

Fact Sheet – Autoimmune Disease

Over 50 different autoimmune diseases have been identified, affecting 3-5% of the population of Europe and North America. Autoimmune disease treatment has traditionally represented a field characterised by the use of dated therapeutics that sub-optimally treat their target diseases, often providing symptomatic relief rather than disease modification. An aberrant T-cell response is now known to underlie a number of major autoimmune diseases, including rheumatoid arthritis, psoriasis, multiple sclerosis, and inflammatory bowel disease, and the preferred approach for new treatments for these disorders is modulation of T-cell function. The advent of biologics has initiated a transformation in the therapeutic approach to immunology. However, this new wave of medicines has benefited some conditions more than others, and, given that many biologics suffer from significant shortcomings such as very high cost, inconvenient administration, hepatotoxicity, and increased risk of infection and malignancy, there is a widely recognised need for alternative, orally bioavailable, small-molecule therapies. Xention has a particular interest in developing new therapies for rheumatoid arthritis and psoriasis. Rheumatoid arthritis is a progressive chronic inflammatory disease of the peripheral joints affecting ~6 million people worldwide, of which fewer than 50% are ultimately unable to continue to work or function normally. Psoriasis is a skin disease that affects approximately 2.5% of the world's population. The disease is characterised by epidermal hyperproliferation, vascular dilatation, and inflammation, leading to the clinical features of red, elevated, scaly plaques.

These diseases represent a very substantial unmet medical need. To address this need Xention is developing well-tolerated, orally bioavailable, Kv1.3 potassium channel blocking drugs that target specific autoimmune responses without promoting generalised immunosuppression.

Kv1.3 – A Target for Autoimmune Disease

The role of autoreactive late-stage effector-memory T-cells (TEM) in the pathogenesis of a variety of autoimmune diseases including rheumatoid arthritis, psoriasis, multiple sclerosis, IBD and others is well established. Activation of these cells is followed by substantial up-regulation of Kv1.3 channel expression and, as a result, Kv1.3 becomes the predominant route of potassium efflux from the cell. Thus, selective blockade of Kv1.3 causes membrane depolarisation and inhibition of Ca²⁺ influx, leading to inhibition of cytokine production and cell proliferation. Experimental evidence has shown that inhibition of Kv1.3 selectively suppresses TEM cell function while leaving other T-cell populations intact. This promotes suppression of disease relevant T-cells without a global generalised immunosuppression. This is expected to result in new safe, effective and well-tolerated treatments.

Xention's Kv1.3 Programme

We have applied our ion channel approach to discover and optimise modulators of Kv1.3 that have high potency and excellent selectivity against non-target channels. Using our approach of incorporating electrophysiology into the lead optimisation process we have optimised three lead series and identified compounds not only with excellent potency and selectivity characteristics, but also compounds with good ADME and bioavailability properties that are suitable for further development.

In Vitro and in vivo Proof of Concept Studies

We have used a model that examines the proliferation of effector memory T-cells to examine the ability of our Kv1.3 blockers to prevent antibody-stimulated proliferation (below, left hand panel) and demonstrated that a small molecule Kv1.3 channel blocker is able to potently inhibit T-cell proliferation.

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Furthermore we have used the in vivo acute-contact dermatitis (ACD) model to examine the efficacy of our small molecules in the delayed-type hypersensitivity skin reaction mediated by TEM-cells. In the rat ACD model, following initial sensitization, rechallenge with oxazolone results in Kv1.3^{HIGH} CD8⁺CD45RC⁺ TEM-cells infiltrating the ear causing it to swell. Similar to psoriasis, the model is characterised by IFN γ production and epidermal hyperplasia. A Xention compound, when dosed orally, was effective in significantly reducing ear-swell in this model by a similar magnitude as the Kv1.3-selective peptide-toxin ShK (see below, right hand panel). The ACD assay is not only a model of psoriasis but also other type 1-cytokine pattern autoimmune diseases such as rheumatoid arthritis and MS.

These data provide proof-of-concept data for an orally active Xention compound that is potentially effective in the treatment of psoriasis and other autoimmune diseases.

