

# Alzheimer's drug trial explores gut-brain link

With new avenues of research exploring the link between the gut and the brain, **AN INNOVATIVE ALZHEIMER'S DRUG** from China offers clues.

**Dementia affects around 50 million people** with 10 million new cases annually, more than half due to Alzheimer's disease. While patient numbers are expected to triple by 2050, few therapeutic strategies have shown promise to date. With new studies hinting at a more complex story, Meiyu Geng, a professor of pharmacology at the Shanghai Institute of Materia Medica Chinese Academy of Sciences (CAS), decided to look at Alzheimer's disease through the lens of the gut-brain axis.

**WE ARE VERY EXCITED THAT SODIUM OLIGOMANNATE IS THE FIRST NEW DRUG IN 17 YEARS TO HAVE BEEN APPROVED ANYWHERE IN THE WORLD FOR TREATING ALZHEIMER'S PATIENTS**

## REFRAMING ALZHEIMER'S DISEASE THERAPIES

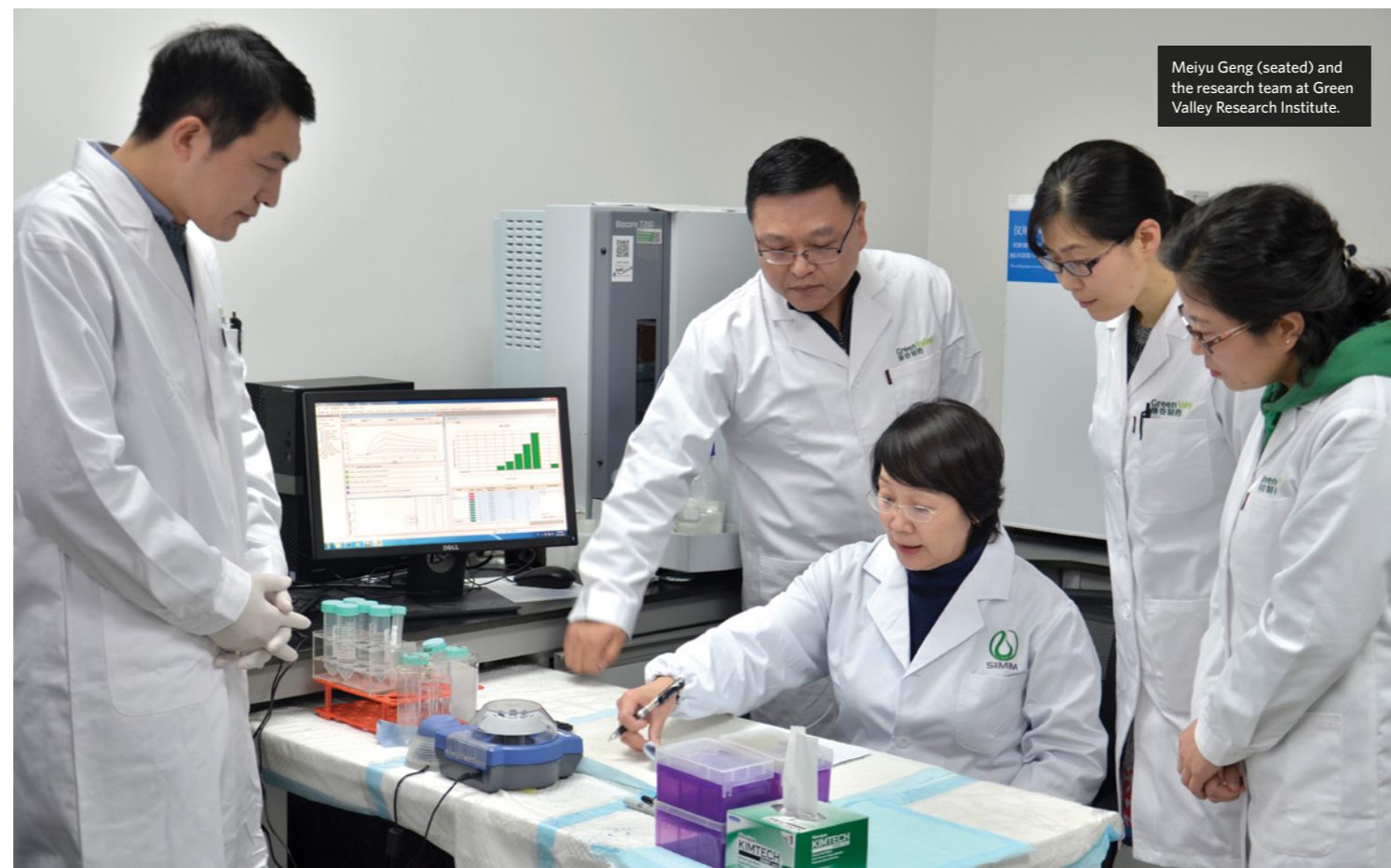
Traditional Alzheimer's disease drug research targets the amyloid- $\beta$  peptide, which gradually forms clumps in the brain; as well as the

neurofibrillary tangles due to the hyperphosphorylation of the tau protein, considered central in Alzheimer's disease's pathology.

