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The battle to own the CRISPR–Cas9 gene-editing tool

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Millions suffer from devastating genetic disorders like cancer, muscular dystrophy, cystic fibrosis, sickle cell anaemia, Huntington's disease and many others. Imagine the pain and suffering that could be avoided (not to mention the healthcare costs) if we could cure these diseases simply by rewriting the genetic code of patients. This is the promise of the CRISPR-Cas9 gene-editing technology.

Billed as the most exciting breakthrough in biomedical research since the dawn of genetic engineering in the 1970s, the CRISPR-Cas9 gene editing tool has huge scope to improve understanding of human and animal disease and its treatment (photo: iStock.com/cosmin4000).

Billed as the most exciting breakthrough in biomedical research since the dawn of genetic engineering in the 1970s, the CRISPR-Cas9 gene-editing tool has huge scope to improve understanding of human and animal disease and its treatment. It has the potential to revolutionize medicine and agricultural research. The race to develop commercial applications of CRISPR-Cas9 in healthcare, agriculture and industry, however, has thrust the technology, its pioneers, the institutions they work for and a clutch of startups in which they are involved into a high-stakes legal battle over who actually invented it and when. The outcome will determine who controls the technology and where the highly lucrative economic benefits it promises to generate will flow.

The technology and how it came about

Ever since Watson and Crick identified the DNA double helix, scientists have been searching for ways to better understand the role that DNA plays in the genetic make-up of living organisms. The CRISPR tool is a huge step forward. Compared to existing research tools, it offers a relatively quick, easy, reliable and cheap way to target and edit specific genetic sequences.

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. It is a natural defence mechanism that allows bacterial cells to detect and destroy the viruses that attack them.

The CRISPR mechanism was first identified as a “general purpose gene-editing tool” in a scientific paper published by scientists Erik Sontheimer and Luciano Marrafinni from Northwestern University, Evanston, Illinois, USA in 2008. The scientists filed for a patent but their application was rejected because they were unable to reduce it to any practical application, *Science*’s Jon Cohen writes.

But CRISPR really began to create a buzz, with the publication in June 2012, of a scientific paper by Emmanuelle Charpentier, a French microbiologist then working at the University of Vienna and now at the Max Planck Institute for Infection Biology, Germany and Umeå University, Sweden, and Jennifer Doudna at the University of California, Berkeley, USA. Their paper outlined how CRISPR, with the help of an enzyme called Cas9, can be transformed into a tool to edit genes. Specifically, how CRISPR-Cas9 can be used to cut DNA in a test tube. They filed their first CRISPR-related patent application in May 2012. It is still under review.

Six months later, in January 2013, scientists at the Broad Institute of the Massachusetts Institute of Technology (MIT) and Harvard University, led by Feng Zhang, reported that they had found a way to use CRISPR-Cas9 to edit the cells of mammals, further fuelling interest in its potential to generate new and more effective medical treatments. The Broad researchers filed their first CRISPR-related patent application in December 2012 and paid for a fast-track review process. Eleven additional patent applications were filed to bolster the claim that they were the first to invent a CRISPR system to edit mammalian cells, Jon Cohen notes. In April 2014, the United States Patent and Trademark Office (USPTO) granted the Broad team a patent on their CRISPR technology.

Jennifer Doudna (top left) at the University of California, Berkeley, USA, and Feng Zhang (top right) at the Broad Institute of the Massachusetts Institute of Technology (MIT) and Harvard University, have each undertaken pioneering work in relation to CRISPR-Cas9. They and others are currently embroiled in a legal firestorm over who owns commercial or IP rights in the technology. (Photos: Keegan Houser/UC Berkeley and Justin Knight Photography).

The battle for ownership

The grant of the patent to the Broad team triggered a legal firestorm. Professor Jake Sherkow of the New York Law School characterizes it as “an absolutely humungous biotech patent dispute”.

