Australian
ALZHEIMER'S
RESEARCH
Foundation

2019 Annual Report

Year in Review

Alzheimer's is one of the most important public health issues we currently face. Together with our supporters, we remain committed to continue our fight for memories and to our vision, mission, objectives and values.

Our Vision

A world in which Alzheimer's disease no longer exists.

Our Mission

To support research that makes Alzheimer's disease treatable and preventable.

Our Objective

The Australian Alzheimer's Research Foundation becomes a self-sustaining Foundation that raises funds to support Alzheimer's disease research.

Our Values

For our stakeholders and customers we will always focus on supporting Alzheimer's disease research; act with integrity; be transparent in everything we do; and celebrate our achievements.

Our key pillars are:

- Research focused on understanding, preventing, diagnosing and treating Alzheimer's and other neurodegenerative diseases.
- Revenue sustainability through diversification of funding support, fundraising, grants and research fee-for-service activity, including industry supported clinical trials.
- Community engagement related to education and awareness.
- Strengthening partnerships and national presence.

To ensure our continued operations and sustainability we will always have a clear and shared understanding of our risk appetite and have mechanisms in place to ensure we operate within this; ensure appropriate policies and procedures are in place and complied with; maintain strict financial discipline; and refuse to compromise on quality and competence in anything we do and represent.

459,000

An estimated 459,000 Australians are living with dementia

250

250 Australians are diagnosed with dementia each day

1,076,000

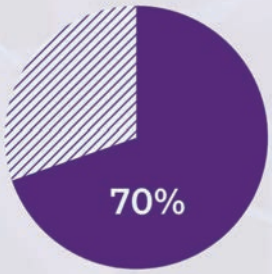
Without a medical breakthrough, over 1,076,000 Australians will develop the disease by 2058

There is **NO** cure

Australian Bureau of Statistics (2018) Causes of Death, Australia, 2017 (cat. No. 3303.0)2 The National Centre for Social and Economic Modelling NATSEM (2016) Economic Cost of Dementia in Australia 2016–2056 Alzheimer's Disease International

52%

52% of residents in Australian Government subsidised aged care facilities have dementia



70%

Approximately 70% of people with dementia have Alzheimer's disease

3 Seconds

Every three seconds someone in the world develops dementia

2nd

Alzheimer's is the second leading cause of death in Australia

Australian Bureau of Statistics (2018) Causes of Death, Australia, 2017 (cat. No. 3303.0)2 The National Centre for Social and Economic Modelling NATSEM (2016) Economic Cost of Dementia in Australia 2016–2056 Alzheimer's Disease International

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Chairman's Report

ENZO SIRNA AM

As reflected in the new constitution, following my six consecutive years as Chairman of the Australian Alzheimer's Research Foundation, I shall be stepping down from my role which I have been privileged to perform.

As an inaugural member of the Foundation since 2001, which was formerly recognised as the McCusker Alzheimer's Research Foundation, I have enjoyed being part of the journey to assist the researchers to pursue their goals, with the ultimate aim to hopefully find the cure for this debilitating disease. The progression over the years, while not always easy, has been maintained with momentum and having had oversight of the many associated challenges, while Chairman, increased my resolve to better assist our researchers in their efforts to find a cure.

Our vision is still very much to see a world in which Alzheimer's disease no longer exists, and our mission clearly articulates the importance of supporting research that makes Alzheimer's disease treatable and preventable.

In reviewing our strategic plan for 2020-2025, the Foundation has refreshed its statement of purpose:

To strengthen the awareness, strategic partnerships, opportunities and funding support to the Prof Ralph Martins' core research team, and to approved key projects to further enhance Alzheimer's disease research.

We are all aware of the significant role, recognition and respect that Prof Ralph Martins and his team have in Alzheimer's disease research, both at a state, national and international level. It is therefore important for the Foundation to maintain its focus on providing this support for the research and the proposed key goals for the next five years include:

- *Research focused on understanding, preventing, diagnosing and treating Alzheimer's and other neurodegenerative disease;*
- *Revenue sustainability through diversification of funding support, fundraising, grants and research fee-for-service activity, including industry supported clinical trials;*
- *Community engagement related to education and awareness; and*
- *Strengthening partnerships and national presence.*

It is also important to maintain high level research and to this end, among the many integral research study projects, the Foundation is pleased to note that Prof Ralph Martins is leading a key study (called AU-ARROW) over the next five years involving over 600 participants. This international clinical trial will determine the efficacy of combining lifestyle factors such as diet, exercise and brain training to reduce the risk of Alzheimer's disease. Prof Martins has been awarded a $3.1 million dollar NHMRC Medical Research Future Fund grant from the Federal Government, and this has been further complemented by an additional $3.4 million dollars from Alzheimer's Association in the United States. The significance of the contributions towards the study indicates the high regard for Prof Martins and his team and the Foundation is keen to maintain its support to help their research efforts to assist in reducing the incidences of this debilitating disease, as well as maintaining the continued focus on early diagnosis. The study will have a truly international link with the involvement of key stakeholders in the United States and in Europe.

Our clinical trials division has also been an important focus for our Foundation and I would like to recognise the efforts of Dr Roger Clarnette, our Medical Director and Principal Investigator, who with his team, are responsible for the trialling of drugs for potential use in people with early diagnosis of Alzheimer's disease.

The Foundation remains grateful to all those who have supported our endeavours over the many years. These include the many donors, sponsors, supporters and ambassadors. We are indebted to the initial longstanding contributions made by the McCusker family to support Prof Ralph Martins and his research, and the ensuing partnership with the Delroy family in assisting us to provide a solid platform from which to grow. With the additional support of many other generous contributors, including, Helen Sewell, Margaret Cowlan, Ron Bennetts and Wesfarmers, the Foundation has been able to proceed with confidence in many of its key research projects.

While it is difficult to list everyone, I would like to express to you all, my sincere gratitude for your contribution and your belief in our cause, to seek prevention and ultimately a cure for this dreaded disease. Your support has given us the confidence to maintain our impetus in assisting the research teams in their continued progress towards a cure.

I would like to express my gratitude to the operational arm of the Foundation, which during my term as Chairman, has been under the guidance of Jenny Gill, Dr Judy Edwards, Bruce McHarrie and Liza Dunne. I have appreciated working with all of you and recognise the efforts you and your team members have all made to overcome the many challenges faced during our journey and to ensure we continue to maintain a focus on our key aims and objectives.

I am also appreciative to past and present members of the Board who have admirably accepted their governance requirements and responsibilities as directors and who have provided many voluntary hours of their time to ensure the important strategic and operational oversight of the Foundation.

Thank you all in sharing the journey with me during my term as Chairman and I do hope that the Foundation continues to be highly regarded for its continued and concerted efforts which will hopefully lead to the prevention and cure of Alzheimer's disease worldwide.

Enzo Sirna AM
Chairman

Board Members

ENZO SIRNA AM
Chairman

DR TERRY BAYLISS
Deputy Chair

ROD O'DEA
Treasurer
Chair of the Foundation's Future Fund

PROF RALPH MARTINS AO
Director of Research

DR MICHAEL QUINLAN AO
Chair of the Foundation's Scientific Advisory Committee

JENNY DAY
Board Member

ROB DAVIES
Board Member

TIM ANDREW
Board Member

GRAEME PRIOR
Board Member

CEO's Report

LIZA DUNNE

The Australian Alzheimer's Research Foundation is a not-for-profit organisation supporting Alzheimer's research focused on understanding the disease, prevention and ultimately, a cure.

Alzheimer's is a complex and multifactorial disease that slowly and progressively destroys the brain and can be influenced by a range of genetic and environmental factors. It must be tackled from all fronts and I continue to be inspired by the dedication of the researchers focused on achieving solutions to address this debilitating disease.

In 2019, the Foundation continued to provide Western Australians with the opportunity to take part in clinical trials with international pharmaceutical companies for potential new therapies for Alzheimer's disease. Our income in this area increased 49% in 2019 compared with 2018, with a number of pharmaceutical companies ramping up their trials as a result of some promising initial data. One of these trials was with American biotechnology company Biogen, and we were extremely encouraged to learn that Biogen will be pursuing regulatory approval from the FDA for the investigational drug aducanumab after finding a reduction in cognitive and functional decline in people taking the high dose of the drug.

A significant income source in 2019 was a Lotterywest grant for our clinical trial investigating the role of testosterone on cognitive health in older men. This study is well underway, seeking to recruit 200 men in WA and NSW and is due for completion at the end of 2021. Our sincerest thanks to Lotterywest for their financial support of this research project.

Two of our large contract research programs concluded in 2018 resulting in a lower overall income in 2019. We continue to focus on keeping all overheads as low as possible and in 2019, 82% of the Foundation's income was directed to research activities. These included:

- salaries for research staff
- accommodation
- laboratories
- equipment
- insurance
- research governance and ethics support
- imaging and other research services provided by third parties

I would like to take this opportunity to thank everyone who donated to the Foundation in 2019, community organisations who raise money on our behalf and to our corporate supporters. The funds you provide are absolutely vital to our organisation and we thank you for your financial support and encouragement. No matter how large or small, your support is greatly appreciated.

