

Alzheimer's disease **RESEARCH**



Assoc Prof John Kwok



NeuRA (Neuroscience Research Australia) is one of the largest independent medical and clinical research institutes in Australia and an international leader in neurological research.

Diseases of the brain and nervous system pose the greatest health, economic and social burden of any disease group because they are chronic, debilitating and have no known cures.

Medical research is the cornerstone of efforts to advance the health and wellbeing of families and the community. Our dedicated scientists are focussed on transforming their research into significant and practical benefits for all patients.

WHAT WE KNOW ABOUT ALZHEIMER'S DISEASE The hallmarks of Alzheimer's disease are seen in the brains of affected people. There are distinctive deposits of an abnormal form of a protein in the space between brain cells called plaques. Research around the world is focussed on understanding how these plaques are formed, how they injure brain cells, and the formulation of drugs that delay or reverse plaque formation.

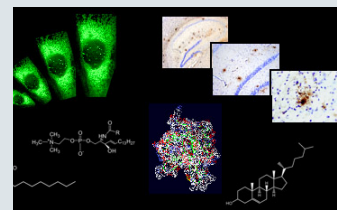
ABOUT OUR RESEARCH Our genetic code is made up of combinations of letters, 'G' 'A' 'T' and 'C'. Small variations in the 'spelling' of the DNA code underpin the variation in our genes that play an important role in whether we develop neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Our research aims to identify the mutations or 'misspelling' of the cause and susceptibility of Alzheimer's genes and understand mechanisms by which genetic alterations in these genes can lead to disease.

WHAT WE HAVE DISCOVERED
Environmental effects on Alzheimer's disease.

Our susceptibility to Alzheimer's disease is a combination of genes and environment and there is a list of genes that contribute to increased risk. There is increasing knowledge of how we can modify inherited risk including a diet rich in dark green vegetables, regular exercise and an active mind. We have discovered that two genes, GSK3B and MAPT, act together to control crucial processes in the cell in order for it to stay alive. Genetic alterations interact to increase the risk for late-onset Alzheimer's disease.

At least one lifestyle factor, cigarette smoking, has a significant effect on how the genes interact. We believe smoking exerts its effect through the "epigenome" which can be considered the way in which the environment can change the way a gene expresses itself. The epigenome acts as 'accents' in our genetic code, modifying the way the four letters are pronounced. The epigenome is an important phenomenon, as it allows us to affect our genes by altering our lifestyle, even if we can't change the genetic code itself.

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CURRENT PROJECT: PROGRESS IN ALZHEIMER'S DISEASE RESEARCH – RARE GENETIC CHANGES SHOW THE WAY

Despite major progress over the last thirty years, we still do not have a drug to stop or slow down the Alzheimer's disease process in the brain. But have we been starting treatment too late, in effect shutting the stable door after the horse has bolted?

For the last five years, NeuRA researchers have been part of an international study called DIAN – the Dominantly Inherited Alzheimer Network. DIAN participants are a very special group. They belong to families where Alzheimer's disease is inherited because of a causative genetic mutation: the children of an affected parent have a 50-50 chance of inheriting the gene and hence developing the disease, usually quite young, between their early thirties and mid-fifties.

DIAN showed that the beginnings of the disease process can be seen in brain PET scans and spinal fluid measures 15 to 20 years before people would develop symptoms. These results were published in a landmark paper in The New England Journal of Medicine in 2012. Australia is a small country in population terms but 82 of the more than 300 participants in DIAN world-wide are Australian, including 28 participants from NeuRA.

The PET scans found amyloid deposits beginning to accumulate in the brains of people carrying the family genetic mutation at least 20 years before the age that their parent had developed symptoms. The scans of their brothers and sisters who did not carry a mutation had no amyloid deposition. Similarly, spinal fluid studies showed increasing amounts of a protein called tau in the spinal fluid of mutation carriers, beginning about 15 years before symptom onset age. The next step in our research is to use these indicators of disease activity, or biomarkers, to measure the effect of drug treatment aimed at preventing or slowing the Alzheimer's disease process before it causes symptoms. Clinical trials have already begun in the USA and NeuRA is on track to join these trials in mid-2014.

If these drug treatments are shown to prevent symptoms in people with the genetic form of Alzheimer's disease, they should also be applicable in the wider community. The families with this rare disease are giving hope not only to their own descendants, but to us all!

CURRENT PROJECT: DO LIFESTYLE FACTORS PROVIDE PROTECTION?

Models that carry mutant versions of the presenilin or amyloid precursor protein genes develop deficits in their memory and the hallmark amyloid plaques in their brains as they age. Dr Tim Karl is using these mouse models to test several lifestyle factors, such as exercise and mental stimulation, that may be protective against Alzheimer's disease. Dr Karl will provide mice with exercise wheels, or more toys to stimulate their minds, and then observing whether these mice are less likely to develop features of Alzheimer's disease.

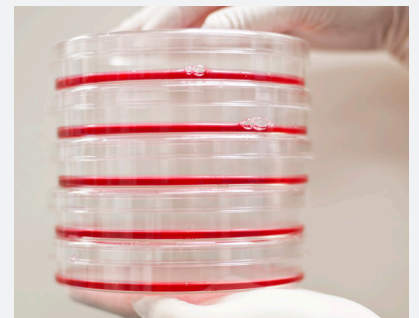
CURRENT PROJECT: NEW TREATMENTS IN THE PIPELINE

We have identified a molecular pathway controlled by the SIGMAR1 gene, which may be important in the movement of molecules within a cell. When not functioning properly, the gene can alter key biochemical pathways involved in Alzheimer's disease and other neurodegenerative disorders. We have identified a panel of drugs that act on the SIGMAR1 gene product and which are currently being used in clinical practice to treat other disorders besides Alzheimer's disease. We will test each one of these compounds to determine which of them result in significant improvement of the treated animal models. As these compounds are already approved by the governing bodies for use in humans, we can rapidly move to the next stage of clinical trials without costly pre-clinical testing.

CURRENT PROJECT: RISK AND PROTECTIVE FACTORS IN OLDER ABORIGINAL POPULATIONS

Indigenous Australians have a marked lower life expectancy than the general population with increased heart related diseases, obesity, smoking and physical inactivity, all which contribute to their increased risk of dementia. A project run by Prof Tony Broe, examines our current knowledge about risk and protective factors and for cognitive growth and cognitive impairment and decline in the older Aboriginal population. The specific aims of the project will be to examine the burden of dementia in Aboriginal people 45 years and over in urban and rural communities, their needs within the communities and current systems of care and support.

While we hope you find this brochure useful, it is always important to discuss any questions about Alzheimer's disease or its treatment with your doctor or other health care provider.



HOW YOUR SUPPORT HELPS

We are able to make significant advances due to the dedication and generosity of countless people who come to NeuRA every day - research participants, families, carers and supporters. Your donation or bequest will play a key role in allowing us to continue to work towards transforming the lives of all Australians through medical breakthroughs. For further information on how you can support our research phone 1300 888 019 or make a secure donation at neura.edu.au/donate.



NeuRA
Discover. Conquer. Cure.