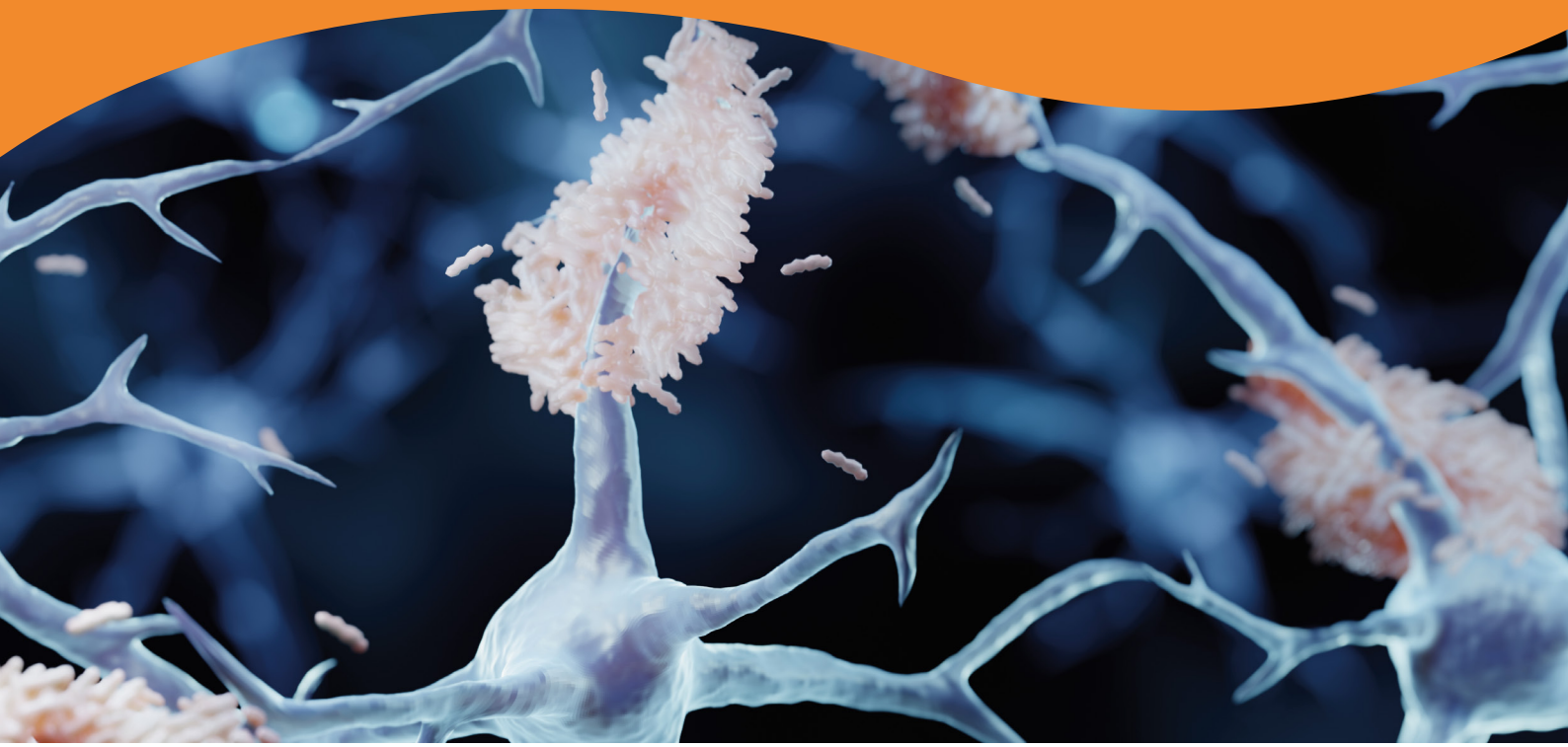
Research Project
By Dr Michael Healy

Dementia Australia™
Research Foundation



Understanding protein toxicity offers hope for new Alzheimer's disease research pathways

What is the focus of the research?

Investigating an unknown protein complex essential for maintaining the health of brain cells, in the hope that by understanding its biology, researchers can develop targeted dementia treatments.

Why is it important?

Alzheimer's disease is a debilitating neurodegenerative condition that devastates families and communities. All attempts to find a cure or slow its progression have failed. Dementia is the second-leading cause of death in Australia and by 2025 it is expected to cost our economy $18 billion.

We urgently need new treatments that act on the disease's underlying molecular pathologies. Scientists know that the development of Alzheimer's disease involves the gradual accumulation and toxicity of proteins amyloid beta and tau in the brain. But they still don't fully understand how or why this occurs.

One critical pathway that can influence the rate of amyloid beta production and the clearance of accumulated toxic material is known as "membrane trafficking". This is the process by which membrane "cargo" (proteins and lipids) is moved around the cell. When this process fails, toxic proteins accumulate, and Alzheimer's disease develops.

Membrane trafficking is like a postal service. Cargo (protein and lipids) in our cells have labels (amino acid sequences). These labels are recognised by postal workers (protein trafficking complexes) and loaded into delivery trucks (membrane vesicles) that facilitate the delivery of cargo to the right place at the right time. If everything runs smoothly, proteostasis of our cells is maintained. But failures in these delivery systems result in the accumulation of toxic proteins that cause the death of cells. This

is particularly important in neurons, which are highly sensitive to blocks in protein trafficking.

In this project, Dr Healy will investigate an essential protein complex (postal worker) known as Commander. It is a master regulator of a specific membrane trafficking pathway called protein recycling. One of its important cargos is the Amyloid Precursor Protein (APP), which is central to Alzheimer's disease pathology. By understanding the structure and function of this protein complex, he hopes to provide greater clarity on its role in maintaining cellular proteostasis and what goes wrong in disorders, including Alzheimer's disease. The results of this project may open new avenues for the development of therapeutics that treat its underlying cause.

How will this happen?

Stage 1: the Commander complex requires a partner called SNX17, which binds APP and other important cargos. To understand how these function, Dr Healy will use biochemical and computational methods to characterise how they interact with each other at atomic resolution.

Stage 2: to paint a complete picture of how Commander functions, Dr Healy will combine modern structural biology techniques, including cryo-electron microscopy and computational modelling, to study details of this protein complex in human cells. He hopes it will allow him to develop new drugs or molecules that can enhance its neuroprotective role.

What is proteostasis?

The maintenance of the right amount of protein at the right place in the cell. Proteostasis is achieved by many different large protein complexes that control the membrane trafficking system. When these fail, toxic proteins like amyloid beta and tau accumulate, resulting in cell death and severing of key neuronal connections.

What will this mean for dementia research?

- A greater understanding of the underlying cause of Alzheimer's disease
- Potential new targets for treatment development.

> **"To effectively treat Alzheimer's disease, first we must understand the underlying processes."**
>
> **— Dr Michael Healy**

Who's undertaking the research?

Dr Michael Healy, The University of Queensland

Dr Healy completed his undergraduate degree at The University of Queensland, where he was introduced to Professor Brett Collins, a field leader in understanding the structure and function of membrane trafficking machineries. Since then, Dr Healy has completed his honours and PhD projects in Professor Collins' lab, collecting multiple high-impact publication and speaking requests along the way. In addition, he has been awarded several scholarships, including the AINSE Postgraduate Research Award to support his investigations of the Commander protein complex.

The title of Dr Healy's project is *Protein homeostasis in Alzheimer's disease: molecular basis for APP trafficking by the SNX17-Commander protein complex.*