BIOCENTURY

POLITICS, POLICY & LAW | REPRINT FROM MAY 30, 2022

CRISPR's other patent interference

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CRISPR-based gene editing has been an IP battleground for the past decade, and the conflicts don't end at therapeutic applications in human cells. A quieter fight over inventorship has been brewing among the small group of companies editing bacterial cells for human therapeutics.

The fight for editing rights in bacterial cells involves a limited set of applications, a subset of the technology and a few biotech players, at least for now. However, the outcome could have broader implications for patent eligibility and how claims can be challenged.

SNIPR Biome ApS, Eligo Bioscience S.A.S. and Locus Biosciences Inc. are involved in a series of IP disputes, including an interference case reminiscent of the high-profile fight for eukaryotic CRISPR editing rights between the University of California and the Broad Institute of MIT and Harvard. The difference is that the newer disputes center on the set of therapeutic applications that fall outside the scope of the original eukaryotic IP — editing pathogenic bacteria and the bacteria that make up the human microbiome.

The original CRISPR patent conflicts, which are still being fought between the UC and the Broad, involve claims specific to the use of CRISPR-Cas9 gene editing in eukaryotic cells, including human cells, using a single guide RNA to direct the nucleases to a target site in the genome.

The majority of human therapeutic applications for CRISPR-Cas9 fall under those claims, but drug developers have identified an opportunity to expand beyond editing in human cells to indications that may be addressed by targeting bacteria instead.

"In 2015, we were actually working in the eukaryotic CRISPR space," said Jasper Clube and Christian Grøndahl, co-founders of SNIPR. "We realized there was a lot going on in the eukaryotic space, but IP-wise, not specific to prokaryotes."

IP that did exist at the time covering the use of CRISPR to kill bacteria was a patent application filed in 2013 by researchers at Rockefeller University and published in 2014. Rockefeller licensed the application to Eligo.

Though the Rockefeller patent was filed earlier than related IP filed by other parties, the examination was slower.

Clube and Grøndahl told BioCentury that SNIPR was the first company to get patents issued covering broad use of CRISPR gene editing tools in the microbiomes; the patents were filed before it was clear how exactly the company would use the IP.

Its early patents cover editing in any bacterial cells with any Cas enzyme for selective antibacterial applications.

The primary applications that have since emerged include microbiome modulation, where the gene editing tool can precisely tune microbiome colonization to change or eliminate disease-related strains. Another application is combating antimicrobial resistance by selectively targeting pathogenic bacterial strains while sparing the microbiome.

In both cases, a layer of antibacterial selectivity is added when the CRISPR machinery is delivered into the target cells by viruses called bacteriophages that naturally kill specific bacterial strains or species. SNIPR and Locus are delivering CRISPR with bacteriophages, while Eligo is using bacteriophage capsid-derived vectors dubbed phagemids that preserve the selective targeting of bacteriophages but do not replicate or kill the bacteria themselves.

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> XAVIER DUPORTET, ELIGO

SNIPR and Eligo are involved in an ongoing interference case in the U.S., the outcome of which should provide some clarity on inventorship and freedom to operate for companies working in the CRISPR microbiome space.

During the first round, the U.S. Patent Trials and Appeals Board (PTAB) determined that Rockefeller was first to invent, and invalidated five SNIPR patents. SNIPR is appealing the decision.

SNIPR's Clube, who is the company's chief intellectual property officer, believes the outcome of that case could have broader implications for the industry by better defining when an interference may be used.

There are also several smaller disputes between the three parties, including re-examination requests, that will help shape the IP landscape.

Interference timelines

The interference case evaluated overlapping claims from the Rockefeller patent application filed in 2013 and five SNIPR patents with filing dates beginning in 2015; however, SNIPR's claims were issued first.

The Rockefeller application covers bacterial editing with Type II CRISPR systems using phagemids. The SNIPR patents broadly cover bacterial editing with any CRISPR system and any delivery vehicle.

"Based on the application filed in 2013, the USPTO declared another interference, this time in the prokaryotic field," said Eligo co-founder and CEO Xavier Duportet.

The interference, which the USPTO declared in June 2020, set out to determine whether Rockefeller or SNIPR was first to invent gene editing of specific bacteria in a bacterial mixture using a CRISPR system that's delivered with a phagemid.

PTAB sided with Rockefeller and Eligo in November, recognizing its earlier priority, upholding its patent and invalidating the five SNIPR patents in a critical win for Eligo.

According to Duportet, one reason the Rockefeller University patents took more time to review is that "one of the main examiners was involved in the eukaryotic CRISPR cases, so granting patents in the CRISPR field got more complicated."

PTAB's decision, if it withstands the appeal, means Eligo's claims in the patent involved in the interference would be issued.

It also means that a patent application from the same Rockefeller patent family, with claims that were allowed but suspended pending the results of the interference, should be issued, according to Eligo. According to Duportet, those claims are broader, are not specific to Type II CRISPR systems, and also cover bacterial editing with other CRISPR systems including CRISPR-Cas3. Eligo would also be eligible to pursue additional subject matter involved in the interference.

