Bruton’s tyrosine kinase (BTK) regulates inflammasome activation in Motor Neurone Disease (MND)

Sara Jose1, Natalie, J. Groves1, William D. Godfrey3, Katerina Z. Hanton1, Nanthini Jayabalain1, Pamela A. McCombe1, Robert D. Henderson4, Fredrick J. Steyn1,2, Shyuan T. Ngo3,4, Trent M. Woodruff2, Richard Gordon1,2

1Translational Neuroscience Laboratory, UQ Centre for Clinical Research, The University of Queensland, 2UQ School of Biomedical Sciences, 3 Australian Institute for Bioengineering and Nanotechnology, 4 Queensland Brain Institute, (QBI)

Motor neuron disease (MND) is a neurodegenerative disorder that currently affects 2000 Australians. Chronic immune activation and ongoing inflammation are key drivers of disease progression in MND (Deora et al., 2017). The aim of the study is to evaluate the role of Bruton’s tyrosine kinase (BTK) as a therapeutic target and molecular switch for inflammasome activation in experimental model of MND. It will also evaluate if BTK inhibitors (BTK-I), could be an effective treatment strategy for MND.

Methods
We utilised the SOD1G93A animal model of MND, to study BTK activation in experimental MND. Further, the SOD1G93A mouse model of MND was used to conduct acute and chronic dosing studies with BTK inhibitor drugs. We utilised NSC34 motor neuron cells and primary microglia for in vitro studies.

Background and Aims
Motor neuron disease (MND) is a neuromuscular disorder that currently affects 2000 Australians. Chronic immune activation and ongoing inflammation are key drivers of disease progression in MND (Deora et al., 2017). The aim of the study is to evaluate the role of Bruton’s tyrosine kinase (BTK) as a therapeutic target and molecular switch for inflammasome activation in experimental model of MND. It will also evaluate if BTK inhibitors (BTK-I), could be an effective treatment strategy for MND.

Results
Figure 5: The BTK pathway is highly activated in the SOD1 model of MND
A. Western blots for active pBTK (Y223) activation loop in spinal cord lysates from wildtype and SOD1 mice b. Densitometric band quantification of active BTK (Y223) from wildtype and SOD1 littersmates demonstrating significantly increased (***p<0.001) BTK signalling in the SOD1 MND model.

Conclusion
Strong BTK transcriptional upregulation and pathway activation occurs in animal models of MND at the sites of degeneration. BTK inhibition with orally active drugs can prevent neuronal death and inflammasome activation in cellular models. Efficacy studies with BTK inhibitors are currently underway to evaluate the potential for disease modification.

Significance
BTK signalling regulates multiple mechanisms relevant to MND pathology
BTK inhibition could be a promising therapeutic strategy for disease modification in MND.