

# A Cutting-edge IP Litigation: the European Front of CRISPR Patent War

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**C**RISPR/Cas9 is a gene editing technology that is revolutionising the way that scientists design biomedical research. In addition to this, CRISPR/Cas9 is opening promising avenues for applications in gene therapy, manufacturing, and agriculture. The commercial and disruptive potential of this invention is so promising that it sparked a 'gold rush' towards patenting CRISPR/Cas technologies. Two principal players weighed in to define the CRISPR/Cas9 patent landscape in the US: the University of California Berkeley (UCB) and the Broad Institute, a joint MIT-Harvard research institute [1]. This ultimately led to a high-profile patent battle in front of the US Patent Trial and Appeal Board, where the Broad Institute prevailed in the first instance [2]. The dispute, however, continues worldwide. In this Communication, I will focus on the European front of this litigation; the problem being not only who owns this technology in Europe, but also what are the potential impacts of patent conflicts between academic institutions on European policy and law.

## *A song of CRISPR and Cas*

Others have more extensively narrated how a niche field of research, an 'immune system' found in bacteria, became the next big thing in genome editing [3,4]. CRISPR stands for 'clustered regularly interspaced palindromic repeats' and describes a region in prokaryotic genomes where arrays of repeated near-palindromic sequences—nucleic acid sequences, e.g. GACGTC, where the complementary strand (CTGCAG) is the mirrored image of the primary one—are interlaced with short variable sequences. Scientists first acknowledged the existence of such genomic patterns in the bacterium *Escherichia coli* in 1987, and in many other prokaryotes (either archaea or eubacteria) over the next decade. In the mid-2000s, multiple authors suggested that CRISPR acts as a 'bacterial adaptive immune system' [3]. A few years later, multiple CRISPR-associated proteins (Cas) were described as effectors of this function in prokaryotes. Among Cas proteins, Cas9 has been characterised extensively from a biochemical and biological point of view.

At this point, one could use patents to tell the recent story of CRISPR/Cas9 systems. This approach might be less appealing than the (often controversial) ‘heroic’ narrative of CRISPR [3], but it also permits to avoid (cherry) picking which scientists provided major contributions towards understanding this system [4]. The players that are sectioning the patent landscape of CRISPR/Cas are also dividing a ‘pie’ worth tens of millions of USD [1], but are not the only people who contributed to the science behind this technology.

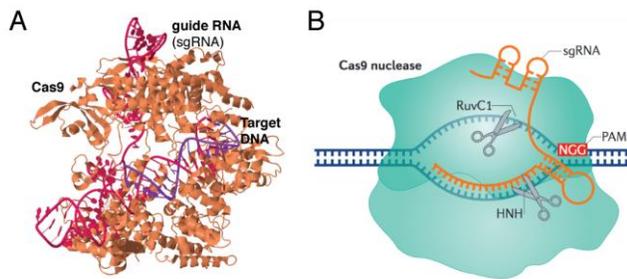
The first attempt at patenting CRISPR/Cas dates back to 2008 [5], when Luciano Marraffini and Erik J. Sontheimer from Northwestern University demonstrated that CRISPR/Cas could cut DNA – and could potentially be used to interrupt horizontal gene transfer from/to pathogens. The authors abandoned this patent due to a lack of sufficient experimental evidence; however, Marraffini would later become a key actor in the Broad/UCB patent battle in Europe. The first successful CRISPR patent application was filed by a Lithuanian researcher, Virginijus Šikšnys, in March 2012 [6]. This patent is, however, widely overlooked in most ensuing CRISPR patent battles as it contains claims on a CRISPR-RNA system created in vitro—not genetically encoded like the Broad/UCB one.

Another fundamental patent application was filed in May 2012 [7]. It came from Jennifer Doudna, a structural biologist at UCB, and Emmanuelle Charpentier, who was at the time a microbiologist at Umeå University in Sweden.

The collaboration of the teams led by the two women made it possible to engineer a CRISPR/Cas9 system to induce a targeted double-stranded DNA cleavage in vitro [8]. Figure 1 shows the mechanism of this DNA editing technology. The plot twist in this story was a patent filed by Feng Zhang at the Broad Institute in December 2012, that contained claims on a protocol to apply CRISPR/Cas9 system for genome editing in eukaryotic cells [9]. Later on, his team published a study in Science, where they were able to edit the genome of murine and human cells [10]. With an expensive patent gamble, the Broad Institute collaboration fast-tracked its application to the US Patent and Trademark Office (USPTO) [1]; the patent was accepted in 2014, while the one from UCB is still pending.

