2013
ANNUAL REPORT

McCUSKER
ALZHEIMER'S
RESEARCH FOUNDATION INC

THANKS
TO ALL OUR SUPPORTERS…

Alzheimer's disease is one of the most important public health problems we face. It has a devastating impact on individuals and their families, the community and the economy. Unfortunately, compared to many other major health areas such as heart disease and cancer, it receives little funding for research to discover treatments.

Emerging trends in Alzheimer's disease statistics are amazing.

- There are 4.6 million new cases every year.
- The number of people with Dementia is expected to double every 20 years and is projected to reach 115 million by 2050, with 81.1 million patients by 2040.
- 43% of cases need significant care (equivalent to a Nursing Home.)
- Total estimated worldwide cost of dementia in 2010 was $US604 billion or nearly 1% of global GDP.
- "If Alzheimer's were a country, it would be the 18th largest economy based on GDP."
- Within 2 decades dementia will be the third greatest source of health and residential aged care spending – approx. 1% of GDP
- Spending on Dementia will surpass any other health condition

In 2010 dementia affected 23,000 WA people and this figure will rise to 61,000 by 2030. It is estimated that by 2050 there will be an estimated 125,000 cases in WA with 18 new cases every day. It is predicted that the most rapid growth in WA will occur in the next 10 years

The support given by the public to the fight against Alzheimer's disease is of the utmost importance. Without the very generous contributions of time and money made by individuals and corporations, the major research being undertaken here in WA, at the McCusker Alzheimer's Research Foundation, would struggle.

We are very grateful to our many supporters who share our vision of a world where Alzheimer's disease is treatable and preventable and our belief that the research occurring here in WA can make major contributions to defeating Alzheimer's.

We are especially thankful to the McCusker family, particularly Malcolm, Carolyn and Tonya for their tremendous support and assistance over many years. Special mention must also be made to Hollywood Private Hospital and Edith Cowan University whose contributions of laboratory space, salaries and funding of research costs are invaluable.

Particular thanks go to a number of significant donors who are acknowledged personally by Enzo Sirna in his Chairman's Report.

We are grateful to community groups such as Lions clubs WA, Rotary and Freemasons who support our efforts to find a cure for Alzheimer's disease. Our developing partnership with the Lions Clubs International (WA) is particularly appreciated.

Volunteers make an invaluable contribution. Their contributions as research volunteers and assistance in fund raising and promotion are critical to our efforts. Special thanks go to the volunteers of the Lions McCusker Committee who work tirelessly to support and promote the work of Professor Martins and his team.

Finally, there are many more important supporters that have not been singled out, however we wish to acknowledge their generous support, along with the support of many members of the public.

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Board of Director 2013

Seated from left: Rob Davies, Professor Ralph Martins; Enzo Sirna, Dr Terry Bayliss
Standing from left: Peter Stephens, Deborah Doncon, Jenny Day, Assoc. Professor David Groth, Ron Bennetts, Russell Delroy.

CHAIRMAN'S REPORT - ENZO SIRNA

Since its inception, the McCusker Alzheimer's Research Foundation has maintained a constant and important presence in assisting our research team, so capably led by Prof. Ralph Martins, in its goal to find prevention and ultimately, a cure for Alzheimer's disease.

The importance of this world class research has not been underestimated by the 2013 Members of the Board of the McCusker Alzheimer's Research Foundation. The Board has recognised the challenges associated with the escalating research demands and the commitment required to give Prof. Martins and his team maximum opportunities to continue to be key research contributors at a world level.

The Board also values key partnerships in assisting with the delivery of outcomes linked to our research. These partnerships allow the quality of research to be progressed not only at a state level, but also at national and international levels with far reaching benefits. It is a recognised fact the McCusker Alzheimer's Research Foundation has one of the world's richest databases associated with its projects and clinical trials, allowing for greater depth and quality of research as Prof. Martins and his team strive, with excellence, in their endeavour to find a cure for this ever growing disease, with 4.6 million new cases of Alzheimer's disease diagnosed each year.

Prof. Martins and his research team work closely with Dr Roger Clarnette and the Clinical Trials Division with the aim of bringing important clinical trials to Western Australia. Among these we have the Testosterone and Fish Oil Study (where over 3000 people registered interest to participate, but only 200 chosen to be assessed), the Tommorrow (Tomm40) Study, the Nutritional Supplements Study (investigating Biocurcumax and Amlamax), the Australian Imaging, Biomarkers and Lifestyle (AIBL) Project and the Karviah Study (in conjunction with Anglican Retirement Homes in Sydney).

Furthermore, the purchase of a new PET CT Scanner in 2013, due to an innovative partnership with Oceanic Medical Imaging, the McCusker Alzheimer's Research Foundation and the estate of the late Dr. Jean Murray-Jones, will enhance Alzheimer's disease neuro imaging. The PET CT Scanner permits shorter scan times, decreased radiation exposure and will assist in getting quicker results with more accurate scanning.

In order to maintain the essential and ongoing support at an operational level, the Board has identified essential requirements which will need to be implemented as soon as possible to keep pace with the rapid expansion in the research area. It has therefore commenced a review process aimed at strengthening its infrastructure and providing a key platform for the implementation of future strategic planning requirements.

The McCusker Alzheimer's Research Foundation is indebted to its many

benefactors, partners, donors, organisations and sponsors who believe in the cause and who continue to support our endeavours. We are particularly grateful to our Patron, His Excellency, Malcolm McCusker AC CVO QC, to Mrs Tonya McCusker and to Carolyn McCusker, for their unwavering support of the Foundation. The McCusker family has been the backbone of the Foundation for many years and has inspired many other benefactors to contribute as well. The Board also recognises the significant contribution by our Vice-Patron, Mrs Terrie Delroy and her family.

Every contribution made to the Foundation, no matter how big or how small, whether financial or in kind, is gratefully accepted because it all helps in achieving our goals. While it is always difficult to list everyone, I would like to make particular mention of Mrs Helen Sewell and the Johanna Sewell Memorial Fund, Mr Ron Geary and Mrs Glenys Geary, Mr Michael Gregg, the Rotary Club of West Perth, the Stan Perron Charitable Trust, Wesfarmers, the Freemasons, the Lions McCusker Committee, the Cliff Richard's Joondalup Support Ladies Group, the Lions Clubs of WA and those who have supported the Foundation through "Everyday Hero". The Board recognises and truly appreciates your ongoing support and significant contributions.

The Board is also grateful for the significant partnerships established with Hollywood Private Hospital and with Edith Cowan University. Furthermore, the Board would like to recognise Lotterywest for the generous contribution towards the new neuroscience building (of which the McCusker Foundation will be a key partner) and the Government of Western Australia for assisting with our cause.

The McCusker Foundation is pleased to have Maggie Beer as an ambassador for our cause and her presence is always inspirational. The fundraising dinner held at the Perth Convention Centre in December 2013, "Maggie Beer and the Five Chefs", was a huge success and we are indeed grateful for the support received by some of Perth's leading chefs, including Chris Taylor, Alain Fabregues, Neal Jackson, Giuseppe Pagliaricci and Richard Taylor. Franklin Tate provided excellent wines for the evening and Eric Ferrari also assisted with the beverages, providing the mineral water and the beer. I would like to recognise the efforts of John Maiorana in coordinating the chefs, food and beverages to ensure the success of the evening.

Our annual fundraising dinner at Maurizio's Restaurant is always a success and Maurizio Di Ciano and his team, supported by Michael Tamburri for the wines, are to be applauded for the excellence of the food and beverages and the wonderful atmosphere created, with the highlight being the musical interlude by the "Musicantes".

Other successful fundraising events included the Sportsman's Lunch, organised annually by the Claremont Nedlands Lions Club, with part proceeds donated to the McCusker Foundation and the Golf Day at the Royal Perth Golf Club.

The McCusker Alzheimer's Research Foundation was pleased to collaborate with Alzheimer's Australia (WA) for the World Alzheimer's Day and the combined event held at the Government House Ballroom was very well received.

I would like to thank all members of the Board, the Executive, staff, Prof. Martins and the research team for your considerate and passionate commitment to a very important cause. I am also appreciative of the support you have given me as a very privileged Chairman of the McCusker Alzheimer's Research Foundation. I would also like to acknowledge the commitment of our previous Chairman, Mr Graham Nixon, who retired in 2013, but who worked tirelessly for the Foundation for so many years.

In conclusion, I am informed Ms Jenny Gill, our Executive Manager, will be retiring in July 2014. On behalf of the Board, I would like to thank her most sincerely for her loyalty and involvement with the Foundation and wish her well in her retirement.

If anyone has been inadvertently left out of my report, please accept my sincere apologies but understand that your contribution retains the highest of respect and value for the Foundation. ”

RESEARCH REPORT

Prof Ralph Martins
Director of Research

The past year has seen considerable growth in the research work undertaken by our team. The most exciting outcome was the commencement of the Tommorrow (Tomm40) international clinical trial in early Jan 2014, with our site only the second in the world starting this massive undertaking – following 500 to 600 people for five years (see below). This success built on work carried out over the previous two years with the Prepare study. This work is undertaken entirely in our Stirling Highway premises. As a result during late 2013 the Foundation established the McCusker Hollywood Private Hospital Research Centre enabling all our other ongoing clinical projects to be undertaken at the Hollywood site. These achievements reflect the invaluable support received from our study participants, our donors and the McCusker Foundation. This support enabled our research team to achieve a number of important milestones in 2013.

DIAN (Dominantly Inherited Alzheimer's disease network) Study: The McCusker Foundation/ECU team is one of only fourteen worldwide investigating people (and families) who have or are at risk of early onset, inherited Alzheimer's disease. Some of our study participants are in their 30s and have now developed this devastating disease, so this is quite a confronting study. Our participants are very generous in attending for follow up as the study involves a large battery of assessments and tests. The information learned from this group, who develop a rapid, severe form of Alzheimer's disease, is invaluable, as well as providing insight into the more common older onset disease. Arising from the DIAN study is the opportunity for some of our DIAN participants to join the new trial below. At this stage we are one of only a few places in Australia to participate in this work.

DIAN Clinical Trial: Current DIAN participants who meet particular onerous criteria will be eligible for this new Clinical Trial. This will be an international intervention trial which will assess three new drugs thought to be helpful in the early stages of Alzheimer's disease. Prof Martins and A/Prof Roger Clarnette, from the Foundation's Clinical Trials Division, are now involved in negotiations regarding criteria for eligibility of participants for this study. This study has now received its approvals and will commence in May 2014.

Nutritional Supplements Trials: Work continues investigating two nutritional supplements, **BiocurcumaxTM** the active ingredient in the Indian curry spice turmeric and a strong anti-oxidant, and Amlamax, concentrated Indian gooseberry. The **BiocurcumaxTM** trial is assessing whether this spice prevents memory loss and the final 50 participants will also undergo brain imaging to help clarify our findings. In the **Amlamax** study we are recruiting participants who have their cholesterol monitored as it is thought that **Amlamax** may help raise good cholesterol and potentially protect both the head and heart from disease! This trial is well under way with nearly 50 people having completed the study already.

KARVIAH – Kerr Anglican Retirement Village (ARV) Initiative in Ageing Health: KARVIAH is examining the physical and dietary health of 200 older people dwelling in Independent Living Units within a Sydney retirement village. One hundred participants will then go on to the stage two curcumin component evaluating **BiocurcumaxTM** (as above) over a 12 month period. This study has commenced recruitment and will move to stage two during 2014. It is led by Prof Martins in conjunction with the ARV's Dementia Consultancy and Research Manager as well as our UWA PhD student, Kathryn

"My team and I have moved forward on a number of very exciting fronts in 2013. For this we are very appreciative of the marvelous support we receive from our many supporters and the public during the year."

Goozee, and is receiving invaluable support from both the Anglican Retirement Village and McCusker Foundations.

Testosterone and Fish Oil (DHA) Trial: This project involves 200 male participants and is a ground breaking trial testing laboratory and anecdotal evidence that testosterone and DHA help delay or prevent the onset of Alzheimer's disease. This will be a worldwide first in terms of combining these substances. To date our 3000 volunteers interested in participating have been screened and brain imaging is now being utilized to assess eligibility. The study will run for 56 weeks with men receiving a testosterone injection every eight weeks.

Memory Study: This project is a 15 year duration project and we have 800-900 participants. In each case we have a record of their memory and blood tests over time. In some circumstances where the individual has passed away we also have details of their post mortem brain studies. This bank of data will be an invaluable resource as new markers of the disease are discovered.

TOMMORROW study: During 2012/13 our group conducted the Prepare study for USA based Zinfandel Pharmaceuticals, in which we recruited and assessed 1300 potential participants for the Tommorrow study. This new study, which commenced in January 2014, has now been taken over by the large Japanese pharmaceutical company Takeda. The trial will determine whether a drug usually used in type two diabetes can help delay the onset of Alzheimer's disease. It will also test the validity of a genetic biomarker TOMM 40. It will run over five years with the Foundation/ECU team center one of three in the world designated Tier One (major) sites. This is a unique prevention trial in that it utilizes a commonly available medication to test its potential to prevent the onset of Alzheimer's disease.

PhD completions: I am proud to announce that three of our PhD students completed their theses with flying colors. Dr Belinda Brown investigated participants in the Australian Imaging Biomarkers and Lifestyle (AIBL) study of Ageing and demonstrated that exercise protects the brain with people who are genetically predisposed obtaining the greatest benefit. Dr Tejal Shah undertook a clinical trial to determine the benefits of different types of exercise and computer based brain training. She demonstrated that both exercise and specific brain training programs were independently beneficial and together these benefits were synergistic. Dr Shaun Frost has undertaken pioneering work to determine whether the eye can play a role in the diagnosis of Alzheimer's disease and has published some exciting results in support of his thesis. All three of them are now playing important roles in the Foundation's ongoing research programs.

I am indebted to the McCusker Alzheimer's Research Foundation Inc., which continues to provide tremendous support to our research. This includes the very generous quarterly contribution to the CRC for Mental Health, enabling our projects to expand by attracting matching funds; as well as support for our Stirling Highway lab; our new McCusker Hollywood Private Hospital lab; and many of our staff.

I am also blessed to have an extremely talented and dedicated team of highly capable and enthusiastic researchers, and we can all be very proud of their efforts. A very big thank you is extended to all of our donors, both small and large. Your interest, friendship and support are critical to our work and you share in our considerable successes.

