Progress Report

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Title of Project: *Developing the amyloid precursor protein as a neuroprotective agent against traumatic brain injury.*

Summary: We were very fortunate to have received a grant from the Brain Foundation in 2015 to aid us in our investigations developing a neuroprotective agent against traumatic brain injury (TBI). TBI causes more deaths in Australians under 45 years of age than any other cause and to date there is no therapy to ameliorate this injury. We have recently published a series of in vivo studies to convincingly demonstrate that the amyloid precursor protein (APP) has a protective role against TBI. We have also identified the specific region in APP that is responsible for this protective activity. Our work has established APP to be a viable and novel therapeutic for treating TBI. The Brain Foundation Grant we received in October 2015 has enabled us to undertake further studies to improve the protective activity of APP in order to make it a better therapeutic molecule for the treatment of TBI.

With the help of the Brain Foundation Grant we have been able to design APP analogues with enhanced heparin binding activity using structure based design, and have tested their neuroprotective activity in a well established rodent TBI model. We are three quarters of the way through our planned studies and so far our results have demonstrated that the “positive” mutants, with higher heparin binding activity, have increased neuroprotective properties and are more effective in ameliorating TBI in our rat model which is very exciting. These results will be presented at the Australasian Neuroscience Society and the 7th Australian Neurotrauma Symposium in Hobart in December 2016.

Published manuscript
Plummer S, Van den Heuvel C, Thornton E, Corrigan F, Cappai R. 2016. The neuroprotective properties of the amyloid precursor protein following traumatic brain injury. Aging Dis,7(2), Pg 163-179.

Submitted manuscript
The Amyloid Precursor Protein derivative, APP96-110, is efficacious for up to 5 hours following intravenous administration after traumatic brain injury

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Hypothesis vs Findings

- This project plan is aimed at further understanding the mechanism by which APP exerts its neuroprotective activity in TBI. We hypothesised that it has to do with its ability to bind to heparin molecules.
- The research plan has two primary aims: (1) To design APP analogues with enhanced heparin binding activity using structure based design, and (2) to test their neuroprotective activity in a well established rodent TBI model.

Our findings certainly indicate that the APP analogues with higher heparin binding activity, have increased neuroprotective properties and are more effective in ameliorating TBI in our rat model.

Unanswered Questions

We are almost three quarters of the way through our planned studies so there are still some experiments to do. We are yet to complete the immunohistochemical assessment of nerve injury markers on the injured brain tissue this is planned for November / December. Results from the immunohistochemical assessment will hopefully confirm the neurological outcome data we have gathered.

What these research outcomes mean

We are focusing our efforts on APP96-110 in order to advance APP as a neuroprotective molecule against TBI. The end result of this project will be the ability to further develop APP as a potential therapeutic agent against TBI.

Please submit this report as a PDF using the following naming convention:

Lastname Firstname – Simplified Project Title

For example: Smith Jane – The anatomy of the Brain.PDF