**TURNING POINT** Fellowship lets physicist explore exotic states of matter **p.653**

**FACEBOOK** The latest in careers advice and information **www.facebook.com/naturejobs**

**NATUREJOBS** For the latest career listings and advice **www.naturejobs.com**

VISUAL MOZART/GETTY

MEDICAL RESEARCH

# Gene-therapy reboot

*Safer, more efficient methods to deliver therapeutic genetic material are generating jobs for savvy scientists.*

**BY LAURA CASSIDAY**

In the early 2000s, gene therapy seemed to be on life support. The once-promising technique, which uses engineered viruses and other methods to shuttle genes into human cells to fix DNA errors, faced a setback after an 18-year-old man died during a clinical trial in 1999. Later analysis showed that the virus carrying the DNA fixes had triggered a massive immune reaction that caused the man's organs to shut down.

But after years of troubled times, the field is on the move again. Success stories, an infusion of venture capital and regulatory approval in the European Union have revitalized the field and made scientists experienced in the technology hot commodities once more. "The field has really started to take off again," says Harry Gruber, chief executive of Tocagen, a gene-therapy company based in San Diego, California. The number of people working in gene therapy has grown enormously, he says, and that is going to continue.

Gene therapies generally use viruses to deliver the gene of interest to cells. The viruses — retroviruses, lentiviruses and adeno-associated viruses, among others — are defanged by removing harmful genetic sequences then engineered to contain the therapeutic gene sequence. When the virus encounters human cells, it inserts its genetic material into the human genome.

The first gene-therapy recipient, in 1990, was a four-year-old girl who had a genetic disorder known as adenosine deaminase (ADA) deficiency. The treatment, which used a retrovirus, seemed to work, although the effects were temporary and the girl continued to need treatment.

Still, the trial established that the procedure was safe and at least moderately effective, and the following decade saw the technique burgeon in hundreds of trials. But then the 18-year-old man died, and in 2002, a trial in France was shut down when a boy with an immune disorder known as X-linked severe combined immunodeficiency (X-SCID) developed leukaemia because of how the retrovirus had inserted itself into the genome. Three other boys in the French trial, and one in a similar UK SCID trial, ultimately developed leukaemia. Regulatory agencies in France, Germany, the United States and the United Kingdom suspended all trials that used techniques similar to that in the French study.

The X-SCID trial did have some successes, however. Nine of the ten boys in the French trial who received the therapy were cured of their deadly disease. And of the four who developed leukaemia, three were successfully treated with chemotherapy.

After a careful risk–benefit analysis, the agencies eventually lifted the restrictions and issued new safety guidelines. But investors and the public were badly shaken. Concerns about playing God resurfaced. Many first-generation gene-therapy companies folded, because the liabilities of the technique seemed to overwhelm the returns.

Yet researchers persevered. They worked to develop vectors that would insert themselves into the genome more precisely, and thereby avoid disrupting important genes. Gradually, success stories started to emerge.

At the University of Pennsylvania in ▶

Philadelphia, for example, researchers led by Carl June, director of translational research at the Abramson Family Cancer Research Institute, have seen promising results in clinical trials for chronic lymphocytic leukaemia (CLL) and acute lymphoblastic leukaemia (ALL).

Their approach involves isolating a patient's T cells and infecting them with a lentivirus that causes the cells to produce an antibody-like protein, or chimeric antigen receptor (CAR), on their surface, which binds to a protein on the surface of B cells. When the modified T cells were infused back into patients' bodies, they multiplied and attacked cancerous B cells. Almost half of the 32 adults with CLL responded to the therapy, and 19 of 22 children and all five adults with ALL experienced complete remissions, although some have since relapsed.

