GENE THERAPY

# Industrial strength

*After a series of setbacks, genetic therapies are finally moving beyond small academic trials towards approval as treatments.*

BY ERIC BENDER

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In the original flurry of public excitement about gene therapy 20 years ago, one of the main attractions of treating patients by delivering DNA or RNA to their cells was the hope that these agents could be created quickly.

"It seemed to be a way to shave years off the development of therapeutics," recalls Nick Lemoine, a molecular oncologist and director of the Barts Cancer Institute at Queen Mary University of London. Small-molecule drugs often take 15 years to reach approval. But in bringing the first gene therapy for breast cancer into clinical trials, "we went from proof of concept through clinical study in five years", he says.

Lemoine and his colleagues published their results in 1999, but just a few months later, a teenage volunteer died in another gene-therapy trial, targeting a metabolic disease, at the University of Pennsylvania in Philadelphia. The viral vector that delivered the package had unexpectedly unleashed a fatal immune storm. In the next few years, several young participants in French and UK clinical studies designed to treat severe combined immunodeficiency ('bubble-boy' syndrome) were diagnosed with leukaemia, thought to have been accidentally induced by the therapies.

As these events accumulated, companies working on gene therapy began to fold or switch their attention to other treatments. "These high-profile adverse events in gene-therapy trials had a snowballing effect," says Katherine High, a haematologist and president of Spark Therapeutics in Philadelphia. "There were serious questions about whether gene therapy would ever make it."

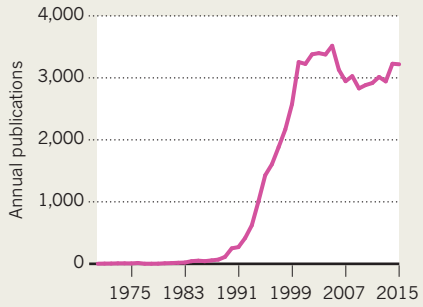
Despite the poor outcomes and plunging investment in gene therapy, academic researchers kept plugging away (see 'Academic mettle'). They developed safer and more effective delivery mechanisms, and tested them in a steady stream of clinical trials involving handfuls of patients. So far, more than 2,300 gene-therapy trials, most of them small-scale academic studies, have been carried out across a wide variety of disease targets and approaches. These trials "have the ability to powerfully reorient the field", says High. "We are learning to be realistic about safety and what the vector can and cannot do."

These small steps are paying off. In the biotech boom that followed the recession of 2008, industry came back to gene therapy. Dozens of start-ups found sponsors in big drug companies or raised money through stock offerings. In one striking example, Juno Therapeutics, based in Seattle, Washington, reached a market capitalization of US$4 billion in 2014, within about a year of its founding.

But few gene therapies have yet been approved. The first was Gendicine, a treatment for head and neck cancer approved in China in 2003. In 2012, the European Medicines Agency (EMA) gave its blessing to Glybera, a gene therapy from UniQure of Amsterdam, to

## ACADEMIC METTLE

The number of gene-therapy research papers published has remained strong despite setbacks in clinical trials. All papers between 1970 and 1978 focused on ethical issues.




SOURCE: FRED LEDLEY

treat an extremely rare disease that inflames the pancreas. But Glybera — perhaps the most expensive drug in history — is not considered a commercial success.

This year, the EMA also approved GlaxoSmithKline's Strimvelis, a paediatric gene therapy that targets a rare immune disorder. The US Food and Drug Administration (FDA) has yet to approve any gene therapies, although treatments for rare genetic eye and blood diseases and blood cancers are considered likely candidates for approval in the next few years.

Submissions for approval have mostly stalled because of a lack of suitably designed clinical trials, says Christian Meyer, chief medical officer at UniQure. "It's only in the last couple of years that industry-sponsored programmes have achieved the quality, robustness, safety and risk benefit at the levels necessary to gain regulatory approval," he says. "That is changing the game."

Gene therapy still brings huge concerns about safety, long-term efficacy and cost. But the first full generation of this highly precise form of medicine could soon be with us.

### DELIVERIES GO VIRAL

Gene therapies vary dramatically, but they all face one huge challenge: enforcing genetic change in their target cells.

"Gene therapy is actually three things: delivery, delivery and delivery," says Eithan Galun, director of the Goldyne Savad Institute of Gene Therapy at the Hadassah Medical Center in Jerusalem. "The core issue is really how much you bring where and when."

James Wilson, director of the gene-therapy programme at the University of Pennsylvania, agrees. "Delivery is always the rate-limiting step in all of these biologics," he says.

Wilson led the University of Pennsylvania trial that produced the 1999 fatality. Most early studies used vectors based on retroviruses, which carry their genetic cargo as RNA, but Wilson's trial used an adenovirus. He went on to spearhead the development of adeno-associated viral (AAV) vectors, which are now used in most gene therapies undergoing clinical testing.

