Is the CRISPR Treat Worth Two Licenses?

By Adelaide Leitzel and Neal Roach

Rivalries between universities do not always play out on football fields or basketball courts. Off the field, research scientists from the University of California at Berkeley are battling against scientists from Broad Institute of Harvard and MIT, with a multi-billion dollar industry at stake. This CRISPR high stakes drama is being played under the United States Patent and Trademark Office (USPTO) rules of engagement. Just as competitive athletes know you have to play the officials, the patent attorneys in the fight over what is referred to as CRISPR technology are doing the same. In the first round it appears the Harvard/MIT team has the edge with the USPTO officials. Luckily for Berkeley, this competition is not one and done. In this article, we look at several questions about this fight: What is CRISPR technology and why is it important? What happened in round 1 and what's next? What does this fight mean for life sciences businesses?

CRISPR Technology

Living things make proteins and compounds from the instructions encoded in their DNA. If the instruction set is altered, the consequences can range from delightful to dire. For example, alterations in the gene encoding medium chain acyl dehydrogenase (MCAD), a protein involved in using medium chain fatty acids, can cause patients to experience extreme hypoglycemia and death. If it were possible to edit DNA, cells could make healthy products instead. In molecular biology's early days, tools to alter DNA were unwieldy and difficult. The tools lacked precision; altering DNA was more like using a bludgeon than a scalpel. The development of in vitro recombinant cloning techniques improved the tools, but researchers still relied on semi-random techniques to edit DNA. More recently, tools like Zinc-fingers and Talens allowed researchers to target certain DNA sequences. Unfortunately, designing Zinc-fingers and Talens for some DNA targets was considerably easier than for others. The discovery of clustered regularly interspersed short palindromic repeat (CRISPR) sequences made this task much simpler. Using a CRISPR sequence and an associated protein, Cas9, allows very specific DNA targeting. Like Zinc-finger and Talens systems, the CRISPR-Cas9 system utilizes the cell's own processes to repair and edit DNA. Unlike Zinc-finger and Talen systems that require designing DNA-specific protein components, the CRISPR-Cas9 system uses short pieces of RNA to target a DNA sequence. Sequence homology between the short RNA pieces and target DNA allows the short RNA pieces to bind near each other on a cell's DNA. The resulting RNA structure recruits Cas9; the Cas9 enzyme cuts DNA at the target site. The cell's machinery attempts to fix the DNA but the repair alters the DNA sequence at the target site. CRISPR's short RNAs allow precise DNA targeting and are easier to design than Zinc-fingers or Talen proteins.

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CRISPR is not the first molecular tool that edits DNA, but CRISPR's target specificity and price point have generated much publicity. There are now thousands of CRISPR-related publications. The most obvious applications of gene editing are in medicine, with the hope that CRISPR can lead to the treatment or eradication of many genetic diseases. CRISPR technology could also lead to breakthroughs in agriculture.

The Berkeley-Broad Dispute

To understand what happened in round one of the Berkeley-Broad Big Dance, we have to look back to 2012. As early as June 2012, Jennifer Doudna (UC Berkeley) and Emmanuelle Charpentier (Helmholtz Center for Infection Research) were discussing CRISPR-Cas9 systems engineered "to target and cleave any dsDNA sequence of interest."[1] Shortly thereafter other groups suggested similar findings "pave the way for development of unique molecular tools for RNA-directed DNA surgery."[2] Within a year, Harvard's Dr. Feng Zhang, later of the Broad Institute, published an improved version of the Cas9-cRNA system.[3] In the 2013 article, Zhang referred to the CRISPR-Cas9 system as "a robust and versatile tool**,"** citing, among others, Doudna's work.

While the academics were publishing, they were also filing patent applications. In May 2012, Doudna

1. Jinek *et al,* 2012. "A Programmable Dual-RNA-Guided DNA Endonucleas in Adaptive Bacterial Immunity" *Science* 337:816-821.

2. (Gasiunas *et al*, 2012. "Cas9-crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria," *PNAS* E2579-E2586).

