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Targeting cortisol to treat Alzheimer's disease and cognitive impairment

Biotech company Actinogen Medical is developing Xanamem, a drug designed to inhibit the increased production of cortisol in the brain, which has been linked to cognitive decline and Alzheimer's disease.

Alzheimer's disease, a chronic neurodegenerative condition leading to rapid cognitive decline, currently cannot be prevented, treated effectively or cured. Already the leading cause of death in the UK and with almost 50 million sufferers worldwide—a number set to double every 20 years—Alzheimer's disease is poised to become the next global public health crisis. In the US alone, the cost of managing the condition is estimated to reach $1 trillion by 2050.

Alzheimer's disease is characterized by the presence of amyloid plaques, an abnormal protein buildup in the brain resulting in irreversible nerve cell degeneration and eventual cell death. Over the past two to three decades, the principal target for drug development by the research community has been amyloid-β. Despite massive investment, however, the efficacy of drugs that target this peptide has been marginal at best, and new drugs with the potential to reverse the decline in brain function or slow disease progression are urgently needed. "What is required is a new approach involving novel targets and the recognition that effective treatment will require combination therapy," said Bill Ketelbey, CEO of Actinogen Medical, a biotech company that develops innovative treatments for the cognitive decline associated with neurodegenerative and metabolic diseases.

Xanamem targets raised levels of cortisol

Actinogen's Alzheimer's disease drug candidate, Xanamem, has been developed in response to robust evidence of a strong association between chronically raised levels of cortisol and the development of Alzheimer's disease. Cortisol is a steroid hormone normally produced in times of physical and mental stress. Persistently elevated cortisol levels in the brain, however, can become toxic to neurons. Data from several major studies have consistently shown an association between increased cortisol levels and the cognitive decline that occurs with the neurotoxicity in the brain. "There is a large and growing set of epidemiological data in both humans and animals indicating that reducing cortisol in the brain is a promising new approach to slowing, or even preventing, the cognitive decline associated with Alzheimer's disease and other disorders," said Ketelbey.

Through a novel mechanism of action, Xanamem selectively inhibits the activity of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) (**Fig. 1**), an enzyme that converts inactive cortisone into its active form cortisol; 11β-HSD1 is present in high concentrations in the hippocampus and the frontal cortex, areas of the brain most associated with recent memory and behavior, and most affected by Alzheimer's disease. "Other molecules that systemically target 11β-HSD1—in adipose tissue or the liver, for example—have not proved beneficial in treating Alzheimer's disease, largely because they have struggled to access the brain and reduce local cortisol levels," said Ketelbey. "Such molecules appear to achieve little more than 10% inhibition of 11β-HSD1 in the brain, whereas Xanamem, which has been specifically designed to cross the blood–brain barrier, is expected to inhibit the enzyme's activity by 50%."

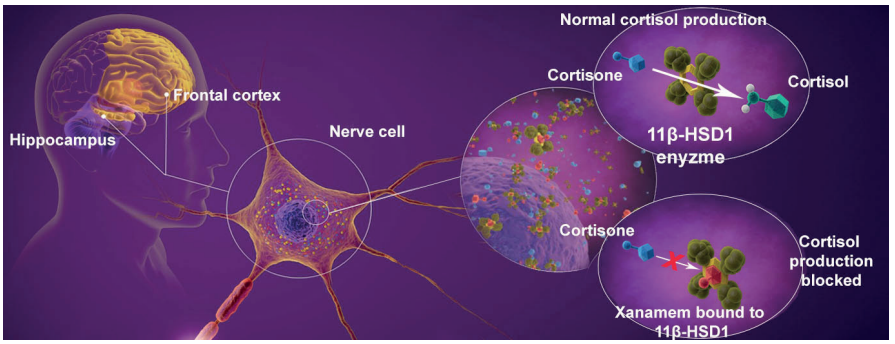

Fig. 1 | Mechanism of action of Xanamem. Xanamem selectively inhibits the activity of 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), an enzyme that converts inactive cortisone into its active form cortisol; 11β-HSD1 is present in high concentrations in the hippocampus and the frontal cortex.

Promising clinical results

Preclinical studies demonstrate that Xanamem is both symptomatic and disease-modifying; in mouse models of Alzheimer's disease, administration of Xanamem resulted in a significant improvement in cognition after only 28 days, continuing for 41 weeks. Phase 1 clinical studies demonstrated that the orally administered drug is safe and well tolerated in humans. And topline results from XanADu, a major international double-blind, randomized, placebo-controlled phase 2 study of Xanamem in mild Alzheimer's disease (currently recruiting), are expected by mid-2019. "The implications of a positive signal from XanADu to the future understanding and treatment of Alzheimer's disease are immense and, with the addition of a number of new studies, we are confident we will have a substantial data package available next year to clearly define Xanamem's future development," said Ketelbey. "We are anticipating that Xanamem will be used in combination with other Alzheimer's disease therapies with little or no competition in what is a vast and growing market."

With the link between chronically raised cortisol and cognitive decline having also been identified in patients with type 2 diabetes, Parkinson's disease, schizophrenia, Cushing's syndrome, depression, and post-traumatic stress disorder (PTSD)—as well as in normal aging—Xanamem's novel mechanism of action offers multiple additional opportunities. "We are evaluating Xanamem for future development in a number of significant indications, including diabetes and PTSD," said Ketelbey. "If effective, Xanamem could also have an enormous impact on the global burden of these diseases."

Actinogen's management team and scientific advisory board include world-renowned Alzheimer's disease and dementia researchers and industry specialists in drug development and clinical trial management. In recognition of its potential, the company has recently received substantial institutional investment allowing it to expand its development program. Actinogen is interested in partnering with academic and commercial parties to progress Xanamem's development in Alzheimer's disease and the additional indications involving cortisol-associated cognitive impairment. "We have a vast array of potential opportunities for cognitive enhancement," said Ketelbey. "Targeting elevated cortisol with our novel, first-in-class drug candidate could offer a clinically meaningful solution for millions of patients and their families."

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