Immunomodulatory peptides from edible plants

Ong ST,* Chang SC,* Tanner M,* Ng XR, Bankula K, Morales R, Chen MW, Luo D, Patel D, Yasmin S, Nguyen HM, El Sahili A, Lescar J, Charman S, Goggi J, Robbins EG, Wulff H, S. Kuyucak, Norton R, Beeton C, Chandy KG

Cysteine-rich peptides from scorpions and sea anemones that block the T cell potassium channel $K_v1.3$ suppress terminally-differentiated effector memory T cells (T_{EM} cells) that are implicated in many different autoimmune diseases. Dalazatide, an analogue of the sea anemone peptide ShK, has progressed to human clinical trials where it alleviated symptoms of psoriasis in a clinical trial. Here, we describe cysteine-rich plant defensins from edible foods that share remarkable sequence and structural similarity to $K_v1.3$ -blocking scorpion peptides. We developed novel analogues that are remarkably resistant to proteases and stable over a wide pH range. These peptides suppress T_{EM} cells at picomolar-to-nanomolar concentrations, and treat disease in rat models of rheumatoid arthritis and atopic dermatitis when administered by subcutaneous injection on alternate days. They do not cause local or systemic toxicity when repeatedly administered over 2 weeks at 10-times the therapeutic dose. Interestingly, they do not block $K_v1.3$, $K_{Ca}3.1$ or 87 other molecular targets including receptors, transporters, enzymes and other channels that we have tested. In summary, we have developed novel T_{EM}-suppressing peptides with excellent pharmacokinetic, biodistribution and safety profiles, but are yet to define a molecular target.