Dementia, including Alzheimer's disease, is the second leading cause of death in Australia and has no cure. The prevalence of the disease is increasing, exacerbated by our ageing population. Now more than ever we must continue to provide funding for multi-pronged research into finding relief for those with the disease and for future generations.

Research into understanding the disease is critical for the development of therapies, diagnostics and preventative strategies. Low cost, early diagnostics enable therapies to have the best opportunities for success and our work on the potential utility of retinal imaging to diagnose Alzheimer's continues. With approximately 30% of dementia being preventable, our support for research into the role of exercise and sleep as preventative strategies is critical.

Importantly the research programs we support also provide an opportunity for students to gain experience and knowledge in Alzheimer's research, to ensure we have a growing pool of expertise in the future. Some of the student research projects are profiled in this report.

Thank you to everyone - staff, researchers, volunteers, study participants and donors - who work tirelessly to ensure the future looks brighter for us all.

Liza Dunne
CEO

2019 Financial Snapshot

TOTAL INCOME $3.6 M

29% DONATIONS & FUNDRAISING
$1,056,630

16% GRANTS
$556, 827

43% CLINICAL TRIAL & RESEARCH INCOME
$1,541,022

6% OTHER INCOME
$215,505

6% INCOME FROM TENANT
$222,762

TOTAL EXPENSES $2.8 M

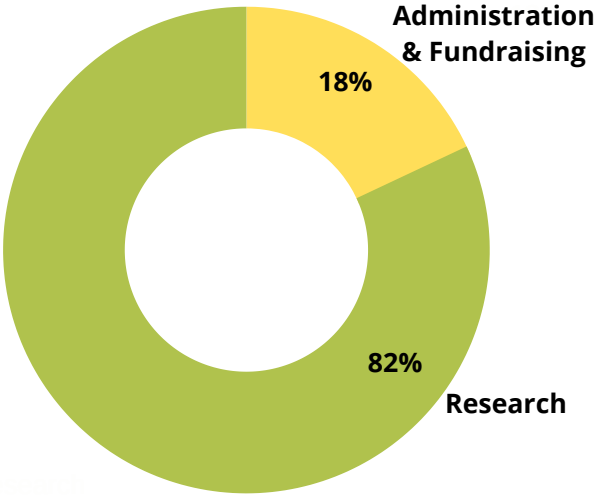
21% ACCOMMODATION EXPENSES
RESEARCH FACILITIES, LABORATORIES, OFFICES
$608,419

5% ADMINISTRATION & FUNDRAISING
EXCLUDING SALARIES
$156,851

41% EMPLOYEE COSTS
$1,170,237

31% RESEARCH EXPENSES
EXCLUDING SALARIES
$891,544

2% INSURANCE
$65, 384



In 2019, 82% of the Foundation's income was directed to research activities including research facilities, salaries and third party services.

The audited financial statements are available on request.

The Personal Impact

Mel is one of our generous supporters and is learning to live with Alzheimer's disease in her family right now. This is Mel's story:

Learning about Alzheimer's disease and how it will eventually affect Mum has been really hard. **I know we'll lose her long before we should.**

My mum has had many traumas in her life, but found happiness and kindness with her second husband, who sadly died shortly after being diagnosed with cancer. As the grief from her husband's death eased somewhat, the forgetfulness she had been having did not go away. After several tests, the doctor told her she had **Alzheimer's disease.**

She had her driver's licence revoked and had to rely on others to take her out of the house. She started walking to the shops, just to get some company as she sat among strangers. As the Alzheimer's progressed, those walking visits gave her family stress – would she be able to get home? One night I was talking to her on the phone and she said she was in the dark – she'd forgotten to turn on the lights as the evening had started. She put down the receiver, to go and turn them on – but then couldn't find the lights nor phone, so wandered alone in the pitch black of her house, until I could get there and let myself in with my key, and turn the lights on for her.

Mum now lives in a nursing home, where she gets a lot of care. Each visit she remembers us less and less. She of course had a lot of joy in her life as well – two children, friends, family, and she loved her hobbies of gardening, sewing, crafting, and socialising. **Every single day I wish there was a cure for Alzheimer's.**

Sincerely,

Mel

THE RESEARCH

The Australian Alzheimer's Research Foundation has a long history of providing support for vital research into Alzheimer's disease.

We provide world class research facilities and funding support for a broad range of Alzheimer's disease research programs under the leadership of Professor Ralph Martins.

WA Memory Study (WAMS)

Professor Ralph N. Martins AO, BSc, PhD
A/Prof Hamid R. Sohrabi, BSc, MSc (Hons), PhD
Mr Kevin Taddei, MSc
Dr Michael Weinborn, PhD
Dr Stephanie Rainey-Smith, PhD

The Western Australia Memory Study (WAMS) is a longitudinal study examining the relationship between self-reported worries about memory and cognitive functions, and actual decline in such abilities.

The WA Memory Study started in 1996 by Prof Ralph Martins and his team to serve three important aims:

- To identify factors influencing cognitive functions in ageing;
- To follow up the longitudinal trajectory of cognitive change in ageing;
- To identify biological and clinical changes that can be used for screening those at higher risk of Alzheimer's disease.

The WA Memory Study also provides an invaluable platform for affiliated researchers, their students and volunteers to collect data, to learn clinical and neuropsychological assessments and to investigate new hypotheses on cognitive ageing and risk of dementia. It is also a service to the community by providing neuropsychological and clinical assessments to those who have been referred to us from community sources and clinical settings.

Since 1996 the study has been actively recruiting participants from the Perth metro area as well as rural Western Australia. In 2019, the WAMS published several papers on the relationship between self-reported concerns about memory, personality, and age-related cognitive impairment. Currently, the WAMS is collecting data to validate several measures developed here in WA.

One of these measures assesses the frequency and severity of self and partner's reported decline in memory and other cognitive abilities. The measure is expected to identify those at earliest stage of risk for future dementia and cognitive impairment. This measure, the McCusker Subjective Cognitive Impairment (McSCI, pronounced Maksee) Inventory, is named after the McCusker family for their generous support of the WAMS over the years. A paper describing the McSCI and its results on over 500 participants is under preparation and will be submitted for publication in mid-2020. Our current data on the McSCI shows that this measure is capable of differentiating memory complainers from non-complainers and those with and without cognitive impairment. Following the publication, we hope that McSCI will be incorporated into the assessment battery of other studies for further validation.

In addition, using the WAMS data we have developed a measure for olfactory memory to assess human's memory for odours.

We are testing this measure further to see if it can be used in identifying those at higher risk of developing Alzheimer's diseases.

In addition, our hearing and dementia collaboration with Ear Science Institute has been very promising with a new PhD student and a submitted manuscript on the WAMS hearing data. Such collaborations are vital for the continuation of the WAMS and future funding.

The WAMS' team is very grateful to our participants, donors, volunteers and students for the critical contribution to this study.

The Foundation is committed to supporting the next generation of researchers in Alzheimer's disease and the WAMS provides an excellent opporunity for this.

The WA Memory Study Team

Back row (L-R): Louise Pivac, Alexander Mladenovic, Jo Shaw, Mike Weinborn, Hamid Sohrabi, Kevin Taddei
Front row(L-R): Rasangi Seneviratne, Georgia Martins, Rachael Mumme

STUDENT PROFILES
WA MEMORY STUDY

Rasangi Seneviratne

PhD Candidate, UWA

Supervisors:
A/Prof Michael Weinborn, UWA
A/Prof Hamid Sohrabi, Murdoch University
Prof David Badcock, UWA
Prof Ralph Martins, ECU

My research is looking at smell memory and how it relates to your brain, cognition and behaviour. We think smell memory might be more sensitive to early signs of disease than just labelling or detecting a smell. To examine this further, we developed a new, comprehensive test that looks at how people can learn smells over time, and how people can remember smells after a short and long delay period. We also looked at the benefits of cues and prompts. This test was found to be very reliable, and we found that it relates to other measures of memory (e.g. verbal and visual), and even predict a decline in brain health and daily life after 18 months. Overall, our results suggest that this new measure of smell memory could be used to help detect and predict changes in your brain, thinking abilities and daily life.

Pamela Lam

Masters Student, ECU

Supervisors:
Dr Craig Speelman, ECU
A/Prof Hamid Sohrabi, Murdoch University
Prof Ralph Martins, ECU

My research project is exploratory in nature. It focuses on assessing if there are any differences between participants who experiences mild cognitive impairments, and participants who do not. Specifically, I am looking to see if there is a difference in the rate of decline between the two groups in specific subdomains; such as attention, learning, memory encoding and memory retrieval. I hope this will yield greater understanding in the area of cognitive decline in Australia's rapidly ageing population.

