Neurodegenerative disease and metals: Case Study

Neurodegenerative diseases such as Alzheimer's, Motor Neurone and Parkinson's disease affect millions of people around the world and place an enormous burden on the Australian healthcare system. Researchers from The Florey Institute of Neuroscience and Mental Health (The Florey), The University of Melbourne and QIMR Berghofer Medical Research Institute have undertaken long-term investigations into how metal ions may impact these diseases and are trialling treatments that could delay their progression.

Origin

The formation of abnormal proteins in the brain was long suspected to be a contributor to the development of neurodegenerative diseases. Although these abnormal protein formations are frequently seen in people diagnosed with neurodegenerative diseases such as Alzheimer's disease, many individuals with abnormal protein formations do not go on to develop such conditions.

As a PhD student in Melbourne in 1989, Professor Ashley Bush became interested in dementia diagnosis and treatment while also working as a mental health clinician. An early discovery made by Bush was that the major forms of protein found in Alzheimer's disease are influenced by interactions with metal ions such as iron, copper and zinc.

In the mid-2000s another long-time researcher of the role of metal ions in neurodegenerative diseases, Associate Professor (A/Prof) Anthony White and his colleagues demonstrated that certain organic molecules had the potential to redistribute copper within the brain. He teamed up with A/Prof Kevin Barnham, Professor Paul Donnelly and A/Prof Peter Crouch to investigate the therapeutic potential of this approach to treat various neurodegenerative diseases.

'It has always been a mystery with Alzheimer's as to why everyone with the disease has got amyloid in the brain but not everyone with amyloid has Alzheimer's disease'

Professor Ashley Bush

Grants and Investments

NHMRC
NHMRC and its National Institute for Dementia Research have supported the following researchers to study the role of metal ions in neurodegenerative disease. Support has been provided through a range of Project, Program and Development Grants, and also individual fellowships as listed below:

Professor Ashley Bush:

- Medical Postgraduate Scholarship, 1989
- Research Fellowships, 2001, 2011 and 2016
- Australia Fellowship, 2011.

Associate Professor Anthony White:

- Career Development Fellowship, 2004.

Associate Professor Kevin Barnham:

- Career Development Fellowship, 2003
- Research Fellowships, 2006 and 2011.

Associate Professor Peter Crouch:

- Career Development Fellowship, 2015.

Dr Scott Ayton:

- NHMRC – ARC Dementia Research Development Fellowship, 2016
- Career Development Fellowship, 2020.

Other Grants and Investments
Work on metal ions by these researchers has also received funding from a wide range of public and private sources, including a Betty Laidlaw Motor Neuron Disease (MND) Research Grant to A/Prof Crouch. Prof Bush is co-principal investigator on a National Institutes of Health (NIH) grant to study the impact of brain metal burden on dementias.

Commercialisation

Professor Bush and A/Prof Barnham are long-term collaborators at The University of Melbourne/ The Florey, a collaboration made possible by NHMRC Program Grants and other funding since 1999. In 1997, Bush co-founded Prana Biotech (now Alterity). The company was listed on the ASX in 2000 and the NASDAQ in 2002. Barnham helped invent drugs for the company for the treatment of Alzheimer's disease. Prana/Alterity continues to develop first-in-class therapies to treat neurodegenerative diseases.

In research begun in 2005, findings from Barnham, Donnelly and White allowed them to patent the use of CuATSM, a synthetic molecule that contains copper, for the treatment of neurodegenerative disease. In 2013, Collaborative Medicinal Development (CMD), a privately held United States (US)/Australian biopharmaceutical company, licensed the patent from The University of Melbourne. Bush is Chairman of the Scientific Advisory Board of CMD, whose external advisors include Crouch, Barnham and Donnelly, among others. CMD has begun progressing the use of the molecule to human trials and has recently reported promising benefits in the treatment of MND and Parkinson's disease (PD).

Bush, Ayton and colleagues have a broad and deep collaborative network, including on the 'ADIRON Study', whose iron imaging discovery was made possible using technology developed by CSIRO and with funding from the Cooperative Research Centre for Mental Health.

Trials and Results

Deferiprone to Delay Dementia (The 3D Study)
New research by Bush, Ayton and colleagues from The Florey has found that iron build up in the brain might contribute to Alzheimer's disease. A Phase II trial of the anti-iron drug Deferiprone in a cohort of Alzheimer's patients is underway to test whether conservatively lowering brain iron slows or stops deterioration in the disease.

ADIRON Study
Bush, Ayton and colleagues are developing new imaging tests that assess levels of iron in the brain, which have been found to indicate the rate of deterioration caused by Alzheimer's disease.

PBT434 study (through Prana/Alterity)
There is no known treatment for slowing disease progression in Multiple System Atrophy (MSA) or Progressive Supranuclear Palsy (PSP). The molecule PBT434 targets iron build-up in the affected brain regions and shows protective benefits in animal models of these diseases. Prana/Alterity began a Phase I clinical trial of PBT434 in mid-2018 to ascertain the optimal drug dose. A further study of patients with MSA and PSP is planned. In early 2019, the US Food and Drug Administration (FDA) granted Orphan Drug designation to PBT434 for the treatment of MSA.