Kevin Taddei

The Dominantly Inherited Alzheimer's Network (DIAN) study

Researchers:
Researchers Mr Kevin Taddei, Dr Hamid Sohrabi, Dr. Veer B. Gupta, A/Prof Simon M. Laws, Dr. Florence Lim and Professor Ralph Martins
PhD student: Miss Pratishtha Chatterjee

The McCusker Alzheimer's Research Foundation and Edith Cowan University are one of the sites for the Dominantly Inherited Alzheimer's Network (DIAN) study. This US$16 million international Network was established by the National Institute on Aging of the National Institutes of Health (US) to bring together researchers who study genetic forms of Alzheimer's disease (AD). The study is seeking 400 volunteers worldwide who are members of families in which AD is dominantly inherited, meaning that about 50% of the individuals in each generation of a family develop AD, generally before age 60. These rare forms of AD are caused by a mutation in one of 3 known genes. Each child of an affected parent has a 50% chance of inheriting the mutation. If they do, they will develop the dementia of AD at about the same age as their parent. Siblings who do not have the mutation have no greater risk of developing AD than someone without a family history of AD and will participate in DIAN as part of a comparison group for their mutation-carrying siblings. Individuals participating in DIAN are not required to know whether or not they carry a mutation. Should they wish to learn their mutation status through genetic testing following genetic counseling, DIAN can assist with this process.

Research suggests that brain changes may occur years before actual Alzheimer's symptoms are detected. The major goal of DIAN is to study these changes in people who carry an AD mutation to determine how the disease process develops before there are any symptoms. Ultimately, knowledge gained from DIAN may lead to tests that detect people who still are normal but are at very high risk of developing dementia caused by AD. It is on this basis, and supported through preliminary research by Drs Gupta and Lim, that an NHMRC grant application led by Prof Martins, with significant contributions by A/Prof. Laws, has been submitted for funding in 2015. All DIAN participants will be members of families with dominantly inherited AD caused by a known mutation and may be ideal candidates to participate in future studies of drugs that have the potential to halt the AD process and prevent dementia.

Presently, there are 14 DIAN study sites: 8 in the US, one in England, three in Australia, and two in Germany. Research volunteers travel to one of the sites for the studies, which are repeated every few years. It is expected that each round of DIAN studies will take between 3 and 5 days to complete. Participants may benefit from the opportunity to talk with persons knowledgeable on the autosomal dominant form of Alzheimer's disease.

The Australian sites include the McCusker Alzheimer's Research Foundation & Edith Cowan University, Prince of Wales Medical Research Institute, University of New South Wales, Mental Health Research Institute of Victoria and the University of Melbourne.

In 2013, we, at the McCusker Alzheimer's Research Foundation and Edith Cowan University, recruited 1 new participant and performed 12 follow-up assessments on previous participants from Australia and overseas (plus 12 remote follow-up assessments). As of March 2013 DIAN had recruited 378 participants worldwide with Perth contributing the third most to date, with 31 participants. So far we delivered our commitments to the DIAN study by recruiting the number of patients required from each site. It should be noted that each patient will spend at least a week with us to go through all the assessments including medical, neurological and neuropsychological tasks as well as fasted and non-fasted blood samples, brain imaging and lumber puncture, if they consent to do so.

An interesting, recent development of DIAN is that a clinical trial for potential prevention and treatment agents will take place and will be undertaken by the different DIAN sites, including Australia. These trials are aimed at increasing the quality of life, delay the process of neurodegeneration and potentially treating the disease. Only participants enrolled in the current DIAN study prior to June 1, 2012 may be recruited into the first DIAN trial. The DIAN baseline data will be utilized as run-in data for the trial. For participants interested in the DIAN trial, it has already commenced in the US and will start in mid 2014 in Australia, participants must be enrolled into the current ongoing DIAN study right away.

Further information about DIAN can be found at:

www.dian-info.org or please contact Athena Paton at the McCusker Alzheimer's Research Foundation Inc on **(08) 9347 4200**, by fax (**08) 9347 4299,** mobile **0418 939 233** or email: **athenapaton@bigpond.com.**

The McCusker Cognitive Complaints Inventory (McCi) McCusker Alzheimer's Research Unit: Memory Complainer Study

Key Researchers (ECU/McCusker):
Dr Hamid R Sohrabi; Professor Ralph Martins

Dr Hamid Sohrabi

Proper screening of those individuals at risk of developing dementia is a challenging task hindering accurate clinical diagnosis and successful clinical trials. If we find a way to screen for the at-risk individuals then we can examine new preventions on the most suitable participants. Having suitable participants in a trial allows for examining the efficacy of our preventive measures on delaying the onset of Alzheimer's neurodegenerative process(s) that is currently irreversible. The self-reported decline or complaint about memory, attention, decision making, judgment, and language and so on is a good indicator for detecting at risk individuals. However, current measures assessing self-reported changes have not proved to be valid and reliable as they are associated with depression and personality traits rather than actual memory or cognitive functions. As such, we have been working on a comprehensive measure that not only measures various cognitive functions but is significantly associated with actual cognitive performance. The McCusker Cognitive Complaints Inventory or McCi (pronounced Maxi) is such a measure. It is still a work in progress and we will examine its first version in our clinical studies by mid-2014.

A/Prof Simon Laws

Biomarker discovery: Towards the early diagnosis, prediction and monitoring of Alzheimer's disease.
CRC Project.

Researchers (ECU/McCusker):

The Biomarker Research Team: A/Prof. Simon M. Laws, Dr. Veer Bala Gupta, Dr. Stephanie Rainey-Smith, Dr. Andrea C. Wilson, Dr. Florence Lim, Dr. Eugene Hone, Mr. Steve Pedrini, Mr. Kevin Taddei, A/Prof. Chiou-Peng Lam, and Prof. Ralph Martins

Students:

Ms Michelle Tegg (Masters), Ms Rhona Creegan (PhD), Ms Samantha Gardener (PhD), Ms Pratishtha Chatterjee (PhD), Ms Tenielle Porter (PhD), Mr James Nelson (Honours)

Collaborators:

AIBL and CRC for Mental Health collaborators, including; University of Melbourne/Florey Institute for Neuroscience and Mental Health (Prof. Colin Masters, Prof. Ashley Bush, Dr. Noel Faux, Dr. Alan Rembach), CogState (Dr. Paul; Maruff), the CSIRO (Dr. Bill Wilson, Dr. James Doecke, Dr. Samantha Burnham), the Australian Neuromuscular Research Institute (Prof. Frank Mastaglia and Dr. Soumya Ghosh) and the University of Western Australia (Prof. Assen Jablensky). Dementia Collaborative Research Centre– Early Diagnosis and Prevention (DCRC-EDP, Canberra). International collaborators: Prof. Hans Foerstl, Dr. Panos Alexopoulos (Technical University of Munich), Dr. Robert Perneczky (Imperial College, London)

Program Aims: Use multiple discovery approaches to identify biomarkers (substances used as an indicator of a biological state), such as proteins and lipids in plasma or genetic factors, whose measurable levels or frequencies are altered between healthy and AD individuals. This approach, when utilised in the thoroughly characterised Australian Imaging Biomarkers and Lifestyle (AIBL) Study of Aging cohort and the DIAN cohort stands the best chance of capturing the most sensitive and specific panel of biomarkers, which have the potential to diagnose, predict and/or monitor AD. Any diagnostic panel requires cross-validation against other neurological disorders to determine disease specificity. With the advent of the CRC for Mental Health we will now have the opportunity to cross validate against other disorders such as Parkinson's disease and Schizophrenia subtypes, and in doing so help our collaborators identify markers that may assist with the diagnosis of these disorders.

Significance: Advances in medical treatments and lifestyle interventions for AD mean the discovery of biomarkers for a reliable method of detecting/predicting the disease, at an early stage, is paramount. The identification of such biomarkers will allow for current and future prevention and treatment strategies to be initiated when they are most effective and will also have applications in the monitoring of medical and lifestyle interventions.

Our Approach - Major findings and future directions: Our on-going multidisciplinary research program combines a wealth of clinical data available through AIBL with different biological discovery approaches listed below, with significant funding from the CRC for Mental Health.

Protein Discovery (Proteomics): "Targeted proteomics" work is focused on the analysis of individual protein biomarkers such as amyloid beta, apolipoprotein E, apolipoprotein J, cortisol, Insulin Degrading Enzyme (IDE) and Brain-derived neurotrophic factor (BDNF) in AIBL plasma. The results obtained from these biomarkers have shed light on their significance in AD and need further longitudinal comparisons together with other potential biomarkers with diagnostic value. We have validated a number of potential protein biomarkers on advanced MSD (Mesoscale) technology in our lab recently and are currently analyzing new protein biomarkers on this platform. Our focus is on the common top hits obtained from recent blood biomarker based studies in characterized population cohorts with AD participants, including AIBL. The candidate protein biomarkers, mentioned above, when validated in the AIBL cohort, have the potential to be combined to create multiplex assays that will greatly facilitate achieving the research programs overall aim of identifying optimal biomarker panels. So, in parallel to the above project, we are also undertaking an in-house multiplex assay development project to assess combination of multiple analytes within a single assay. In addition to the plasma, we are also assessing the use of platelets as an alternative source of potential AD biomarkers in collaboration with DCRC-EDP. Further, in our "Discovery proteomics" stream, we are carrying out relative and absolute quantitation of differentially expressed proteins in AD compared to controls and Mild Cognitive Impaired participants in the AIBL cohort and presymptomatic and symptomatic compared to non-carriers in the DIAN cohort using Mass spectrometry and 2-Dimensional Gel electrophoresis methods. This project will help us identify additional candidate markers to be incorporated in our "AD biomarker panel".

Lipid Discovery (Lipidomics): The successful 2010 NHMRC project grant, awarded to Prof. Martins, A/Prof. Laws and Dr. Gupta, provides the backbone

to this research, which commenced in 2011. Dr. Florence Lim, whose pilot study significantly contributed to the awarding of the grant, is working closely with PhD students Ms. Rhona Creegan (near completion), Ms. Samantha Gardener and Ms. Pratishtha Chatterjee in undertaking this work, which involves the profiling of plasma lipids using a state-of-the-art platform unique in Australia and based at ECU. This screening of plasma lipids, when combined with clinical data from AIBL, will allow for lipid profiles to be determined in relation to disease status, clinical phenotypes (e.g. memory performance or brain imaging) and lifestyle factors (e.g. diet and exercise). Currently, lipids in over 2000 samples spanning the first 18-months of the AIBL study had been profiled and results are currently being tabulated. The results obtained from these lipid biomarkers need further longitudinal comparisons together with other potential biomarkers with diagnostic value. This work will be augmented with continued support from the CRC for Mental Health extending this lipid profiling to subsequent time points in the AIBL study, to help us determine how lipid profiles change over time and with disease progression. Samples from the DIAN cohort are currently being lipid-profiled. The results obtained from these lipid biomarkers might provide insight into the earlier lipid changes in AD.

Gene Discovery (Genomics): This third and most recent addition to our 'multiomic' approach, led by A/Prof. Laws, has rapidly expanded through bringing core infrastructure components of this research 'in-house'. Not only has this significantly reduce costs and increased productivity but also it has allowed this small group to establish itself as the central genotyping hub for both the AIBL study and the CRC for Mental Health. The Genomics Group is responsible for undertaking routine genotyping in addition to fee-for-service and collaborative 3rd party genotyping requests, which is now generating revenue for the benefit of the McCusker Alzheimer's Research Foundation. In general terms the Genomics program focuses on two streams of research, Discovery and Validation. These streams work synergistically to focus on the identification of genes and underlying genetic factors, which will help identify additional biomarker candidates as well as increasing our understanding of the pathways leading to the disease. These genomic approaches will aim to identify new genes involved in early onset and sporadic AD as well as the screening of genes in the Australian population. The Discovery stream, funded through the CRC for Mental Health utilizes "Next-generation Sequencing" approaches to sequence the coding regions (regions that hold information for translation into, for example, proteins in the body) across the entire human genome. This study uses a population enrichment approach whereby we selected "super-controls" and compared them to both individuals with Alzheimer's disease and Parkinson's disease – allowing us to identify disease specific variations in genes that have the highest functional relevance. This study, the validation of its findings and study of the functional consequences is the focus of the genomics group's inaugural PhD student – Ms. Tenielle Porter – and preliminary findings were presented in March 2013 at the AD/PD international conference in Florence, Italy. These initial findings have led to the awarding of a Mason Foundation grant, to A/Prof Laws and A/Prof Verdile, to study the functional impact of some of these gene variations and the submission of an NHMRC grant for funding in 2015. The Validation stream is the core stream that underlies the genomics research program, where newly discovered genetic variations or a priori candidate genes, either from our group or published by others are screened in our own Alzheimer's cohorts and those of our collaborators in Germany and the United Kingdom. With our collaborator Professor Paul Maruff (CogState) we have shown that variation in the BDNF gene can mediate the rates of memory loss and neuropathology. Through the work of our recently completed honours student, Ms Sara Garin, we have identified variants in steroid synthesis genes not previously linked to AD, work that has been submitted for presentation at the Alzheimer's Association International Conference in Copenhagen in July 2014. In addition to determining genetic associations with disease, a focus of this research program is assessing what genes may help determine how an individual responds to a disease intervention, as well as what genes are affected by the intervention, whether the intervention be pharmacological or lifestyle related (e.g. diet). These fields of research, pharmacogenomics and nutrigenomics, respectively, are of increasing importance in AD research especially as we move closer to our goal of early diagnosis. An understanding of therapy response will help ascertain the best mode of intervention for a given person. A collaborative research project, between the genetics and lifestyle programs, sees the co-supervision of an honours student (Mr James Nelson) by A/Prof Laws and Drs Rainey-Smith and Brown, which is investigating whether specific gene variants differentially impact the beneficial effects that exercise and diet provide that our group has previously reported. This hopefully represents the first of many projects in this growing area of research.

Dr Giuseppe Verdile

Developing agents that selectively target the enzyme responsible for beta amyloid generation

Researchers (Curtin/ECU/McCusker):
Dr Giuseppe Verdile,
A/Prof David Groth,
Mr Mohammad Imran Khan
(PhD Student commenced in 2012),
Mr Gorcin Kruejsepi (honours student commenced in 2014)
and Professor Ralph Martins

Collaborators:
Professor Paul Fraser
(University of Toronto, Toronto)
A/Prof Maho Morishima
(Hokkaido University, Japan)
Dr Imre Berger (EMBL, Grenoble, France)
Dr Christianne Berger Schaffitzel (EMBL, Grenoble, France)

Background

The enzyme, gamma secretase is a major target for developing appropriate specific therapeutic agents for Alzheimer's disease. The enzyme is responsible for the production of a protein called beta amyloid, which has a central role in Alzheimer's disease pathogenesis. The majority of drugs that have been developed targeting the enzyme have failed due to its many other functions within cells. A better understanding of gamma-secretase function and structure is required if it is to be pursued as an appropriate target. Using the latest advanced techniques, the project will provide significant insight into the function and structure of the enzyme, and thus can be used to develop more specific drugs directed at gamma secretase.

