FIGHT MND.

A/Prof Anthony White

Researcher.
A/PROF ANTHONY WHITE

IMPACT Project.
PATIENT MONOCYTE-DERIVED MICROGLIA FOR PRECISION TREATMENT OF NEUROINFLAMMATION IN MND

Where do you work?

QIMR Berghofer Medical Research Institute, Queensland.

Can you summarise your research experience and background?

I have spent more than twenty years researching degenerative diseases of the brain, including motor neuron disease, and dementia. My research has focused on understanding the underlying disease pathways and developing potential therapeutic treatments for these diseases. This has included research experience at University of Melbourne, and Imperial College of Medicine in the UK. Now, much of my research is done in close collaboration with researchers in Finland and Italy.

What has been your favourite scientific finding so far?

My favourite and most important scientific finding was when my research team demonstrated the therapeutic potential of copper-delivery agents that were developed in collaboration with Profs. Paul Donnelly and Kevin Barnham, University of Melbourne. This led to the development of copper-ATSM, which is now in clinical trials for MND.

What is the current focus of your research laboratory?

We are now developing new human, and patient-focused cell models of MND and dementia. These are urgently needed to improve drug targeting, especially to individual patients, and improving the success of drug translation into the clinic.

How did you identify that monocyte-derived microglia could be beneficial for developing new treatments for MND?

Once we had developed the model system through a lot of great work by Dr Hazel Quek in my group, we already had a strong collaboration with Prof. Vincenzo La Bella in Italy, who heads an ALS research centre in Palermo. We were both very excited at the prospect of examining microglia generated from people with MND/ALS and were able to achieve this through the collaboration. We didn't know what to expect, but the initial experiments identified key changes in the function of the microglia from people with ALS.

What excites you about this approach to developing new treatments?

This is really the best approach available to characterise the differences between MND/ALS patient microglia and matched controls in a time and cost-effective model. It also will allow a clinically applicable approach to testing new and re-purposed drugs, and allow us to determine if there are patient-to-patient differences in drug action. This patient-oriented approach cannot be achieved on a suitable scale with any other system at present.

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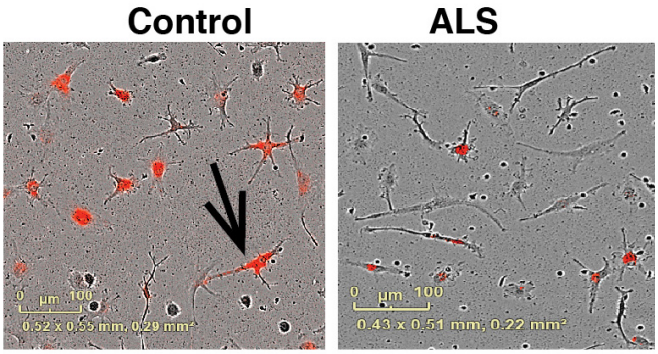
What will this funding allow you to achieve?

The funding will be an extraordinary boost for us and we are very excited to receive this wonderful support from FightMND. The funds will allow us to gain a strong insight into how microglia differ between people with MND and healthy controls, and identify patient-specific changes that can be targeted. We will also be able to set up a drug screening platform to search for new and re-purposed drugs to target individual patients. This will put us in a great position to boost clinical translation of drugs for treatment of MND.



The difference between phagocytosis (uptake of red particles) in MND/ALS microglia compared to control.

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We are developing a unique assay platform that will allow, for the first time, the testing of immune-modulating drugs on individual patient brain immune cells (called microglia). Microglia provide the main form of immune defence in the brain, and their function is compromised in MND. A major issue in developing new drugs for treating MND is the diverse nature of the disease course and the individual patient genetic background and lifestyle. These factors have a major influence on how the immune system, including microglia, acts in each person. This diversity has contributed to the failure of many drugs in clinical trials designed to normalise microglia function in MND.

To overcome this problem and provide better outcomes for people with MND, we need a lab-based test that allows us to examine drug effects on each person's own microglia in a rapid and reproducible manner.

Our advanced cell-based platform will allow drugs to be tested for efficacy on individual patients, and allow real-time monitoring of drug efficacy across the disease course and during clinical trials. The approach will help select appropriate patients for clinical trials of new drugs, avoiding unnecessary treatment of people who are less likely to benefit, and enabling these patients to be involved in alternative treatment options. Our platform is generated using microglia grown from human peripheral blood monocytes. This approach is highly cost-effective and rapid compared to other methods for preparing human microglia. These microglial cells can be screened with different drugs to enhance their protective functions, allowing us to determine which drugs will likely benefit each patient.

OBJECTIVE:

- Demonstrate that microglia from MND patients can be used to screen for potential inflammatory modulating compounds in 'real-time', and personalise MND treatment.

OUTCOMES:

- Devise a rapid and cost-effective patient-specific drug targeting scheme to normalise immune cells in MND patients.
- Using microglia from MND patients, identify patients best suited for clinical trials of newly developed drugs aimed at normalising the function of immune cells in the brain.