CORPORATE COUNSEL
An ALM Website
corpcounsel.com | April 25, 2016

A Breakthrough Technology is Caught in an Epic Patent Battle

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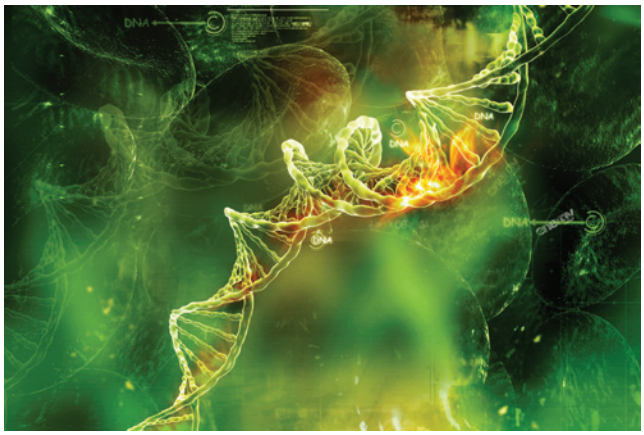
In the last couple of years, a new gene editing technique called CRISPR has taken biology by storm. Scientists worldwide are using CRISPR to turn off, turn on and alter genes in living cells. CRISPR is so precise that it is expected to turn into a promising therapy for correcting genes in people, thereby curing devastating illnesses. Gene editing startups have burst onto the scene and industry has jumped in to develop this technology for therapeutic use. But CRISPR is now embroiled in a massive patent fight between the research institutions that lay claim to the technology. In January, the Patent Trial and Appeal Board (PTAB) declared an interference, an arcane and largely obsolete proceeding, to decide who was first to invent CRISPR gene editing in eukaryotic cells (using Cas9, a CRISPR associated protein), and thus who may be able to profit from its far-reaching applications.

Gene Editing Takes Off

CRISPR, which is pronounced *kris-per* and stands for Clustered Regularly Interspaced Palindromic Repeats, is a bacterial defense system for fending off invading viruses by targeting their DNA. Scientists co-opted and engineered this system for gene editing. The technique uses RNA guide sequences to target DNA of interest and the Cas9 protein to bind and cleave the selected DNA. The cut DNA can then be repaired using a template of a scientist's choosing to insert new DNA, providing a "find and replace" functionality. Since the first publication of CRISPR/Cas9 mammalian gene editing in 2013, scientists have used CRISPR/Cas9 to make human cells immune to HIV, modify the genomes of monkeys, inactivate 62 viruses in the pig genome to pave the way for safe organ transplants and cure mice of a rare liver disease, among a vast number of other applications. CRISPR also is revolutionizing agriculture. The journal *Science* chose CRISPR as its 2015 Breakthrough of the Year.



CRISPR has also raised the specter of designer babies.

Patent Battle Heats Up

Though many scientists across the globe have contributed to the discovery of CRISPR, two teams have received the most attention: the University of California team led by Jennifer Doudna at Berkeley and her colleague Emmanuelle Charpentier; and the team led by Feng Zhang at the Broad Institute and MIT. The PTAB will determine which team was the first to invent CRISPR/Cas9 gene editing in eukaryotic cells, including human cells.

Doudna's team published its studies (available online in *Science*, June 2012) showing that Cas9 could cut purified DNA in vitro and could be reprogrammed using an RNA guide sequence to cut any selected target DNA, "highlight[ing] the potential to exploit the system for RNA-programmable genome editing." Zhang's team then published its work (available online in *Science*, January 2013) reporting mammalian gene editing in mouse and human cells. Zhang's publication quickly became the most-cited paper in the field, and his reagents for gene editing have

been distributed to the research community worldwide.