## INDUSTRY INTEREST

In 2012, the university and the pharmaceutical firm Novartis in Basel, Switzerland, announced a partnership to study and commercialize the technology. The partnership, which will grant Novartis an exclusive worldwide licence to therapies based on CAR technology, will help to build a Center for Advanced Cellular Therapies on the university's campus. It will also fund the establishment of new labs and the hiring of scientists at the bachelor's, master's and PhD levels, says Bruce Levine, director of the university's clinical cell and vaccine production facility. He says that the alliance is an example of a growing trend of partnerships between industry and academia that are likely to increase demand for researchers. Another partnership that garnered media attention was the 2013 collaboration between the biotechnology company Celgene in Summit, New Jersey, with the Baylor College of Medicine in Houston, Texas, to develop gene therapies for cancer.

***"We are ramping up at an extraordinary rate."***
Bruce Levine

"We are ramping up at an extraordinary rate, due in large part to the Novartis alliance, but also to our other cell- and gene-therapy programmes," says Levine. "I half-joke to my colleagues when we're going to meetings that I should wear a badge that says, 'Ask me about the positions we have open.'" He says that "dozens" of positions are open, and that they are looking for people with a degree in a biology-related field and experience in developing and manufacturing gene and cell therapies. Also, strong record-keeping skills are a must owing to the extensive documentation required for the manufacturing of gene-therapy products for clinical trials.

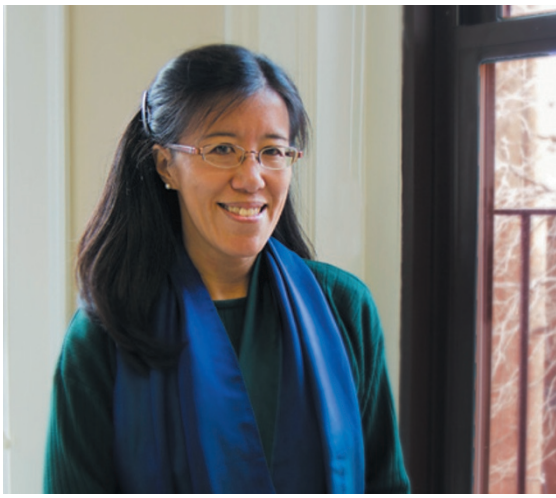
People who want to move into gene-therapy research would do well to consider eye disorders, says Robert MacLaren, a surgeon at the University of Oxford's Nuffield Laboratory of Ophthalmology in Britain. "About one-third of genetic diseases manifest themselves in the retina," he says. Retinal cells are also easy to access and can be efficiently targeted with adeno-associated viruses (AAV), which are less likely to trigger an immune reaction or cause cancer than other viruses. "We're in the early stages, but undoubtedly the eye will be the most logical target organ for gene therapy," he says. "And I think what we learn about gene therapy in the eye will help us to apply the techniques much more effectively to other diseases."

MacLaren's trial of gene therapy for choroideremia, a rare, inherited form of blindness, triggered much excitement when the results were published in *The Lancet* in March (R. E. MacLaren *et al. Lancet* **383,** 1129–1137; 2014). Choroideremia is caused by a mutation in a gene called CHM that causes pigment cells in the retina to gradually stop working and die. MacLaren's team inserted a functional copy of CHM into an AAV and then injected it into one retina in each of six men with varying degrees of visual acuity. Five of the men showed improvements in their ability to see a dim light in the dark, and the two patients with the most severe choroideremia were able to read additional lines on an eye chart. These improvements have been sustained in the two years since the single treatment.

Researcher Samantha de Silva recognized the enormous potential of gene therapy for the eye. She had earned a medical degree and was completing her residency in ophthalmology at Oxford Eye Hospital, UK, when her career path veered in an unexpected direction. She heard about MacLaren's upcoming gene-therapy trial and was fascinated. "I really wanted to be involved in gene therapy because it has a great potential to benefit patients," she says. So she took time off from her residency to pursue a PhD in MacLaren's lab. Three and a half years later, she is in the final stages of her thesis project on gene therapy for retinal degeneration. After she completes her residency, she hopes to combine her research with a career in clinical ophthalmology.

These successes have helped to restore investor confidence in the field. "The investment community has started showing up again at scientific conferences for gene therapy," says Gruber. "The attendance went from basically all scientists to about five investors for every scientist."

