Novel Peptide Inhibitors of the Kv1.3 Potassium Channel Demonstrate Efficacy in an Anterior Uveitis Model

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1. Background and Rationale

Dalazatide (SHK-186) and KPI-190, a topicaly administered peptide in the Shk family, are potent inhibitors of Kv.1.3, a voltage-gated potassium channel that is expressed on activated autoreactive effector memory T (TEM) cells. Because Kv.1.3 expression is selectively upregulated on activated TEMs, which are most often found at the sites of inflammation in autoimmune disease, but not activated naive or central memory T cells, it is a novel and attractive target for the treatment of many autoimmune diseases. SHK-186 is the first blocker of the Kv.1.3 channel to enter clinical trials and has shown to be well tolerated with no serious adverse events reported in three Phase I human trials.

Previous work has shown that subcutaneous administration of SHK is effective in preventing disease in multiple models of autoimmune disease. For organ specific diseases such as those affecting the eye, localized administration would be desirable. Here we report on the evaluation of the therapeutic effect of SHK when administered topically to the eye in a model of anterior uveitis. SHK was able to readily cross the cornea and accumulate in the aqueous fluid in the anterior chamber of the eye at levels above those predicted to have a therapeutic effect. Preventative topical treatment with SHK reduced clinical disease parameters, inflammatory cell infiltration and histopathological changes. Infiltration of Kv.1.3 positive CD4 T cells was blocked by SHK treatment. These results suggest that blockade of TEMs by targeting the Kv.1.3 channel could be a novel strategy to treat ocular autoimmune diseases including anterior uveitis, Sjogren’s syndrome and dry eye disease.

*Dalazatide is being jointly developed by KPI Therapeutics Inc and its sister company Kineta Inc.

2. SHK Peptides Target Kv.1.3 Channels on Autoreactive Effector Memory T Cells

By selectively targeting T cells that cause autoimmune attack, SHK-186 and KPI-190’s MOA is more broad than cytokine targeting therapies but safer than immunosuppressive drugs.

Key differentiators:
- Novel MOA
- Immune sparing
- Targets major autoimmune disease markets
- Potent, stable small peptides
- Excellent safety profile
- Broad intellectual property

Kv.1.3 and KCa.3.1 are K+ channels needed to maintain membrane potential (by allowing K+ efflux) during T cell activation and the requisite increase in intracellular Ca2+. While KCa.3.1 is important in activation of naive and central memory T cells, Kv.1.3 is only highly expressed in activated effector memory T cells.

3. Pathogenic T Cells in Autoimmune Eye Diseases

- Non-infectious uveitis and dry eye are ocular diseases where autoreactive T cells play a major role in both etiology and chronicity (Stein et al., 2013).
- Sjogren’s patients with dry eye have infiltrating eye surface Th1 and Th17 cells (Stein et al., 2013).
- In animal models of uveitis and dry eye, particularly in those that are chronic models and that most closely resemble human disease, a key role for effector memory T cells has been demonstrated (Oh et al., 2011; Chen et al., 2014).
- Cyclosporine A emulsions have beneficial effects in dry eye syndrome but lack poor penetration and do not selectively target pathogenic T cells.

4. Topically Administered Shk Peptides Penetrate into the Anterior Chamber

"Penetration into the eye is a major challenge in ocular drug development"

SHK-186 in aqueous fluid, day 7

KPI-190 in aqueous fluid, day 7

Ocular topical administration of SHK-186 or KPI-190. SHK-186 and KPI-190 were formulated in an aqueous saline solution (pH 7.4) and administered topically three times a day to the eyes of Lewis rats for seven consecutive days. Aqueous fluid was harvested on day 8 and SHK concentration assessed by direct ELISA quantification. This dosing regimen did not produce any observable adverse effects. Dosage of up to 5% SHK-186 three times a day for up to 5 days did not result in any observable histopathological changes either (not shown).

5. SHK-186 Reduces Disease in Model of Autoimmune Anterior Uveitis

![Graph showing efficacy of SHK-186 in anterior uveitis model](image)

SHK-186 efficacy in an animal model of Experimental Autoimmune Uveitis (EAU). Lewis rats were immunized with bovine melanin associated antigen in complete Freund’s adjuvant to induce EAU. Disease progress was monitored by observing and scoring miosis, iris structure and function, the presence of cells and flare in the anterior chamber by slit lamp (Table). Animals treated with 1% SHK-186 topically three times per day developed significantly less severe clinical symptoms during the peak of disease (A). SHK-186 treatment also lowered the number of infiltrating cells observed in the aqueous fluid (B).

6. Histopathology and Immunohistochemistry

Histopathology and immunohistochemical evaluation of SHK-186 in the EAAU rat model. A-C. Hematoxylin and eosin (H&E) staining of anterior chamber. Increased infiltrating cells in vehicle treated only. (D,E) Kv.1.3+ cells (red) CD3+ cells. Sections of the ciliary body.

7. Current Status and Future Plans

KPI-190
- Potent Kv.1.3 inhibitor
- CMC scale up and stability underway
- Currently looking at Kv.1.3 expression in corneal impressions from patients with dry eye
- Planning proof-of-concept efficacy dry eye studies
- Planning Phase 1 clinical program

Dalazatide
- Six month chronic toxicology studies conducted in rat and cyno monkey
  - Established safety margin range >20X
  - No target organs of toxicity identified
  - NOAEL was highest dose tested
- Dalazatide is immune sparing in host resistance models
- SAD and MAD Phase 1 clinical studies completed n healthy volunteers
- Phase 1b proof-of-concept trial completed in patients with active plaque psoriasis

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Developing game-changing drug platforms in autoimmunity and chronic pain.