The ethics of access to patented biotech research tools from universities and other research institutions

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As universities and public research organizations increasingly partner with industry to fulfill their 'third mission' of innovation activities for economic and societal benefit, they have ethical obligations to ensure access to patented research tools, especially CRISPR–Cas9 technology.

In industry, patents have traditionally been used as barriers, incentives, and negotiation tools in commercial transactions. Academic institutions such as universities and public research organizations (PROs), however, base science and technology development on information sharing, as openness is considered critical to the growth of knowledge. In the life sciences, stronger patent regimes, newer technologies such as biotech, and changing industrial structures have increased patenting activities by academic institutions. The underlying climate in which universities and PROs are encouraged to actively engage in the industrialization and commercialization of research therefore brings to the forefront the critical issue of their ethical obligation of ensuring access to their patented biotech research tools[1].

The commercialization of innovation arguably detracts from academic institutions' primary mission of creating public goods, where this is understood to be goods available to all. Here, we propose two models that can improve access to research results patented by universities and PROs. One model is based on the setting up of systematic flexible licensing systems by universities and PROs. The other is based on federal government use of intellectual property laws and policies to regulate access to publicly funded research results held by universities and PROs. The models are proposed as solutions that could allow academic institutions to fulfill their core mission of providing research, education, and dissemination while also pursuing the legitimate third mission of innovation and commercialization. Furthermore, we shed light on the ethical obligation of universities and PROs to provide access to patented biotech research tools while pursuing this threefold mission. We discuss whether this differs from other biotech patent issues concerning the inherent justification of the patent system, which is the promotion of innovation for societal benefit.

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CRISPR–Cas9 and the co-production of science and society

Clustered, regularly interspaced, short palindromic repeats (CRISPR) and its associated enzymes such as CRISPR-associated protein 9 (Cas9) is a new technology platform for genome editing, now widely used in research areas such as gene therapy, drug screening and development, and agricultural biotech. A dispute is currently being arbitrated by the US Patent and Trademark Office between the major inventors of the CRISPR–Cas9 technology[2]. The dispute relates to important aspects of access by universities and PROs to inventions and research results. It also relates to the so-called third mission of innovation and commercialization[3]. Patent protection and control are at the heart of this mission, and the management of this mission by universities and PROs is therefore of great societal importance. So is the question of whether these organizations are capable of combining co-production of commercial products and services through patented inventions with their essential mission of education, research, and dissemination. The CRISPR–Cas9 technology exemplifies some of the hurdles public knowledge holders must overcome to effectively manage the incorporation of the third mission into their other activities.

The publication of the CRISPR–Cas9 construct by a group led by Jennifer Doudna and Emanuelle Charpentier in 2012 revealed the potential of the technology as a research tool[4]. Subsequent studies demonstrated how the CRISPR–Cas9 construct could be applied in an easy way as a genome editing tool to a wide range of organisms. Doudna's and Charpentier's home institutions, the University of California, Berkeley, and the University of Vienna, respectively, excited by the discovery and its possibilities, together filed a patent application in late 2012 (ref. 5).**[AU: sentences 1 and 2 revised to include Doudna's and Charpentier's names; reword as desired]** Only a few months after, a research group at the Broad Institute, MIT, and Harvard College filed a patent application on the CRISPR–Cas9 construct based on the research and publication of neurologist Feng Zhang[6]. In his patent, Zhang showed that CRISPR–Cas9 could edit DNA in eukaryotic and mammalian cells[7]. Due to legal technicalities in the US patent system, the lawyers prosecuting Zhang's patent application were able to have the patent granted before Charpentier and Doudna's patent application, **[AU: patent application not just from Berkeley; have replaced Jinek's name with Charpentier's, okay?]**creating a messy legal situation. These overlapping patent applications are the subject of a dispute that for some time has created uncertainty regarding the ownership of the access rights to the inventions.

