Faculty of Health Sciences

2021 Australian Government Research Training Program Scholarships
Strategic Project Profile

PROJECT TITLE: Mechanisms of progressive degeneration after mild traumatic brain injury

FIELD OF RESEARCH CODE: 1109

PROJECT SYNOPSIS:

Mild traumatic brain injury (mTBI) can result in secondary degeneration of initially undamaged tissue. This phenomenon is associated with oxidative DNA damage and debilitating neurological dysfunction\(^1\)\(^-\)\(^3\). Myelin-producing oligodendrocytes, the essential signal conductors within the brain, are vulnerable to oxidative stress-induced DNA damage and their dysfunction may underlie much of the pathology of secondary degeneration\(^2\)\(^,\)\(^4\). In other diseases which share neurodegenerative features with mTBI, oligodendrocytes with oxidative DNA damage attempt to re-enter the cell-cycle and die soon after\(^5\). However, it is unknown whether this occurs in repeated mTBI, whether newly-derived or pre-existing oligodendrocytes are more vulnerable and whether loss contributes to dysfunction. The knowledge gained in this project will facilitate development of new treatments that stop oligodendrocyte cell-cycle re-entry at the onset of secondary degeneration and potentially prevent progression to pathology. This project will use an established model of mTBI to determine (1) how
oligodendrocytes die following mTBI, (2) the contribution of this death to loss of myelin structure and function and (3) whether relevant inhibitors can prevent behavioural deficits.

Overall hypothesis: mTBI initiates oxidative DNA damage and aberrant cell-cycle re-entry in pre-existing oligodendrocytes, compromising myelin integrity and neurological function

Aim 1: Determine the contribution of pre-existing and newly-derived oligodendrocytes with oxidative damage to abnormal myelin production following mTBI

After injury, newly-derived oligodendrocytes have a reduced capacity to myelinate, manifesting as structural abnormalities such as de-compacted (loose) myelin. We have found that pre-existing oligodendrocytes produced less myelin following injury than when under healthy conditions. However, it is unknown whether that myelin was de-compacted, and therefore a major contributor to poor outcomes.

Transgenic mice will be used to assess changes to myelin 12 weeks post-mTBI. Brain tissue will be assessed using the following visual techniques:

- Immuno-transmission electron microscopy: myelin integrity
- Immunogold particles: DNA and oxidative damage, and cell-cycle re-entry

Aim 2: Determine whether oligodendrocyte damage or degeneration of neuron axons initiate functional deficits

We have demonstrated structural and functional changes to myelin early after injury, prior to axonal and functional loss. However, we do not know if oxidative damage to oligodendrocyte DNA and/or abnormal cell-cycle re-entry is the initiating event of axon degeneration and subsequent functional loss in mTBI.

Newly-derived oligodendrocytes will be labelled, enabling visualisation of their myelin sheaths. Immunohistochemistry will then be used to determine whether:

a. axons ensheathed with myelin (wrapped with myelin) from newly-derived oligodendrocytes are degenerated

b. degeneration coincides with oxidative damage to DNA or other markers of altered function.

To ascertain which events initiate functional deficits, behavioural deficits will be assessed at each time point following mTBI, and related to early oligodendrocyte and/or axon pathology and neuron loss.

Aim 3: Inhibitors will be administered, which may provide proof-of-principle that the disease mechanisms identified are causative of functional loss.

References


FEASIBILITY AND RESOURCING – DESCRIPTION OF THE SUPPORT THIS PROJECT WILL RECEIVE:

CI Fitzgerald provides expertise in TBI and established model systems, with published data demonstrating feasibility for each aim of the Project. Post-doctoral researchers and PhD students with expertise in methods, models and analyses are present for continuous support. The project is NHMRC funded and related research aims are presently underway, guaranteeing immediate project commencement. Facilities include a dedicated wet lab, new confocal microscope, specialized tissue preparation suite, cryostat, tissue culture suites, luminescence/absorbance/fluorescence plate reader, and multiple fluorescence microscopes. The Perron Institute provides additional resources and the Sarich Institute features a new bio-resources facility on site.

THE SIGNIFICANCE OF THE PROJECT/ PROGRAM FOR THE ENROLLING SCHOOL OR INSTITUTION:

The proposed project falls within the key theme of Neuroscience for the Curtin Health Innovation Research Institute. Traumatic brain injury and neurodegeneration are a strength for the Faculty of Health Sciences and this project will build on this strength to provide an excellent training environment with high visibility. The project aligns with the Mission for Traumatic Brain Injury, a $50 million dollar initiative from the Australian Federal Government of which CI Fitzgerald is the proposed Chair of the Expert Advisory Panel. The project is NHMRC funded and will contribute to a track record of achieving research aims.

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