Modulating a hypothalmic switch to treat obesity

THERAPEUTIC: Obesity and Metabolic Disorders

Product Type	Small molecule drug candidate – repurpose or NCE
Indication/ROA	Obesity – intra-nasal (reformulation existing drug) or oral NCE
Target/MoA	A hypothalamic protein tyrosine phosphatase (PTP) 'switch', regulated by glucocorticoids (GC), modulates insulin sensitivity and weight loss. CNS-targeted blocking of TCPTP (via GC-receptor antagonism) reset in diet-induced obesity (DIO) re-sensitizes arcuate nucleus (ARC) neurons to insulin, increases energy expenditure and white adipose tissue (WAT) browning leading to weight loss. Combined with targeting PTP1B to re-sensitize ARC neurons to leptin, this represses feeding and leads to synergistic and sustained weight loss and improved glucose metabolism.
Development Stage	Targets validated through intra-nasal administration of TCPTP inhibitor (or GC antagonist) and PTP1B inhibitor; in preclinical efficacy studies; re-profile existing marketed drugs/drug candidates for i.n. delivery.
Brief Description & Differentiation	Central targeting of the hypothalamic PTPs is a new approach to increase insulin and leptin signalling, increase WAT browning and energy expenditure **and** repress feeding for the treatment of metabolic disease and obesity. Inhibiting TCPTP and PTP1B in ARC neurons is highly efficacious in promoting weight loss in obesity and improving glucose metabolism, even without lifestyle modifications.
Research Team	Prof Tony Tiganis (Monash BioMedicine Discovery Institute)
Intellectual Property	PCT/AU2018/050588 - METHODS AND COMPOSITIONS FOR THE TREATMENT OF OBESITY
Key Publications	Dodd *et al*., (2015) Leptin and Insulin Act on POMC Neurons to Promote the Browning of White Fat. *Cell 160*:88-104. Dodd *et al.,* & Tiganis T. (2017) A hypothalamic phosphatase switch coordinates energy expenditure with feeding. *Cell Metab 26*, 375-393.
Future	Re-profile TCPTP and PTP1B inhibitors for i.n. administration and formal preclinical studies

➢ Key Data

Monash researchers have identified a novel hypothalamic PTP switch linking GC to insulin receptor signalling.

- Elevated ARC PTP1B & TCPTP promote cellular leptin & insulin resistance.
- Elevated ARC PTP1B & TCPTP contribute to the maintenance of obesity, systemic insulin resistance & hyperglycemia.
- Intranasal delivery of TCPTP (*via* GC antagonist) increases WAT browning and energy expenditure while PTP1B inhibitor represses feeding to promote weight loss and improve glucose metabolism in obesity.

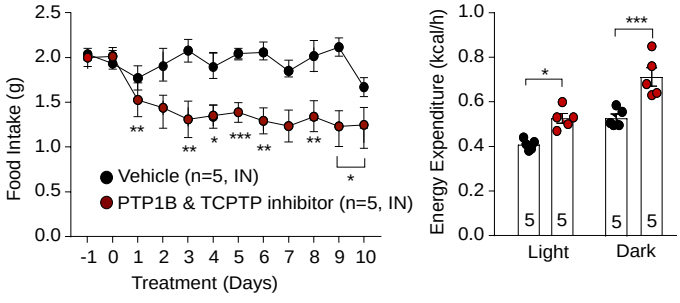

Figure 1: *Once daily Intranasal Delivery of TCPTP and PTP1B inhibitors promotes weight loss in DIO*

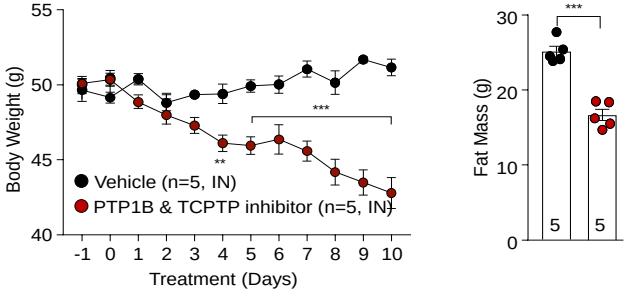

Figure 2: *Once daily Intranasal Delivery of TCPTP and PTP1B inhibitors promotes weight loss in DIO*