Progress

The initial stage of this project involves re-constructing the enzyme in an insect cell culture model. We use this model to generate large amounts of the enzyme so that it can be purified and undergo analysis to determine its structure, which currently remains to be determined. A PhD student, Mr Sudarsan Krishnaswamy was recruited to undertake this project in 2007. Initial attempts at re-constructing the enzyme failed however, after many subsequent attempts we finally succeeded at re-constructing all 4 components that make up the enzyme. This success was possible through our collaborations with Dr Imre Berger from the European Molecular Biology Laboratories (EMBL), Grenoble, France who is an expert at reconstructing complex proteins and identifying their structure. Sudarsan spent 3 months in his laboratory where he learnt advanced molecular biological techniques that he brought back with him. Sudarsan successfully completed his thesis, which was favourably received, and graduated in 2010. His work is currently being drafted into a manuscript and contributed to data that was included in a project grant, submitted to the National Health and Medical Research Council (NHMRC). In 2012, we recruited a PhD student (Imran Khan) to continue this work.

We are moving to the next stage of the project which is to continue to collaborate with Dr Berger to purify the enzyme and determine its structure and identify areas within the enzyme that are critical for its activity to generate beta amyloid, in order to develop specific drugs targeting beta amyloid. We are currently collaborating with a team of internationally recognized, well respected scientists to tackle this project. The team includes Professor Paul Fraser (University of Toronto, Canada), A/Professor Maho Morishima (Hokkaido University, Japan), Dr Imre Berger (EMBL, Grenoble, France) and Dr Christiane Berger-Schaffitzel (EMBL, Grenoble, France). The PhD student will work in Drs Berger and Berger-Schaffitzel's labs to progress the work required. An honours student has also been recruited from Curtin University. Supervised by Assoc. Professors Verdile and Groth and Professor Fraser. This project aims to identify areas within the enzyme that are critical for its activity.

As well as using this model to determine the structure of the enzyme we also aim to develop it as a rapid screening method of drugs trying to reduce beta amyloid production. Another feature of the enzyme is that it also acts on other proteins that are important in cell function. Its multi-functional nature is a major reason for the failure of the majority of drugs that have been developed targeting this enzyme. These drugs have shown severe side-effects in pre-clinical trials.

By comparing the effect of potential therapeutic agents on enzyme activity on a number of proteins that are acted on by the enzyme, we can rapidly identify those that specifically target beta amyloid without altering the production of the other proteins. This will ultimately generate more specific drugs for the disease.

Enhancing the clearance of beta amyloid

Dr Veer Gupta

Researchers (ECU/McCusker):
(ECU/McCusker) Mr Kevin Taddei, Dr Veer Gupta, Dr Ian Martins, Dr Renae Barr, A/Prof Giuseppe Verdile, A/Prof Simon Laws, Dr Prashant Bharadwaj, Miss Elham Teimoori (PhD Student), Ms Tenielle Porter (Honours Student), , A/Prof David Groth, Miss Linda Wijaya, Mr Mike Morrici, and Professor Ralph Martins

Collaborators:
Professor Sam Gandy (Mount Sinai, Medical School, New York); Professor Paul Fraser (University of Toronto, Toronto)

Graduated Student:
Ms Tenielle Porter received first class honours and now has joined our laboratory as PhD student.

In addition to the over-production of beta amyloid, the impaired clearance (or removal) of this toxic protein from the brain plays a key role in its accumulation in the AD brain and the resulting neurodegeneration. As such enhancing the clearance of beta amyloid from the brain is a potential therapeutic strategy that we are currently investigating.

In collaboration with Professor Sam Gandy (now of Mount Sinai School of Medicine, New York) and funded by the prestigious funding agency, the National Institute of Health (NIH) in the US, we investigated the role of the genetic risk factor for AD, APOE ε4, in impairing beta amyloid clearance in the brain and the periphery. Here we showed that mice containing the APOE ε4 gene did not clear/degrade beta amyloid as well as those mice that didn't contain the gene, providing evidence that the presence of this gene impacts how efficiently, beta amyloid is cleared. In 2010, we received NHMRC funding to continue this research to investigate mechanisms by which APOE ε4 impairs clearance/degradation of beta amyloid in liver cells (the liver is the major organ that degrades beta amyloid).

In 2010, we also received NHMRC funding to assess the efficacy of a novel small peptide, (which we identified and showed to neutralize beta amyloid toxicity) at enhancing the clearance of beta amyloid in the presence of the APOE-ε4 gene. Preliminary data with this peptide (which we refer to as amyloid neutralizing agent- ANA) shows that it binds beta amyloid and we will now determine if administering this peptide to a mouse model of AD, can reduce the accumulation of beta amyloid in their brains and promote its degradation/ clearance by peripheral organs such as the liver. Dr Renae Barr has been investigating the activity of this peptide further to provide further insight into how the peptide could be modified to generate a more potent agent. This work was presented at the Combined Biological Sciences Meeting, 2012 held in Adelaide. A provisional patent (P1078AU000) on this work was filed in September 2012. Based on evidence from our laboratory that our peptide binds Aβ, we are also exploring its potential as a specific imaging agent of not only amyloid plaques but the intermediates that accumulate early in the disease process, small beta amyloid aggregates called oligomers.

We are also investigating another mechanism by which beta amyloid can be efficiently cleared/degraded by cells. Evidence exists that a pathway within the cell called autophagy plays an important role in a number of neurodegenerative diseases including Huntington's disease and AD. This pathway appears to have a role in removing protein aggregates from the cell. Dr Prashant Bharadwaj, developed a yeast model to show for the first time that autophagy is involved in the degradation of beta amyloid. Prashant also showed that a drug that is currently in human clinical trials called Latreperdine (previously known as Dimebon) can enhance the degradation of beta amyloid in yeast cells by activating autophagy. Our collaborator Professor Gandy showed similar results in neuronal cells and in mice. This work was presented by Dr Verdile at the Society for Neurosciences meeting (Washington), November 2011 and the Alzheimer's Association International Conference (AAIC) in Vancouver in July 2012. These findings have now been published in the journals Journal of Alzheimer's disease and Molecular psychiatry. We will be evaluating whether latreperdine related molecules have greater potency in activating autophagy and enhancing beta amyloid clearance in cell culture. This work will be undertaken by and Dr Prashant Bharadwaj, under supervision of A/Prof Giuseppe Verdile.

Prashant's data was key to successfully obtaining NHMRC funding for this project, in which

Enhancing the clearance of beta amyloid

funding commenced in 2011. The NHMRC funding allowed us to employ Prashant as a post-doctoral fellow to continue this work. The project will extend these findings to assessing the ability of Latrepirdines to activate autophagy in neuronal cells and its ability to enhance the clearance of beta amyloid from the brains of mouse models of AD. A PhD student, Miss Elham Teimoori (supervised by Professor Ralph Martins, Dr Giuseppe Verdile and Dr Prashant Bharadwaj) has been recruited for this work and commenced in 2011. Recently an honours student (Miss Tenielle Porter), supervised by A/Prof Giuseppe Verdile and Dr Prashant Bharadwaj and A/Prof David Groth, completed her honours with first class and showed that latrepirdine also regulated beta amyloid aggregation. This work was presented at the Australian Society for Medical Research (ASMR) Symposium and the COMBiol conferences held in Perth. The findings have been prepared as a manuscript and will be submitted to the Journal Biochemical and Biophysical Research Communications. Tenielle has continued working with our group and has joined as a PhD student. Supervised by A/Professors Simon Laws, Giuseppe Verdile and David Groth, her project aims to identify and study the function of genetic variations ("polymorphisms") that are closely linked to AD risk. Preliminary data has identified a gene involved in a cellular pathway involved in the removal of beta amyloid. This data was included in an NHRMC grant submitted in 2014.

Professor Ralph Martins with some of his team members.

Developing a Zebrafish Model for Alzheimer's Disease: Towards developing a high-throughput drug screening tool.

Researchers:
(ECU/McCusker): Miss Mengqi Chen (PhD Student), Mr Avdesh Chaudhary (PhD Student) A/Prof Giuseppe Verdile, A/Prof David Groth), A/Prof Simon Laws, Miss Tenielle Porter (PhD Student) and Professor Ralph Martins

Collaborator:
Dr Michael Lardelli (The University of Adelaide).Prof Matthew Martin Iverson (The University of Western Australia)

Graduated Student:
Mr Avdesh Chaudhary

The current drugs for AD only temporarily treat disease symptoms without targeting the underlying pathology and cause of neurodegeneration. Therefore, new treatments for the disease are urgently required. The overall aim of this project is to develop a novel animal model for AD that can facilitate rapid screening in pre-clinical stages of drug development.

The use of current mice models to validate potential therapeutic agents are limited to only assessing one or two drugs, thereby slowing down the progress of drug development. Further, the majority of drugs that show benefits in transgenic mouse models fail in human clinical trials. It is clear that further in vivo screening of potential therapeutic agents is required prior to entering clinical trials. In addition, a model that will allow rapid screening of numerous drug agents/libraries will be of great benefit to increase the capacity and potential to identify and validate effective treatments, in pre-clinical stages of drug development. Features of the zebrafish make them a particularly attractive model; in particular, their rapid development, availability in large numbers and lower maintenance costs (1/1000th that of mice). These features facilitate the development of a cost effective high-through put in vivo drug screening tool.

Once developed, the AD zebrafish model will provide the appropriate model to rapidly screen and identify drugs that target the underlying pathogenesis of the disease.

Progress

During the past 4 years we have established a small PC2, AQIS approved aquatic facility at the School of Medical Sciences, Edith Cowan University. The majority of this time period was spent setting up the facility and establishing wild-type zebrafish lines. During this period we also undertook preliminary experiments to show that the pathological beta amyloid species, Aβ42 induces cell death in zebrafish embryos. Although, these findings provided first evidence to show that beta amyloid is toxic to zebrafish, the concentrations used in the preliminary study were supraphysiological and do not represent the levels observed in an AD brain. This project will extend these studies to develop a more physiological model that exhibits pathological hallmarks more closely representing that occurring in the AD brain. Our PhD student, Miss Mengqi Chen, undertook this work and is in the final stages of completing her thesis. The students' scholarship was co-funded by the West Perth Rotary club and McCusker Foundation. Mengqi for the first time showed that an enzyme that degrades beta amyloid plays an integral role in fish development. Furthermore, this student has shown that zebrafish have similar enzyme activity to humans. This work was presented at the Alzheimer's Association International Conference (AAIC) in Vancouver in July 2012 and at the Society for West Australian Neuroscientists (SWAN) conference in Perth. A manuscript of the work is being prepared. Another PhD student, Mr Avdesh Chaudhary, developed assays that assess learning and memory in zebrafish. These assays will be essential in providing a functional assessment that can be implemented in a screening of potential drug agents. A manuscript was published in the Journal of Alzheimer's disease outlining the use of two methods called the colour preference box and T-maze to assess the colour preference of zebrafish. The results show that zebrafish prefer certain colours over others. This information is essential in designing further assays assessing memory and learning in zebrafish. Avdesh has also developed a high throughput functional assay to assess embryo behaviour. Avdesh successfully completed his thesis in 2013 and has obtained a post-doctoral position at

Developing a Zebrafish Model for Alzheimer's Disease: Towards developing a high-throughput drug screening tool.

the prestigious Max Planck Institute in Frankfurt, Germany.

Mengqi and Avdesh also played essential roles in maintenance of the zebrafish and our zebrafish facility. This includes zebrafish husbandry to provide efficient embryo production. The protocols in which they have developed were recently published in a novel concept for a journal, the Journal of Visualised Experiments. The article is a step by step guide to maintaining a zebrafish facility and outlines optimal conditions to breed zebrafish and is useful for researchers' world-wide who are considering establishing a zebrafish research facility. More recently two additional PhD students, Mr Imran Khan and Ms Tenielle Porter, have taken up the role of maintaining the Zebrafish facility in addition to their respective PhD projects. This significant contribution they have made is very much appreciated and acknowledged by Prof Martins and the senior members of his team.

We continue utilizing the zebrafish as a model to understand gene function. The data generated by Mengqi has also provided preliminary data for a NHMRC project grant application that was submitted on March 2013. The grant identifies genetic variants associated with increased AD risk and investigate their functions in cell culture and in vivo using zebrafish. Our honours student, Ms Tenielle Porter, who completed her studies with first class honours, was successful at obtaining a scholarship to undertake a PhD at ECU in 2013. This will be supervised by A/Prof Simon Laws, A/Prof Giuseppe Verdile and A/Prof David Groth as she undertakes this project. Further, Prof. Martins and A/Profs Verdile and Laws were among a team of WA researchers who were awarded an ARC LIEF grant of $400k to establish a larger Zebrafish facility that will not only support our increased research utilization of Zebrafish, but that also of the entire WA research community.

Dr Michael Lardelli, (Adelaide) and A/Prof Giuseppe Verdile have been collaborating for many years on the role of proteins called presenilins that are essential in the production of beta amyloid. They have discovered that a certain variant of the presenilin protein has an impact on beta amyloid accumulation in the brain. The levels of this variant in the brain increase under conditions of oxidative stress and high cholesterol and this is associated with increases in beta amyloid levels. Drs Verdile and Lardelli, in collaboration with Dr Matthew Sharman, will investigate the role of this presenilin variant in beta amyloid metabolism, and using zebrafish, identify critical sites within the protein that are responsible for its activity. This has implications in the development of agents that selectively attenuate beta amyloid levels. An NHMRC project grant was recently awarded to A/Prof Verdile, Dr Lardelli and Dr Sharman to fund this work, which commenced in 2014.

The support of Perpetual is acknowledged through their grant to the McCusker Alzheimer's Research Foundation.

The potential of testosterone as a therapeutic strategy for AD

Prof Ralph Martins

Researchers:
Professor Ralph Martins Dr Eka Wahjoepramono (PhD Student) A/Prof Giuseppe Verdile, Mr Kevin Taddei, A/ Prof Simon Laws, Dr. Hamid Sohrabi, Dr. Stepahnie Rainey-Smith, Miss Linda Wijaya, Ms. Kathryn Quirke, Ms Prita Riana Asih (Honours student)

Collaborators:
Dr Malcolm Carruthers (Centre for Men's Health, London)

Graduated Student:
Dr Eka Wahjoepramono successfully completed his PhD in 2012

Several studies have reported that compared to controls, men with AD and other dementias have lower serum testosterone levels. Professor Martins, together with Professors Almeida and Gandy have shown that reducing blood levels of testosterone in men is associated with an increase in blood levels of beta amyloid. In addition, supplementing neuronal cells in culture with testosterone has been shown to reduce beta amyloid levels and attenuate its toxicity. Taken together, these studies suggest that the reduction in testosterone during aging could contribute to the development of, and the underlying causes of AD.

This project investigated the role of testosterone in beta amyloid production and assesses testosterone replacement therapy in animal and human clinical study as a potential therapy for the effective treatment of AD. The work is part of a PhD undertaken by Dr Eka Wahjoepramono, a neurosurgeon from Siloam Hospital, Lippo Karawaci, Tangerang, Indonesia.