The current understanding of the role of public knowledge holders is expressed by Sheila Jasanoff, professor of science and technology studies at the Harvard Kennedy School, in the idea of the co-production of science and society, which indicates how scientific and societal activities interact and shape each other[8].**[AU: Jasanoff's first name and affili-**

ation added in keeping with journal style] CRISPR–Cas9 technology is an example of how access to science is shaped by the society with which we interact. Jasanoff argues that the concept of co-production may be used to describe how the "domains of nature, facts, objectivity, reason, and policy cannot be separated from those of culture, values, subjectivity, emotion, and politics"[8]. Justin Biddle, a professor of philosophy at the Georgia Institute of Technology, supports this by suggesting that although patenting is meant to incentivize research in areas such as biotech and life sciences to promote the development of knowledge, it often has the opposite effect[9]. Biddle argues that science should therefore be reorganized, because inventions in patents have been used to prevent or forbid research into biotechnologies and have therefore imposed restrictions on science. The lack of access to new scientific contributions furthermore limits the possibility of universal validation. The expectation that research is beneficial to society and that scientists should contribute to society by producing knowledge that is useful in the creation of commercial products and services demonstrates two seemingly contradictory aspects of the co-production of science and society. **[AU: revised to shorten and remove jargon; reword if needed.]**

The question of whether it is appropriate for academic institutions, whose mission is to disseminate research and knowledge, to own patent rights that potentially restrict access, therefore becomes pertinent. Patent ownership involves a trade-off between exploiting exclusive rights in a competitive commercial market and ensuring sufficient scope for positive benefits to the public. This trade-off is often decided by researchers at universities and public research organizations who hold the patent. This may well be suboptimal and has led to a number of national legislative regulations, the US Bayh–Dole Act being one of the greatest influences upon the legislation that governs the intellectual property framework for universities and technology transfer[10]. The Act has led to reform and an increased focus on university technology transfer. However, it has also been controversial, with critics suggesting that a number of legislative and federal interventions need to be imposed to achieve a better and more socially efficient transfer of knowledge from universities to industry and others[11,12].

Political demands for greater societal impact are widely recognized as being a key driver of research organizations' collaboration with industry to create new products and services. An essential aspect of this collaboration is the control of and access to research results and innovations, with patents being recognized as being one of the main tools for facilitating control and access[13]. But intellectual property mechanisms could inherently lead to a conflict of interest for universities and PROs between broad dissemination and provision of access to research, and the filing of patent applications that impose restrictions on the use of research.

The CRISPR–Cas9 research tool exemplifies the conflict of interest that can arise between universities' core and third mission activities, as well as their difficulty in navigating them[14]. Access to the CRISPR–Cas9 patents is currently solely granted to specific spinoff companies established by the stakeholders in the patent dispute, namely UC Berkeley and the Broad Institute[15]. Other academic institutions, PROs, and even commercial entities that want to use and develop the tool could, therefore, be hindered by these patents. The ethical issues of the management of access to patented biotech products therefore need to be explored. The current paradigm in academic technology transfer stresses the creation of startup companies in which both inventors and universities hold equity. This form of spinoff technology transfer model works well for inventions that are developed and commercialized by a single entity that can focus all of its efforts on one or a few projects, as in the early development of human therapeutics, which are then acquired and commercialized by major pharmaceutical companies. But does this model work as well for an enabling technology such as CRISPR? It is reasonable to propose that CRISPR must be widely disseminated to both the nonprofit and for-profit sectors if the expected explosion in gene editing is to occur and the promise of this groundbreaking technology is to be realized.

Access to research tool patents from universities and PROs

Though CRISPR–Cas9 is an exciting and powerful tool that may lead to ways to identify, repair, or treat inborn and acquired genetic errors, it is, however, subject to a debate on its controversial technological uses. Suggestions for preventing certain uses include regulation and controlled distribution through well-defined "ethical" licenses[16]. **[AU: sentence splitting okay?]**Patent protection has been an important commercial incentive mechanism for biotechnologies such as PCR, recombinant DNA, and short interfering RNA (siRNA). Research tools of this kind that are used in high-throughput screening methods, biological assays, ligand binding methods, and antibody-specific marker detection are very suitable for patent protection. However, there are concerns regarding the practice of including reach-through claims in research tool patents, which allows earlier patented inventions to claim coverage of downstream inventions and raises the problem of research tool patents covering more than is justified by the initial invention[17,18]. For example, patents for methods that use antibody detection may therefore cover antibodies not yet identified, a patent for a new screening method might cover the use of ligands or similar that have no defined specificity and biological assays might cover targets that have not yet been shown to functionally work.