The AAVs are small viruses that typically provoke very little immune response and can be modified to carry 'corrected' single-stranded DNA. But AAV therapies do not integrate into the chromosomes, so they work best with cells that do not divide, such as those in the brain or retina — in dividing cells, the non-replicating DNA delivered by AAVs would eventually be lost. Although their small size means that they are unable to carry larger genes, the viruses are typically infused into the blood or injected directly into tissue, where their relatively small genetic cargo is not a problem.

Modified lentiviruses, a retroviral group that includes HIV, are also sometimes used in gene therapy, and these do integrate into chromosomes. The lentiviral sweet spot is in modifying cells that are taken from the body, treated and then reintroduced, says Philip Gregory, chief scientific officer at Bluebird Bio in Cambridge, Massachusetts. "They are very good at transducing new information into the genome of otherwise difficult-to-modify cells."

Lentiviral vectors can carry larger genetic cargoes than AAV vectors. But there is a downside. "What we can't control with lentiviral vectors is where that integration happens," Gregory says. This gives rise to safety concerns, because something important to the cell might be disrupted, although he adds that no such serious effects have arisen in the clinic so far.

Treatments built on re-engineering the herpes simplex virus 1 (HSV-1) can exploit its ability to target the nervous system, says molecular geneticist Joseph Glorioso at the University of Pittsburgh in Pennsylvania. He and his colleagues have made encouraging progress in using HSV-1 vectors to treat pain by increasing the expression of endogenous opioids. They believe that approaches involving HSV-1 are well suited for dealing with many illnesses of the brain.

The gene-editing technologies that have exploded onto the scene in the past few years — notably CRISPR–Cas9 — promise to accelerate and improve the precision of many forms of gene therapy. Gene editing makes it possible to combine gene corrections or handle genes that are too big for standard viral vectors to carry. In July 2016, an *ex vivo* T-cell trial targeting lung cancer at Sichuan University's West China Hospital in Chengdu, received ethics approval, and it is expected to be the first study to use CRISPR in humans. Other groups aim to do genomic editing *in vivo*. Editas Medicine in Cambridge, Massachusetts, for example, expects to launch a clinical trial using CRISPR to treat a rare eye disease in 2017.

### RARE DISEASES

Most clinical work using gene therapy has pursued disorders that are driven by rare mutations to a single known gene, such as diseases of the eye, the blood and the central nervous system. Several factors place the outer retina among the most likely targets, says Jean Bennett, an ophthalmologist at the University of Pennsylvania. The retina is small, easily accessible and its changes can be measured by high-resolution imaging. Moreover, researchers can test therapies on one eye while using the second as an experimental control. And several rare genetic conditions that affect the retina can be studied in dogs, where they occur naturally.

Bennett, who has been working on retinal illnesses since the 1980s, launched a small trial in 2007 for inherited blindness driven by mutations in the *RPE65* gene. Success in that study allowed Bennett and her colleagues to push ahead with a larger study in collaboration with Spark Therapeutics — an effort that demonstrated improved vision in a phase 3 trial of 31 patients in 2015. Spark Therapeutics expects to file for FDA approval by the end of 2016. "This might be the first gene therapy approved in the United States, which would be very exciting, and would make a path for other people to develop treatments for other blinding diseases," says Bennett.

Blood diseases have also been prime targets, partly because of the ability to tap into decades of experience in working with blood stem cells to treat blood cancers. In June 2016, Spark Therapeutics revealed that in a small early trial to treat haemophilia B, all four participants generated enough of the blood clotting factor that is damaged in the disease to skip regular injections of the factor. The following month, BioMarin Pharmaceutical of San Rafael, California, reported highly encouraging results for a gene therapy for haemophilia A, the most common form of the disease.

*"Gene therapy is actually three things: delivery, delivery and delivery."*

If these preliminary results are sustained and repeated across large numbers of patients, gene therapy may offer a single-shot 'cure' for many people with haemophilia. "The successes in haemophilia are pretty remarkable, although it remains to be seen how enduring these treatments are," says Glorioso, who was not involved in the trials.

Treatments are also steadily moving ahead for rarer single-mutation blood illnesses, such as thalassaemia and sickle-cell disease, says Gregory. These treatments remove the patient's own blood stem cells, replace the β-globin gene with a corrected copy, and re-infuse the cells. In late 2015, Bluebird Bio reported encouraging results in a few such people, and two with thalassaemia no longer required blood transfusions to stay healthy. Other companies are also seeing positive early signs from trials in these diseases.

Gene therapies can also tap into the blood's ability to carry proteins to other organs. Bluebird Bio is using this approach to treat cerebral adrenoleukodystrophy, an illness of the central

RANA SAJID HUSSAIN/PACIFIC PRESS/LIGHTROCKET VIA GETTY

nervous system that affects one in 20,000 male births worldwide and that gained prominence through the 1992 film *Lorenzo's Oil*. Modified blood stem cells travel to the brain and produce enough corrected protein to stop damage from the disease, which is caused by a mutated gene called *ABCD1*. A Bluebird Bio trial in 2016 demonstrated this effect in 16 of 17 boys.

