Patent protection for CRISPR: an ELSI review

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INTRODUCTION

Much has been written about the power of CRISPR—the workhorse genetic-editing system first elucidated in 2012—and the public’s interest in it, both as a piece of science and an ethical battleground.1 But there has also been extensive interest in the variety of intellectual property issues surrounding CRISPR, including a heated patent dispute between two of the technology’s originators, Jennifer Doudna (UC Berkeley) and Emmanuelle Charpentier (Max-Planck), on one side, and Feng Zhang (Broad Institute) on the other.2 While the intellectual property disputes concerning CRISPR are far from over—indeed, like Tolstoy’s War and Peace, new characters central to the dispute continue to materialize3—five years of hindsight has given some perspective on their ethical, legal, and social implications.

This brief essay reviews several of these issues: (i) difficulties with interinstitutional collaborations, especially for lucrative ‘translational’ technologies; (ii) the rise of for-profit ‘surrogate’ companies to manage university licensing; and (iii) the use of patents as a means of private governance to prevent potential abuses, such as ‘gene drives’,

1 See eg Antonio Regalado, Engineering the Perfect Baby, MIT TECH. REV., Mar. 5, 2015, https://www.technologyreview.com/s/535661/engineering-the-perfect-baby/ [https://perma.cc/AT7T-FM8Y] (accessed Nov. 13, 2017) (discussing public perceptions of CRISPR); see generally CRISPR-CAS: A LABORATORY MANUAL (Jennifer Doudna & Prashant Mali eds., 2016) (teaching the method of using CRISPR for gene editing).
2 See eg Jacob S. Sherkow, What the CRISPR Patent Dispute Is All About, SCI. AM., Dec. 12, 2016, https://blogs.scientificamerican.com/guest-blog/what-the-crispr-patent-dispute-is-all-about/ [https://perma.cc/BA88-VUEN] (accessed Nov. 13, 2017) (synopsizing the CRISPR patent dispute).
3 See Jon Cohen, CRISPR Patent Battle in Europe Takes a ‘Wild’ Twist with Surprising Player, Science News, Aug. 4, 2017, http://www.sciencemag.org/news/2017/08/crispr-patent-battle-europe-takes-wild-twist-surprising-player [https://perma.cc/SZG3-CHRB] (accessed Nov. 13, 2017) (describing a new, fundamental CRISPR patent in Europe owned by MilliporeSigma).
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seed-saving restrictions for agriculture, and germ-line human engineering. It concludes with several observations—and prescriptive recommendations—for patent protection related to academic, collaborative, cutting-edge research.

**THE CRISPR PATENT DISPUTE**

Since the first U.S. patent applications were filed for an engineerable CRISPR system in 2012, the IP landscape has become significantly more crowded, with several researchers contending a few significant battlements. To date, three groups of scientists have emerged as holders of foundational patents covering CRISPR-Cas9: Jennifer Doudna (UC Berkeley) and Emmanuelle Charpentier (now at Max-Planck, but at Umeå University, Sweden, at the time of her contribution to the invention), Feng Zhang (Broad Institute), and Virginijus Šikšnys (Vilnius University, Lithuania). Contrary to popular belief, Šikšnys was the first of the three to file a patent application covering his variation on the technology. Šikšnys filed for his patent on March 20, 2012, although it did not issue—that is, it was not formally granted by the U.S. Patent and Trademark Office (U.S.P.T.O.)—until May 2, 2017. For a number of reasons, Šikšnys’ contributions—both to the science CRISPR and the technology’s patent dispute—have been overlooked. But Šikšnys’ patent covers using CRISPR-Cas9 through an in vitro, pre-assembled Cas9: RNA complex—also known as CRISPR ribonucleoproteins—an important iteration of the technology for a variety of applications.

More famously, Doudna and Charpentier first filed their fundamental patent application covering CRISPR-Cas9 on May 25, 2012. Their original patent application contained over 150 claims—particular ways to practice the invention that defined the application’s boundaries—and was notably unspecific with respect to cell type. Nonetheless, Doudna and Charpentier’s patent attorneys pegged their clients’ invention broadly, as the use of a single-guide RNA to mediate the editing of genomic DNA. It was the ease, flexibility, and precision of this advance that has largely thrust CRISPR into the lay lexicon.
During the pendency of Doudna and Charpentier’s application in the USA, Zhang also filed a U.S. patent application—directed specifically to eukaryotic applications of CRISPR-Cas9. 12 The principal improvement of Zhang’s methods over his predecessors was the use of a nuclear localization signal and, separately, codon optimization to natively express Cas9. 13 But Zhang’s attorneys fast tracked his application through the U.S.P.T.O., a relatively expensive and strategically risky process. 14 As a consequence, Zhang’s patent—even though it was filed after applications from Doudna, Charpentier, and Šikšnys—was issued first in the USA. 15 That quandary gave rise to the now-famous patent dispute in the USA, the first round of which was won by Zhang. 16 The remainder of it is still being appealed; a decision is expected in late 2018. 17

