

ity is compromised in government. They can fiercely protect university independence. And they can defend peers who become political targets for speaking up (17).

We maintain hope that these concerns will not be realized. But the scientific community is well positioned for what may lie ahead. Already, scientific societies have asked the Trump Administration to appoint a science adviser and more than 5500 scientists have signed a letter asking the Administration to uphold scientific integrity (18). Alarms must sound when science is silenced, manipulated, or otherwise compromised. When science is sidelined from policy decisions, we all lose. ■

REFERENCES AND NOTES

1. L. M. Krauss, *New Yorker*, 13 December 2016; www.newyorker.com/tech/elements/donald-trumps-war-on-science.
2. S. Otto, *The War on Science: Who's Waging It, Why It Matters, What We Can Do About It* (Milkweed Editions, Minneapolis, MN, 2016).
3. UCS, "Preserving scientific integrity in federal policy-making: Lessons from the past two Administrations and what's at stake under the Trump Administration" (UCS, Cambridge, MA, 2017); www.ucsusa.org/preservingscientificintegrity.
4. C. Mooney, *The Republican War on Science* (Basic Books, New York, 2005).
5. Office of Inspector General, Department of the Interior, *Investigative report: On allegations against Julie MacDonald, Deputy Assistant Secretary, Fish, Wildlife, and Parks* (Department of Interior, Washington, DC, 2006); <https://www.doi.gov/sites/doi.gov/files/Macdonald.pdf>.
6. A. C. Revkin, "Bush vs. the laureates: How science became a partisan issue," *New York Times*, 19 October 2004, p. F1; www.nytimes.com/2004/10/19/science/19poli.html.
7. UCS, Scientist statement on restoring scientific integrity to federal policy making (UCS, Cambridge, MA, 2004); www.ucsusa.org/our-work/center-science-and-democracy/promoting-scientific-integrity/scientists-sign-on-statement.html#WErynFUrKuk.
8. UCS, "Voices of federal scientists" (UCS, Cambridge, MA, 2007); www.ucsusa.org/sites/default/files/legacy/assets/documents/scientific_integrity/Voices_of_Federal_Scientists.pdf.
9. E. Williamson, *Washington Post*, 1 May 2007; www.washingtonpost.com/wp-dyn/content/article/2007/05/01/AR2007050101920.html.
10. F. Grifo et al., *Federal Science and the Public Good* (UCS, Cambridge, MA, 2008); www.ucsusa.org/sites/default/files/legacy/assets/documents/scientific_integrity/Federal-Science-and-the-Public-Good-12-08-Update.pdf.
11. G. Goldman et al., "Progress and problems: Government scientists report on scientific integrity at four agencies" (UCS, Cambridge, MA, 2015); www.ucsusa.org/scientistsurvey.
12. U.S. Environmental Protection Agency, *FY 2015 Allegations* (EPA, 2015); <https://www.epa.gov/osa/fy-2015-allegations>.
13. W. Wagner, E. McGarrity, *Bending Science: How Special Interests Corrupt Public Health Research* (Harvard Univ. Press, Cambridge, MA, 2012).
14. P. Ryan, *A Better Way* (2016); <http://paulryan.house.gov/top5issues/a-better-way-our-vision-for-a-confident-america.htm>.
15. Office of Management and Budget, "Draft report to Congress on the benefits and costs of federal regulations and agency compliance with the Unfunded Mandates Reform Act" (OMB, 2015); https://obamawhitehouse.archives.gov/omb/infocore/regpol_reports_congress/.
16. A. A. Rosenberg et al., *Science* **348**, 964 (2015).
17. M. Halpern, M. Mann, *Science* **348**, 479 (2015).
18. UCS, *An open letter to President-elect Trump and the 115th Congress* (UCS, Cambridge, MA, 2016); ucsusa.org/trumpscientistletter.

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BIOTECHNOLOGY AND LAW

CRISPR, surrogate licensing, and scientific discovery

Have research universities abandoned their public focus?