Many other clinical studies are under way for genetic disorders of the central nervous system. AveXis, a biotech company based in Chicago, Illinois, for example, reported encouraging early results in May 2016 from a trial with 15 people with spinal muscular atrophy — a neuromuscular disease that is the leading genetic cause of infant death.

**Blood transfusions are the standard treatment for thalassaemia, but gene-therapy trials are promising.**

## CANCER TREATMENT DONE TO A T

The gene therapies that have drawn most headlines so far are adoptive T-cell transfers, in which the patient's immune T cells are re-engineered before being injected back. These treatments are making rapid progress against difficult-to-treat blood cancers — although some of the headlines report patients who died in trials.

There are two main forms of engineered T cell: chimaeric antigen receptor (CAR) T cells and T-cell receptor (TCR) T cells. The CAR T cells have a receptor that is modified both to grab onto specific tumour cells and to react more violently to them, and have shown "remarkable success in curing difficult-to-treat leukaemias", Glorioso says.

Dozens of research organizations and companies are pursuing this approach to treat various blood cancers, but the path forward is not entirely smooth. In July 2016, Juno Therapeutics disclosed that the FDA had suspended the clinical trial of its CAR T agent for acute lymphoblastic leukaemia after three patients died. The deaths were apparently caused by a drug given in preparation for treatment, rather than by the CAR T cells themselves, and the FDA quickly gave permission to restart the trial without that compound.

The TCR T cells, which are given the ability to recognize specific proteins either on the tumour cell's surface or inside it, require more individualized tailoring than CAR T cells. They are used in far fewer clinical studies, and these are generally not as advanced, but they may offer a much broader repertoire of disease targets, says Hans Bishop, chief executive officer of Juno Therapeutics.

Solid tumours present additional challenges for engineered T cells, which must travel to the tumour and combat the microenvironment around it while leaving healthy cells mostly untouched. Bishop contends, however, that thanks to research now being done by several groups, "the evidence is tilting more towards TCRs than CARs". He also expects engineered T cells to show "increasing cure rates for some malignancies" over the next few years.

As regulatory agencies consider approving gene therapies, researchers expect them to balance the trade-offs between risks and benefits as they do for other new drugs. "Most of these diseases have terrible prognoses and no current therapies in any other form," Gregory points out. "The FDA encourages you to go straight to patients where the risk–benefit ratio is appropriate."

## MAKING IT TO MARKET

There is one huge difference between gene therapy and small-molecule drugs or biologics, however: once a gene therapy is administered, you cannot stop the treatment. "We need to follow patients for many years to figure out how long does the therapy last, and do safety concerns emerge that we don't know today," says Meyer.

Additionally, almost all of the clinical trials of gene therapies so far have been so small and short that the treatments' full effects are not yet known. "I worry that we could open up a floodgate of potential problems if something is overlooked," says Bennett. "It's important to go stepwise, to be sure we understand the safety and efficacy."

Some researchers draw an analogy to the long clinical pathways followed by other new therapies. For instance, the monoclonal antibodies that began to appear 30 years ago brought deep concerns about safety and manufacturing issues, says Bishop. Scores of studies by a large number of labs and companies, ultimately put those fears to rest. "I think you will see a very similar trajectory in our field."

No single discovery or technology will change everything overnight, says High. "It is wrong when people try to convince you that they have a silver bullet that will solve things for gene therapy," she says. High emphasizes the need for a deep understanding of the biology of illnesses, especially as the field starts to address conditions that have more complex genetic contributions. "We need more physicians who know a whole lot about a disease and will work with us," she says.

Then there is the vexing issue of economics. Gene-therapy advocates need to be prepared for the astronomical costs of many gene therapies. Glybera treatment, for example, is nominally priced at about US$1.2 million, but the drug is thought to have been bought for that amount just once.

Therapies that successfully treat fatal, rare diseases will sustain high price tags, says Karen Aiach, chief executive of Lysogene in Paris. Aiach founded the company to develop a gene therapy for Sanfilippo syndrome — a rare neurological disease that affects her daughter. But she concedes that expense is a major issue. "We need to think about new business models, finding the right pricing scheme and the right reimbursement scheme," she says.

High costs may raise huge concerns but they will not necessarily stop people paying, even for diseases such as haemophilia where other treatments are available. "One injection and you're done, so what do you charge for that?" asks Glorioso. "It actually may be cheaper than caring for a patient for a lifetime."

"Gene therapy is a classic disruptive technology," says Wilson. "It's so different, and it will impact the entire practice of medicine. But we as a society will figure it out. We'll have some successes, we'll have some failures. It's still science, we're still learning, this is not routine. We're at the very beginning." ■

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## CORRECTION

The Outlook article 'Industrial strength' (*Nature* **537,** S57–S59; 2016) incorrectly stated that the 1999 trial at the University of Pennsylvania was based on a retrovirus, it was in fact based on an adenovirus.