Findings from the animal studies indicate that testosterone replacement at physiological and higher doses reduces beta amyloid levels in both the blood and the cerebrospinal fluid, which could possibly be a result of clearance of beta amyloid from the brain into the blood. This work was published in the Journal of Alzheimer's disease (Wahjoepramono Wijaya et al., 2008, Journal of Alzheimer's disease, 15: 129-37.

The human clinical study, undertaken in Indonesia, involved 50 men with memory complaints and low levels of testosterone, who are administered cream containing placebo or testosterone for a total of 56 weeks. The recruitment and neuropsychological assessment of these men have been completed and blood samples have been collected and Eka successfully completed his thesis in 2012. One of the major findings is the demonstration that testosterone administration increased the more potent form of testosterone (DHT) and improved memory in elderly men who were deficient in this hormone. These results were presented at the AD/PD conference in Florence in March 2013 and manuscripts outlining the major findings are currently being prepared.

In addition an open labeled study has continued in Perth with 25 men recruited. The data from these men clearly demonstrate that testosterone treatment lowers beta amyloid levels in 4 months in most of the men in this study and lowers the hormone LH, a major contributor to Alzheimer's disease, in all participants. A manuscript describing these results is currently in preparation. Our findings thus far indicate that this approach provides a promising avenue for effective prevention and treatment of Alzheimer's disease, which has the advantage over other agents of being rapidly implemented following successful clinical trials, as it is a drug that is already on the market.

We will be undertaking a 56 week randomised double blinded placebo-controlled trial to assess the benefits of testosterone in 200 male subjects with Pittsburgh Compound B (PiB) PET brain imaging positivity. Results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing have revealed that one-third of asymptomatic elderly individuals (over the age of 60 years) show the presence of

The potential of testosterone as a therapeutic strategy for AD

Aβ in the brain (PiB-PET positive). It is suggested that therapy aimed to reduce the neurodegenerative process should be commenced in pre-symptomatic individuals with high PiB. Therefore we will enrich for 200 PiB-PET positive men to participate in this trial. This trial will be the first to assess the effect of testosterone supplementation on cognition, plasma beta amyloid levels, brain glucose metabolism (FDG-PET imaging) and brain amyloid load (PIB-PET imaging). Testosterone will be in the form of an injection. Testosterone or placebo will be administered every 8 weeks. A number of parameters will be measured at baseline (before treatment), mid-way during the trial (26 weeks) 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, brain imaging, including MRI, FDG-PET (to determine if there are improvement in brain glucose metabolism), and PIB-PET (to determine if there is lowering of brain amyloid load). In addition, blood plasma beta amyloid levels and blood biochemistry will be assessed every two months. CSF beta amyloid levels will be assessed at baseline and 56 weeks. Brain scans will to be conducted at baseline and 56 weeks.

Work is also continuing to identify agents that can increase testosterone and other neuronal specific steroids in the brain. Our former PhD Student, Dr Anna Barron, now a research fellow at the National Institute of Radiological Sciences in Japan, identified compounds that can increase brain steroid production and reduce amyloid deposition and improve cognition in mice. However, these compounds are thought to have toxic side effects. In collaboration with Dr Barron and Dr Andrew Katsifis (Royal Prince Alfred Hospital, Sydney), we are now trialing in cell culture the ability of similar compounds to enhance brain steroid production. An honors student, Ms Prita Asih has been recruited to undertake this work and is supervised by A/Prof Giuseppe Verdile, Dr Veer Gupta and Dr Robert Trengrove (Murdoch University).

Hormonal changes associated with ageing have been implicated in the increased risk of developing Alzheimer's disease. Many studies have provided evidence to show that low levels of oestrogen or testosterone increase the risk of developing AD. This effect may be due to these hormones altering the levels of beta amyloid (Aβ, a molecule that is thought to be central to AD pathogenesis. Sex hormones are under the control of complex feedback loops that involve hormones called gonadotropins. High levels of the gonadotropin, luteinizing hormone (LH), have also been implicated in the increased risk of developing AD and in disease pathogenesis. The clinical significance of LH and the sex hormones and their relative contribution to the pathogenesis of AD remain to be determined. This is an ongoing project that investigates the role of LH in AD pathogenesis and assesses in animal studies the use of gonadotropin lowering agents as a therapeutic strategy for this disease.

In 2004, we published findings showing that LH can increase the production of beta amyloid in neuronal cells. In a small study of elderly men (40) we have recently shown that increases

Investigating the Role of Gonadotropins in the Pathogenesis of Alzheimer's Disease

Prof Ralph Martins

Researchers:
A/Prof Giuseppe Verdile, Dr Eka Wahjoepramono (PhD Student), Mr Kevin Taddei, Ms Linda Wijya, A/Prof Simon Laws, Ms Prita Riana Asih and Professor Ralph Martins

Graduated Student:
Dr Eka Wahjoepramono successfully completed his PhD in 2012.

in blood levels of LH are associated with increases in blood levels of beta amyloid, providing further evidence the LH can modulate beta amyloid levels. We published these results in 2008 in the Journal of Alzheimer's disease (Verdile et al., Journal of Alzheimer's Disease. 14:201-208). In addition we showed that age related increases in LH serum levels are associated with a reduction in cognition in a large cohort (n=450) of elderly women without dementia which provides further evidence for a role for LH in AD risk (Rodrigues et al., 2008; Journal of Alzheimer's disease. 13:267-274). Access to samples and data from AIBL study provided an opportunity to extend our initial results to investigate associations between sex steroid and gonadotropins and plasma A 40 and A 42 and cerebral amyloid deposition (as assessed by PIB-PET brain imaging). We have shown that testosterone and LH impact on plasma A 40 and A 42 levels and cerebral amyloid deposition at different clinical stages of cognitive decline in men. We have shown a significant positive correlation between increases in LH and amyloid accumulation (as assessed by PiB-PET brain imaging) in a cohort of subjective memory complainers (SMC). Increasing evidence is suggesting that SMC may be an important clinical feature before the onset of clinical symptoms of cognitive impairment is evident. The correlation between LH and amyloid deposition is lost at the stages when cognitive impairment is evident (MCI and AD). This result also suggests that increases in serum LH levels may have a greater impact on AD pathology at earlier stages in the disease process. These findings were recently published, by A/Profs Verdile and Laws, in the journal Molecular Psychiatry. Data collection for an 18 month follow-up has recently been collected and a 36 month followup will commence soon. These follow-up studies will determine if these associations still hold with conversion of mild cognitive decline (MCI) to AD.

In an NHMRC funded project, we investigated potential mechanisms by which LH could impact on AD pathogenesis. This project was completed in early 2010. Some of the most significant results included the finding that a more potent analogue of LH impaired memory in a mouse model for AD and also increased the levels of beta amyloid within the brain of these animals. These results have been presented at a number of conferences (including Alzheimer's Association International Conference and the Japan Neuroscience Society). These findings were also recently published in a journal that is listed in the top 10 journals in the field of endocrinology (Barron, Verdile et al., 2010, Endocrinology 151(11):5380-8). Similar results were shown in another rodent model where the direct exposure of LH to the brain resulted in accumulation of beta amyloid, possibly through activating a signaling pathway in the brain. These findings were published in Neuroendocrinology (Wahjoepramono, Wijaya et al. 2011, 94:313-22). Overall, this project has provided significant evidence for a role of LH in AD risk and pathogenesis through experimental methods that have seperated the actions of sex hormones from gonadotropins. Further insight into these mechanisms will provide therapeutic or preventative strategies for AD.

Dr Tejal Shah

PEACS Study – Effects of physical activity and cognitive stimulation on plasma beta amyloid and on cognitive functioning in the elderly

Researchers:
Dr Tejal Shah (PhD Student), A/Prof Giuseppe Verdile, and Professor Ralph Martins

Graduated Student:
Dr Tejal Shah

With the rising tide of elderly population there is a marked increase in the incidence of AD among these populations globally. With no current effective treatment, there is a major focus on either preventing or delaying the onset of AD. Researchers all over the world are targeting lifestyle as a prime factor that could play a vital role in diverting the course of AD. This lifestyle includes staying physically and mentally active, eating a healthy diet and also staying socially engaged.

There is now robust observational literature available demonstrating that people who are mentally and physical active can ward off the risk of dementia, however, there are very few clinical trials conducted on healthy community dwelling older adults that actually show that physical and mental exercises administered over a fixed duration with certain intensity and frequency can truly avoid the risk of cognitive decline in the healthy elderly. Such a trial would enable us to establish the clinical significance of these non Pharmacological strategies and may take us a step further in understating the pathological course of AD as well as a potentially providing us pathways for therapeutic approach.

With these goals in mind, a pilot study referred to as the PEACS (physical activity and cognitive stimulation) study was designed. The PEACS study recruited 224 volunteers that were allocated into a physical activity group, a brain training group, a combination group that includes physical activity and brain training and a control group. The 16 week intervention study was designed with a battery of assessments at baseline (prior to intervention), at 8 weeks and 16 week time points. These assessments included neuropsychological tests, blood biomarkers, body composition scans (which measures body mass and fat) and brain imaging to investigate brain glucose uptake in certain regions of the brain. Furthermore, two types of brain training software programs-auditory and visual were implemented.

The findings from the study showed that compared to the control (non-training group), a combination of physical activity and cognitive brain training (using computerized software programs that have been validated in clinical trials), showed improvements in certain cognitive domains (particularly verbal memory). The improvement in verbal memory was maintained on follow-up after completion of the training, suggesting long lasting effects on this particular cognitive domain. In addition novel data is presented to suggest that the order in which auditory or visual stimulation is administered via these brain training programs can impact on the amount of benefits obtained in certain cognitive domains. Although improvements observed with the combination of physical activity and cognitive stimulation did not correlate with changes in blood biomarkers, associations were observed with increased cerebral glucose metabolism, indicating that the benefits obtained are due to improvements in neuronal activity.

The results presented here contribute to the body of knowledge that is leading to a better understanding and development of physical activity and cognitive training as a protective factor for cognitive decline and AD. It also provides pilot information that is useful for the design of future intervention trials utilizing physical activity or cognitive training.

A PhD student, Dr Tejal Shah, under the supervision of Professor Ralph Martins and A/Prof Giuseppe Verdile, undertook the study. Tejal recently successfully completed here PhD and will graduate in 2014 . The work has been presented at the Alzheimer's disease International Conference (London) in March 2012 and at the Alzheimer's Association International Conference (AAIC) in Vancouver, Canada in July 2012 and Society for Neurosciences in San Diego. Manuscripts outlining these findings have recently been submitted for publication.

Miss Samantha Gardener

Impact of Nutrition on Cognition and its Association with Blood and Brain Alzheimer Disease Related Biomarkers

Researchers:
Miss Samantha Gardener (PhD student), Dr Stephanie Rainey-Smith and Professor Ralph Martins

The focus of the current research climate is shifting from understanding Alzheimer's disease (AD) pathology and diagnosis, to primary prevention and intervention strategies. Early detection combined with intervention strategies could reduce disease effects. Diet represents one potential intervention strategy accessible to all. Recent reports suggest adherence to the Mediterranean diet (MeDi) may affect AD risk and the progression of pre-dementia syndromes to overt dementia. Adherence to other dietary patterns such as the western diet has been shown to correlate with risk factors for AD. However, the investigation of dietary factors, AD risk and disease course, is a relatively young field of research and there is a critical need for data collected from a well-characterised ageing cohort.

The aim of this project is to investigate the association between dietary patterns and cognition, and other blood and brain AD biomarkers. The study will include analysis of dietary, cognitive, functional, behavioural and physical assessments within the AIBL cohort at a baseline visit and at 18, 36 and 54 month follow up assessments. Levels of known AD risk factor markers which may be affected by nutrient intake in the diet, will be analyzed. Dietary assessment involves analysis of data acquired from administration of the Cancer Council of Victoria food frequency questionnaire and the CSIRO food frequency questionnaire (CSIROFFQ).

A MeDi score was generated for each participant (0-9 point scale): higher scores indicate higher adherence. A western and prudent diet score was assigned to each participant using factor analysis to establish the dietary pattern.

In October 2012 we published a paper in Translational Psychiatry titled 'Adherence to a Mediterranean Diet and Alzheimer's disease Risk in an Australian Population'. This reported cross sectional results showing that healthy control participants have a higher adherence to the MeDi than AD and mild cognitively impaired participants. Currently we are working on longitudinal analysis from the baseline and 36 month follow up assessment and finding associations between the three dietary pattern scores and cognitive decline (measured from the neuropsychological test battery participants complete at each follow up assessment). Our results, which will be published in early 2014, indicate a beneficial effect of the MeDi and a detrimental effect of the Western diet on memory and thinking abilities over 3 years. We have commenced analyses that we believe will provide insight into the mechanisms underlying the observed effects.

There are currently no Alzheimer's-specific diet questionnaires available to the research community. To address this deficit, we have added questions to an online food frequency questionnaire designed by the CSIRO that focus on foods and beverages of particular interest to AD researchers. The modified questionnaire is currently undergoing a 'validation study' involving AIBL participants which evaluates the repeatability and reliability of this FFQ with the new questions, and will compare daily intake of foods measured from the answers to the FFQ with daily intake of foods measured from four day weighed food records. Once this 'validation study' is complete, the modified CSIROFFQ will be completed by the whole AIBL cohort at the 90 month follow up assessment.

Our work has been presented at several conferences including the Lifestyle Approaches for the Prevention of Alzheimer's disease Conference in Perth, Western Australia in March 2012, the Alzheimer's disease International Conference (London) in March 2012, the Alzheimer's Association International Conference in Vancouver, Canada in July 2012 and the Dementia Collaborative Research Centres Conference in Canberra, Australia in September 2012 and in Brisbane in September 2013. An abstract has been submitted to present our longitudinal results at the Alzheimer's Association International Conference in Copenhagen, Denmark in July 2014.

Dr Stephanie Rainey-Smith

Combinational nutritional supplement therapies in the prevention of Alzheimer's Disease

Researchers:
Dr Matthew Sharman (University of Tasmania)
Dr Stephanie Rainey-Smith (McCusker Fnd, ECU)
Dr Binosha Fernando (ECU)
Professor Ralph Martins (McCusker Foundation, ECU)

In Collaboration with:
A/Prof Gerald Munch (University of Western Sydney)
A/Prof Marcus Wenk (National University of Singapore)
Prof Barry Halliwell (National University of Singapore)
Prof R Vijayalakshmi (National Brain Research Institute, India)

Significance of the project: Lifestyle modifications such as dietary interventions, and physical activity programs, have long played a central role in the management of several diseases such as cardiovascular disease, diabetes and cancer. It is well known that one of the most important lifestyle factors, diet, strongly influences the incidence and outcome of major age-related pathologies. Diet can also strongly influence the risk of developing late-onset Alzheimer's disease, with several studies across the world showing that fruits, vegetables and fish oils are associated with improving health and decreasing an individual's risk for developing Alzheimer's disease. This is supported by research which shows that low dietary intake of fruits, vegetables and fish oils increase your risk for developing late-onset Alzheimer's disease. If nutritional-based complementary and alternative medicine (CAM) therapies could be developed to prevent or delay the onset for Alzheimer's disease, the impact on disease burden could be substantial. However, these CAM therapies need to be critically evaluated for their mechanisms, efficacy and safety. The development of effective preventative strategies for the treatment of Alzheimer's disease is critical if we are to reduce the number of people that are expected to develop Alzheimer's disease over the next 50 years, due to the rapidly aging population.