By **Jorge L. Contreras¹** and **Jacob S. Sherkow²**

Several institutions are embroiled in a legal dispute over the foundational patent rights to CRISPR-Cas9 gene-editing technology, and it may take years for their competing claims to be resolved (1–4). But even before ownership of the patents is finalized, the institutions behind CRISPR have wasted no time capitalizing on the huge market for this groundbreaking technology by entering into a series of license agreements with commercial enterprises (see the figure). With respect to the potentially lucrative market for human therapeutics and treatments, each of the key CRISPR patent holders has granted exclusive rights to a spinoff or "surrogate" company formed by the institution and one of its principal researchers (5, 6). Although this model, in which a university effectively outsources the licensing and commercialization of a valuable patent portfolio to a private company, is not uncommon in the world of university technology transfer, we suggest it could rapidly bottleneck the use of CRISPR technology to discover and develop useful human therapeutics.

Several patterns emerge from the web of transactions shown in the figure (we make the documents used in our analysis available at <https://dataverse.harvard.edu/dataverse/crisprlicenses>). The right to use CRISPR techniques has been divided into three broad "fields of use": (i) basic, non-commercial research; (ii) development and sale of tools (kits, reagents, and equipment) that aid CRISPR-based gene edit-

ing; and (iii) development, sale, and use of therapeutics and treatments using CRISPR techniques. This last field broadly covers the most commercially significant applications and includes gene editing to develop agricultural products, veterinary medicine, and human diagnostics and therapeutics.

Precisely demarcating these fields of use—especially for a flexible, broadly applicable technology like CRISPR—and awarding appropriate license grants can be challenging. Nonetheless, the institutions have largely granted non-exclusive licenses with respect to noncommercial research and tools development. This means that licensees, including academic researchers, are permitted to engage in these activities, but do not have the right to market and sell products derived from their research. It also

means that the CRISPR patent holders are free to grant licenses for their respective technologies to other research institutions. However, in the case of therapeutics and treatments, with few exceptions, exclusive licenses to surrogate companies (Editas, Caribou, or CRISPR Therapeutics) prevent the institution from granting similar licenses to other companies without the surrogate's permission. Caribou's exclusive license covers all fields of use, and it has in turn granted an exclusive license in the field of human therapeutics to Intellia Therapeutics.

SURROGATE LICENSING AND CRISPR

The companies to which the patent-holding institutions grant exclusive licenses effectively stand in as surrogates for the institutions themselves. These surrogates control a large and lucrative field for the exploitation of the licensed technology, and have significant freedom both to exploit it themselves and to seek partners and sublicensees. The surrogates take on the role of the patent owner and retain a lion's share of the resulting profits. Many

"The institutions controlling CRISPR patent rights have delegated [them]... to surrogate companies, which determine...[who] will be able to exploit [them]."

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universities prefer this model because it gives them a substantial share of profits with minimal risk through, for example, equity stakes in their researchers' surrogate companies (7, 8).

The surrogate licensing model, in theory, permits the university to focus on a broader range of commercialization projects with a limited staff, and delegates the job of licensing to experts focused on the relevant technology. Although a university could license its rights individually to the range of commercial enterprises illustrated in the figure, it is often more efficient to grant rights in bulk to a single company and let that company scour the market for viable licensing candidates. The university profits from its equity interest in the surrogate and from any royalties that are generated by the technology.

In addition, the individual investigators, who often have a substantial equity interest in the surrogate company, stand to profit far more than they otherwise would. For all of these reasons, the surrogate licensing model has become popular with universities, investigators, and companies across a wide range of technologies (7, 8).

We reviewed all of the CRISPR surrogate license agreements made publicly available through filings with the U.S. Securities and Exchange Commission, requests under state and federal "freedom-of-information" acts, and through press releases and public announcements. In each of the principal surrogate licenses that we reviewed, the patent-holding institution has granted its surrogate the exclusive right to use CRISPR to develop human therapeutics targeting any of the 20,000+ genes

that comprise the human genome. Because no single company could develop, test, and market therapeutics on the basis of even a fraction of the entire human genome, the surrogates are authorized and expected to sublicense their rights to others.

