Research Project
By Dr Liviu-Gabriel Bodea

Dementia Australia™
Research Foundation

Alleviating Alzheimer's disease by removing toxic immune cells in the brain

> **Each step towards a better understanding of Alzheimer's disease is instrumental in finding novel treatments for this terrifying disease**
>
> — Dr Liviu-Gabriel Bodea

What is the focus of the research?

Investigating how microglia, the brain's immune cells, become toxic in Alzheimer's disease and if removing them decreases brain damage that causes cognitive decline.

Why is it important?

Alzheimer's disease is the most common form of dementia. It erases memories and steals years from people's lives.

It is not a normal part of growing old, but ageing is our biggest risk factor. As Australia's population ages, the number of people who develop Alzheimer's disease is set to grow exponentially. This will put significant strain on the healthcare system and cause tremendous distress for millions of families.

Although researchers have made valuable discoveries about a brain with Alzheimer's disease, they still don't understand how it begins and progresses. Hallmarks of Alzheimer's disease include the abnormal build-up of proteins called amyloid beta and tau within the brain, which lead to cognitive decline. This build-up sparks the activation of microglia to fight infection and inflammation.

Microglia remove harmful deposits in the brain associated with Alzheimer's disease. However, they're also involved in the development of Alzheimer's disease. Unfortunately, we don't know why. One theory is that as microglia age, they're less able to remove these abnormal deposits. They can become senescent and toxic. Given that a person's risk of developing Alzheimer's disease also increases with age, understanding this mechanism is critical for the development of new treatments.

Although previous treatment strategies have investigated microglia's role in Alzheimer's disease, Dr Bodea will explore these cells in the

context of ageing. For the first time in research, he will use mice with Alzheimer's disease to investigate the changes microglia undergo during ageing and in disease that cause them to become senescent. He will then examine if removing them decreases Alzheimer's disease-related brain damage.

To do this, Dr Bodea will use a highly sensitive technique which he developed to validate these results using brain samples from humans with and without Alzheimer's disease. Dr Bodea will repurpose a drug that is currently being tested in bone marrow cancer to remove the senescent microglia in the mice.

The results will provide a clearer understanding of how Alzheimer's disease progresses, making an important contribution to the development of ground-breaking treatments.

How will this happen?

Stage 1: monitor the brains of mice with Alzheimer's disease to identify changes in microglia that cause them to become more senescent than normal.

Stage 2: remove the senescent microglia in mice by feeding them a diet containing the repurposed anti-cancer drug. Evaluate the protective effects of removing the senescent microglia in the treated mouse brains.

What are senescent cells?

Senescence is the term for old and damaged cells that have stopped dividing. This occurs due to DNA damage, exposure to various toxins and through the ageing process. Senescence is protective against cancer; when damaged cells die, they can't keep dividing and cause tumours to develop.

Normally, senescent cells are cleared away via a process called autophagy. But as we age, this process stops happening as efficiently. Senescent cells accumulate and can secrete toxic, inflammatory substances that induce ageing in the healthy surrounding cells. As senescent cells continue to build up, so too does inflammation, which is highly associated with Alzheimer's disease.

What will this mean for dementia research?

- A better understanding of microglia's role in the development of Alzheimer's disease.
- The potential to develop treatments that act on the removal of senescent microglia.

Who's undertaking the research?

Dr Liviu-Gabriel Bodea, University of Queensland

Dr Bodea leads the Microglia in Health and Disease Research Team at the Clem Jones Centre for Ageing Dementia Research, within the Queensland Brain Institute, University of Queensland. A brain cell biologist, he studies how microglia and surrounding cell types work together to accomplish their functions in health and disease.

Dr Bodea was the recipient of a University of Queensland Research Stimulus Fellowship from 2021-2022 and the Peter Hilton Early Career Fellowship in Ageing Dementia Research from 2014-2019, under the mentorship of world-renowned leader in Alzheimer's disease research, Professor Jürgen Götz.

The title of Dr Bodea's project is *Rejuvenating microglia to alleviate Alzheimer's disease.*