Hadeel Tarawneh

PhD Candidate, UWA

Supervisors:
Dr Dona Jayakody, ESIA
A/Prof Wilhelmina Mulders, UWA
Prof Ralph Martins, ECU
A/Prof Hamid Sohrabi, Murdoch University

There has been a strong association between auditory function and cognitive function. In fact untreated hearing loss has been identified as a modifiable risk factor for developing dementia. Changes in the way the brain processes sound have been tied to changes in cognitive function that are associated with Alzheimer's disease (AD). Therefore, by looking at changes in auditory functions in individuals at risk of developing AD, we could be able to differentiate between those who are at high risk of developing AD. In this project I will be investigating auditory functions in populations at risk of developing Alzheimer's disease using non-invasive measures of the brains electrical responses to sound. I will be investigating the measures of electrical responses to sound in relation to biological markers of AD, obtained using genetic testing, blood biomarker testing and neuroimaging. Through this research we are better able to establish whether using these objective measures of auditory function can be used as a quick, non-invasive, and inexpensive screening tool for early Alzheimer's disease.

Rachael Mumme

PhD Candidate, UWA

Supervisors:
A/Prof Michael Weinborn, UWA
A/Prof Stephanie Rainey-Smith, ECU
Prof Romola Bucks, UWA
Paul Maruff, Cogstate Ltd

Improving our ability to detect Alzheimer's disease in its earliest stages is an exciting research avenue that holds promise for early disease identification and the ability to trial new intervention methods. Currently, we most commonly use a person's average level of performance on tests of memory (or other thinking skills) to detect a decline in their thinking ability. A new method, which my research focuses on, is looking instead and the variability of their performance. It is thought that this new way to look at a person's test performance may appear earlier in disease progression than a drop in their average level of performance. To explore this theory, my research is investigating the ability of performance variability to predict those who will later develop Alzheimer's disease, as well as, whether this variability has a relationship with the long term build-up of amyloid in the brain, a common feature of Alzheimer's disease.

Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing

Professor Ralph N. Martins AO, BSc, PhD
A/Prof Hamid R. Sohrabi, BSc, MSc (Hons), PhD
Mr Kevin Taddei, MSc
Dr Stephanie Rainey-Smith, PhD
A/Prof Simon Laws, PhD
Dr Michael Weinborn, PhD

AIBL is a study of over 2,500 people, some of whom have been followed for over 8 years, to determine which biomarkers, cognitive characteristics, and health and lifestyle factors determine subsequent development of symptomatic Alzheimer's disease (AD).

The AIBL Study commenced in 2006, includes two sites (Perth and Melbourne), and has resulted in more than 260 publications with over 2500 citations per year. The contribution of AIBL to Alzheimer's and dementia research led to an application by its investigators, including Prof Ralph Martins, for a national initiative. This application was successfully funded in 2019 by the National Health and Medical Research Council, resulting in the launch of the Australian Dementia Network (ADNeT), which is a milestone in supporting future clinical trials into the prevention or treatment of dementia.

The clinical and cognitive assessments as well as brain imaging, blood biomarkers and lifestyle data collected as part of the AIBL Study have significantly increased our understanding of Alzheimer's pathology in the brain, effective methods of tracking very early cognitive decline, and establishing the best window of opportunity for implementing drug and lifestyle interventions.

Papers published in 2019 using AIBL data (listed at the end of this report) include groundbreaking findings on blood biomarkers for Alzheimer's disease and the performance of a group of older adults we consider as 'super-agers'. These individuals are the AIBL Study participants who perform significantly better than their peers, and maintain their high-level performance over time. It is hoped that this research will provide important information regarding optimal brain ageing which can be the target of future therapies. As always, we are incredibly grateful to the participants of the AIBL Study for their commitment and dedication which has helped to significantly advance research into the early detection and causation of Alzheimer's disease.

aibl The Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing

The AIBL study is internationally recognised for its significant contribution to the global understanding of Alzheimer's disease.

ADNeT

Kevin Taddei
Research Associate, School of Medical and Health Sciences, Edith Cowan University

The Australian Dementia Network (ADNeT) is the largest single research program funded to date through the NHMRC's $200 million Boosting Dementia Research Initiative, with $2 million additional support from philanthropic organisations the Wicking Trust and the Yulgilbar Foundation.

ADNeT brings together the country's top researchers to create a sustainable, translational research infrastructure to drive ongoing, high quality research and clinical care for Australians living with, or at risk of, cognitive impairment and dementia.

Dementia is Australia's second leading cause of death. Without a medical breakthrough, the number of Australians with a diagnosis of dementia is expected to increase to over 530,000 by 2025 and over 1.1 million by 2056. Other challenges to the sector include service fragmentation and the lack of unified standards to improve dementia diagnosis and care in the Australian context.

To address the problem, ADNeT brings together Australia's leading researchers and stakeholders to:

- Establish an integrated network of dementia researchers, clinicians, service providers, industry, and consumers to drive this priority national translational research initiative
- Develop and maintain a clinical quality registry (CQR) that can track, benchmark and report on the quality of clinical care of people with dementia and mild cognitive impairment to drive quality improvement, identify suitable and willing persons for clinical trials, and systematically collect longitudinal data for research on the determinants, epidemiology and trajectory of cognitive decline
- Establish a national network of Memory Clinics to optimise the assessment of cognitive disorders and improve specialist access for all Australians
- Develop a large, highly-characterised cohort of people with dementia, or at increased risk of dementia, to populate a Trials-Ready Cohort for participation in cutting-edge clinical trials and to study the natural history of dementia
- Connect with existing infrastructure supporting clinical trials in Australia to enhance the capacity for state-of-the-art assessments and the conduct of clinical trials nationwide
- Integrate Australian research with the international effort to prevent or effectively treat dementia

Led by Professor Chris Rowe, ADNeT is comprised of 25 investigators, 12 institutions and a broad spectrum of government, clinicians and consumer advisors.

ADNeT is supported by the NHMRC National Institute for Dementia Research, the Wicking Trust, Yugilbar Foundation, Dementia Australia and Austin Health.

Partner institutions are drawn from across Australia, including the University of Melbourne, University of New South Wales, Monash University, Edith Cowan University, CSIRO, Flinders University, SAHMRI University, University of Sydney, NeuRA, Macquarie University, QIMR Berghofer and University of Tasmania.

Professor Ralph Martins and his team at Edith Cowan University, will lead the site in Western Australia contributing to two key initiatives: ADNeT-Clinics to improve diagnosis of dementia via a national network of memory clinics with close links to primary care; and ADNeT-Trials to develop a large, highly-characterised cohort of people with dementia, or at increased risk of dementia, to populate a Trials-Ready Cohort for participation in cutting-edge clinical trials.

Australian Dementia Network
REGISTRY. CLINICS. TRIALS.

ADNeT brings together the country's top researchers to create a sustainable, translational research infrastructure to drive ongoing, high quality research and clinical care for Australians living with, or at risk of, cognitive impairment and dementia.

Dominantly Inherited Alzheimer's Network (DIAN) Study

The DIAN study in an international, multi-site collaboration investigating the progress of various biomarkers of Alzheimer's disease in a group of individuals with mutation in a gene causing young onset, familial type of the disease.

Prof Ralph Martins

Director of Research Chair in Ageing and Alzheimer's disease, Edith Cowan University

Kevin Taddei

Research Associate, School of Medical and Health Sciences, Edith Cowan University

A/Prof Hamid Sohrabi

Associate Professor , School of Psychology and Exercise Science, Murdoch University

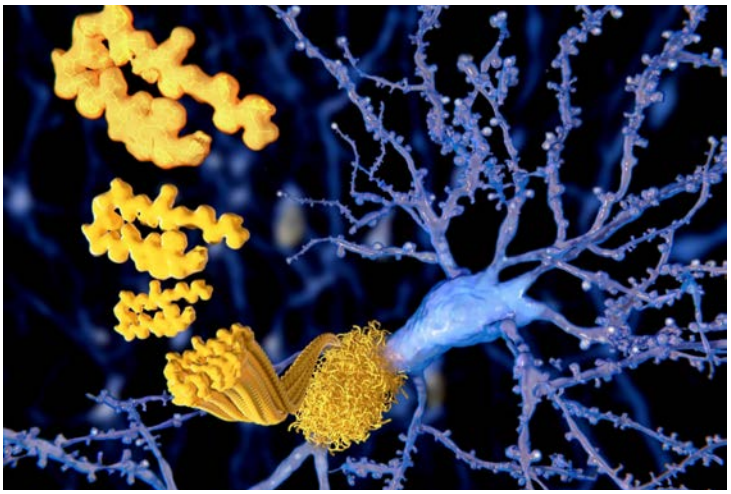
The WA Site of the DIAN Study undertook this collaboration with the support of the Australian Alzheimer's Research Foundation in 2011 and has contributed to a long list of achievements recognised worldwide, including the first blood-based biomarkers panel to identify those at higher risk of developing the disease and a clinical trial on preventing the disease, which our Clinical Trials Division is participating in.

