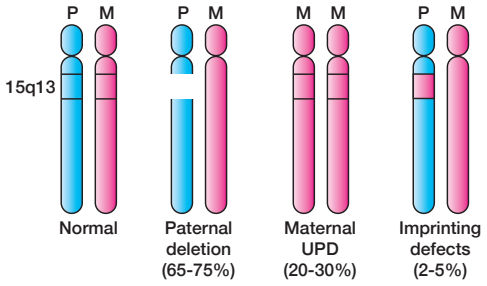
Walter+Eliza Hall Institute of Medical Research
DISCOVERIES FOR HUMANITY

Precision epigenetics: silencing SMCHD1 to treat Prader-Willi syndrome (PWS)

- **There is currently no treatment available that targets the genetic cause of PWS.**
- **We showed that Smchd1 deletion in committed cells causes selective gene reactivation at the PWS cluster.**
- **Seeking partners to progress the development of SMCHD1 inhibitors as a potential PWS therapy.**

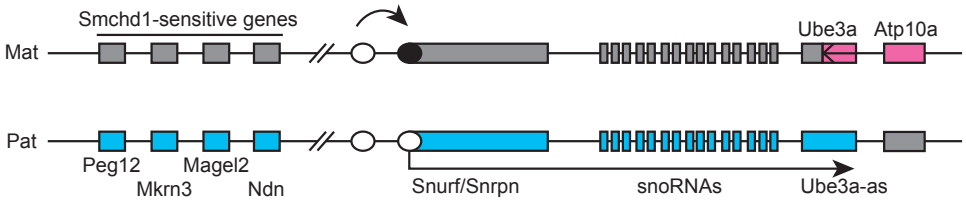
The opportunity

PWS occurs due to mutations in the paternal allele causing a failure to express critical genes in the PWS cluster. It affects one in 10,000 newborns and medical care per patient costs around $30,000-$66,000 annually. Current treatments target symptoms instead of the genetic cause of PWS.



The technology

SMCHD1 represses PWS critical genes on the maternal allele.



We showed selective gene reactivation of PWS genes following genetic deletion of Smchd1, suggesting that SMCHD1 could be a potential PWS therapy target (Table 1).

Table 1: Selective gene reactivation from Smchd1 deletion

Smchd1 binding sites	Embryos	Committed cell
Hox clusters	Failed silencing	Silencing maintained
X chromosome	Failed silencing	Silencing maintained
PWS cluster	Failed silencing	Gene reactivated (maternal allele)

Opportunities for partnership

We are seeking a partner to co-develop SMCHD1 inhibitors.

We have:

- Foremost experts in SMCHD1, a world-class structural biology program and an excellent understanding of SMCHD1.
- A lead SMCHD1 inhibitor and *in vitro* neural cell assays to conduct initial testing.

We are seeking investments to:

- Enable the *in vivo* validation of SMCHD1 inhibition in PWS mouse model.
- Expand on proof-of-concept experiments in patient iPSC-derived hypothalamic neurons.
- Further progress lead optimisation for our SMCHD1 inhibitor medicinal chemistry program.

Scientific team

Associate Professor Marnie Blewitt
Division head, Epigenetics and Development division

Associate Professor James Murphy
Division head, Inflammation division

Partnering opportunities

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At the Walter and Eliza Hall Institute our multidisciplinary research teams are focused on solving complex biological questions by integrating expertise in bioinformatics, clinical translation, computational biology, epidemiology, genomics, medicinal chemistry, proteomics, structural biology and systems biology. Our innovative science expands and improves the understanding of human biology and enables the translation of this new knowledge into novel therapies that benefit patients worldwide.

Project pipeline - available for partnering

	Project	Mode of action*	Target validation	Hit discovery	Lead generation	Lead optimisation	Indication
Cancer	Targeting minor class splicing	Inhibitor					Mutant K-Ras, B-Raf tumours
	Targeting EBV malignancies	Inhibitor					Burkitt's lymphoma
	Treating drug resistant cancers	Inhibitor					Cancer
Immune health and infection	pDC therapy for lupus	Inhibitor					Systemic lupus erythematosus
	RIPK2: Intercepting Inflammation	Inhibitor					Inflammatory bowel disease
	Rethinking CD52	Biologic					Autoimmunity
	SOCS mimetic	Inhibitor					Inflammatory bowel disease
	A complete cure for HBV	Inhibitor					Hepatitis B
	Novel malaria vaccine	Vaccine					Malaria
	Toxoplasma vaccine	Vaccine					Animal health: Toxoplasmosis
	Precision prebiotics	Prebiotic					Inflammation
Healthy development and ageing	Precision epigenetics	Inhibitor					Prader-Willi Syndrome
	FSHD epigenetic therapy	Activator					Facioscapulohumeral dystrophy
	Improving retinal detachment outcomes	Inhibitor					Ophthalmology

*Activator or Inhibitor refers to small molecule compounds

To discuss partnering opportunities, please contact **Dr Anne-Laure Puaux**, Head of Commercialisation, by email **partnering@wehi.edu.au**.