Who Owns CRISPR IP?

The question of intellectual property hovers insistently over any conversation about democracy, for the obvious reason that those who own a technology have a strong hand in shaping its outcomes. The IP question is also, unfortunately, not so easy to answer, since numbers of patent applications and awards grow incessantly, since IP can be claimed on CRISPR-Cas components, applications, vectors, and delivery, among other elements, and since a vicious 7-year battle over foundational CRISPR IP remains unsettled.

Despite their discovery in the 1980s in E. Coli, CRISPR sequences remained somewhat mysterious until the early 2000s, when The CRISPR-Cas9 that Philip Horvath and Rodolphe Barrangou at Danisco (later acquired by DuPont) and colleagues discovered in yogurt bacteria that CRISPRs were related to infection by viruses and subsequent immune defense (Barrangou et al., 2007). DuPont filed a number of patents on this technique, placing Danisco as one of the earliest CRISPR patent holders in the early CRISPR research history — yet for yogurt culturing, rather than genome editing (IPStudies, 2018).

IP rights on the genome editing tool came into the picture in 2012. At that time, two apparently independent discoveries kicked off a dispute that NYU patent expert Jacob Sherkow (2015) has called a "monumental event" in generating core CRISPR IP.

Two principal research groups say the insight to use CRISPR-Cas9 in higher organisms was theirs first. One team was led by Doudna of the University of California and Emmanuelle Charpentier of Vienna University who filed a patent application in May 2012 outlining how CRISPR-Cas9 could be used to precisely cut isolated DNA in any organism. The other team, led by Feng Zhang of the Harvard/MIT Broad Institute filed its first patent application in December, showing how the CRISPR-Cas9 system could be adapted to specifically edit DNA in eukaryotic cells such as plants, livestock, and humans. The Broad team also expedited their request, and because the

US Patent Office had not yet switched to a "first-to-file" system (which occurred later in 2013), the first CRISPR patent was granted to the Broad Institute in 2014 (Sherkow, 2015; Ledford, 2016).[1]

To contest this decision, the UC filed what is known as an "interference claim." Its lawyers argued that the Broad's application for use in eukaryotes was a subset of the UC's wider claim — and therefore "interferes" with the UC's patent. For the next three years, a vicious contest between the universities ensued, with patent amendments, decisions appeals, and lawyers on both sides fighting for IP rights anticipated to be worth billions. In February 2017, a ruling by the Patent Trial and Appeal Board of the US Patent Office put a temporary halt on the legal merry-go-round: the use of CRISPR-Cas9 in eukaryotes, it said, is "separately patentable" from the use of CRISPR-Cas9 in all cells (*Nat. Biot., 2017*; Han, 2017; Sanders, 2017). Although the UC appealed that decision, asserting that the Patent Board's ruling was based on several errors, in 2018, the US Court of Appeals found no evidence that the Patent Board had mishandled or misanalyzed the case, and affirmed the judgement of "no interference-in-fact" (Cross, 2018).

Hailed as a win for Broad, this decision meant that the Broad's eukaryotic patent would stand as a separately patentable invention from the UC's claims (which were still pending). But by early 2019, the tide had turned again to potentially favor the UC. In April, the US Patent Office finally approved patent No. 10,266,850, the UC's foundational patent from 2012 involved in the interference (Sanders, 2019a). Though significant for its starring role in contested IP, this patent was by this time part of a suite of key CRISPR-Cas9 patents that the UC had applied for and were starting to trickle in.[2] By July 2019, the UC had been granted a total of 10 patents from the USPTO,

[1] Another key factor that led to Broad's award, according to Colorado State University professor Greg Graff, was their method of patent application. Unlike the UC, which filed a very long patent including more than 120 claims, Broad broke up its initial requests into several shorter patents, "like chapters in a book." Because of the way that the USPTO reviews and requests revisions on patent applications, the latter approach is more expeditious.