Despite this, it is still unlikely that any of the surrogate companies could explore a significant fraction of the potential human health applications that CRISPR could enable, even with a range of experienced commercial partners and collaborators. If an unlicensed company has the expertise and wherewithal to develop a novel human therapy using CRISPR—even if that therapy concerns a previously unexplored gene—that company might not be able to obtain the sublicense necessary to undertake this work. In some instances, such as the license to Editas from the Broad Institute of MIT and Harvard, the institution retains some right to entertain proposals from other companies if the surrogate is not pursuing work on a specific gene and does not plan to do so in the future. The scope of this limitation, however, is narrow and still leaves all "unclaimed" portions of the genome in the surrogate's hands.

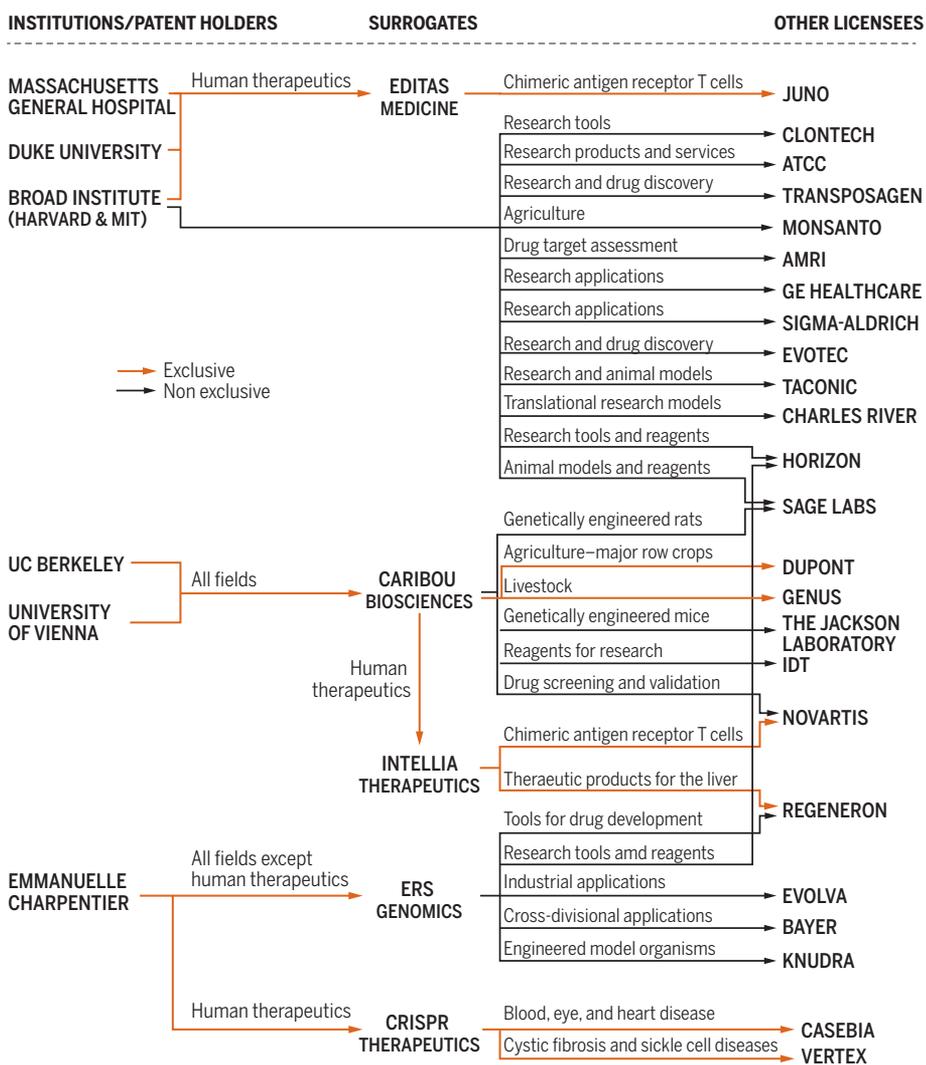
Further, traditional contractual safeguards against overbroad exclusive licenses will likely work poorly under this model. Diligence milestones, for example, require an exclusive licensee to demonstrate progress toward commercialization of a licensed technology (often through the achievement of various regulatory hurdles, testing, and trials). But a surrogate can easily show some progress in some subset of a broader field to meet this requirement, even if it does not intend to, or cannot, pursue all aspects of the licensed field. Giving one company an exclusive right to use CRISPR to develop human therapies targeting every segment of the human genome could thus limit the creation of potentially beneficial therapies.

