CRISPR Cas9–Licensing What Can't Be Licensed

By Ulrich Storz

A new gene engineering technology has recently made it through the media, not only because of its technical advantages, but also because it is in the focus of an epic patent battle between two academic institutions.

The technology bears the cryptic name "CRISPR Cas9," and allows the manipulation of genes (so called "gene editing") with so far unseen simplicity and efficacy. Dana Carroll of the University of Utah said for this reason that CRISPR Cas9 has brought about the "democratization of gene targeting."[1]

Probably, she made such statement also to work out a difference to a similar technology called Zinc Finger Nucleases, which Carrol has actively worked with, and which, besides being technically more challenging, were vigorously monopolized by a company called Sangamo Biosciences, by means of a proprietary library, and a restrictive patent licensing policy encompassing also non-commercial and academic use.[2]

CRISPR Cas9 holds great promise not only for basic scientific research, but also for the generation of new plant varieties bearing advantageous features, for the generation of specific cell lines for cancer therapy, and even for the repair of fatally mutated genes in human embryos, to name a few potential applications.

The Interference Proceedings

While, in the past 20 years, many researchers contributed, stepwise, to develop this technology, two parties are oftentimes cited as being the key players that made the technology accessible to the scientific community, namely Emanuelle Charpentier & Jennifer Doudna of University of Vienna and UC Berkeley (called Berkeley hereinafter) on the one hand, and Feng Zhang of Broad Institute and MIT (called Broad hereinafter) on the other.

While, in a nutshell, Charpentier and Doudna demonstrated the general usability of CRISPR Cas9 for gene editing in bacteria, and provided a facilitated approach (in which two RNA molecules called crRNA and tracrRNA were combined to form a chimeric sgRNA), Zhang showed how it can be transferred into eukaryotes, *i.e.*, more complex cells and organisms.

Accordingly, Berkeley filed a patent application first, and Broad came later. However, Broad requested expedited examination, and for that reason, obtained granted patents first, both in the United States and Europe. Berkeley was somewhat taken by surprise by this development, and initiated a so-called interference proceeding before the USPTO, in which they declared that they would be entitled to all of the benefits derived from Broad's patents.

■ Ulrich Storz,
Senior Partner,
Michalski Hüttermann & Partner Patentanwälte mbB
Düsseldorf, München
E-mail: st@mhpatent.de

Both consortia have early on realized the huge commercial potential of this technology, and have transferred outlicensing activities almost exclusively to commercial entities specifically founded for this purpose.

The resulting legal battle was fought with an intensity that has so far been unwitnessed in the academic sector. Editas, which is the commercial entity Broad has appointed to outlicense its rights, reports to have spent about 15 mn USD only for the first instance of the interference.[3]

It appears that the money was not spent in vain, because in February 2017 the USPTO eventually decided in favor of Broad. In the decision, the USPTO emphasized that in their patent application, Berkeley had not provided an enabling disclosure to justify patent claims on the use in the complex cells and organisms that Broad focused on.

Further, the USPTO emphasized that Doudna had repeatedly stated that after completing their pioneering studies in bacteria, she was not sure if the system would work in eukaryotes as well.[4]

Dissatisfied with this decision, Berkeley went into appeal, which is now pending.

Does the Winner Take it All ?

One thing which is surprising is that, in the media, the USPTO's first instance decision was commented as being a "winner takes it all" outcome for Broad.[5] The use in complex cells and organisms, which is explicitly claimed in the Broad patents, is certainly commercial-

1. R. Coontz, "And Science's 2015 Breakthrough of the Year is..." *Science News*, Dec. 17, 2015.

2. C. Scott, "The Zinc Finger Nuclease Monopoly." *Nature Biotechnology* 23, 915 - 918 (2005).

3. S. Begley, "CRISPR Patent Fight: The Legal Bills Are Soaring." *Stat News*, August 16, 2016.

4. M. Jinek, *et al.*, "RNA-programmed Genome Editing In Human Cells." *eLife* 2013;2:e00471.

5. H. Ledford, "Broad Institute Wins Bitter Battle Over CRISPR Patents." *Nature* 542, 401(2017).

Table 1- Selected licensees of UC Berkeley and Broad			
Applicant	**Key Patent/ Application**	**Licensing Agent**	**Exclusive Licenses To**
Berkeley	EP2800811 US2014068797	Caribou Biosciences ERS Genomics Intellia Crispr TX	Novartis (CAR T cells) Casebia (blood, eye, heart) Vertex (cystic fibrosis, sickle cell anemia) Regeneron (liver) DuPont (crops) Genus (livestock)
Broad	US8697359 EP2771468	Editas	Juno TX (CAR T cells)

ly more attractive than the mere use in bacteria, but the claims that Berkeley currently pursue before the USPTO are not restricted to the use in bacteria—hence, covering also the use in higher organisms.[6] While a decision on their U.S. patent claims is suspended until a final decision in the interference has been reached, a patent with a relatively unrestricted scope—excluding *in vivo* applications but encompassing in vitro use in eukaryotic cells—scope has recently been awarded to Berkeley by the European Patent Office (EP2800811).

