‘Bubble boy’ gene therapy reignites commercial interest

Industry interest reignited by increased safety and efficacy of lentiviral gene therapies in several severe combined immune deficiencies.

In mid-April, researchers described how eight infants with X-linked severe combined immune deficiency (SCID-X1), better known as ‘bubble boy’ disease, were cured by a gene therapy. Scientists from St. Jude Children’s Research Hospital and the University of California, San Francisco (UCSF) used an autologous lentiviral gene therapy to deliver a functional interleukin receptor common gamma chain gene to the patients’ hematopoietic stem cells ex vivo. Once transplanted, the cells restored patients’ immune systems, including T cells, B cells and natural killer cells (*N. Engl. J. Med.* **380**, 1525–1534, 2019).

These positive clinical data have shifted attention back to a field that, despite its successes, has failed to attract investor interest. That may now be changing.

Last August, Mustang Bio licensed the lentiviral gene therapy platform from St. Jude’s, renaming it MB-107. And since the April publication, several companies have come knocking to discuss sublicensing opportunities. “So, there are clearly other people who are interested in getting into this space,” says Manuel Litchman, president and CEO of the Massachusetts-based firm.

Meanwhile, Orchard Therapeutics, a London-based startup, announced clinical success of its own in February with a lentiviral fix for adenosine deaminase (ADA)-SCID, the second most common form of the disease, after SCID-X1. Reporting at the 2019 Transplantation and Cellular Therapy Meetings in Houston, Texas, Donald Kohn, an Orchard scientific cofounder from the University of California, Los Angeles, showed that two years after treatment all 20 youngsters who received the company’s OTL-101 therapy had recovered and maintained fully functioning immune systems. By comparison, around one-third of patients in a historical control arm, who received hematopoietic stem cell transplants, required rescue transplants or enzyme replacement therapy.

David Vetter (1971–1984) was called the ‘bubble boy’ because of the plastic enclosures used to protect him from possible infection. He was born with severe combined immune deficiency and lived for 12 years in isolation at Texas Children’s Hospital. Credit: Science History Images / Alamy Stock Photo

“It’s exciting times,” says Adrian Thrasher, another Orchard cofounder from University College London’s Great Ormond Street Institute of Child Health, UK. “SCID is eminently treatable with these technologies, and over the next five to ten years we’re going to see their entry into mainstream medicine, rather than just in very specialized, experimental trials—so that’s cool.”

It’s been a long time coming. Researchers first began testing SCID gene therapies in the clinic nearly three decades ago, and commercial disappointment followed (*Nat. Biotechnol.* **34**, 600–607, 2016). Safety concerns raised in the early 2000s with the first-generation vectors added to industry caution, too. In the world’s first two studies of gene therapies for SCID-X1, 6 of 20 patients developed vector-induced leukemia, brought on by insertional activation of cancer-related proto-oncogenes. One young patient died. “It set the whole field back,” says David Williams, CSO of Boston Children’s Hospital in Massachusetts.

Those setbacks cast a pall over ex vivo gene-corrective remedies—one that in 2005 led Williams to cofound the Transatlantic Gene Therapy Consortium, a group that later spawned Orchard (*Nat. Biotechnol.* **34**, 578, 2016). Regulators halted further clinical testing of gene therapies for many years.

Further hampering clinical progress was the fact that first-generation gene therapies using gammaretroviral vectors for SCID helped correct T cell defects but failed to restore other immune functions. Now, thanks to lentiviral vectors—and especially the newer conditioning protocols that ensure sustained engraftment of gene-modified cells—the therapeutic strategy may be curative.

Lentiviruses became the ex vivo gene therapy vector platform of choice for both efficacy and safety reasons. From an efficacy standpoint, these HIV-based vectors are better at transducing rare, non-dividing cell populations—including hematopoietic stem cells of the bone marrow—than the gammaretroviral systems derived from Moloney murine leukemia viruses used in earlier SCID therapies. Gene transfer is also faster with lentiviruses, shaving a couple days off the laboratory culturing steps.

In terms of safety, the lentiviral vectors in the latest generation gene therapies seem to avoid the adverse outcomes that arose in earlier trials. When used as a vector to deliver a gene payload, lentiviruses tend to

Table 1 | SCID gene therapies in clinical development

Product	Sponsor	Disease	Mutated gene	Vector/cryopreservation	Status
Strimvelis	Orchard Therapeutics	ADA-SCID	*ADA*	Retroviral/no	Approved in Europe
OTL-101	Orchard Therapeutics	ADA-SCID	*ADA*	Lentiviral/yes	Phase 1/2
TYF-ADA	Shenzhen Geno-Immune Medical Institute	ADA-SCID	*ADA*	Lentiviral/no	Phase 1/2
MB-107	Mustang Bio	SCID-X1	*IL2RG*	Lentiviral/yes	Phase 1/2
G2SCID	Boston Children's Hospital, UCLA Mattel Children's Hospital, Great Ormond Street Hospital	SCID-X1	*IL2RG*	Lentiviral/no	Phase 1/2
TYF-IL-2Rg	Shenzhen Geno-Immune Medical Institute	SCID-X1	*IL2RG*	Lentiviral/no	Phase 1/2
AProArt	University of California, San Francisco	Artemis-deficient SCID	*DCLRE1C*	Lentiviral/yes	Phase 1/2
	Leiden University Medical Center	RAG1-SCID	*RAG1*	Lentiviral/yes	Planned

insert themselves within genes and away from transcription start sites, as retroviruses preferentially do. The latter process can trigger cancer if the integration occurs near proto-oncogenes. What's more, lentiviral vectors built on a self-inactivating HIV backbone contain deletions in the long terminal repeats thought to have driven dysregulated gene expression in the patients who developed leukemia with first-generation retroviral vectors.

