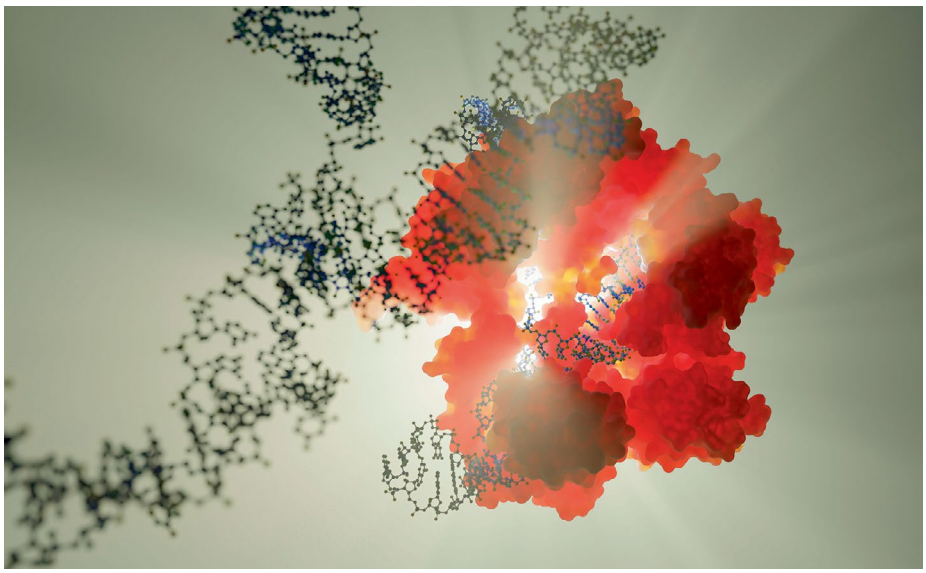
Prime editing deal flurry to nail down patent rights

The prime editing field is booming, with companies making strategic decisions to avoid an IP showdown.

By Carrie Arnold



The Cas9 system, shown here, is good at wiping out a defective gene, but for therapeutics, a system that inserts the correct gene is a better option.

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Tome Biosciences came out of stealth mode on 12 December with a haul of over $200 million to develop the company's gene editing platform. Tome's first order of business was to snap up Replace Therapeutics to expand its toolkit to one equipped to make gene edits in DNA sequences big and small.

Tome's own genomic technology, mediated by an integrase, is well suited to large DNA up to tens of thousands of kilobases long. Replace's CRISPR–Cas9 ligase-mediated platform, by contrast, is adept at inserting and deleting small DNA sequences of 10–100 base pairs. Having both of these technologies in its pocket, says Tome CEO Rahul Kakkar, means that the company can potentially replace an entire gene with a wild-type version rather than correct a defective version, and without requiring double-stranded breaks in DNA.

The merger, worth $65 million up front and potentially up to $185 million total for Replace, is one of the largest acquisitions in the booming prime editing field. Although Kakkar says that the acquisition was driven not by patent coverage but to expand Tome's gene editing toolkit, such proactive steps to ensure a company is on solid footing with intellectual property (IP) rights before diving deeper into drug development would not be misplaced, says University of Illinois biotech patent attorney Jacob Sherkow.

IP supremacy battles tend to be drawn out. The patent dispute over the original CRISPR–Cas9 technology between the Broad Institute and the University of California, for example, dates back to 2012 and has yet to be fully resolved. For next-generation genome editing technologies, potential patent skirmishes around base and prime editing are also likely, says Sherkow.

For treating genetic diseases, systems that target and correct — rather than destroy — are likely to prevail. Traditional CRISPR–Cas9, although precise, is limited because it must make double-stranded cuts in the DNA to execute a repair. Also concerning are the off-target effects — greater than 50%, by some estimates — as well as CRISPR's way of destroying DNA rather than fixing it. "It's a key limitation that prevents it from being a platform from which we can actually start making disease therapies for broad populations," says Kakkar.