A qualified patent practitioner would assume that Berkeley's patent would therefore encompass both the use in bacteria and the *ex vivo* use in higher organisms, meaning that Broad's patent would be "dependent" on the patent assigned to Berkeley.

General Licensing Issues

In the patent world, such situation (where a later patent claims an invention which is an improvement of a more fundamental invention claimed in an earlier patent) is rather the rule than the exception. As a result, the owner of the earlier patent can block the other party completely, while the owner of the younger patent can at least block the other party from using the improvement.

For this reason, it appears likely that, in the end, third parties wanting to use CRISPR Cas9 for ex vivo applications in higher cells or organisms, will need a license from both patent estates. In a press conference, Jennifer Doudna explained the situation by laconically stating that Broad "has a patent on green tennis balls" while Berkeley would receive "a patent on all tennis balls."

This is where another remarkable point of this complex issue comes into play. As said, both consortia have transferred the rights to outlicense the technology to commercial entities almost exclusively[7]—something which is quite unusual in the university sector. Both Berkeley and Broad are signing members of the so-called Nine Points Document, which is a declaration signed by leading universities[8] comprising a code of conduct regarding the outlicensing of patented technologies. In said document, the universities are encouraged "to use approaches that balance a licensee's legitimate commercial needs against the university's goal (based on its educational and charitable mission and the public interest) of ensuring broad practical application of the fruits of its research programs."

Some authors have stated that, by deliberately handing over almost all outlicensing rights to commercial partners, both universities have de facto bypassed their own self-obligation.[9]

The said commercial partners have been extremely successful in acquiring third party capital, either by an IPO or in the form of venture capital. They have also been very successful in deploying licenses regarding specific applications of the technology to third parties. In some cases, these licenses are exclusive licenses. See Table 1.

On their website, Broad claims to pursue a very open licensing policy, advertising that they provide non-exclusive access to companies to use CRISPR in their own commercial research, as well as to research tool companies. However, for human therapeutics, they state that they have decided that exclusivity be necessary to encourage sufficient investments needed to render the respective applications ready for the bedside. While there might be some truth in this rationale, this means that for some of the most promising and publicly demanded applications, Broad has decided to exclude the majority of potential users from exploiting this technology.

Broad's commercial partner, Editas, has for example awarded an exclusive license to use the technology in a new, promising type of anti-cancer cell therapy, called CAR T-cells, to Juno Therapeutics. One of Berkeley's commercial partners, Intellia Therapeutics, has likewise granted an exclusive license for the same application to Novartis.

Now, in case Berkeley's U.S. patent is granted, and the above situation of dependencies materializes, No-

6. US20140068797, pending claims can be found here: https://register.epo.org/ipfwretrieve?apn =US.201313842859.A&lng=en.

7. J.L. Contreras and J.S. Sherkov, "CRISPR, surrogate Licensing and scientific discovery." *Science* 355 (6323) 698, (2017).

8. *http://www.autm.net/autmmain/media/Advocacy/Documents/Points_to_Consider.pdf.*

9. J.L. Contreras and J.S. Sherkov, CRISPR, surrogate Licensing and scientific discovery. Science 355 (6323) 698, (2017).

vartis would need a license from Juno, and vice versa, to be able to actually use the technology—hence, each exclusive licensee would have to grant a sublicense to the other party.

What is, however, more concerning is that the CAR T field is a very broad one which cannot fully be explored by even a giant like Novartis. The licensing policy the two universities apply could thus lead to a situation where exclusive licenses are actually broader than what the licensee can do therewith—something that is precisely not intended by the Nine Points Document, because it may actually block the full and unlimited exploration of a groundbreaking technology, much to the disadvantage of public interest.

License Restrictions for Ethical Motifs

Because CRISPR Cas9 dramatically facilitates genetic manipulation of cells and organisms, it has often been critizised as making ethically questionable applications, like germ line therapy, too simple.[10] In this regard, the CRISPR Cas9 complex has yet another remarkable licensing anecdote to offer. One of Broad's direct licensees is Monsanto (recently acquired by Bayer), who have obtained a non-exclusive license for agricultural applications, including the genetic modification of plant varieties.