[2] The first CRISPR patent issued to UC Berkeley (U.S. 10,000,772) was awarded on June 9, 2018, and the ninth and tenth (U.S. 10,358,658 & 10,358,659) on July 23, 2019. In terms of scope, several of these patents cover specific components or uses. For example, the fifth patent (U.S. 10,301,651) addresses techniques that enable sequence-specific repression or activation of gene expression in all types of cells. Collectively, the UC's 8 patents as of July 2019 cover compositions and methods that allow for targeting

with 5 more expected in coming months (Sanders, 2019b). Patents for the wide use of CRISPR-Cas9 in all cell types had also already been issued to the UC team by the European Patent Office (representing more than 30 countries) as well as by China, the UK, Japan, Australia, New Zealand, and Mexico.

Back in 2016, when the CRISPR patent wars were still fairly new, Sherkow told NPR radio that such struggles are to be expected. CRISPR, he said, is "arguably the biggest biotechnology breakthrough in the past 30 to 40 years and controlling who owns the foundational intellectual property behind that is pretty important" (Harris, 2016). Yet not even Sherkow probably anticipated the knock-down-drag-out fight it has turned out to be.[3] In June, 2019, in a move that surprised many, the US Patent Board opened a *new* interference case, this time declaring interference between 10 existing US patent applications and multiple previously issued Broad Institute patents. The current action jeopardizes 13 of the Broad's 15 CRISPR-Cas9 US patents and one application[4] and signals that the USPTO will again crack open the issue of who first invented CRISPR-Cas genome editing in eukaryotic cells. In a press statement, Eldora L. Ellison, lead patent strategist on CRISPR matters for UC and a director at Sterne, Kessler, Goldstein & Fox said, "We are confident that the USPTO will ultimately recognize that the Doudna and Charpentier team hold the priority of invention specific to eukaryotic cells, as well as other settings covered by previous patents" (UC Public Affairs, 2019; GenomeWeb, 2019).[5]

and editing genes in any setting, including within plant, animal, and human cells, as well as modulating transcription.

[3] In 2018, when the US Court of Appeals gave its ruling, Sherkow told *C&EN*: "This is almost certainly the end of this particular patent dispute" (Cross, 2018).

[4] The Broad Institute holds a total of 29 key CRISPR-Cas9 patents in the United States and Europe (Broad, 2019).

[5] Adding yet more drama to the fight over foundational IP, on July 19, 2019, MilliporeSigma, one of the world's largest life science companies, petitioned the USPTO to open an interference proceeding over CRISPR-Cas9 patents the company applied for in 2012 and patents that UC has applied for or received (Begley, 2019).

This contest over core IP notwithstanding, researchers at universities and companies worldwide continue to apply for CRISPR patents. Dow and DuPont, prior to their merger, were already leading industry CRISPR IP holders (Egelie et al., 2016), and this dominance continues today under the helm of Corteva Agriscience, which became a major license holder of foundational CRISPR-Cas IP when DowDuPont split into three separate companies in 2019 (Corteva, 2019; Kerr, 2019).[6] According to statistics kept by the Broad Institute, the USPTO has issued more than 80 patents with claims to CRISPR and/or Cas9 to more than 300 inventors from nearly 60 applicant organizations (Broad, 2019). Using different metrics, IPStudies, a company that offers independent IP studies and analytics, counts some 3,800 CRISPR patent families in 2019, up from 90 in 2014. "With now nearly 200 patent families published every month, we see a burst in CRISPR application patents, in particular from China, in all fields ranging from agriculture to therapeutics" (IPStudies, 2019). While some of these applications "follow on" from foundational patents, others are carving out new foundational territories with novel compositions and methods. For example, scientists are developing new CRISPR systems that do not use Cas9 at all but instead rely on miniature Cas variants like Cas12, Cas 13, Cas14, and CasX (eg. Liu et al., 2019).

Licensing democracy?