As a veteran in the field, Gruber has a broad view of its opportunities for researchers. In 1987, he co-founded Viagene, one of the world's first gene-therapy companies, in San Diego. The company had some early successes in treating melanoma and was acquired by Chiron in 1995. But growing concern about gene therapy during the early 2000s and a subsequent acquisition by Novartis in 2006 meant that the research was halted. In 2007, Gruber and several colleagues founded Tocagen.



**Dinah Sah says that candidates would ideally have industry experience in adeno-associated viruses.**

VOYAGER THERAPEUTICS

He notes that renewed investor interest has spurred the founding of companies and the growth of existing ones like his, leading to a proliferation of jobs. "We have openings for scientists in almost every department in our company, at several educational levels," he says. He also says that gene therapy is a multidisciplinary activity and as such, there are opportunities for people with a variety of degrees, including molecular biologists, cancer biologists, biochemists, pharmacologists, clinical researchers and engineers.

Voyager Therapeutics in Cambridge, Massachusetts, is another company benefiting from the renaissance. Launched in February with the help of US$45 million from Third Rock Ventures in Boston, Massachusetts, the start-up aims to treat disorders of the central nervous system, such as Parkinson's disease and motor neuron disease, by boosting or inhibiting the expression of genes linked to the conditions. The company uses AAVs to deliver the therapeutic genes to the brain.

## TOP OF THE HEAP

Unlike other popular vectors, AAVs can target non-dividing cells, such as those in the central nervous system. Their genomes do not readily integrate into the target cell's genome, so the cancer risk is minimal and they are less likely to trigger an immune reaction than other types of virus. "AAVs have been used in more than 1,300 patients in clinical trials, and no serious adverse events have emerged," says Jeff Goater, vice-president of business development at Voyager. "I think it's fair to say that they have risen to the top of the heap in terms of the viral vector of choice for a number of therapies."

Dinah Sah, senior vice-president of neuroscience at Voyager, says that the company is advertising for scientists, specifically those with expertise in working with AAVs as well

as knowledge of biology and diseases of the central nervous system. In addition, skills in molecular biology and protein chemistry are highly valued. "We'd prefer someone with a PhD or someone with a master's or bachelor's degree who has at least seven years of industry experience," she says.

Goater agrees that industry experience is prized but says that most of the candidates with AAV experience tend to come from academia, not industry. As recently as five years ago, he says, gene-therapy companies were focusing on other viruses and much of the work on AAVs was being done at universities. People interested in working in the gene-therapy field should therefore gain experience with this up-and-coming vector, he advises.

Perhaps the biggest boost to the field came in 2012 when the European Medicines Agency approved Glybera (alipogene tiparvovec) for the treatment of lipoprotein lipase (LPL) deficiency in patients with severe or recurring pancreatitis. Glybera uses an AAV to deliver a working copy of the LPL gene to muscle cells. It joins Gendicine, a recombinant adenovirus approved in China in 2003 for head-and-neck squamous-cell carcinoma, as the only gene therapies to obtain regulatory approval thus far.

"The approval of Glybera dramatically changed the landscape in the field of gene therapy," says Jörn Aldag, chief executive of UniQure, Glybera's developer in Amsterdam. "It's the first time that both pharma companies and investors recognized that gene therapy is here to stay."

Aldag hopes to obtain US Food and Drug Administration approval for Glybera by 2017. UniQure also has therapies for diseases such as haemophilia and Parkinson's disease in clinical trials. The company has grown from 45 employees in 2012 to 140 employees, and expects to add 50 more to its workforce by the end of the year, Aldag says.

