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THE BATTLE FOR CRISPR CONTROL

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Introduction

On September 10, 2018, the United States Court of Appeals for the Federal Circuit issued a decisive ruling on *Regents of University of California v. Broad Institute, Inc.* which confirmed the Patent Trial and Appeal Board's (PTAB) decision of "no interference-in-fact" between the patents of The University of California and The Broad Institute. Members of these two institutions were foundational in the development of the DNA editing technique known as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), and the arguments centered on whether The Broad Institute's patent which claimed CRISPR only for eukaryotic cells (namely, human, animal, and plant) fell under The University of California's patent which claimed CRISPR for all cell types, but only showed examples in prokaryotic (namely, bacterial) cells. A brief look at this ruling and the history behind it will show the importance of effective patent and claim writing and the lessons learned from this patent litigation.

What is CRISPR and Why is it Important?

CRISPR is a DNA (DeoxyriboNucleic Acid) sequence consisting of multiple short base pair palindromic sections with varying DNA sequences inside of these palindromic sections. DNA is the backbone of life and made up of a number of different building blocks known as base pairs which combine to form a single strand of DNA. Two complementary strands bind together to form the iconic double helix structure of DNA. There are four base pairs which make up DNA, which are given the names A, T, C, and G, and a palindrome of these base pairs (such as ATA) is what constitutes a palindromic section.

CRISPR was initially discovered in the early 1990's in archaea and bacterial cells, and their function was later discovered to be a defense mechanism against viruses or other cellular invaders. Viruses insert sections of their own DNA into a cell's DNA so that when the cell's DNA is replicated, the viral DNA is also replicated and more viruses are produced. As a defense against this, the palindromic sections are placed around the viral DNA, such that the CRISPR section includes the viral DNA capped on either end with palindromic sections. These CRISPR sections helps guide a bacterial enzyme known as Cas9 to the invading viral DNA, which then cuts the viral DNA sections out prior to their insertion into the cell's DNA. Once cut, the DNA section is either replaced by the cell with random base pair sequences, leading to an un-functioning DNA section, or by using DNA sequences which are programmed to fit into the section which was removed.

In 2012 two separate groups, the first lead by a collaboration between Jennifer Doudna at The University of California at Berkeley and Emmanuelle Charpentier at The Laboratory for Molecular Infection Medicine in Sweden, and the second lead by Virginijus Siksnys at Vilnius University, showed how this CRISPR/Cas9 system could be modified to target and cut out any DNA section in prokaryotic (namely, bacterial) cells. Then, in 2013, Jennifer Doudna, Feng Zhang at The Broad Institute, and George Church at Harvard University each separately published papers showing how the CRISPR/Cas9 system could be used in eukaryotic cells (namely, human, animal, and plant). These papers opened up the possibility to use this system to treat diseases involving DNA mutations by either deleting or replacing the damaged DNA section and also enabled easier genetic alteration of plants. As evidence of the importance of these discoveries, billions of dollars have already been invested in the various companies which were started based on this technology.

Patent History

In May of 2012, The University of California filed a Provisional Patent Application, which has since issued as US Patent No. 10,266,850, and claimed various engineered CRISPR/Cas9 systems as well as the method of using CRISPR/Cas9 technology for editing DNA. US Patent No. 10,266,850 does not claim a specific cell type, and while it discusses in the specification the possibility of using in CRISPR/Cas9 in eukaryotic cells, the only data shown is for prokaryotic cells. Shortly after this, in December of 2012, The Broad Institute filed a Provisional Patent Application which has since issued as US Patent No. 8,697,359, among others, and claims various engineered CRISPR/Cas9 systems and the method of using CRISPR/Cas9 technology for editing DNA specifically in eukaryotic cells. Even though The University of California filed first, The Broad Institute had paid for fast-tracked examination, and their patent was granted in April 2014, even before the examination of The University of California's patent in 2015. In April of 2015, The University of California requested an Interference Proceeding of it's pending Application (Application No. 13/842,859) with The Broad Institute's Patents.

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Did You Know?

In the United States, Genetically Modified Organisms, or GMOs, are defined as organisms which have foreign DNA material added into their DNA. Such modifications require approval by the Food and Drug Administration, which significantly increases the cost and thus the barrier of entry for companies producing these organisms. However, if one uses techniques such as CRISPR, which simply removes a section of DNA, these organism are not considered GMOs, and do not require approval by the FDA. In contrast, the European Union considers both the addition and deletion of DNA material to be GMOs, and thus both require approval by the European Food Safety Authority.

