The emerging patent landscape of CRISPR–Cas gene editing technology

Knut J Egelie, Gregory D Graff, Sabina P Strand & Berit Johansen

Early views on the control of the CRISPR–Cas disruptive enabling technology and access for follow-on commercial applications.

The progress in biomedical research over the last four decades has been accompanied by a steep rise in patent filings[1]. Yet, the patenting of biotechnology inventions, especially those related to human genes, has raised ethical, legal and economic concerns, leading to the 2013 decision by the United States Supreme Court in *AMP v. Myriad Genetics* to ban patents on naturally occurring genetic sequences in the US, changing the landscape of patenting biotech inventions[2]. Patenting by universities and public research organizations (PROs) has raised concerns about the effect of such patents on the progress of science and the advancements of technology. On the other hand, many patented university inventions have created grounds for the biotech industry to develop products and services of enormous benefit to society. The challenge, therefore, is to find the right balance between providing sufficient openness for further scientific investigation and, at the same time, sufficient control to provide incentives for private innovation and commercial development. How universities and PROs view their social mission, in particular, when it comes to transferring knowledge, is crucial to striking this balance. Arguably, the objective should not simply be to maximize an institution's licensing revenues, but rather to integrate its licensing program with its overall social and economic mission[3]. Considering recent developments in genome editing technology, we follow other scholars in asking whether earlier models developed by university licensing programs for facilitating access to previous biotech breakthroughs should be considered and emulated in the case of CRISPR-Cas genome editing tools[4–6].

Genome editing is a powerful tool in basic biological research that has been pursued for years, given its promise for a wide range of potential commercial applications. A recent breakthrough in genome editing by academic scientists, using clustered, regularly interspaced, short palindromic repeats (CRISPR) and the CRISPR-associated protein 9 (Cas9), has again put universities in a central and controversial position. Patent filings by academic institutions claiming key components of the CRISPR–Cas technology have created concern among scientists and legal experts that they might deter or slow down the development and utilization of the technology[4,5] by establishing proprietary control over what may be considered an essential research tool. There have long been arguments that patents within biomedicine inhibit the open access that is vital to scientific research[7–10]. However, in several key cases, universities have demonstrated that through good management of intellectual property, it is possible to establish a workable balance between access and control for essential research tools[11].

Since 1980, when the US Supreme Court ruled that living organisms modified by genetic engineering could be patented[12], there have been many biotechnological breakthroughs where patent protection has played a major role in the development of the technology. Herbert Boyer at the University of California (UC), San Francisco, and Stanley Cohen at Stanford University invented and filed a patent for a method to produce recombinant DNA in bacteria[13,14]. Upon filing the Cohen–Boyer patents, Stanford created a pioneering licensing program that provided a predictable legal framework for using their inventions. Non-exclusive licenses were available to both companies and academic institutions, but on different terms. This licensing program collected substantial royalty revenues for the universities, which were re-invested in research and research infrastructure. Stanford's licensing program became a model for other universities[15]. Similarly, in the invention of co-transformation of eukaryotic DNA, by Wigler, Silverstein and Axel[16], Columbia University succeeded in controlling the patents and making them available for both researchers and industry[17]. Small interfering RNA (siRNA) is another example of a major breakthrough in biotech by universities using technology protected by patents[18–20]. Three of the four institutions involved in the early developments of siRNA agreed to provide a free license to their patents to academic scientists who make other siRNA molecules in the laboratory. They also granted non-exclusive licenses to companies selling these molecular components[21]. The maintenance of access to these research tools by the scientific community together with the broader trajectories of commercial innovation that ensued underscore the importance of these university licensing strategies[11]. This analysis seeks to determine whether the CRISPR-Cas case is similar enough to those of recombinant DNA, co-transformation and siRNA to suggest that similar flexible non-exclusive licensing arrangements could strike the right balance between access and control.

CRISPR–Cas9: the technology

In the late 1980s, Ishino and colleagues at Osaka University discovered unusual repeating

Knut J. Egelie and Berit Johansen are in the Department of Biology, Norwegian University of Science and Technology, Trondheim, Norway; Gregory D. Graff is in the Department of Agricultural and Resource Economics, Colorado State University, Fort Collins, Colorado, USA, and the Department of Technology Management and Economics, Chalmers University of Technology, Gothenburg, Sweden; and Knut J. Egelie and Sabina P. Strand are in the Technology Transfer Office, Norwegian University of Science and Technology, Trondheim, Norway.
e-mail: knut.egelie@ntnu.no

