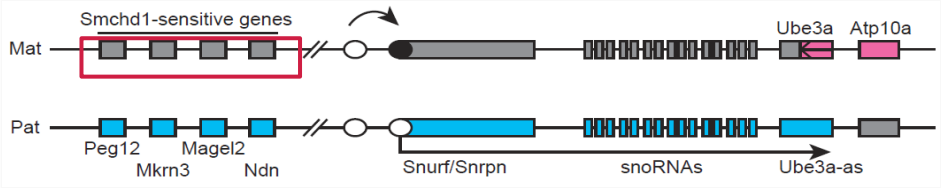
Precision epigenetics: drug discovery program - SMCHD1 inhibition to treat Prader-Willi Syndrome (PWS)

The Problem

- PWS is characterised by hypotonia, developmental delays, hyperphagia and insatiable appetite, obesity, reduced stature and scoliosis, intellectual disability and challenging behavioural disorders. These 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 available.

Mouse PWS cluster



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.
- WEHI team has shown that **SMCHD1 deletion in mouse neural stem cells reactivates PWS critical genes in the maternal allele** but does not affect other Smchd1 targets.
- Only current active program to undertake this approach, which has the potential to effectively treat multiple symptoms of this syndrome by targeting the cause.

Our Program

- 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.
- Ultimate goal: **Develop a small molecule clinical candidate to address the genetic cause of PWS**. ASO treatment is also now possible.

Our Team

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