NONEXCLUSIVITY AND RESEARCH TOOLS

CRISPR is a broadly applicable, enabling technology platform, similar in many respects to "research tools": equipment, reagents, and methods that enable a broad range of downstream research (9). Exclusive rights in research tools are generally unnecessary for commercialization of downstream products developed using them. Rather, exclusive licenses are only needed with respect to specific therapeutic uses discovered using those tools. For example, a molecular drug target may be discovered using research tools like the polymerase chain reaction (PCR) but then require considerable and costly product development, clinical trials, and regulatory

CRISPR-CAS9 licensing agreements

Exclusive licenses to surrogates for human therapeutics limit access to CRISPR as a platform technology.



approval before it can be marketed (9).

For this reason, in 1999 the U.S. National Institutes of Health (NIH) recommended that patents on research tools developed using federal funding be licensed nonexclusively to promote their greatest utilization, commercialization, and public availability (9). In 2007, eleven major U.S. research universities—including the University of California, Berkeley (UCB), Harvard, and Massachusetts Institute of Technology (MIT), all of which have made CRISPR patent claims—committed to a set of core licensing values, known as the “Nine Points,” one of which states that universities should make patented research tools as broadly available as possible (10).

Although CRISPR is not necessarily a “research tool” in that its function is generally not to enable downstream research, it is a broadly applicable “platform” technology—like stem cells or the Internet—that could enable innumerable specific applications. To that end, foundational CRISPR patents, like patents covering research tools, should be licensed and disseminated as widely as possible especially when developed with public funding by universities operating in the public interest (11–14).

“Platform technologies such as CRISPR should be recognized as offering the same potential for industry-wide innovation and discovery as traditional research tools.”

To their credit, the UCB and the Broad Institute have not sought to limit academic research through their exclusive CRISPR licenses (1). Both have made many of their CRISPR research tools available freely or cheaply through AddGene, a nonprofit organization in service of academic and nonprofit institutions (1, 14). Likewise, as noted above, the institutions have granted nonexclusive licenses in the area of tool development.

But the exclusive licenses granted to the institutions’ surrogates for human therapeutics limit access to CRISPR as a platform technology, potentially hindering competition and creating innovation bottlenecks. For example, the Broad’s surrogate, Editas, has granted Juno Therapeutics an exclusive license to develop a host of CRISPR therapies—across multiple genes—using chimeric antigen receptor T cell (CAR-T) technology (15). This broad license threatens to complicate both research and development for CRISPR-based

CAR-T technologies for gene targets chosen by Juno, but that neither Editas nor Juno have the bandwidth to pursue. In other instances, overly broad exclusive licenses may hinder research into socially valuable—but unprofitable—therapeutics, such as those indicated for rare diseases or treating illnesses prevalent in disadvantaged populations or regions, a separate yet equally important principle advanced in the Nine Points document.

Situations like these—in which exclusive licenses have the potential to extend beyond that which can be developed—are precisely what the NIH guidelines and the Nine Points sought to avoid. Yet the surrogate licensing model adopted by the CRISPR patent-holding institutions seemingly allows them to circumvent this prescription by ceding licensing authority to private companies not bound by the guidelines and Nine Points.

