Novel, highly potent peptides that are selective inhibitors of the Kv1.3 potassium channel, an important pharmaceutical target in autoimmune diseases. The Monash peptides offer potential clinical advantages due to selectivity for Kv1.3 which reduces off-target side effects and can be developed as recombinant products, supporting GMP scale production.

- Novel ‘best in class’ peptides that are highly potent (low pM affinity) and selective inhibitors of Kv1.3 (and not Kv1.1)
- Can be manufactured recombinantly and suitable for GMP-scale production
- Clinical ‘Proof of Mechanism’ of related peptides demonstrated in Phase 1b clinical study
- Potential for formulation as an injectable for weekly or monthly administration

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.

ShK peptide, derived from the venom of the sea anemone, is one of the most potent inhibitors of Kv1.3 channels, with an IC50 of 11pM.

Recently, Dalazatide (ShK-186), a derivative of ShK, displayed encouraging clinical activity in a Phase 1b study in patients with active plaque psoriasis. Dalazatide was administered at doses of 30μg or 60μg twice weekly by subcutaneous injection for four weeks, then four weeks of follow-up. While the study was not powered to assess clinical efficacy, improvements in several relevant clinical disease endpoints were noted.

However, because Dalazatide includes non-protein amino acids and linkers, it cannot be expressed recombinantly and must be manufactured synthetically.

THE TECHNOLOGY

Researchers from the Monash Institute of Pharmaceutical Sciences and collaborators have designed new analogues of peptides derived from sea anemone and scorpion venom. The resulting peptides 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 all other ion channels, offering potential safety benefits. They also offer potential manufacturing advantages as they are chemically more stable and can be produced more cheaply by recombinant expression.

Intellectual property: Two patent applications, PCT/AU2015/000487 and PCT/2013/001249, have been filed claiming composition of matter of novel peptides and their use for the treatment of autoimmune diseases.

THE OPPORTUNITY

Monash is now seeking partners to progress the development of these Kv1.3 inhibitory peptides and associated formulations.