The management of intellectual property involves more than the stimulation of innovation. It primarily involves not ownership of individual emerging technologies, but governance in a wider sense, including the consideration of the cost of the technology, its availability, who is to have access, transparency of development, and who will control further developments, private institutions, or political authorities[19]. The 'tragedy of the anticommons' postulated that the distribution of knowledge within biotech and biomedicine could be unbalanced by the filing of patent applications. Furthermore, when multiple owners each have the right to exclude others from access to a scarce resource, no single owner has an effective privilege of use[20,21]. The anticipated and theoretical results of the anticommons hypothesis have, however, not significantly materialized in practice. On the contrary, we see successful efforts by industry and academia to reach workable solutions whenever biotech patents have seemed to block subsequent developments rather than incentivize them. **[AU:OK?]**Recent data on the influence of patents and other intellectual property rights upon scientific research and development indicates a more complex picture. Those in the scientific community appear to ignore patents and possible infringements of the patent rights of others. This could establish a norm and so promote the sharing of research results among academic scientists[22]. Concern about anticommons and patent thickets are possibly overstated because of academics evoking the research exemption rule, which they believe to be a safe harbor[23].

There are, however, concerns that the research exemption practice exercised by university and PRO employees is too liberal. The argument is that universities and PROs have not, in the past, entered into commercial agreements relating to patented research results in a commercial structured manner. They have mostly used such research results for academic research and not in commercial activities. These arguments become less convincing as universities and PROs increase their commercial activity. A 2002 US Court of Appeals

for the Federal Circuit decision rejected the "experimental use defense" in a patent infringement lawsuit[24]. The decision suggests that overlooking the patent rights of others may not be acceptable even for academic researchers. The research exemption may therefore not be a safe harbor, at least not in the United States where the research exemption is interpreted more restrictively than in Europe[25].

Can CRISPR–Cas9 inventions learn from history?

The transfer of control of patent ownership to commercial entities by organizations that owned the initial CRISPR–Cas9 invention, as described in recent studies[15,26], raises the issue of how organizations controlling patents use their privilege to grant other operators access to the invention through licensing and other types of agreements, and of the consequences of this transfer of intellectual property control from public nonprofit organizations to private interests. **Figure 1** highlights the main CRISPR–Cas9 patent holders and the number of their filed patent applications. The figure shows that organizations, institutions and industries are creating patent portfolios to gain control of the CRISPR–Cas9 system[26].