The U.S. interference decision, however, stands apart from the rest of the world. As detailed—excellently—by Knut Jørgen Egelie and his colleagues at Norwegian University of Science and Technology—the global CRISPR patent landscape is varied. 18 Europe has now officially sided with Doudna and Charpentier over Zhang, although opposition proceedings at the European Patent Office have just begun. 19 And China, too, recently sided with Doudna and Charpentier. 20 These conflicting decisions are further complicated by a set of interlocking license agreements from the inventors’ biotech companies, with a great deal of uncertainty playing out in the global commercial sector for CRISPR. 21 Unraveling those agreements, and the issues raised by the patenting of the technology in the first instance, speaks volumes about the values and pitfalls of patents in the research enterprise.

INTERINSTITUTIONAL COLLABORATION

One notable aspect of the CRISPR patent dispute is that it is, by and large, a dispute between academic research institutions. It pits lawyers representing the University

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12 See U.S. Patent No. 8,697,359 (noting a provisional application date of Dec. 12, 2012).
13 Id. (‘The invention comprehends the expression of two or more gene products being altered and the vectors of the system further comprising one or more nuclear localization signal(s) (NLS(s))…. The invention further comprehends the Cas9 protein being codon optimized for expression in the eukaryotic cell.’).
14 Petition to Make Special Under Accelerated Examination Program, U.S. Patent Application No. 14/054,414 (Oct. 15, 2013).
15 Compare U.S. Patent No. 8,697,359 (Zhang’s issued patent) with U.S. Patent Application No. 13/842,859 (Doudna and Charpentier’s patent application); see also Jacob S. Sherkow, The CRISPR Patent Interference Showdown Is On: How Did We Get Here and What Comes Next?, STAN. CTR. L. & BIOSCI. BLOG, Dec. 29, 2015, https://law.stanford.edu/2015/12/29/the-crispr-patent-interference-showdown-is-on-how-did-we-get-here-and-what-comes-next/ [https://perma.cc/7WZB-2L44] (accessed Nov. 13, 2017) (explaining the genesis of the dispute).
16 Broad Institute, Inc. v. Regents of the University of Cal., Patent Interference No. 106,048, 2017 WL 657415 (P.T.A.B. Feb. 15, 2017).
17 Kevin E. Noonan, Berkeley Files Opening Brief in CRISPR Appeal, PATENT BLOG, July 31, 2017, http://www.patentdocs.org/2017/07/berkeley-files-opening-brief-in-crispr-appeal.html [https://perma.cc/57GX-8UMX] (accessed Nov. 13, 2017).
18 Knut J. Egelie et al., The Emerging Patent Landscape of CRISPR-Cas Gene Editing Technology, 34 NAT. BIOTECH. 1025, 1025 (2016).
19 European Patent No. 2,800,811 (filed Mar. 15, 2013); see also Sharon Begley, University of California’s CRISPR Patent Win in Europe Likely to Be Challenged, STAT NEWS, Mar. 28, 2017, https://www.statnews.com/2017/03/28/crispr-university-of-california-patent/ [https://perma.cc/E8ZB-Q4FF] (accessed Nov. 13, 2017) (reporting on upcoming challenges).
20 Chinese Patent No. 104,854,241.
21 Jorge L. Contreras & Jacob S. Sherkow, CRISPR, Surrogate Licensing, and Scientific Discovery, 355 SCIENCE 698, 699 (2017).
of California against lawyers representing the Broad Institute of MIT and Harvard. To be sure, university rivalries are common. But because universities share among themselves a larger mission to create and disseminate knowledge to the public, litigiousness among them has been historically rare.

University-against-university patent disputes, like CRISPR, complicate interinstitutional research agreements on several levels. First, they have the potential to chill formal interinstitutional research collaborations among universities if the institutions cannot agree on intellectual property issues beforehand. Universities may simply be unwilling to enter into such agreements in the first instance, or, perhaps more punitively, discourage their faculty from informally developing such networks. While the empirical evidence for such a diminishment in collaborative efforts is slight—difficult to demonstrate, in part, because it requires the proof of opportunities not taken by universities—some recent survey data have found that ‘institutionally mandated [materials transfer agreements] put sand in the wheels of a lively system of intra-disciplinary exchanges of research tools’. Aside from this, there is substantial anecdotal evidence of institutional difficulties in creating such agreements. It stands to reason that, at least in some instances, these difficulties have ended some collaborations before they could begin. More immediately, this is a current issue with the CRISPR patent dispute given some internal dissention between Doudna and Charpentier’s respective institutions concerning the intellectual property involved. Although Doudna and Charpentier filed their joint patent application in 2012, their institutions did not formally assent to a cross-licensing agreement until December 2016. If assenting to a cross-licensing agreement, the institutions would have to agree on intellectual property issues beforehand. This raises a question about the tradeoffs between the value of insights derived from inter-university collaboration and the costs incurred due to licensing complexity.