Within the DIAN Study larger cohort we also have a very unique group of individuals with a mutation that causes haemorrhagic stroke and is known as the Dutch-type hereditary cerebral amyloid angiopathy [D-CAA] (previously known as "Hereditary cerebral hemorrhage with amyloidosis, Dutch type [HCHWA-D])". Of note D-CAA is actually the young onset of a similar condition commonly seen in older adults that is considered a silent cause of stroke.

Prof Martins' Lab and a team in the Netherlands are the only groups worldwide with access to D-CAA participants. In 2016, A/Prof Sohrabi attended a conference on CAA in London that was organised by Prof Steve Greenberg (Boston General Hospital, USA) and Prof Mark van Buchem (Leiden University Medical Centre, the Netherlands). His meeting with these two leading CAA researchers resulted in further collaborative work aimed at future clinical trials for this condition. To further the collaboration, Prof Martins, A/Prof Sohrabi and Mr Taddei visited the Lab in the Netherlands and discussed the potential of a clinical trial on these individuals with an international team of scientists who gathered in Leiden to discuss the design of this trial.

Prof Martins and his team will continue this collaboration and are working towards the clinical trial commencement in the next few years.

DIAN
Dominantly Inherited Alzheimer Network



Investigators examined the onset, sequence, and rate of progression of biomarker and clinical measures across the spectrum of Alzheimer disease, using the Dominantly Inherited Alzheimer Network study.

Diabetes and Alzheimer's Disease

A/Prof Giuseppe Verdile

Associate Professor, School of Pharmacy and Biomedical Science, Curtin University

Dr Prashant Bharawaj

Research Fellow, School of Medical and Health Sciences, Edith Cowan University

Type 2 diabetes represents a major Alzheimer's disease risk factor and with the number of Australians with diabetes expected to double in the next 5 years and diabetics at a 2 fold increase risk of developing dementia, it will be a major contributor to the predicted increase in the prevalence of Alzheimer's disease in this country.

Type 2 diabetes is a progressive disease in which tissues in the body become resistant to the normal effects of insulin ("insulin resistance") and thereby have reduced capacity to utilise blood sugar (glucose) for metabolic functioning. As the disease progresses, the ability of a group of cells in the pancreas called islets to produce enough insulin is gradually lost. In addition, another amyloid called islet amyloid polypeptide (IAPP) [also called amylin] builds up in the islets. Overall, these features of type-2 diabetes result in disruptions in metabolism, tissue energy production and increases in blood glucose levels (hyperglycemia) that can lead to significant complications.

In collaboration with Professor Paul Fraser and his team from the University of Toronto, we have shown in a mice models that Aβ and pTau can accumulate in pancreatic islets, promote insulin resistance in tissue such as muscle and contribute to high blood glucose levels. These findings support a novel scenario where accumulation of Aβ and pTau can directly promote type 2 diabetes. This in turn, may potentiate a cycle that can exacerbate neuronal dysfunction and Alzheimer's disease pathology in the brain. In collaboration with Prof Philip Newsholme (Curtin University), A/Prof Verdile is co-supervising a PhD student (Mrs Joanne Rowels) who's project is understanding how this process occurs. Our recent findings suggest that the build-up of amylin can potentiate this process and Dr Prashant Bharadwaj has shown a potential mechanism by which this can occur: through an interaction with Aβ. Amylin has also been found in the brain and Dr Bharadwaj has shown that the interaction with Aβ can exacerbate neuronal death (Bharadwaj et al., submitted to Scientific Reports). These mechanistic studies are critical in understanding how diabetes may impact on the brain to promote Alzheimer's disease pathology.

Type 2 diabetes can also promote insulin resistance in the brain and diabetics have reduced cognitive functioning and greater brain atrophy (shrinkage) compared to non-diabetics. Inducing type 2 diabetes in animal models also promote pathology observed in Alzheimer's disease, namely the accumulation of the proteins, amyloid-β (Aβ) and phospho (p)Tau. Alzheimer's disease patients can also show insulin resistance and disruptions in blood glucose levels, however, whether this feature in Alzheimer's disease is a cause or consequence of Alzheimer's disease pathology remains unclear.

A study led by A/Profs Giuseppe Verdile and Simon Laws have shown that insulin resistance is associated with reductions in cognitive functioning and increases in cerebrospinal fluid (CSF) levels of Tau. This association was stronger in females and is consistent with previous epidemiological studies that indicated that females with type 2 diabetes were at greater risk of dementia than men with type 2 diabetes. Our findings were published in Scientific Reports (Laws et al., 2017) and have implications for understanding when and how type 2 diabetes impact on AD biomarkers and disease progression. A PhD student (Miss Amy Woodfield) supervised by A/Prof Giuseppe Verdile, A/Prof Simon Laws and Dr Tenielle Porter will be undertaking further analysis to determine how insulin resistance impacts on cognition over time and further understand the relationship we have observed between insulin resistance and Tau accumulation.

Pictured above (L-R) Dr Tenielle Porter, Madeline Peretti, Andre Vieira, A/Prof Simon Laws, Lidija Milicic, Mehrane Mehramiz, Michael Vacher.

Genetics and Alzheimer's Disease

A/Prof Simon Laws, School of Medical and Health Sciences, Edith Cowan University

The Australian Alzheimer's Research Foundation is delighted to be providing Lidija with an annual top-up scholarship to support her PhD research.

People in the early stages of Alzheimer's disease may soon have access to personalised treatment advice, tailored to their genetic profile, to help slow the progression of this debilitating condition.

A team led by Edith Cowan University's Associate Professor Simon Laws has received funding from the National Health and Medical Research Council (NHMRC) to examine the interplay of genetic and lifestyle factors impacting the rate of memory decline among Alzheimer's sufferers.

Genetics has been well established as a key contributor to Alzheimer's disease risk, but 20 years ago few thought lifestyle factors had much to do with the condition. There is now evidence that both genetic and lifestyle factors can impact Alzheimer's risk. The aim of this research is to determine how genetic and lifestyle factors interact with each other, which may determine the rate at which people in the early stages of Alzheimer's disease suffer cognitive decline and changes in the brain.

Understanding this interaction could lead to the development of personalised advice for early-stage sufferers about which specific lifestyle changes would provide them with the most benefit and help delay the onset of symptoms. One person's genetic profile may mean that they should focus on modifying their diet, whereas another person should perhaps focus on exercise or sleep.

This comprehensive study will build on previous research from fellow ECU researchers, including Drs. Stephanie Rainey-Smith, Belinda Brown and Hamid Sohrabi that identified important lifestyle factors influencing the risk of developing Alzheimer's disease, such as diet, sleep and depression. Moreover, it particularly builds on the developing evidence that their interaction with genetics is key.

Lidija Milicic
PhD Candidate, ECU

Supervisors:
A/Prof Simon Laws, ECU
Dr Tenielle Porter , ECU
Dr Michael Vacher, UWA

I began working as a research assistant for the Collaborative Genomics Group in 2015, which is when my interest in genetics and dementia research flourished. Alzheimer's disease is the second leading cause of death in Australia and has devastating consequences to the sufferers and their families. Being part of a small team focused on understanding the integral role that genetics plays in defining risk for Alzheimer's disease, I began to appreciate the complexity of this disease and realised that I wanted to be one of the scientists contributing to make a difference.

In 2017, I did my honours degree and I have commenced my PhD, under the supervision of A/Prof Simon Laws. In recent years, there has been a heightened interest surrounding the potential role of methylation patterns (the attachment of a molecule to DNA, which changes the expression of a gene) in many diseases, including Alzheimer's disease. My PhD thesis will focus on examining the role methylation may play in defining Alzheimer's disease risk. Specifically, we hope to identify individuals within the population at risk of the disease and determine how those methylation patterns may influence disease symptoms and progression.

AU-ARROW

The **AU**stralian-Multidomain **A**pproach to **R**educe Dementia **R**isk by Pr**O**tecting Brain Health **w**ith Lifestyle intervention **(AU-ARROW)** study

Professor Ralph N. Martins AO, BSc, PhD
A/Prof Hamid R. Sohrabi, BSc, MSc (Hons), PhD
Mr Kevin Taddei, MSc
Dr Stephanie Rainey-Smith, PhD

Alzheimer's disease is characterised by loss of brain cells, manifested as cognitive decline leading to dementia. Current research shows that prevention is the best approach to the disease.

Our previous findings on diet, sleep, cognitive stimulation and physical exercise have shown that these lifestyle factors can significantly change the course of the disease in the brain. Furthermore, a preliminary trial of a multi-modal treatment comprising prescribed diet, exercise, cognitive stimulation and vascular risk monitoring has shown significant benefits. These findings have led to a global initiative for dementia risk reduction, known as World Wide FINGERS (WW FINGERS). The AU-ARROW study is the Australian adaptation of WW FINGERS to examine whether this multi-modal treatment can show benefits in Australian cohorts.