A base editing tool discovered by scientists in David Liu's lab at the Broad Institute made the first inroads towards correcting genes. It goes about changing individual DNA bases, from C to T or A to G. The method relies on the original Cas9 guides, used to target the changes to the correct spot, fused to a nickase version of Cas9 enzyme that makes only single-stranded DNA breaks.

Prime editing, first published in 2019, fuses a catalytically inactive Cas9 endonuclease with an engineered reverse transcriptase and a guide RNA that encodes both the genome target and the intended edit. Both base and prime editing are being developed for use as therapeutics by a number of biotech companies. Despite the widespread use of these gene editing tools, scientists and industry are pursuing alternatives that will not infringe existing patents. Companies like Tessera Therapeutics hold that their platforms, which are based on retrotransposon machinery instead of adaptations of CRISPR–Cas, do not run afoul of Prime Medicine's patents; some of Liu's lab members allegedly noted the potential overlap in other interviews. Subsequent prime editing patents filed by Liu and included in the package of technologies licensed by Prime Medicine include a nickase.

Freedom to operate can come at a hefty price. Vertex Pharmaceuticals had to pay Editas Medicine $100 million in licensing fees for a non-exclusive license of their CRISPR technology used in a recently approved sickle cell treatment. Access to patented technologies is a major driving force behind the mergers, acquisitions and partnerships in the gene writing and editing world, according to Sherkow.

"It is an absolute gobsmacking sum of money. And that is something that is worth thinking about as to whether or not that is a lesson for others in the field": whether they should postpone dealmaking and licensing to so late in the process, he says.

Jonathan Gootenberg and Omar Abudayyeh were both PhD students in Feng Zheng's lab at the Broad Institute during those heady days,

and the pair took it upon themselves to create a gene editing system that could insert large DNA sequences of tens of thousands of kilobases. The pair worked to combine a Cas9 nickase to make single-stranded DNA cut with a programmable serine integrase and reverse transcriptase, which they dubbed PASTE (programmable addition via site-specific targeting elements) that was published in November 2022 in *Nature Biotechnology*. The PASTE patent was awarded jointly to MIT, Abudayyeh and Gootenberg in February 2023; they subsequently licensed it to their own startup, Tome Therapeutics.

To Gootenberg, PASTE overcomes some of the major limitations inherent in both CRISPR 1.0 and prime editing because these methods can only develop a single therapeutic to address a single mutation, when many genetic diseases, such as cystic fibrosis, involve a variety of mutations. Tackling each individual mutation with CRISPR–Cas9 or prime editing would be prohibitive in both cost and time.

"A lot of people are left with no solution when you're playing a correction game," Gootenberg says. "With PASTE, it doesn't matter what mutation somebody has. It's a single drug that's applicable to anyone with that disease."

Gootenberg and Abudayyeh both say that PASTE is conceptually and technologically different from prime editing, calling it a "method for programmable gene insertion." The PASTE system also uses an integrase as well as a reverse transcriptase. Liu is less convinced. "It seems reasonable to assume that if other parties were to commercialize a technology that uses prime editing, they may need a license to prime editing patents," Liu wrote in an email.

Liu shares similar concerns about Tessera's retrotransposon-based gene editing system. The lack of peer-reviewed publications from Tessera makes it impossible to judge the precise details of their methods, but the process — described by the company as writing therapeutic messages into the genome — is a non-viral technology that uses mobile genetic elements to make targeted genetic changes without double-stranded breaks. It uses a guide RNA to steer the gene-writing protein machinery to the desired DNA sequence. A nickase makes a single-stranded cut and a reverse transcriptase inserts the desired sequence from the provided template. Tessera was founded by Flagship Pioneering and received $300 million in 2022 from a broad investor syndicate. A Tessera spokesperson declined to comment for this article.

Sherkow, an expert on CRISPR patents, says that an invention is considered patentable if it meets three criteria: novelty, utility and non-obviousness. Teams from Tome and Prime have already received patents, thus potentially fulfilling all three criteria. Other genome editing technologies will likely be able to demonstrate the first two with minimal difficulty, Sherkow says. It's the last criterion that is likely to prove a sticking point, he says. Non-obviousness "is the most tortured of all the patent doctrines out there," he says, because applicants must show that the improvements to existing inventions were not trivial or obvious to an average user. Whether Tome and Tessera's work will be considered non-obvious next to prime editing in a potential legal challenge "is the $64 million question," says Sherkow.