See Broad Institute, Inc. v. Regents of the University of Cal., Patent Interference No. 106,048, 2017 WL 657415 (P.T.A.B. Feb. 15, 2017).

See eg Greg Emmanuel, The 100-Yard War: Inside the 100-Year-Old Michigan-Ohio State Football Rivalry (2005) (writing on the historic rivalry between the University of Michigan and The Ohio State University).

See Jacob H. Rooksby, The Branding of the American Mind 122 (2016) (examining university patent prosecution and assertion).

Jacob S. Sherkow, Pursuit of Profit Poisons Collaboration, 532 Nature 172, 173 (2016).

Id.

27 Zhen Lei, Rakhi Juneja & Brian D. Wright, Patents Versus Patenting: Implications of Intellectual Property Protection for Biological Research, 27 Nat. Biotech. 36 (2009).

28 See eg Gideon D. Markman et al., Innovation Speed: Transferring University Technology to Market, 34 Res. Pol’y 1058, 1064 (2005) (‘[C]ross-university collaborations . . . . may introduce another layer of complexity to licensing and thus add time to the transfer process. This raises a question about the tradeoffs between the value of insights derived from inter-university collaboration and the costs incurred due to licensing complexity.’); Mel I. Mendelson & Mark Rajai, Students Patents on Inter-University Projects, Proc. Am. Soc’y Eng’r Educ. Ann. Conf. & Exposition 6.904.1, 6.904.1–6.904.2 (2001) (describing the difficulties in establishing a patent agreement for student projects between Loyola Marymount University and East Tennessee State University); Dianne Nicol & Jane L. Nielsen, Patents and Medical Biotechnology: An Empirical Analysis of Issues Facing the Australian Industry, Centre for Law and Genetics Occasional Paper No. 6 105 (2003), http://ssrn.com/abstract=2583508 [https://perma.cc/W978-583Q] (describing interinstitutional IP tensions among Australian universities). But see Timothy Caulfield et al., Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies, 24 Nat’l Biotech. 1091, 1093 (2006) (‘Finally, the data concerning the increasing secrecy of university researchers seem to indicate that there may be a conflation of patenting and commercial and/or scientific competition as the cause of this trend. It appears that academic researchers are becoming more secretive, but that is not shown to be attributable to the patenting process, suggesting that the solution might not reside in modifying patent policy.’).

29 CRISPR Therapeutics, Intellia Therapeutics, Caribou Biosciences and ERS Genomics Announce Global Agreement on the Foundational Intellectual Property for CRISPR/Cas9 Gene Editing Technology,
agreement for a single piece of technology has proved difficult, it is unclear how the two institutions will deal with one another on future collaborations.

Second, even with some friction between universities over obtaining patents for their researchers’ work, it has been rare for universities to sue one another regarding inventorship—until now. In 2011, for instance, the University of Utah sued the Max-Planck Institute concerning inventorship over a foundational group of patents concerning RNA interference technology. And since 2012, Stanford University and the Chinese University of Hong Kong have battled one another over lucrative patent rights to noninvasive prenatal genetic diagnostics. That dispute—despite several rounds of appeals—is still ongoing. Such patent disputes are costly, high stakes, and high profile. And while the CRISPR patent dispute itself is not a cause of such conflict, it has become emblematic—and potentially prophetic—of the tenor of such disputes today. Avoiding them in the first instance is a sensible institutional priority. But that sometimes comes at the cost of avoiding one’s colleagues.

Third, even apart from the administrative institutional level, patent disputes like these damper the culture of scientific collaboration, clearly something of tremendous import to modern science. Putting a price on a loosely defined culture of scientific collaboration is difficult—its loss is difficult to quantify. Nonetheless, many of the most significant breakthroughs of the past century arose in part from a culture of scientific openness and collegiality. Abandoning that in favor of inuring patent rights to researchers from a single institution seems, at best, unwise. Relatedly, it may erode scientists’ penchant for honest, if critical assessments, of their own work among collaborators and colleagues. A key piece of evidence used in the U.S. CRISPR patent interference against the University of California was a single one of Doudna’s public statements that her collaborators ‘weren’t sure if CRISPR/Cas9 would work in eukaryotes—plant and animal cells’. That statement has now echoed throughout laboratories across the USA as a cautionary tale against critical reflections of one’s work—at least while patents are pending.

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30 CARIBOU BIOSCI., Dec. 16, 2016, http://cariboubio.com/in-the-news/press-releases/crispr-therapeutics-intellia-therapeutics-caribou-biosciences-and-ers [https://perma.cc/T6HG-P6DB].