In their license agreement with Monsanto, Broad excluded an array of specific applications, namely

(i) performing gene drives that spread altered genes quickly through populations;

(ii) creating sterile 'terminator' seeds, which would impose a serious financial burden on farmers who would be forced to buy new seeds each year; and

(iii) conducting research directed to the commercialization of tobacco products, which might increase the public health burden of smoking.

Further, Broad's outlicensing partner, Editas, agreed to not use or outlicense the technology to modify human germ cells or embryos for any purpose or to modify animal cells for the creation or commercialization of organs suitable for transplantation into humans.

Such ethically motivated constraints imposed by the licensor have been discussed as a helpful step to fill a legal grey area that quickly developing technologies bearing ethical risks leave behind during their triumphal procession, before lawmakers can react.[11]

In any case, while CRISPR Cas9 has already made its way through the academic laboratories, the current patent and licensing situation creates uncertainly with small and medium sized enterprises considering to use the technology, not only because of the question where to apply for such license (Berkeley or Broad, or both ?), but also with regard to the exclusivity issue. In the past five years, we could witness an exponential increase of third-party patent filings related to applications of CRISPR Cas9, which even increases said uncertainty. These factors combined may become a true obstacle in the process of bringing products and technologies that rely on CRISPR Cas9 to the consumer, or the patient.

Is the Time Ripe for a Patent Pool?

The somewhat murky situation regarding potential licenses has furthermore triggered voices that urged to establish a patent pool providing non-discriminatory access to the technology.[12] MPEG-LA, which has been active in forging patent pools covering different consumer electronics technologies like MP3, has recently set up a new pool to collect patents covering CRISPR Cas9 technologies, and is now inviting companies to feed in their CRISPR related patents—not only those which covering the basic enabling technology, but also those which cover applied technologies and the like.

While such pools have proven to be a pragmatic solution in the consumer electronics sector, they might not do justice to a field like human therapy, where the investments that have to be made, and the risk to fail, are higher than in any other sector, and where product lifecycles are much longer than they are in consumer electronics.

For this reason, it has been suggested, instead of establishing such pool, to grant exclusive licenses not for an entire field, like CAR T, but only for the application in a specific gene and/or disease, and provided the respective licensee has the capacity and intent to fully exercise such license.[13]

Still, Broad has recently announced that, together with MIT, Harvard University, and Rockefeller University, it would join discussions to contribute part of their CRISPR Cas9 IP to the suggested pool, for most other types of commercial research, including agriculture. The patents suggested not only include the 12 U.S. patents that list as inventor Feng Zhang, but also more broadly relevant CRISPR patents and applications related to the technology.[14]

9. J.L. Contreras and J.S. Sherkov, CRISPR, surrogate Licensing and scientific discovery. Science 355 (6323) 698, (2017).

10.CRISPR Controvers—CRISPR has brought gene editing into the mainstream—but where should we draw the line? The translational scientist. #0116.

11. J. Guerrini *et al*, "The Rise Of The Ethical License." *Nature Biotechnology* 35, 22–24 (2017).

12. L. Horn, "Patent Pools For CRISPR Technology." *Science*. 2017 Mar 24;355(6331):1274.

13. J.L. Contreras and J.S. Sherkov, "Response on Horn," *Science*. 2017 Mar 24;355(6331):1274.

14. Broad Inst Press release of 10 July 2017.

Further Players

However, Berkeley has so far not signaled that they would joint the initiative. And, there are other parties that will probably have a word to say.

Table 2 gives an overview of the players that have patent estates for basic CRISPR Cas9 technologies, with the respective priority dates and some key aspects (new features are marked with grey shades), and Figure 1 shows a timeline of the earliest priority dates of these estates, and their key features (again, new features are marked with grey shades). These estates will be discussed briefly in the following.

It seems that three further players—Toolgen, Vilnius University and Sigma Aldrich, plus a co-applicant of Broad, Rockefeller University, all of which have been somewhat under the public radar so far, have become members of the club of basic CRISPR Cas9 patent owners. Public access to basic CRISPR Cas9 technologies might hence not depend on Berkeley's and Broad's consent alone.