The claims approved in Liu's 2019 patent for prime editing cover "a method for site-specific modification of a double-stranded target DNA sequence" involving a programmable DNA binding protein such as Cas9 fused to a reverse transcriptase or other polymerase and a prime-editing guide RNA. Because Liu was first to the finish line in this area, he was able to carve out large indications for prime and base editing. Improvements or additions to prime editing that meet the novelty, utility and non-obviousness criteria will almost certainly make narrower, more specific claims, Sherkow says, which narrows the conditions under which users of that technology would need to pay licensing fees. This means that while users of prime editing will need a license from Prime Medicine, users of Tome's or Tessera's platforms may need licenses from both Prime Medicine and Tome or Tessera.

Tome's Kakkar notes that issues of licensing do not become an issue until a company goes to sell a drug. Researchers can (and do) use these technologies without paying any fees, as long as nothing is being sold. That's why Vertex didn't complete a licensing agreement with Editas Medicine and the Broad Institute until after their sickle cell gene therapy was approved in December 2023 — and perhaps why the fees were so steep, according to Daniel de Boer, founder and CEO of ProQR Therapeutics, an RNA editing technology company.

"From a strategic perspective, patents are really important and potentially driving [these] partnerships," says de Boer, pointing to ProQR's June 2023 non-exclusive license agreement with Eli Lilly and a January 2024 partnership with the Rett Syndrome Research Trust as examples. Both endeavors will utilize ProQR's Axiomer platform, which uses synthetic RNA oligonucleotides designed to harnesses the human cell's copies of adenosine

News in brief

First gene-edited pig kidney transplant

Surgeons at Massachusetts General Hospital have transplanted a pig kidney into a living person for the first time. On 16 March, a 62-year old man with end-stage kidney disease received a kidney from a genome-edited pig developed by eGenesis. The humanized pig organ was taken from a genetically engineered Yucatan miniature pig carrying a total of 69 gene edits designed to increase compatibility between the pig graft and its human recipient. The changes in the genome were of three types: knockouts of three genes involved in glycan antigen synthesis to avoid acute rejection; inserts of seven human transgenes involved in pathways that regulate immunity, coagulation and complement; and inactivation of porcine endogenous retroviruses to avoid their transmission and integration into the recipient.

Xenotransplants — ones from animal to human — have long been considered as a potential solution to the chronic shortage of organs for transplantation, but progress has been slow, with only a few successful examples of xenotransplants surviving for a few months in nonhuman primates. In recent years, the first person to receive a genetically edited pig heart from the company Revivicor, a subsidiary of United Therapeutics, lived for two months; a second transplant recipient lived for six weeks. Revivicor introduced 10 genetic modifications in the pigs to ensure the organs do not grow too big, to avoid blood clots, and to limit rejection.

The go-ahead for eGenesis's pig kidney transplant came from the US Food and Drug Administration 'Expanded Access' program. At the time *Nature Biotechnology* went press, the organ recipient was recovering well, the kidney was filtering and there was no sign of rejection. Long-term follow up will define whether gene-editing tools have ushered in the possibility of using pigs as human organ donors. eGenesis is also co-developing human-compatible porcine livers as an ex vivo perfusion system to support patients with liver failure. The porcine livers carry the same three types of genetic modification as the porcine kidneys.

deaminase RNA specific (ADAR) to transform an A to a G. This type of up-front arrangement benefits both parties since pharma will have guaranteed access to technology at a lower cost and the developers can get earlier payouts, de Boer says.