Led by Prof Ralph Martins and his team and collaborators in Sydney and Perth, the project has been supported by the NHMRC Medical Research Future Fund and the US Alzheimer's Association. The study will commence in the second half of 2020 and will take 3 to 4 years to complete. The AU-ARROW clinical trial brings Australia into the international initiative for dementia risk reduction and optimising cognitive function across the ageing lifespan.

The AU-ARROW is closely aligned with the US-POINTER study, a major partner of the WW-FINGERS and will be conducted across two sites in Australia: the Macquarie University Health Clinics, Sydney, NSW and the Sarich Neuroscience Research Institute, Edith Cowan University, Perth, WA. The study will recruit 600 individuals in total across the two sites, aged 60-79 years, who are at higher risk of dementia. Participants will be randomised into two groups including a multi-modal treatment plan and a control group. While part of an international collaboration, AU-ARROW has a unique and innovative set of biomarkers including eye imaging that will be a major contribution in assessing treatment effects.

"The results of this study could have large-scale implications for clinical care, treatment and prevention of Alzheimer's disease.

Preventative measures to protect brain health are becoming increasingly important with our ageing population and the fast-growing number of older Australians at risk of dementia."

Professor Martins

The AU-ARROW project will be supported by the Australian Alzheimer's Research Foundation. The Perth team includes Prof Ralph Martins AO, Mr Kevin Taddei, Dr Stephanie Rainey-Smith, and Dr Samantha Gardener from Edith Cowan University and A/Prof Hamid Sohrabi and Dr Belinda Brown from Murdoch University.

Sleep Improvement Study

Dr Stephanie Rainey-Smith, PhD
School of Medical and Health Sciences, Edith Cowan University

Dr Stephanie Rainey-Smith
Senior Research Fellow, School of Medical and Health Sciences,
Edith Cowan University

Lead investigator: Dr Stephanie Rainey-Smith (ECU)
Associate Investigators: Prof Romola Bucks (UWA), A/Prof Michael Weinborn (UWA), Prof Ralph Martins (ECU and MqU), Dr Melissa Ree (UWA)
Study coordinator: Ms Jo Shaw

The Sleep Improvement Study is an intervention study which aims to assess whether memory and thinking (cognition) and neuroimaging biomarkers of brain health are improved following a cognitive behavioural therapy intervention targeted at improving sleep.

Compelling evidence indicates that sleep is a critical contributor both to cognitive health and to neurobiological changes in the ageing brain. Yet this study fills an important knowledge gap by being one of only a few to explore the utility of interventions to improve sleep as a preventative approach to decrease Alzheimer's disease risk. The results collected to-date as part of this study show great promise, with significant improvements in measures of executive function and memory, and increased brain glucose metabolism (a marker of brain health), coupled to the improved sleep occurring post-intervention. Notably, in 2019, Dr Stephanie Rainey-Smith was awarded an internationally competitive project grant from the Alzheimer's Association (US) thereby enabling her to enrol additional participants into the study.

STUDENT PROFILES
SLEEP IMPROVEMENT STUDY

Ms Nadia Soh
PhD Candidate, UWA

Supervisors:
Dr Stephanie Rainey-Smith, ECU
A/Prof Michael Weinborn, UWA
Dr Melissa Ree, UWA

With the ultimate aim of improving overall quality of life, and reducing the risk of Alzheimer's disease, Nadia's research will examine an important yet relatively unexplored area of poor sleep – the discrepancy between subjective (self-report) and objective sleep assessments, which is commonly experienced in insomnia. This discrepancy often includes an underestimation of total sleep time, and overestimation of time to fall asleep and wake after sleep onset. Specifically, Nadia's research will explore the relationship between subjective self-reported sleep disturbance and objective cognitive deficits, and the underlying neurophysiological mechanisms behind this relationship. This knowledge may help inform the development of future treatments.

Mr Matt Hyett
PhD Candidate, UWA

Supervisors:
A/Prof Michael Weinborn, UWA
Prof Ralph Martins, ECU
A/Prof Brandon Gavett, UWA
Prof Michael Breakspear, University of Newcastle

Matt is currently a second year student in the Master of Clinical Neuropsychology/PhD program at UWA. Matt is involved in the Sleep Improvement Study, conducting neuropsychological testing of participants and performing quality assurance checks on collected data. Matt's research focuses on clarifying neurobiological links between depression and neurodegenerative disorders such as Alzheimer's disease. Part of his PhD will use data from the AIBL study to examine whether symptoms of low mood, cognitive functioning, and associations between different brain regions predict cognitive decline in healthy older adults.

Ms Louise Pivac
PhD Candidate, ECU

Supervisors:
Dr Stephanie Rainey-Smith, ECU
A/Prof Michael Weinborn, UWA
Dr Samantha Gardener, ECU

After two years working as a research volunteer, on the Western Australian Memory Study and the Sleep Improvement Study, Louise commenced her PhD studies in February 2020. Using state of the art methodologies, Louise is investigating the effect of sleep on cognition, and whether brain glucose metabolism and Amyloid-β deposition impact this relationship. Ultimately, she will use data from the Sleep Improvement Study to investigate whether those individuals with improvement in sleep quality, following a sleep-specific cognitive behavioural therapy program, gain observable improvement in cognition and markers of brain health determined using brain imaging. This research has the potential to provide a safe and widely applicable method for maintaining healthy brain ageing.

Mr Alex Mladenovic
PhD Candidate, UWA

Supervisors:
A/Prof Michael Weinborn, UWA
Dr Stephanie Rainey-Smith, ECU
Prof Romola Bucks, UWA

Alex is involved in the Sleep Improvement Study, conducting neuropsychological testing of participants and performing quality assurance checks on collected data. Alex's research aims to improve understanding of how night to night variability in sleep develops over time, and whether this corresponds to changes in various forms of cognition (e.g., attention, episodic memory and executive functioning) or biomarkers of brain health (e.g., beta-amyloid burden or cortical thickness). The results will tell us if night-to-night variability is more reliable than averages of sleep characteristics in predicting changes to cognition and brain health over time.

Exercise

Dr Belinda Brown
Research Fellow, School of Psychology and Exercise Science, Murdoch University

Accumulating evidence supports a role for exercise in protecting the brain as we age. Nevertheless, there is still more we need to learn about what type of exercise is best for the brain and how we can keep people engaged in exercise in older adulthood.

We have recently completed the **Intense Physical Activity and Cognition (IPAC)** study, undertaken as a collaboration between Murdoch University and the Australian Alzheimer's Research Foundation. We recruited 99 individuals to undertake either six month high-intensity exercise or moderate-intensity exercise (or to enter a no exercise control group), and evaluated the effect of exercise on memory and thinking and indicators of brain health from brain scans.

The data is currently undergoing analysis, but we can report that individuals that had higher levels of cardiorespiratory fitness at baseline, were also performing better on tasks assessing memory and executive function (organisational thinking and planning skills). We also noted some influence of genetics on these associations, where we were more likely to observe a relationship between fitness and memory in individuals of certain genetic make-ups. This type of research pertains to a long-term research aim of ours, where we aim to gather sufficient evidence to be able to provide individually tailored exercise, based on genetic factors.

Although work from our team, and others, indicates that exercise can improve brain health and reduce dementia risk, we know that participants tend to stop exercising once an intervention finished. Our team has recently been awarded a Dementia Collaborative Research Centre-Dementia Australia grant, that we will use to investigate the effect of high-intensity exercise on the brain, this time with the aim of creating a long-term behaviour change toward exercise. Our intervention will include ongoing education regarding exercise, and various behavioural change techniques. This study is due to commence in May 2020.

Natalie Frost

PhD Candidate, UWA

Supervisors:
A/Prof Mike Weinborn, UWA
Dr Belinda Brown, Murdoch University

There is extensive research that reports regular physical activity as a protective factor against age related neurodegeneration and cognitive decline. However, we still don't know why or how physical activity protects against this type of decline. To answer some of these questions, my research looks at the most beneficial physical activity intensity level for cognitive protection, as well as measuring brain regions that appear most amenable to physical activity mediated change. Specifically, the main focus of my research is to try to understand optimal exercise intensity levels by assessing changes in Executive Function following a high-intensity exercise intervention (versus moderate intensity and no exercise) in older adults. As Executive Functions allow us to think before we act, resist impulsive responses, focus attention, reason, problem-solve, shift-between competing demands or priorities, and view circumstances from new and varied perspectives, it is unsurprising that decline in this area of cognition is linked with poor quality of life and decreased ability to live independently. Consequently, interventions such as ours that that aim to slow or prevent Executive Function decline have the potential not only for preservation of cognitive function, but preservation of overall quality of life and independent living as well.

Shaun Markovic

PhD Candidate
Murdoch University

Supervisors:
Dr Belinda Brown , Murdoch University
Prof Melinda Fitzgerald, Curtin University
A/Prof Jeremiah Peiffer, Murdoch University
Dr Brendan Scott, Murdoch University

My PhD is focused on the cognitive and neurological implications of concussion when sustained later in life and whether lifestyle-related habits and behaviours such as physical activity and sleep could influence cognitive recovery following a mild injury to the brain. After achieving confirmation of candidature and gaining ethical approval to begin collecting data in late 2019, I am currently in the process of recruiting and enrolling both acutely concussed older adults (aged between 50 and 80), as well as age-matched healthy controls for the rest of 2020.