31 Univ. of Utah v. Max-Planck-Gesellschaft zur Foerderung der Wissenschaften E.V., 851 F.3d 1317 (Fed. Cir. 2017).

32 Bd. of Trustees of the Leland Stanford Jr. Univ. v. Chinese Univ. of Hong Kong, 860 F.3d 1367 (Fed. Cir. 2017).

33 Johan Bruneel, Pablo D’Este & Ammon Salter, Investigating the Factors That Diminish the Barrier to University–Industry Collaboration, 39 RES. POL’Y 858, 859–60 (2010) (noting that IP conflicts act as a barrier to collaboration).

34 See Sherkow, supra note 25, at 173.

35 See eg Clyde A. Hutchison, III, DNA Sequencing: Bench to Bedside and Beyond, 35 NUCLEIC ACIDS RES. 6227, 6230 (2007) (describing the collaboration to engineer DNA sequencing between Maxam and Gilbert); E.M. Tansey & P.P. Catterall, Monoclonal Antibodies: A Witness Seminar in Contemporary Medical History, 38 MED. HIST. 322, 327 (1994) (describing the collaborative efforts of the discovery of antibodies); James D. Watson & Robert Mullan Cook-Deegan, Origins of the Human Genome Project, 5 FASEB J. 8, 9 (1991) (discussing the collaborative efforts of the Human Genome Project).

36 Broad Institute, Inc. v. Regents of the University of Cal., Patent Interference No. 106,048, 2017 WL 657415 (P.T.A.B. Feb. 15, 2017).

37 Michael Eisen, Patents Are Destroying the Soul of Science, It Is NOT JUNK (Feb. 20, 2017), http://www.michaileisen.org/blog/?p=1981 [https://perma.cc/2VME-PUS8] (accessed Nov. 13, 2017)
Lastly, patent conflicts’ hindrance of interinstitutional collaborations may simply be costly. Today, some research benefits from economies of scale, such as where expensive equipment can be shared among institutions.\(^{38}\) The New York Genome Center, for example, is a joint venture among several New York-area research institutions: NYU, Columbia, Cold Spring Harbor Laboratories, to name a few.\(^{39}\) This arrangement allows researchers at these institutions to share a fleet of Illumina X Ten sequencers, the total cost of which—including operations—runs into the millions of US dollars.\(^{40}\) Where research funding is diminishing—as is sadly the case in much of the Anglophone world\(^{41}\)—universities may foolishly hesitate to engage in similar cost-saving arrangements in the short-sighted hope of avoiding future patent lawsuits.\(^{42}\) One would hope that the CRISPR patent dispute teaches others that such myopia isn’t warranted.

**SURROGATE LICENSING**

Interinstitutional tensions aside, the CRISPR patent dispute raises some significant issues concerning patent licensing and commercialization—agreements between universities and commercial entities over the use and development of CRISPR. In CRISPR’s case, both the Broad Institute and the University of California have employed a system of ‘surrogate licensing’: ‘outsourcing the licensing and commercialization of a valuable patent portfolio to a private company.’\(^{43}\) It is that company—rather than university—that takes responsibility for licensing the included patents to commercial researchers, including biotech startups and large pharmaceutical developers.\(^{44}\)

At the same time, the surrogate is frequently working to develop the technology itself.\(^{45}\) This is certainly true for CRISPR. The University of California has delegated the entirety of its licensing rights to Doudna’s inventions to Caribou Biosciences, which in turn has granted an exclusive license to develop human therapies to Intellia Therapeutics.\(^{46}\) The Broad Institute, meanwhile, has employed Editas Medicine as its surrogate for human therapeutics; the institute retains control over non-commercial and

\(\text{\textsuperscript{38}}\) Karla Hernandez-Villafuerte et al., *Economies of Scale and Scope in Publicly Funded Biomedical and Health Research: Evidence from the Literature*, 15 *Health Res. Pol’y & Sys.* 3 (2017) (reviewing the sometimes conflicting evidence for economies of scale in biomedical research).

\(\text{\textsuperscript{39}}\) *Institution Founding Members, New York Genome Center*, [http://www.nygenome.org/about-us/#our-members](http://www.nygenome.org/about-us/#our-members) (accessed Nov. 13, 2017).

\(\text{\textsuperscript{40}}\) *The New York Genome Center Purchases Illumina Hiseq X Ten Sequencing System, New York Genome Center*, Jan. 22, 2014, [http://www.nygenome.org/wp-content/uploads/HiSeq-X-Ten-NYGC-Press-Release-FINAL.pdf](http://www.nygenome.org/wp-content/uploads/HiSeq-X-Ten-NYGC-Press-Release-FINAL.pdf); [https://perma.cc/G4KZ-6EAF](https://perma.cc/G4KZ-6EAF) Jacob S. Sherkow, *Cancer’s IP*, 96 N.C. L. REV. (forthcoming 2018) (manuscript at 14-16), [https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2928241](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2928241) (discussing the cost of sequencing operations).

