MARMOSETS: A KEY TOOL FOR UNRAVELING BRAIN DISORDERS

Genetically modified marmosets are proving vital FOR UNDERSTANDING AND TREATING BRAIN DISEASE, aided by advancements in genome-editing technologies.

The common marmoset may be small enough to fit in the palm of a hand, but the diminutive stature of these monkeys belies their enormous significance in unraveling the intricate mysteries of human brain diseases.

These primates are making a big impact in the scientific community, offering invaluable insights into neurodegenerative and psychiatric conditions that have long confounded researchers, such as Alzheimer's and Parkinson's diseases, autism spectrum disorders and motor neurone disease. Common marmosets are proving to be a vital key to unlocking the secrets of the human brain.

Among monkeys, marmosets offer many advantages over other potential models. They are smaller and easier to house than macaques or baboons. Their rapid growth and quick sexual maturation help to expedite breeding programmes. And their complex social behaviours closely mirror those of humans, with intricate family structures and sophisticated communication patterns.

GREATER ACCURACY

The genetic similarity between these New World monkeys and humans also allows researchers to deploy advanced genome-editing tools to create precise and targeted modifications, mirroring specific conditions found in humans with much greater physiological and molecular accuracy than conventional rodent models allow.

"There is no other genetically modified animal model that so precisely mimics human brain disorders," says Hideyuki Okano, a neuroscientist at the Keio University School of Medicine in Tokyo and head of the Laboratory for Marmoset Neural Architecture at the RIKEN Center for Brain Science (CBS) in Wako, Japan.

Okano, Erika Sasaki and their colleagues made international headlines when, in 2009, they developed the first transgenic marmosets, each engineered to carry a jellyfish gene that made the animals' cells glow green under a special light[1]. Notably, these monkeys passed on the glowing gene to their offspring, demonstrating that stable genetic manipulations were possible and paving the way for more elaborate primate models of human disease[2].

Building on this success — and as part of the Brain/MINDS project, a 40 billion yen (US$350 million), ten-year initiative aimed at mapping the marmoset brain and developing new disease models — Okano's team has since created marmosets bearing mutated copies of genes linked to Parkinson's disease and Rett syndrome, a severe autism-related developmental disorder. His close collaborators Sasaki, a geneticist at the Central Institute for Experimental Animals in Kawasaki, Japan, and Takaomi Saido of RIKEN CBS have spearheaded efforts to make marmoset models of Alzheimer's disease as well.

At the heart of these groundbreaking endeavours lie a few critical genetic-modification techniques.

For their Parkinson's disease model, the researchers employed an older virus-mediated delivery system to introduce mutated copies of a human gene called *SNCA* into the genetic makeup of marmosets.

The expression of this faulty gene triggers the accumulation of a troublesome protein known as alpha-synuclein within the marmoset's brain. This buildup disrupts and ultimately destroys the neurons responsible for producing dopamine, a vital signaling neurotransmitter that is essential for smooth movement. As a result, the marmosets exhibit symptoms that strikingly resemble those observed in humans with Parkinson's.

Being primates, marmosets can offer insights into the human brain that cannot be obtained from rodents.