3. Ran *et al* 2013. "Double Nicking by RNA-guided CRISPR Cas9 for Enhanced Genome Specificity," *Cell* 154(6):1380-1389.

et al filed a provisional patent application claiming a CRISPR-Cas9 system. Doudna and her group filed subsequent applications, including a provisional application in October 2012 that described the CRISPR-CAS9 system in eukaryotic cells. Eukaryotic cells are the advanced cell type found in mammals and plants; eukaryotic cells are of considerable market interest. In March 2013, the Berkeley group filed a nonprovisional application claiming priority to its provisional applications, shortly before a major rule change in the Patent Office. Under the new rules, patents are awarded to the first applicants to file a patent application for their invention rather than the first applicants to invent a technology. Additionally, the Berkeley group filed an international (PCT) application. The Berkeley applications claimed the CRISPR-Cas9 system for editing DNA. The Berkeley group's PCT application published in November 2013, and their U.S. application published on March 13, 2014.

Meanwhile, on the East Coast, Broad Institute filed a provisional application in December 2012 and additional provisional applications throughout 2013; Broad filed its first non-provisional application in December 2013. Broad's applications specifically required the CRISPR Cas9 system be used in eukaryotic cells. Broad's applications targeted commercially relevant aspects of the invention. Limiting the invention to eukaryotic cells carved a tunnel in Berkeley's existing claims through which Broad is driving a Mack truck. With a February 18, 2014 new continuation application Broad filed a request for prioritized examination. During patent prosecution Berkeley's international publication and underlying provisional applications were cited against the Broad application. Broad provided the Patent Office with evidence that after Berkeley's filing date, the Berkeley inventors made cautionary, self-deprecating comments about CRISPR technology. Broad argued the contemporaneous comments indicated the Berkeley inventors did not expect the CRISPR method to succeed in eukaryotic cells. Broad argued that although Berkeley claimed methods of editing DNA in any environment, Berkeley did not have a method of editing DNA in eukaryotic cells. Broad's prioritized applications were examined, and a patent issued to Broad on August 5, 2014; additional patents also issued to Broad from other prioritized applications.

Before examination began in the Berkeley application, a third-party submitted a list of references including a patent issued to a Broad inventor and a Notice of Allowance for a Broad application. Berkeley promptly began discussions with the Patent Office. Berkeley did not concur with the Patent Office. After all, the academic world was proclaiming Doudna's CRISPR Cas9 system breakthrough technology. Broad did not concur with the academic perspective, even asking the Patent Office to disregard the "media noise." An Interference proceeding was declared between the Berkeley applications and Broad's patents. Interference proceedings determine who was first to invent a claimed invention. Issued patents are presumed to be valid, so Broad's later filed, earlier issued patents gave Broad the edge. Rather than deciding if the Berkeley group had invented methods of editing DNA in eukaryotes before the Broad-Harvard team, the Patent Office's Board of Patent Appeals and Interferences studied Broad's issued claims and Berkeley's pending claims. The Board assessed whether Broad and Berkeley claimed the same invention. Broad's issued claims are limited to eukaryotic cell uses; Berkeley's broader claims are directed toward methods of editing DNA, without limit to cell type. In February, the Patent Office Board declared there was no interference because Broad's patents are limited to eukaryotic cells while Berkeley's claims encompass methods of editing DNA in any cell type. Both Broad and Berkeley claimed victory. Berkeley's lead inventor, Jennifer Doudna, announced the Patent Office Board's decision allows her applications to move forward and that companies wanting to use the CRISPR Cas9 method commercially would need a license from both Broad and Berkeley.