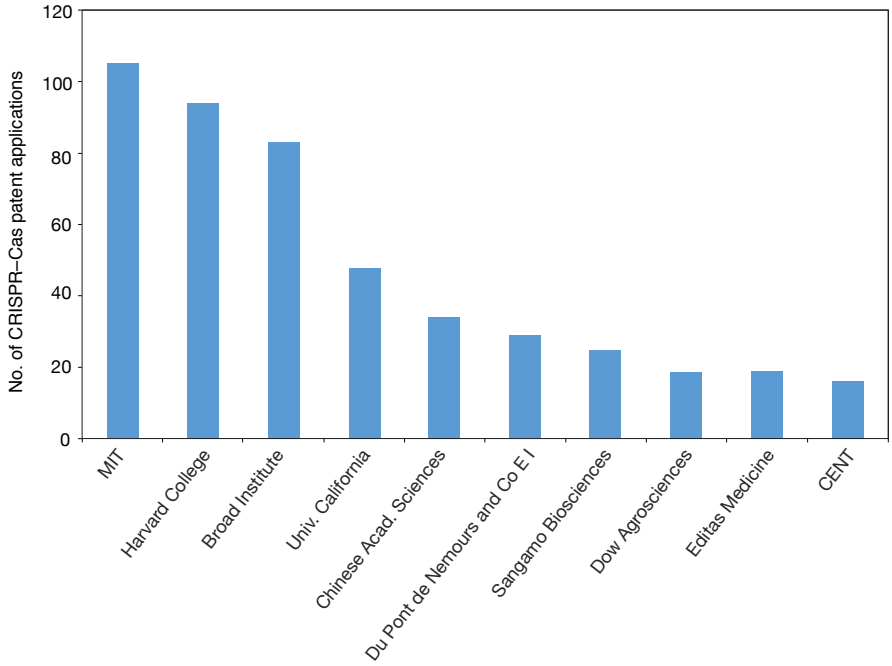

Figure 1 Top ten patent holders and the number of CRISPR–Cas9 patent applications filed. The list is based on a search of key words "CRISPR" and "Cas9" in the Thomson Innovation patent database. The number of total inventions represents separate patent families where each family represents one unique invention.**[AU: add DWPI to legend, if needed; it has been deleted from figure] [AU: spell out CAS and CENT]**

The patent dispute between UC Berkeley and the Broad Institute concerns the scope of some of their CRIPSR–Cas9-related patents. UC Berkeley claims their patents cover a genome-editing tool in any type of cell, although the US patent court currently only grants coverage as far as prokaryotes. The Broad Institute, however, claims to have invented the use of CRISPR–Cas9 to cut DNA specifically in eukaryotic (including human) cells and says that their patent application therefore applies to eukaryotic use of CRISPR–Cas9. The court's opinion is that UC Berkeley has not specified their patent for eukaryotes in general or humans specifically and that their patent is not infringed by the Broad Institute's patent.

The outcome of this dispute is highly significant as it will determine which research institution controls the fundamental CRISPR–Cas9 technology patents, and therefore the commercialization of pharmaceutical industry inventions arising from its use. UC Berkeley has appealed the patent court's decision, with the final outcome still unknown.

Both the Broad Institute and UC Berkeley have entered into a partnership with Addgene, a nonprofit organization aiming to provide access to biotech research tools for academic institutions[27], including the CRISPR–Cas9 system. This move appears to compensate for possible monopolistic control and licensing of their patent portfolio, with non-commercial access being granted to universities and other nonprofit organizations for further research. Even so, the CRISPR–Cas9 patents are still under the control of one or a few parties, a control that is open to the bias of the parties' interests. Single industry interests can also, wittingly or unwittingly, be granted exclusive access to parts of the CRISPR–Cas9 portfolio and use this access solely to benefit their business interests. The social construct of the controlling parties' intellectual property management therefore needs to be questioned.

The history of biotech provides us with evidence that patents can be managed in a way that provides both industry and public R&D with access to inventions. One example is the invention and patenting of a method to produce recombinant DNA in bacteria by Herbert Boyer of the University of California, San Francisco, and Stanley Cohen of Stanford University[28,29]. Stanford established a licensing program that provided a predictable legal framework for using their inventions at the same time as it filed the Cohen–Boyer patents. The program, which provided new methods for academic research organizations to grant industry partners access to their inventions[30], made non-exclusive licenses available to industry and to academic institutions and included a predictable royalty scheme for commercial use.

The Stanford licensing program has been successfully used by other research organizations—such as Columbia University for its so-called Axel patents—to control patents and make them available to both researchers and industry[31]. Another example of patent-based licensing of a major biotech breakthrough is small interfering RNA (siRNA)[32,33]. Three of the four academic institutions involved in the early development of siRNA agreed to provide free patent licenses to scientists who made other siRNA molecules in the laboratory and to grant non-exclusive licenses to industries that were commercializing molecular components based on their intellectual property[34]. There are, therefore, several examples of organizations that have managed to successfully balance access to research and open academic dissemination with a more proprietary commercial development of products and services.

