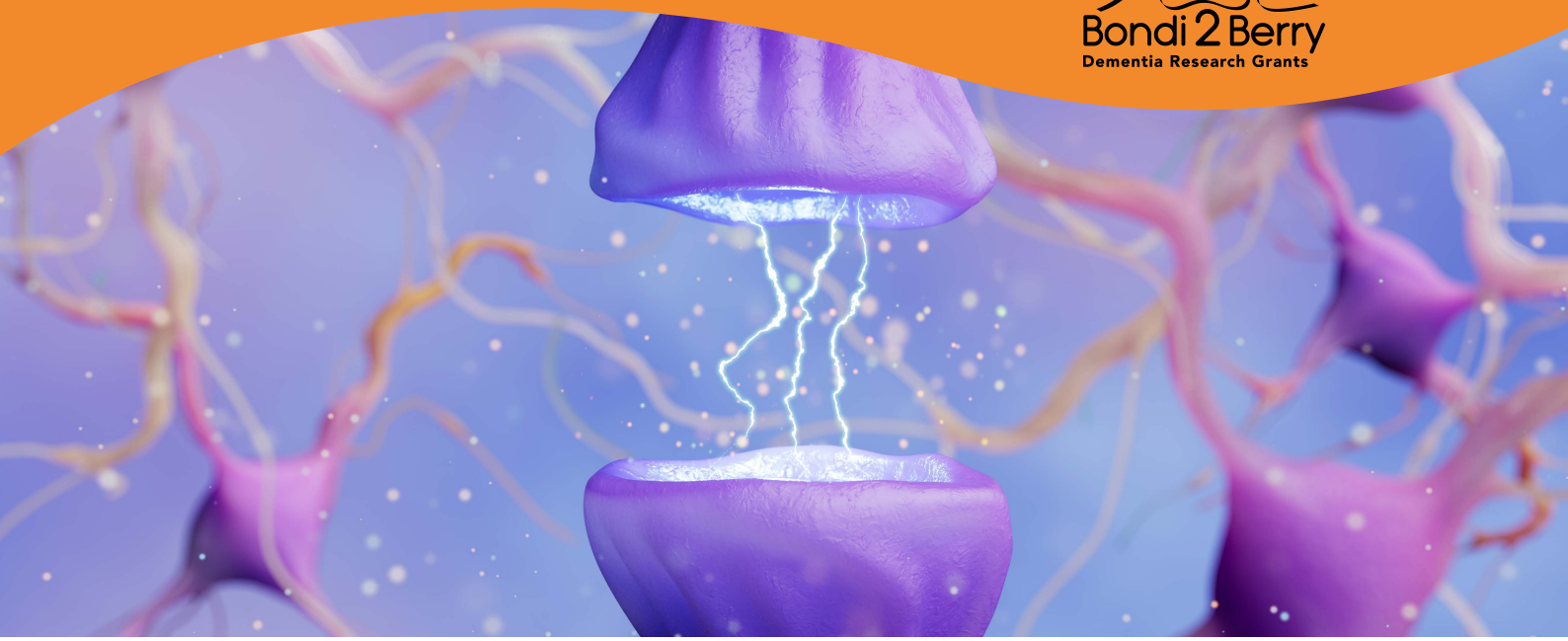
Research Project
By Dr Janet Van Eersel

Dementia Australia™
Research Foundation

Bondi 2 Berry
Dementia Research Grants



Preclinical development of specific tau-binding compounds to target underlying disease mechanisms for the treatment of dementia

What is the focus of the research?

To identify novel chemical structures that can inhibit Tau:Fyn interactions, and that can be used to ultimately develop a new treatment for Alzheimer's disease.

What is Tau?

Tau is a protein in the brain.

It is thought that Tau's role in Alzheimer's disease may be due to excessive interactions with another protein known as Fyn. Together, Fyn and Tau set off a cascade of events that lead to overstimulation of neuronal brain cells, eventually causing cell death. It is vital that ways to stop either the presence of one or the interaction of both are explored.

How will this happen?

Stage 1: Use a DNA-encoded library (DEL) screening to identify compounds that can disrupt interactions between Tau and Fyn, by focussing on identifying compounds that can bind to Tau at sites across the protein and those that can specifically bind to the Fyn-interacting domains of Tau.

Stage 2: Evaluate, distinguish and catalogue compounds that can bind to the Fyn-interacting domain of Tau and those that bind to Tau elsewhere on the protein.

Stage 3: Test binding hits in cell culture models (in vitro) to determine their potential usefulness.

Stage 4: Test the most promising candidates in primary neurons.

Stage 5 (option 1): Assess the effects of Tau:Fyn interaction inhibitors in mouse models (in vivo) using electroencephalography (EEG). primary neurons.

Stage 5 (option 2): Modify the binding hits to specifically remove the Tau protein.

Why is it important?

Dementia is the second leading cause of death in Australia, with hundreds of thousands of families currently devastated by its impact. Alzheimer's disease and frontotemporal dementia are two of the most common causes of dementia.

Unfortunately, there is as yet no effective treatment or cure for either of these disorders. This means the development and testing of new therapies is vital.

Although these two dementias are quite distinct from one another, in both conditions, a protein known as Tau is thought to play a central role in the disease process.

Traditionally, treatments for Alzheimer's disease have focused on targeting amyloid-beta (Aβ) peptides and their associated plaques. Unfortunately, many of the Aβ clinical trials have failed and so the focus has turned towards new disease pathways including Tau-targeting therapies.

Dr Van Eersel and her team are hopeful that if interactions between Tau and Fyn could be disrupted or reduced in the brains of people with dementia, this would provide therapeutic benefits.

What will this mean for Dr Van Eersel's team?

It's vital that Dr Van Eersel's team conducts in vivo testing of the new compounds. Significant data that they need to carry this out will be obtained during this study. After this project, they will be able to use their findings to seek further funding, and develop an Investigational New Drug regulatory package to engage with pharmaceutical companies for clinical testing and commercialisation.

Why are mice 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.

What will this mean for people with dementia?

- Potential to take part in future clinical trials.
- Potential therapeutic benefits in their lifetime.
- Hope that there may be a cure someday.

What will this mean for the medical industry

- Identification of potential new drug candidates for the treatment of Alzheimer's disease.
- Groundwork laid for pre-clinical testing and clinical trial testing.
- Potential therapeutic leads to help people with Alzheimer's disease.

How will this research help to progress a new drug?

The first step towards the development of a new drugs is identifying a molecule that can bind to a Tau with high affinity.

New technology called DEL will allow the target samples in Dr Van Eersel's study to be tested against a whole library of compounds to identify these binders. It will test 14 billion compounds in a single reaction!

Because DEL is faster, more cost effective, more efficient, and screens more deeply than other methods, drug candidates found with the results of this study should be able to move more quickly into clinical trials.

Who's undertaking the research?

Dr Janet Van Eersel, Macquarie University

Dr Janet van Eersel is a group leader in the Dementia Research Centre in the Department of Biomedical Sciences of the Faculty of Medicine and Health Sciences at Macquarie University. She received her PhD from the Department of Pathology at the University of Sydney in 2010 before continuing her work on dementia at the Brain and Mind Research Centre, and eventually moved to UNSW where she worked in the Dementia Research Unit headed by Prof Lars Ittner.

Bondi 2 Berry
Dementia Research Grants

Dr Van Eersel and Dementia Australia Research Foundation would like to acknowledge the support of Bondi2Berry and Bondi2BlueMountains in making this research possible.