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To this point, the technology known as CRISPR-Cas9 has been a science project, a research tool with enormous potential—and significant questions to answer—on which venture capitalists have placed bets by forming a group of startups. The jackpot: CRISPR-Cas9, a method of performing precise genetic surgery, might yield treatments for a wide array of previously intractable diseases.

We're still a long way from anybody claiming that prize, though; no CRISPR-Cas9 therapy has ever been tested in a human being, and a whole lot could go wrong when that happens. Emerging technologies, after all, go through their ups and downs. But today some of the biggest names on Wall Street and elsewhere are showing that they like the odds by handing the largest round of funding yet to a CRISPR-Cas9 startup.

Cambridge-based Editas Medicine is announcing a $120 million Series B round led by Bill Gates's chief advisor for science and technology, Boris Nikolic. The list of financiers teaming with Nikolic reads like a rolodex of so-called crossover investors, who invest in both public and private entities, and corporate venture arms. Among them: Deerfield Management, Viking Global Investors, Fidelity Management & Research, T. Rowe Price Associates, Google Ventures, Jennison Associates, Khosla Ventures, EcoR1 Capital, Casdin Capital, Omega Funds, Cowen Private Investments, and Alexandria Venture Investments. Editas' founding VC backers—Flagship Ventures, Polaris Partners, and Third Rock Ventures—also pitched in, as did Partners Innovation Fund.

Nikolic, who is joining Editas' board, made the investment through what's been called "bng0," a new U.S.-based investment company backed by "large family offices with a global presence and long-term investment horizon" and formed specifically to invest in Editas. CEO Katrine Bosley confirmed that Gates is one of the individuals investing in Editas alongside Nikolic.

To be clear, while this is a significant round, it's not even close to the largest financing round for a biotech startup. During the latest boom, we've seen messenger RNA drug developer Moderna Therapeutics haul in a record $450 million. And the now-public cancer immunotherapy company Juno Therapeutics (NASDAQ: JUNO)—which Editas recently partnered with—got $310 million last year before taking itself public.

But the round is still the largest financial investment made yet in a CRISPR-Cas9 startup, adding to the quickly gathering momentum of the field's fledgling companies. Intellia Therapeutics and CRISPR Therapeutics (both of which have operations in Cambridge) were both formed after Editas, and both

have made strides as well: Intellia raised a $15 million Series A last year and then cut a broad collaboration with Novartis in January. CRISPR hauled in $64 million in April in a round that was led by Celgene (NASDAQ: CELG) and the venture arm of GlaxoSmithKline. Caribou Biosciences of Berkeley, CA, too, is part of the fray, having recently raised an $11 million Series A of its own.

Editas has become the first of the group not only to attract crossover backers, but to begin discussing the diseases that its targeting. Its first program, Bosley says, is a potential treatment for a form of leber congenital amaurosis (LCA), a genetically driven blindness. It's a different form of the LCA than the gene therapy company Spark Therapeutics (NASDAQ: ONCE) is targeting; Bosley says the one Editas is going after can't be solved by gene therapy.

Beyond that, and Editas's ongoing immuno-oncology work with Juno, Editas has done some very early work in Duchenne muscular dystrophy and is exploring ways to repair a mutant hemoglobin gene—something that could have an impact in a range of bleeding disorders. That doesn't mean this is where Editas will ultimately focus—Bosley notes, for instance, that there are big technical challenges of producing an effective CRISPR-Cas9 therapy for Duchenne—but it's a glimpse into the company's thinking.

Bosley won't estimate how long it'll be before the first Editas therapy begins human testing, noting that the company is in the midst of preclinical work, testing its technology in patient cells. "We have a little bit more work to do before we can really be explicit about a specific timeline," she says.

Does that mean a few years? "I don't think it'll take that long," she says. "We'll move sooner than that if we have a construct that's good enough."

For those new to the story, CRISPR-Cas9 is a two-part system derived from a defense mechanism that bacteria use to fend off viruses. Think of it as a pair of molecular scissors (an enzyme called CRISPR-associated protein 9, or Cas9) being carried into a cell's nucleus by a strand of RNA that serves as a guide (clustered, regularly interspaced short palindromic repeats, aka CRISPR). Once there, the scissors may be able to snip out a defective gene, and perhaps replace it with a new, functioning one. In the case of Editas's LCA program, for instance, Bosley says the company aims to make two specific cuts in two different DNA sites to eliminate the genetic mutation causing the disease.