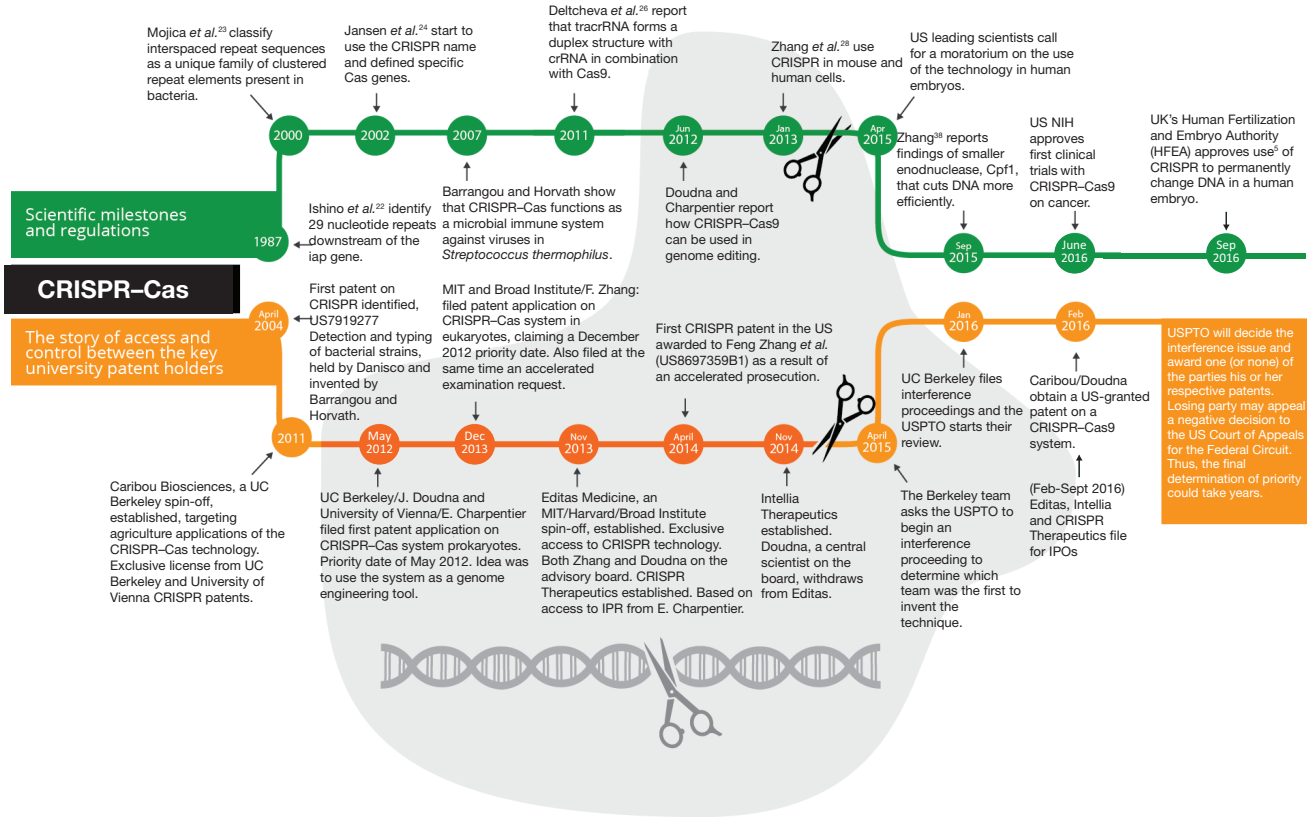

Figure 1 CRISPR–Cas scientific and regulatory milestones (upper strand) as well as milestones in patenting activity (lower strand). IPR, intellectual property rights.

sequences in the DNA of certain bacteria[22]. They were arranged as direct repeats, but at the time they were uncharacterized and their biological significance was not known. In 2000, Mojica *et al.* classified such interspaced repeat sequences as a unique family of clustered repeat elements, found to be present in >40% of sequenced bacteria and 90% of archaea[23]. The use of the CRISPR name and identification of specific Cas genes came about in 2002, by Jansen *et al.*[24]. Later in the 2000s, Philippe Horvath, Rodolphe Barrangou and colleagues at the Danish dairy company Danisco (recently acquired by DuPont) were working with CRISPR in *Streptococcus thermophiles* and found it to be very useful in preventing contamination by viral pathogens in the beneficial bacteria cultures for making yogurt, cheese and similar products[25].

In the CRISPR system, the Cas9 enzyme is an essential part of the larger construct in which an RNA molecule guides the targeting of any possible matching DNA sequence and is actually used to specify the site of cleavage that is critical. Emmanuelle Charpentier, at the time at the University of Vienna, identified the role of the Cas9 enzyme in *Streptococcus pyogenes* in 2010. Her team found that this enzyme was very efficient in cutting DNA[26]. She then teamed up with Jennifer Doudna, a molecular biologist working on the CRISPR system at UC Berkeley. Their collaboration and their complementary experience resulted in a paper describing the CRISPR–Cas9 system and how it could be used for genome editing[27].

While this work by the group at Berkeley revealed the potential of the technology as a

Table 1 CRISPR–Cas inventors in terms of numbers of patent families distributed in their first filed country as represented by their priority filing

Inventors	Organization	Total inventions
Feng Zhang	Massachusetts Institute of Technology, Harvard College and Broad Institute	56
Fei Ran	Massachusetts Institute of Technology, Harvard College and Broad Institute	23
Le Cong	Massachusetts Institute of Technology, Harvard College and Broad Institute	18
David R. Liu	Harvard College	16
Guihua Lu	Pioneer Overseas Corp., Qingdao Livestock Veterinarian Res. Inst.	12
Guanfan Mao	Pioneer Overseas Corp.	12
Yang Gao	Pioneer Overseas Corp.	11
Wei Wang	Pioneer Overseas Corp.	11
Xiping Wang	Pioneer Overseas Corp.	11
Steven R. Webb	Dow AgroSciences LLC, Sangamo Biosciences Inc.	11
Jennifer A. Doudna	Univ. California, Caribou Biosciences Inc.	5
Emmanuelle Charpentier	Univ. California and Univ. Vienna	2

CRISPR–Cas inventors in terms of numbers of patent families distributed in their first filed country represented by their priority filing and further their family member countries. Doudna at UC Berkeley and Charpentier, who was at the University of Vienna at the time of filing some of these applications, have the earliest priority date among the key applications.

