



## Project: Mechanistic Basis of Cognitive Impairment in Cholestatic Liver Disease

*'I am incredibly proud and honoured to be receiving the Dr Falk Core Student Bursary. Grants like this enable students like me to do research during medical school and our training as junior doctors. I think it's important that healthcare professionals are able to step outside of the clinical aspect of their job to explore research.'*

*'Completing the research that Dr Falk and Core are supporting me with has enriched my knowledge and enhanced my skillset, providing me with tools that I can take forward into clinical practice and my future career. It has also enabled me to experience research first hand, and I now know that this is something that I wish to take forward through my working life.'*

*Katherine McKay is just completing an intercalated Masters by Research of Medical Sciences at the Institute of Cellular Medicine at Newcastle University.*

'I've become increasingly interested in liver disease throughout medical school. When the liver fails the effects are multisystem and devastating, and I am fascinated by how the liver influences other body systems. As I read more about the autoimmune liver diseases, and the huge impact of symptoms on quality of life, I became evermore excited by the opportunity to undertake this research project.

'Primary Biliary Cholangitis (PBC) is a chronic liver disease in which autoimmune damage of bile ducts causes impaired flow of bile. Toxic bile acids cause progressive damage to the bile ducts and liver. Eventually, patients suffer liver failure potentially requiring transplant. Patients experience itch and fatigue as well as cognitive symptoms, including memory and concentration problems, which are significant and debilitating. The mechanisms behind these cognitive symptoms have not been elucidated, nor have any effective treatments been identified.

'Progress is being made in treatments of PBC, with therapeutic compounds currently under trial. Unpublished work from the lab showed that mice which have undergone bile duct ligation (BDL) surgery show problems with cognition similar to PBC patients.

Prophylactic treatment with one of these compounds significantly improved symptoms compared to untreated BDL mice.

'We are examining samples from these mice to uncover the mechanism behind the symptoms. We are assessing liver, blood and brain to investigate whether there are changes in inflammation and working to establish whether there is a change in the bile composition and the impact on other tissues, in particular whether certain bile acids cause damage to or protect brain tissue. The work so far suggests that a change in inflammation is not the driving factor. 'In addition, a study is being organised to assess patients with PBC. The aim of this is to characterise in detail patients with and without cognitive impairment such that a trial of new compounds can have useful outcomes to measure the effectiveness of any potential drug. The hope is that combining these two approaches could lead to more effective treatments for patients.'

### *Ms McKay's supervisor, Professor David Jones comments:*

'Katherine is a really outstanding medical student and is one of the "stars" of her year. It has been a real pleasure working with her to develop the project. She has shown a real aptitude for translational research, having a very clear sense of the value of linking mechanistic research with patient-facing work. She has played a significant role in the shaping of this project which I think is an extremely exciting one, with real potential.'