Thirty years ago, Alzheimer’s disease (AD) was considered an uncommon disorder, attracting little attention from a medical fraternity busy tackling other pressing health problems such as cancer and cardiovascular disease.

In 2017, more than 50 million people worldwide are currently affected by AD, and the disease is poised to become the next global health crisis. Despite the dedication of many in this field, developing drugs for AD has proved particularly challenging. There are currently only four drugs to treat the disease, all of which provide limited symptomatic benefit – none prevent disease progression. Actinogen Medical, a Sydney biotechnology company, is taking on this challenge with its candidate drug Xanamem, using insights from 25 years of AD drug development.

A fundamental shift in the approach to AD research has helped shed light on a disease process that can start a decade or more before the onset of symptoms. AD drugs tested in the past may have failed because they were used too late in the disease to have much effect. Also, the β-amyloid plaques, which for more than 30 years have been considered responsible for the neurodegeneration characteristic of AD, may in fact be a sign of the disease rather than the cause. This shift away from the amyloid hypothesis has opened the door to fresh approaches and the pursuit of new avenues of investigation.

One such avenue being pursued by Actinogen Medical is the association between chronically raised cortisol and the development of AD. Healthy, elderly individuals with high plasma cortisol levels were significantly more likely to develop AD than those with low cortisol levels, and those with concomitant β-amyloid plaques were at even greater risk, studies showed.

Actinogen Medical is developing Xanamem, a centrally active drug designed to reduce brain cortisol through inhibiting the enzymatic activation of cortisol by 11β-HSD1. In a mouse model of AD, Xanamem was effective in improving cognitive function and clearing amyloid plaques from the brain. Notably, improved cognitive function was observed after only four weeks of treatment, and was maintained for at least 41 weeks. While many drugs 2017 showed early promise in animal models failed in human trials, these results, together with the evidence from the AIBL study and many others, support the hypothesis that reducing brain cortisol presents a very rational target for the treatment of this devastating disease.

Many drug candidates have been tested in AD, with very few successes, but while these failures have been frustrating and expensive, the Alzheimer’s research community has gained valuable insights into drug research in AD through these failures. These insights have been instrumental in refining the design of Actinogen Medical’s study for Xanamem in AD. XanADu (www.ClinicalTrials.gov: NCT02727699) is Actinogen Medical’s Phase II safety and efficacy study of Xanamem in patients with mild Alzheimer’s disease. XanADu is a double-blind, randomised, placebo-controlled study of 174 patients at 20 sites across Australia, the United Kingdom and the United States.

The XanADu patient cohort has mild Alzheimer’s (MMSE 20-26), no longer responding to standard best care. While newly diagnosed patients are more likely to respond to medication, the downside is the difficulty in measuring a response to treatment in such a relatively ‘well’ patient. To address this, the trial includes ADCOMS1 as a co-primary endpoint alongside ADASCog14.

XanADu is believed to be the largest global Alzheimer’s trial ever run by an Australian biotechnology company. Patient recruitment and treatment commenced in 2017 and is on track to enrol the last patient in the fourth quarter of 2018, with top-line results expected in early 2019. If the results from XanADu demonstrate that Xanamem is effective in the treatment of mild AD, it will be one of the most meaningful global medical breakthroughs in this disease in many years.