MONASH University

GI-directed immunomodulatory therapeutics

THERAPEUTIC: Autoimmune diseases

Product Type	Small molecule drug candidate
Indication/ROA	Inflammatory bowel diseases (IBD)
Target/MoA	Next generation GI-selective $S1P_1$-modulators directly target the mesenteric lymph node (MLN) and decrease dose requirement for efficacy while minimizing systemic exposure.
Development Stage	Advanced (patentable) leads bearing newly defined lymph-directing elements with nM potency and *in vivo* efficacy (T-cell trafficking) at <1.5 mg/kg.
Brief Description & Differentiation	Our GI-selective $S1P_1$-modulators are designed for direct uptake into the MLN from the gut lumen following oral administration. Biasing drug exposure through lymphatic-uptake achieves GI-specific immunosuppression. • Clinically validated target ($S1P_1$) in IBD. • Advanced lead series of GI-specific $S1P_1$ receptor modulators with newly defined features for promoting uptake into MLN. • Biased exposure addresses the adverse CV and non-specific immunosuppressive effects of available $S1P_1$-modulators such as fingolimod.
Research Team	Prof. Bernie Flynn and Prof. Christopher Porter (Monash Institute of Pharmaceutical Sciences)
Intellectual Property	Novel, patentable - composition of matter
Key Publications	Undisclosed
Future	Complete lead optimization, validate efficacy (colitis) and safety advantages → select drug candidate

➢ Key Data

Monash $S1P_1$-modulators show significant lymphatic uptake (> 20 fold higher lymph levels than fingolimod) and excellent efficacy in supressing T-cell trafficking while having low uptake into the blood, as desired (Fig 1). Despite being 1000-fold less potent, $S1P_1$-A (EC_{50} 1000 nM) exhibits similar efficacy on circulating T-cell levels (from MLN) in rats at the same dose (1-5 mg/kg) as do fingolimod (EC_{50} 1 nM) and another orally bioavailable $S1P_1$-selective drug, $S1P_1$-B (EC_{50} 3 nM). This effect is linked to the massively greater exposure to MLN seen with $S1P_1$-A relative to the other two drugs (**Fig. 1**). Lead optimization has led to improved S1P potency whilst retaining high lymphatic uptake (compounds 1-3, EC_{50} 10-80 nM) and a marked improvement in blocking T-cell trafficking over $S1P_1$-A *in vivo* (**Fig. 2**).

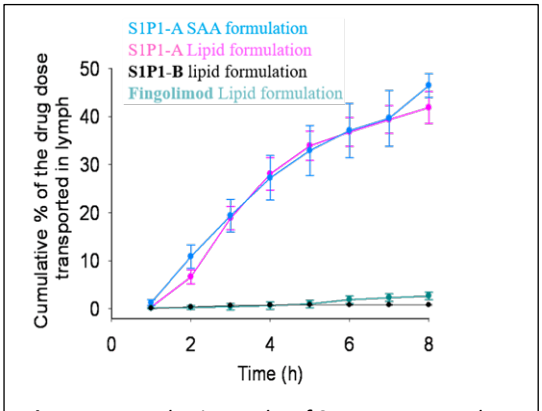

Figure 1: *Lymphatic uptake of $S1P_1$-A compared to systemically-distributed $S1P_1$-B and fingolimod.*

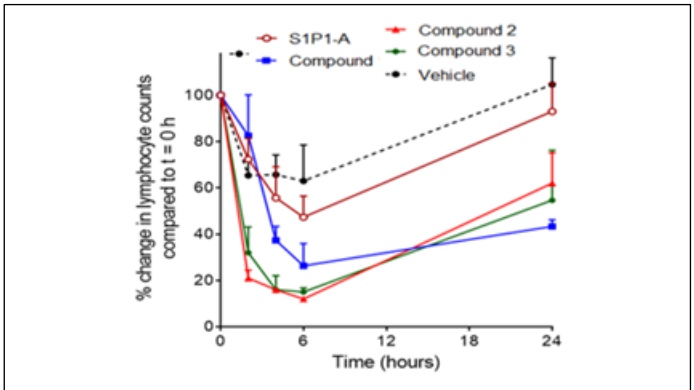

Figure 2: *MLN-directed S1P-receptor modulators, Compounds 1-3, exhibit markedly greater lymphopenia than $S1P_1$-A at 1.5 mg/kg.*