Reasonable access to CRISPR–Cas9 technology under current patent practices will be determined by the ability of the patent holders to provide flexible licensing and other strategies that ensure further development of the technology. Both Columbia and Stanford recognized that charging too much for licenses would discourage potential licensees and increase the likelihood of third parties challenging the validity of patents in the court. Despite the differences in their models, Columbia and Stanford placed no restrictions on the use of patents by researchers at nonprofit institutions. Stanford's concept for licensing (known as the "ethical commercialization" of intellectual property created by the university[35]) has been expanded

by leading academic institutions such as the Broad Institute and UC Berkeley by free-of-charge use of patented inventions in academic research being facilitated through material transfer agreements (MTAs) via the Addgene nonprofit clearinghouse. Besides the Stanford and Columbia 'self-regulation' models, other examples of initiatives for providing broader public access to biotech and life science patents include the Medicines Patent Pool (MPP)[36], a shared patent pool administrated by the World Health Organization that draws together new academic research and patented commercial pharmaceutical research results, the pooled resources being made available to parties that make low-price generic HIV drugs that are distributed solely in developing and poor countries; the Pool for Open Innovation against Neglected Tropical Diseases, established in 2009 by GlaxoSmithKline and Alnylam Pharmaceuticals, later joined by MIT and several other academic institutions; and the Public Intellectual Property Resource for Agriculture (PIPRA), founded in 2004 by the Rockefeller Foundation in response to concerns that, due to patents, public investment in agbiotech that benefits developing countries was experiencing delays, high transaction costs and lack of access to important technologies[37,38]. PIPRA's patent pool provides open-access to plant transformation technologies through consolidating patent rights in marker-free vector systems, plant transformation systems having been licensed to and deployed in both commercial and humanitarian applications in the United States and Africa.

In 2016, a patent pool and global licensing program for the CRISPR-based technology platform was announced by MPEG LA, an intellectual property rights management company. The Broad Institute and Harvard have submitted 22 of their CRISPR–Cas9 patents to the patent pool. CRISPR technology is still in its early infancy and whether this patent pool can be successful remains to be seen. If successful, the pool could create a one-stop shop for commercial users wanting to license CRISPR-based patents and so avoid users having to navigate a complex patent and licensing landscape. Patent pools such as MPEG are furthermore subject to industry-standardized technologies, applications and streamlined non-exclusive license programs—the opposite status of CRISPR technology today.

Models such as the ones above can serve as alternatives to self-regulation models. Sharing research tools is important in ensuring that research with low profit potential but high societal benefits continues. The question, however, remains whether voluntary arrangements are sufficient to guarantee access and ensure that academic organizations and PROs as patent holders share and disseminate their knowledge.

The prospects of future access to patented research tools

There are good reasons for arguing that, by itself, voluntary self-regulation of access is insufficient to prevent knowledge access challenges. One alternative could be the strengthening of the general access requirement in patent grants and making the models used by Stanford and others mandatory. The potential of CRISPR–Cas9 to be a fundamental technology for innovation raises ethical arguments for societal control of the use of the technology and for ensuring reasonable access at an affordable price. This is particularly important for innovations that should benefit the developing world.

An important aspect of societal control of access to technology and knowledge is that this control should not slow innovation, but stimulate it. Patents are dependent on the dynamics of technological developments and societal changes, and must therefore be under continuous revision. Although systemic in their regulative form, they involve normative questions concerning moral standards, which will also need to be the argument for a balanced access scheme to new technologies such as the CRISPR–Cas9 platform.

University and research organization involvement in business creation and other commercial activities expands the social value creation responsibility they bear. We propose two models to help these organizations manage this responsibility.

First, we propose a self-regulation model in which universities and research organizations balance their broader social responsibilities with commercial activities by providing access to patented research tools and methods via transparent license models. Universities, acting on behalf of the public, engaging in highly profitable licensing agreements is an untenable situation. Universities should therefore pursue broad and nonexclusive licenses for research tools and use simple and predictable agreements. The model should be based on licenses that minimize fees and unreasonable restrictions such as reach-through royalties. Universities should, in a self-regulation model, provide access to research tools such as CRISPR through different entities like spinoff companies and ventures in a way that balances revenue with further R&D access. Exclusive licensing to a surrogate company granted by a university will, as for CRISPR–Cas9, create concentrated control of the use of the technology in a for-profit entity that has both short and long-term goals that are likely to be in conflict with the broad dissemination of the technology. Thus, universities and research organizations must continue to explore the more solidaric sharing of licensing models, involving non-exclusive alternatives in combination with clear research exemptions. Non-exclusivity could provide a broader social sharing alternative for creating access to both for-profit and nonprofit parties.