The burgeoning geographic, technical, and sectoral complexity of CRISPR development adds to the challenge of answering 'who owns CRISPR?' But the more significant factor in configuring ownership and use rights is the licensing landscape (see Allen and Overy, 2017). In 2011, the UC granted an exclusive CRISPR-Cas9 license to Caribou Biosciences, Doudna's own spinoff firm (Egelie et al., 2016). In 2015, Caribou announced a cross-licensing arrangement with DuPont. As

[6] The formation of DowDuPont in 2017 had represented a major consolidation of IPR in agricultural gene editing applications, as it brought together Dow AgroSciences, with claims to uses of CRISPR-Cas in crop and weed genomes, and DuPont, which had its own patents in agricultural CRISPR alongside IP rights garnered through exclusive licensing with Caribou/UC. With the spinning off from DowDuPont, Corteva now controls key CRISPR-Cas IP rights, including the power to grant licenses and enter into joint ventures.

part of this "strategic alliance," DuPont received exclusive IP rights for CRISPR-Cas9 use in row crops and non-exclusive rights in other agricultural and industrial applications (Caribou, 2015). On the Harvard/MIT side, the first major moves were in medicine, but by September 2016, it made its first move into agriculture with Monsanto licensing non-exclusive global rights for CRISPR-Cas9 use in seed development (Begley, 2016).

In general, while the UC and Caribou have taken the approach of exclusively licensing the IP under their control to DuPont (now Corteva Agriscience), the Broad Institute has been more catholic, providing an array of non-exclusive licenses to Monsanto, BASF, Syngenta, and other corporations. This approach, Broad suggests, is more democratic than exclusive licenses:

> When licensing IP to industry, non-profit institutions should, in general, favor non-exclusive licenses over exclusive licenses. In general, non-exclusive licenses maximize innovation by enabling creativity and competition among many parties (Rozen, 2016).

Both universities justify their IP activities as serving "in the public interest," as envisioned by the 1980 Bayh-Dole Act. With the passage of Bayh-Dole, Congress fundamentally shifted the incentive structure governing research and development by allowing publicly funded institutions to own inventions resulting from federally sponsored research, and to license those inventions to the private sector (Boettiger and Bennett, 2006). Some celebrate Bayh-Dole as a uniform framework critical for the successful transfer of technology from university to industry, and a catalyst for economic growth. This perspective is clearly seen in the Broad's framing of its CRISPR licensing approach:

> Congress's purpose was clear: It felt the American public would be better served by such a system, because grantee institutions would be more knowledgeable and more vigorous in ensuring that the IP was licensed to industry to benefit consumers—including patients.

Critics, however, argue that Bayh-Dole has had seriously deleterious effects on the nature of public interest research in the US. By enabling universities to route tax-payer funded innovations to the private sector, they suggest, Bayh-Dole sanctioned what amounts to a public subsidy to agribusiness. More subtly, the incentive structure enabled corporations to begin exerting significant backwards pressure on the R&D pipeline: what was valuable to commodify began to discipline the scope of research that universities undertook — including which crops, traits, and farming systems were important, and which could be ignored (Eisenberg, 1996; Kloppenburg, 2004; Glenna et al., 2007).

While the legacy of Bayh-Dole remains contested (Boettiger and Bennett, 2006), less controversial is the legal framework it provides for the flow of CRISPR IP: The main university patent holders have established a now-familiar pattern for licensing CRISPR to downstream developers. First in the chain are the universities and individual researchers with foundational patent rights (eg. Broad, UC, Vienna University, Emmanuelle Charpentier, Vilnius University). Next are so-called "surrogate companies" like Caribou Biosciences and ERS Genomics to which the main CRISPR patent owners have granted exclusive rights to seek further investments and licensing opportunities (Contreras and Sherkow, 2017). Finally, there are commercial developers, large and small, who have acquired CRISPR rights for a variety of agricultural applications. Terms of these licenses contain "a huge diversity of possibilities," says Greg Graff, a professor at the University of Colorado, Boulder who studies CRISPR IP. Some of the contracts are specific to microbial uses, for example. Others are specific to crops types, such as DuPont's exclusive license from Caribou for developing row crops.