The stakes are clearly very high. Whoever owns the commercial or IP rights to CRISPR-Cas9 has the potential to generate huge financial returns and to decide who gets to use it.

Each of the pioneering researchers and their respective institutions has a stake in a handful of start-ups which have attracted millions of investment dollars to translate CRISPR-Cas9 systems into new treatments for a broad range of genetic diseases. They include Intellia Therapeutics (UC Berkeley), Caribou Sciences (J. Doudna), CRISPR Therapeutics and ERS Genomics (E. Charpentier) and Editas Medicine (Broad Institute).

An analysis of the CRISPR-Cas9 commercial landscape by *Science*’s Jon Cohen reveals that a web of often overlapping licenses have already been granted by CRISPR startups for many applications in medicine, agriculture and industry.

The Bayh-Dole Act

Under the 1980 Bayh-Dole Act universities in the United States are able to hold IP rights in inventions arising from federally-funded research. But guidelines developed by the U.S. National Institutes of Health advise that these technologies should be licensed under “reasonable terms and conditions” to ensure they are available to support further biomedical research. Both UC Berkeley and the Broad Institute readily offer non-exclusive licenses for purely scientific research, notes Megan Molteni in *WIRED*. But anyone seeking to commercialize a CRISPR-related product needs to obtain a sublicense from one of the CRISPR startups.

But with the scope of the exclusive licenses they hold covering the 20,000 or so genes in the human genome, some question whether these companies alone can possibly develop all of the technology's potential applications. What will be the impact on other biotech companies that want to commercialize CRISPR-related products. Will the fact that they need to obtain an additional sublicense from these companies put a brake on innovation?

The patent interference procedure

In April 2015, UC Berkeley, representing E. Charpentier and J. Doudna, requested a patent interference proceeding against the patents granted to the Broad Institute. The USPTO's Patent Trial and Appeal Board (PTAB), responsible for hearing such cases, granted the request. Hearings began in January 2016.

Patent interference procedures are effectively "administrative trials to determine which of two (or more) parties invented something first," writes Jake Sherkow. The procedure is a vestige of the first to invent system existing in the United States up to March 2013 when it was superseded by the America Invents Act. The United States now grants patents on the basis of a "first to file" system. As the disputed CRISPR-related patents were filed prior to March 2013, they qualified for a patent interference procedure. "Typically a USPTO patent interference proceeding comes into being when different patent applications filed before the USPTO by different inventors may potentially overlap as the same invention," notes Joe Stanganelli in *Bio IT World*.

The question before the PTAB was whether the work of the Broad Institute researchers was novel or whether it was "the next *obvious* step to take, and/or fundamentally based on *prior art*", Joe Stanganelli explains.

On February 12, 2017 the PTAB handed down its decision. It stated that the patents granted by the USPTO to the Broad Institute for the use of CRISPR-Cas9 in editing mammalian cells (eukaryotic genomes), did not overlap or interfere with patent claims filed by the UC Berkeley team for the use of the system in any environment (see box). The PTAB thus ruled that Zhang's patent claims were not obvious considering the information provided in UC Berkeley's US patent application.

The PTAB's decision means that the Broad Institute will be able to keep its US patents which claim methods of using CRISPR-Cas9 in mammalian cells (eukaryotes). It also means that UC Berkeley can keep its US patent application, which claims methods of using CRISPR-Cas9 in any cells. While this may be good for the two institutions, it spells "maximum uncertainty" for the biotech business community, for whom it is unclear whether they need to get licenses from both universities, notes Kevin Noonan, partner at McDonnell Boehnen Hulbert & Berghoff in Chicago, USA, in *Nature*.

