cells transduced centrally in Leiden with a lentivirus to correct RAG-deficient SCID, caused by mutations in *RAG1*.

Both RAG1 and Artemis regulate the process by which immune cells randomly assemble different gene segments to generate a diversity of antigen receptors—and there's evidence to suggest that gene therapies designed to correct these protein deficiencies require finer tuning of transgene expression levels than viral remedies for ADA- or X-linked SCID. For that reason, Scott McIvor and Branden Moriarity at the University of Minnesota–Twin Cities have begun exploring the use of gene editing to correct rather than replace a working version of the *DCLRE1C* gene. Using CRISPR–Cas9 or precision base-editing will ensure a natural level of protein expression for patients with Artemis-deficient SCID, McIvor notes.

Although CRISPR technologies have their own on- and off-target safety concerns, this approach should completely eliminate the possibility of insertion-related gene activations, a risk associated with any integrating viral vector. "In the future, we won't be treating these diseases using a randomly integrating gene-addition approach," McIvor says. "We'll be going into the endogenous gene and correcting the mutation."

Matthew Porteus, a gene-editing expert at Stanford University, demonstrated the feasibility of this strategy in April when his team reported successful repair of *IL2RG* in hematopoietic stem cells isolated from six affected patients—with no evidence of off-target mutations. Porteus and his colleagues used the CRISPR–Cas9 technique with a cDNA template delivered via a non-integrating adeno-associated viral (AAV) serotype 6 vector. Luigi Naldini and Pietro Genovese from the San Raffaele Telethon Institute described a similar gene correction strategy for SCID-X1 in 2017 (*Sci. Transl. Med.* **9**, eaan0820, 2017).

Porteus has approached a few companies about advancing the CRISPR-based treatment into the clinic, but all have declined, citing a lack of market potential for such an AAV therapy in light of the latest MB-107 data. "They haven't been interested because the lentiviral work has looked so good," he says.

Still, with the St. Jude-turned-Mustang vector inserting itself into a handful of genetic hotspots, including tumor suppressors such as *NF1* and *PTEN*, there remains the possibility that recipients of that gene therapy could develop cancer-related complications down the road. Although patients in the initial adult trial of MB-107 are now 4–7 years out with no vector-associated adverse effects—and additional safety reassurances come from up to 9 years of follow-up data on a similar lentiviral gene therapy to treat Wiskott–Aldrich syndrome—the recent publication on babies treated with MB-107 tracked the patients for only 0.5–2 years, and the oncogenic events in the early SCID-X1 trials occurred between 2.5 and 15 years after therapy.

And so Porteus remains committed to testing his CRISPR-based therapy in patients. Together with Malech, he is now working to secure government funding to conduct the necessary preclinical studies to enable a first-in-human trial of his CRISPR-based fix. "While there are a lot of promising results" with lentiviral gene therapies for SCID, Porteus says, "it's not like it's a done deal." ❐

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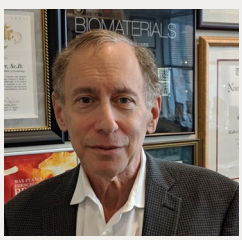
PODCAST

First Rounders: Robert Langer

Robert Langer is the David H. Koch institute professor at the Massachusetts Institute of Technology. He also runs a lab and is cofounder of more than 40 biotech companies. His talk with *Nature Biotechnology* covers the death of his father, his experience teaching high school science and math, and the requirements for launching a successful biotech. https://www.nature.com/nbt/podcast/index.html



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Protein degraders, from clinic to crops

Bayer and Arvinas have joined forces to develop a new class of agents that degrade proteins rather than inhibit them. The overall deal, announced on June 4, includes $110 million in upfront cash to work with Arvina's protein-degrading PROTAC (PROteolysis-TArgeting Chimeras) technology to find new therapeutics for cardiovascular, oncology and gynecology indications. The deal also extends to agricultural uses, with Bayer and Arvinas launching a Crop Science joint venture. The aim is to develop novel protein-degrading molecules to fight weeds, insects and other agricultural pests. Unlike traditional small molecules that aim to inhibit the target protein's active site, Arvina's PROTACs harness the ubiquitin proteasome system to destroy the target molecule. PROTACs are bifunctional small molecules that use one arm to bind a target and the other to bind an E3 ubiquitin ligase. Once a PROTAC brings together the target protein and the E3 ligase, the enzyme ubiquitinates the target protein, tagging it for disposal. In agriculture, PROTAC technology also has the potential to rekindle crop-protection mechanisms that have become ineffective due to resistance, according to Bayer. Other companies focused on targeted degrader chemistries for clinical applications include C4 Therapeutics and Kymera Therapeutics. In April, Arvinas became the first company to take this approach to the clinic, when it began dosing patients in a phase 1 trial for the treatment of metastatic castration-resistant prostate cancer with the drug ARV-110. Results are expected in the second half of 2019. The company also has plans for testing this drug against breast cancer, and a phase 1 clinical trial planned for the third quarter of 2019.

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"What right to try has done, and what one-patient bills like this will do, is put us back into a position where we have to justify FDA's existence to society." Bioethicist Holly Fernandez Lynch, University of Pennsylvania, comments on how the US FDA, under pressure from Congress, is allowing a patient with amyotrophic lateral sclerosis (ALS) to receive an antisense drug developed by researchers at Columbia University that has undergone no safety testing. (*STAT*, 31 May 2019)