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 inhibit tau:fyn interactions, and can be used to ultimately develop a new treatment for Alzheimer's disease.

Why is this 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 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, so the focus has turned towards new disease pathways, including Tau-targeting therapies.

Dr van Eersel is hopeful that disrupting the interactions between tau and another protein called fyn in the brains of people with dementia will provide therapeutic benefits.

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 the protein 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 focusing on identifying compounds 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) in vitro cells.

Stage 5 (option 2): modify the binding hits to enhance the removal of tau protein.

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.

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 does this project get us closer to a treatment?

The first step towards the development of a new drug is identifying a molecule that can bind to 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 van Eersel is a group leader in the Dementia Research Centre in the Faculty of Medicine, Health and Human Sciences at Macquarie University. Her team's main aim is to develop novel therapeutics for dementia and other neurological disorders, including immunotherapies, gene therapies and small molecules.

She received her PhD from the Department of Pathology at the University of Sydney in 2010 before continuing her work on dementia at the Brainand Mind Research Centre, and eventually moved to University of New South Wales, where she worked in the Dementia Research Unit until 2018.

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