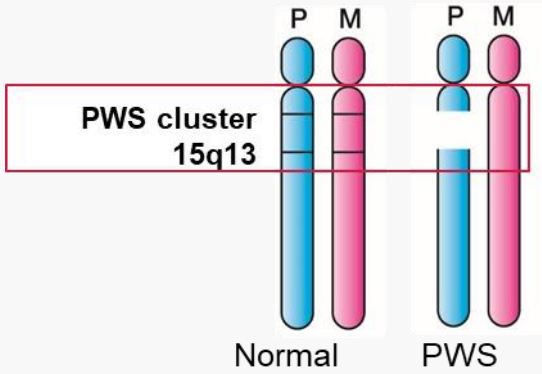
Precision epigenetics: SMCHD1 inhibition to treat Prader-Willi Syndrome (PWS)

The Problem

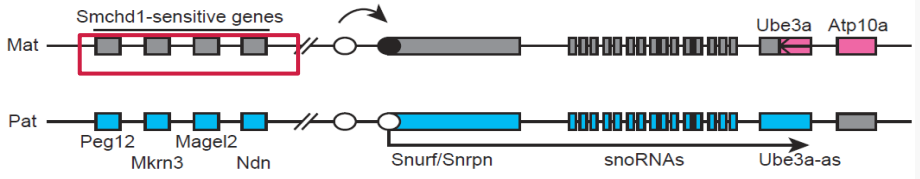
- PWS symptoms stem from a defect in the hypothalamus of the brain. Symptoms are identified at infancy and are life-long.
- Genetic disorder caused by failure to express critical PWS genes in paternal allele; affects 1 in 10,000 newborns.
- Current treatments target some symptoms; no treatment targeting the genetic cause is available.



The Solution

- Almost all PWS patients have a functioning set of PWS genes on the maternal side. SMCHD1 is an epigenetic regulator that switches off the maternal PWS genes.
- We have shown that SMCHD1 deletion in mouse neural stem cells reactivates PWS critical genes in the maternal allele but does not affect other Smchd1 targets.
- Our goal is to develop a small molecule clinical candidate to address the genetic cause of PWS. ASO treatment is also now possible.

Mouse PWS cluster



Our Program

- Only active program to undertake this approach, which has the potential to effectively treat multiple symptoms of this syndrome by targeting the cause.
- Chemistry: Preliminary screen and full-deck biochemical screen completed, medicinal chemistry currently in progress. Identified two hit series, currently being elaborated.
- Biology: SMCHD1 deletion being undertaken to determine activation of PWS cluster in human cells and mouse models. Use of tool compounds will aid the next steps.

Our Team

Prof. Marnie Blewitt, SMCHD1
Prof. James Murphy, Structural Biology
Dr. Nicholas Liau, Venture Scientist, WEHI Ventures

David Segal, PhD, Business Development Lead
segal@wehi.edu.au