ADVERTISEMENT FEATURE

FOCAL POINT ON GENOME EDITING AND GENE THERAPY IN JAPAN

PRODUCED IN PARTNERSHIP WITH JICHI MEDICAL UNIVERSITY

A BOOM TIME FOR GENE THERAPIES AND GENOME EDITING TOOLS

CHANGES TO THE OUTLOOK FOR RESEARCHER-INITIATED GENE THERAPIES IN JAPAN should help bring significant advances to important work, say experts.

Gene therapy researchers and genome editing experts say they have been the surprise beneficiaries of an increased interest in Japan in novel treatments, spurred by separate advances in induced pluripotent stem (iPS) cells.

In 2012, Japanese researcher, Shinya Yamanaka, won a Nobel Prize for his contribution to developing induced pluripotent stem (iPS) cells. University of Tokyo neurosurgeon, Tomoki Todo, says the subsequent 2014 amendment of Japan's Pharmaceuticals and Medical Devices Law to install a system that gives rapid conditional approval to particular regenerative medicine products was mostly aimed at stem cell treatments. However, a slightly different set of treatments, gene therapies, were also included under the regenerative medicine banner, and commercial entities quickly began to look more closely at both fields in Japan.

Then in 2015 Japan implemented the Sakigake system, which flags promising therapies at comparatively early stages of development and gives them priority for clinical trial consultation and review, alongside a fast-track drug approval system for breakthrough medical products. "For researcher-initiated development it was previously quite difficult to get company sponsorship until the end of clinical trials, when we had good results," says Todo, whose latest gene therapy, an edited virus that targets and kills cancer cells, was flagged for development under the Sakigake system in 2016. He's currently working on this oncolytic virus, known as G47Δ, with Japanese pharmaceutical company, Daiichi-Sankyo. "Companies would usually join at the final stage. But now, once we have Sakigake designation, companies are quite interested in joining earlier, which is a good thing," says Todo. G47Δ was the world's first third-generation oncolytic virus to go to clinical trial.

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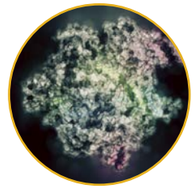
1

A 2015 to 2017 clinical trial, led by Takanori Yamagata, used **VIRAL VECTORS** to deliver a gene therapy to five patients with aromatic L-amino acid decarboxylase deficiency. All improved, some able to walk, stand or run in ways not observed in the lead up to treatment.

2

A new **CRISPR-CAS9**, SpCas9-NG, published on in 2018 by a group that included the University of Tokyo, is being heralded for its ability to increase the targeting range of CRISPR technology.



CLOCKWISE TOP LEFT: Juan Gaertner/Science Photo Library; MOLEKUUL/Science Photo Library; Kateryna Kon/Science Photo Library

More controversial is the 2014 system, which allows regenerative medicines for serious conditions go to market in a probationary manner after only small clinical trials. A number of academics have criticized the lack of requirement for double-blind clinical trials. Nonetheless, a surge, since 2014, of therapeutic companies setting up in Japan suggest the relaxing of regulations has contributed to Japan's commercial appeal.

Gene therapies had moved forward in the 1990s, but clinical trials using viral vectors — viruses that deliver gene therapies into the body — experienced a setback after two deaths exposed safety issues, including inflammation and cancer risks. Researchers went back to the lab, and for a while gene therapy advances slowed.

Based north of Tokyo, Jichi Medical University's Professor Keiya Ozawa agrees that in 2014 the focus was stem cells. "A significant number of researchers left gene therapies to work on iPS cells," he says. But Ozawa had been working on new adeno-associated viral (AAV) vector gene therapy delivery methods since 1995, initially in collaboration with a former National Institutes of Health (NIH) colleague, Gary Kurtzman, who became involved in founding AAV start-up, Avigen. Using the company's technologies, Jichi became a major centre for AAV vector study.

As a result, two gene therapy treatments for neurological diseases have reached small clinical trials at Jichi, one on Parkinson's and one on aromatic l-amino acid decarboxylase deficiency, a rare disease characterised by severe neurologic dysfunction that leaves patients with minimal motor skills. Both reported significantly improved function.

Globally, gene therapies are also entering a new era. After a number of successful clinical trials, in 2018 the US government removed NIH special oversight rules on gene therapy studies and began considering gene therapy drugs for approval in the same way as other medications. In January 2019, the FDA indicated that it had been considering more than 800 applications for preclinical development or clinical studies for gene therapies.

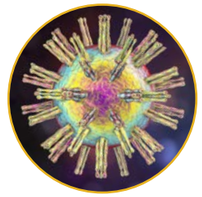
To support these efforts are a small vanguard of Japanese gene editing and gene therapy start-ups that all took off after 2014, and have recently begun attracting millions of dollars in government and investor funding. These include two 2015 entries to the market, EdiGene and EditForce, and Bio Palette, founded in 2017, among others. The latter is beginning to make its presence felt on the world stage, signing a 2019 cross-licencing deal on mutagenesis-based gene editing systems with Beam Therapeutics, a United States-based start-up using technologies developed at the Massachusetts Institute of Technology and Harvard University.

Japan has a lot to offer in terms of gene-editing expertise, says University of Tokyo Professor Osamu Nureki. Part of the founding team at EdiGene, Nureki also has links with Beam Therapeutics through Beam co-founder Feng Zhang, who pioneered the use of CRISPR in human cells. In 2018, the two researchers published on SpCas9-NG, an engineered CRISPR system that broadens the regions of the genome that can be edited. In an article in *Nature* this year, Jin-Soo Kim, the director of the Center for Genome Engineering at Seoul National University, mentioned SpCas9-NG alongside mutagenesis-based gene-editing as his pick of technologies to watch in 2019.

The persistence of some key gene therapy research centres in Japan and the convergence of a heightened interest from commercial parties, both locally and internationally, is timely, says Ozawa. "Many gene therapies are now close to the stage of commercialization, and much more attention should be paid to gene therapy approaches here," he says. ■

3

The first third-generation **HERPES SIMPLEX VIRUS TYPE 1**, engineered to kill cancer cells, has been submitted for approval in Japan to treat brain tumours.



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