Research Project
By Dr Janet Van Eersel

Dementia Australia Research Foundation

ROYCE SIMMONS FOUNDATION

Developing a revolutionary dementia treatment that targets the build-up of toxic protein in the brain

What is the focus of the research?

Developing a next-generation dementia treatment that acts on the abnormal build-up of a protein called tau between brain cells that causes cognitive decline.

Why is it important?

This project will use cutting-edge technology to transform the development of future dementia treatments. The abnormal clumping of tau is found in the brains of people with Alzheimer's disease and frontotemporal dementia. At first, these clumps are small. But as disease progresses, they mature into large "neurofibrillary tangles", which scientists initially believed caused brain cells to die. However, exciting new research suggests that it's the initial, smaller clumps that are responsible for cell death and subsequent cognitive impairment.

This discovery has major implications, since drugs that are currently in clinical trials are designed to target and dissolve the mature neurofibrillary tangles. These drugs may cause the release of the small, toxic tau clumps that were safely trapped away in mature tangles.

Dr van Eersel's project aims to create the next generation of tau-targeting drugs that act specifically on the smaller clumps, not the tangles. By combining mouse models and her newly developed lead compound, this may be the most promising drug candidate to date.

How will this happen?

Stage 1: test a new lead chemical compound designed to prevent the formation of toxic tau clumps (without disturbing existing mature clumps) on genetically modified mice that develop tau pathology and exhibit dementia-like symptoms. Test at two and four months with either the new compound or a control to determine any cognitive improvements.

Stage 2: harvest the mouse brains to assess any changes in the amount of tau clumping. Researchers to continue refining the compound to achieve greater clinical results and generate new compounds.

Stage 3: partner with a pharmaceutical company to further test the compound for toxicity, dosage and potential drug interactions, to begin carving a path towards clinical trials.

What will this mean for the medical industry

- Tau testing methodology that is at the forefront of early drug discovery.
- Rapid detection of more specific, next-generation tau-clustering inhibitors.
- Potential for significant clinical benefits for modern medicine.
- New compound candidates that can be further developed for clinical trials.

> **We believe we can possibly prevent the death of brain cells and potentially stop tau from spreading.**
>
> **— Dr Janet van Eersel**

From mouse to man

Drug testing must undergo many rigorous phases of research before approval for use in humans. Mouse trials are within the "pre-clinical" phase. If a treatment is successful within this phase, there's still a long way to go before your doctor can write you a prescription. The drug candidate undergoes several more years of rigorous testing, so researchers can show it is safe and effective for use in humans. They then apply to the government's regulatory body, the Therapeutic Goods Administration, for approval to use in the next phase – human clinical trials.

There are four phases of clinical trials, which encompass the initial safety testing on a small group of people, through to studying the effectiveness of the drug and any adverse side-effects after it has been approved for public use. In general, it takes many years and billions of dollars for a drug to go from mouse trials to prescription pads.

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 University of Sydney in 2010 and continued her work on dementia at the Brain and Mind ResearchCentre. She has also carried out her research at the University of New South Wales' Dementia Research Unit.

The title of her project is *Pre-clinical development of next-generation tau aggregation-inhibitors for the treatment of dementia.*

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