We have previously demonstrated in an animal model of Alzheimer's disease, that both a Green Tea diet and a Fish Oil diet were able to reduce the levels of beta-amyloid in the brain and cerebrospinal fluid. However, the Fish Oil diet which is high in the omega-3 essential fatty acids resulted in significantly greater reductions in beta-amyloid levels compared to the Green Tea diet. Based on these initial findings we have now begun work investigating whether combinations of a number of nutritional-based-CAM compounds have a great effect on reducing the pathology caused by Alzheimer's disease in an animal model. Some of the compounds we are currently examining include, EGCG (a compound extracted from Green Tea), curcumin (the main ingredient extracted from the spice turmeric), DHA (one of the main components in fish oil), ALA (a natural antioxidant) and Short Chain Fatty Acids (manufactured in the gut following intake of dietary fibre).

Major Findings to date: Work on this project is still ongoing, with a number of different dietary combinations being trialed in a mouse model of Alzheimer's disease. Analysis of samples is currently underway and expected to be completed in 2014. This work is critical to establish the efficacy of these potential therapies, before progressing to clinical trials in humans. The development of effective preventative strategies for the treatment of Alzheimer's disease is critical if we are to reduce the number of people that are expected to develop Alzheimer's disease over the next 50 years, due to the rapidly aging population. This is an exciting approach that builds on our long-term understanding of both different antioxidants and beta amyloid metabolism resulting in a combination of these compounds to provide maximal synergy. If the current animal study is successful, it has the advantage of being able to progress rapidly to clinical trials as these antioxidants are food products known to be very safe for human consumption.

This project is funded by a National Health & Medical Research Council Complementary and Alternative Medicine Strategic Grant as well as a grant from the Hollywood Private Hospital Research Foundation.

The Effect of Physical Activity on Cognition, the Development of Alzheimer's disease and Associated Blood Biomarkers (AIBL study)

Dr Belinda Brown

Researchers:
Dr Belinda Brown, Dr Stephanie Rainey-Smith and Professor Ralph Martins

The objective of this research is to determine the effect of physical activity on factors associated with the development of Alzheimer's disease (AD). More specifically, we are evaluating the relationship between physical activity and AD biomarkers (biological markers of disease) that have been measured in both the blood and brain (via neuroimaging). We have also investigated the association between physical activity and performance on memory and cognitive functioning tasks.

Data used in this research has been collected from the Australian Imaging Biomarkers and Lifestyle (AIBL) Study cohort. All participants undergo memory testing, blood collection and complete detailed lifestyle and physical activity questionnaires. A subset of individuals also wore Actigraph activity monitors for seven consecutive days, which enables us to accurately capture the quantity and intensity of physical activity that our participants are undertaking. A further group of individuals completed brain imaging, including positron emission tomography with Pittsburgh compound B (known as PiB PET; to measure brain amyloid) and magnetic resonance imaging (MRI).

To date, we have reported promising results that suggest physical activity is an important protective factor for Alzheimer's disease. Our findings indicate that people undertaking higher levels of physical activity have lower levels of the toxic beta-amyloid protein in their blood. We also report a similar finding in the brain, with higher exercising individuals having lower levels of beta-amyloid, as measured PiB PET brain imaging. Furthermore, it appears that genetics plays a role in this association, with carriers of the APOE 4 allele (a genetic risk factor for AD), receiving the greatest benefit from physical activity.

In addition to physical activity influencing important Alzheimer's disease biomarkers, we have also demonstrated that intense physical activity is associated with better memory and cognitive function. This may be due to an increase in hippocampal volume, the structure of the brain important for learning and memory, which we have also found to be associated with higher levels of physical activity.

We aim to build on this research by investigating the mechanisms in which physical activity is changing levels of amyloid in the brain. It will also be important to identify the level (i.e. intensity) of physical activity that is most beneficial to brain health, and thus an exercise intervention trial is currently being designed. Collectively, the current research, and proposed future research, will be used to establish physical activity as a protective factor against AD.

A pilot clinical study to evaluate the potential of a nutritional extract Amlamax TM on raising HDL levels

Key Researchers:
Dr Stephanie Rainey-Smith (McCusker A.R. Foundation, ECU)
Dr Hamid Sohrabi (McCusker A.R. Foundation, ECU)
Dr Tejal Shah (McCusker A.R. Foundation, ECU)
Mr Kevin Taddei (McCusker A.R. Foundation, ECU)
Professor Ralph Martins ((McCusker A.R. Foundation, ECU)

In Collaboration with:
Dr Benny Antony (Arjuna Natural Extracts, Kerala, India)
Dr Binu Kuruvilla (Arjuna Natural Extracts, Kerala, India)

Significance of the project:

One of the most prevalent lifestyle-associated diseases today in Western society is cardiovascular disease. A growing body of literature also indicates that the presence of cardiovascular disease is associated with increased risk of developing late-onset Alzheimer's disease. Considerable evidence has been provided in support of the notion that increases in total plasma cholesterol, low-density lipoprotein-cholesterol (LDL-C), and decreased high-density lipoprotein-cholesterol (HDL-C) known risk factors for cardiovascular disease, are also associated with increased Alzheimer's disease risk. Numerous studies have demonstrated that elevated total plasma cholesterol results in increased deposition of beta-amyloid in the brain and increases individuals' risk for developing Alzheimer's disease. Thus, one factor which may link cardiovascular disease and Alzheimer's disease is HDL-C, as epidemiological studies have reported that high concentrations of HDL-C or "good" cholesterol (>1.5mMol/L) may also be protective against Alzheimer's disease.

Previous work performed at the McCusker Alzheimer's Research Foundation/ECU, by Dr Kristyn Bates and colleagues has demonstrated a relationship between HDL-C levels and beta-amyloid levels in 198 study participants, providing further evidence for a link between cardiovascular disease and Alzheimer's disease. This has suggested that strategies designed to improve cardiovascular health, namely raising HDL-C levels, may protect against cognitive decline and Alzheimer's disease. While drugs that lower cholesterol and LDL-C levels are currently being considered and tested as potential therapies for the treatment of Alzheimer's disease, there are no effective drugs available to raise HDL-C levels - although, HDL-C levels are known to be modified by a number of environmental factors, including diet and exercise.

The Indian plant Amla (Emblica officinalis) commonly known as Indian gooseberry has widely been utilized in traditional Ayurvedic medicine preparations for use against a variety of disease conditions. The natural herbal extract Amla has been recently identified for its ability to increase HDL-C levels. As low HDL-C levels are thought to be an important risk factor for late-onset Alzheimer's disease this has an important implication for future work.

Project Progress

We have commenced a study evaluating in a pilot clinical trial, the effectiveness of this herbal Amla Extract on raising HDL-C levels in a population of subjects with low HDL-C levels. This study also aims to determine whether directly raising HDL-C levels can result in a decrease in plasma beta-amyloid levels. This work is being conducted in collaboration with Arjuna Natural Extracts Ltd., a global manufacturer and exporter of herbal and spice extracts, located in Kerala, India. This Amla extract, known as AmlamaxTM was developed by the R&D lab of Arjuna Natural Extracts Limited. Amlamax is a reconstituted dry extract from fresh fruits of Amla and has recently shown remarkable results in increasing HDL-C levels in patients with dyslipidemia. However, its possible role in helping to decrease Alzheimer's disease risk has not been previously explored. The findings from our pilot study will contribute towards assessing the ability of the Amla extract to effectively treat patients identified as having low HDL-C levels, and subsequently evaluating the potential role of Amla in helping to decrease the risk of developing late-onset Alzheimer's disease. At the time of writing 49 trial participants have completed a 6 month course of Amlamax or placebo.

Evaluation of the Nutritional Extract Biocurcumax (BCM-95) to Preserve Cognitive Functioning.

Key Researchers:
Dr Stephanie Rainey-Smith (McCusker Fnd, ECU)
Dr Hamid Sohrabi (McCusker Fnd, ECU)
Dr Tejal Shah (McCusker Fnd, ECU)
Mr Kevin Taddei (McCusker Fnd, ECU)
Professor Ralph Martins (McCusker Fnd, ECU)

In Collaboration with:
Dr Benny Antony (Arjuna Natural Extracts, Kerala, India)
Dr Binu Kuruvilla (Arjuna Natural Extracts, Kerala, India)

Significance of the project:

Curcumin, the main bioactive ingredient of the Indian curry spice turmeric has been reported to have many beneficial effects including showing promise as a neuroprotective agent in the prevention of Alzheimer's disease (AD). Epidemiological studies have suggested curcumin is protective against cognitive decline, whilst animal studies have shown that mice, genetically predetermined to develop AD and fed a diet rich in curcumin, exhibit significantly reduced beta amyloid levels. Moreover, curcumin has been shown to be clinically safe with no adverse effects reported following administration of doses up to 8g/day. However, the low bioavailability of curcumin in the body (due to poor absorption and uptake) has limited its clinical impact. Indeed, a recent clinical trial for AD, 6 month administration of 1-4 g/day, had no significant effect on cognitive impairment. Consequently, methods to increase the oral bioavailability of curcumin are a subject of intense current research. Reconstituting curcumin with the non-curcuminoid components of turmeric has been found to increase the bioavailability substantially. BiocurcumaxTM, is a novel bio-enhanced preparation of curcumin. Human studies have shown increased (7-fold) bioavailability of BiocurcumaxTM compared to curcumin.

Project Progress

We commenced work in September 2011, within the McCusker Foundation, evaluating in a pilot clinical trial, the ability of this nutritional extract BiocurcumaxTM to preserve cognitive function in subjects with memory complaints, over a 12 month period. This study also aims to determine whether BiocurcumaxTM can alter plasma and brain beta-amyloid levels. This work is being conducted in collaboration with Arjuna Natural Extracts Ltd., a global manufacturer and exporter of herbal and spice extracts, located in Kerala, India. BiocurcumaxTM was developed by the R&D lab of Arjuna Natural Extracts Limited. The ability of BiocurcumaxTM to prevent cognitive decline, alter Alzheimer's disease-related biomarkers, and therefore its potential role in helping to decrease the risk of developing late-onset Alzheimer's disease has not been previously explored. At the time of writing 88 participants have completed the 12 month study. An additional 35 participants have undergone an added component of the study where the amyloid load in their brain is visualised (using PiB-PET brain imaging) immediately prior to commencement of the BiocurcumaxTM or placebo regimen. These 35 participants will undergo a second brain scan immediately following cessation of the BiocurcumaxTM or placebo regimen; this will enable the effect of BiocurcumaxTM on brain amyloid load over 12 months to be examined. We are currently in the process of recruiting the final 35 participants for this study.

COLLABORATIONS

CRC

The CRC for Mental Health has 20 participant organizations, each of which brings a unique set of skills to the discovery program.

Educational Institutions
Edith Cowan University
The University of Melbourne
The University of Western Australia
Research Organizations
CSIRO
Florey Neuroscience Institutes
Mental Health Research Institute
National Ageing Research Institute
Commercial Entities
Alzhyme Pty Ltd
CogState
Lawley Pharmaceuticals
Nucleus Network
Oceanic Medical Imaging Pty Ltd
Pfizer Inc
Health Care Providers
Austin Health
Barwon Health
Hall and Prior
Mercy Health Aged Care
Philanthropic Organizations
Alzheimer's Association
McCusker Alzheimer's Research Foundation Inc
Parsemus Foundation

International:

Collaboration has been ongoing for the last 16 years with ***Professor Sam Gandy initially from Farber Institute for Neurosciences, Thomas Jefferson University Philadelphia and now with Professor Gandy at the Mount Sinai Centre for Cognitive Health in New York*** into an interdisciplinary approach to Alzheimer Drug discovery. The collaboration with Professor Sam Gandy has resulted in his visit in 2000 to the University of Western Australia as the Raine Visiting Professor and several joint publications including a publication in JAMA and the subsequent 4 month (April-July 2003) visit to Professor Gandy's Farber Institute by Professor Ralph Martins to further progress our ongoing collaborative partnership.

Close collaboration has been established since 2004 with Dr Markus Wenk and Dr RH Yang from the National University of Singapore. Project entitled "Lipodomics of neuronal membranes – Identification of lipids involved in neurosecretion and neurodegenerative diseases.

Professor Martins and Associate Professor Giuseppe Verdile have an ongoing collaboration with Professors Peter Hyslop and Paul Fraser from the University of Toronto to identify genetic risk factors in Alzheimer's disease. This collaboration has involved exchange of students and staff between Western Australia and the American and Canadian institutes.

An ongoing collaboration with ***Professor John Morris and Professor Randy Bateman from the Washington University*** was established in 2006. This resulted in collaboration on the DIAN Clinical Study and DIAN Clinical Trial.

Professor Judith Miklossy from the University Institute of Pathology, University of Laussanne in Switzerland and latterly from Center for NeuroVirology and Cancer Biology, College of Science and Technology, Temple University, Philadelphia has supplied 200 brain samples from post-mortem confirmed Alzheimer's disease cases for biochemical and genetic studies. This collaboration has resulted in several publications.

COLLABORATIONS

The role of oestrogen in Alzheimer's disease is being undertaken in collaboration with ***Professor Suzanne Craft from the University of Washington.***

The structure and function of the amyloid precursor protein in Alzheimer's disease is being studied in collaboration with ***Professor Toshihara Suzuki of Tokyo University, Japan.***

A study into the role of gonadotropins in the development and progression of Alzheimer's disease is being undertaken in a joint collaboration with ***Ass. Professor Craig Atwood from Wisconsin University Maddison Medical School, USA.***

Collaboration has been instituted with ***Professor D. Allan Butterfield from the Dept of Chemistry and Center of Membrane Sciences, University of Kentucky, Lexington USA.*** This collaboration is to study oxidative stress in Alzheimer's disease and this resulted in one of our PhD students spending 6 months with Professor Butterfield investigating the protective effects of apoE isoforms on Abeta induced oxidative stress in cell culture.

Collaboration is ongoing with ***Associate Professor Joachim Hallmayer from Stanford University Department of Psychiatry and Behavioural Science*** to identify genetic and molecular risk factors in neurodegenerative diseases. This collaboration has resulted in several papers.