Box 1 Methodology

We identified all inventions filed in all jurisdictions around the world with a priority date after 2000 that refers to any aspect of CRISPR and Cas9 technology, including uses, methods of preparation and compositions of matter. The main intention is to identify what entities are in a position to control access to the CRISPR–Cas9 platform, as well as the scope of geographical jurisdictions and technical areas in which the breakthrough and follow-on inventions are being filed. Our methodology follows four major steps:

Search. Using Thomson Innovation's Data Analyzer software, an initial search acquired a small, high-relevance sample including core known CRISPR–Cas9 patent documents both pending and granted. This sample was analyzed by text-mining algorithms to identify key words and terms of art as well as candidate technology classification codes, and tested these for appropriateness. Those were then used to seed iterated searches that assembled a well-balanced collection that covers the field of interest robustly while keeping unwanted topics to a minimum. This search strategy resulted in an initial set of 2,356 patent families. Once the data set was built, further 'de-noising' was performed by removing patent records through manual review and algorithmically, based upon occurrence of non-relevant keywords and/or technology classifications. This narrowed the final collection to 1,456 patent publication records (93 patent grants, 1,363 published patent application relating to CRISPR–Cas9, which collapsed into 604 patent families as determined by the Derwent World Patent Index (DWPI) patent family includes all 'equivalent' patent applications and granted patents worldwide that represent the same invention).

Entity clean-up. Assignee names appearing on patent documents are often inconsistently spelled and/or formatted. To the extent possible, these were regularized.

Categorization. Patent records were placed manually into technology categories, according to a taxonomy developed by the authors, using the information present in patent titles, abstracts, claims or technology classification codes.

Analysis of patent families. Analyses to address the primary questions of interest count the number of inventions, as represented by DWPI patent families in the data, which ensures that a single invention is not counted multiple times when represented by different patent applications in different jurisdictions.

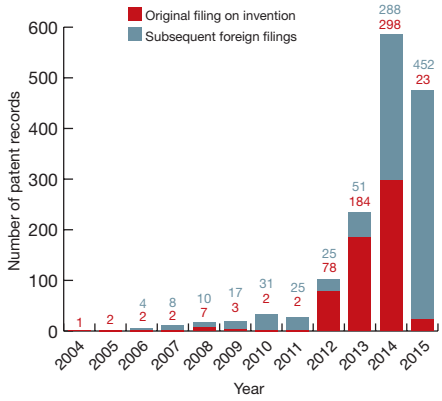

Figure 2 The number of CRISPR–Cas9 inventions, as represented by patent families, by year of original priority filing for each patent family, together with a count of subsequent foreign filings that expand already existing patent families. From 2012 there is notably increased activity. The apparent decrease in 2014 of original filing of inventions is due to the 18-month publication lag for patent applications. For this reason, the numbers of original priority applications for the most recent 18 months are not observable.

gene-editing tool, a number of *in vitro* proof-of-principle studies by Zhang and colleagues at the Broad Institute and the Massachusetts Institute of Technology (MIT) followed in 2013, showing that Cas9 may be targeted to genes in bacteria, human cell lines, cultured stem cells and zebra fish[28]. These studies demonstrated that CRISPR–Cas9 is a simple and efficient method to edit the genome of any organism. **Figure 1** illustrates the critical scientific and technical steps in the development of the CRISPR–Cas9 technology platform as well as the legal and commercial milestones.

CRISPR–Cas has emerged as a highly flexible research tool for genome editing and is already transforming biological and biomedical research. The system enables researchers to precisely manipulate the genome in a number of different ways[29]. A particularly exciting future direction is the medical use of the system for directly treating genetic disorders by correcting disease-causing mutations[30]. As summarized by Doudna and Barrangou, the potential for CRISPR applications is huge and will "affect almost every aspect of life, and provide inspiration for future technological breakthroughs"[31]. Yet, a number of challenges remain to be overcome to realize the tool's full potential for gene therapy and other applications. Among these, appropriate delivery strategies must be established, off-target effects need to be diminished and precisely detected, and repair strategies have to be designed. Furthermore, this breakthrough technology also requires ethical, societal and regulatory considerations in securing responsible use of the CRISPR–Cas technology.

It has been widely publicized that several organizations have been filing patents over fundamental parts of the CRISPR–Cas9 system[4,5]. Recognizing the possibilities of the discovery by Doudna and Charpentier of how the Cas9 enzyme can be directed to cut specific sites in isolated DNA, UC Berkeley and the University of Vienna together filed a US patent application in late 2012 (ref. 32). Just a few months later, MIT and the Broad Institute filed the first of several patent applications for work by Feng Zhang showing that CRISPR–Cas could edit DNA in eukaryotic and, even more specifically, in mammalian cells[33].

MIT, the Broad Institute and Harvard fast-tracked their patent applications through the US Patent and Trademark Office (USPTO) and, although they were filed later than the UC Berkeley and University of Vienna application, received granted US patents while the Berkeley/Vienna application was still pending. Upon noticing this, UC Berkeley then filed a request for interference proceedings against the granted patent, arguing on the grounds that it makes some of the same claims as the Berkeley/Vienna application and, moreover, that Doudna and Charpentier had come up with these aspects of the invention prior in time to Zhang and the team at Broad, MIT and Harvard[34]. USPTO interference proceedings can take time and, even after the patent office issues a decision, can be appealed by the losing party. The result has been a period of uncertainty during the formative period of the technology's adoption regarding who, if anyone, ultimately holds rights to the core CRISPR–Cas9 invention and thus control over access to the technology platform.

Evaluating the global CRISPR–Cas patent landscape

We identified all inventions filed in all jurisdictions around the world with a priority date after 2000 that refers to any aspect of CRISPR–Cas9 technology, including uses, methods of preparation and compositions of matter (**Box 1**). Our results show that the rapid growth in filings started in 2012 (**Fig. 2**), essentially simultaneously with the two leading research groups publishing their breakthroughs in the scientific literature[27,28].