#### *CRISPR Total War*

Both UCB and the Broad Institute claim an engineered CRISPR-Cas9 system for use in genome editing. Doudna and Charpentier’s patent does not specify the cell types to which it might be applied, while Zhang’s patent claims specific use on eukaryotic cells. If we represent the two patents as Venn diagrams, the claims of the latter patent might be a subset of the former. And to be patentable, an invention must be novel considering the information already available to the public (the ‘prior art’), show non-obvious inventive step from already patented inventions, and it must be fully disclosed.



**Figure 1 CRISPR-Cas9 mechanism.** A) Cas9 (orange) is a Cas protein with multiple functions: in nature it complexes with targeting RNA derived from a CRISPR cluster (crRNA) and a second, structural RNA called tracer RNA (tracRNA). The group from Doudna and Charpentier proved that these two RNAs can be replaced with a single guide RNA (sgRNA, magenta) [8]. B) The RNA-protein complex then unwinds the double helix and scans the genome until it reaches a sequence which 1) is complementary to the spacer region of crRNA and 2) is adjacent to a sequence motif called a PAM site. After sequence recognition, Cas9 cleaves double-stranded DNA three bases upstream of the PAM sequence from both sides leaving blunt-ends, which are hotspots for homologous recombination (fundamental to gene knock-ins) or small sequence deletions that might lead to gene knock-out. *Panel A from Streptococcus pyogenes Cas9 structure resolved with X-ray diffraction (PDB:4008). Panel B adapted by permission from Macmillan Publishers Ltd: Nat. Rev. Mol. Cell Biol, doi:10.1038/nrm.2015.2 © (2016).*

In 2016, UCB filed an interference to the USPTO stating that the Broad's patent is an 'obvious' derivation from their own. This action opened a high-level international patent war between Cambridge (MA) and Berkeley. The focal point being whether it would be trivial to use the system developed in vitro by Doudna and Charpentier in eukaryotic cells. The Broad Institute managed to convince the US Patent Trial and Appeal Board that its patent is a non-obvious application of the system patented by UCB [2]. The ruling opened a scenario in the US where both the UCB (when awarded) and Broad patents might be valid for commercial application in agriculture or human gene therapy. UCB has since filed an appeal to the decision of the USPTO, but their decision is still pending [2].

The war for CRISPR/Cas9 is not over yet, because each Regional/National Patent Office is a distinct battlefield. For example, in 2017 China took sides with Doudna and Charpentier, granting them a patent for the use of CRISPR/Cas9 in vitro and in all types of cells [2]. This came after the European Patent Office (EPO) also granted the two scientists a CRISPR/Cas9 patent with broad claims (EP2800811) in May of the same year.

#### *CRISPR goes to Crete*

When moving to the Old Continent, the dispute over CRISPR patents becomes labyrinthine, with no Ariadne's thread in sight. Multiple players are in the arena, along with Doudna and Charpentier, and Zhang. Some are to be

expected—such as Vilnius University, the home institution of Virginijus Šikšnys, inventor of a non-genetically encoded CRISPR technology—others are not. Of note is Merck’s subsidiary company MilliporeSigma, which was granted a patent for a CRISPR-based knock-in strategy specific for genome editing in eukaryotic cells (EP3138910). EPO’s decision caused surprise among American commentators [11]. MilliporeSigma’s patent—also granted in Australia, Singapore, and Canada—covers claims very similar to those presented by the Broad Institute [10], but was filed six days prior.

The EPO awarded the European equivalent of the patent at the centre of the American dispute to the Broad Institute back in 2015 (EP2771468) following an international patent application naming the Broad Institute, MIT and Harvard as applicants. The application was filed in December 2013 claiming a priority date of December 2012—i.e. the date the patent was first filed to the USPTO [12]. Claiming priority means that the novelty of the patent is to be established as if it were filed on the priority date (December 2012), and not on the filing date (December 2013) [13]. In this story, dates are as fundamental as reading.

