SWEETER OPTIONS FOR ALZHEIMER'S RESEARCH

A CARBOHYDRATE-BASED ALZHEIMER'S DRUG from marine algae and a 'sugar bank' of carbohydrate compounds illustrate the innovation of a Chinese pharmaceutical company.

Alzheimer's disease remains widely misunderstood by the community. A widespread belief is that the disease just concerns the brain, but for Chinese pharmaceutical company, Green Valley, a fresh perspective linking the gut and the brain has paid off. In 2019, the company's carbohydrate-based GV-971 became the first new therapeutic drug in the past 17 years approved for use in China to treat mild to moderate Alzheimer's disease.

A complex and chronic disorder, Alzheimer's disease causes degeneration of cells in the brain that results in a gradual, eventually severe, cognitive and functional impairment. It is the leading cause of dementia for people over 60 years old. The World Health Organization estimates that globally more than 55 million people have dementia and the number is likely to increase to 139 million by 2050 as the world's population ages. Beyond the numbers of people directly affected by Alzheimer's disease are millions more, as families, healthcare and societies take up the increasing burden of patient care.

Current therapeutics for Alzheimer's disease offer some short-term relief to patients by treating the symptoms, but fail to reverse or slow the progression of the disease. These drugs target two markers in the affected brain—the increase of both β-amyloid proteins and neural fibre tangles caused by hyperphosphorylation of the Tau protein.

The many failures of late-stage clinical trials of these therapeutic strategies show that new thinking is needed for treating Alzheimer's disease, says Green Valley researcher, Xinyi Wang, and colleagues in a 2019 article in *Cell Research*.

THE GUT-BRAIN LINK OFFERS NEW OPTIONS

The link between the brain and the gut in Alzheimer's disease and other chronic diseases has come to light. Meiyu Geng, a professor of pharmacology at the Shanghai Institute of Materia Medica Chinese Academy of Sciences (CAS), noted an imbalance in the gut microbiota and the development of amyloid plaques in the brain of Alzheimer's patients. After more than two decades of research, she exploited this link and developed GV-971, a low-molecular acidic oligosaccharide compound made from an extract of marine brown algae.

The drug reconditions dysbiosis of gut microbiota and inhibits the abnormal increase of specific metabolites of the gut microbiota. "This in turn reduces peripheral and central inflammation as well as deposition of β-amyloid and hyperphosphorylation of Tau protein in the brain," Geng says.

A phase III clinical trial ran in China with 818 patients from 2014 to 2018 with the results published in Alzheimer's *Research & Therapy* in 2021. In April 2020, the FDA approved a global multi-centre phase III clinical trial, known as the GREEN MEMORY Study, that will run for 5 years across 14 countries and areas targeting more than 2,000 patients with mild to moderate Alzheimer's disease: 88 clinical centres globally had already signed up by the end of July. After the 52-week double-blind treatment period, a 26-week open-label period will follow. This suite of studies is expected to finish by 2025.

NEW PRODUCTION FACILITY AIMED AT GLOBAL SUPPLY

Green Valley is now constructing a facility that will significantly increase the production capacity of GV-971, along with a range of other carbohydrate drugs, to meet the anticipated medication needs of more than two million Alzheimer's patients.

When completed in 2024, this facility will be the third of Green Valley's production sites alongside its Qingpu base in Shanghai and Benxi base in Liaoning Province and is of considerable strategic importance, explains Songtao Lv, chairman of Green Valley.

"The new facility will play a critical role in fulfilling the mission of promoting a Chinese original and innovative drug on the global market, and bringing new hope to the patients around the world," says Lv. "To be ready to enter the global supply chain, the facility is being constructed in line with international production and quality standards, specifically those of China, United States and the European Union."

A WORLD CLASS SUITE OF SWEET COMPOUNDS

Furthering Green Valley's investigations into chronic and complex diseases is an internationally leading 'carbohydrate bank'. "The structure of carbohydrate chains is extremely complex and diverse. These energy substances, structural substances and information molecules underpin almost all physiological and pathological processes of life," explains Jing Zhang, director of the biology department at the Green Valley Research Institute. "Therefore, the ability to regulate this system provides unlimited imagination for the treatment of chronic and complex diseases."

This carbohydrate compound library is a large database of simple and complex carbohydrates, such as oligosaccharides and polysaccharides, extracted and synthesized from various species—many used in traditional Chinese medicine for centuries— including land and marine plants, microorganisms and animal tissues.

The world class carbohydrate bank will support Green Valley's unique carbohydrate drug research and development pipeline.

With growing incidence of Alzheimer's disease it is crucial to expand therapeutic options.

For each sample in the database there is a comprehensive list of information including drug use site, polysaccharide composition, polysaccharide connection, biological activity, mechanism of action, active biomarkers and other factors. "This rich database has enabled Green Valley to establish a unique carbohydrate drug research and development pipeline that includes dozens of preclinical lead compounds," explains Zhang. These compounds are the potential source of therapeutics for many major and complex diseases, such as cancer and neuropsychiatric and autoimmune diseases.

The global disease spectrum has vastly changed over the past 30 years, says Zhang, with chronic and complex diseases becoming one of the major threats to human health. Green Valley Research Institute aims to take a holistic view to explore the pathogenesis of these diseases and to seek new health solutions for these challenges.■

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