Interstate:

Ongoing collaboration has been established with Dr Lautenschlager and Professor Forstl into identification of biomarkers for cognitive decline in subjective memory complainers.

Ongoing collaboration has been established with the three major research groups working on Alzheimer's disease in Australia led by ***Professor Colin Masters at the University of Melbourne, Associate Professor Peter Schofield from the Garvan Institute in Sydney and Professor Tony Broe from the Prince of Wales Medical Research Institute, Sydney, New south Wales.***

Dr Elizabeth Milward from the University of Newcastle New South Wales, ongoing research into 'Iron-related genes and neurodegenerative disorders".

Local:

Collaboration is ongoing with ***Professor Alan Harvey (Department of Anatomy, University of Western Australia)*** on the development of animal models for Alzheimer's disease.

Collaboration is ongoing with ***Professor Dharmarajan from the CSIRO Western Australia*** on studying the function of beta amyloid. This seminal work has been published.

University of Melboiurne.

Research is ongoing ***Dr Ian Martins (ECU)*** who has a strong background in lipoprotein research which is aimed at obtaining a better understanding of the molecular mechanism(s) by which apolipoprotein E acts as a major risk factor for Alzheimer's disease.

Professor David Bruce and Dr Bu Yeap from University of W.A. School of Medicine and Pharmacology, Fremantle Hospital, Effect of androgens on cognitive function and evolution of dementia in older men.

Collaboration has been established with ***Professor Leon Flicker from the Department of Geriatric Medicine and Professor Osvaldo Almeida from the University Department of Psychiatry, Queen Elizabeth II Medical Centre,*** to undertake an intervention study in patients with memory disorders.

Collaboration has recently been established with ***Professor Gary Hulse, from University of Western Australia's Unit for Research and Education in Drugs and Alcohol*** to analyse the effectiveness of a therapeutic agent for Alzheimer's disease.

A collaboration has been established with ***Professor Vijay Jayasena from the School of Public Health, Curtin University, Associate Professor Roz Walker and Associate Professor Juli Coffin from the Centre for Research Excellence in Aboriginal Health and Wellbeing, Telethon Institute for Child Health Research, Professor Sven Silburn, Centre for Child Development and Education Menzies School of Health Research and Professor Carmela Pestell, School of Psychology, University of Western Australia*** to develop Innovative foods that will potentially prevent chronic disease in Aboriginal children.

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Doré V, Villemagne VL, Bourgeat P, Fripp J, Acosta O, Chetélat G, Zhou L., **Martins RN**, Ellis KL, Masters CL, Ames DA., Salvado O, Rowe CC. Cross-sectional and longitudinal analysis of the relationship between Aβdeposition, cortical thickness and memory in cognitively unimpaired individuals and in Alzheimer's disease. Archives of Neurology 2012. Accepted September.

Carrillo MC, Rowe CC., Szoeke C., Masters CL., Ames D., O'Meara T., Macaulay SL., Milner A., Ellis KA., Maruff P., Rainey-Smith SR., **Martins RN**, Bain LJ, Head RJ. Research and Standardization in Alzheimer's Trials: Reaching International Consensus. Alz and Dementia 2012. Accepted November 2012

PROFESSOR RALPH MARTINS GRANTS AWARDED

Australian Research Council. LIEF Grant. Hunt DM, Martins R, Verdile G, Laws S, Lister R, Collin SP, Pavlos N, and Davies WIL. Establishing a zebrafish facility in Western Australia. ARC LE140100116. 2014: $400,000

Mason Foundation National Medical Program Project Grant. Laws SM, Verdile G. "Validation of genetic variants and their functional implications in Alzheimer's Disease" 2014: $40,000

ECU Early Career Researcher Award, 2013:: $10,000, "Protective role of autophagy genes in Alzheimer's disease", Dr. Bharadwaj P

FCHS Research Grant ($9982) for "Angels and Demons" – Phylomers® as novel candidates targeting toxic aggregates in Alzheimer's Investigators: Dr R Barr (ECU), Prof R Martins (ECU), Dr G Verdile (ECU), Prof Paul Watt (Phylogica Ltd), Dr R Hopkins (Phylogica Ltd).

Hollywood Private Hospital Research Foundation RF062 Efficacy of Biocurcumax and Docosahexaenoic acid (DHA) in slowing accumulation of Beta Amyloid and preventing cognitive decline in an older population. Martins RN, Goozee K. Rainey-Smityh S. & Pedrini S. November 2012 $15,000.

Neurotrauma Research Program Grant: Head Injury & Testosterone Study (HIT) RN Martins, H. Sohrabi, NW Knuckey, M Weinborn, M Carruthers, N, Lenzo, K. Taddei $148,701 1 year 2013.

ECU- Small Faculty Grant : Genome wide screening of oligomer Aβtoxicity using a yeast gene deletion library. Bharadwaj P. Martins RN. 2012 $10,000

ECU- Small Faculty Grant : Serum beta-Amyloid 1-42, olfactory functioning and cognitive decline in the elderly; Hamid Sohrabi, RN Martins, 2013. $ 7500

ECU- Small Faculty Grant for Early Carrier Researchers: Personality dimensions and increased risk of late onset Alzheimer's disease; Hamid Sohrabi, 2013; $ 15000

INVITED PRESENTATIONS

Invited by Roma Lester to make a presentation to the ORA Womens' Cultural Group, Jewish Centre in Perth February 12, 2013. Latest Advances in Alzheimer's disease.

Presentation entitled Alzheimer's disease development, Early Detection and Life Style Prevention Factors – The Australian Imaging Biomarker & Lifestyle Study (AIBL) at the Health Aging – Strategies to Meet Healthy & Lifestyle Challenges Singapore. March 2013.

Invited by Roma Lester to make a presentation to the ORA Womens' Cultural Group, Jewish Centre in Perth February 12, 2013. Latest Advances in Alzheimer's disease.

Presentation entitled Alzheimer's disease development, Early Detection and Life Style Prevention Factors – The Australian Imaging Biomarker & Lifestyle Study (AIBL) at the Health Aging – Strategies to Meet Healthy & Lifestyle Challenges Singapore. March 2013.

Invited to present a talk at the 6th Annual Biopharma Asia Convention, Santosa Singapore March 18-21 2013. Presentation entitled: Developing disease modifying therapeutic peptides and diagnostics for Alzheimer's disease.

Presentation at the AD/PD Conference in Florence March 10th 2013 entitled: Testosterone and Luteinizing Hormone Levels; Association with Alzheimer's disease Related endophenotypes & therapeutic Efficacy in a Pilot study.

Presentation at the AD/PD Conference in Florence March 10th 2013 entitled: Testosterone and Luteinizing Hormone Levels; Association with Alzheimer's disease Related endophenotypes & therapeutic Efficacy in a Pilot study.

Invited as Plenary speaker at the Science of Nutrition in Medicine and Healthcare Sydney New South Wales May 3- 5th 2013. Two presentations:

1. Role of testosterone & Luteinizing Hormone on the Pathogenesis of Alzheimer's Disease (30 mins)

2. Early diagnosis and prevention of AD: The Australian Imaging Biomarkers and Lifestyle Study of Ageing (30 mins)

Invited to make a presentation to members and guests at the South of Perth yacht Club at their Prestigious Spring Fundraising Luncheon for the year. Mrs Tonya McCusker also presented at this luncheon. September 12, 2013.

Invited by Alzheimer's Australia (South Australia) to present at the "Mindful of Dementia" conference in Port Lincoln and at the Queen Elizabeth Hospital in Adelaide, a talk entitled Alzheimers Disease – Development, Early Detection, and Lifestyle Prevention Factors" October 2- 5 2013.

Invited by UNI HealthCare to give the keynote presentation at the EQUIP Expo Claremont Showgrounds November 22 & 23rd 2013, Entitled "Understanding Alzheimers".

While there is currently no cure for Alzheimer's disease, there are five prescription drugs approved to treat its symptoms. These drugs modestly improve symptoms but do not alter disease progression. No new drugs have been approved by the TGA or FDA for Alzheimer's disease treatment since 2003 despite numerous clinical drug trials worldwide. Novel pharmacological agents that slow or halt the progression of AD are therefore desperately needed.

The Clinical Trials Department (CTD) of the McCusker Alzheimer's Research Foundation has been conducting clinical drug trials since 2003 with Associate Professor Roger Clarnette as Principal Investigator. A/Prof Roger Clarnette is a Consultant Geriatrician at Fremantle Hospital and Director of their specialised Memory Clinic with expertise and particular interest in memory loss and Alzheimer's disease. He has been the Principal Investigator for more than 50 clinical trials over a period of 20 years.

There are promising new treatments for Alzheimer's disease being tested by the CTD. We are currently trialing new treatments for the very early or prodromal stage of Alzheimer's disease. It is known the pathology of the disease commences 10-20 years before the onset of clinical symptoms warranting early intervention and early treatment. Testing new treatments in mild to moderate Alzheimer's disease have not proven effective probably because the brain damage is difficult to reverse at these stages and a slowing of disease progression may be all that is possible. The DIAN-TU-001 trial will enroll participants at our site with a rare genetic form of Alzheimer's disease when they are cognitively normal or have mild cognitive impairment. Patients chosen for the trial will test drugs that may prevent the buildup of beta amyloid plaques in their brains and therefore prevent the disease. Understanding this rare early onset form of Alzheimer's disease may provide clues to decoding the most common age related sporadic form Alzheimer's disease and therefore help develop new dementia treatments.

The CTD plays an important part in The McCusker Alzheimer's Research Foundation's vision of a world without Alzheimer's disease. Our goal is to eliminate Alzheimer's disease through the advancement of research and to provide and enhance care and support for all affected. The trial participants and their families receive medical care and support provided by a multidisciplinary team who are experts in this field. Participants also gain access to new treatments which may benefit them and will definitely benefit future generations by adding to the body of scientific knowledge in this area.

If you or someone you know is interested in participating in a clinical trial please call 93896433 and speak to one of the study coordinators.

All trials are double blind, randomised, parallel group, placebo controlled multicentre trials. During 2013, the Clinical Trials Division was engaged in the following clinical trials:

MERCK SHARP & DOHME CORP

An Efficacy and Safety Trial of MK-8931 (SCH 900931) in Subjects with amnestic Mild Cognitive Impairment (aMCI) due to Alzheimer's Disease (Prodromal AD)

This is a 24 month trial of 1500 participants in subjects with amnestic mild cognitive impairment due to Alzheimer's disease (or prodromal Alzheimer's disease) The study medication is a potent -site APP cleaving enzyme 1(BACE1) Inhibitor so may reduce beta-amyloid production in humans and potentially slow progression in subjects with prodromal AD. The trial enrolls subjects who meet the criteria for prodromal AD defined as subjects who have amnestic aMCI and are positive for an AD biomarker. The primary biomarker to be used for this study is cortical amyloid load measured with a PET scan using an investigational ligand flutemetamol. We require participants for this trial in 2014.

TauRx THERAPEUTICS LTD

TRx-237-015: Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, 15-Month Trial of Leuco-methylthioninium bis(hydromethanesulfonate) in Subjects with Mild to Moderate Alzheimer's Disease

This 15 month trial is being conducted in 120 study sites worldwide with a recruitment target of 833 participants. The primary development of the study medication methylthioninium (MT) in Alzheimer's disease is focused in its activity as a Tau Aggregation Inhibitor. The Tau hypothesis is that processes leading to abnormal aggregation of Tau protein lead to the formation of tangles within the nerve cells in the brain and lead to clinical dementia. The Protein Aggregation Inhibitors target the underlying pathology of dementia with the aim of modifying or halting disease progression and an ultimate goal of prevention. We require participants for this trial. Recruitment is ongoing.

The DIAN-TU-001 Prevention Trial (Dominantly Inherited Alzheimer's Network)

A Phase II/III randomized, double-blind, placebo-controlled, multi-centre study of 2 potential disease modifying therapies in individuals at risk for and with dominantly inherited Alzheimer's Disease.

This 4 year study of 210 participants worldwide will assess the safety, tolerability and biomarker efficacy of gantenerumab and solanezumab in subjects who are known to have a rare Alzheimer's disease-causing mutation by determining if treatment with the study drug improves primary and secondary outcome disease-related biomarkers. The 2 drug treatments being administered are humanised anti beta amyloid peptide antibodies which may prevent, inhibit or reduce the accumulation of beta amyloid. Gantenerumab is given as an injection and solanezumab is given intravenously (IV) every month for 24 months in this study. Participants will have 8 PET scans (PIB, FDG and Florbetapir F-18) 9 MRIs, lumbar punctures as well as cognitive testing throughout the study to assess the outcome measures.

ROCHE PRODUCTS PTY LIMITED

Protocol Number: WN25203D Multicenter, randomised, double-blind, placebo-controlled, parallel-group two year study to evaluate the effect of subcutaneous Gantenerumab on cognition and function in prodromal Alzheimer's Disease.

770 subjects were selected worldwide who met the criteria of memory impairment and reduced CSF A 1-42 levels so have likely Prodromal AD. The study medication is a human anti beta amyloid peptide antibody which may prevent, inhibit or reduce the accumulation of beta amyloid. Subcutaneous study treatment are given every 4 weeks for 26 administrations and the total treatment duration is approximately 2 years. There is optional participation in Part 2 of the study for years 3 and 4 with monthly study treatment.

- There are 11 ongoing patients and 3 patients have withdrawn.
- Recruitment has finished. We were the top recruiter in Australia for this study

F.HOFFMAN-LA ROCHE LTD

A Phase 2 multicentre, randomised, double-blind, parallel-group, placebo-controlled study to investigate the efficacy and safety of RO4602522 added to the background therapy of the acetylcholinesterase inhibitors donepezil or rivastigmine in patients with moderate severity Alzheimer's Disease

This study medication is a selective inhibitor of MAO-B being tested in patients with moderate severity Alzheimer's disease to ascertain its capacity to improve cognition, functionality and behavior in this population. The study medication is given for 12 months added to background AD treatment. A total of 354 patients have been recruited worldwide for this study which was the recruitment target.

SERVIER

1. Protocol Number: CL2 38093 011 - Efficacy and safety of 3 doses of S38093 (2, 5 and 20mg/day) versus placebo in patients with mild to moderate Alzheimer's Disease. A 24-week international, multicentre, randomised, double-blind, placebo-controlled phase IIb study followed by a 24 week extension period

The purpose of this trial is to assess the efficacy and safety of S 38093 versus placebo in patients with mild to moderate AD. The primary objective of this study is to assess the efficacy of 3 fixed doses of S 38093 (2, 5 and 20 mg/day) versus placebo after 24 weeks of treatment, on cognitive performance measured with the ADAS-Cog 11-items in patients with mild to moderate AD.

Recruitment has finished for this study.

