Research Grants 2025

Alzheimer's disease | Discovering drivers of Alzheimer's disease using metabolomics

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Dementia is the second leading cause of death of all Australians.1 Dementia is an umbrella term encompassing different brain disorders that cause loss of memory, language, and other thinking skills to the degree that they impact on a person's daily life. There are several causes of dementia, with Alzheimer's disease (AD) being the most common for older Australians. AD is typified by the toxic build-up of 2 proteins in the brain called tau and amyloid beta (A□). There is no known cure or effective treatment to reverse the disease.

Fifty million people worldwide are living with dementia, a number projected to triple by 2050.2 Currently, AD diagnosis is supported by specialized resource-heavy tests like brain scans and spinal fluid sampling. In the face of this expected surge in dementia cases, developing accessible diagnostic tests and treatments — blood tests and tablets — is essential.

Despite decades of research, significant gaps exist in our understanding of the disease-causing processes that drive AD. For instance, it remains unclear what triggers AD to develop, what drives the death of brain cells, what factors cause cognitive impairment to emerge, and why some people decline much faster than others. To answer these questions, we must understand at a chemical level the changes that are happening between molecules like proteins and genetic material in the brains of people with AD. Without this nuanced understanding, developing accurate diagnostic tests and therapies will be impossible.

In a pilot sub-study of a recently completed phase II placebo-controlled drug trial of SAMe (a putative anti-tau drug), we aim to analyse blood samples to explore the metabolomic changes that occur in people with Alzheimer's disease (AD) over 6 months.

Funding has already been secured to support another pilot sub-study in which we will use cutting-edge technology to perform a proteomics analysis of our samples. By adding this proposed metabolomics analysis, we will be able to leverage our proteomics data to molecularly profile our samples with exquisite granularity. Combining these powerful, complementary techniques in a novel multiomics approach, we will be ideally positioned to reveal new insights into AD's underlying mechanisms, with exciting opportunities for biomarker and drug development.

Grant $12,000

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Progress Report

This project investigates the biological drivers of Alzheimer's disease (AD) using metabolomic analysis of blood samples collected during The SAMe Study, a phase 2, randomized, multi-centre, placebo-controlled clinical trial of S-adenosyl methionine (SAMe) in people with mild cognitive impairment or early dementia due to AD. While the broader scientific program includes planned proteomic analyses, this grant specifically supports the metabolomic component of the work.

At the time this grant was awarded, The SAMe Study was ongoing. Over the past 12 months, the clinical study has now been completed. All baseline and six-month blood samples have been collected, processed, and stored, and the clinical dataset has been finalised. The primary manuscript reporting the clinical and biomarker outcomes of The SAMe Study is currently under peer review.

With the primary clinical study now complete and the main findings progressing toward publication, the project is entering its next phase. The sample set generated by The SAMe Study is now ready for multiomic investigation. To date, the grant has not yet been accessed and the multiomic analyses have not commenced, with work intentionally sequenced to begin following completion of The SAMe Study.

Hypotheses and Aims

This project was founded on the hypothesis that measurable changes in blood metabolites occur over relatively short timeframes in early AD, reflecting both the natural biological progression of the disease and potential treatment-related effects. Specifically, the project aims to test the following hypotheses:

1. People with early AD demonstrate metabolomic changes over six months as part of the natural history of the disease, detectable through paired longitudinal sampling.

2. SAMe supplementation influences disease-relevant biochemical pathways—particularly those related to methylation, antioxidant synthesis, and neuronal metabolism—even if such effects are not reflected in conventional downstream AD biomarkers such as phosphorylated tau species.

By applying untargeted metabolomic profiling to paired baseline and six-month samples, this project aims to identify upstream biochemical changes that may precede, modulate, or fail to translate into changes in established plasma biomarkers.

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Preliminary Results

The SAMe Study demonstrated that SAMe supplementation was safe and well tolerated over six months. However, there were no significant differences between the SAMe and placebo groups in established AD blood biomarkers, including phosphorylated tau species (p-tau181 and p-tau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP). There were also no significant differences in cognitive performance as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

Although these results indicate that SAMe did not produce detectable disease-modifying effects using conventional biomarkers over the study period, they provide critical context for the metabolomics project. Standard AD biomarkers reflect downstream consequences of complex biochemical cascades. The absence of change in these markers does not exclude the possibility that SAMe influenced upstream biochemical pathways that were not directly measured.

Importantly, The SAMe Study has generated paired blood samples, collected at baseline and after six months, from people with early AD treated with SAMe under rigorous clinical trial conditions. These samples offer a unique opportunity to investigate short-term metabolomic changes associated with both the natural progression of early AD and exposure to SAMe.

Key Questions Yet to Be Answered

Completion of The SAMe Study has sharpened several critical unanswered questions that this metabolomics project is specifically designed to address:

1. Why did SAMe not alter conventional AD biomarkers? Was there insufficient biological engagement, or were relevant effects confined to upstream biochemical processes not captured by p-tau, NfL, or GFAP measurements?

2. Did SAMe influence metabolic pathways despite unchanged downstream biomarkers? Metabolomic profiling may detect alterations in substrates, intermediates, or pathway flux that do not result in measurable changes in canonical AD biomarkers over six months.

3. What metabolomic changes occurred over six months as part of early AD progression in placebo-treated participants? Defining short-term disease-related metabolic change is essential for interpreting treatment effects and identifying candidate biomarkers of progression.

These questions cannot be addressed using targeted biomarker approaches alone and require unbiased, large-scale metabolomic analysis of paired longitudinal samples.

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Future Directions and Implications

The SAMe Study has yielded a rare and valuable research asset: paired blood samples collected before and after six months in a placebo-controlled trial of people with early AD, including a world-first cohort treated with SAMe. This dataset provides a unique opportunity to interrogate AD biology at a fundamental biochemical level over a clinically relevant timeframe.

Importantly, the availability of paired longitudinal samples enables integrated proteomic and metabolomic interrogation, allowing complementary insight into molecular pathways and their downstream biochemical consequences. While proteomics characterises changes in protein expression and signalling, metabolomics captures the products, substrates, and intermediates of these processes, providing a direct readout of pathway activity.

The neutral clinical findings from The SAMe Study underscore the need to understand treatment biology more deeply. By identifying which metabolic pathways were unchanged, subtly altered, or unexpectedly affected, this work can clarify why SAMe did not demonstrate efficacy at the tested dose and duration, and whether upstream biological effects occurred that were not reflected in conventional biomarkers.

The outcomes of this project have the potential to:

- Reveal previously unrecognised metabolomic changes occurring over six months in early AD
- Identify metabolite biomarkers that reflect biological effects not captured by conventional assays
- Inform the rational design of future SAMe trials through improved selection of biologically meaningful endpoints
- Advance the development of scalable blood-based tools to study and monitor AD biology

With The SAMe Study complete and samples ready for analysis, this project is timely, well positioned, and highly relevant. The planned metabolomic analyses represent a critical next step in translating rigorous clinical trial data into deeper biological understanding, aligned closely with the RMH Neuroscience Foundation's mission to advance neuroscience research and improve outcomes for people living with brain disease.