In 1997, Geng began searching for a sugar-chain compound to compete with glycosaminoglycan in the formation of amyloid- $\beta$  fibres, thereby reducing their toxicity and deposition in the brain.

She investigated a range of factors and other studies linking Alzheimer's disease and gastrointestinal microbiota. For example, gut flora is linked to the activation of microglia (non-neuronal cells throughout the brain and spinal cord), as well as the enhancement of residential neuroinflammation resulting from peripheral immune cells infiltrating the brain. In 1999, she identified a brown marine algae extract, oligomannate, which therapeutically harnesses the abnormal production of amino acids, and the infiltration of immune cells to the brain. Re-establishing the gut-flora balance can inhibit the abnormal increase of specific metabolites of this gut microbiota, and reduce peripheral and central inflammation.

Working together with Chinese pharmaceutical company, Green Valley, her 22-year effort resulted in



Meiyu Geng (seated) and the research team at Green Valley Research Institute.

sodium oligomannate, orally administered as a capsule. Approved in China by the National Medical Products Administration (NMPA) in November 2019, GV-971 became the first Alzheimer's disease drug to be marketed since 2003. Having completed a nine-month phase III trial in 2018 in China covering 818 patients across 34 public hospitals, sodium oligomannate began a global phase III trial in October 2020 targeting at least 2,000 patients at 200 medical centres worldwide. The trial is expected to be completed by 2025.

"We are very excited that sodium oligomannate is the first new drug in 17 years to have been approved anywhere in the

world for treating Alzheimer's patients. We are grateful to our patients and families who are the real heroes in the fight against this debilitating disease," said Songtao Lv, chairman of Green Valley. "We look forward to continuing this journey to bring this treatment to patients around the world."

The challenge for manufacturing sodium oligomannate includes the high structural complexity and diversity of these carbohydrate-based drugs, compared to those based on proteins and nucleic acids. Green Valley, which has been engaged in the development, production and commercialization of carbohydrate drugs since its establishment in 1997, was

convinced of the clinical value of carbohydrate drugs, and reached out to Geng.

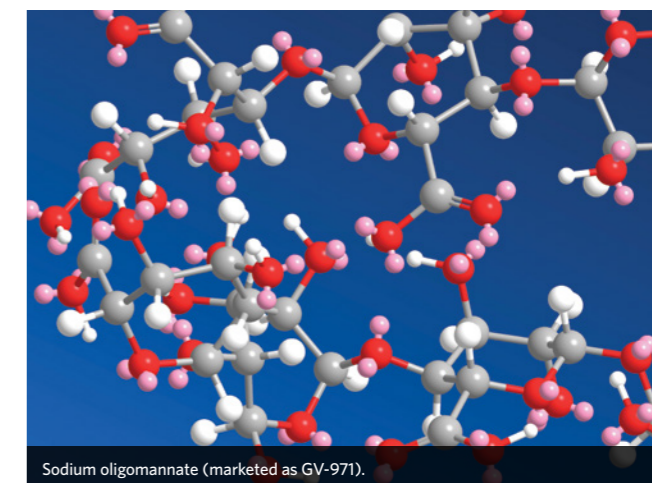
"I chose to work with Green Valley, whose ongoing support is backed by their vision for and investments in developing and manufacturing carbohydrate-based drugs," she said. Her hope is that sodium oligomannate will one day delay the progression of mild to moderate Alzheimer's disease along with recovered cognition functions maintained in the long-term.

## FORGING A COLLABORATIVE FUTURE

In 2019, her study on the effect of sodium oligomannate in mice, and the association between dynamic changes of gut microbiota and

neuroinflammation at different stages of Alzheimer's disease development, was published in *Cell Research*. The paper, featured on the cover of the October 2019 issue, also detailed the possible mechanistic links between intestinal microbiota and neuroinflammation via metabolites, suggesting how gut microbiota patterns and amino acid-derived metabolites are important for the infiltration of specific immune cell types. After publication of the paper, Geng was listed by *Nature* among the 'Ones to Watch 2020'.

The paper, however, attracted criticism from an editor of *Cell Research* about the large number of drug targets claiming to produce the therapeutic



Sodium oligomannate (marketed as GV-971).



World-class facilities at Green Valley help overcome obstacles to the production of carbohydrate drugs.

effects described, and the lack of associated side effects. Concerns were also raised that the team's prior papers on GV-971 that did not support the 2019 paper were not cited.

As Geng explained, sodium oligomannate's development is a testament to the shifting focus in China from developing follow-on to 'first-in-class' drugs. Like many pioneers, Geng has faced scepticism from the dominant line of thinking.

In a reply also published in *Cell Research*, Geng pointed out other drugs with multiple targets, such as metformin, a widely used oral type II diabetes drug, that achieved desired therapeutic effects by targeting multiple pathways. Her team countered that the uncited

papers were excluded due to insufficient relevance to the 2019 paper.

"In contrast to our critics' approach towards Alzheimer's disease's therapeutic target, I believe in scientific models like ours to test unprecedented hypotheses, and to map new therapeutic strategies targeting conditions and links less obvious," she said.

"This takes concerted efforts among scientists and experienced industry partners, such as Green Valley, to break through existing barriers." ■

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