Differentiated approach giving biased exposure of S1P₁-receptor modulators to mesenteric lymph nodes (MLN) in the development of a GI-specific immunosuppressant for the treatment of inflammatory bowel disease (IBD).

- Clinically validated target (S1P₁) in inflammatory bowel disease (IBD).
- New approach to addressing the adverse cardiovascular (CV) effects and non-specific immunosuppressive effects of current S1P₁-modulators through biased exposure.
- Advanced lead series of S1P₁ receptor modulators with newly defined features for promoting lymphatic update into MLN.

THE CHALLENGE

The lipid metabolite sphingosine-1-phosphate (S1P) plays a number of critical roles in regulating immune responses and CV functions by signaling through five G-protein coupled receptors, S1P₁-5. Over the last ten years S1P₁-receptor modulators have emerged as useful treatments for autoimmune disease. They exert their immunosuppressive function by blocking T-cell egress from lymph nodes. The first S1P₁-receptor modulator to be approved for the treatment of multiple sclerosis (MS), fingolimod (Gilenya, Novartis), is a non-selective drug (hits multiple S1P₁-receptors) that suffers from adverse cardiovascular (CV) effects (bradycardia, macular oedema).

Several pharma groups have generated S1P₁-selective modulators and demonstrated their efficacy in Phase II clinical trials for treatment of MS and IBD (Crohn’s disease and colitis). However, the adverse effect profile is similar to that of fingolimod, where the S1P₁ subtype is apparently responsible for both efficacy and adverse CV-effects. This has hampered the development of these second-generation S1P₁-targeting drugs and many have been withdrawn from clinical trials.

Systemically distributed S1P₁-modulators suppress immune responses from all lymph nodes, not just those associated with autoimmune reactions, resulting in adverse effects linked to opportunistic infections.

THE TECHNOLOGY

The Monash team led by A/Prof Bernard Flynn has developed a different approach to S1P₁ receptors, relying on biased exposure to MLN.

Since the disease-associated immune responses in IBD are mounted from the MLN in the gut wall, biasing drug exposure to these through lymphatic-uptake of suitably designed S1P₁-modulators offers the opportunity to achieve GI-specific immunosuppression. This approach involves direct uptake of suitably designed S1P₁-modulators into the mesenteric lymph from the gut lumen, following oral administration. These features also minimize the systemic distribution of drugs, reducing their adverse effects on CV tissue and other lymph nodes.

The team has identified a candidate (S1P₁-A) S1P₁-selective modulator that fits the physicochemical properties for lymphatic uptake, with low uptake into the blood (Fig 1). Despite being 1000 fold less potent, S1P₁-A (S1P₁ EC₅₀ 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 (EC₅₀ 1 nM) and another orally bioavailable S1P₁-selective drug, S1P₁-B (EC₅₀ 3 nM). This effect is linked to the massively greater exposure to MLN seen with S1P₁-A relative to the other two drugs (Fig 1).

The team has undertaken drug lead optimization to improve potency towards S1P₁ whilst retaining high lymphatic uptake and has progressed several new leads (Compounds 1-3, EC₅₀ 10-80 nM). These compounds also and show a marked improvement in blocking T-cell trafficking over S1P₁-A in vivo (Fig 2).

THE OPPORTUNITY

Monash University seeks a commercial partner to bring the lead candidates to clinical studies.

**Figure 1:** Lymphatic uptake of S1P₁-A compared to systemically-distributed compounds S1P₁-B and fingolimod.

**Figure 2:** New, potent, MLN-directed S1P₁-receptor modulators, Compounds 1-3, exhibit markedly greater lymphopenia than does S1P₁-A at 1.5 mg/kg.

Intellectual property: Provisional application on the new composition of matter is pending.

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