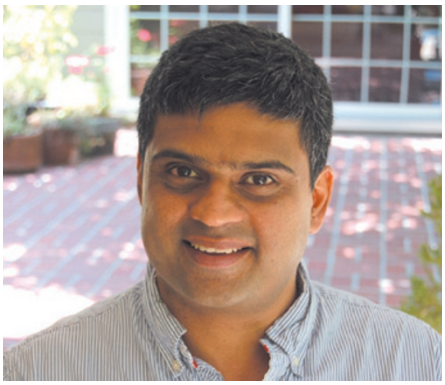
Although opportunities seem to be on the rise, some are likely to remain cautious — what is to prevent the bubble from bursting again? Levine cites an information-technology concept known as the Gartner Hype Cycle. "Whenever there's a new technology, it goes from a peak of inflated expectations, to a trough of disillusionment, to a slope of enlightenment, and a plateau of productivity," he says. "Gene therapy is now in the enlightenment stage."

Levine says that the current period of growth is different from that in the 1990s because of the accumulated clinical experience. "Thousands of people have now been treated with gene therapy," he says. "And we have much better tools, techniques and equipment than we had back then." ■

**Laura Cassiday** *is a freelance writer in Hudson, Colorado.*

# TURNING POINT
# Ashvin Vishwanath

*Ashvin Vishwanath, a condensed-matter physicist at the University of California, Berkeley, received a Guggenheim fellowship in April for his exceptional scholarship. It will allow him to spend several months trying to fabricate the exotic states of matter that result from interactions between quantum particles. He describes how reaching out to colleagues in other fields transformed his career.*



**Why choose a career in physics?**
Growing up in India, I realized that it was not common to pursue a pure-science career. I did my master's at the Indian Institute of Technology Kanpur, where 90% of students were engineers. My choice of condensed-matter physics was also unusual — my peers were more attracted to particle physics or string theory. I wanted to be able to conduct experiments to test my theories.

**How did you approach your PhD?**
I did my PhD at Princeton University in New Jersey on high-temperature superconductors — specifically, how their structure differs from that of regular superconductors. The electrons look like a pair of dumb-bells rather than a pair of circles as in other types of superconductors. My thesis explored the consequences that arise from this pattern. No single one of my PhD papers was spectacularly received, but my colleagues noticed that I was doing a lot of work independently — framing problems and finding solutions on my own as well as working with my adviser and other postdocs. I got a number of postdoc offers.

**How did you choose which postdoc to accept?**
I made my decision on the basis of potential collaborators, because I felt I would do better science working with someone that I could discuss and generate ideas with. During my PhD, I noticed a paper by Senthil Todadri, a condensed-matter physicist at the Massachusetts Institute of Technology (MIT) in Cambridge. I e-mailed him with some questions, and we launched a collaboration on superconductivity. We got to know each other scientifically and, ultimately, I accepted a postdoc at MIT so that we could continue our work — I had the right instinct for what was important for a longer-term perspective.

**What did you work on?**
We studied the properties of phase transitions and showed that a seemingly implausible phase transition in superconductors became plausible at the quantum level. The e-mail that led to this collaboration and to this breakthrough finding was therefore a turning point for me.

**Did you jump at the opportunity to apply for tenure-track jobs?**
No. A few universities encouraged me to do so, but I wanted to spend as long as I could as a postdoc — I didn't think I had a discovery that was significant enough to give me the momentum necessary to start a successful lab. Eventually I landed a job at the University of California, Berkeley, which let me delay my start by a year to get more time as a postdoc. It was during that year that Senthil and I, along with other collaborators, discovered a new phase transition in a magnet, which is a relevant starting point for work in high-temperature superconductors. Had I rushed into a faculty position, I would have missed one of the most productive times of my career. When I'm making career decisions, focusing on the science has always worked best for me. Ten years on, I keep returning to the research questions I asked during my postdoc.

**What will you do with the fellowship?**
My group proposes the existence of states of matter that have properties that currently exist only in theory. These states obey the laws of nature, but I want to see if we can realize them in a material or synthetic system made of atomic gases. For example, I want to find a system that is a three-dimensional analogue of graphene.

**Could this fellowship be a turning point?**
Yes. If we can eventually make these materials, it would be huge. That's the dream of every theoretical physicist — to one day bring together a beautiful theory and the experiments to prove it. ■

INTERVIEW BY VIRGINIA GEWIN