FIGHT MND.

Researcher.
A/PROF JOSEPH NICOLAZZO

IMPACT Project.
CHARACTERISING BLOOD-BRAIN BARRIER DYNAMICS TO ENHANCE DRUG DELIVERY AND OPTIMISE MEDICINE USE IN MND


A/Prof Joseph Nicolazzo

Where do you work?

I am an Associate Professor and Associate Dean, Graduate Research, at the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, and a researcher at Monash Institute of Pharmaceutical Sciences.

What is your research experience and background?

I trained as a pharmacist and have always been interested in how drugs accessed different parts of the body. My PhD focused on how drugs could be absorbed across the buccal mucosa as an alternative route to oral drug delivery, a research area in which I am still active. My current major research interest, however, is understanding how drugs and endogenous agents are trafficked across the blood-brain barrier (BBB) and how this alters in neurodegenerative diseases - a better appreciation of these phenomena will assist in identifying approaches to more effectively deliver drugs to their site of action in the brain, given the restrictive nature of the BBB in preventing drug access to the central nervous system.

How did you come to work in MND research?

In my BBB research program, I have mainly focused on Alzheimer's disease. In 2018, I was invited to present my findings on the BBB in Alzheimer's disease at the Australasian MND Symposium. I was not only taken by the enthusiasm of the MND research community, but I was particularly touched by the number of individuals with MND at the symposium rightly advocating for more research to cure this disease. I felt that applying my BBB experience to MND could therefore benefit the many individuals with MND by accelerating the drug development process for MND therapeutics.

Can you describe the research your team is currently pursuing?

My research focuses on identifying how the trafficking of drugs across the BBB alters in neurodegenerative disease, particularly Alzheimer's disease and now MND. In this research project, we will use both mouse models of MND and stem-cell based BBB models to assess whether the levels of drug transporters are altered in MND and whether this leads to altered brain uptake of drugs and naturally-occurring molecules.

How can the blood-brain barrier be used to improve MND treatments?

By understanding if BBB drug transporters and drug access to the brain are altered in MND, we will be able to identify approaches that may be exploited to enhance brain access of drugs in MND. One of the major barriers to the clinical success of potential therapeutics for brain diseases is their inability to cross the BBB. By identifying which BBB drug transporters are increased, we can design drugs or delivery vectors to overcome the restrictive nature of the BBB and improve the potential for new drugs to reach their site of action within the brain.

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What excites you about induced-pluripotent stem cell models?

The ability to develop a BBB model based on stem cells derived from individuals with MND means we can, for the first time, recapitulate a biological barrier present in individuals with MND. This should enhance the translation of results obtained in the laboratory and accelerate the application of our drug delivery approaches into the clinical domain.

How will this funding impact on your work?

This funding will really allow our research group to extend the knowledge we have gained on the BBB in Alzheimer's disease to MND, another major neurodegenerative disease. I strongly believe that, due to the funding provided by FightMND, we can identify novel ways to target therapeutics to the brain, overcoming one of the major barriers in central nervous system drug development. This will ultimately bring us one step closer to a therapeutic solution for MND.

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In order for any potential therapeutic for MND to exert its disease-modifying effect, it needs to reach the brain. However, the ability of a drug to cross from the bloodstream into the brain is extremely low given the presence of a protective lining between the blood and brain; the blood-brain barrier (BBB). Based on what is known about the healthy BBB, researchers attempt to trick shuttles present on the BBB to carry drugs across the BBB; this has not resulted in success to date as the levels of such BBB shuttles are likely to be modified in MND, as they are in other brain diseases, altering drug uptake capacity and questioning the utility of these targeting approaches.

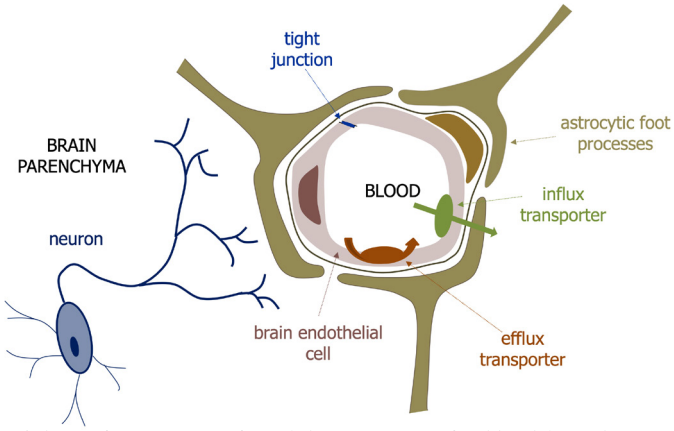
Altered brain uptake of drugs is also a concern for the multiple medicines that individuals with MND are prescribed for other conditions, which may place them at a greater risk of drug-induced brain toxicity. Knowing changes to altered brain dynamics in advance can lead to tailoring of the dosages of these non-MND medicines to minimise their potential for brain toxicity. Therefore, this IMPACT project will lead to approaches that increase the brain uptake of drugs intended to treat MND, but also minimise the brain uptake of drugs not intended to reach the brain, increasing the quality of life of individuals with MND.

OBJECTIVES:

- Evaluate the BBB status in MND, focusing on understanding which shuttles are increased or decreased. This will provide an understanding of which shuttles should be exploited for carrying therapeutics across the BBB specifically for MND.
- Assess which classes of drugs have modified access to the brain in preclinical models of MND. This will provide insight for advancing drug design to optimise their uptake in the brain of MND patients.

OUTCOMES:

- Identify pathways that give therapeutics optimal access to the brain in MND, for greater efficacy, and limit the entry of harmful drugs to minimise side-effects.
- Develop a blood-brain barrier model using stem cells from MND patients, that assesses the ability of novel preclinical therapeutics to transfer from the blood to the brain



Schematic representation of the BBB separating blood from the brain parenchyma with influx (green) and efflux (red) transporters (or shuttles).