The top ten patent assignees, including several leading academic institutions and corporations, account for 240 of the 604 inventions (40%) for

Table 2 Distribution of CRISPR–Cas patent applications in various areas of technology

High level technical segments	MIT/Harvard/Broad/ Zhang group	Doudna/Charpentier/UC Berkley–California Vienna group	Dow/DuPont
CRISPR–Cas9 components	56	13	9
CRISPR–Cas activity	10	1	12
Vectors	47	6	8
Delivery	19	0	1
Application	51	7	9

The CRISPR technology landscape can be divided into five main technology areas of high patent activity. These categorizations are based on the accumulation of the two inventor groups comprising researchers from MIT, the Broad Institute and Harvard, and UC Berkeley and the University of Vienna, as well as the patent portfolio of the two companies DuPont and Dow AgroSciences that have announced intentions to merge.

which patent applications have already been filed in the newly emergent field of CRISPR–Cas technologies (**Fig. 3**). Most notable are assignee institutions in the Boston academic cluster, consisting of the Broad Institute, MIT, Harvard, as well as Editas Medicine, which is a commercial spin-off from MIT and the Broad Institute. Together, these account for ownership of 131, or over 20%, of all CRISPR–Cas inventions to date. The University of California has a smaller patent portfolio, consisting of 14 patent families. These inventions, however, potentially include some of the central aspects of the CRISPR–Cas technology platform.

Commercial assignees have taken less ground in the early phases of the CRISPR–Cas patent landscape. The only large corporations ranked in the top ten are Dow AgroSciences and DuPont Nutrition Science, together holding 33 inventions. In late 2015 DuPont acquired Danisco, one of the pioneers in CRISPR[35,36] that dominates a major agricultural field of application, the dairy industry, and renamed it DuPont Nutrition Science. Recently DuPont announced an agreement with the team of Virginijus Siksnys at Vilnius University, working on how Cas proteins cut DNA in bacteria[37], with two patents filed in 2012. DuPont also signed an exclusive license with Caribou Biosciences, a startup out of UC Berkeley created to develop applications of its gene editing technology. Dow AgroSciences has claimed uses of CRISPR–Cas in agriculture, including editing crop and weed genomes. Recently, the parent corporations, DuPont and Dow, announced their intention to merge, which will further consolidate control over applications of genome editing in both crop and animal agriculture. Another commercial entity on the list is Cellectis, a French biotech company, which has a portfolio of its own gene editing technology and holds exclusive licenses to a broad patent from the Pasteur Institute and Boston Children's Hospital for gene editing in cells *in vitro*. Furthermore, Cellectis's US subsidiary Calyxt, formerly Cellectis Plant Sciences, has acquired exclusive worldwide rights to gene targeting technology from the University of Minnesota granting Calyxt and Cellectis worldwide rights to patents covering the use of CRISPR–Cas technology in plants.

Thus academic institutions, through their licensing, spin-offs and commercial partners are largely in control of medical applications of CRISPR–Cas. But larger industry players, with Dow and DuPont at the forefront, already appear to be more in control of the technology's agricultural and food applications.

National level filings are most numerous in the United States (**Fig. 4**), as inventions involving CRISPR–Cas are mainly taking place at US organizations. The years 2004–2011 saw only minor patent filing activity on CRISPR technology around the world, as the main breakthroughs[27,28] were not until 2012. After that, though, came the rapid increase of patent applications in the US and a year later in China. By 2013 and 2014, the priority applications already made in the US began spawning many foreign filings in other jurisdictions, including Europe and Asia. Danisco started to file applications in its home country of Denmark on the CRISPR-Cas system.

In analyzing the leading individuals listed as inventors on CRISPR-Cas patents (**Table 1**), we find that the most prolific are academic scientists from the Broad Institute, MIT and Harvard. The competing scientists at UC Berkeley and the University of Vienna have contributed far fewer inventions. Also among the top ten inventors, interestingly, are five scientists working for Pioneer Overseas Corp., a subsidiary of DuPont focused on crop genetics.

Supplementary Table 1 further demonstrates that the US is the primary focus for filings by the leading inventors, but Europe is a major target as well as Canada, Australia and Korea. Most patent holders appear to be pursuing a strategy

Table 3 Sub-categories of main technology categories

Technical categories	Detailed technical categories	Total inventions	MIT/Harvard/ Broad/Zhang group	Doudna/ Charpentier/UC Berkeley–Vienna group	Dow/ DuPont
CRISPR–Cas9 components	CRISPR RNA	139	14	4	6
	tracrRNA	63	11	0	0
	gRNA	212	38	7	3
	PAM	56	8	2	0
	Cas9 enzyme	121	25	0	0
Total		591			
CRISPR–Cas9 activity	RNA-Cas complex	54	6	0	4
	Spacer integration	10	1	0	3
	Cas cleavage	31	3	1	5
Total		95			
Vectors	Expression vectors	94	7	4	0
	Bacterial	12	0	0	2
	Viral	97	28	1	2
	Plasmid	132	27	2	7
Total		335			
Delivery	Liposome	30	10	0	1
	Nanoparticle	33	16	0	0
	Exosome	16	12	0	0
	Microvesicle	16	11	0	1
Total		95			
Application	Gene editing	78	19	2	1
	Gene therapy	105	23	3	1
	Drug discovery	10	4	0	0
	Diagnosis	79	11	0	0
	Regulating	70	6	3	3
	Targeting	167	24	3	5
Total		509			

We have divided the five main technology categories into sub-categories to analyze which specific technical areas are controlled by which of the different patent holders. PAM, a protospacer adjacent motif.