Interference Decision

The Interference proceeding focused mainly on the question of whether taking The University of California's system and using it in a different cell type was obvious or not. It was admitted that The University of California's system was published and known before the filing of The Broad Institute's patent, thus constituting prior art. Thus, if the cell type jump was obvious, an interference proceeding would ensue, which would almost certainly have shown The University of California to be the first inventors of the system. But, if the cellular jump was non-obvious, a judgment of "no interference-in-fact" could be issued and the interference proceeding would not need to take place.

The University of California argued that their Patent Application discussed and encompassed both prokaryotic and eukaryotic cell types and that there was a reasonable expectation of success going from prokaryotic to eukaryotic cells. This reasonable expectation of success was based on: 1) Comparisons of this technology to similar technologies which worked in both cell types, 2) The fact that this system already had worked in various different non-native organisms or cell types, and 3) That multiple groups immediately tried and had success using this system in eukaryotic cells. Based on these reasonable expectations of success, The University of California argued that this cell type jump was obvious.

Conversely, The Broad Institute argued that the cell type jump was non-obvious by showing: 1) Comparative technology that failed in the jump from prokaryotic to eukaryotic cells, 2) Statements by The University of California's authors as well as other contemporaries which discuss the difficulty and unknown success of transferring the CRISPR/Cas9 system to eukaryotic cells, and 3) Pointing out the fact that The University of California did not show any data to demonstrate that it did work in these cells, but just stated that it potentially could, indicating that it was not as obvious or easy as they were claiming.

Ultimately, the PTAB sided with The Broad Institute and determined that The Broad Institute's Patent did not infringe upon The University of California's patent application as a person of ordinary skill in the art would not have had a reasonable expectation of success and thus the cell type jump was non-obvious. The Federal Circuit upheld the PTAB's decision, stating that they did not re-weigh evidence but only looked to see if there was sufficient evidence to support the PTAB's decision, which was affirmed.

Lessons Learned

While these decisions were a clear blow to The University of California patents and the companies based off of them, after the dust has settled and the money has been spent, what can be learned for future patents dealing with cutting edge technology like this one? Below are some key take-away points:

1. Know what you are patenting versus what you want to patent - The University of California's patent was designed to cover CRISPR technologies in all cell types, however, a large portion of the data in their specification and consequently their claims dealt with prokaryotic cells, thus limiting the enforceability of their patent on eukaryotic cells. Thus, when drafting a patent it is important that the inventors and their agents are on the same page as to what the invention currently does and what other embodiments the patent is designed to cover. In this case, if The University of California had tried to claim their system specifically for eukaryotic cells, there would likely have been a rejection due to inadequate description, as their specification did not show how to complete the CRISPR process in these cell types.

2. Know what is at stake - For both parties, the implications of this case initially seemed massive. If interference was found, The Broad Institute's patent would likely have been invalidated and they would be forced to pay royalties to The University of California for use of the CRISPR/Cas9 system. If interference was not found, the main monetary enterprises of this technology, disease prevenation and genetically modified plants, both of which are eukaryotic cells, would be solely in the hands of The Broad Institute. To make matters worse, it turned out that Vilnius University filed a Provisional Application weeks before The University of California's application, which has since issued into US Patent No. 9,637,739, and could potentially invalidate what is left of The University of California's patent. However, since the initial filing and subsequent proceedings, many groups, including both The Broad Institute and The University of California, have come up with new CRISPR systems which do not use Cas9 and are more selective, more efficient, and outside of the patent space of both of these patent classes. So while CRISPR/Cas9 was the first in this field, it certainly does not appear it will be the only or the best player, which leads to questions about the value of this litigation in the long run. These types of questions and analyses are important to consider in the midst of intensive patent litigations, keeping the end goal and the value of that end goal in mind.

3. Be careful what you say - Admissions by the inventors regarding the difficulty they experienced transferring this system from prokaryotes to eukaryotes was a large factor in the PTAB's decision to issue a "no-interference" ruling. For future cases, this can be an avenue for those looking for "no-interference" rulings, so be careful what things are said publicly and written down in terms of the applicability or scope of a potential invention, especially ones like CRISPR which have far reaching and lucrative possibilities.

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