Further Player 1: University of Vilnius

On May 2, 2017, the USPTO issued another basic patent to the University of Vilnius, which has an earlier priority date than both the Berkeley estate and the Broad estate (see Figure 1), and which claims CRISPR Cas methods for *in vitro* applications, yet without disclosing or claiming the chimeric sgRNA (see Table 2). The patent claims the use of a crRNA, and a tracrRNA, and hence could be considered to form the foundations on which the Berkeley patent stands (which claims the chimeric sgRNA made from fusing the crRNA and the tracrRNA).

It is difficult to judge whether or not methods using the chimeric sgRNA would fall under the scope of the Vilnius patent, because, strictly speaking, such methods still use a crRNA, and a tracrRNA, even when the two are combined to form the chimeric sgRNA.

It is in this context noteworthy that in a continuously updated press release,[15] Broad refers to a couple of patent applications having an earlier priority date than the Broad estate, with, *inter alia*, an application assigned to Vilnius University, and the Berkeley application, disqualifying them as "speculating about the potential utility of CRISPR," showing "only that purified Cas9 protein and a certain purified RNA could cut a short piece of DNA in a solution in a test tube." Even after their U.S. patent was granted, Broad's press release continued to state that "the USPTO rejected the Vilnius application as not having significantly more than a study of the natural system and failing to describe invention."

Indeed, the USPTO issued a final rejection against the Vilnius application in October 2015. However, in the subsequent prosecution, the applicants submitted amended claims which then were found patent eligible. This development adds one further patent estate to the scenario which has to be considered by potential licensees.

This passage was only recently modified, to state that "the USPTO granted method claims to use of CRISPR-Cas9 systems assembled *in vitro* in one of the Vilnius applications." In fact, Broad's general PR tactics have been critizised by many, among others, by Michael Eisen of the University of California who critisized an article on the history of Cispr Cas 9 Broad's director Eric Lander has published in 2016[16] as "science propaganda at its most repellent."[17]

Further Player 2: Toolgen

Toolgen is a Korean company which focuses on the development of genome editing technology and products for biomedicine. Toolgen has a CRISPR Cas9 related patent family which, as regards the priority date (October 23, 2012), ranks third after Vilnius University (March 20, 2012) and Berkeley (May 25, 2012). See Figure 1.

However, Toolgen's patent family is the first patent estate that has disclosed the use of CRISPR Cas9 in eukaryotes, by means of nuclear localization sequences (NLS). While a Korean patent has already been granted (KR101706085), the respective European (EP2912175) and U.S. counterparts (US2015344912, US2015322457) are still pending.

Further Player 3: Sigma Aldrich

A company which was not on the radar of many to be a player in the CRISPR Field is Sigma Aldrich. The company has recently received a grant for an Australian patent protecting the fundamental CRISPR technologies (AU2013355214, now under opposition by three strawmen), plus a European patent (EP3138910, opposed by only one strawman, presumably acting on behalf of CRISPR Therapeutics).

As regards the priority date (December 6, 2012), Sigma Aldrich ranks fourth after Vilnius University (March 20, 2012), Berkeley (May 25, 2012) and Toolgen (October 23, 2012), but before Broad. See Figure 1.

Yet what makes Sigma Aldrich's portfolio so relevant is that it has disclosed the use of CRISPR Cas 9 in eukaryotes, by means of a Nuclear Localization Sequence (NLS) already in the priority document. See Table 2.

This is what Broad has always claimed to be its pio-

15. *https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process*.