MND and PD trials
Barnham, White, Donnelly and Crouch developed and tested CuATSM over a 15-year period. The Florey, The University of Melbourne and Bio21 Institute, in conjunction with CMD, have tested the potential of the CuATSM molecule to treat MND and PD in Phase I trials. Data from both trials revealed promising benefits. Phase II trials have now commenced.

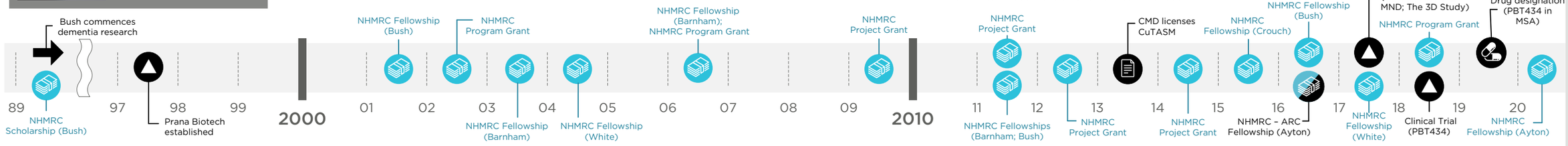
Outcomes and Impact

Research funded by NHMRC, and undertaken by The Florey, The University of Melbourne and QIMR Berghofer, has significantly increased our understanding of neurodegenerative diseases. This research is internationally recognised as ground breaking and has influenced the research programs of a new generation of researchers.

This research is leading the way to the development of screening tests for Alzheimer's that can be undertaken in middle age, and new drug approaches being actively tested in proof-of-principle clinical trials.

CuATSM has been repurposed as a drug by scientists at The Florey and the School of Chemistry and Bio21 Institute at The University of Melbourne and has shown promise as the first disease modifying treatment for MND and PD.

Application of these research findings could improve the quality of life of Australians with Alzheimer's disease, MND, PD and other neurological disorders, and relieve the substantial economic and personal costs of these diseases.



Professor Ashley Bush

Ashley Bush is Professor of Neuroscience at The University of Melbourne and Director of the Melbourne Dementia Research Centre at The Florey. He is Co-Director of Biomarker Development for The Australian Imaging, Biomarkers and Lifestyle Study of Ageing. Professor Bush has authored over 450 publications and 29 patents, and is rated in the top 1% of neuroscience researchers in the world for high impact citations.

A/Prof Kevin Barnham

A/Prof Barnham is associated with The Florey, and the Department of Pharmacology and Therapeutics at The University of Melbourne. He is the Head of the Neurotherapeutics Laboratory at The Florey and a scientific advisor for CMD and Prana/Alterity. His work focuses on investigating diseases such as Alzheimer's, Parkinson's and Motor Neurone Disease. He holds a PhD in bioinorganic chemistry from the University of Queensland.

A/Prof Anthony White

Associate Professor White is an NHMRC Senior Research Fellow and group leader of The Cellular and Molecular Neurodegeneration Laboratory at the QIMR Berghofer. He and his research group investigate the cellular processes of neurodegenerative diseases and the potential treatment of these disorders. He completed post-doctoral research at Imperial College, London and worked at The University of Melbourne from 2003-2016. He has obtained over $10 million in competitive research funding and co-founded a start-up biotech company, Procypra Therapeutics.

A/Prof Peter Crouch

Peter Crouch is Associate Professor and Laboratory Head in the Department of Pharmacology and Therapeutics at The University of Melbourne. He heads the Neurodegenerative Disease Laboratory at The University of Melbourne, which researches potential new therapeutics. He is an expert on MND and a scientific advisor on the biology of neurodegenerative diseases for CMD. A/Prof Crouch received his PhD from La Trobe University in 2002.

Dr Scott Ayton

Dr Scott Ayton is an NHMRC Career Development Fellow, Head of the Translational Neurodegeneration laboratory, and Deputy Director of the Melbourne Dementia Research Centre at The Florey. He completed his PhD at The University of Melbourne in 2012. Dr Ayton's research encompasses both laboratory and clinical research relating to neurodegenerative diseases such as Alzheimer's and Parkinson's diseases in order to investigate mechanisms, discover biomarkers, and develop therapeutics. He has a particular interest in iron neurochemistry and the cell death pathway called ferroptosis.

Professor Paul Donnelly

Paul Donnelly is a Professor in the School of Chemistry at The University of Melbourne, where he heads the Donnelly Group at the Bio21 Molecular Science and Biotechnology Institute. He completed his PhD at The University of Western Australia and was previously a post-doctoral Junior Research Fellow at the University of Oxford. His group's research focuses on the application of synthetic inorganic chemistry to biology as well as investigating the role of metal ions in biology.

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