UC filed a provisional patent application on the work of Doudna's team in May 2012. The Broad Institute filed its application in December of that year. The Broad then requested accelerated examination of its patent application. In April 2014, the Patent and Trademark Office (PTO) awarded the Broad a patent on CRISPR/Cas9 gene editing, followed by many additional patents. In granting the Broad's patents, the PTO considered the international counterpart of UC's patent application and agreed that it did not anticipate or make obvious CRISPR/Cas9 gene editing in eukaryotic cells.

UC then asked the PTAB to declare an interference between twelve Broad patents (and one application) and UC's patent application. Although the America Invents Act eliminated interferences for patents filed after March 15, 2013, the CRISPR applications were filed earlier and are therefore subject to these complex proceedings. In declaring the interference, the PTAB designated UC as the senior party, since it filed its application first, providing it with a number of procedural advantages over its junior party rival.

The interference is still in its infancy and the PTAB has only recently authorized motions on certain threshold issues. It allowed the Broad to argue that the two parties' claims don't actually interfere and that UC's claims are not supported by its application. It allowed UC to file a motion to substitute the description of the interfering subject matter and denied UC's request to file a motion arguing that the Broad's patents were obtained through inequitable conduct. While the stakes are undoubtedly high for the teams and institutions, the interference likely will take years to complete.

The fight over CRISPR/Cas9 gene editing also is heating up across the Atlantic. The European Patent Office (EPO) granted the Broad six patents. The first issued in February 2015. Nine parties have now opposed it. Another issued in April 2015, and eight parties have opposed that one. An argument before the EPO for revoking the patents is that they are not inventive over Doudna's 2012 article. The oppositions will take years to resolve. UC's patent application remains pending before the EPO.

CRISPR Goes to Market

There is no doubt that CRISPR-based gene editing promises to be incredibly lucrative, and investors have already begun to fund CRISPR's practical applications. Editas Medicine, founded by Zhang and Doudna, among others, raised $94.4 million in its February 2016 IPO. That was in addition to $120 million that Editas raised in 2015 from private investors, including Bill Gates. Editas holds a license to the Broad's CRISPR/Cas9 patents and plans to start clinical trials sometime in 2017 – the first to use CRISPR to edit the DNA of a person – for treatment of a rare genetic condition causing blindness.

Doudna has thrown her support behind a rival gene editing company, Intellia Therapeutics (launched by Caribou Biosciences, which Doudna co-founded), with a license to her IP. In April 2016, Intellia filed for an IPO to raise up to $120 million. It has already raised $85 million and has a partnership with Novartis focusing on ex vivo applications of CRISPR/Cas9. Intellia also entered into a collaboration with Regeneron Pharmaceuticals Inc. to develop CRISPR/Cas9 in vivo therapeutics. Charpentier co-founded CRISPR Therapeutics, a startup that has raised $89 million from investors, including Celgene Corporation. It has joined forces with Bayer to develop CRISPR/Cas9 therapies. Vertex Pharmaceuticals Inc. also has teamed up with Charpentier's company.

Further complicating the landscape, Zhang published a paper in September 2015 detailing the discovery of the Cpf1 protein, which could replace Cas9 in CRISPR-based gene editing. Cpf1 is smaller than Cas9, making it easier to deliver into cells for gene editing. It also cuts DNA in a different way, increasing the efficiency and accuracy of editing. And because the patent claims in the current disputes require use of Cas9, Cpf1 offers gene editing opportunities separate and apart from the CRISPR/Cas9 patent battle.

The Road Ahead

CRISPR/Cas9 gene editing is transforming research and also holds the potential for correcting genetic mutations in patients. But as with many breakthrough innovations, from the telephone to the television, the patent battle ahead looks to be bitter and long. Gene editing research, however, is surging forward. The use of the Cpf1 protein may provide its own patent rights, and diminish the stakes of the current patent disputes. In addition, with CRISPR-based gene editing still in its infancy, further tools may be discovered, and, in any case, new developments are needed before these tools can be used in patients. As a result, the impact of the current disputes on who ultimately profits from CRISPR's gene editing applications is far from certain. And the battles are far from over.

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