The Australian Alzheimer's Research Foundation is delighted to be providing Shaun with an annual top-up scholarship to support his PhD research.

Autophagy Dysfunction in Alzheimer's Disease

Dr Prashant Bharawaj
Research Fellow, School of Medical and Health Sciences,
Edith Cowan University

Autophagy or "self-eating" is a waste removal process that recycles damaged protein and organelles in cells. Autophagy is impaired in Alzheimer's disease and is implicated in the increased accumulation of beta amyloid and tau protein aggregates.

The autophagy pathway is highly conserved from yeast to mammalian cells and Dr Bharadwaj originally developed a high-throughput yeast model for investigating autophagy mediated clearance of beta amyloid, a protein that accumulates in the Alzheimer's disease brain. Using this yeast model, Dr Bharadwaj screened 182 autophagy genes and identified a gene, SNF4 that reduced the levels of beta amyloid aggregates. These findings were published in Molecular and Cellular Neuroscience and the first to demonstrate a role for SNF4 in regulating beta amyloid levels.

Dr Bharadwaj also determined whether expression of PRKAG2 (Protein Kinase AMP-Activated Non-Catalytic Subunit Gamma, human homolog of yeast SNF4), is altered and if it is associated with impaired autophagy and accumulation of beta amyloid in post-mortem brain tissues of patients with Alzheimer' disease, Frontotemporal dementia, Lewy body dementia and in healthy controls.

Dr Bharadwaj demonstrated that gene expression of PRKAG2 was increased 3-fold in Alzheimer's disease brain and its protein levels positively correlated with beta amyloid accumulation in the brain. These findings were published in the Journal of Alzheimer's disease and the first to identify a role for PRKAG2 gene in Alzheimer's disease. Overall, these findings by Dr Bharadwaj suggest that impaired autophagy and increased expression of PRKAG2 could be a response to beta amyloid accumulation in the Alzheimer's disease brain. Dr Bharadwaj is undertaking further analysis to determine whether PRKAG2 is a reliable and sensitive blood biomarker for early detection of autophagy dysfunction in Alzheimer's disease.

In another study, Dr Bharadwaj developed a novel neuronal cell model to assess clearance of beta amyloid and tau which was published in Molecules. Dr Bharadwaj has also identified a new autophagy modulator from screening a library of small molecules using this model as a high-throughput screening tool and was invited to present this finding at the Alzheimer's and Parkinson's Diseases (ADPD) conference at Lisbon, Portugal in 2019. Dr Bharadwaj also received an Artificial Intelligence Molecular Screen award from Atomwise. Inc, a US based drug development company to develop novel autophagy compounds for treatment of Alzheimer's disease.

Blood Biomarkers Lipidomics

Dr Florence Lim
Senior Research Fellow, School of Medical and Health Sciences, Edith Cowan University

Lipids play an essential role in all mammalian systems. Previous lipidomics studies have identified multiple lipid classes and species such as phospholipid and ceramide metabolism may be involved in Alzheimer's disease (AD) pathogenesis.

The Australian Imaging, Biomarker and Lifestyle (AIBL) study of Ageing enabled us to examine lipid metabolism in AD. In this study, we together with Professor Peter Meikle and Kevin Huynh from the Baker Heart and Diabetes Institute investigated whether altered lipid metabolism associated with increased age, gender and APOE status may contribute to the development of AD by examining these risk factors in the plasma of healthy controls and also clinically diagnosed AD individuals.

This study extends our existing knowledge of the relationship between lipidome and AD and highlights the complexity of the relationships between lipid metabolism and AD at different ages and between men and women. This has important implications on how we assess AD risk and also for potential therapeutic strategies involving modulation of lipid metabolic pathways.

As part of the NHMRC grant through Professor Peter Meikle titled "A systems epidemiology approach to define metabolic and genomic determinants of Alzheimer's disease", we will be examining platelet lipidomics and its association with AD. This analysis will be performed on samples obtained from 5 timepoints (baseline, 18, 36, 54 and 72 months) of the AIBL cohort.

Blood Biomarkers Proteomics

Dr Eugene Hone
Senior Research Fellow, School of Medical and Health Sciences, Edith Cowan University

Mr Steve Pedrini
Senior Research Fellow, School of Medical and Health Sciences, Edith Cowan University

The primary objective of our research is focused on uncovering a specific blood-based signature that can detect Alzheimer's disease in the early stages or even before the clinical onset. Recent studies have indicated that in the brain, biochemical changes take place years before the appearance of the earliest symptoms, but the current methods to detect such changes are either expensive or invasive and cannot be used on a daily basis.

The development of a blood-based biomarker panel for the early diagnosis of the disease would allow for early treatment of patients in the initial phases of the disease, when therapies are said to be more effective.

Our research team has recently published a study examining inflammatory molecules in the journal Scientific Report. We measured a broad spectrum of inflammatory molecules in the blood of participants who were either healthy, or had mild cognitive impairment, or were Alzheimer's affected. We found that two of these inflammatory molecules belonging to the class of cytokines (IL-10 and IL-12/23p40) were associated with the disease. Our study indicated that these two molecules displayed differences between the groups of participants. However, our work also showed that we need to identify other biomarkers to improve the sensitivity of the test. Our data also indicate that we need those additional blood biomarkers of Alzheimer's disease to ensure that the test is accurate and produces a reliable result to aid with the diagnosis of the disease. Our ongoing research is committed to identifying the optimal set of blood biomarkers in our quest to make the diagnosis of Alzheimer's disease more accurate, less costly, faster and less stressful.

Testosterone Study

TotAL Study: A 56 week, Double-Blind, Randomised Study to Evaluate the Efficacy of **T**estosterone, With and Without **o**mega **t**hree (DHA) Supplementation on Cerebral **A**myloid **L**oad in Men with Subjective Memory Complaints

One of the proposed reasons for cognitive decline and Alzheimer's disease is the age-related decline in sex hormones. Research indicates that the relatively abrupt loss of estrogen and progesterone at menopause in women and the more gradual decrease in testosterone in aging men are likely risk factors for Alzheimer's disease.

Hormones are chemical messengers that travel in the bloodstream and regulate complex processes within the body including growth, metabolism, appetite and reproduction. They are also very important for brain function for example facilitating neuronal (brain cell) connections to allow memory processing, consolidation and retrieval and protect the brain from inflammation or oxidative stress. Imbalances in hormone levels can influence behaviour and promote diseases such Alzheimer's disease and type 2 diabetes.

During ageing, there is a normal decline in sex hormone levels. Previous studies have indicated that testosterone replacement reduces beta amyloid levels in both the blood and the fluid that surrounds the brain (cerebrospinal fluid) and suggests that the reduction in testosterone during ageing could contribute to the development and underlying causes of Alzheimer's disease.

The findings from previous research encouraged the team to investigate further the impact of testosterone treatment on the associations observed between luteinizing hormone and testosterone and brain amyloid load. As a result, we have established a clinical trial to assess the effect of testosterone treatment on brain amyloid load and cognition in men over 60 years of age. The study is being conducted in Perth and at Macquarie University in NSW.

The study is targeting men who have testosterone levels at the low end of normal and who have subjective memory complaints. Eligible participants will receive 13 months of treatment. A number of parameters will be measured at baseline, during the trial and the end of the trial (56 weeks). The parameters to be measured will include neuropsychological assessments to assess whether benefits to cognition and memory are observed, and brain imaging, including MRI, FDG-PET (to determine if there are improvement in brain glucose metabolism), and Amyloid-PET (to determine if there is lowering of brain amyloid load).

The Testosterone Study Team

Back row (L-R) : Shane Fernandez, A/Prof Hamid Sohrabi, A/Prof Roger Clarnette, Dr Vicky Tee, Dr Christina Di Camillo, Kevin Taddei
Front row (L-R): Marie Todd, Kimberly De man, Dr Erin Bell, Dr Lin McVee

STUDENT PROFILE
TESTOSTERONE STUDY

Sherilyn Tan
PhD Candidate
UWA

Supervisors:
A/Prof Michael Weinborn, UWA
A/Prof Hamid Sohrabi, Murdoch University
Professor Ralph Martins AO, ECU

An increasing body of literature suggests a positive, neuroprotective effect for testosterone on cognition in older men. However, randomized clinical trials examining the effects of testosterone supplementation on cognitive function have been inconclusive. The aim of this meta-analysis was to investigate the potential for testosterone supplementation to prevent cognitive decline in otherwise cognitively healthy older men, by examining the differential effects of testosterone supplementation on cognitively healthy older men in randomized clinical trials. A comprehensive search of electronic databases, conference proceedings, and grey literature from 1990 to 2018 was performed to identify randomized clinical trials examining the effects of testosterone supplementation on cognition before and after supplementation, in cognitively healthy individuals.

