Research Project
By Dr Kristie Stefanoska

Dementia Australia™
Research Foundation

Saving memories by reversing brain protein damage in Alzheimer's disease

What is the focus of the research?

Investigating whether developing a treatment for a protein that becomes impaired in Alzheimer's disease can prevent brain cell death and cognitive decline.

Why is it important?

Australians are living longer than ever. In just 30 years our life expectancy has risen from 73 to 83, with no signs of slowing down. Developments in medicine and technology have given us treatments for many previously deadly diseases, so we can remain healthy, active and engaged in society well into old age. Unfortunately, we still don't have a cure or any effective treatments for dementia, which is the greatest health issue for Australians aged over 65.

Growing old is our biggest risk factor for Alzheimer's disease and other forms of dementia – and Australia's population is ageing. While scientists have some understanding of what happens in the brain during the disease process, there is still a long way to go before it is no longer a devastating diagnosis. We know that the toxic accumulation of a brain protein called tau is underlying in Alzheimer's disease. It destroys the structure of brain cells and prevents important nutrients from reaching parts of the brain. Those parts eventually shrink and die, resulting in cognitive decline. However, we don't know why or how this occurs.

In this project, Dr Stefanoska will increase the research field's understanding of Alzheimer's disease development by investigating how tau-induced brain cell death contributes to cognitive decline. Previous research showed that a brain protein called NSF is impaired by toxic tau and this may contribute to the development of neurological diseases. Dr Stefanoska wants to determine whether treating impaired NSF can prevent brain cells from dying and improve cognition. The results of her project will pave the way for more informed approaches to developing drug treatments for cognitive impairment in Alzheimer's disease.

How will this happen?

Stage 1: use mice that recapitulate tau-mediated dementia and optimise the activity levels of NSF to improve their cognitive function. Assess their cognitive function by performing a series of behavioural tests. This will define the protective function of regulating NSF activity.

Stage 2: attempt to understand how the interaction between pathogenic tau and NSF interrupts NSF function to drive inflammation in brain cells that eventually causes a programmed form of cell death. Using healthy (non-pathogenic tau) and dementia (pathogenic tau) mice, researchers will inhibit their NSF activity to understand how blocking NSF results in programmed cell death - and whether this process is tau dependent.

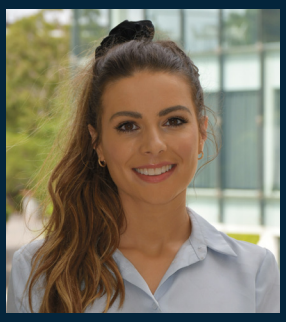
Stage 3: investigate how different forms of pathogenic tau control NSF activity and brain cell death. Use different versions of pathogenic tau and study the impact on NSF levels and brain cell death. Also use versions of tau that cannot be modified at disease-associated sites to determine the protective function of inhibiting disease-associated modifications in tau.

What will this mean for dementia research?

- Vital knowledge on how the tau/NSF association contributes to Alzheimer's disease.
- New avenues to develop treatments that delay or reverse cognitive decline.

How does tau become toxic?

Tau is a protein that is important for brain health. It binds to and releases from the skeletal structure of nerve cells, called microtubules. This facilitates the movement of cargo important for transporting nutrients and proteins along brain cells. The activity of tau is controlled by a modification, known as phosphorylation, that is either added or removed from tau. In dementia, crucial sites on tau become overly phosphorylated – a process called hyperphosphorylation – causing it to form clumps and become toxic. As disease progresses, these clumps become neurofibrillary tangles, which destroy the microtubules, preventing important factors from moving around the cell. This is what causes cognitive impairment.



Who's undertaking the research?

Dr Kristie Stefanoska, Flinders University

Dr Kristie Stefanoska received her PhD in neuroscience in 2020 and is currently a Scientia Professor Henry Brodaty fellow (Dementia Australia Research Foundation) and an Alzheimer's disease fellow (BrightFocus Foundation) within Flinders University. Dr Stefanoska is an expert in neuroscience and dementia and has made considerable contributions to the field as an early career researcher. Her research focuses on understanding the function and contribution of tau to physiologic and disease-associated processes. In 2021, Dr Stefanoska was awarded a Dementia Australia Research Foundation grant to study abnormal 'master' sites on tau in Alzheimer's disease.

The title of Dr Stefanoska's project is *A tau-associated factor to enhance memory function and prevent neuronal cell death.*

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