AAV vector expertise behind new clinical trials

A long history of research on safe and efficient delivery has put JICHI MEDICAL UNIVERSITY at the centre of a number of important gene-therapy clinical trials for neurological disorders.

Four gene-therapy clinical trials starting in 2020 will make use of improved delivery viruses from Jichi Medical University to tackle serious neurological disorders.

Adeno-associated viral (AAV) vectors are viruses used to deliver gene therapies to different cells. They are considered one of the field's most effective delivery tools.

AAVs show particular promise in the treatment of neurological disorders, including Parkinson's disease, amyotrophic lateral sclerosis (ALS), and aromatic L-amino acid decarboxylase (AADC) deficiency, due to their low toxicity, mild stimulation of immune responses, and ability to cross the blood–brain barrier.

At Jichi Medical University, in Tochigi, north of Tokyo, much research has focused on establishing the safety and long-term efficacy of AAV vector-mediated gene therapies, including navigating problems such as ectopic gene expression and long-term persistence. After more than 20 years, those efforts are bearing fruit.

"We have seen remarkable results from clinical trials using AAV vectors for AADC gene transfer," says Shin-ichi Muramatsu, a pioneer of AAV vector research and a professor in Jichi Medical University's Neurology Department.

"Children with AADC deficiency at a hospital in Taiwan showed improvement in motor function, while other patients in Japan have also shown recovery of swallowing and respiratory functions, and, in some cases, even cognitive functions."

Such successes have contributed to the growing recognition of gene therapies as viable treatment strategies in Japan. Clinical trials starting in 2020 for neurological conditions, including Parkinson's disease, ALS, GM2 gangliosidosis and spinocerebellar ataxia type 1 have been approved for funding by the Japan Agency for Medical Research and Development (AMED).

Muramatsu points out that Jichi Medical University — including the aforementioned AADC work by Takanori Yamagata's group at Jichi's paediatric hospital — is currently the only Japanese centre conducting clinical studies using AAV vectors.

Muramatsu has been at the forefront of this area for decades. In the mid-1990s, while working as a visiting associate at the National Institutes of Health (NIH), he sequenced AAV3, one of eleven types of AAV vector, and subsequently developed other vectors for tissue-specific targeting. Most recently, he has been working on optimizing AAV vectors for haemophilia B and for liver-directed gene therapies, and has led pre-clinical studies on rare diseases including Niemann Pick Disease Type C and ornithine transcarbamylase (OTC) deficiency.

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"We are also now exploring ways to combine AAV vectors with gene-editing tools such as CRISPR/Cas9," he says. Such hybrid technologies could overcome the capacity limitation (roughly 4.5 kilobases) of AAV vectors and eventually help treat a wider range of diseases associated with larger genes, such as haemophilia A and Duchenne muscular dystrophy.

Although developing gene therapies involves balancing safety interests, Muramatsu says the field will expand, and AAV vectors should improve results. ■

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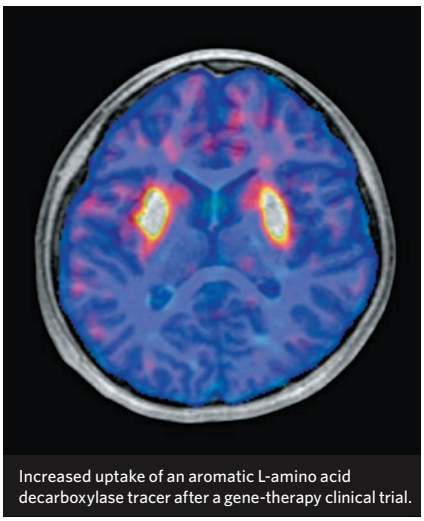
Jichi Children's Medical Center in Tochigi Prefecture, north of Tokyo.



Increased uptake of an aromatic L-amino acid decarboxylase tracer after a gene-therapy clinical trial.