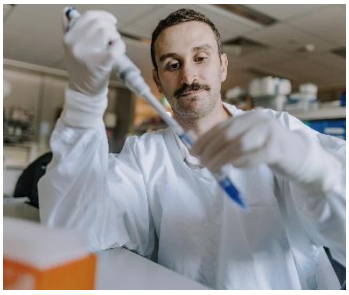
Dementia
RESEARCH COMMUNITY

Research by:
Dr Simon Maksour
The University of Sydney

Project title
Enhancing Microglial Tau Clearance via AAV-Mediated Gene Therapy

About the researcher



I am a stem cell biologist and neuroscientist, and my passion lies in understanding the earliest changes that occur in neurodegenerative diseases, including Alzheimer's disease, frontotemporal dementia and motor neurone disease, to develop new treatment strategies for these conditions. I use stem cells from people living with these diseases and grow them into nerve cells in the dish, including neurons, microglia and organoids, to identify these changes and test new therapies.

Project summary
In many forms of dementia there is the build-up of toxic protein clumps of a protein called tau, which spreads throughout the brain and damages nerve cells, causing them to eventually die. The brain's immune cells, called microglia (Image 1), normally breakdown these clumps of tau, but in dementia this process is impaired. This project aims to deliver a gene therapy to microglia to restore the ability to clear toxic tau clumps.

Project detail
There are still no effective treatments or cure for dementia. Changes in the brain include build-up of toxic forms of proteins including amyloid and tau. To date, treatment approaches have largely focussed on removing brain amyloid.

Newly approved treatments are only mildly effective in slowing progression of symptoms and have significant side effects. Thus, there is an urgent need for new treatment approaches. Even more pressing, there are no current treatments for Frontotemporal dementia, which is directly linked to toxic tau build up.

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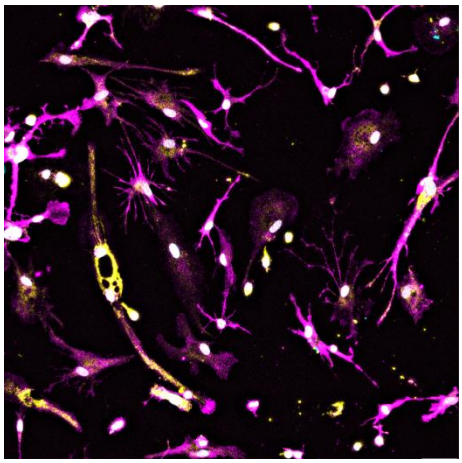
The brain's immune cells, called microglia, are normally responsible for clearing these toxic protein clumps, including tau and amyloid, however they become impaired early in disease and fail to do this job across all forms of dementia.

What if we could restore the function of microglia and improve the brains own defence mechanisms against toxic clumps of tau?

This project will test whether a novel gene therapy delivered directly to abnormally functioning microglia can restore the ability to clear toxic tau clumps and protect neurons (Image 2) from dying. It will also test the effectiveness and safety of the gene therapy in the laboratory in microglia and organoids (Image 3) generated from stem cells of people with Alzheimer's disease and Frontotemporal dementia.

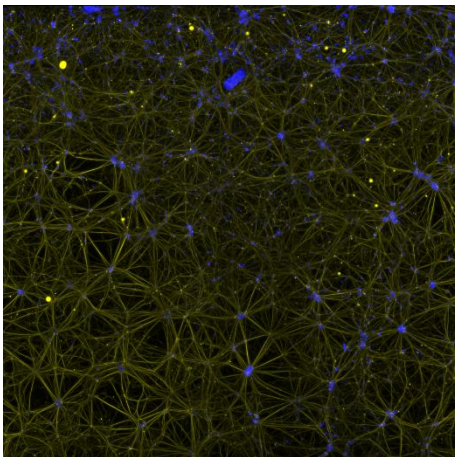
This platform has the potential to develop a transformative gene therapy that can be used to treat multiple forms of dementia, and open new avenues for safe and effective treatment.

Image 1: Microglia



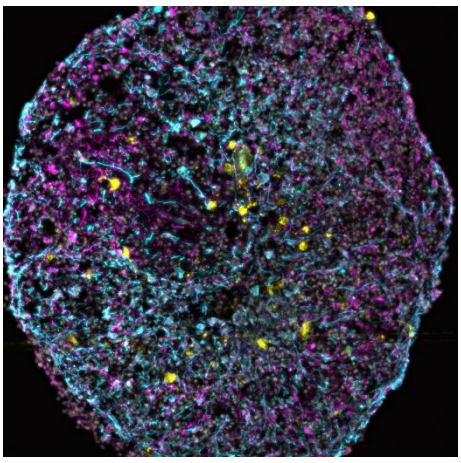
The brains immune cell, grown in the dish in the lab.

Image 2: Neurons



Neurons grown in a dish that have self organised into an intricate network.

Image 3: 3D Organoid



Three of the main neural cell types growing together (neurons in magenta, microglia in yellow and astrocytes in cyan)