2. Efficacy and safety of 3 doses of S 38093 (2, 5 and 20mg/day) versus placebo, in co-administration with donepezil (10mg/day) in patients with moderate Alzheimer's Disease. A 24-week international, multi-centre, randomized, double-blind, placebo-controlled phase 11b study.

This trial is using the same study medication as the previous trial with no extension phase. We have 3 patients participating in this 6 month treatment study and are still looking for suitable participants.

TROPISETRON

A randomized, double-blind, placebo-controlled, sequential cohort, multi-centre study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of F03 in subjects with mild cognitive impairment due to Alzheimer's Disease.

This 8 week treatment study of 36 participants is a Phase 1b/2a study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics and preliminary efficacy of oral F03 (tropisetron) compared to placebo in males and females with Mild Cognitive Impairment due to Alzheimer's Disease. Tropisetron is a currently approved anti-emetic drug in 49 countries across the world, including Australia.

This study will commence in 2014.

DIAN Clinical Trial Unit

Chief Investigator: Prof Randall Bateman
Washington University School of Medicine

Researchers (ECU/McCusker): A/Prof Roger Clarnette and Professor Ralph Martins

Sponsor: Washington University School of Medicine

Pharmaceuticals Collaborators:
Eli Lilly and Company
Hoffmann-La Roche
Alzheimer's Association (USA)
National Institute on Aging (NIA)
Avid Radiopharmaceuticals

Autosomal-dominant Alzheimer's disease is a rare but aggressive form of Alzheimer's disease that result in memory loss and other cognitive problems in individuals aged 30-60yrs old. The DIAN Clinical Trial aims to examine the efficacy of drugs potentially able to change the course of the disease. The DIAN Trial will examine if these drugs can prevent the disease, treat the symptoms, or delay its onset and whether they are safe, tolerated by patients, and are effective. The study started by screening potential participants at the Washington University School of Medicine in St. Louis, Missouri USA, in late 2013. Our Perth site will be the first in Australia to start this clinical trial. To be eligible for this study participants must be offspring of a patient with one of the three known Alzheimer's related gene mutations and have been registered for the study.

alzhyme

"Commercialising technologies to prevent Alzheimer's disease"

Alzhyme Pty Limited is a biotechnology company specialising in the development of novel drugs and diagnostics for the effective detection, prevention and treatment of Alzheimer's disease.

Alzhyme was formed in December 2002 out of the University of Western Australia to commercialise the research of Prof Ralph Martins and his team,. Alzhyme was established through initial capital investment from its founding shareholder and Chairman, Mr. Harold Clough. Alzhyme is seeking to raise additional capital to advance its pipeline of technologies through pre-clinical development.

Today, Alzhyme has four patent application families and four development project streams:

1. Peptides to enhance peripheral clearance of -amyloid as a treatment for Alzheimer's disease. Jointly funded with federal government support.
2. Peptide therapeutic treatments for early intervention in Alzheimer's disease.
3. Diagnostic imaging agents for early detection of Alzheimer's disease.
4. Partnership in a major new clinical trial of testosterone for the prevention of Alzheimer's disease (in collaboration with the CRC for Mental Health and the McCusker Alzheimer's Research Foundation)

Therapeutic Pipeline

Through the research efforts of Prof Ralph Martins and his team, Alzhyme has identified a family of peptides that specifically neutralize the damaging potential of beta-amyloid in the brain. Accumulation of beta-amyloid in the brain is believed by many to be of major importance in the pathogenesis of Alzheimer's disease. Alzhyme's lead peptide candidate has been shown to significantly inhibit beta-amyloid-induced neurotoxicity in several animal models.

Through Prof. Martins and his team, Alzhyme is working to establish that the Alzhyme peptides can be used to progressively reduce beta-amyloid in the brain through a process known as peripheral clearance. Importantly this process obviates the need for the Alzhyme peptides to cross the blood brain barrier.

The research group is also developing an orally available analogue of the Alzhyme peptide for the treatment of Alzheimer's disease.

Diagnostics

In parallel to its therapeutic program of research, Alzhyme has is committed to improving early diagnosis of Alzheimer's disease.

The pathological processes of Alzheimer's disease begin many years before clinical symptoms are observed. Early, cost-effective diagnostic methods have the potential to minimise the enormous impact that Alzheimer's disease will have on health, quality of life and healthcare costs through:

- accurate diagnosis of Alzheimer's disease early in the disease course and before significant memory loss occurs;
- earlier and more appropriate treatment and management of Alzheimer's disease patients;
- identification of mild cognitive impairment patients likely to progress to Alzheimer's disease;
- improved management of clinical trials by facilitating better and earlier patient recruitment;
- monitoring of the response to treatment with new disease modifying therapies being developed.

Alzhyme is collaborating to develop a diagnostic tool involving the use of Alzhyme proprietary peptides. Because the Alzhyme peptides bind to a specific site within the human beta-amyloid protein, with the successful radio labeling of the compound, the potential exists for the development of an early diagnostic and imaging test for Alzheimer's disease, using Positron Emission Tomography (PET) imaging techniques. Alzhyme peptides are being developed as a radiopharmaceutical agent to image amyloid deposits in the brains of living patients.

CRC for Mental Health and Testosterone Clinical Trial

Alzhyme joined the McCusker Foundation as one of the founding participants in the successful bid for the CRC for Mental Health, which commenced in July 2011 and was launched in November 2011. The CRC allows researchers from all over Australia to collaborate on two major programs: neurodegeneration and the psychoses. Prof. Martins will head major AD studies in the neurodegeneration program. Alzhyme and the McCusker Alzheimer's Research Foundation will conduct two of the initial research projects related to Novel Therapeutics for AD – Testosterone Trial and Novel Peptide. The CRC is funded for seven years and the institutions involved will receive $23 million of Commonwealth funding in this timeframe.

As part of the CRC for Mental Health, Alzhyme will participate in the major testosterone clinical study commenced in 2013. Prof. Martins' research group will conduct the clinical trial to assess the role of testosterone and DHA in preventing the development of AD in patients with Subjective Memory Complaint (SMC). If the outcome of the study is positive there is the potential to develop and commercialise a combination therapy for the prevention of AD in patients with Subjective Memory Complaint (SMC).

Alzhyme and the McCusker Alzheimer's Research Foundation Inc

Alzhyme is proud to have had a long association with Professor Martins and the McCusker Alzheimer's Research Foundation Inc including having an Access and Option pipeline agreement in place since 2009. This gives Alzhyme a first-right-to acquire and commercialize intellectual property for the treatment and diagnosis of Alzheimer's disease arising out of the Foundation and Alzhyme with a wonderful opportunity to increase its R & D pipeline and reduce development risk.

By establishing such productive partnerships and pursuing an integrated pipeline approach encompassing diagnostic imaging agents and disease-modifying drugs, Alzhyme expects to meaningfully impact the Alzheimer's disease market, and help ease the suffering of millions of patients, creating a future in which Alzheimer's is a treatable disease.

More information can be found at www.alzhyme.com

Jenny Gill
Executive Manager

2013 started in a flurry of activity. In mid-January the Minister for Health Dr Kim Hames launched our Testosterone and Fish Oil study recruitment drive. As a result we had 3000 men register their interest. This will be a worldwide first in terms of combining these substances. The study will run for 56 weeks and has the support of the WA Government and private funding, which is very much appreciated.

The New Year also saw the arrival of our new PET Camera in which the Foundation has an interest. As a result brain imaging can now be more regularly and conveniently undertaken. This has assisted our ongoing AIBL (Australian Imaging, Biomarkers and Lifestyle) Project as it is allowing us to compare brain scans with eye scans in a sub group of AIBL participants, to try and develop a simple diagnostic eye test. The AIBL project is now regarded internationally as a cutting edge project because of the cooperation of our participants as well as the data that is starting to emerge. The purchase was made possible by an innovative partnership between Oceanic Medical Imaging, (a private medical imaging provider) the McCusker Alzheimer's Research Foundation and the estate of the late Dr Jean Murray- Jones. Dr Jean Murray-Jones (1921 – 2009) was a pioneering Western Australian woman, recognised for her strong interest and commitment to improving the health and welfare particularly women.

Sir Cliff Richard, Knight Bachelor, OBE has had personal experience with Alzheimer's disease, his mother, Dorothy, aged 87, died after a decade with Alzheimer's disease. Sir Cliff said by speaking publicly about his mother's battle with Alzheimer's, he is significantly boosting efforts to raise

awareness of this devastating disease. Sir Cliff is a Patron of Alzheimer's Research UK. We were fortunate to be able to attend Sir Cliff's concert held at the Sandalford Winery earlier this year, courtesy of Peter, Debra and Gary Prendiville. The Cliff Richard's Joondalup Support Ladies Group, led by Susan Lynch, have been fundraising throughout the year for the Foundation, and Sir Cliff presented a cheque to His Excellency, Patron of our Foundation. Our sincere thanks go to these wonderful ladies for their ongoing support.

Maggie Beer, Celebrity Cook and food producer, is a strong supporter of the Foundation launching the KARVIAH study in Sydney in 2012. Maggie was very kind to offer her services for two fundraising events in Perth in 2013 – **"Valentine's Day Cocktail with Maggie Beer"** and **"Maggie Beer and 5 Chefs,"** Our sincere thanks for these events go to the Perth Arena, Perth Convention and Exhibition Centre; Deborah Kennedy, Maurizio Di Cino, Michael Tamburri; Musicantes; John Mairiorana; Franklyn Tate; Alain Fabregues; Neal Jackson; Giuseppe Pagliaricci; Chris Taylor; Richard Taylor and all of our supporters.

ECU scientists lead the way on Alzheimer's research – supported by the McCusker Alzheimer's Research Foundation. Research Fellow **Assoc Prof Giuseppe Verdile** has received $536,949 from the National Health and Medical Research Council. A team led by ECU's School of Medical Science Research Fellow, Ass/Prof Giuseppe Verdile has received one of just six grants - and the only one in WA – from the National Health and Medical Research Council (NHMRC) to look at therapies for dementia. Assoc Prof Verdile will conduct the study with co-investigators Dr Michael Lardelli from the University of Adelaide and Dr Matthew Sharman from the University of Tasmania. Assoc Prof Verdile is part of ECU's Neuroscience Research Group, led by the Inaugural Chair in Ageing & Alzheimer's, Professor Ralph Martins. Poscript: In January 2014 Assoc Prof Verdile moved to Curtin University.

Perth Convention Bureau ASPIRE Program
The Perth Convention Bureau, with its major stakeholders, the City of Perth and Tourism WA, annually convenes the Aspire Scholarship and Professional Development Awards. The Awards offer financial support for the professional development of non-profit association members and university staff through attendance at an international conference within their discipline. One of the benefits of International conferences secured by the program is the sharing of substantial knowledge, international profiling and advancement of the state's many sectors of expertise.

Winner: Dr Hamid Sohrabi, Postdoctoral Research Fellow at the School of Medicine at ECU
Dr Hamid Sohrabi is a postdoctoral research fellow in Professor Ralph Martins' laboratory at ECU, investigating different aspects of Alzheimer's disease. This award enabled him to participate in the Alzheimer's Association International Conference (AAIC) in Boston, United States in July last year. Dr Sohrabi is supported in his work by the McCusker Foundation.

Due to the overwhelming success of our Inaugural Golf Day, we held another very successful event again last year at the Royal Perth Golf Club. We are extremely grateful to the Commonwealth Bank of Australia who came on-board as our Naming Sponsors for the second time. We held our Annual Fund Raising Dinner at Maurizio's Restaurant in Fitzgerald Street. VIP Guests included His Excellency Malcolm McCusker, Governor of Western Australia, Dott. Adriano Tedde, Consul of Italy in WA and West Coast Eagles favorite, Dean Cox. We sincerely thank all who contributed to the success of this annual event

The Foundation is extremely grateful for the contributions of the Lions Clubs in Western Australia. Their ongoing support is invaluable to Professor Ralph Martins work. The **Lions McCusker Committee** meet monthly, not only to brain-storm fund-raising options, but also to discuss strategies to spread the work of the Foundation to the community. The Claremont Nedlands Lions Club held their Annual Sportsman's Lunch with part proceeds being donated to the Foundation. Michael Thompson very kindly donated his time as MC for the event, with David Wirrpanda attending as guest speaker.

The community are availing themselves of the **EVERYDAY HERO** website which enables them to spread the word of the Foundation, inspire support and raise money for Alzheimer's research and for this, we thank you all for your most generous support.

National Science Week 2013 Events:
10-17Aug 2013. Researchers set up an information stall to raise awareness in the community of the current medical research in Alzheimer's disease (Science week Launch event, Perth Cultural Centre, 10Aug), they also held a public lecture series entitled "Battling Alzheimer's disease: From Diagnosis to Care and Prevention" followed by tours of the research lab. (ECU, Joondalup campus.)

BOARDS MEMBERS 2013

His Excellency Mr Malcolm McCusker AO CVO QC (Patron)
Mrs Terrie Delroy (Vice Patron)

Mr Enzo Sirna AM (Chairman)
President Italo–Australian Welfare and Cultural Centre

Dr Terry Bayliss (Deputy Chair and Representing Hollywood Private Hospital)
Manager Development Projects and Research, Hollywood Private Hospital.

Mr Rob Davies (Treasurer)
Accountant. Actively involved in fundraising for the Foundation through the Lions Club of Bullcreek and the Lions McCusker partnership.

Professor Ralph Martins AO (Director of Research)
Director of Research, Sir James McCusker Alzheimer's Disease Research Laboratory.

Mr Peter Stevens
Chartered Accountant, former Company Director.

Assoc Prof David Groth (Representative Scientific Advisory Committee)
Biomedical Science Curtin University of Technology.

Mr Ron Bennetts
Former partner of a leading international advisory group; board member of a variety of not for profit organisations; published author in the field of finance, stock market, real estate and financial planning. Chair of the Foundation's finance committee.

Mr Russell Delroy
Managing Director of a boutique resource fund, board member of variety of private companies and not for profit organisations

Ms Deborah Doncon
Extensive experience as a CEO and membership of boards of management.

Ms Jenny Day
Chief Executive Officer of the Community Development Foundation.

Mr Larry Lopez
Partner, Australian Venture Consultants with extensive experience in executive management and membership in public, private and non-profit boards of management

Assoc Prof Giuseppe Verdile (Alternate Director of Research)
Deputy Director of Research, Principal Research Fellow McCusker Alzheimer's Research Foundation.

Ms Jenny Gill
Executive Manager, McCusker Alzheimer's Research Foundation.

Board notes

In accordance with the Constitution, Board sitting fees are not payable to any member. No Board member sought to be reimbursed for any expense incurred on behalf of the Foundation.

Indemnity Insurance

The Foundation has indemnity insurance cover up to $10 million in aggregate to protect funds, board members, staff and volunteers against claims for damage and other legal actions.

McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC

FINANCIAL REPORT

FOR THE YEAR ENDING DECEMBER 31, 2013

McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC

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McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC

BALANCE SHEET

31 December, 2013

		2013 $	2012 $
CURRENT ASSETS			
Cash on Hand		3,601	993
Cash at Bank	(Note 2)	2,074,016	2,339,011
Receivables		124,919	119,454
Work in Progress		45,000	-
Other Receivables		22,056	54,205
Investment – Shares at Cost	(Note 4)	1,341,346	1,360,853
TOTAL CURRENT ASSETS		3,610,938	3,874,516
NON CURRENT ASSETS			
Property, Plant & Equipment	(Note 3)	3,855,997	3,528,661
Loans - Other		-	95,583
TOTAL NON-CURRENT ASSETS		3,855,997	3,503,324
TOTAL ASSETS		7,466,935	7,498,760
CURRENT LIABILITIES			
Trade Creditors & Accruals	(Note 5)	566,233	439,795
Unexpended Capital Grant		2,265,405	2,175,713
Other Creditors		9,594	4,629
Provision for Employee Leave Entitlements		36,627	28,004
TOTAL CURENT LIABILITIES		2,877,859	2,648,141
LONG TERM LIABILITIES			
Provision for Employee Leave Entitlements		33,165	23,171
Loan		50,000	50,000
TOTAL LONG TERM LIABILITIES		83,165	73,171
TOTAL LIABILITIES		2,961,024	2,721,312
NET ASSETS		**$ 4,505,911**	**$ 4,777,448**
EQUITY			
Endowment Reserve		2,000,000	2,000,000
Capital Reserve		2,404,841	2,404,841
Retained Earnings		101,070	372,607
TOTAL EQUITY		**$ 4,505,911**	**$ 4,777,448**

McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC

STATEMENT OF INCOME AND EXPENDITURE

For The Year Ended December 31, 2013

		2013 $	2012 $
Total Income		2,703,994	2,001,469
Total Expenditure		(2,975,531)	(2,454,945)
Net Operating Loss		(271,537)	(453,476)
Income Tax Expense	(Note 1d)	-	-
Loss From Ordinary Activities After Income Tax Expense		(271,537)	(453,476)
Retained Earnings at Beginning of Year		372,607	826,083
Retained Earnings at 31 December, 2013		**$ 101,070**	**$ 372,607**

McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC

DETAILED PROFIT & LOSS STATEMENT

For The Year Ended 31 December, 2013

	2013 $	2012 $
INCOME		
Conference Registration	-	15,855
Grants	3,035,624	2,144,049
Donations	570,426	1,295,440
Fundraising & Events	68,457	46,422
Lions Club of WA	40,228	79,280
Interest	81,458	97,525
Investment Income	383,060	89,519
Sundry Income	835	9,099
Clinical Trials Income	789,311	399,993
Unexpended Grant Income C/Fwd	(2,265,405)	(2,175,713)
TOTAL INCOME	**2,703,994**	**2,001,469**
EXPENSES		
Accounting	33,438	25,093
Audit Fees	3,840	3,600
Advertising & Media	28,905	34,503
Bank Fees	2,878	3,596
Cleaning	11,429	10,934
Computer / Internet Expenses	12,439	25,646
Consulting Fees – Medical	934,725	892,485
Courier & Freight	2,922	720
Depreciation	267,323	135,643
Donations	4,000	-
Equipment Purchases	25,094	-
Fundraising	4,375	17,502
Hire / Lease of Equipment	3,271	12,151
Insurance	51,123	59,036
Investment Management Fees	3,752	-
Legal Fees	22,505	4,992
Medical Procedures & Supplies	300,880	56,776
Office Equipment & Expenses	24,843	12,443
Patient Amenities & Travel Reimbursement	21,536	43,997
Postage, Printing & Stationery	64,992	62,544
Professional Services	25,125	141,936
Rates, Strata Fees & Land Tax	14,358	14,762
Rent & Outgoings	72,507	32,256
Repairs & Maintenance	25,342	11,863
Research	79,761	28,702
Salaries & Wages	788,832	559,112
Scholarships	6,300	30,620
Security	7,237	-
Staff Amenities	6,400	9,007
Staff Training	1,617	9,440

McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC

DETAILED PROFIT & LOSS STATEMENT

For The Year Ended 31 December, 2013

	2013 $	2012 $
Subscriptions	4,096	-
Superannuation	70,630	59,547
Sundry Expenses	3,621	15,272
Telephone	23,519	16,560
Travel & Accommodation	2,263	102,720
Utilities – Electricity & Water Charges	19,647	18,487
TOTAL EXPENSES	**2,975,531**	**2,454,945**
OPERATING LOSS	**($ 271,537)**	**($ 453,476)**

McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC

Notes To and Forming Part of the Financial Statements For The Year Ended 31 December, 2013

1. Statement of Significant Accounting Policies

The Board has prepared the financial statements on the basis that the McCusker Foundation for Alzheimer's Disease Research Inc (the "Foundation") is a non-reporting entity because there are no users who are dependant on its general purpose financial reports. This is a special purpose financial report prepared in order to satisfy the financial reporting requirements of the *Associations Incorporation Act WA (1987).*

The financial statements have been prepared in accordance with the mandatory Australian Accounting Standards applicable to entities reporting under the *Associations Incorporatiuon Act (1987*) and the significant accounting policies disclosed below, which the Board have determined are appropriate to meet the needs of members. Such accounting policies are consistent with the previous period unless stated otherwise.

The financial statements have been prepared on an accruals basis and are based on historical costs unless otherwise stated in the notes. The accounting policies that have been adopted in the preparation of the financial report are as follows :

(a) **Incorporation and Constitution**

The Foundation was incorporated in accordance with the provisions of the Associations Incorporation Act 1987 (section 9(1) on January 27, 2000.).Registration No A1005460A. The Constitution was finalised by way of special resolution and came into effect as from November 21, 2001- Document No 954353/15962552.

(b) **Donations and Fundraising Income**

Donations and fundraising monies received, by their nature can be recognised only when they are recorded in the books. Such items as donations are brought to account on a cash basis or where they are received other than in cash, when ownership passes to the Foundation.

(c) **Cash**

Cash for the purposes of the Balance Sheet includes cash on hand, at bank and deposit.

(d) **Taxation**

The Foundation is registered with the Australian Taxation Office (ATO) for both Australian Business Number (ABN) and Goods and Services Tax (GST). Registration ABN: 34 575 647 667

The Foundation is exempt from income tax under the provision of sub-division 50.B of the Income Tax Assessment Act 1997 as amended.

As the Foundation is for public benevolent and non-profit making the ATO allows any donations over $2.00 as tax deductible. This was by way of endorsement as a Deductible Gift Recipient (DGR) under subdivision 30.BA of the Income Tax Assessment Act 1907.

Notes To and Forming Part of the Financial Statements For The Year Ended 31 December, 2013 (continued)

(e) **Non Current Assets and Depreciation**

Office equipment is carried at cost, less, where applicable, any accumulated depreciation. The depreciable amount of all fixed assets is depreciated over the useful loves of the assets to the Association commencing from the time the asset is held ready for use.
All assets are depreciated over their useful lives to the Foundation commencing from the time the asset is held ready for use.

The depreciation rates used for each class of depreciable assets are:

Class of Fixed Asset	Depreciation Rate
Equipment	20%
Computer Equipment	30%

(f) **Impairment of Assets**

At each reporting date, the Board reviews the carrying values of the Foundation assets to determine whether there is any indication of that those assets have been impaired. Impairment losses are recognised in the Income Statement.

(g) **Employee Benefits**

Provision is made for the Foundation's liability for employee benefits arising from services rendered by employees up to balance date. Employee benefits expected to be settled within one year together with benefits arising from wages, salaries and annual leave which may be settled after one year , have been measured at the amounts expected to be paid when the liability is settled plus related on costs.

Contributions are made by the Foundation to an employee superannuation fund and are charged as expenses when incurred.

(h) **Goods & Services Tax (GST)**

Revenues, expenses and assets are recognised net of the amount of GST, except where the amount of GST incurred is not recoverable from the Australian Taxation Office. In these circumstances the GST is recognised as part of the cost of acquisition of the asset, or as a part of an item of expense. Receivables and payables in the Balance Sheet are shown inclusive of GST.

(i) **Going Concern**

The financial statements have been prepared on a going concern basis. The Foundation is dependant upon continuation of donations and fundraising income, for the pursuit of its objectives.

Notes To and Forming Part of the Financial Statements For The Year Ended 31 December, 2013 (continued)

	2013 $	2012 $
2. Cash at Bank		
Business Cheque Accounts		
- Commonwealth - Admin	340,405	297,363
- Commonwealth - Grants	169,365	701,504
- NAB	31	15,564
- NAB Clinical Trials	61,011	61,792
- NAB Other	28	121
- Other	3,176	151
Term Deposits		
- Commonwealth Bank	1,150,000	409,890
- Macquarie	350,000	852,626
	$ 2,074,016	**$ 2,339,011**
3. Plant and Equipment		
Land & Buildings at Cost		
- Suite 22, Hollywood Medical Centre	1,015,107	1,015,107
- Unit 2, 142 Stirling Highway	1,865,720	1,865,720
	2,880,827	2,880,827
Research Equipment at Cost	1,897,831	1,309,348
Less Accumulated Depreciation	(961,847)	(697,869)
	935,984	611,479
Office & Computer Equipment at Cost	45,075	59,065
Less Accumulated Depreciation	(33,118)	(32,702)
	11,957	26,363
Furniture and Fittings at Cost	40,724	18,782
Less Accumulated Depreciation	(13,495)	(8,759)
	27,229	9,993
	$ 3,855,997	**$ 3,528,661**

McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC

Notes To and Forming Part of the Financial Statements For The Year Ended 31 December, 2013 (continued)

4. Investments	2013 $	2012 $
Morgan Stanley Portfolio Account - Investment in listed Shares and Trusts at cost	**$ 1,341,346**	**$ 1,360,853**

The market value of investments held at **31 December, 2013 was $1,499,569**

The market value of investments held at **21 March, 2014 was $1,480,281**

5. Payables

Current		
Creditors	546,544	426,595
Accruals	19,689	13,200
Unexpended Capital Grant	2,265,405	2,175,713
Aust Taxation Office - PAYG Witholding	9,594	4,629
Employee Holiday Pay Provision	36,627	28,004
	$ 2,877,859	**$ 2,648,141**
Non Current		
Loan – Unsecured, Non Interest Bearing	50,000	50,000
Employee Long Service Leave Provision	33,165	23,171
	$ 83,165	**$ 73,171**

6. Contingencies

The Foundation has no known contingent liabilities or capital commitments at reporting date.

7. Events Occurring After Balance Date

There has been no material or significant events subsequent to 31 December, 2013 which have materially affected the operations or the financial position of the Foundation.

McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC

STATEMENT BY MEMBERS OF THE COMMITTEE

The Committee has determined that the Foundation is not a reporting entity and that this special purpose financial report should be prepared in accordance with the accounting policies outlined in Note 1 to the financial statements.

In the opinion of the Committee, the financial report:

(a) Presents a true and fair view of the financial position of the McCusker Alzheimer's Research Foundation Inc. at 31 December, 2013 and its performance for the year ended on that date; and

(b) At the date of this statement there are reasonable grounds to believe that the McCusker Alzheimer's Research Foundation Inc will be able to pay its debts as and when they fall due.

This statement is made in accordance with a resolution of the Committee and is signed for and on behalf of the Board by:

Enzo Sirna
Chairman

Jenny Gill
Executive Manager

Dated : 8th April, 2014

INDEPENDENT AUDIT REPORT

TO THE MEMBERS OF THE

McCUSKER ALZHEIMER'S RESEARCH FOUNDATION INC.

Report on the Financial Report

I have audited the accompanying financial report, being a special purpose financial report, of the McCusker Alzheimer's Research Foundation Inc.("the Foundation") which comprises the balance sheet as at 31 December, 2013, the income statement, and detailed income & expenditure statement for the year then ended, a summary of significant accounting policies, other explanatory notes and the statement by members of the committee.

Committee's Responsibility for the Financial Report

The committee of the Foundation is responsible for the preparation and fair presentation of the financial report and have determined that the accounting policies described in Note 1 to the financial statements, which form part of the financial report, are appropriate to meet the requirements of the *Associations Incorporation Act (WA) 1987*, and are appropriate to meet the needs of the members. The committee's responsibilities also include designing, implementing and maintaining internal control relevant to the preparation and fair presentation of the financial report that is free from material misstatement, whether due to fraud or error; selecting and applying appropriate accounting policies; and making accounting estimates that are reasonable in the circumstances.

Auditor's Responsibility

My responsibility is to express an opinion on the financial report based on my audit. No opinion is expressed as to whether the accounting policies used, as described in Note 1, are appropriate to meet the needs of the members. I conducted my audit in accordance with Australian Auditing Standards. These Auditing Standards require that I comply with relevant ethical requirements relating to audit engagements and plan and perform the audit to obtain reasonable assurance whether the financial report is free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial report. The procedures selected depend on the auditor's judgement, including the assessment of the risks of material misstatement of the financial report, whether due to fraud or error. In making those risk assessments, the auditor considers internal control relevant to the entity's preparation and fair presentation of the financial report in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of accounting estimates made by the trustees, as well as evaluating the overall presentation of the financial report.

The financial report has been prepared for distribution to members for the purpose of fulfilling the committee's financial reporting obligations under the *Associations Incorporation Act (WA) 1987*. I disclaim any assumption of responsibility for any reliance on this report or on the financial report to which it relates to any person other than the members, or for any purpose other than for which it was prepared.

Liability limited by a scheme approved under Professional Standards Legislation
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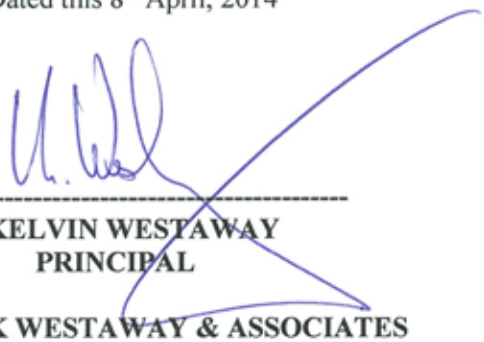
Kelvin Westaway

The audit opinion expressed in this report has been formed on the above basis. I believe the audit evidence I have obtained during the conduct of my audit is sufficient and appropriate to provide a basis for my audit opinion.

Auditor's Opinion

In my opinion, the attached financial report presents fairly, in all material respects the financial position of the McCusker Alzheimer's Research Foundation Inc as at 31 December, 2013 and of its financial performance for the year then ended in accordance with the accounting policies described in Note 1 to the financial statements.

Dated this 8th April, 2014



KELVIN WESTAWAY
PRINCIPAL

K WESTAWAY & ASSOCIATES
REGISTERED COMPANY AUDITOR

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