# ARMI EXTERNAL SEMINAR SERIES 2024

MONASH University | ARMI AUSTRALIAN REGENERATIVE MEDICINE INSTITUTE

## SMCHD1: From fundamental biology to translational target

Professor Marnie Blewitt – Acting Deputy Director, WEHI

**Abstract**

Epigenetic silencing is a fundamental process critical for normal development that has been the focus on my group's research. In this talk I'd like to focus on how we can use this knowledge to identify and test new ideas for how to treat incurable diseases. In this case, I will focus on the neurodevelopmental disorder Prader Willi syndrome (PWS) that currently has no effective treatment. PWS is caused by lack of expression of a suite of genes on chromosome 15, whose expression is exclusively derived from the paternal allele due to genomic imprinting. Since all patients harbour the maternal epigenetically silenced allele, a potential therapeutic approach that targets the underlying cause of disease is to activate expression from the maternal allele by inhibiting its epigenetic silencing. Evidence from other neurodevelopmental syndrome suggests intervention in the neonatal period could have beneficial effects, likely because brain development is still ongoing.

We are working on SMCHD1, which we have previously shown silences the PWS cluster in mice, as well as the *Hox* genes and several other autosomal clustered gene families, alongside the inactive X chromosome in females. In this talk I will present our current evidence from mouse and human studies relating to SMCHD1 as a drug target for Prader Willi syndrome. While SMCHD1 is essential for gene silencing at all its targets during early embryonic development, we have found that removing SMCHD1 after this stage, at a time and in a tissue relevant to disease treatment, has very limited effects on gene expression. This reveals interesting aspects of the different stages of epigenetic control, pertinent to disease treatment more broadly. Importantly for us, the PWS cluster of genes remains sensitive to removal of SMCHD1 in the neural system both *in vivo* in mice and in Prader-Willi patient iPS cell-derived neural progenitors. These data suggest that SMCHD1 may indeed be a relevant drug target for Prader Willi syndrome.

**Bio**

Marnie's lab focuses on understanding the mechanisms of epigenetic control, and how such mechanisms can be manipulated in the context of disease. She uses functional genetic screens to identify epigenetic regulators, which she started as a PhD student with Emma Whitelaw at The University of Sydney (2005). Marnie took up a NHMRC Post-doctoral fellowship with Doug Hilton at WEHI in 2005 to work on the novel protein SMCHD1 that she identified in her PhD. In 2010, Marnie established her lab at WEHI, and in 2017 became a Division head, leading a group of labs focused on gene regulation.

Her lab works on the fundamentals of epigenetic silencing alongside targeting epigenetic regulators for the treatment of rare diseases. The highlight awards Marnie's work has attracted are the Australian Academy of Sciences Ruth Stephens Gani medal (2009) and more recently the 2024 Biochemical Society International Prize. Marnie is currently Acting Deputy Director and a NHMRC Leadership fellow.

## EVENT DETAILS

**DATE:**

14th May 2024

**TIME:**

12:30pm

**VENUE:**

Room G19
15 Innovation Walk
Monash University
Clayton Campus

**HOST:**

A.Prof. Edwina McGlinn

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