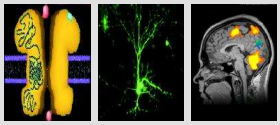

CHARACTERIZATION AND RESCUE OF NEURONAL DYSFUNCTION

April 25th - 26th, 2023

Session 2 **Mechanistic insights into psychiatric and affective disorders**

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Identification of neuro-epigenetic dysfunction that underpin cognitive deficits caused by exposure to maternal infection

Exposure to maternal infection *in utero* is an established major risk factor for offspring, leading to their altered neurodevelopment and associated disorders. This risk is thought to be mediated by epigenetically-driven transcriptomic changes in the fetal brain. However, understanding of the underlying mechanisms is lacking, preventing step change progress in identifying novel interventions for at-risk groups. Our overarching hypothesis is that exposure to maternal infection induces distinct alterations in fetal neuro-epigenetic mechanisms leading to neuronal dysfunction caused by changed expression of genes that result in cognitive dysfunction in offspring. Our project aims to test this hypothesis using a rat model of neurodevelopmental disorders that traces the origin of induced changes from acute changes to placental function and fetal brain development to changes in adolescent and adult behaviours associated with epigenetic and transcriptomic changes of genes regulating neuronal development and function.

We show that raised maternal inflammatory profiles associate with reduced amino acid transport across the placenta and affect fetal brain development. These initial patterns are manifest in altered DNA methylation profiles in the prefrontal cortex, differences in oligodendrocytes and parvalbumin interneurons resulting in GABAergic disinhibition and associated behavioural differences analogous to patient symptomology. We also illustrate how novel analytical tools such as behavioural cluster analysis enables us to dissociate individuals who respond from those who don't respond to effects of maternal infection.