\(\text{\textsuperscript{41}}\) See Simon Parkin, *Brexit Is Quietly Strangling Science*, *Bloomberg*, Aug. 8, 2017, [https://www.bloomberg.com/news/features/2017-08-08/brexit-guts-british-sciences-and-risks-graphene-innovation](https://www.bloomberg.com/news/features/2017-08-08/brexit-guts-british-sciences-and-risks-graphene-innovation) [https://perma.cc/9VD9-WVNV] (accessed Nov. 13, 2017).

\(\text{\textsuperscript{42}}\) See Sherkow, supra note 25, at 173; ROOKSBY, supra note 24, at 126.

\(\text{\textsuperscript{43}}\) Contreras & Sherkow, supra note 21, at 698.

\(\text{\textsuperscript{44}}\) Id. at 698–99.

\(\text{\textsuperscript{45}}\) Id.

\(\text{\textsuperscript{46}}\) Id.
non-human therapy uses.\textsuperscript{47} Surrogates, therefore, ‘control a large and lucrative field for the exploitation of the licensed technology, and have significant freedom both to exploit it themselves and seek partners and sublicensees’. \textsuperscript{48}

This system of surrogate licensing—while not unique to CRISPR—sets up several obvious conflicts. Surrogates may very well be unwilling to sublicense their technology to smaller biotech companies—who, in a very real sense, are rivals to the surrogate.\textsuperscript{49} Smaller companies seeking to develop similar uses of CRISPR to that studied by, say, Editas are unlikely to receive patent licenses to do so—at least on favorable terms.\textsuperscript{50} Surrogates are also not invested with the same public duty as their related academic institutions. Their duties, especially if they are publicly traded companies—as are Editas, Intellia, and Emmanuelle Charpentier’s own company, CRISPR Therapeutics—are to their shareholders.\textsuperscript{51} In both real and legal terms, this duty tacks toward profit maximization rather than, say, advancing scientific knowledge or public access to the downstream products of their research—ideals typically lauded by research institutions.\textsuperscript{52} With respect to this conflict between public-facing goals and shareholder value, Michael Eisner, former CEO of Disney, put it best: ‘We have no obligation to make history. We have no obligation to make art. We have no obligation to make a statement. To make money is our only objective’. \textsuperscript{53} Lastly, surrogate licensing—even when functioning well—may ‘bottleneck’ the commercial development of the underlying technology.\textsuperscript{54} Surrogates may grant exclusive sublicenses that are too broad relative to their licensees’ contributions; this blocks others from developing competing technologies.\textsuperscript{55} Surrogates may also grant licenses to disease indications or areas of the genome far greater than any sublicensee can work at any given time.\textsuperscript{56} To be sure, bottlenecking is a serious problem with respect to university licensing as well.\textsuperscript{57} But universities are frequently more invested in nonexclusive licenses to commercial developers than for-profit surrogates.\textsuperscript{58}

ETHICAL LICENSING AND ENFORCEMENT

Most of the commentary on the CRISPR patents has been negative—and, in particular, the negative side of patenting the products of academic research.\textsuperscript{59} But—aside from money—there are some significant social positives as well. At their core, patents

\begin{footnotesize}
\begin{enumerate}
\item Id.
\item Id. at 700.
\item Id.
\item Id.
\item Id.
\item See Mark J. Roe, Corporate Short-Termism—In the Boardroom and in the Courtroom, 68 Bus. L. 977, 993 (2013) (noting the conflict between short-term shareholder value and long-term scientific research).
\item Id.
\item Kim Masters, Keys to the Kingdom 103 (2000).
\item Contreras & Sherkow, supra note 21, at 700.
\item Id.
\item Id.
\item Id.
\item See Ian Ayres & Lisa Larrimore Ouellette, A Market Test for Bayh-Dole Patents, 102 Cornell L. Rev. 271, 279–80 (2017) (noting deadweight losses with exclusive university licensing).
\item Id. at 275.
\item See eg Contreras & Sherkow, supra note 21, at 698; Egelie et al., supra note 18, at 1030–31; Sherkow, supra note 25, at 173.
\end{enumerate}
\end{footnotesize}
are rights to exclude others from practicing the claimed invention.60 The corollary to this axiom is that patents therefore allow their owners to dictate to the rest of the world how to use the inventors’ technology.61 This power to direct others’ research can be harnessed for societal good.62 Where the claimed technology raises ethical or social concerns, patent holders have the right to tell their technologies’ users to behave ethically and to provide access to downstream inventions.63 In this sense, patents—when used well—can function as a powerful form of private governance.64