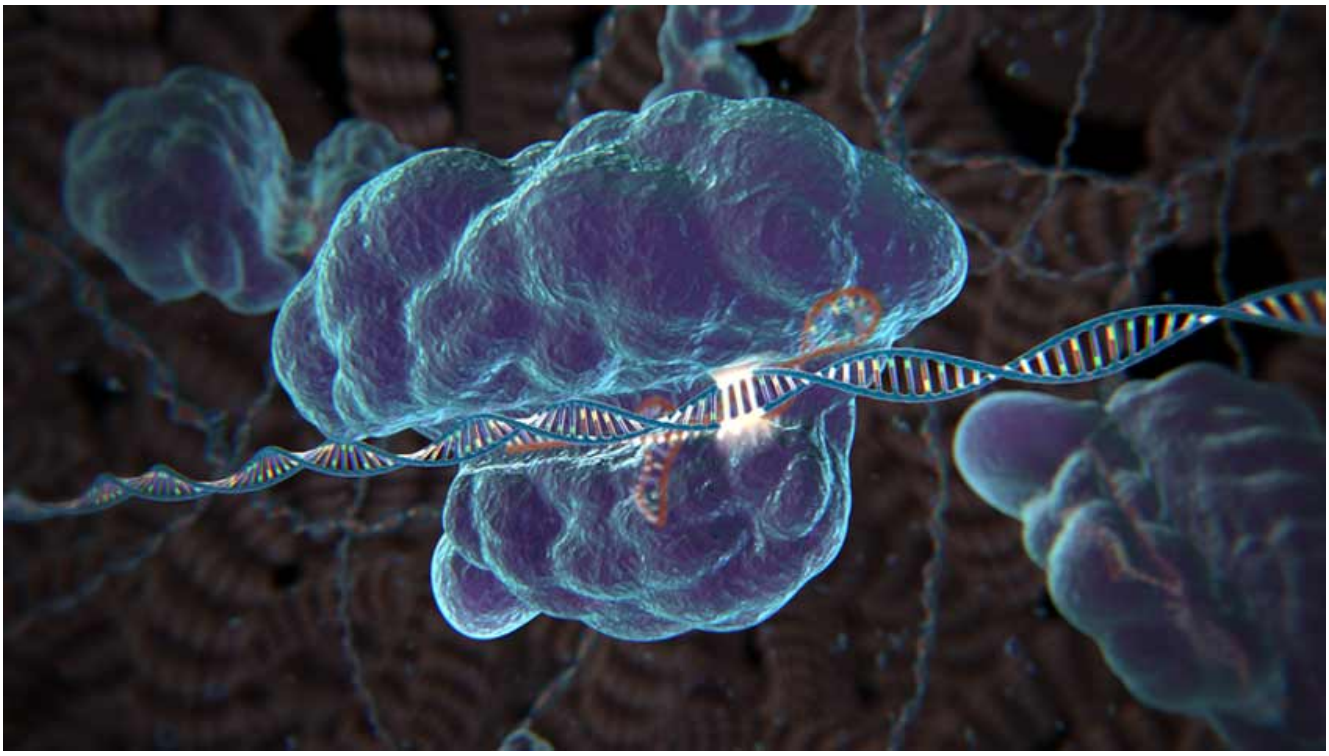
Summary of the PTAB's Decision on Motions

The decision states: "Broad provided sufficient evidence to show that its claims, which are all limited to CRISPR-Cas9 systems in a eukaryotic environment, are not drawn to the same invention as UC's claims, which are all directed to CRISPR-Cas9 systems not restricted to any environment. Specifically, the evidence shows that the invention of such systems in eukaryotic cells would not have been obvious over the invention of CRISPR-Cas9 systems in any environment, including in prokaryotic cells or in vitro, because one of ordinary skill in the art would not have reasonably expected a CRISPR-Cas9 system to be successful in a eukaryotic environment. This evidence shows that the parties' claims do not interfere."

Why we should be interested in CRISPR-Cas9

The CRISPR-Cas9 gene-editing system has the potential to “change the way life sciences researchers edit and engineer the DNA of virtually any living thing on the face of the earth,” explains Professor Jake Sherkow.

