Research Project
By Dr Daryl Ariawan

Dementia Australia™ Research Foundation

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Dementia Research Grants

Pioneering peptide treatment to prevent brain cell death in Alzheimer's disease

What is the focus of the research?

Using innovative peptide technology to target and block the toxic effects of a protein that kills brain cells and causes cognitive decline in people with Alzheimer's disease.

Why is it important?

Toxic clustering of brain proteins called tau and amyloid beta are key players in the development of Alzheimer's disease. This clustering causes the death of brain cells, which leads to the cognitive decline that erases memories and devastates families. Tau and amyloid beta are being studied in thousands of laboratories around the world. Unfortunately, we aren't any closer to a cure or any effective treatments that prevent or slow disease progression.

A number of clinical trials of drugs that act on amyloid beta have failed, making tau the new alternative treatment. Using brand-new peptide technology, which she developed, Dr Ariawan will test a treatment that acts on the toxic effects of tau clusters to prevent brain cells from dying. Peptides are small chains of protein building blocks strung together. Their structure shares similarities with the natural proteins found in humans, making them a low-risk treatment option. She will examine the peptide treatment's effectiveness in human brain tissue using brain organoids, aka "mini brains", in a petri dish. These 3D tissue samples are created from stem cells and partially simulate human brain function.

If successful, Dr Ariawan believes this treatment will improve the symptoms of Alzheimer's disease and delay its progression. The results of this study will be used to attract interest from major pharmaceutical companies, so this promising new therapy can be prepared for clinical trial testing.

> **"Peptide therapeutics are the future."**
>
> **— Dr Daryl Ariawan**

How will this happen?

Stage 1: inject mice genetically engineered to have Alzheimer's disease with a single dose of the treatment. Determine the correct dosage required by monitoring their brain function using EEG. Treat more Alzheimer's disease mice with the new dosage and monitor them for four months. Assess their spatial learning and memory using a water maze. Collect their brains for further examination.

Stage 2: determine that the treatment's effectiveness translates to human brain tissue by testing it in the brain organoids.

Stage 3: if successful, prepare the treatment so it can be administered orally to humans. To cross the blood brain barrier, the treatment must pass through the digestive system in-tact, so it can be absorbed into the bloodstream.

What will it mean for the medical field?

- A potential drug candidate to trial on humans.
- An effective treatment that slows or stops the progression of Alzheimer's disease.
- A greater understanding of the disease process.

From mouse to man

Drug testing must undergo many rigorous phases of research before it can be used on humans. Mouse trials are within the "pre-clinical" phase. If a drug candidate is successful here, there's still a long way to go before your doctor can write you a prescription. It will undergo several more years of rigorous testing, so researchers can show its safety and efficacy. They then apply to the government's regulatory body, the Therapeutic Goods Administration, for approval to use in the next phase – human clinical trials.

There are four phases of human trials, which encompass the initial safety testing on a small group of volunteers, through to studying the drug's effectiveness and adverse side-effects after it has been used publicly. In general, it takes 10-15 years and billions of dollars for a drug to go from mouse trials to prescription pads.

Who's undertaking the research?

Dr Daryl Ariawan, Macquarie University

Dr Ariawan is a postdoctoral research fellow at the Dementia Research Centre, Macquarie University. She works with Professor Lars Ittner on developing novel peptide therapeutics to treat Alzheimer's disease. Dr Ariawan's research focuses on blocking the tau-mediated toxicity pathway in Alzheimer's disease. Before joining the Dementia Research Centre, she completed her PhD in medicinal chemistry at the University of New South Wales, where she worked on small molecule and peptide therapeutics for cancer. In 2021, Dr Ariawan was awarded an NHMRC Ideas Grant to research the protein TDP-43 in frontotemporal dementia and motor neuron disease.

The title of Dr Ariawan's project is *Pre-clinical development of novel cell-penetrating peptides to block tau-associated neurotoxicity for the treatment of dementia.*

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