CJD Foundation Research Grant 12-month Progress report

Risk of cancer from reduced expression of PrPC-implications for prion disease treatment.

Associate Professor Victoria Lawson, Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, The University of Melbourne, Victoria, Australia

We are grateful for the funding received from the CJD Foundation to facilitate our investigation of risk of cancer from reduced expression of PrPC-implications for prion disease treatment.

Below is a summary of the progress that has been made towards the aims of our project.

Aim 1
To investigate the effect of PrPC expression on low- and high-grade glioma development low grade (LGG) and high grade (GBM) tumors have been induced in Prnp+/+, Prnp+/- and Prnp-/- mice. Tissues have been collected and processed for analysing the effect of PrPC on the pathology of low grade tumors in cohort 1 (Figure 1) and tissue will be collected for analysis of high grade gliomas in late February. Tumors have been induced for survival studies (cohort 2) and will be collected and processed as mice show signs of disease over the next 6-12 months.

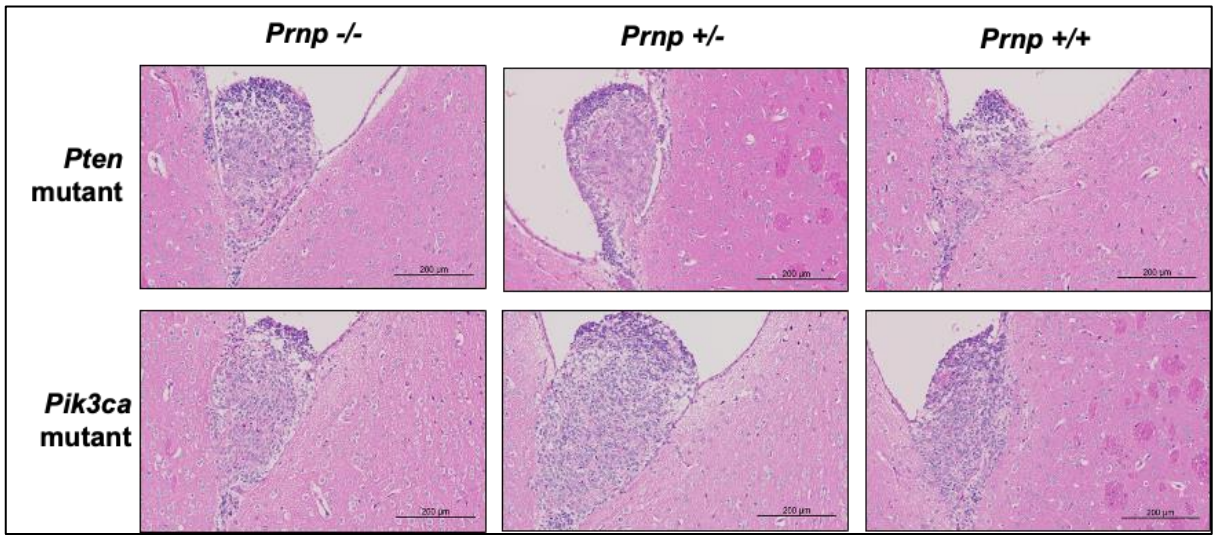

Figure 1. Representative tumours in the sub ventricular zone in the brains of mice that develop low grade tumors (Pten or Pik3ca mutations) in Prnp+/+, Prnp+/- and Prnp-/- mice. Tissue was collected at 6-weeks post tumor induction by tamoxifen mediated Cre-recombination. Tissue will be analysed for tumor phenotype, PrPC production and processing and gene expression by spatial RNA-seq (10xgenomics-Aim 2).

Aim 2

To investigate changes in PrPC mRNA expression, protein production and processing in tumors of different glioma grades we have induced tumors and collected tissue for spatial RNA-seq analysis. This change from the original proposal to detect PrPC mRNA expression changes and localisation using in situ hybridisation (RNA-scope) has been made possible through the award of a 10X Genomics Fellowship to Ms Shana Portelli, a PhD student working on this project. This fellowship has provided a discount on reagents required for mRNA gene expression and access to equipment and expertise that we will use to look at changes in expression of the whole genome, including PrPC mRNA expression in tumors induced in high and low grade tumors of Prnp+/+, Prnp+/- and Prnp-/- mice. To date tumors have been induced, tissue collected and processed for low grade tumors and high grade tumors have been induced with tissue to be collected and processed at the end of February (Figure 1). All samples will then be sequenced and analysed.

Aim 3

To investigate the effect of PrPC protein expression and processing on the features of cancer that determine malignancy we have expressed full length (FL) and cleaved (C1) forms of PrPC in 2/6 and 5/6 neural progenitor cell lines (Figure 2).

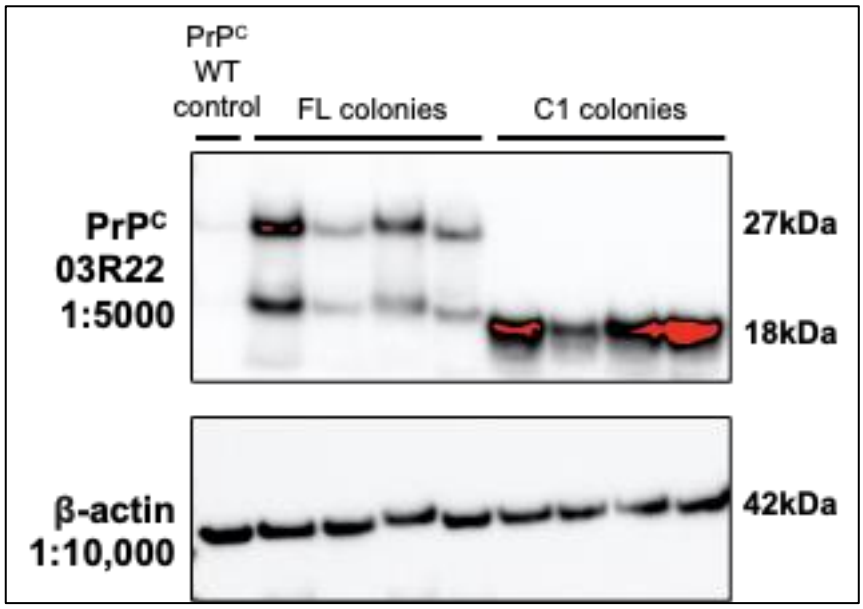

Figure 2. An example of expression of full length (FL) and cleaved (C1) PrPC expression in neural progenitor cells derived from Prnp-/- mice. Overexpression of FL and C1 can be compared to PrPC expression in neural progenitor cells derived from Prnp+/+ mice (WT control lane).