RECONCEPTUALIZING CRISPR LICENSING

Given the potential bottlenecks created by the current surrogate licensing model, UCB, Harvard, and MIT should broaden access to CRISPR technology for human therapeutics. Given that the technology is developing rapidly and, in some instances, now being disputed among the parties, there is still time to do so. This dynamism in CRISPR’s patent landscape should provide the impetus for these institutions—and their surrogate companies—both to amend their existing agreements and to cross-license their respective patent rights to one another. And these cross-licenses need not be exclusive.

As an example, Broad and UCB could reserve their rights to license CRISPR to other commercial firms engaged in therapeutic research on areas of the genome that their surrogates do not have a reasonable plan to develop. The institutions could thus open up larger swaths of the genome to beneficial commercial research. Both UCB and Broad have recently shown some attraction to this approach by announcing limited cross-licensing agreements with other institutions, albeit not with one another (16, 17). A more flexible licensing approach would result in greater competition and innovation in the marketplace—in the spirit of the Nine Points agreement.

The emergence of CRISPR as an important new platform technology should also prompt NIH to update its guidelines regarding the licensing of federally funded inventions. Platform technologies such

as CRISPR should be recognized as offering the same potential for industry-wide innovation and discovery as traditional research tools. A similar updating of, and recommitment to, the Nine Points may also be in order.

As the National Academies of Science have noted, “the first goal of university technology transfer involving (intellectual property) is the expeditious and wide dissemination of university-generated technology for the public good” (12). The institutions controlling patent rights in CRISPR have delegated that responsibility to surrogate companies, which determine how many or few commercial firms will be able to exploit it. We urge these institutions to rethink their use of exclusive, surrogate licenses across the entire genome. Those institutions should ensure that any exclusive licenses are narrowly drawn to specific genes, to maximize competition in the development of the revolutionary technology they have created. ■

REFERENCES AND NOTES

1. J. S. Sherkow, *Nature* **532**, 172 (2016).
2. J. S. Sherkow, *Nat. Biotechnol.* **33**, 256 (2015).
3. H. Ledford, *Nature* **537**, 460 (2016).
4. K. J. Egelie, G. D. Graff, S. P. Strand, B. Johansen, *Nat. Biotechnol.* **34**, 1025 (2016).
5. License agreement between the President and Fellows of Harvard College, the Broad Institute, Inc., and Editas Medicine, Inc. (29 October 2014).
6. Exclusive License between Caribou Biosciences, Inc., and the University of Vienna and The Regents of the University of California for methods and compositions for RNA-directed target DNA modification and for RNA-directed modulation of transcription (16 April 2013).
7. L. Pressman et al., *Nat. Biotechnol.* **24**, 31 (2006).
8. J. Carter-Johnson, J. S. Carter-Johnson, J. L. Contreras, in *Bioinformatics Law: Legal Issues for Computational Biology in the Post-Genome Era*, J. L. Contreras, A. J. Cuticchia, Eds. (American Bar Association, 2013), pp. 97–112.
9. NIH, *Fed. Regist.* **64** (246), 72090 (1999).
10. Association of University Technology Managers, in the *Public Interest: Nine Points to Consider in Licensing University Technology* (AUTM, Washington, DC, 2007).
11. I. Ayres, L. L. Ouellette, *Cornell Law Rev.* **102**, 271 (2017).
12. National Research Council, *Managing University Intellectual Property in the Public Interest*, S. A. Merrill and A.-M. Mazza, Eds. (National Academy Press, 2010).
13. A. K. Rai, R. S. Eisenberg, *Law Contemp. Probl.* **66**, 289 (2003).
14. L. McGuire, *Nature* **534**, 37 (2016).
15. Collaboration and license agreement between Editas Medicine, Inc., and Juno Therapeutics, Inc. (25 May 2015).
16. Caribou Biosciences, CRISPR Therapeutics, Intellia Therapeutics, Caribou Biosciences, and ERS Genomics announce global agreement on the foundational intellectual property for CRISPR/Cas9 gene editing technology [press release] (2016); <http://bit.ly/2jWnkON>.
17. Editas Medicine, Editas Medicine extends CRISPR genome editing leadership through licensing of new CRISPR technologies [news] (Editas Medicine, 2016); <http://bit.ly/2k8CMN>.

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