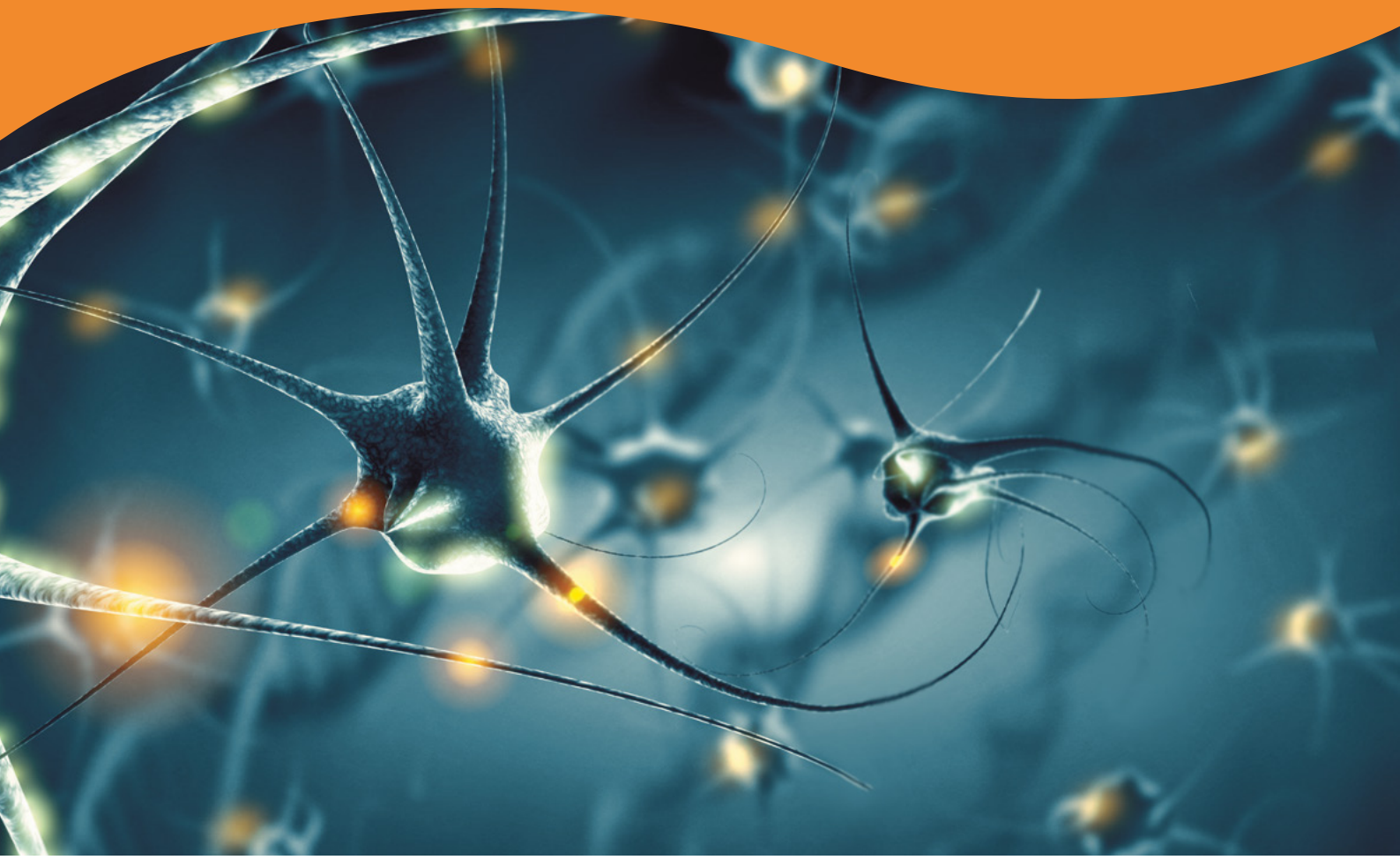
Research Milestone
By Dr Arne Ittner

Dementia Australia™
Research Foundation



A novel neuro-protective mechanism in Alzheimer's disease

What was the aim?

To find out how the molecule p38gamma protects brain cells from amyloid toxic signals.

How did this happen?