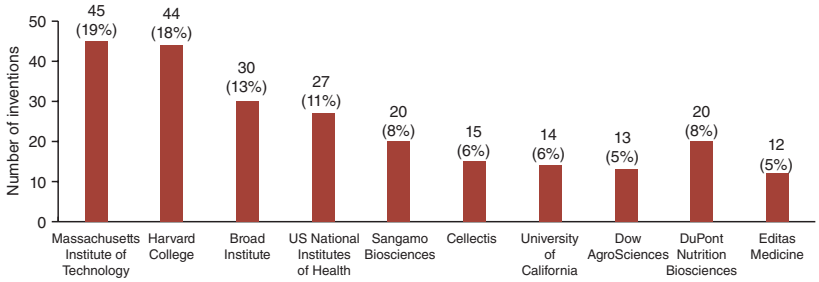

Figure 3 Top ten patent holders and the number of patent applications each filed (percentage each of the total). MIT is on top, followed by Harvard College and the Broad Institute. The list of the top ten patent holders is based on a search of key words CRISPR and Cas9 in the patent database from Thomson Innovation. The number of total inventions represents separate patent families where each family represents one unique invention. The unit is the 'number of inventions'. It counts patent families, each of which encompasses the set of granted patents as well as published patent applications for a given invention.

of keeping a worldwide option open for their patent portfolios.

A technical analysis of the documents in the data set divides the CRISPR–Cas technology landscape into five high-level categories: (i) CRISPR–Cas9 components, (ii) CRISPR–Cas9 activity, (iii) vectors, (iv) delivery and (v) applications (**Table 2**). Of these, CRISPR components dominate the patent landscape in terms of sheer numbers, with 591 inventions (priority applications). Among these, guide RNAs (gRNA) are the most common type of component of the CRISPR technology platform with a total of 212 inventions (**Table 3**). CRISPR–Cas9-mediated genome editing relies on gRNAs that direct site-specific DNA cleavage by the Cas9 protein. The gRNA is composed of two RNAs termed CRISPR RNA (crRNA) and trans-activating crRNA, which can be combined in a chimeric single guide RNA (sgRNA) specifically designed for its target and purpose. Currently, tens of thousands of such gRNA libraries have been created. As such these are both distinct from and complementary to most other targets in the patent landscape, which explains why there would be many distinct patent applications filed.

The second most prevalent category found are applications, and the most heavily patented are targeting applications. The CRISPR–Cas9 and appurtenant gRNA are used to obtain and facilitate more precise targeting to perform better DNA cleavages.

The invention portfolios by technology category from the two competing academic groups, in Cambridge and Berkeley, and the corporate portfolio of a potentially merged Dow and DuPont, are quite different (**Table 3**). Yet there is similarity in the high volume areas of each, particularly the "CRISPR–Cas9 components" segment, and specifically in "gRNAs." But while the Zhang group has filed 19 inventions in the 'Delivery' segment, the Doudna/Charpentier group does not have any.

The key patents in the interference dispute at the USPTO were categorized by this analysis into different technology segments. The patent granted Broad/MIT/Harvard[33], US8697359, combines multiple technology categories (**Tables 2** and **3**), including the gRNA and Cas9 enzyme components, Cas cleavage activity, viral expression, liposome and nanoparticle delivery, and, finally, targeting and gene therapy applications. The Berkeley/Vienna patent application in the dispute[32], US20140068797, is categorized more narrowly within our schema, involving just one component—a protospacer adjacent motif—and an expression vector.

The technology focus of the combined corporate portfolios of Dow and DuPont is different from that of the two main academic groups, with more relative emphasis around CRISPR–Cas activity, but also involving CRISPR RNA components and plasmid vectors.

How important is the outcome of the patent interference to the future of gene editing?

The claims by both parties in the dispute cover adaptations of the CRISPR–Cas system, for use in both prokaryotes and in eukaryotes, including mammals, broadly. However, at the time of filing only Zhang had been able to show use in eukaryotes explicitly. There are four scenarios of what might follow from the USPTO office action:

(i) UC Berkeley and University of Vienna are favored in the interference proceedings. The USPTO then examines the Berkeley/Vienna patent. It is granted, for both prokaryotes and eukaryotes, as their broader claim is considered to be sufficiently supported. MIT/Broad/Harvard lose their initial patents.

(ii) UC Berkeley and University of Vienna are favored in the interference proceedings. The USPTO then examines the Berkeley/Vienna patent. It is granted, but only for prokaryotes, as their broader claim for eukaryotes is not considered to be sufficiently supported. The USPTO then amends the MIT/Broad/Harvard patents to cover the other use, for eukaryotes, including mammals.

(iii) UC Berkeley and University of Vienna are favored in the interference proceedings. The USPTO then examines the Berkeley patent, but it is not granted at all. MIT/Broad/Harvard retain their patents as already examined and granted.

(iv) MIT/Broad/Harvard are favored in the interference proceedings. The USPTO does not examine the Berkeley/Vienna patent, and therefore it is not granted. MIT/Broad/Harvard retain their patents as already examined and granted.