Partnerships and deal-making abound in other gene editing biotechs, too. Arbor Biotechnologies has identified a suite of nucleases of different sizes and containing different protospacer-adjacent motifs (PAMs) that the company can use to perform a range of gene editing tasks. By combining several different PAMs, CEO Devyn Smith says Arbor can reduce off-target effects. "We let evolution do the initial work and then we'll take it from there to make it a therapeutic," says Smith. He says that some of the nucleases Arbor has discovered for its next-generation gene editors have only a 1–2% homology to Cas9. This uniqueness means that, although Smith is watching the outcomes closely, he remains confident in the validity of his own patents. And in January 2024, Arbor teamed up with 4D Molecular Therapeutics to co-develop and co-commercialize gene editing therapies for amyotrophic lateral sclerosis, a motor neuron disease.

To avoid patent infringement, companies scour the microbial kingdom for RNA-guided nucleases and nickases. Research Triangle Park's Life Edit Therapeutics, spun off from AgBiome and now wholly owned by Elevate-Bio, has done just that. Life Edit's co-founders Clare Murray and Tedd Elich acknowledge Liu's original work on both base and prime editing, but say they are confident their discoveries do not run afoul of his patents, citing two nuclease patents they have already been granted, with several more pending. "Obviously we're very aware of existing IP out there, and our nucleases are evolutionarily distinct from the foundational patents," says Elich. "Our nucleases are orthogonal to each other as well as to the other nucleases out there, meaning they don't share a guide sequence, for example."

This distinctiveness is powerful not just from the patent law aspects, Murray says, but also in their ability to perform a wide range of gene editing. In February and May of 2023, Life Edit signed deals with Moderna and Novo Nordisk, respectively. Whether another patent showdown is imminent remains to be seen, Sherkow says. "It's a really exciting time in the field with all the technologies, and I think there's a lot of therapies that are going to be able to treat patients," says Abudayyeh.

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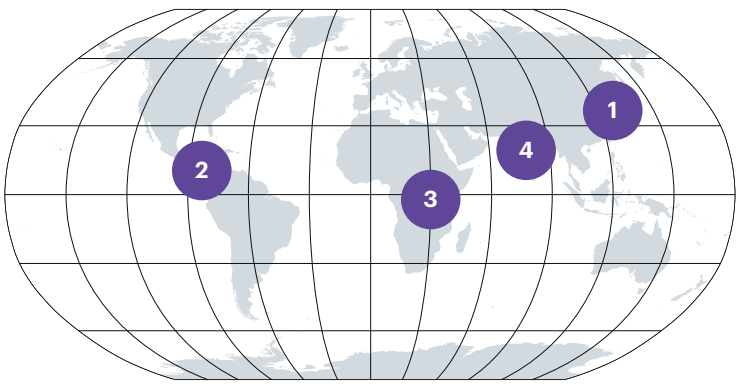
Biotech news from around the world

1. SOUTH KOREA
The Ministry of Health and Welfare selects Johnson & Johnson's JLABS to operate the country's global accelerator platform. JLABS will engage with various local incubators and collaborators in the startup ecosystem to offer venture development programs, stimulate employment and encourage commercialization to enhance the global competitiveness of Korea's life sciences sector.

2. COSTA RICA
Costa Rica revises its biotech regulatory framework to ease restrictions on gene editing and other new breeding techniques. Experts say a banana variety resistant to yield-reducing fungal diseases sigatoka and *Fusarium* wilt could be the first genome-edited product commercialized in Costa Rica later this year.

3. RWANDA
Rwanda partners with CEPI, Ginkgo Bioworks, BioNTech and IQVIA to create a 'disease intelligence system' for monitoring biological threats. If a novel pathogen is detected on arriving international flights from the analysis of wastewater or nasal swab samples, the end-to-end biosecurity infrastructure aims to deliver a vaccine within 100 days, an effort aligned with CEPI's 100 Day Mission, a global effort embraced by the G7 and G20.



4. INDIA
The first human clinical trial of a gene therapy for hemophilia A (FVIII deficiency) begins in Vellore, India. The treatment uses a lentiviral vector to express a *FVIII* transgene in the patient's own hematopoietic stem cells, which, once differentiated, will produce FVIII, is supported by the government's Department of Biotechnology, Bangalore-based Institute for Stem Cell Science and Regenerative Medicine, Emory University and Christian Medical College, Vellore.