This is certainly the case with CRISPR, the ethical and social issues of which have been explored at length.65 One potentially problematic use of CRISPR is its use in ‘gene drives’, a daisy chain of genetic editing that essentially forces future generations to inherit and subsequently pass on only a single variant of a particular gene.66 The concern, as detailed by Kevin Esvelt, is that gene drives, because they are forcibly heritable, become difficult to control once put in place.67 Should later research find negative, unintended effects of the particular genetic variant driven through the population, it may simply be too late.68 To that end, Esvelt and others have proposed patenting the use of CRISPR-based gene drives to, essentially, prevent others from using the technology without rigorous scientific and ethical controls.69 The legal mechanics of enforcing patent protection in this manner leave some gaps that likely need to be addressed. But Esvelt’s proposal suggests, at a minimum, that patenting controversial technologies is one possible tool to further their ethical use.

In other cases, rather than using patents to ethically restrict access to controversial technologies, patents can be used to ethically promote access to the same. That is, patent holders can demand licensees promise that they make their technology available to broad segments of society, and on fair terms.70 This is largely the case with Monsanto’s license from the Broad Institute covering the use of CRISPR-Cas9 for a variety of agricultural purposes. That license essentially requires Monsanto to allow its farmer customers to save and resow seed from one season to the next, in contrast to some of

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60 See 35 U.S.C. § 271(a) (2012) (‘[W]hoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.’).
61 See Tania Bubela, Jenilee Guebert & Amrita Mishra, Use and Misuse of Material Transfer Agreements: Lessons in Proportionality from Research, Repositories, and Litigation, 13 PLoS Biol. e1002060 (2015) (linking patents’ greater rights to exclude with the lesser right of limiting the underlying inventions use—typically through material transfer agreements).
62 Christi J. Guerrini et al., The Rise of the Ethical License, 35 Nat. Biotech. 22, 22 (2017).
63 Id. at 23.
64 Id. at 22 (‘By prohibiting uses the patent holder deems unethical, a patent license can function as a tool of private governance.’).
65 See eg Regalado, supra note I.
66 See Ed Yong, One Man’s Plan to Make Sure Gene Editing Doesn’t Go Haywire, July 11, 2017, ATLANTIC, https://www.theatlantic.com/science/archive/2017/07/a-scientists-plan-to-protect-the-world-by-changing-how-science-is-done/532962/ [https://perma.cc/WSS8-BWC8] (accessed Nov. 13, 2017) (discussing Esvelt’s proposal).
67 Id.
68 Kevin M. Esvelt, Strategies for Responsible Gene Editing, PROJECT SYNDICATE, Jan. 25, 2016, https://www.project-syndicate.org/commentary/crispr-gene-drive-editing-rules-by-kevin-m–esvelt-2016-01 [https://perma.cc/ZP3A-89CX] (accessed Nov. 13, 2017).
69 See Yong, supra note 66.
70 See Guerrini et al., supra note 62, at 23.
Monsanto’s past practices. Requiring this of Monsanto provides greater access to the fruits of CRISPR technology to farmers, who would otherwise be required to purchase expensive new seed each year from Monsanto. In the therapeutics context, similar license restrictions could be used, in theory, to require price controls, access plans, or that research and development funds be used, in part, to develop treatments for neglected diseases.

And, perhaps counterintuitively, patents could also be used to ensure research access to a variety of technologies. Patent holders can publicly commit to refuse to enforce their patents against researchers or academic institutions. In the USA, these frequently take the form of ‘patent pledges’—‘commitments made voluntarily by patent holders to limit the enforcement or other exploitation of their patents’. Doing so both prevents others from patenting—and suing others—on the same technology, and dissuades less ethically minded competitors from entering the field. Patent holders can also use open licensing systems to researchers interested in developing and sharing the technology for the public good. In the CRISPR context, this non-commercial use is mediated through a non-profit organization, AddGene, a company that provides access to CRISPR constructs and plasmids through a standardized Biological Materials Transfer Agreement (BMTA). AddGene’s BMTA’s contains patent licenses for academic use of the underlying technology.

To be sure, these restrictions have the potential for abuse. One scientist’s ethical restriction is another’s unethical impediment to research. The Wisconsin Alumni Research Foundation (WARF), for example, owns many patents directed to human embryonic stem cells (hESC), methods of use and propagation and therapies potentially derived from their use. But facing public controversy over the technology—and a moralistic Congress then threatening to restrict federal funding covering the technology—WARF has imposed restrictions on its hESC patent licenses concerning their technology’s use in connection ‘non-human embryos’. These restrictions have aroused some ire among the scientific community, many of whom view the limitations not as an ethical fence, but an impermissible walling off of secular research for religious purposes.