This isn't the first gene editing technique to emerge; Sangamo Biosciences (NASDAQ: SGMO) and its zinc finger nuclease platform have the most advanced gene editing candidate, a potential therapy for HIV in Phase 2 testing. But CRISPR-Cas9 has taken the medical world by storm because of how easy it is to use, and the broad potential it may have. CRISPR technology has already been used to modify the genomes of plants and animals, but that ease of use has also led to some serious ethical questions. One of the field's pioneers, UC Berkeley's Jennifer Doudna, and several others have called for a

moratorium on using CRISPR-Cas9 to edit the human germline—making changes to sperm, eggs, and embryos that would then be passed along to future generations—and have warned against altering humans for non-medical reasons.

There are also some practical concerns when it comes to using CRISPR-Cas9 for therapeutics. How can a therapy using this technology be delivered into the body effectively? Will it safely do its work, or cut DNA in the wrong places? One wrong snip—a so-called off-target effect—could cause serious unintended consequences, and ensuring that this doesn't happen is just one of the technical challenges that have to be faced before a CRISPR-Cas9 drug begins human testing. One need only look at the up and down history of gene therapy and RNA interference drugs to see the roller coaster likely ahead as researchers try to figure out how to use CRISPR-Cas9 for therapeutics.

While Bosley acknowledges the challenges to come, she notes that part of the excitement surrounding CRISPR-Cas9 is that it's come at a time when "our knowledge of the genome is just at a fundamentally different place" than it was many years ago. She adds that a lot of progress has been made to combat potential off-target effects, like figuring out the exact right size of the RNA guides and which types of Cas9 enzymes to use. Meanwhile, Editas co-founder Keith Joung has developed a tool called "Guide-Seq" to track instances of unintended DNA cuts.

And as for delivering these treatments, Editas "isn't trying to reinvent the wheel," Bosley says. Rather, it's looking to proven delivery methods—at least initially. For the LCA program, it's delivering a CRISPR/Cas9 using adeno-associated virus, a delivery vector that has been used by a number of gene therapy companies. It could use other established delivery technologies, like lipid nanoparticles (often used to shepherd RNA interference drugs into the body) or electroporation (in which an electric pulse creates tiny holes in cells that allow drugs to gain entry).

Still, delivery is "a critical challenge in this field, there's no question about that," she says.

A patent battle between Editas and Doudna's group at UC Berkeley is also part of the mix. The U.S. Patent and Trademark Office awarded the first CRISPR-related patent in April 2014 to the Broad Institute of MIT and Harvard for work led by the Broad's Feng Zhang (an Editas co-founder). The Berkeley group is fighting the patent, claiming it made the invention first. Doudna's work is licensed to Caribou, which in turn has licensed use of its technology for human therapies to Intellia. The work of Doudna's co-inventor, Emmanuelle Charpentier, is licensed to CRISPR. And Doudna herself was an Editas co-founder, but as MIT Technology Review first reported, later cut ties with the company. When asked about the patent case, Bosley didn't give an update directly, but said that the company has a "broad portfolio of IP" that it's licensed in, and that it's developing patent applications from its own internal work as well.

All of which is why the progress of Editas and its rivals will be so closely watched, and why the financing today marks such a noteworthy step for the

technology. Crossover backers have been increasingly active during the biotech boom, joining up with early stage companies to lay the foundation for a number of public offerings. Editas has become the first of the CRISPR-Cas9 group to amass that kind of support, but deciding when to take the leap to the public markets is critical, particularly for a company with a new and unproven technology. Moderna executives, for instance, contended that they were not thinking of an IPO in the short term when they raised $450 million.

Bosley also brushed off thoughts of an IPO, at least in the short term. While Editas will almost certainly have to tap Wall Street at some point to build the broad type of company it hopes to be, there's much work to be done first. That means adding a significant number to its roughly 40-person staff, refining its strategy, and using some of that $120 million to bring several programs to clinical testing.

"We are on a marathon here at Editas," Bosley says. "As much as we think there's some nearer term possibilities of things we might be able to address in a more straightforward way, there's a lot to do to really develop the platform."

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