Flexibility is needed when managing a new research tool invention. New research will, in most cases, have limited commercial potential; however, a smaller subset of that research could be the basis for forming a new company. Effective commercialization can determine which is which, and design the appropriate licensing deal. Non-exclusive licensing is not morally superior to exclusivity; both are simply tools that have their place depending on the nature of the invention. Exclusive licenses, furthermore, often cover only a particular field of use, not every application. Through the noncommercial organization Addgene, the Broad Institute provides access to CRISPR–Cas9 to nonprofit researchers. While not perfect, as private companies will still gain exclusive control of commercial products and possibly follow-on inventions, it does create an awareness that access for further research is important and necessary. In the self-regulation model, university management needs to take active control and engage in the commercial activities of publicly funded research. By introducing top-down managed, flexible licensing models that suit both commercial projects and the broader social needs, publicly funded research could be more accessible for all stakeholders in the third mission era of universities and PROs.

A second option is a federal-regulation model based on state control and government-centralized utilization of patented innovations from universities and PROs that relate to technology platforms of major importance to society. The federal-regulation model must involve purpose-targeted and balanced licensing solutions specifically designed for broad technology and knowledge dissemination. Technologies such as CRISPR–Cas9 should be available widely to those who want to explore, develop, and use the technology. Federal governments should therefore develop license conditions and practices that safeguard access to publicly funded disruptive technologies to realize both their economic and social potential.

Through legislation such as the Bayh–Dole Act of 1980, the US government explicitly endorses the exclusive control by universities of inventions resulting from state-funded research. However, while such legislation is intended to accelerate further development and commercialization of ideas and inven-

tions under federal funding, government has not provided any clear national strategies, processes, tools, or resources to support the transition of innovations from academia into the commercial market. There are some exceptions to this. The EU Framework program, the EU Horizon 2020 Program[39], and the more specific Lambert Agreements[40] in the UK are targeted at a better balanced utilization of co-produced research and technologies. These programs are examples of license conditions and models provided by federal institutions to safeguard broader access to and control of university created inventions based on federal funded research. They are, however, purely contractual models. Foundational technology patents such as the CRISPR platform must be implemented into[**AU: meaning no clear; please reword to clarify sense of 'implemented into…'**] broader society based on clear long-term federal strategies and policies. This is particularly important where technologies are developed with public funding by universities operating in the public interest. This is where universities and governments should explore access and sharing models in the management and utilization of intellectual property.

Both models have drawbacks. The first provides little or no public control over knowledge and research results as a common good. This type of transfer of power from the public is a necessary aspect of the patent system, but becomes problematic when the technology in question is of fundamental significance to further innovations, as is the case with CRISPR–Cas9. In addition, leaving the responsibility for reasonable access to the patentee may give too much power to one institution. Historical precedent arguably shows that universities and research organizations could establish access in ways that promote rather than prevent innovations for the common good. There is, however, no future guarantee that similar access will be provided. Adding to this is the question of whether this monopoly is fair, taking into consideration that the knowledge necessary for the patented technology is derived from publicly funded public research, and from the discoveries and inventions initiated by the research of others. One can also question whether self-regulation is sufficient to overcome patent thicket problems, as the patentee will be prone to prioritize the interests of their institution before those of the common good.

The second model can be criticized for over-regulation and creating unnecessary bureaucracy, with no guarantee that this will achieve the intention of balanced patent access rights. In this respect, it can also lead to a "loopholes in moralities" problem caused by the transfer of moral responsibility from the agent to an external governmental body[41]. The result could be that the patent owner has no separate responsibility to provide access if external regulations are inefficient, which is contrary to the societal obligations of universities and PROs as public institutions.

In conclusion, we propose that strategies based on the self-regulation model, where universities and PROs provide access to research through balanced licensing models, and the federal-regulation model, where access is provided through state regulations, should be further explored and developed when universities and research organizations are involved in the patenting and commercialization of technology platforms that have fundamental social significance. Such strategies should result in guidelines on licensing practices that are consistent with the pursuit of both economic profit and the activation of social value.

COMPETING INTERESTS

The authors declare no competing interests.

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