third parties the responsibility (and the benefits) of licensing management.

Whether these models will continue to diversify or winnow down to a simpler set of options remains to be seen. The diversity of models now being employed (or proposed) may be attributed to the complexity of genome-editing technologies, the plethora of possible applications, the legal uncertainty from ongoing disputes and inconsistencies among jurisdictions, or some combination of these factors. The diversity certainly arises from the endemic challenges of the technology's dual nature, being both a powerful research tool and an essential component of downstream commercial products. This diversity in models may also be considered simply as a natural progression of the sophistication of licensing regimes in a maturing knowledge economy. Time—and the progression of the technology under such licensing regimes—will tell.

The Public Domain

The norms of open science have long prevented secrecy or claims of IP, largely due to the incentives and pressures that exist to publish new discoveries in a way that enables others to validate and corroborate the veracity of those discoveries (31). Today, university scientists (or at least their technology transfer offices) understand that if, in the rush to claim scientific priority, an idea is published, it may no longer be considered novel under patent law (118), effectively depositing it in the public domain. Some have advocated for intentional strategies of defensive publication to secure technologies in the public domain for wider use and application (11, 14). Similarly, as patents expire, the inventions they protected revert to the public domain for anyone to use (11). Practically speaking, a vast body of knowledge resides in the public domain. Analogously, many biological materials are freely accessible from public repositories and banks, and enormous amounts of data are available from public databases (15).

Such intellectual resources have provided the foundation for advances in genome editing (119). Yet the public domain is vulnerable to expropriation or enclosure, especially along the frontiers in rapidly growing fields like genome editing. One recent notable experiment in using the public domain explicitly in order to encourage commercialization is the Open Science initiative at the Montreal Neurological Institute, which consists of an institution-wide commitment to open access publication and free provision of data, software, and materials (105). The initiative also includes a promise to refrain from filing of patents in favor of alternative, open commercialization strategies (105). With respect to genome editing, the initiative includes a program to make CRISPR-knockout neuronal cell lines derived from induced pluripotent stem cells and all the protocols involved freely available (105). But these efforts center on specific applications of genome editing. By contrast, to date, none of the core inventions of genome editing have been left in the public domain.

Maintaining Open Access with Contracts and Material Transfer Agreements

A growing number of initiatives in biotechnology, many of which involve CRISPR or other genome-editing technologies, have devised openness-preserving strategies using contractual mechanisms. Addgene has become the primary source for exchange of plasmids containing ZFN, TALEN, and CRISPR components, distributing them broadly to researchers under the terms of the UBMTA, with highly efficient options for electronic MTA approval and even automated approval under established institutional accounts (69). While this model has been highly effective in advancing research, one of the main challenges has been the blanket restriction against commercial users, inherited from the UBMTA, which some have argued disproportionately disadvantages small startup companies from academic institutions and thus generally hampers commercialization (68). To that end, the BioBricks Foundation has helped develop a new standardized MTA that it terms the OpenMTA. In contrast to the UBMTA, the OpenMTA removes restrictions on further transfer to third parties, including transfer to commercial users, in particular small biotechnology startup companies that originate from university research laboratories (68). Despite this seeming appeal, the new OpenMTA has yet to be implemented.

Apart from MTAs, the BioBricks Foundation has also developed an open model for the synthetic biology research community through the BioBrick Public Agreement, essentially an IP nonassertion user agreement for accessing and sharing standardized molecular biology components. Like the OpenMTA, the nonassertion provisions apply to both commercial entities and academics (52).

The global network of influenza virus researchers and vaccine companies, under the auspices of the World Health Organization's Global Influenza Surveillance and Response System (GISRS), have devised a novel two-tiered system of agreements designed to formalize and preserve the sharing practices that had originated within that scientific community. These agreements directly serve a commercial end: the seasonal development of commercial flu vaccines (70). However, the flu network's IP model does not appear to have been replicated in other research communities or for other technologies to date.