Importantly, too, the overreliance on patents as vehicles promoting the ethical uses of technology may crowd out other equally effective—and less restrictive—forms of control. Patents, of course, are not the only means of private governance to reign in ethically unruly technology. The BioBrick Foundation, a research platform for

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71 Id. at 24.
72 Id.
73 Cf. Rebecca S. Eisenberg & W. Nicholson Price, Promoting Healthcare Innovation on the Demand Side, J. L. & BIO SCI. 3, 18 (2017) (noting that health care payers have the information and incentives to impose demands on drug developers).
74 Jorge L. Contreras, Patent Pledges, 47 ARIZ. ST. L.J. 543, 546 (2015).
75 See Id.
76 AddGene UBMTA, ADDGENE, https://www.addgene.org/terms/1047/ [https://perma.cc/ZGSK-4YFP] (accessed Nov. 13, 2017).
77 John M. Golden, WARF’s Stem Cell Patents and Tensions Between Public and Private Sector Approaches to Research, J. L. MED. & ETHICS 314, 314 (Summer 2010).
78 Id. at 319.
79 Id. (‘In any event, outside researchers do not seem always to have distinguished, or to have been able to distinguish, between ethical and proprietary motivations for WARF’s restrictions, which a number of researchers have contended were overly burdensome or intrusive.’).
‘synthetic biology’, famously abandoned patents as a tool for ethical governance in favor of standardized, contractual, materials transfer agreements—namely, the BioBrick User Agreement (BUA). The BUA itself contains, in essence, ethical restrictions—notably, § 5, which prohibits ‘intentionally harmful, negligent, or unsafe uses’. While the enforceability of the agreement is questionable, it stands testament to the possibility of private ethical governance of platform technologies outside of patent assertion. In any event, the contrast among the WARF hESC patents, AddGene’s BMTA, and the BUA demonstrates that, like CRISPR itself, patents are tools that can be used for good or for ill. At a minimum, ethically responsible patent pledges demonstrate the capacity of using patents as a tool for the public good.

CONCLUSIONS

In many ways, the ethical, legal, and social issues of CRISPR patenting are idiosyncratic. It is not often that a ground-breaking genetic engineering technology is invented, with monumental import to therapy, human reproduction, and social order. And it is perhaps rarer still that such an important technology becomes the subject of a contentious patent dispute among some of the world’s highest esteemed research institutions. Nonetheless—despite claims that the CRISPR patent dispute is a unique event—there are some greater lessons to be learned about the ethical, legal, and social implications of intellectual property in research science.

The first, and perhaps most important for day-to-day scientific practice, is that patents—their promises and pitfalls—should not ruin research collaborations. Science, and molecular biology in particular, is largely a team sport. Researchers seeking to make the most significant advances in their fields must increasingly turn to others at the fringe of their disciplines for help. In biology, this is perhaps best exemplified by the recent explosion of collaboration between molecular geneticists and computer scientists, the informational yields of which have been tremendous. Even in the CRISPR context itself, it’s worth reiterating that the two warring factions made their advances through collaborative efforts, despite patent disputes within research groups: Doudna with Charpentier; and Zhang with Luciano Marraffini of Rockefeller University.

80 The BioBrick User Agreement, BioBricks Foundation, https://biobricks.org/bpa/users/agreement/ [https://perma.cc/Y6HD-9WXA] (accessed Nov. 13, 2017) [hereinafter BUA]; see also David Singh Grewal, Before Peer Production: Infrastructure Gaps and the Architecture of Openness in Synthetic Biology, 20 STAN. TECH. L. REV. 143, 180–187 (2017) (exhaustively describing the BUA and its implications).
81 BUA, supra note 80.
82 Although CRISPR’s magnitude, as a biological tool, is not unique. Recombinant DNA, the discovery of hESCs, and the engineering of monoclonal antibodies have similarly challenged law, science, and ethics when they were first announced. See generally GEORGE CHURCH AND ED REGIS, REGENESIS: HOW SYNETHETIC BIOLOGY WILL REINVENT NATURE AND OURSELVES (2012) (discussing each of these technologies and their impact on synthetic biology).
83 Janet D. Stemwedel, The Objectivity Thing (Or, Why Science Is a Team Sport), SCI. AM., July 20, 2011, https://blogs.scientificamerican.com/doing-good-science/httpblogsscientificamericancomdoing-good-science20110720the-objectivity-thing-or-why-science-is-a-team-sport/ [https://perma.cc/ENR9-SDYE] (accessed Nov. 13, 2017).
84 See Jacob S. Sherkow, Negativating Invention, 2011 BYUL. REV. 1091, 1118–19 (describing the innovation trend to combine widely disparate fields of art).
85 Minoru Kanehisa & Peer Bork, Bioinformatics in the Post-Sequence Era, 33 NAT. GENET. 305, 305 (2003) (discussing the rise of bioinformatics as a scientific discipline); Saurabh Vishnubhat & Arti K. Rai, When Biopharma Meets Software: Bioinformatics at the Patent Office, 29 HARV. L. & TECH. 206, 206–07 (describing the rise of bioinformatics as a field of innovation).
University.\textsuperscript{86} CRISPR research has now largely become international in scope despite a thicket of global and interinstitutional patent issues.\textsuperscript{87} It is doubtful that further advances could be made without such teams. Patent incentives should not act as collaborative disincentives.