A final sample of 14 eligible randomized clinical trials met inclusion criteria. A comparison of placebo versus treatment groups pre- and post-supplementation showed improvements in the treatment group when cognitive scores were considered as a whole. In individual cognitive domains, testosterone supplementation appeared to improve cognitive performance on measures of psychomotor speed and executive function. Overall, our findings support the potential for testosterone supplementation as a preventative measure against cognitive decline, although the effect sizes were small. These findings warrant further observational studies and clinical trials of good methodological quality, to elucidate the effect of testosterone supplementation on cognition.

The Australian Alzheimer's Research Foundation is delighted to be providing Sherilyn with a scholarship to support her PhD research.

Sodium Butyrate and Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder characterised by progressive cognitive decline and neuropathological features, including abnormal deposition of β-amyloid (Aβ) peptides, intracellular neurofibrillary tangles, and neuronal death.

Dr Binosha Fernando
Research Fellow, School of Medical and Health Sciences, Edith Cowan University

Identifying therapeutics which can reduce memory deficits at an early stage of the disease has the advantage of slowing or even reversing disease progression before irreversible brain damage has occurred. Consequently, in this study, we investigated the ability of the histone deacetylase (HDAC) inhibitor sodium butyrate (NaB) to attenuate memory deficits in the 5xFAD mouse model of Alzheimer's disease following a 12 week feeding regimen.

Butyrate is a short chain fatty acid (SCFA). These are small organic acids resulting mainly from the anaerobic fermentation of indigestible polysaccharides (ex; fibre) in human gut. The main short-chain fatty acids that are produced are valeric (C5), butyric (C4), propionic (C3) and acetic (C2). SCFAs may attenuate Alzheimer's disease by serving as substrates for energy metabolism, and providing an alternative energy source to reduce neuronal dysfunctions in Alzheimer's disease and other neurodegenerative conditions. They are also important to reduce cholesterol, insulin resistance and to reduce cancer cells. However, little is known whether SCFAs may modulate cognition and pathology of Alzheimer's disease at its early stage.

In this study we used 5xFAD mice which demonstrate a unique time course of Aβ pathology, developing Aβ plaques as early as 2 months. Mice were assigned to either a control diet or a NaB-supplemented diet which was administered at either 5 mg/kg/day, or 15 mg/kg/day for 12 weeks (each group, N=15). Supplementation commenced at an early disease stage (8-10 weeks of age). Behavioural testing (contextual and cued fear conditioning) was undertaken, and brain Aβ levels measured, at the end of the 12 week intervention. NaB had profound effects on Aβ levels and on associative learning and cognitive functioning. A 40% reduction in brain Aβ levels and a 25% increase in fear response in both the cued and contextual testing was observed in the NaB-treated animals compared to the control group. In summary, Butyrate treatment improves associative learning and cognitive functions in Alzheimer's disease mouse models whilst reducing the amyloid beta load in the brain at early stages of the disease. These findings suggest that NaB warrants further investigation as a potential therapeutic agent in the treatment of cognitive deficits associated with early stages of Alzheimer's disease.

CLINICAL TRIALS DIVISION

The Australian Alzheimer's Research Foundation conducts clinical trials into new investigational therapies for Alzheimer's disease.

Under the leadership of Dr Roger Clarnette, the Foundation is working with international pharmaceutical companies, trialling new drugs that may ease the suffering for those diagnosed with Alzheimer's disease.

Clinical Trials Division

A/Prof, Roger Clarnette
Australian Alzheimer's Research Foundation

A/Prof Roger Clarnette
Medical Director,
Australian Alzheimer's Research Foundation

The Foundation's Clinical Trials Division conducts clinical trials for some of the world's leading pharmaceutical companies to test potential treatments for people at risk of, or diagnosed with, Alzheimer's disease.

The Foundation is a vital part of the search for new treatments to slow the progression of and treat Alzheimer's disease.

Clinical trials are an essential part of medical research. In order for new medications to make it onto the market, they must first undergo meticulous testing to determine overall safety and effectiveness. These trials offer hope for many people and an opportunity to help researchers find better treatments for others in the future. They also provide an opportunity to potentially access the latest therapies being researched internationally for Alzheimer's disease.

Based at the Hollywood Specialist Centre in Nedlands, the Clinical Trial Division is staffed by study coordinators, nurses and medical practitioners. The unit is supervised by Associate Professor Roger Clarnette, a senior specialist physician at Fremantle Hospital who has a particular interest in memory loss and Alzheimer's disease.

The Clinical Trials Division Team

(L-R) Dr Cheryl Chen, Paula Mather, Dr Cate Mansfield, Allae Saade

A snapshot of the therapeutic trials the Clinical Trials Division was involved in throughout 2019 are summarised on the following pages.

ABBVIE AWARE M15-566 (PHASE 2)

A Phase 2 Multiple Dose, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABBV-8E12 in Subjects with Early Alzheimer's Disease

- Humanized immunoglobulin G4 (IgG4) monoclonal antibody against human microtubule-associated protein tau (ABBV-8E12)

Approximately 400 participants worldwide with early Alzheimer's disease between 55 to 85 years of age were eligible to participate in the study according to the selection criteria. Upon completion of screening and baseline procedures, eligible subjects were randomized to one of the three ABBV-8E12 dose arms (300 mg, 1000 mg or 2000 mg) or placebo in a 1:1:1:1 ratio. Doses are administered every 4 weeks via IV infusion. The Foundation screened sixteen participants, with nine successfully enrolling.

ABBVIE AWARE EXTENSION M15-570 (PHASE 2)

Open Label Extension Study for Patients with Early Alzheimer's Disease (AD) Enrolled in Study ABBV-8E12

- Humanized immunoglobulin G4 (IgG4) monoclonal antibody against human microtubule-associated protein tau (ABBV-8E12)

Participants that complete the AbbVie AWARE M15-566 study have the opportunity to enrol in the extension study.

ANAVEX2-73-AD-004 (PHASE 2B/3)

A Phase 2b/3, Double-Blind, Randomized, Placebo-Controlled 48-week Safety and Efficacy trial of ANAVEX2-73 for the Treatment of Early Alzheimer's Disease

- Sigma-1 (σ1R) and muscarinic receptors agonist (ANAVEX2-73)

In addition to evaluating the effects on cognition and functioning, ANAVEX also explores sleep outcomes, behavioural and psychological symptoms, changes in daily functioning of participants and changes in caregiver burden. Safety assessments include pharmacokinetic (PK) assessments and blood markers of Alzheimer's disease pathophysiology before and after treatment.

Anavex was a highly anticipated trial due to the publicity it received nation wide from the promising results seen in earlier phases of research. The Foundation screened sixteen participants, enrolling twelve.

ANAVEX2-73-AD-004 EP (PHASE 2B/3)

Open Label Extension Study for Patients with Early Alzheimer's Disease (AD) Enrolled in Study ANAVEX2-73-AD-004

- Sigma-1 (σ1R) and muscarinic receptors agonist (ANAVEX2-73)

Participants that complete the ANAVEX2-73-AD-004 study have the opportunity to enrol in the extension study.

BIOGEN ENGAGE 221AD302 (PHASE 3)

A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

- Human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ) (Aducanumab)

Biogen terminated this trial in March 2019 due to a futility analysis finding the study was unlikely to meet efficacy targets. A further detailed analysis of the results has shown that those treated with the highest dose of study drug showed improved outcomes in cognition and functioning which became worldwide news. A re-dosing study was announced in December 2019.

BIOGEN EMBARK 221AD304 (PHASE 3B)

Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (aducanumab) in Subjects with Alzheimer's disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205

- Human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ) (Aducanumab)

This open-label, single arm clinical study is being conducted to assess the long-term safety and efficacy of aducanumab in participants with Alzheimer's disease who were actively participating in previous aducanumab studies. It is a two-year study involving monthly infusions of aducanumab.

The study is expected to start in April 2020. Four participants will be eligible for enrolment.

COGRX SHINE COG0201 (PHASE 1B/2)

A randomized, double-blind, placebo-controlled, parallel-group, phase 2 study to evaluate the safety and efficacy of CT1812 in subjects with mild to moderate Alzheimer's disease

- Highly brain penetrant sigma 2/PGRMC1 antagonist (CT1812)

In 2017, the Australian Alzheimer's Research Foundation took part in the Phase 1 study of CogRX. Due to promising results the drug was put on fast track status and a Phase 1b/2 commenced in late 2018. The Foundation is the highest recruiting site in Australia while also maintaining a low screen failure rate. Recruitment is temporarily suspended awaiting release of further grant funding. We already have numerous people eager to participate once it reopens. The Foundation screened fifteen participants with ten successfully enrolling.

EISAI CLARITY BAN2401 (PHASE 3)

A Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study With an Open-Label Extension Phase to Confirm Safety and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease

- BAN2401 is a humanized IgG1 monoclonal antibody that binds to soluble Aβ aggregates.

The Australian Alzheimer's Research Foundation was selected for this study in December 2019, with recruitment to open in May/June 2020.