16. E. Lander, "The heroes of CRISPR," Cell. 2016 Jan 14;164(1-2):18-28.

17. *https://twitter.com/mbeisen/status/687703268953214976.*

Figure 1

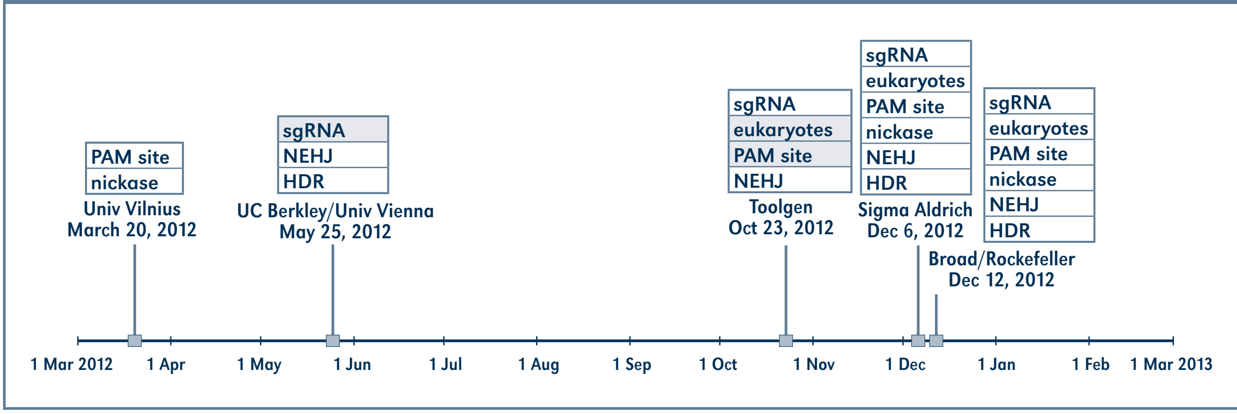


Table 2

Time rank	Applicant	Priority date	Disclosure: Nickase mutant/single strand breaks	Chimeric sgRNA	Application in eukaryotes	PAM site	NHEJ/ HDR	Key patent (example)	Restrictions of scope	Remarks
1	Univ Vilnius	20.03.2012	yes (1)	no	no	yes	no/no	US9637739	Scope of U.S. Patent restricted to in vitro use. Unclear (but likely) whether sgRNA embodiments are encompassed	(1) point mutation in RuvC, or HNH, e.g. D31A, H868A and N891A
2	Berkeley	25.05.2012	no	yes	yes/no (1)	no (1)	yes/yes	EP2800811	Scope of EP Patent restricted to in vitro or in a cell ex vivo use, but not excluding use in eukaryotic cells	(1) but examiner found it was implicitly disclosed
3	Toolgen	23.10.2012	no	yes	yes/yes	yes	yes/no	KR20150101476	Broad scope, not restricted to in vitro ex vivo or prokarytic use	Only granted in Korea so far
4	Sigma Aldrich	06.12.2012	yes (1)	yes	yes/yes	yes	yes/yes	EP3138910	Restricted to use in eukaryotes	(1) Cas9-dreived endonuclease has optionally only one functional nuclease domain (either RuvC or HNH)
5	Broad/ Rockefeller	12.12.2012	yes (1)	yes	yes/yes	yes	yes/yes	US8697359, EP2771468, EP2840410 et al	Restricted to use in eukaryotes	(1) point mutation in RuvC, D10A, H840A, N854A, N863A

neering feature over the Berkeley portfolio, in which such transfer from prokaryotes into eukaryotes was not yet disclosed or enabled at the priority date.

Hence, the recent development regarding Sigma Aldrich's portfolio could make an already complicated IP situation even more complicated. In appears that the recent allowances Sigma Aldrich has obtained might compromise Broad's position, in particular because Sigma Aldrich was purchased by Merck Millipore in 2015.

Interestingly, in the manuals of their CRISPR kits, Sigma Aldrich provides a use license agreement in which it is stated that the "product and its use are the subject of one or more of the following patents controlled by The Broad Institute (...) U.S. Patent Nos. 8,697,357; 8,771,945 (...)." It would be interesting to see how Merck Millipore will position itself against Broad's patents in the future.

Further Player 4: Rockefeller University

The arrival of University of Vilnius and Sigma Aldrich as new players was not the only event that complicated licensing matters in CRISPR Cas. In the opposition proceedings against Broad's European Patent EP2771468, with nine (!) opponents, the Opposition Division (OD) took the position that the subject patent would not be eligible to claim the priority of a number of priority applications (called PR1, PR2, PR5, and PR11), mainly because inventor Luciano Marraffini, a researcher of

Rockefeller University (called Rockefeller hereinafter) who was coinventor/coapplicant of the said applications (which are U.S. provisionals, hence inventors and applicants are the same), had not transferred his priority rights to Broad's PCT application, which formed the basis of Broads' granted EP patent.

Impact on Broad's EP Patents

The OD found only the priority claim to third priority document valid. The loss of the earliest priority claim rendered prior art applicable which otherwise would not count, for being post published. On the basis of this conclusion, the OD found that in particular the independent claim of the patent would be anticipated by two prior art documents which were published in between,[18] and would hence not be novel. See Figure 2. Because the loss of the priority claim seems to affect other corresponding EP patents from Broad's family as well, which all refer to the same priority document, the underlying controversy between Broad and Rockefeller, which so far has not really made it into the public, could become fatal.

Indeed, Feng Zhang of Broad Institute did not only collaborate with Jennifer Doudna (Berkeley) and Emmanuelle Charpentier (Vienna) in the good old days, but also with Rockefeller's Luciano Marraffini—who was named coapplicant in the crucial priority filings. However, something seems to have gone wrong between Rockefeller and Broad.[19]

Table 3 shows different European patents assigned to Broad which rely on the same priority filing and could hence be affected by this issue.