Nonexclusive Licensing for Research Kits and Reagents

An entire category of licenses for commercializing the core CRISPR inventions was offered nonexclusively to a range of companies that specialize in selling research equipment and standardized reagents, including Sigma-Aldrich, GE Healthcare, Takara Bio (formerly Clontech Laboratories), Horizon, and others (28). These companies sell CRISPR products for use in research laboratories, including both academic and commercial research and development. However, the terms of use by those who purchase these CRISPR products are typically quite restrictive. For example, the Sigma-Aldrich end user agreement forbids any clinical or commercial uses, including in human or veterinary diagnostics or therapeutics or in commercial crop applications (122). This effectively results in a two-tiered strategy of nonexclusive licensing upstream, even for commercially oriented research, followed by potentially more restrictive intermediate or downstream licensing that would need to be separately negotiated for any commercial product developed under the research license.

Nonexclusive Licensing for Humanitarian Uses

Similarly, a category of licenses to the core CRISPR inventions has been offered to nonprofit research organizations, particularly in agriculture, that are dedicated to creating technologies for use in developing countries. For example, both the International Maize and Wheat Improvement Center and the International Rice Research Institute have received licenses from the Broad

Institute and Corteva Agriscience (formerly DuPont Pioneer and Dow AgroSciences) for breeding of crops to be used in smallholder agriculture (64, 89). Here, too, whether such a licensing model will extend beyond smallholder agriculture remains to be seen, but it could very well be employed for clear and direct humanitarian efforts in therapeutic and preventative medical uses of genome editing (e.g., for infectious tropical diseases).

Aggregated Nonexclusive Licensing

Another particularly interesting model, given the number of overlapping and competing rights holders, is the aggregated license (55)—a suite of IP rights from multiple owners made available to multiple users. In engineering and information technology, patent pools have long been used to aggregate multiple complementary patents over general-purpose or standardized technologies held by multiple owners for licensing to many users (such as the 4G telecommunications standard). In biotechnology, collective models have recently been proposed to solve similar problems for genome editing (102, 136). In CRISPR, an aggregation of multiple source licenses has been achieved at least within one particular field of use—certain crop plants—through a complex series of licensing arrangements among research institutions and commercial developers (17). This was announced in 2017 as an effort of the Broad Institute and Corteva Agriscience, resulting in a joint licensing framework that brings together patents that both parties had come to control through management agreements, exclusive licenses, cross-licenses, and other means, representing at least a dozen different owners and including all of the core patents over the main CRISPR inventions from the University of California, Berkeley; Vilnius University; and MIT and the Broad Institute (17). This joint licensing framework offers nonexclusive commercial licenses to any and all interested users of CRISPR in crop agriculture, including direct competitors of Corteva in its major markets. While demand for licenses from such frameworks has been low, interest from developers in the field is gaining, and the agreement may serve as a proof of concept for future efforts.

Field-of-Use Exclusive Licenses

One of the main instruments of patent commercialization by universities has long been the exclusive license, whereby a single commercial entity receives all rights to use a patented technology (77). From the perspective of entrepreneurs and investors, such exclusivity is often essential. However, in the case of very broad research tools, like genome editing, no single company can possibly exploit all possible commercial applications of the technology; exclusivity beyond that which can be utilized, necessary or not, is simple waste (8). For this reason, exclusivity is discouraged by a number of public organizations and agencies, including, perhaps most famously, the NIH, whose licensing guidelines discourage the practice (96). In such cases, exclusivity can be narrowed to a single market or field of use in which a licensee has interest, expertise, and capacity, an approach that has been partially used for CRISPR/Cas9 (28). Such field-of-use exclusive licensing is little different from exclusive licensing models for single genes or therapeutic products. Given the increase in maturity in these models, there is hope that technology managers can police some of their worst excesses; the recent and rapid initiation of clinical trials based on CRISPR by three different companies provides some hope in that regard.

Exclusive Surrogate Licensing

Exclusive licensing need not be direct; an interesting commercialization model has emerged in recent decades involving faculty startups that take exclusive licenses to a faculty member's invention, which are then responsible for both commercializing and sublicensing the invention to

others (28). This approach builds on the historic model of third-party patent management of university inventions, as pioneered by the Research Corporation in the early twentieth century, discussed above (91), but with the addition of commercial development by the licensing agent itself. A recent precedent was Alnylam Pharmaceuticals, which was founded by one of the lead inventors in the field of RNAi and which not only offers sublicenses to its RNAi portfolio but also actively develops RNAi-based therapies. Inventors' startup companies have been involved in other genome-editing technologies, including Precision BioSciences (founded at Duke University) in meganucleases and Calyxt (founded at the University of Minnesota) in TALENS, although neither of these companies took a significant role in sublicensing.

