United in Hope: PWS 2025 – Clinical and Scientific Conference Keynote Speaker

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Background: Marnie's lab focuses on understanding the mechanisms of epigenetic control, and how such mechanisms can be manipulated in the context of disease. She received her PhD from The University of Sydney, then undertook a post-doctoral period at WEHI working on the novel epigenetic regulator SMCHD1. This work earned her the Australian Academy of Science Gani medal and the L'Oreal Australia Women in Science fellowship 2009. In 2010, Marnie established her own lab at WEHI. Her recent work on SMCHD1 and mechanisms of epigenetic silencing earned her the Genetics Society of AustralAsia Ross Crozier medal and the Lorne Genome Women in Science award. She is Deputy Director of WEHI.

Presentation Title: Epigenetic activation of the PWS locus as a potential therapeutic approach

Abstract: PWS is caused by the lack of expression of the SNRPN cluster of genes on chromosome 15. These genes are imprinted and only expressed from the paternal allele; however, all patients possess a maternal allele that has the required genetic information, but in an epigenetically silenced state. Thus, an attractive therapeutic option that targets the underlying cause of disease, is to activate the maternal genes.

There are several approaches by which gene activation might be achieved, including inhibiting G9a-based H3K9me3, SMCHD1, DNA methylation, or directly activating expression with dCas9 tethered activators. Each of these present different opportunities and risks. I will present our work on targeting SMCHD1, a chromosomal ATPase and silencer that we have shown binds and silences the PWS maternal allele. We have shown in vivo in mice and in vitro in PWS patient-derived neural progenitors that targeting SMCHD1 results in gene activation at the PWS cluster, without appreciable effects genome-wide. I will present our findings using the Magel2-LacZ mouse model that suggest targeting SMCHD1 may provide therapeutic benefit.