Table 3

Publication Number	Opponents	Opposition Term
EP2771468	9	November 1, 2015
EP2784162	8	January 8, 2016
EP2764103	7	May 19, 2016
EP2896697	8	June 2, 2016
EP2931898	6	December 9, 2016
EP2898075	6	December 9, 2016
EP2921557	7	April 13, 2017

European patent law demands, in order to validly claim a priority, that either (i) the priority application is assigned to the same party as the actual application, or (ii) the right of priority has been transferred before the actual application has been filed.

Neither of the two seems to be the case in the Broad portfolio because, as it seems, Mr. Marraffini did not transfer his priority rights to Broad, but to Rockefeller. Because, under U.S. law, in a provisional application the inventor is the applicant, inventorship disputes (which play a minor role at the EPO) can easily escalate into applicantship issues—which in the worst case may result in the loss of a priority claim—and, as a consequence, revocation of the patent for lack of novelty.[20]

On January 17, 2018, the OD revoked the patent on the basis of lack of novelty, due to the invalid priority claims, arguing, *inter alia*, that if each joint applicant of a priority application could file an individual patent application a multiplication of proceedings with identical content would result, with different patents protecting the same subject matter, yet having different patent owners. Further, in such case, the different patent applications would constitute state of the art to each other under Articles 54(2) and 54(3) EPC.

The same day, Broad issued a press release stating that the office's position would be "inconsistent with treaties designed to harmonize the international patent process." Broad also filed an appeal against this decision immediately, on January 18, 2018, hoping that the office would "use this case as an opportunity to review and resolve this international inconsistency, not just for CRISPR patents, but for a wider range of European patents and applications that originated as U.S. provisional applications."

In the opposition proceedings, Broad provided expert statements from, *inter alia*, Lord Hoffmann, former UK Law Lord, and Professor Straus, Director Emeritus, Max Planck Institute for Innovation and Competition, to support its position, while the opponents relied, *inter alia*, on a statement of Jay Erstling, fomer Director of the Office of the Patent Cooperation Treaty (PCT).

Quite surprisingly, Rockefeller filed their own U.S. non-provisional applications and EP applications, in which the priority of Broad's provisional applications which name Mr. Marraffini as a coapplicant was claimed, and Broad, MIT were named coapplicants, allegedly without informing them.[21]

In their non-provisional U.S. application US2015184139, Rockefeller has simply copied the

18. P. Mali *et al*, Science. 2013 Feb 15;339(6121):823-6; Hwang WY et al, Nat Biotechnol. 2013 Mar;31(3):227-9.

19. K. Grens, "That Other CRISPR Patent Dispute." *The Scientist*, August 31, 2016.

20. C. Coombes, "How to Avoid Legal Problems in Collaborative Research." *The Scientist*, August 31, 2016.

21. See a letter of Broad's inhouse IP counsel, Ellen Law, to the USPTO of July 7, 2014, with regard to application 14/424,960 (published application US2015184139).

claims of Broads's U.S. patents US8697359 and US8771945, which fail to name Mr. Marraffini as a coinventor, or Rockefeller as a coapplicant, although relying on a provisional application which names Mr. Maraffini as a coapplicant.

The application has been objected by the USPTO examiner for double patenting in view of the two Broad patents, for improper naming of inventors and for being anticipated by Berkeley's application US2014068797—which is surprising, because Broad's US8697359 and US8771945 were granted irrespective of said reference. Rockefeller has countered, *inter alia*, that it would not be the USPTO's role to resolve the underlying inventorship dispute *ex parte*.

Apparently, Broad was not happy about these parallel filings. However, because Rockefeller is named in these patents as coapplicant, the priority problem that threatens the validity of Broad's other European patents would likely not apply here.

Interestingly, one day before the oral proceedings against Broad's first patent started, on January 15, 2018, Broad announced it had settled its disagreement with Rockefeller regarding inventorship and ownership of the respective patent. Broad stated that the parties agreed that inventorship on Broad's eukaryote filings including PCT/US2013/074819, which forms the basis of Broad's opposed patents, will remain unchanged, meaning that Marraffini would not be a named inventor. Broad submitted a copy of this agreeement in the oral proceedings, and demanded consideration thereof, in an attempt to convince the OD that the lacking designation of Rockefeller or Marrafini as a coapplicant of the respective patents was justfied. However, according to the rationale the OD applied, this finding was irrelevant, and could not restore the lacking priority claim.