However, by the time the dispute is resolved, the outcome could prove largely inconsequential. Most of the practical value of the technology may be realized in patent filings protecting follow-on refinements, designed to minimize dependence upon the claims of the initial patents, precisely because of the uncertainty over the validity and provenance of those claims. This kind of situation has been seen before. For example, when the US Supreme Court finally ruled against the *BRCA* gene patents of Myriad Genetics, the impact on the market value of the defendant was modest. Myriad had built a

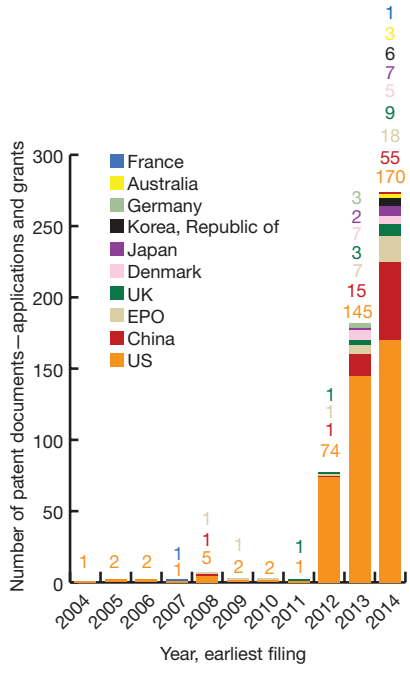

Figure 4 Geographical distribution of patent family filings by date of filing of the priority application for each invention in a given jurisdiction's patent office. Most inventions are filed in the United States, followed by China and the European Patent Office (EPO). The apparent drop in filings in 2015 is due to the 18-month lag between filing and publication of a patent application in most jurisdictions.

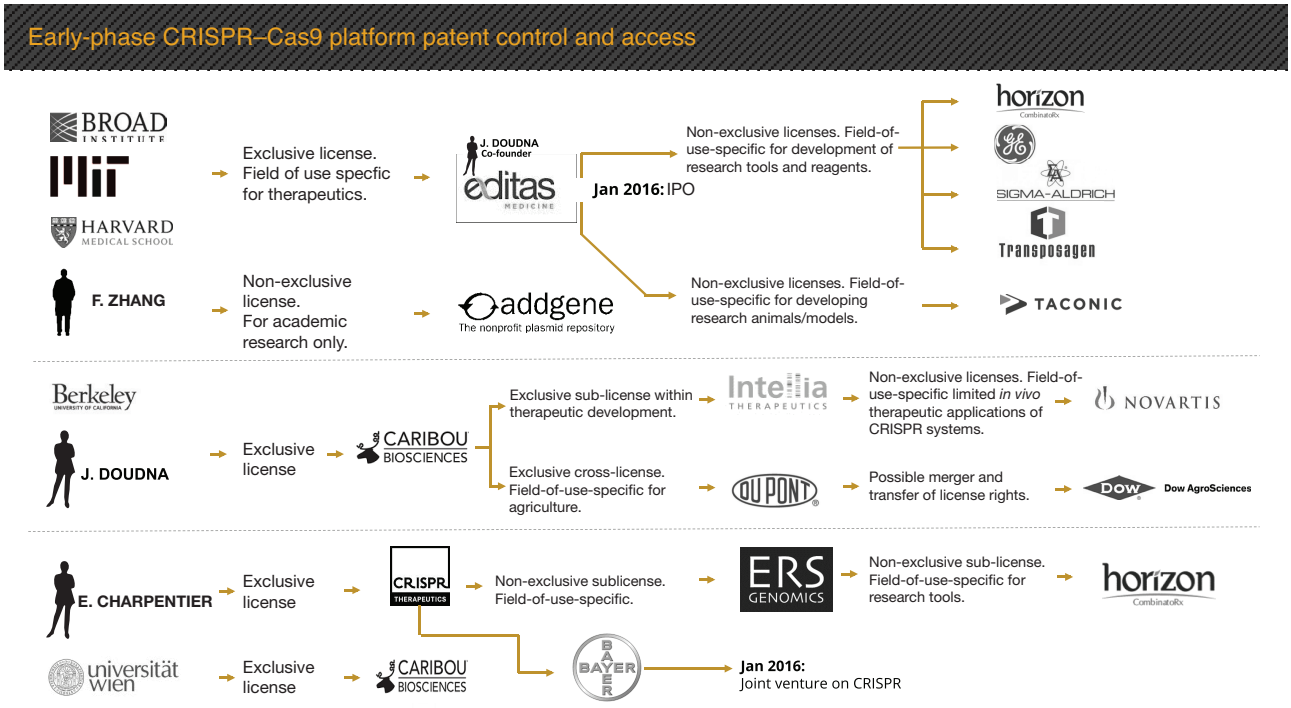

Figure 5 CRISPR–Cas9 initial platform patent holders, licensors, licensees and partners. All three main inventors, F. Zhang, J. Doudna and E. Charpentier and their institutions of employment, are involved in several commercial startup companies. Editas is directly linked to Harvard, MIT and the Broad Institute while Addgene is a nonprofit independent organization linked to MIT and the Broad Institute through a partnership program. Addgene provides access to public and nonprofit research while Editas provides access to commercial companies. UC Berkeley has ownership interests in two startups, Caribou Biosciences and Intellia. University of Vienna was E. Charpentier's employer at the time the initial platform patent was filed, and has licensed its patent to Caribou. E. Charpentier has also licensed some of her patent rights to a Swiss company, CRISPR Therapeutics. Some of the licenses are exclusive, but field of use specific while others are on non-exclusive terms. Source: company and institution websites and van Erp *et al.*[40]

diversified IP portfolio that complemented their business strategy enough so that the loss of a few patents, even key ones, could be withstood. As a current example, Zhang and colleagues have discovered and filed patent protection for a possibly smaller and better alternative to the Cas9 enzyme, the enzyme called Cpf1, reported in September 2015 (ref. 38). This shows that the pace of discovery and development is likely to continue, with a high probability of further improvements. Such portfolio building and diversification is already being used by the MIT/Broad/Harvard group both to position them for the possibility of losing the interference proceeding and to strengthen their overall position if they win.

