LYMPH-DIRECTING PRODRUGS
Offering enhanced oral bioavailability immune cell targeting

A novel lymph-directing prodrug technology based on the structure of natural triglyceride. The prodrug promotes transport to the intestinal lymph and offers potential to enhance oral bioavailability by avoiding first pass hepatic metabolism and to target lymph or lymphocyte-mediated pathologies. In vivo proof of mechanism has been demonstrated.

- A novel technology to enhance drug targeting to the intestinal lymphatics
- Based on a modified lipid-mimetic prodrug with novel approaches to drug conjugation and release
- In vivo proof of mechanism, demonstrating stable transport of the drug to the intestinal lymph and ready reversion to the active parent agent

THE CHALLENGE
The lymphatic system plays a number of key roles in immune response, fluid balance, nutrient absorption, lipid homeostasis, and tumour metastasis. Due to the unique anatomical and physiological characteristics of the lymphatic system, targeted delivery of drugs to and through the lymphatic system offers the potential to improve both pharmacokinetic and pharmacodynamic profiles. For instance, lymphatic drug transport has the potential to:

- enhance oral bioavailability through avoidance of first pass metabolism;
- alter systemic drug disposition (e.g. to enhance drug deposition in adipose tissue and potentially in certain tumours); and
- enhance efficacy against lymph- or lymphocyte-mediated pathologies such as autoimmune disease, transplant rejection and lymphatic tumour metastasis.

Dietary lipids such as triglycerides use a unique metabolic pathway to gain access to the lymph and ultimately, the systemic circulation. Following ingestion, dietary triglycerides are hydrolysed by luminal lipases to release a monoglyceride and fatty acids. These components are subsequently absorbed into enterocytes, where they are re-esterified to triglycerides. The triglycerides are assembled into intestinal lipoproteins and subsequently gain preferential access to the intestinal lymphatics. Within the lymphatics, these lipoproteins enter into systemic circulation where they are preferentially and efficiently taken up by adipose tissue, the liver and potentially certain types of tumour tissues.

THE TECHNOLOGY
Researchers from the Monash Institute of Pharmaceutical Sciences have developed a proprietary lipidated prodrug technology that is stable in the gastrointestinal tract, promotes transport to the intestinal lymph and ultimately, promotes release of the active drug. By altering the composition of the linker that is used to conjugate the drug in the sn-2 position of the glyceride backbone, the pharmacokinetic profile of the drug can be optimised.

The researchers have completed in vivo evaluations of a series of testosterone prodrugs. When compared with commercially available testosterone undecanoate, the Monash testosterone prodrugs demonstrated significantly enhanced (>10 fold) lymphatic transport (Fig.1) and significantly improved (up to > 50 fold) systemic exposure (Fig.2).

THE OPPORTUNITY
Monash seeks partners with drugs that would benefit from delivery with this lymph-directing prodrug technology. The researchers, together with the Faculty of Pharmacy and Pharmaceutical Sciences, have extensive academic and industrial experience in drug absorption, lymphatic transport and drug discovery.

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