It promises a deeper understanding of the way genes function in cells and the development of new and more effective medical treatments and therapies for a range of devastating diseases. By removing the underlying dysfunctional DNA sequences, it could be possible not only to cure these diseases but to ensure these conditions no longer pass to the next generation. Its application in agriculture and industry also promises the development of more robust, disease-resistant plants and animals. So the potential social benefits are huge.



Artistic representation of the CRISPR-associated nuclease Cas9 cutting DNA at a specific target site (photo: Courtesy of McGovern Institute for Brain Research at MIT).

Researchers around the world are already using CRISPR-Cas9 systems to edit genomes, including for edible mushrooms, corn, mice, monkeys, and even human embryos. In June 2016, the U.S. National Institutes of Health approved the first clinical trials using CRISPR-Cas9 on cancer. And in September 2016, the UK’s Human Fertilization and Embryo Authority (HFEA) approved its use to permanently edit DNA in a human embryo.

But CRISPR-Cas9 technology as it currently exists still bears significant risks and needs further refinement, for example in terms of its accuracy and delivery to human cells. It also raises many ethical concerns that deserve serious consideration. After all, it has the potential to radically alter the genetic make-up of humanity. In response to these concerns, Jake Sherkow notes, the Broad Institute has already issued “ethical licenses” to certain licensees to prohibit certain activities deemed contrary to the public interest. Given the time it takes to craft effective policies, he believes this approach offers an effective way “to pause worrisome applications of emerging biotechnologies”.

After the PTAB’s ruling, what next?

Although PTAB ruling may appear to have given the Broad Institute an outright win, the outlook is not quite so clear-cut. The battle over CRISPR-related IP rights looks far from over for various reasons.

First, UC Berkeley is weighing its decision to appeal the PTAB's ruling. It remains convinced that "the Doudna/Charpentier team was the first group to invent this technology for use in all settings and all cell types, and was the first to publish and file patent applications directed toward that invention, and that the Broad Institute's patents directed toward use of the CRISPR-Cas9 system in particular cell types are not patentably distinct from the Doudna/Charpentier invention."

Second, various commentators consider it likely that the parties will eventually come to some sort of settlement involving the cross-licensing of their technology. Given unresolved issues of IP rights ownership of CRISPR vectors – which enable delivery of the mechanism to recipient DNA – this seems likely. "If UC gets patent claims to CRISPR vectors granted, it would have rights to stop others from making, using, or selling them," explains Phillip Webber, biotech patent attorney at the law firm Dehns in Oxford, UK. This would mean that even Editas Medicine, which holds an exclusive license to use Zhang's CRISPR methods, would need to take a license from UC Berkeley.

Third, both the Broad Institute and UC Berkeley have filed and are defending patent applications in Europe. Catherine Coombes, a patent lawyer at HGF in New York notes in *Nature* that European case law may bring about a different outcome from that of the PTAB. If the European Patent Office finds that UC Berkeley's research provided "sufficient motivation", for other researchers to try the CRISPR-Cas9 system in mammalian cells then UC Berkeley's patent may be judged to cover applications in all cell types, giving it the edge over the Broad Institute's patents in Europe.

And finally, many other research groups are also getting in on the CRISPR-Cas9 patenting game. According to IPStudies, a Swiss-based IP management consultancy, more than 900 patent families currently exist, all claiming rights on different aspects of CRISPR-Cas9 systems. As these groups assert their rights, and demand royalties, many more legal battles are likely to ensue both for the Broad Institute and UC Berkeley.

But while the courts continue to grapple with these issues, the science continues to advance. Researchers at the Broad Institute, again led by Feng Zhang, have already identified – and submitted a patent application for – an interesting alternative to Cas9 called Cpf1. This new enzyme offers scientists greater scope to edit the genes of certain bacteria. While no CRISPR-therapy yet exists, there is talk of a number of trials starting this year. So watch this space.

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