Another more extreme possibility is that altogether other gene editing technologies may yet emerge to compete with or possibly even supersede CRISPR–Cas. Again, history has precedents. The strength of the patent position held by the University of Wisconsin and the Wisconsin Alumni Research Foundation (WARF) over human embryonic stem cells was significantly diminished with the discovery of induced pluripotent stem cells. When an area of research becomes intensely charged, such as it was around stem cells in the late 1990s and 2000s, and as it is now around gene editing, the likelihood of other follow-on breakthroughs can increase.

Control of and access to the CRISPR–Cas technology system

As the CRISPR–Cas toolbox becomes more widely used, how is access being provided and managed? One pragmatic question at this point is, how could any of the patent holders actively restrict access to CRISPR–Cas for research use, as it is already widely used in academic laboratories? Scientists routinely pass around tools that they find helpful in the laboratory, often flaunting legal restrictions or institutional requirements. This practice by scientists may be supported by commitments to 'open science', but it may be also be due to the pragmatic awareness that no company, let alone university, would like to go down in history as having sued every other university in the US for patent infringement, a strategic dilemma that Cook-Deegan calls "rational forebearance"[39]. Moreover, the leading academic institutions involved, including the Broad Institute and MIT as well as UC Berkeley, already offer free use of the technologies they control for academic research purposes under material transfer agreements through a nonprofit 'clearinghouse' organization, Addgene.

Generally, we see the technology protected by patents being put under structured control for development of commercial uses, with provisions being made within that structure to allow for broad dissemination for research or non-profit uses[40]. CRISPR–Cas control positions are being used by the leading universities to structure the allocation of access to a range of different commercial entities and non-profits (**Fig. 5**).

The institutional cluster of MIT, the Broad and Harvard have granted exclusive licenses for therapeutic applications of their CRISPR–Cas technologies to their joint commercial effort, the spin-off company Editas. In addition, they offer academic researchers access through Addgene. The UC Berkeley group similarly have granted exclusive license to the startup Caribou Biosciences, which has in turn made exclusive sublicenses to Intellia and Novartis for therapeutic applications, and to DuPont for agricultural and food applications. Also like Broad and MIT, UC Berkeley offers their CRISPR–Cas technology free of charge for academic research, with a range of plasmids from the Doudna lab available via Addgene.

The big question is what happens when researchers at other universities make potentially valuable discoveries of their own using

the research tool they obtained for nonprofit or research use? What are their options for commercializing follow-on technologies? Addgene uses the general terms of the Uniform Biological Material Transfer Agreement (UBMTA), developed in 1995 by technology licensing experts at the US National Institutes of Health in collaboration with the Association of University Technology Mangers (AUTM), to simplify transfers of biological research materials for universities and public research institutions. The UBMTA seeks to solve, to some extent, the issue of 'reach-through' claims: the UBMTA's legal terms state that modifications or new discoveries are owned by the recipient of the biological material and can be licensed for commercial use; yet, inevitably, some of those new commercial applications may fall within the broadly drafted claims of the original patent and therefore require a second, commercial license. This is where serious difficulties could arise with CRISPR–Cas, because many, if not all, fields of commercial use have already been exclusively licensed by the original university owners to their respective commercial partners.

Inventors of follow-on applications made using a CRISPR-Cas technology will most likely need to seek a commercial sub-license from the respective exclusive commercial licensee that controls that technology—Editas, Caribou, Intellia, CRISPR Therapeutics or Cellectis/Calyxt—rather than from the originating university. Yet, these same companies are each aggressively seeking, under pressure from their venture capital backers, to develop products of their own. Editas and Intellia describe their ambitions to 'build alliances,' to 'expand our platform,' or to 'optimize our pipeline.' This sort of business terminology implies intentions to be directly engaged in product development, rather than to license their technology broadly, at arms' length, on non-exclusive terms.

Over the 17 years of the Cohen–Boyer licensing program, Stanford University granted non-exclusive commercial use licenses to 468 companies for the development of an estimated 2,442 new products worth an estimated $35 billion[15]. Genentech, the company founded by Herbert Boyer, was just one of those companies. What would it have looked like if Genentech had an exclusive license from Stanford, and was itself responsible for extending commercial sublicenses to other companies? Would we have the same biotech industry that we do today?

How many of the thousands of potential products to come from CRISPR–Cas gene editing can this small group of startup companies be expected to successfully manage either internally or in close partnership? While the free research licenses available through Addgene are admirable, the permissions they grant typically stop at the door of the recipient university lab. Yet, none of the players involved seem to be discussing plans for a broad, non-exclusive, commercial licensing program that would make the enabling technology platform of CRISPR-Cas efficiently available on fair and reasonable terms for the many commercial applications that are likely to arise.

In cases like the Cohen–Boyer recombinant DNA technology or the Axel co-transformation technology, it was the university licensing offices that stood somewhat above the competitive fray and forged workable licensing programs that struck a balance, however imperfect, between control and access for the multiple commercial applications and ongoing scientific studies that used them. In the case of CRISPR-Cas it appears that the university licensing offices have already abdicated the possibility of playing such a role. How likely is it that the commercial entities now in control will decide that broad, non-exclusive sublicensing is a viable business model?

Note: Any Supplementary Information and Source Data files are available in the online version of the paper (doi:10.1038/nbt.3692).