An agreement between Broad and Rockefeller could have theoretically helped to overcome the priority problem, because when filing the parallel PCT application, Rockefeller named Broad and MIT as coapplicants. Hence, the applications emanating therefrom, incuding granted European patents EP2840140 and EP2825654, do not suffer from the insufficient priority claim, in particular as Marraffini's priority right has been effectively assigned to Rockefeller.

However, Broad's statement that they agreed with Rockefeller that Marraffini would not be a legitimate inventor of this invention is somewhat counterproductive for such solution. Not surprisingly, Rockefeller's EP patents have recently also become subject to oppositions. The first was opposed by five opponents, while the second was opposed by seven opponents. All opponents are strawmen, most of which are opponents against the Broad portfolio. It remains an open question who the strawmen that were not party of the Broad oppositions actually work for. Under the rules of the EPC, Broad can not file an opposition against a patent it is actually the owner of, even if said ownership came unwillingly.

Figure 1 gives an overview about the earliest priority dates of the patent portfolios of the different players discussed herein, and the essential features disclosed in the first priority application.

Other Side Notes from the EP Opposition

In addition to the novelty issues that are caused by the above discussed priority problem, the Opposition Division has further noted that even if the priority claims were valid, at least some of the claims would lack inventive step.

Further, while sufficient enablement has not been addressed by the Opposition Division in their opinion yet, enablement can indeed still become an issue. In a recently published article,[22] the authors discuss that Broad and also Berkeley (and also the other players), have only provided enablement for *Streptococcus pyogenes* Cas9 (SpCas9), yet have received, or are about to receive, patent claims covering all Cas9 orthologues. The authors refer to another paper[23] and argue that therein, it was shown that Cas9 from *Staphylococcus aureus* (SaCas9), which shares just 17 percent amino acid sequence identity with SpCas9, can also be used for genome editing in mammalian cells, while five further Cas9 orthologs cannot, despite being capable of *in vitro* DSB induction. In EPC terms, this is a catchy insufficiency argument. Opponents could argue that, simply because the scope of the claims covers subject matter that is not enabled, the claims would be too broad and hence not disclosed in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

Lessons Learned from Party's Mistakes During Prosecution

Despite the high profile of the involved cases, and the financial resources invested, some of the parties have actually committed quite a few mistakes during prosecution.

1. As discussed, Broad has invested considerable resources to obtain a strong patent position for CRISPR Cas basic technologies. After all, among the different applicants discussed herein, Broad was the last to file but who received granted patents first (due to expedited examination proceedings), and now holds the biggest portfolio of granted CRISPR

22. N. Benjamin, N. Gray and Wm. Spruill, Nat Biotechnol. 2017 35, 630–3.

23. F.A. Ran, *et al*. Nature 520, 186–191 (2015).

Cas patents. It is therefore quite surprising that it slipped Broad's attention that the fact that the two earliest priority applications had named applicants/ inventors which then assigned their priority rights to another entity can actually become fatal for their EP patents. Joint patent ownership often leads to problems, and it is a good idea to avoid it when ever possible.

In the academic sector, joint publication with long author lists are commonplace, but one should rather not adopt this practice when it comes to the filing of patent applications. Further, it appears that Broad's attorneys completely misjudged the requirements the EPO sets to accept a priority claim.

