Novel, highly potent peptide inhibitors of the Kv1.3 potassium channel, an emerging target for autoimmune diseases. The Monash peptides offer numerous advantages, including high Kv1.3 selectivity, minimising the potential for off-target side effects, efficacy across a range of experimental models and high yield production (recombinant or synthetic).

- Novel lead peptide inhibitors of Kv1.3 having high potency (low pM affinity), selectivity (over Kv1.1) and stability
- Clinical ‘Proof of Mechanism’ of related peptides demonstrated in Phase 1b clinical studies
- Suitable for recombinant manufacture GMP-scale production, as well as peptide synthesis
- Multiple therapeutic product opportunities

THE CHALLENGE

Nearly 80 different autoimmune diseases are known, affecting millions of people worldwide. Typically, they are characterised by tissue destruction caused, at least in part, by self-reactive T lymphocytes (T cells). As T cells undergo repeated antigen stimulation they differentiate into terminally-differentiated effector memory T cells (Tem), characterised after activation by high expression of the voltage-gated potassium channel Kv1.3. Conversely, naive and central memory T cells (Tcm) and B cells are less sensitive to the inhibition of Kv1.3 as they up-regulate Kca3.1 channels upon activation.

As a consequence, selective blockers of Kv1.3 are expected to reduce the severity of Tem-mediated autoimmune diseases without inducing generalised immunosuppression. Kv1.3 inhibition is now being actively explored for a range of AI diseases, including rheumatoid arthritis, atopic dermatitis, plaque psoriasis, asthma, IBD and lupus.

ShK peptide, isolated from a sea anemone, is one of the most potent inhibitors of Kv1.3 channels, (IC50 11pM). An analogue of ShK, Dalazatide, has been tested successfully in a Phase 1b study of plaque psoriasis, with twice-weekly subcutaneous injection and is now Phase 2-ready (KPI Therapeutics Inc.).

While this is an important clinical validation of the target, there are significant improvements over this drug candidate that would offer advantages in efficacy, safety and manufacture (for example Dalazatide includes non-protein amino acids and linkers and cannot be expressed recombinantly). Our approach is to develop a best in class Kv1.3 blocker that is potent, cheap to manufacture, and sufficiently stable to better exploit the full range of opportunities in autoimmune diseases.

THE TECHNOLOGY

Researchers from the Monash Institute of Pharmaceutical Sciences and their collaborators have designed two different lead series based on ShK and HsTX1 (from scorpion venom). These lead series are potent and highly selective inhibitors of Kv1.3, with potency in the low pM range.

Compared with Dalazatide, the Monash peptides have enhanced selectivity for Kv1.3 over Kv1.1 and other ion channels, offering potential safety benefits. They also offer potential manufacturing advantages as they are chemically more stable and can be produced cheaply by recombinant expression.

The peptides have demonstrated efficacy in a range of AI disease models, including RA (Fig. 2), where the results support once-weekly injectable administration. We are currently in lead optimisation stage and demonstrating the suitability of these classes for diverse administration routes.


THE OPPORTUNITY

Monash is now seeking partners to complete the optimisation of these Kv1.3 inhibitors and associated formulations, and lead their further development.

Figure 1: ShK-192 (molecular surface representation) docked with a model of the pore-vestibule region of Kv1.3 (ribbon).

Figure 2: Pristane-induced model of RA showing that once-weekly dosing with HsTX1 analogue significantly improves the clinical score.