Notably, Strimvelis—the first ex vivo gene therapy to receive marketing authorization anywhere in the world—does not use a lentiviral system. Developed by scientists at the Milan-based San Raffaele Telethon Institute for Gene Therapy, and later owned by London-based GlaxoSmithKline, the therapy uses the same gammaretroviral vector that was blamed for complications in the early SCID-X1 trials. Fortunately, Strimvelis has been free from these kinds of adverse events—although no one is certain why. "There is something specific about ADA deficiency that fortunately protects patients from leukemia," says pediatric immunologist Alain Fischer, from the Necker Hospital for Sick Children in Paris.

Even so, the gene therapy has been something of a commercial dud. After Strimvelis won European regulatory approval in 2016, just five patients received the product in its first two years on the market. Last year, in light of poor sales numbers—and as part of a larger strategic reorganization—GlaxoSmithKline offloaded Strimvelis and the rest of its gene therapy assets on Orchard in exchange for royalties, commercial milestones and a near-20% equity stake in the company. (According to Orchard's CSO Bobby Gaspar, more patients have since received Strimvelis, but he declined to give specific numbers.)

One explanation for the low uptake is the rarity of the condition: only around 15 new cases of ADA-SCID are diagnosed annually in Europe. Another reason may be the therapy's €594,000 ($667,000) price tag—a cost that could be avoided by enrolling in an ongoing trial with Orchard's lentiviral follow-up, OTL-101, in London.

But one of the biggest impediments to rapid adoption boils down to logistics. Strimvelis, as currently formulated, requires patients to travel to Milan for cell processing, gene correction and reintroduction. That kind of trek and the months-long stay can be hard on young, sick babies. And it presents all sorts of reimbursement headaches for patients who have to cross national borders. If Orchard could decentralize the process, then "you would have a viable commercial product," says David Nierengarten, analyst and managing director at Wedbush Securities.

Enter cryopreservation. Kohn is now wrapping up an Orchard-backed study of OTL-101 in which his team freezes the gene-modified stem cells after lentiviral transduction. The cells then sit in liquid nitrogen until such time as the patient is ready to receive them. "It means that the cells travel, rather than the patient," says Gaspar, "and you only condition the patient and reinfuse the cells when you know you have an optimal product, which gives the patient the best chance of the therapy working."

Orchard is eyeing a 2020 filing date in the United States, with a European application to follow. (According to Litchman, Mustang is aiming for 2021 with MB-107.) If approved, OTL-101 would essentially make Strimvelis obsolete—but the impact of Strimvelis on the field should not be underestimated, experts say. Strimvelis blazed the path to market, gaining an approval with a small number of patients. It also demonstrated the benefit of a conditioning strategy—low doses of the DNA-alkylating chemotherapy busulfan—that is now standard for enhancing the engraftment of gene-modified blood cells. "That made a huge difference," says Harry Malech, genetic immunotherapy section chief at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland.

Before, gene therapies were administered without preconditioning and cell engraftment was so low that most ADA-SCID patients had to remain on enzyme replacement therapy, while SCID-X1 patients recovered only T cell function and needed lifelong immunoglobulin infusions. Now, with a course of busulfan, Strimvelis engraftment is sufficiently effective that patients no longer require enzyme replacement, and many can stop taking immunoglobulin replacement therapy as well. A similar conditioning regimen, along with the better lentiviral gene transfer tool, also likely accounts for the unprecedented efficacy of MB-107, says Malech, who co-led the first study of the treatment in older patients. "Both things are important: the transition to lentiviral and the conditioning."

"It's kind of like making a soufflé," he adds. "It's not going to rise unless you get all the pieces right."

Trials involving gene therapies for other forms of SCID are just getting started—but they too are built on the lentiviral chassis (Table 1). At UCSF, pediatric immunologists Morton Cowan and Jennifer Puck have begun studying a lentiviral vector for Artemis-deficient SCID, a disease caused by mutations that are particularly common among some indigenous communities of North America. After treating three infants, "we're seeing development of corrected B cells, T cells and natural killer cells in these babies. So we're very encouraged," says Puck, who is also involved in testing MB-107.

In the coming months, stem cell biologist Frank Staal from Leiden University Medical Center in the Netherlands also hopes to begin two trials—one at Leiden and Great Ormond, a second at ten sites across Europe and Israel—evaluating cryopreserved stem

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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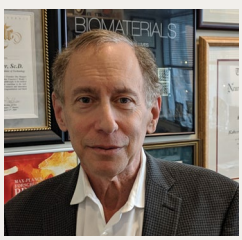
PODCAST

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)