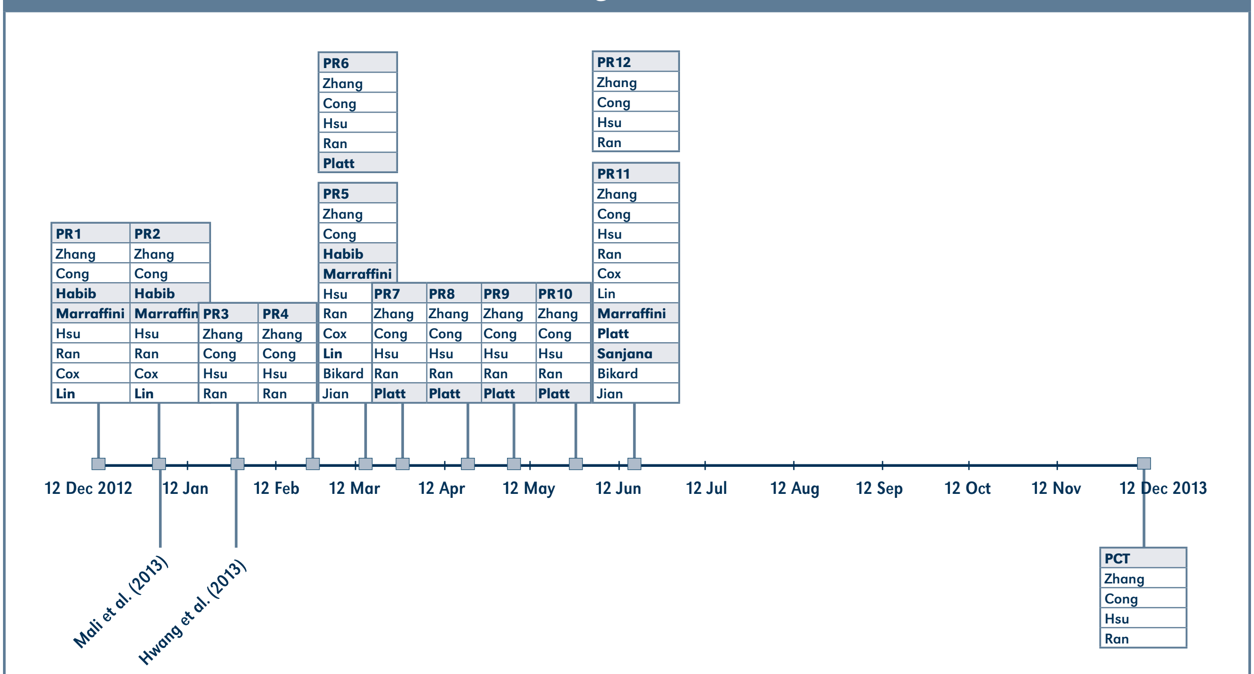
2. Another mystery is why Berkeley used a patent application to initiate the interference which, according to Mrs. Doudna, had already been determined by the examiner to be allowable. The interference led to an immediate stay of the granting process. Berkeley could have brought the application to grant and then filed a continuing application to use it for the interference, to have (i) a granted patent in hand and (ii) an interference running.

3. Berkeley's European patent application was almost refused for lack of novelty because, in their first priority application, the so-called PAM sequence (Protospacer Adjacent Motif) was not yet disclosed. This feature was for the first time disclosed in the second priority application.

The examiner wanted this feature to be in the claims, as he deemed it an essential feature of the invention. In such case, the priority claim to the first and second priority application would have been invalid, and Doudna's and Charpentier's own seminal Science article[24] would have become novelty destroying prior art. As a response to Berkeley's arguments, the examiner later accepted a claim which did not recite PAM. Hence, the original priority claim was restored, probably much to the relief of Doudna and Charpentier. But this moment of shock could have been avoided if the first priority application had been properly drafted, disclosing all essential features of the method.

4. From an academic standpoint, it may appear good practice to commit in an academic article, that, starting from what has been discussed in the article that, this or that future perspective may pose challenges. However, such statement can be used against you if you claim exactly that future perspective in a corresponding patent application, or at least claim that it would be encompassed by the scope thereof. This is what happened when Jennifer Doudna stated that she was not sure if the system she and Emanuelle Charpentier developed would

Figure 2



24. M. Jinek *et al*., Science. 2012 Aug 17;337(6096):816-21.

function in eukaryotes.[25] Hence, what is academically honorable can become detrimental in a patent strategy. So, academic researchers who start founding a business will have to adapt their communication habits. The scrutiny they will be exposed to is a different one than in the academic world

Conclusion

The licensing situation in CRISPR Cas is a complicated one. One should not expect the same development as in Zinc Finger Nucleases, where a combination of technical challenges, exclusive access to a library of enzymes and a restrictive licensing policy slowed down the spreading of the technology, simply because CRISPR Cas9 is so simple to practice and has already made its way through the academic laboratories. However, one may question if we can truly speak of a "democratized technology," in view of the licensing issues that are now surfacing. Potential licensors will have a long way to go to find out where to apply for a license. ■

Disclosure of Potential Conflicts of Interest

The author is involved in opposition proceedings against some of the patent applications mentioned herein.

Disclaimer

The information provided herein reflect the personal views and considerations of the author. They do not represent legal counsel and should not be attributed to Michalski Hüttermann & Partner Patent Attorneys or to any of its clients. Patent numbers and patent lifetimes have been verified with utmost care, but no liability is taken for their correctness.

Available at Social Science Research Network (SSRN): *https://ssrn.com/abstract=3164392*

25. M. Jinek, *et al*., "RNA-Programmed Genome Editing in Human Cells." *eLife* 2013;2:e00471.