Stage 1: Used mice to determine the effects of p38gamma on the onset and progression of memory deficits, and also on amyloid beta levels, amyloid plaque load and related cellular processes.

Stage 2: Used electroencephalography to record and analyse brain activity in Alzheimer's mice without p38gamma.

Stage 3: Used cell culture, biochemistry and a transgenic approach in mice to decipher the role for p38gamma in limiting amyloid toxicity.

Has it been successful?

Yes, the work described a new neuroprotective pathway and — more strikingly — a new function of the tau protein, a major factor in Alzheimer's disease.

Why was this project so important?

Few Australians have not been affected by dementia within their families or social circles. The most prevalent type of dementia is Alzheimer's disease.

Unfortunately, there is neither efficient therapy nor a cure available. This is partly due to the complex nature of this disease. Understanding more about the stages and events underlying Alzheimer's disease is the first important step in developing new therapies and treatments.

Whilst previous research had shown that the toxic signal of amyloid was being caused by changes in brain cell molecules, until this project, researchers were unaware that there were also molecules that could inhibit these toxic signals. This was a significant gap in knowledge that this project has now begun to close.

Dr Ittner's research boldly suggested a molecule which he believed could protect brain cells from amyloid toxic signals - p38gamma. The results of the p38gamma study have completely changed researchers' understanding of the disease because it described a new protective role for the tau protein. Tau was until then thought to only promote amyloid toxicity and the progression of dementia.

What was found?

- Mice without the p38gamma gene have greater cognitive decline and death than those with it, suggesting some protective properties or mechanisms exist.
- Insight into the protective signalling that limits toxic damage of neurons in Alzheimer's disease.
- New information about a critical step in the formulation of tangles that has, until now, been misunderstood.

What is amyloid toxicity?

In a brain with Alzheimer's disease, certain proteins deposit in the brain tissue forming amyloid plaques. Sections of the amyloid plaques are toxic to brain cells, causing them to die. This process is called 'amyloid toxicity'.

> **"This study has completely changed our understanding of what happens in the brain during the development of Alzheimer's disease."**
>
> **– Professor Lars Ittner**

Why is p38gamma important?

Alzheimer's disease is most recognisable as a loss of memory, because of dying brain cells and brain atrophy.

P38gamma is a molecule that can protect brain cells, so understanding how it does this could help researchers find a way to stop, slow or prevent the disease.

What is electroencephalography?

Electroencephalography (EEG) records electrical activity in the brain.

Dr Ittner's study used hippocampal electrodes and subcutaneous telemetric transmitters to record brain waves from mice. Amyloid-beta causes brain waves to form spikes on the EEG. Such spikes also are detected during a seizure.

What was created?

A widely publicised and applauded academic paper in the journal *Science* https://www.ncbi.nlm.nih.gov/pubmed/27856911.

What are the next steps?

Should funding become available, Dr Ittner's team will develop their patented discoveries into a novel treatment and therapeutic tools for humans in the long term. This work is funded by the National Health and Medical Research Council (NHMRC) and the Australian Research Council (ARC).

What will this mean for the future?

- A significantly enhanced understanding of mechanisms that limit toxic signals in brain cells in Alzheimer's disease, and hence greater potential for successful interventions.
- Implementation of new strategies for treatment.
- A greater understanding of the protective role of p38gamma, and hence greater potential for successful treatments.

What sort of mice are used?

In the 1990s, researchers discovered a gene mutation that could be inherited in mice. It's very similar to the gene mutation that's seen in the genetic form of human Alzheimer's disease. It causes plaques on the brain (which are thought to contribute to Alzheimer's disease) and also cognitive deficits.

These mice are often known as APP mice, which stands for 'amyloid precursor protein'.

Besides plaque formation and neuronal loss, human Alzheimer's disease and APP mice share epileptic-type (epileptiform) brain activity, which makes detection on EEG possible.

How do I know the experiments were not cruel?

Dr Ittner's mice based research underwent careful screening and were approved by the University of New South Wales animal ethics committee.

Who undertook the research?

Dr Arne Ittner, University of New South Wales

Dr Ittner is a Post-doctoral Research Associate based at the Dementia Research Unit, School of Medical Sciences, University of New South Wales. He began his two year half funded AADRF fellowship in early 2015.