Will the Patent Office issue patents to Berkeley or will the Broad patents block the Berkeley applications? The Patent Office has declared the Berkeley applications claim a broad genus of inventions while the Broad applications focus on eukaryotes only. Although Berkeley did not limit the claims to eukaryotic cells, by March 2013 the Berkeley patent specification discussed the use of CRISPR Cas9 in "a eukaryotic cell, a eukaryotic single cell organism, a somatic cell, a germ cell, a stem cell, a plant cell" and even a "human cell." While some might suggest that is a fanciful laundry list of desirable cell types, the Berkeley application describes the use of CRISPR Cas9 in human cells and the use of the CRISPR interference system in mammalian cells. The Berkeley application teaches eukaryotic promoters, vectors for use in eukaryotic cells, additional eukaryotic specific instructions and extensive discussion of suitable eukaryotic cell types including animal and plant cells. Undisputedly, the Berkeley application claims the results of RNA programmed genome editing in human cells. The original non-provisional application claims methods of producing a genetically modified eukaryotic cell, and human cell use was described in the January 28, 2013 provisional application. The Berkeley application may contain enough examples to support the argument it enables the invention in all cell types.

Broad relied on the standard practice that U.S. patent applications are available as prior art as of the publication date rather than the earliest effective filing date to overcome Berkeley's application. However, un-

der the patent regulations' other sections, patent applications are available as prior art as of the earliest effective filing date. Broad has pending patent applications to which Broad's issued patents claim priority. Broad's pending patent applications claim methods of editing DNA without the eukaryotic use limitation. The Patent Office has cited Berkeley's patent applications against Broad's pending patent application using Berkeley's earliest effective filing date. Broad's vigorous efforts to distinguish its claims to methods of editing DNA in eukaryotes from Berkeley's claims to methods of editing DNA will make obtaining claims to unlimited DNA editing more difficult. Nonetheless, given Broad's skillful use of the Patent Office rules of engagement, Berkeley should not underestimate Broad's ability to block Berkeley and obtain further patent protection regardless of who was first to invent.

Business Implications of the Berkeley-Broad Battle

The high market potential for CRISPR licenses, the stunning irony of a competitor citing your work as "a robust tool" whilst claiming to have invented the commercially relevant aspects and Berkeley's overseas patent victories, make it unlikely that Berkeley will walk away from the dispute. Berkeley expects to obtain commercially relevant patent coverage. In fact, Berkeley asserts researchers will pay both Berkeley and Broad for CRISPR technology. If Berkeley expects companies to pay twice for the same technology, Berkeley's licensing arm needs to be top-notch.

Are Broad's licensing attorneys as good as their patent prosecutors? Will Berkeley's licensing attorneys be as unlucky as their patent prosecutors? Broad uses the AddGene Material Transfer Agreement for academic researchers. Broad also makes CRISPR materials available for non-human gene editing through non-exclusive licenses. It is likely Broad's non-exclusive licenses will be similar to AddGene's industry Material Transfer license agreement for transfers to for-profit researchers. However, Broad does not disclose costs. Broad has entered into an exclusive right of first refusal license agreement with Editas for treatment of human diseases. Companies that wish to use Broad's CRISPR systems to develop human disease treatments must first submit a development plan to Broad and Editas. If Editas is not pursuing or chooses not to pursue the target, the Broad Institute may consider a license agreement with the company. Doudna from Berkeley also deposits CRISPR plasmids with AddGene for non-commercial uses. Berkeley transferred its commercial use rights first to Caribou, a company founded by Doudna. Caribou has since sub-licensed commercial rights to Intellia Therapeutics.

Where this leaves parties seeking CRISPR licenses is currently in the air. Non-commercial licensing seems straightforward—an institution can license from either Broad or Berkeley, or both. If and when a commercial license is necessary, the potential licensee faces a quandary. Assuming Broad's initial win stands, a license from Broad (after jumping through Editas' hoops) will likely give licensees the rights they need. If Berkeley's appeal is successful or partially successful, a license from Berkeley or its sublicensees may be necessary. One company, MPEG LA, LLC, is attempting to form a patent pool that would permit Broad and Berkeley, and other entities that patent CRISPR-related technologies, to pool their technologies and create "one-stop shopping." This effort remains nascent; neither Broad nor Berkeley have signed on as of this writing. While "wait and see" often does not seem to be helpful advice, in this case it may be the best answer. ■

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