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**Understanding how the glymphatic system contributes to cognitive impairment may lead to new Alzheimer's disease treatment pathways”**

– Dr Zengmin Li



# Brain's waste disposal system a new target for Alzheimer's disease treatment



## What is the focus of the research?

Investigating if impairment of the brain's waste disposal system is responsible for the build-up of toxic proteins that cause cognitive decline in Alzheimer's disease.



## Why is it important?

Dementia is now the biggest health issue for Australians aged 65 and over. Currently, more than 400,000 people are living with this diagnosis and we are still a long way from a cure or any effective treatments.

The build-up of toxic brain proteins in Alzheimer's disease are responsible for the cognitive decline that steals a person's memories and shatters families. Unfortunately, researchers still do not fully understand how or why this happens.

Emerging research has pointed to impairment of the glymphatic system as a cause of toxin accumulation. The glymphatic system is the brain's fluid pathway for waste clearance and an important part of healthy brain functioning. It is largely active during sleep, which is when our long-term memories are formed. To do this, the brain uses co-ordinated brain regions associated with learning and memory, called networks. Deficits in these networks have been shown in humans and rodents with Alzheimer's disease. Two of the most significant symptoms of the disease are memory impairment and sleep disturbances. This suggests a strong relationship between the glymphatic system, brain network functioning and memory consolidation. However, scientists have not studied whether glymphatic function is essential for memory consolidation.

In this project, Dr Li is aiming to understand if suppressing aquaporin 4 (AQP4), a key water

transporter in the glymphatic system, impairs cognitive function. Using mice with Alzheimer's disease, his team will combine advanced imaging and behavioural testing to examine the effects of modifying the glymphatic system on memory. He hopes to identify new avenues for developing treatments that slow or prevent cognitive decline in Alzheimer's disease.



## How will this happen?

**Stage 1:** suppress glymphatic flow in healthy and Alzheimer's disease mice by injecting an AQP4 inhibitor into the hippocampus (the brain region used in learning and memory). Monitor brain changes with MRI, then harvest the brains for further study.

**Stage 2:** insert cannular and electrodes into the hippocampi of new mice. Train mice in a spatial learning task, then suppress their glymphatic function for one week. Perform a memory recall test to determine changes in cognition. Harvest the brains to examine AQP4 and toxin accumulation in the hippocampus.



## What will this mean for dementia research?

- More understanding of Alzheimer's disease pathways.
- Potential to develop new treatments.
- New knowledge of how the glymphatic system works.



## What is AQP4?

AQP4 is a water channel protein that plays an important role in supporting the capacity of the brain to clear waste proteins and other metabolites through the glymphatic system. AQP4 water channel deficiency may contribute to dysfunction in the brain's clearance system. This could lead to a build-up of toxic waste proteins that contribute to the development of Alzheimer's disease and other forms of dementia.



## Who's undertaking the research?

### Dr Zengmin Li, The University of Queensland

Dr Li is a post-doctoral research fellow at the School of Biomedical Sciences, The University of Queensland. After graduating with a Bachelor of Science from Fudan University in China, he was awarded a scholarship from The University of Queensland to study his PhD in neuroscience, which he completed in 2022.

Dr Li's research interests are in understanding how brain networks support learning and memory, how to improve memory via facilitating brain network function, and how this network is impaired in neurodegenerative diseases such as dementia. He has published multiple research papers in this area of research.

The title of Dr Li's project is *Understanding glymphatic contribution to cognitive impairment*.