In 2016, Graff, alongside lead author Knut Egelie and colleagues, published one of the most comprehensive CRISPR IP surveys to date. They found that through their licensing, spin-offs, and commercial partners, the two main academic institutions of UC Berkeley and Broad largely control medical applications of CRISPR-Cas9. By contrast, "larger industry players, with Dow and DuPont at the forefront, already appear to be more in control of the technology's agricultural and food applications" (Egelie et al., 2016; 1028). Others could soon catch up. One to watch is Monsanto/Bayer AG, which in 2018 announced it would invest $100 million over the next five years in a new biotech startup called Pairwise[7] — partly to develop basic CRISPR science and partly to use gene editing "to alter commodity crops, including corn, soy, wheat, cotton and canola, exclusively for Monsanto" (Polansek, 2018). The deal allows Monsanto/Bayer AG to commercialize products from the partnership.

In 2017, just before the Pairwise launch, a major agreement between DuPont Pioneer and Broad — two previously separated halves of the IP camp — were joined. Under the terms of this joint licensing framework, both parties agreed to provide non-exclusive licenses to IP under their control for use in commercial agricultural research and product development. Core CRISPR technology will also be freely available to universities and nonprofit organizations for academic research. On the Broad side, this includes a large collection of CRISPR-Cas9 IP controlled by Broad and its collaborators (including Harvard University, MIT, New York Genome Center, New York University, The Rockefeller University, and the University of Iowa). On the DuPont Pioneer side, it includes a set of exclusive rights for use in agriculture that the company received from Caribou Biosciences (which had obtained them from the UC and the University of Vienna). DuPont Pioneer had also separately licensed rights from Vilnius University in Lithuania, whose IP overlaps with

[7] Among Pairwise's founders is David Liu, a Harvard University professor who pioneered a new form of gene editing called "base editing" which is now widely recognized as part of the next-generation CRISPR toolkit. Liu's involvement with Pairwise also illustrates the porosity of public and private sectors in the CRISPR research and development landscape.

that of UC Berkeley. The company, now Corteva, additionally has its own patents and patent applications (Rozen, 2017).

The companies' and universities' intentions are clear with this approach to licensing CRISPR-Cas9 technology. "The goal," Broad's Chief Business Officer Izzi Rozen wrote in a statement, "is to ensure that scientists in both academia and industry will be able to use CRISPR-Cas9 technology to explore new ways to lift crop yields, improve drought resistance, and reduce reliance on pesticides" (Rozen, 2017). Neal Gutterson, vice president of Research & Development at DuPont Pioneer, called the IP strategy one that puts "the promise of CRISPR-Cas9 technology in the hands of many" (Cameron, 2017). Headlines on the day the framework was announced were even clearer: "*DuPont Pioneer and Broad Institute Join Forces to Enable Democratic CRISPR Licensing in Agriculture*" (ibid).

Democracy is certainly one way to see it. Another perspective suggests that emerging CRISPR patent and licensing landscapes are hewing to familiar patterns of the past 50 years: motivated by IP acquisitions, 30 separate agrochemical firms in the 1970s became six by 2001 (Moretti, 2006), which became just four by 2018 (IPES-Food, 2017). Estimates from 2018 indicate that the top four — Monsanto/Bayer, DowDupont (now Corteva Agriscience), Syngenta-ChemChina, and BASF — controlled 60% of global proprietary seed sales (Howard, 2018). Domination of seed patents in the US has long been even higher, with the (then) top three companies owning 85% of corn patents and 69.6% of non-corn patents (Glenna and Cahoy, 2009; Howard, 2015).

It is certainly possibly that CRISPR will defy these trends, with the aforementioned provisions that make CRISPR freely available to universities and non-profits for academic research. It is also possible that industry consolidation continues despite, or even because of, a boom of 'free' gene-editing in the academic sector. In the context of almost 50 years of US Supreme Court decisions allowing patenting on novel organisms and Congressional Acts enabling public universities to acquire proprietary rights that can be monetized in the private sector, large firms

today can comfortably invest in university research "with the understanding that research results would have patent protection" (Glenna et al. 2007). Having long ago carved out a division of labor between basic university science and industry applications (Kloppenburg 2004), firms have little difficulty transforming licensed technologies into their own patented products, deriving value and power from assuming control over the shape of the commodity form. It is difficult to fathom how CRISPR, powerful as it may be, might help to knock out these structural lock-ins. Who would do it and how?