By contrast, the surrogate licensing model has been vigorously pursued in the case of CRISPR/Cas9 (28), with Caribou Biosciences (and its human therapeutics sublicensee, Intellia Therapeutics) founded by Jennifer Doudna at the University of California, ERS Genomics and CRISPR Therapeutics founded by Emmanuelle Charpentier, and Editas Medicine founded by Feng Zhang at MIT and the Broad Institute. In each of these cases, the startup surrogate received an exclusive license to the fundamental technology, with a charge to sublicense the technology to others. Like exclusive licenses, generally, this surrogate licensing model faces some significant inefficiencies, some of which are putatively policed by the originating universities' rights to "claw back" their rights to the technology if it remains underdeveloped by the surrogate. But underdevelopment is difficult to prove (28).

Other Potential Models: Auctions and Clearinghouses

There are other potential models of interest to scholars and policy makers that have not yet been exercised in commercializing genome-editing technologies. Among these are patent auctions and the related models of clearinghouses or exchanges (8, 84, 102), which have several potential benefits over traditional licensing models, particularly a more efficient price discovery process. But they also have several drawbacks. First among these is that, thus far, patent auctions have facilitated sales transactions, not merely licenses; thus, only patent owners with technologies amenable to outright sale have been interested (65). (However, the question of whether auctions could be extended to at least some types of licensing contracts is worthy of investigation.) Second, true patent auctions have been held infrequently, and the uneven timing of transactions may not fit the rapidly evolving and fast-paced research and development demands of most companies engaged in genome editing.

Online patent exchanges or clearinghouses were avidly pursued by a range of players in the 1990s and early 2000s and promised easier market discovery and greater flexibility of different types of transactions (51). Both auctions and online exchanges, it turns out, can suffer from thin markets and are often unable to offer comprehensive solutions for potential buyers or licensees. Still, as online applications and exchange technologies advance, there may be room for innovation by IP aggregators or hybrid auction-based exchanges, auctioning of standardized licenses, and auctioning in continuous time. If these facilitate greater market liquidity and flexible matching between supply and demand, such models may become viable for biotechnology (55, 84).

IMPLICATIONS OF GENOME EDITING'S PATENT ESTATES AND TECHNOLOGY TRANSFER MODELS

The current diversity in patent estates and technology transfer models provides some insight into what the future may look like. First, there are likely to be an increasing number of entities patenting not only new genome-editing technologies but also new uses and applications of

existing genome-editing technologies. This is demonstrated by the rapidly expanding and diversifying patent landscape for CRISPR, which includes patents covering new engineered nucleases, improvements on older versions of the technology, and new applications for existing components (34). A significant portion of new technology will still come from academia, as has been the case with CRISPR thus far. The success of CRISPR and its variants has encouraged a significant amount of academic research, and patenting of new results by academic institutions will continue.

Increased patenting of forthcoming genome-editing technologies may mean that smaller universities (with tighter budgets, lower research expenditures, and smaller endowments) as well as small venture-capital-backed biotechnology companies will have even stronger incentives to hold out for more stringently enforced and more costly exclusive licenses. For CRISPR, at least, these concerns have been somewhat ameliorated by the financial footing of and competition between the Broad Institute and the University of California—two of the most well-financed research institutions in the world. Meanwhile, there is little evidence that the CRISPR patent dispute between these parties has stymied academic research, although this seems significantly due to the work of Addgene. And it appears that commercial development of the technology is proceeding at a fast clip even with little certainty of freedom to operate downstream. But this will not necessarily remain the case in the longer run.