Another lesson to be drawn is the potential power of scientists—not just lawyers—over the use and abuses of their patents. Researchers often have some significant say in how their home institutions can use their patented technology—from who should receive a license to the royalty rate and terms set for competitors.\textsuperscript{88} Indeed, academic inventors are frequently the founders or co-owners of spinout companies to whom their institutions farm out patent sublicensing work.\textsuperscript{89} Doudna, for example, is the co-founder of Caribou Biosciences, the University of California’s patent surrogate; Charpentier, CRISPR Therapeutics; and Zhang, Editas Medicine.\textsuperscript{90} Inventor researchers with academic spinouts therefore have some control in how their technology will ultimately be used. Scientists with careers otherwise dedicated to the greater good should leverage this power; they should engage with and negotiate with their institutions to responsibly develop the fruits of their efforts. They should not abandon these concerns to university administrators or their companies’ shareholders.

Lastly, the ethical, legal, and social implications of the CRISPR patents have something to say about academic patenting, in general. Currently, a great deal of the academic literature on IP paints patents with a normative brush—patents are ‘good’; patents are ‘bad’.\textsuperscript{91} More nuanced, economically sophisticated discussions of these positions cast them in terms of efficiency.\textsuperscript{92} But the CRISPR patent controversies teaches us that patents, like kitchen knives, are simply tools, without a moral valence separate from their users. Patents, like the CRISPR patents, can be used in ways that impede further research.\textsuperscript{93} Or, they can be used to promote, if not demand, their ethical application.\textsuperscript{94} The patents themselves do not do these things; the outcomes depend

\textsuperscript{86} Jon Cohen, \textit{How the Battle Lines Over CRISPR Were Drawn}, \textsl{Science News}, Feb. 15, 2017, \url{http://www.sciencemag.org/news/2017/02/how-battle-lines-over-crispr-were-drawn} [\url{https://perma.cc/ZMA5-Y2FU}] (accessed Nov. 13, 2017) (describing the relationships between Doudna and Charpentier as well as between Zhang and Marraffini).
\textsuperscript{87} Egelie et al., \textit{ supra} note 18, at 1030–31.
\textsuperscript{88} See Jason Owen-Smith & Walter W. Powell, \textit{To Patent or Not: Faculty Decisions and Institutional Success at Technology Transfer}, 26 J. TECH. TRANSFER 99, 106 (2001) (describing concerns of academic scientists over use of their patented technology); Lynne G. Zucker & Michael R. Darby, \textit{Star Scientists and Institutional Transformation: Patterns of Invention and Innovation in the Formation of the Biotechnology Industry}, 93 PROC. NAT’L ACADEMY OF SCI. USA 709, 709 (1996) (examining that faculty input of star scientists is a significant factor affecting technology transfer offices’ decision to create spinouts).
\textsuperscript{89} See Jorge L. Contreras & Charles R. McManis, \textit{Catalyzing Technology Development Through University Research}, in \textit{Research Handbook on Intellectual Property and Climate Change} 237 (Joshua D. Sarnoff ed. 2016) (describing the creation of spinouts).
\textsuperscript{90} About Us, CRISPR THERAPEUTICS, \url{http://www.crisprtx.com/about-us/scientific-founders-advisors.php} [\url{https://perma.cc/T7UB-MKYN}] (accessed Nov. 13, 2017); Origins, CARIBOU BIOSCIENCES, \url{http://cariboubio.com/origins} [\url{https://perma.cc/SMH8-7KHU}] (accessed Nov. 13, 2017); Our Team, EDITAS MEDICINE, \url{http://www.editasmedicine.com/our-team} [\url{https://perma.cc/UA2W-AUFY}] (accessed Nov. 13, 2017).
\textsuperscript{91} See Mark A. Lemley, \textit{Faith-Based Intellectual Property}, 62 UCLA L. REV. 1328, 1331 (2015) (casting the academic literature in these normative terms).
\textsuperscript{92} See \textit{id}. at 1332–35 (describing some of the economic literature on the ‘patent system’, writ large).
\textsuperscript{93} Contreras & Sherkow, \textit{ supra} note 21, at 698.
\textsuperscript{94} Guerrini et al., \textit{ supra} note 62, at 23.
entirely on who’s wielding them. To that end, the CRISPR patent controversies should encourage researchers to think about how, and by whom, their inventions will ultimately be used—both for those seeking to use them for good or for ill.

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