ROCHE GRADUATE WN29922 (PHASE 3)

A phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy, and safety study of Gantenerumab in patients with early (prodromal to mild) Alzheimer's disease

- *Fully human monoclonal antibody targeting fibrils, and plaques (Gantenerumab)*

This study aims to evaluate the ongoing safety and efficacy of gantenerumab administered as a subcutaneous injection over a 24-month period. The Foundation screened fourteen participants and eight were successfully enrolled in 2019.

NTA THE 3D STUDY DEF-001 (PHASE 2)

Deferiprone to Delay Dementia (The 3D Study): A clinical proof of concept study

- *Iron chelator (Deferiprone)*

The 3D study investigates whether an iron chelator medication, Deferiprone, delays dementia progression in the early stages of Alzheimer's disease. Iron chelators are used in the treatment of conditions such as haemochromatosis and thalassemia, where abnormal iron accumulation is present. In Alzheimer's disease iron accumulates in affected brain regions causing neurotoxicity. Recruitment will commence in 2020.

STUDIES THAT CLOSED IN 2019

Biogen EVOLVE 221AD205 (Phase 2)
This study assessed the safety impact of continuing aducanumab dosing in subjects with asymptomatic moderate to severe findings on MRI related to study drug adminsitration.

EISAI MissionAD E2609-G000-301 (Phase 3)
The study was terminated by the Sponsor following a futility analysis not showing significant effect and a greater incidence of adverse events.

INmuneBio (XPRO-1595) (Phase 1b)
The study was closed at site as nationwide recruitment target was met early.

NOVARTIS GENERATION 1 & 2
CAPI015A2201J/CNP520A2202J (Phase 2/3)
The studies was terminated by the Sponsor who concluded that the potential benefits no longer outweighed the risks.

THANK YOU TO OUR SUPPORTERS

Staying connected with the community is vitally important, providing information about Alzheimer's disease and how funds are being used to support vital research.

We are tremendously thankful to our supporters who enable our research work to continue.

In 2019 we welcomed the Pinnacle Charitable Foundation and Spheria Asset Management as corporate sponsors.

"Spheria Asset Management is delighted to be helping drive cutting edge research into understanding more about cell biology and early stage changes at the onset of Alzheimer's disease. Our partnership with AARF acknowledges the enormous impact of Alzheimer's across our society, with devastating impacts on not only those affected, but also their loved ones. Together with the Pinnacle Charitable Foundation, the team at Spheria is committed to helping AARF explore advances in diagnosis and treatment, and ultimately find a cure for this debilitating disease."

Matthew Booker, Portfolio Manager

OUR SUPPORTERS

Thank you to our generous sponsors and contributors

Donors and Fundraisers
We are always touched by the number of people who donate to, or fundraise for the Australian Alzheimer's Research Foundation. We wish to thank all those individuals who have given to the the Foundation through regular giving, one of our appeals, or through one of our fundraising programs.

Volunteers
Delivering our programs and events would not be possible without the contribution of our wonderful volunteers. We thank our volunteers who have given their time, skills and energy in helping us throughout the year.

Bequests
It's with respect and gratitude that we recognise those who gave a lasting gift to the Australian Alzheimer's Research Foundation via a gift in their Will. Their kindness enables us to fund research that we hope brings us one step closer to an Alzheimer's free world.

Workplace Giving
We would also like to acknowledge those employees who continue to support the Australian Alzheimer's Research Foundation through regular workplace giving and their employers who make it possible. Individual employees contribute regular donations through their pre-tax pay and many employers match these contributions.

In 2019 Alcoa's employee giving program PEACH – Personnel Employed at Alcoa Charity Help – lent its support. PEACH collects regular payroll donations from Alcoa employees and distributes them to worthy West Australian charities and community organisations. In February, PEACH donated funds to the Foundation to purchase a much needed -80°C freezer to enable the long-term storage of blood sample.

Major Giving
We greatly value the wonderful contributions by our major donors and philanthropists in helping us achieve our mission of supporting research that makes Alzheimer's disease treatable and preventable.

In Celebration
The Foundation would like to give their sincerest recognition to everyone who invited their family and friends to make a donation to assist our cause rather than receive presents.

In Memoriam
To everyone who chose to honour a loved one by making a donation to the Foundation in their memory, our sincerest thanks. Your generous gift will enable us to continue supporting leading edge research.

Corporate and Government Partners
With no government funding, our corporate partners are incredible important and their continued support helps to raise awareness of Alzheimer's disease with their employees as well as providing vital financial support for the Foundation. In 2019, we would like to thank all our corporate supporters and the following national and government partners for their on-going commitment to the Australian Alzheimer's Research Foundation.

Wesfarmers kindly continued their sponsorship in 2019 and we greatly appreciate their ongoing support.

Lotterywest support for the Testosterone Study is greatly appreciated.

The CWA of WA elected the Foundation as its 2018-2019 charity partner and raised an astonishing $50,000 through various fundraising activities. We are extremely grateful for their incredible effort.

Our thanks also to The Government of Western Australia, Edith Cowan University, The University of Western Australia, Macquarie University, Pinnacle Charitable Foundation, Spheria Asset Management, Alcoa and Wine & Horses Perth Hills who supported the Foundation in 2019.

Thank you to our generous supporters and partners

COMMUNITY ENGAGEMENT

Community activities to raise funds for the Foundation and bring greater awareness and understanding of the disease are greatly appreciated. We thank everyone for their tremendous support.

'Etching for Moi'

Internationally acclaimed artist Leon Pericles produced a beautiful etching called "Etching for Moi" dedicated to his wife Moira, with all funds donated to the Foundation to support Alzheimer's research. The art work was exhibited at Leon's 50 year Retrospective at the Linton & Kay Gallery and all 150 etchings have been sold. Reproductions are now available and ongoing funds will continue to be donated to the Foundation.

The etching coincided with the production of the documentary 'Storm in a Tea Cup' directed by Nia Pericles and shown on SBS. The documentary and the etching have brought significant awareness to the disease for which we are very grateful.

We would like to thank Leon, his family, the Linton & Kay Gallery and everyone behind the scenes for their tremendous support.

Rockingham Beach Cup

Rockingham Beach Cup held their annual charity event on Sunday 17 November. The Australian Alzheimer's Research Foundation is one of the beneficiaries of this prestigious event and would like to say a huge thank you to the Rotary Club of Palm Beach WA Inc, the City of Rockingham and the Rockingham Beach Cup committee for their amazing efforts. Representatives from the Foundation were in attendance over the weekend to bring much needed awareness to Alzheimer's disease.

Rockingham Beach Cup

Swim for a Reason

Barry Green and a dedicated and fit group of the Stadium Masters Swimmers held their annual Swim for a Reason on Saturday 6 July 2019 at HBF Stadium. These swimmers are not only on top of their exercise regime, they also raised over $5500 for Alzheimer's research.

Country Women's Association of WA

Over the last 12 months the CWA of WA have been supporting the Australian Alzheimer's Research Foundation with a variety of fundraising activities. Heather Allen, State President, CWA of WA, presented Chairman Enzo Sirna with a cheque of $50,000 at the 95th Annual State Conference to help us in our fight for answers into the debilitating Alzheimer's disease. We cannot thank the CWA of WA enough for their generosity and friendship throughout the year.

COMMUNITY ENGAGEMENT

Public Lectures

The Foundation holds Public Lectures each year during September's **World Alzheimer's Month.** These lectures enable the Foundation to inform our research participants as well as the general public on the latest research being undertaken. Our lectures also provide everyone in attendance with the opportunity to meet some of WA's top Alzheimer's researchers. In 2019, approximately 400 people attended our lectures eager to hear the latest developments in Alzheimer's research.

Wine & Horses

Wine and Horses in Perth Hills held their annual charity ride on 12 & 13 October. Approximately 45 horses and riders trekked along the CY O'Connor Pipeline and Kep Trail to Northam. Over 150 people attended the fundraising event after the ride, where dinner, an auction, hot showers and live music were enjoyed by all. Liza Dunne, CEO, attended the event and spoke to the audience about the disease and things we can do to reduce our risk of developing Alzheimer's disease.

Palm Beach Movie Fundraiser

In July 2019 Universal Pictures and the Australian Alzheimer's Research Foundation hosted a fundraising preview screening of the highly anticipated film Palm Beach. Screen legend Bryan Brown was in attendance and spoke about his role as the Foundation's ambassador while also sharing a few amazing stories about his career and life.

A very special thank you to Bryan for his passion towards our cause and for everyone who attended the event and made it a complete success.

HBF Run for a Reason

Congratulations to all the runners who participated in this year's HBF Run for a Reason. Over 40 participants raised nearly $17,000 for the Foundation. Thank you!

SCIENTIFIC PUBLICATIONS

Scientific Publications

Some publications are repeated under mutliple headings

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WAMS & AIBL

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AUTOPHAGY DYSFUNCTION IN ALZHEIMER'S DISEASE

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