At the same time, the more that genome editing diversifies, the more its constituent technologies are likely to diverge rather than interfere and compete with one another. For example, discoveries of new nucleases beyond Cas9 fall outside of the principal patent dispute. More types of genome-editing technologies, especially where they are interchangeable for certain applications, may serve to operate as competing tools (94). In addition, the future of genome-editing technologies is likely to include newer platforms on which developers can build, such as the Broad Institute's prime editing system (1). Rapid development of variants of a genome-editing technology may build a robust marketplace for different uses—and competition for patent licenses. This may ultimately counsel against exclusive licensing or, even where exclusive licenses are pursued, may lead to exclusive licenses essentially competing against one another on terms such as price. Still, dominant patents covering foundational aspects of an original technology may complicate such competition by establishing themselves—by virtue of the patent laws—as necessary components to practice new yet subordinate downstream applications. The ultimate power of any technology platform lies both in its ability to develop a robust competitive marketplace for licenses and in its potential to be optimized for different types of applications.

The Advantages of Diversity

All else being equal, the diversity of models for technology transfer in genome editing is a good thing. It allows for more flexible licensing approaches, which can result in greater competition and innovation (28). It allows institutions to experiment with licensing—to see what works and, where it does not, to improve. It also allows research institutions to mimic approaches that have been successful elsewhere. We think of this as a federalism model of technology transfer, a reference to the way that individual states within a federal system can experiment with different state-level policies and legal approaches in response to their unique circumstances (98). Furthermore, this diversity in models allows customization and optimization depending on the specifics of the technology and its application; for example, the take-it-or-leave-it conditions built into the UBMTA spurred the introduction of the OpenMTA as a more adaptive and flexible approach (68).

At the same time, a diversity in licensing approaches may serve as an apologia for harmful licensing practices. A greater diversity of licensing models, especially for those trafficking in

exclusivity, may encourage more entities to use exclusivity than would have otherwise, which would risk locking up genome-editing technologies. On balance, however, we view diversity as promoting experimentation, given the historical default toward exclusivity. Current licensing experiments regarding CRISPR/Cas9 seem to already be an improvement over older models of pure exclusivity, as seen in RNAi or even ZFNs. We encourage technology managers to continue to experiment.

Technological Pace

An important consideration of patent licensing for genome editing is the speed of development of the technology itself. It stands to reason that when a technology is rapidly advancing, the importance of any given patent estate is potentially limited: Users will likely soon have alternatives, and the benefits of controlling a particular technological platform will wane. For example, the emergence of induced pluripotent stem cells appears to have fundamentally shifted the licensing landscape of human embryonic stem cells (86). For genome editing, the number of CRISPR licensors is likely to increase, thus increasing competition. The advance of CRISPR, coupled with its diffusion and democratization, may prove to be the ultimate example of these dynamics.

For future genome-editing technologies, the rapid pace of development has several implications. First, the particular licensing practices of any given institution may not matter all that much in the end. If one institution adopts a restrictive, exclusive license for its variant of the technology, others will likely be encouraged to adopt more liberal licensing policies for their variants as competitive measures.

Second, even artful patent drafting—writing patents to cover the broadest scope of the underlying invention—will be unable to keep pace with the cutting edge of the technology itself. Barring a few idiosyncratic circumstances, patent applicants cannot claim advances to their inventions that they neither foresaw nor possessed at the time of their invention. This means that it is unlikely that initial broad discoveries in the genome-editing space will result in patents that can be wielded to halt iterative development of the genome-editing technology unforeseen—and undisclosed—by the original inventors.

Third, the global interest in the technology will result in more institutions from more countries filing for patents covering their developments outside the first jurisdiction in which they were discovered. This has the potential to lead to global—and conflicting—patent disputes, as is the case with CRISPR/Cas9 in Europe (39), which may ultimately serve to compel settlement, if not cross-licensing.

In sum, the new enzymes for CRISPR, advances for TALENs, and the current riot of meganucleases all suggest that new techniques for genome editing are routinely introduced and frequently evade attempts of initial inventors to grasp large applications of the technology upon first notice. Much like other areas of licensing, the diversity of models of licensing for genome editing demonstrates that technical substitutes may serve as economic substitutes, too, be it in terms of components, licensing terms, or even licensors.

The Rise of Third-Party Licensing Intermediaries

A final interesting implication of genome editing's technology transfer models is the increasing importance of third-party intermediaries, such as Addgene and the 2Blades Foundation. Before the development of genome editing, patents covering broad uses of platform technology were managed almost entirely by the institutions that developed them and their exclusive licensees. In contravention of universities' broader missions to disseminate the fruits of their research to the public, this approach aligned licensees' profit motives with their universities, in some cases

potentially delaying the commercial development of the underlying technology (35). But off-loading nonexclusive licensing or material transfers to third parties allows some separation between commercial licensees' profit motives and universities' obligations to disseminate technologies developed at their laboratories as widely as possible.