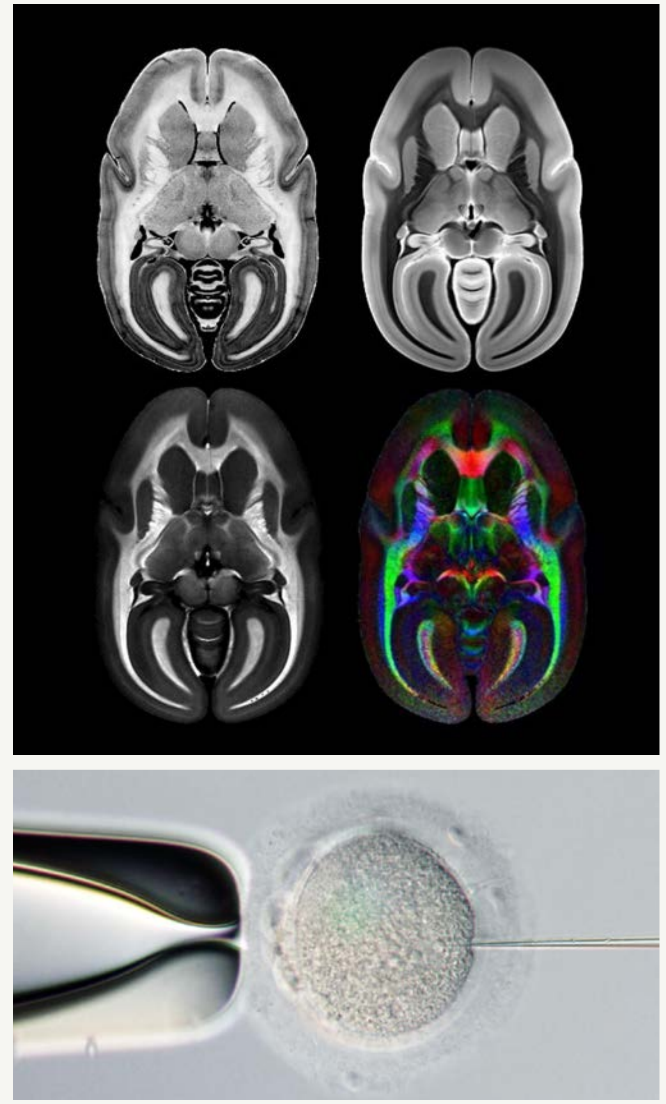
POWERFUL TOOL

Viral techniques work by introducing defective genes at random into the marmoset genome, providing researchers with a powerful tool to investigate the intricate mechanisms underlying certain diseases.

Leveraging this method, a team of researchers from the National Center of Neurology and Psychiatry in Tokyo in 2017 reported the creation of a marmoset model of a rare neurodegenerative disorder called spinocerebellar ataxia. Another group from Germany, in collaboration with Okano and Sasaki, took advantage of viral delivery systems to study the contribution of human genes in brain development.

But newer genome-editing technologies are needed to model diseases in which specific genes within the marmoset genome must be precisely rendered inoperable or manipulated.

Such is the case with Rett syndrome, a disease caused by loss-of-function mutations in a gene called *MECP2*. Okano and his colleagues have leveraged the precision of two different genome-editing tools, including the CRISPR–Cas9 system that functions like a molecular scalpel for DNA, to introduce targeted modifications in the marmoset *MECP2* gene, creating faithful marmoset models that closely resemble the human condition. Others, at the Massachusetts Institute of Technology (MIT) in the United States, used CRISPR editing to create marmosets with mutations in *SHANK3*, another gene implicated in some cases of autism spectrum disorder.



▲ **Top: Images of a marmoset brain. Bottom: Gene editing of embryos allows researchers to investigate the effects of gene variants.**

Meanwhile, Sasaki and her team have deployed a different technology, known as TALENs, along with CRISPR genome editing to amend a gene associated with an inherited form of Alzheimer's disease. The researchers deleted one specific part of this gene, known as PSEN1, and found that the marmosets' cells then pumped out more of a problematic protein called amyloid-beta known to form plaques in the brains of Alzheimer's-afflicted individuals.

"We want to find very early signs of Alzheimer's onset," Sasaki says, "so that we can start to find treatments for preventing the progression to more severe disease."

Assisting these efforts are several complementary technologies, including a digital atlas of the marmoset brain developed through the Brain/MINDS project — complete with high-resolution imaging data along with structural and functional connectivity mapping of brain circuitry patterns — plus automated behavioural tracking systems for monitoring vocal and social interactions under naturalistic conditions.

PHARMACEUTICAL DRAW

Pharmaceutical companies have taken notice of the researchers' progress. "They are very keen to use our models," Okano says. Most experimental drugs for brain diseases fail to offer benefits when evaluated in human patients. But the genetically modified marmosets are likely to provide a better preclinical test of drug efficacy and safety than standard rodent models, Okano says.

As with any scientific research involving non-human primates, ethical considerations abound — and this is especially pronounced when studying genetically modified marmosets designed to replicate the behavioural and cognitive impairments seen in debilitating human brain disorders.

Okano and Sasaki therefore prioritize animal welfare, striving to minimize marmoset suffering while advancing biomedical science ethically. For example, they meticulously screen genetically manipulated embryos prior to implantation, ensuring that only those embryos carrying the intended edits are implanted and contribute to their research projects. ■

REFERENCES

1. Sasaki, E. *Nature* **459,** 523–527 (2009).
2. Okano, H. *Ann. Rev. Neuro.* **44,** 27–48 (2021).

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