Research Project
By Dr Kristie Stefanoska

Dementia Australia™
Research Foundation

Targeting abnormal ‘master’ sites on brain protein offers hope for Alzheimer’s disease treatment

What is the focus of the research?

To investigate if removing disease-promoting sites on tau, a brain protein involved in Alzheimer’s disease, could lead to a new treatment.

Why is it important?

As Alzheimer’s disease progresses, there is an abnormal accumulation of a protein in brain cells called tau.

Tau is important for healthy brain functioning. It binds to the skeletal structure of nerve cells, called microtubles, which facilitate the delivery of nutrients and other important substances to the brain.

But in Alzheimer’s disease, tau undergoes an abnormal modification process called

How does tau modification cause cognitive impairment?

In Alzheimer’s disease, the hyperphosphorylation process makes tau clump together and form neurofibrillary tangles. These tangles cause the microtubles to collapse, destroying neuronal connections and preventing important compounds from reaching parts of the brain. Those parts eventually shrink.

The areas of the brain that shrink determine the type of impairment a person experiences. In most cases the hippocampus, responsible for memory, is affected first. But as the disease progresses and more tangles are formed, more parts of the brain are affected.

hyperphosphorylation, which destroys neurons and causes cognitive impairment. Understanding this modification can help researchers determine what happens or changes during disease so they can prevent it from occurring.

Dr Stefanoska's previous research was the first to discover disease-promoting 'master' sites on tau, where initial modification at these sites causes tau to undergo further abnormal modification. Removing these master sites may reduce hyperphosphorylation and delay disease progression.

This project will model Alzheimer's disease in mice to assess if removing these disease-promoting sites can protect against disease. Dr Stefanoska hopes the results will move us another step closer to finding a new treatment for Alzheimer's disease.

How will this happen?

Stage 1: test the protective effect of removing tau 'master' sites in mice with Alzheimer's disease. This will happen by injecting the mice with a variant of tau that is deficient for these 'master' sites.

Stage 2: investigate the importance of tau modification at the 'master' sites for memory function, by training and testing the mice to find a platform submerged in water.

Stage 3: immunise mice with a compound that targets tau phosphorylation at the 'master' sites, with the goal of reducing their cognitive deficits. This will provide direct insight into the therapeutic potential of targeting or eliminating 'master' site tau phosphorylation.

What will this mean for dementia research?

- Better understanding of how tau switches from a healthy to a diseased state.
- Hope of a new treatment for Alzheimer's disease.
- Targeted prevention and risk-reduction strategies.
- Effective public health messaging aimed at prevention.

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.

The title of Dr Stefanoska's project is *Master sites of tau phosphorylation as treatment targets for Alzheimer's disease.*