This model, in some areas, has been a clear success. Nonprofit academic researchers have simple, easy access to genome-editing materials and permission to use them without needing to go through technology transfer offices or other researchers' (busy) laboratory staff. Addgene employs, instead, a professional staff invested in quality control, documentation, and customer support, unheard of for more informal transfers of biological materials among academic researchers. In addition, third-party intermediaries' boilerplate, take-it-or-leave-it licensing terms cut down—or eliminate, in many instances—the cost of negotiating agreements for materials or reagents. In the case of 2Blades, this extends to commercial developers as well. Technology transfer policies centered on separating academic from commercial licensing without the cost of maintenance, or even nonexclusive licenses for commercial applications, could see third-party intermediaries play a greater role in the future.

DIRECTIONS FOR FUTURE RESEARCH

In this article, we have presented a review of current genome-editing technologies, the variety of models used to mediate technology transfer, and the implications of their development. Several avenues remain for future research in this area to add empirical rigor to some of the generalizations and predictions made here.

First, additional landscaping work for each of the genome-editing technologies described above is needed—and will continue to be on an ongoing basis—given the rapid development of the field. It is of significant interest to many to know which institutions are seeking patent protection on their new technology variants, how those variants differ from prior variants, and to whom such patents are being licensed. More detailed work should also examine the breadth of the claims being prosecuted and the specific terms of the licenses being employed. Even narrow licenses from multiple institutions may nonetheless result in a patent-mediated monopoly for a technology, as seems to have been the case with Sangamo and ZFNs (19). Keeping an eye on such developments would be useful to technology transfer professionals and researchers alike.

Second, research into the funding sources underlying the development of competing technologies would also prove fruitful. Much of the work on technology transfer for genome editing presumes, in large part, that universities and research institutions receive funding almost entirely, in a sense, agnostically through grants; that the stochastic results of such grant-funded research can be patented; and that those patents are subsequently licensed as a means of increasing the potential for commercial uptake. But this assumption discounts or ignores the role that public–private partnerships may play in targeting the development of a technology or, as with genome editing, the role that commercial developers may play in making basic discoveries about the technology themselves. In fact, some of the original research into the mechanisms behind CRISPR, as a bacterial adaptive immune system, was conducted by commercial interests, with the applied engineering work then performed in academic settings (119). Thus, even the leading example of genome-editing technology challenges typical assumptions about the archetypal linear model of innovation.

Third, additional exploration into the feasibility of auctions for licenses would be opportune. Recent academic work suggests that auctions for patent licenses could partially alleviate the tension between exclusivity and commercial development present for university technology transfer policies (8). Whether such a mechanism would be feasible for field-delimited or nonexclusive

licenses to genome editing—facilitated by online connections and algorithms—within a clearinghouse model is worthy of further investigation (129).

Fourth, continued investigation into the successes or failures of IP-free models for genome editing, such as those recently announced by the Montreal Neurology Institute or the BioBricks Foundation, is important (70, 105). Much of the work here presumes that universities will continue to patent their inventions, regardless of the licensing model eventually employed. But this decision is not inexorable, and any demonstration that IP-free models for genome editing both are revenue positive for universities and result in commercial development would be an important development. Recent work on the IP-free nature of the GISRS flu network suggests that such a model is at least possible (70). Whether these are isolated cases or a broader statement about technology transfer remains unclear.

Ultimately, both genome-editing technologies and technology transfer practices have matured. Today, the technology is rapidly diversifying and increasing in power, prestige, and potential. Effectively directing such power for commercial innovation clearly has not simply meant increasing the use of exclusive licensing; the success of third-party intermediaries in reducing friction in research use and encouraging investment in startups has shown otherwise. Rather, understanding genome-editing technologies and models of technology transfer as interacting within a larger system replete with competition and experimentation should counsel technology managers, policy scholars, and scientists alike to continue to forge new paths toward fulfilling the promise of genome editing.

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