SNIPR is appealing on the grounds that an interference shouldn't have been brought in the first place.

The purpose of an interference is to determine which party was first to invent a technology, but the PTO no longer allows claims on a first-to-invent basis. For patents filed after enactment of the America Invents Act (AIA) on March 15, 2013, claims are instead issued based on first-to-file rules.

The foundational eukaryotic CRISPR-Cas9 patents were filed pre-AIA and were subject to an interference procedure to determine first-to-invent status. The timing for the prokaryotic filings from SNIPR and Eligo is less clear.

Eligo's IP was filed just before the law changed, but SNIPR's was filed after. SNIPR is arguing that interferences were abandoned as a way of determining priority before the date of SNIPR's filings, but PTAB is so far not persuaded by the argument. In the initial decision, PTAB said, "[AIA] does not state that no interference could be declared after 16 March 2013."

"All our IP was filed under the new law. It was an erroneous decision that will read out by the end of the year," Clube

said. "Effectively, the USPTO decision has rolled us back. Everybody out there in the U.S. could be subject to the old law in interference."

He added that SNIPR doesn't believe Rockefeller showed enablement of the idea that it was possible to selectively edit bacteria in the microbiome using CRISPR.

SNIPR raised the issue in a motion that PTAB dismissed.

Technology breakdown

The impact of the interference case may extend beyond the claims in Rockefeller's patent, but the competing companies developing CRISPR bacteriophage therapies believe they will still have freedom to operate.

"If Rockefeller were to prevail in an appeal, the allowed claims set covers Cas9 and phagemids. They will get a patent granted that's limited to Cas9 phagemids, and that won't impact our development," said Grøndahl. "In a nutshell, we don't need Cas9 or phagemid, but we want to make sure we stand by our principle."

Locus CFO Joseph Nixon said Locus' technology does not fall under any of the claims involved in the interference. The company believes it has freedom to operate based on opinions from three law firms.

However, Duportet believes some aspects of Eligo's allowed and future claims cover competitors' products.

The technology more relevant to the competitive landscape is the Type I CRISPR-Cas3 system. All three companies are working with that technology.

Cas9 makes double-stranded DNA breaks at the target site, making it a good fit for editing applications in human cells, while Cas3 triggers indiscriminate DNA shredding once it engages its target site in both eukaryotic and prokaryotic cells to kill the target cell.

However, Duportet noted that Cas9 can also effectively kill bacterial cells. He said Eligo has shown that bacterial cells cannot effectively repair double-stranded DNA breaks induced by Cas9, which also leads to DNA shredding and cell death.

Each company is using the same basic technology, but they have their own variations and are targeting different indications. For example, Locus often hijacks the target bacteria's Cas enzyme, rather than delivering it through the bacteriophage, whereas SNIPR is delivering the entire CRISPR complex.

Locus was the first of the three companies to reach the clinic with a product using CRISPR gene editing to target bacteria. It has completed a Phase Ib study of LBP-EC01, a bacteriophage-based CRISPR-Cas3 therapy to treat urinary tract infections caused by E. coli. The company is also developing Cas3 bacteriophage therapies for other infections, and is engineering bacteriophages that target certain tissue-resident bacteria for delivery of therapeutic molecules. It's planning to start a Phase II/III study this year.

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SNIPR began a Phase I study of SNIPR001 to prevent E. coli bloodstream infections in hematological cancer patients. SNIPR001 is a bacteriophage-delivered CRISPR-Cas3 product.

Though both companies are targeting E. coli, Grøndahl said SNIPR isn't focusing on treating bacterial infections broadly at this time because "the business model there is quite challenging."

Instead, it's focusing on oncology and immunology, and addressing life-threatening multi-drug resistant infections in these vulnerable patients with SNIPR001. However, he noted that "10 years from now, people may really get it. There could even be a Moderna moment," when a technology such as CRISPR bacteriophages is needed to address an urgent unmet need.

Eligo has a series of preclinical programs in development, including topical CRISPR-based therapy EB005, which is partnered with GlaxoSmithKline plc (LSE:GSK; NYSE:GSK). Unlike its competitors, which use replicating bacteriophages to help kill the bacteria, Eligo's Eligobiotic platform relies on non-replicating phagemids derived from the bacteriophage capsid to deliver the CRISPR machinery.

The IP landscape for CRISPR editing in bacteria is much broader than the claims in the interference. Eligo has more than 25 patent families covering its technology and portfolio, Locus has more than 40 patents and patent applications across nine families broadly covering CRISPR-Cas3 systems with and without bacteriophages, plus other engineered bacteriophage compositions and methods, and SNIPR has had 20 U.S. patents issued.

The international IP landscape is different. Rockefeller's discoveries exist as prior art, but Rockefeller did not file European IP covering the discovery. SNIPR and Eligo are both pursuing IP in Europe.

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