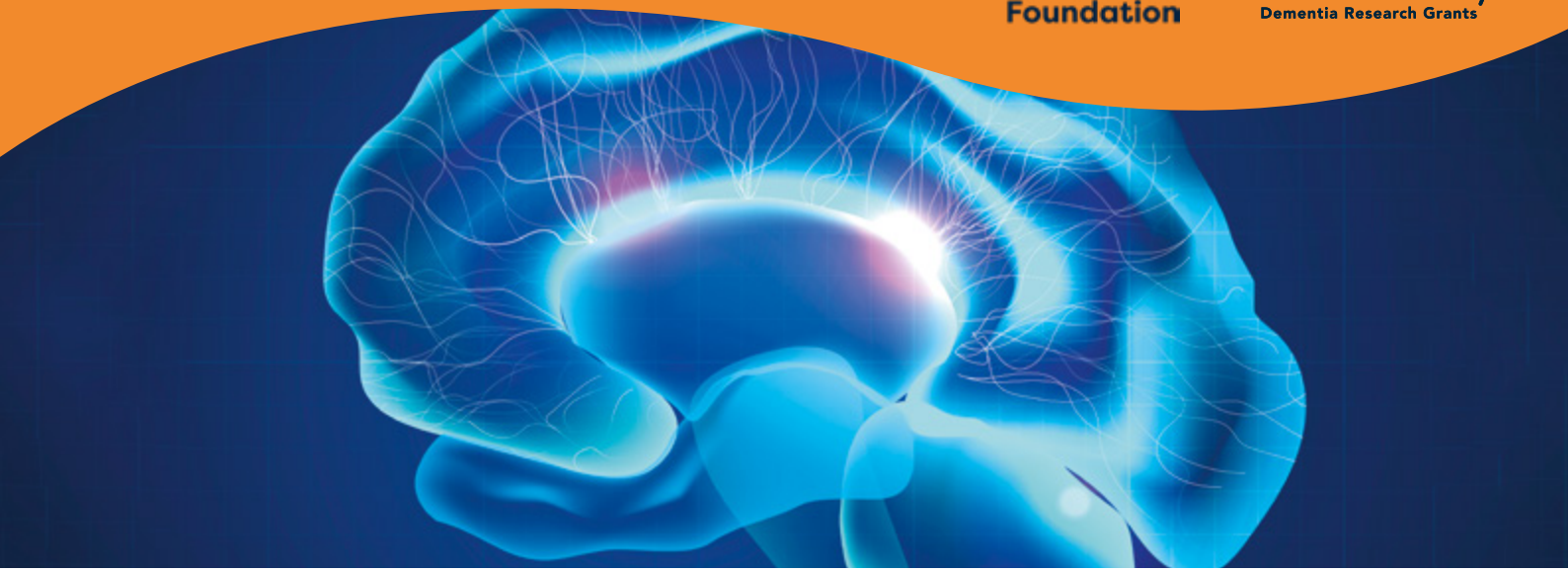
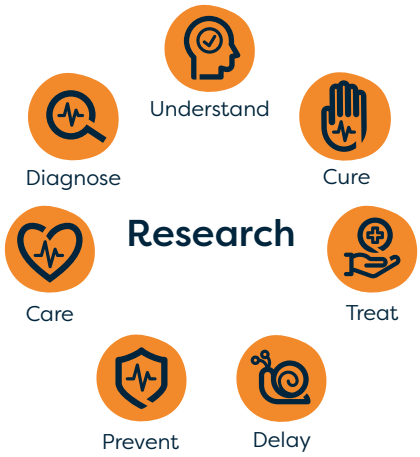
Research Project
By Dr Leah Beauchamp

Dementia Australia Research Foundation

Bondi 2 Berry
Dementia Research Grants



Protein phosphatase 2A methylation as a therapeutic target in Alzheimer's disease



What is the focus of the research?

To determine whether novel compounds that supplement the methionine cycle will increase PP2A methylation and reduce pTau.

How will this happen?

Stage 1: Test the efficacy of a number of compounds which have been designed to increase SAMe levels, in select cells in vitro (outside the body) to determine functionality and target engagement.

Stage 2: Posttreatment, measure PP2A levels, activity and methylation, pTau levels and SAMe levels.

Stage 3: Assess the compounds for efficacy and safety, and select the lead compound(s) for testing in primary cortical neurons.

Stage 4: Assess the pharmacokinetic properties of the compound(s), such as half-life and the ability to cross the blood-brain barrier.

Stage 5: Use in-house technologies to refine the compound(s) and re-test blood-brain barrier permeability.

Stage 6: Test the refined compound(s) in two mouse models, performing behavioural analysis, and testing for cognitive function, hyperactivity, and anxiety.

Stage 7: Perform post-mortem protein sampling of the mice brains to measure PP2A.

What is PP2A?

PP2A is a common family of enzymes in the brain. It is modulated and regulated to prevent untimely activation. Alterations (demethylation) to PP2A occur in affected regions of a brain with Alzheimer's disease. It is suspected that disfunctions in PP2A contribute to pTau which contribute to Alzheimer's disease.

What Is The Methionine Cycle?

Methionine is an amino acid that plays a role in protein structure and metabolism. It is activated during the methionine cycle and becomes S-adenosylmethiwonine (SAMe). The level of SAMe are substantially decreased in a brain with Alzheimer's disease. and hence Alzheimer's disease progressively spreads throughout the brain.

How are they linked?

Dr Beauchamp hopes to find a special compound to supplement the methionine cycle and restore PP2A methylation homeostasis. If this happens, it may result in a reduction of dementia-like endophenotypes in mouse models, and hopefully lead to an opportunity for human trials.

Why is it important?

Alzheimer's disease is a devastating disease accounting for approximately 70% of all cases of dementia. There is currently no cure, nor any particularly effective treatments for Alzheimer's disease, so there is an urgent need for new therapeutic strategies to help people living with it and support families impacted by it.

Tau is a protein that we need throughout life, however, in Alzheimer's disease it changes and becomes sticky, causing the protein to clump in the brain cells and become toxic. Dr Beauchamp's project will develop strategies to correct the biochemical failure that leads to this toxic protein build up.

She believes that promoting the methylation event that drives PP2A activity has real therapeutic potential for Alzheimer's disease, and we are eager to see her results.

What will this mean for people with dementia?

- Potential new therapies for Alzheimer's disease.

What will this mean for the future?

- Data to facilitate further preclinical development.
- Better brain health as we age.measured in early Alzheimer's disease.

Who's undertaking the research?

Dr Leah Beauchamp, The Florey Institute of Neuroscience and Mental Health

Dr Beauchamp is a postdoctoral fellow at Neurotherapeutics Laboratory at The Florey. Her early work has helped to identify potential causes of a common symptom of Parkinson's disease and this is currently being investigated in patients, with the hope of developing a novel diagnostic aid.

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