ACKNOWLEDGMENTS

The authors thank Tushar Khandeka and Rohit Gole (Thomson Reuters) for excellent assistance with patent data; Nancy Eik-Nes at NTNU for invaluable language support and insights; Steinar Kvam at NTNU Technology Transfer Office for his design creativity supporting our figures; Bowman Heiden at Sahlgrenska School of Innovation and Entrepreneurship, University of Gothenburg, and Mats Lundqvist at Chalmers for strategic insights on intellectual property platforms. The authors also wish to express sincere thanks to the following organizations that have contributed to this collaboration as funding and event partners: The Research Council of Norway; VINNOVA.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

1. Moses, H. III *et al. J. Am. Med. Assoc.* **313**, 174–189 (2015).
2. Graff, G.D. *et al. Nat. Biotechnol.* **31**, 404–410 (2013).
3. Association of University Technology Managers. *Nine Points to Consider in Licensing University Technology* (March 6, 2007). http://www.autm.net/AUTMMain/media/Advocacy/Documents/Points_to_Consider.pdf
4. Sheridan, C. *Nat. Biotechnol.* **32**, 599–601 (2014).
5. Sherkow, J.S. *Nat. Biotechnol.* **33**, 256–257 (2015).
6. Van Overwalle, G., van Zimmeren, E., Verbeure, B. & Matthijs, G. *Nat. Rev. Genet.* **7**, 143–154 (2015).
7. Weiner, C. *Sci. Technol. Hum. Values* **2**, 50–62 (1987).
8. Heller, M.A. & Eisenberg, R.S. *Science* **280**, 698–701 (1998).
9. Walsh, J., Arora, A. & Cohen, W. in *Patents in the Knowledge-Based Economy* (eds. Cohen, W.M. & Merrill, S.A.) 285–340 (National Research Council, National Academies of Science, Washington, 2003).
10. Lei, Z., Juneja, R. & Wright, B.D. *Nat. Biotechnol.* **27**, 36–40 (2009).
11. Cook-Deegan, R. & Heaney, C. Annu. *Rev. Genomics Hum. Genet.* **11**, 383–425 (2010).
12. Robinson, D. & Medlock, N. IP & *Technol. Law J.* **17**, 12–15 (2005).
13. Cohen, S.N. & Boyer, H.W. Process for producing biologically functional molecular chimeras. US patent 4237224 (1980).
14. Morrow, J.F. *et al. Proc. Natl. Acad. Sci. USA* **71**, 1743–1747 (1974).
15. Feldman, M.P., Colaianni, A. & Kang, L. in *Intellectual Property Management in Health and Agricultural Innovation: a Handbook of Best Practices*, vols. 1 and 2, (eds. Krattiger, A. *et al.*) 1797–1807 (2007).
16. Axel, R., Wigler, M.H. & Silverstein, S.J. DNA construct for producing proteinaceous materials in eucaryotic cells. US patent 6455275 (2002).
17. Colaianni, A. & Cook-Deegan, R. *Milbank Q.* **87**, 683–715 (2009).
18. Elbashir, S.M. *et al. Nature* **411**, 494–498 (2001).
19. Tuschl, T. *et al.* RNA sequence-specific mediators of RNA interference. EU patent 2028278 (2014).
20. Chi-Ham, C.L., Clark, K.L. & Bennett, A.B. *Nat. Biotechnol.* **28**, 32–36 (2010).
21. Esmond, R.W. & Chung, A.K.-H. *Nanotechnol. Law & Bus.* **11**, 15–28 (2014).
22. Ishino, Y., Shinagawa, H., Makino, K., Amemura, M. & Nakata, A. *J. Bacteriol.* **169**, 5429–5433 (1987).
23. Mojica, F.J., Díez-Villaseñor, C., Soria, E. & Juez, G. *Mol. Microbiol.* **36**, 244–246 (2000).
24. Jansen, R., Embden, J.D., Gaastra, W. & Schouls, L.M. *Mol. Microbiol.* **43**, 1565–1575 (2002).
25. Barrangou, R. *et al. Science* **315**, 1709–1712 (2007).
26. Deltcheva, E. *et al. Nature* **471**, 602–607 (2011).
27. Jinek, M. *et al. Science* **337**, 816–821 (2012).
28. Cong, L. *et al. Science* **339**, 819–823 (2013).
29. Harrison, M.M., Jenkins, B.V., O'Connor-Giles, K.M. & Wildonger, J. *Genes Dev.* **28**, 1859–1872 (2014).
30. Hsu, P.D., Lander, E.S. & Zhang, F. *Cell* **157**, 1262–1278 (2014).
31. Barrangou, R. & Doudna, J.A. *Nat. Biotechnol.* **34**, 933–941 (2016).
32. Doudna, J.A. *et al.* Methods and compositions for RNA-directed target DNA modification and for RNA-directed modulation of transcription. US patent 20140068797 (2014).
33. Zhang, F. CRISPR–Cas systems and methods for altering expression of gene products. US patent 8697359 (2014).
34. USPTO. CRISPR interference proceeding, Broad Institute/MIT/Harvard College vs. University of California and University of Vienna. https://acts.uspto.gov/ifiling/PDFfromDocumentum?No=106048&docTy=NOTICE+TO+DECLARE+INTERFERENCE&action=getContentByDocType (11 January 2016).
35. Bubela, T. *et al. Nat. Biotechnol.* **31**, 202–206 (2013).
36. Grushkin, D. *Nat. Biotechnol.* **34**, 13 (2016).
37. Gasiunas, G. *et al. Proc. Natl. Acad. Sci.* **109**, 2579–2586 (2012).
38. Zetsche, B. *et al. Cell* **163**, 759–771 (2015).
39. Fore, J., Wiechers, I.R. & Cook-Deegan, R. J. *Biomed. Discov. Collab.* **1**, 7 (2006).
40. van Erp, P.B.G., Bloomer, G., Wilkinson, R. & Wiedenheft, B. *Curr. Opin. Virol.* **12**, 85–90 (2015).