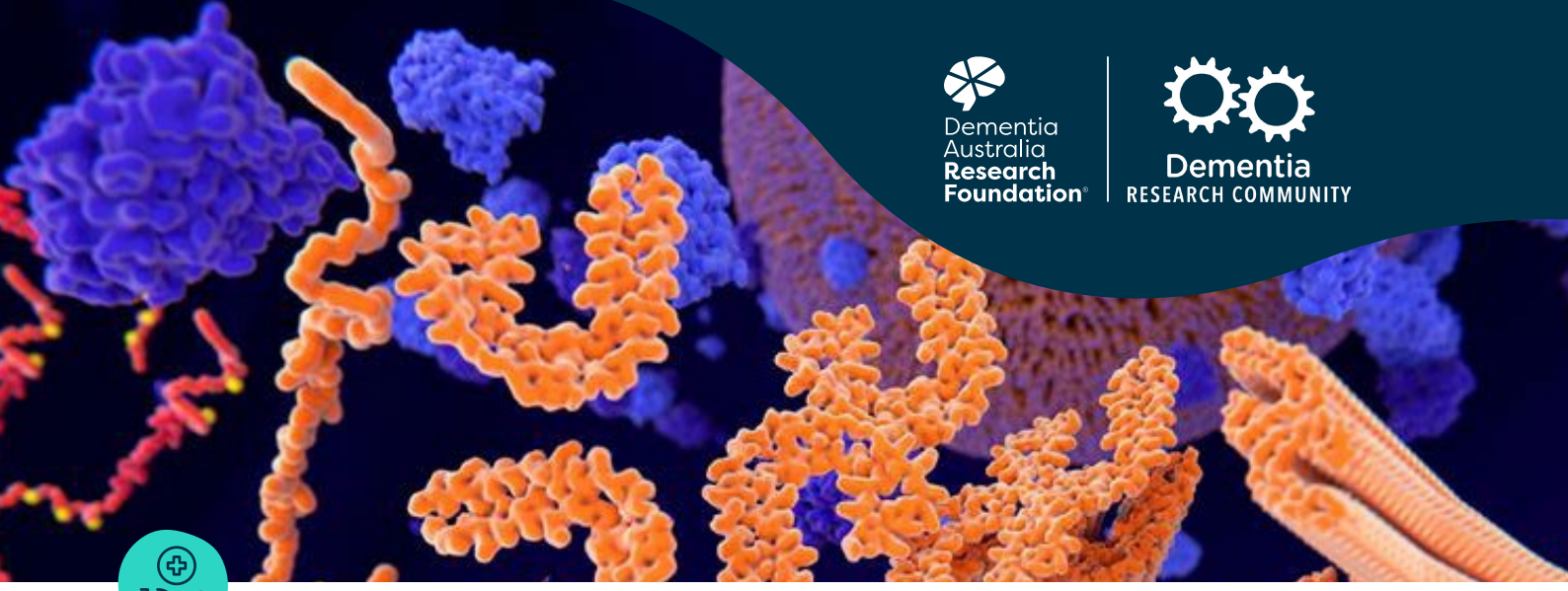

Dementia Australia Research Foundation

Dementia RESEARCH COMMUNITY

Treat

Targeting new cellular pathways for treatment of Alzheimer's disease

RESEARCH PROJECT BY
Dr Esteban Cruz

What is the focus of the research?

Developing a new treatment strategy that uses autophagy, the body's cellular recycling system, to degrade a toxic protein involved in Alzheimer's disease.

Why is this important?

Alzheimer's disease is the most common form of dementia and remains without a cure. The disease is characterised by the accumulation of toxic proteins in the brain, including tau, which forms tangles inside brain cells and disrupts their function. These tau tangles are strongly associated with disease progression and severity, especially in later stages of Alzheimer's disease.

What is tau?

Tau is a protein normally involved in stabilising the internal skeleton of brain cells. In Alzheimer's disease, tau becomes abnormal and forms tangles inside brain cells disrupting crucial cell processes. This leads to cell damage and death.

What is autophagy?

Autophagy is a natural process used by cells to break down and recycle unwanted or damaged components. It's like a cellular clean-up crew, helping maintain a healthy balance of proteins and cellular structures. In Alzheimer's disease, autophagy becomes impaired, allowing harmful proteins like tau to build up.

Despite decades of research, most tau-targeting therapies have struggled to produce meaningful results in clinical trials. So, there is an urgent need for new therapeutic strategies that can more effectively reduce toxic tau build-up in the brain.

Dr Cruz will explore a new approach: harnessing autophagy, the brain's natural recycling system, to selectively break down

Who's undertaking the research?

DR ESTEBAN CRUZ

The University of Queensland

Dr Cruz is an early-career researcher at the Queensland Brain Institute, The University of Queensland. His work focuses on developing targeted therapies for Alzheimer's disease by integrating protein engineering with neuroscience. He has led the development of new antibodies and autophagy-based approaches to clear toxic proteins from the brain. His broader research interests include improving therapeutic delivery to the brain, with a particular focus on antibody-based technologies for the treatment of neurodegenerative diseases.

The title of Dr Cruz's project is *Targeted autophagosomal degradation of tau to treat Alzheimer's disease*.

Dr Cruz and Dementia Australia Research Foundation would like to acknowledge Dementia Research Community for making this project possible.

toxic tau aggregates. By directing tau to this degradation pathway, Dr Cruz aims to reduce its toxic function and restore brain cell health. This will pave the way for treatments that could slow or even reverse the progression of Alzheimer's disease.

How will it happen?

STAGE 1

Discovering how to guide proteins to the autophagy degradation pathway

Study the domains within proteins that naturally direct waste to the autophagy (cell death) pathway, aiming to identify the cellular elements responsible for this recruitment.

STAGE 2

Design and develop tau-targeting degraders

Engineer proteins that combine tau-targeting domains with identified cellular elements from Stage 1 that are responsible for directing proteins to autophagosomes for degradation. These constructs will function as guides that selectively recruit tau into the cell's waste disposal pathway.

STAGE 3

Test degrader function in cells

Use live cell models to assess whether the tau degraders designed in Stage 2 reduce toxic tau accumulation and restore cell health. These methods will also identify the most effective constructs for further testing.

What will it mean for dementia research?

- A novel therapeutic strategy to eliminate toxic tau protein accumulation.
- A way to harness the autophagy process for long-term disease control.
- New tools to study autophagy in neurodegenerative diseases.
- The potential for a next-generation therapy that slows or reverses disease progression.