Opponents of the Broad Institute’s patent in Europe have found a winning argument, based on a technical difference between European and US patent law, which led to the revocation of the patent on 17th January 2018. One of the priority documents, dated 2012 (US application 61736527), named Luciano Marraffini, at the

time at Rockefeller University in New York, as co-inventor with Zhang, while the application included only the latter as inventor. This mismatch is not coming out of the blue, but is the result of a non-conventional parallel patent dispute between Broad Institute and Rockefeller University, solved through arbitration in January 2018 [14]. According to European rules, the names of inventors listed on priority documents and on the filed application must be identical in order to claim priority (in the US, at least one of the inventors must be present in both documents). This technicality meant that the application could not claim priority date and its effective date became the filing date. The Broad application lacked novelty over the prior art in December 2013 (see for example [10]) and ultimately had to be revoked.

The Broad Institute is appealing the decision on the grounds that the EPO has rules contradicting international patent treaties. However, it is unlikely that the EPO is going to defy decades of patent case law to accommodate Broad’s requests [13]. Nonetheless, this revocation does not directly affect the many follow-up CRISPR patents that the Institute still holds in Europe. Thus, at the moment multiple institutions are in possession of key patents with similar claims on CRISPR/Cas9 in Europe. This situation is probably not going to have a winner-take-all solution, and it is likely that multiple players will share rights to the technology [13].

#### *CRISPR patents, academia, and policy making*

The CRISPR patent war is not just a fascinating

story for people interested in Intellectual Property law. At its core, there are fundamental issues related to the role of academic institutions in the commercialisation of their research, the consequences of ‘academia becoming business’ [1, 2, 15, 16], and the role of policy makers in addressing this issue (if need be).

Patents are a contract between inventors and society, where one side discloses their invention to the public, and the other grants them the negative right to protect the invention for a definite period of time. This, in turn, incentivises people to create new tools or processes that might benefit society as a whole; patents serve as a powerful tool to drive scientific innovation. The link between legal protection of inventions and innovation has been recognised for a long time, for example the United States Constitutional Convention introduced an ‘Intellectual Property clause’ in the U.S. Constitution (Article I, Section 8, Clause 8) as early as 1787.

However, advantages become less clear when academic institutions are pushed towards patenting—or rather, exclusive licensing—and commercialising their research. The CRISPR patent dispute is defining a quite unprecedented scenario where a plethora of (mostly academic) players, each with partially overlapping claims on a technology, are present in different regional/national markets. One aspect of this problem is that universities, the patent owners, transfer licensing rights to their private ‘commercial arms’ (a.k.a. spin-off companies)

according to the practice of surrogate licensing [2, 15]. Compared with the past decades, this is a novel approach to the commercial exploitation of academic research [16] and it might be related to changes in the availability and distribution of research funding. Some scholars have warned that a convoluted licensing situation might end up hindering the development and commercial availability of CRISPR-derived biomedical technologies, since a handful of private companies would retain exclusive licensing rights to the technology [1, 15].

A second crucial point we need to focus on is the potentially detrimental effect that these litigations have on interinstitutional collaboration and on the way in which academic research is run. Again, the CRISPR example is paradigmatic, as it disclosed manual examples of toxic behaviours in academia: from downplaying the role of other groups in developing CRISPR/Cas9 [1], to using Prof. Doudna’s critical analysis of her own work as a key argument against UCB patent claims [2]. In the long run, the fear of patent clashes might hold back institutions from collaborating—in particular when potentially profitable technologies are on the table. This would betray one of the main assets of scientific research: collegiality.

Funding bodies and policy makers might have a pivotal role in avoiding the emergence of a ‘patent or perish’ culture in applied research. For instance, they could respectively adopt or

promote the adoption of evaluation criteria that would favour applicants providing forms of open licensing, such as patentleft (the patent analogue of copyleft), alongside standard ones. Another possibility is to encourage the use of patents to exert ways of 'private governance' [2] on their commercial derivations that would favour communities. For example, Monsanto's license from the Broad Institute for agricultural applications of CRISPR/Cas9 requires the multinational company to allow the practice of saving and resewing seeds from one season to the next [17]. A policy-driven push on academic institutions towards open and ethical licensing, if matched with policies that encourage a fairer distribution of funding, might discourage research institutions from pursuing time- and money-intensive patent wars and put the focus back on openness and scientific collaboration.

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