Dalazatide (ShK-186), a Kv 1.3 Inhibitor that Targets Effector Memory T Cells: Ex vivo studies in Pediatric Systemic Lupus Erythematosus

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1. Dalazatide Targets Kv1.3 Channels on Autoreactive Effector Memory T cells, Evidence of Kv1.3 in Human Disease

- Kv1.3 and KvCa3.1 are K+ channels highly expressed on activated T effector memory cells (TEM), is essential for T cell activation, and is a novel target for the treatment of autoimmune disorders. ShK-186 (dalazatide) is a specific, highly potent peptide inhibitor of Kv1.3 that has recently entered clinical development. Previous reports associated TEM activation with the development of SLE. Urinary T cells in active lupus nephritis patients specifically have exhibited an effector memory phenotype. These findings suggest there is a potential for dalazatide efficacy in treating SLE.

- Methods: Peripheral blood from pediatric patients with SLE and healthy controls were studied. Ex vivo Kv1.3 expression was assessed on T lymphocyte subsets by flow cytometry. The effect of dalazatide on cytokine production in vivo in a dose-dependent fashion in TEM, but not naive cells from SLE patients and healthy controls. In the CCR7-low CCR7-high TEM subset, inhibition of TNF expression was detected. Expression of Kv1.3 on urinary lymphocytes was measured by immunofluorescence.

- Results: Kv1.3 was upregulated on CD4+TEM from SLE patients with active disease (mean ± 4.54% @ 15 min) compared to and to patients with inactive disease (mean ± 3.12% @ 13 min; p=0.055), or to controls (mean ± 2.95%). A larger effect on Kv1.3 expression was detected in CD8+TEM (active mean ± 6.22%, inactive mean ± 1.97%, p=0.164; control ± 2.47, p=0.241). Dalazatide at concentrations of 10 µM-100 µM decreased proinflammatory cytokine production ex vivo in a dose-dependent fashion in TEM, but naive cells from SLE patients and healthy controls.

- Ongoing chronic tox studies suggest an attractive long term safety profile ideal for chronic use to prevent flares.

- Conclusion: In vitro studies suggest that Kv1.3 on TEM may be a treatment target for SLE without negatively affecting other T cell subsets necessary for normal immune function. In addition, Kv1.3 expression may be useful as a biomarker of disease activity in SLE.

3. Case for Dalazatide in Lupus and Vasculitis

- Unmet needs in lupus and vasculitis:
  - Current therapies including steroids, cyclophosphamide, mycophenolate cause long term problems and do not prevent flares.
  - Current biologic therapies Rituximab and Belimumab have incomplete efficacy.

- Opportunity for dalazatide therapy in SLE patients:
  - During flares of disease, lupus nephritis patients show an increase of urinary (16-kD) TpA (Yuasa et al., 2020).
  - Kv1.3 is in the main K+ channel responsible for Ca2+ homeostasis in hyperactive SLE T cells (Yuasa et al., 2020).
  - Blocking Kv1.3 with ShK-186 could return hyperactive T cells to a resting state.
  - Carboxyl-terminal splicing and MSQA complementary to T cell directed drugs.
  - Ongoing chronic tox studies suggest an attractive long term safety profile ideal for chronic use to prevent flares.

6. Immunofluorescence studies of Kv1.3 in Lupus Nephritis patient samples

In vitro activated CD4+ Tmem cells express Kv1.3

Urinary lymphocytes of a Lupus nephritis patient express Kv1.3

4. Dalazatide (ShK-186) Effect on Cytokine Expression Assays

Cytokine A CD4+T EM (Active SLE)

Cytokine A CD4+T EM (Inactive SLE)

Cytokine B CD4+T EM (Active SLE)

Cytokine B CD4+T EM (Inactive SLE)

Cytokine C CD4+T EM (Active SLE)

Cytokine C CD4+T EM (Inactive SLE)

For questions about bileaf’s” ShK-186 patents, contact Chelsea Steen, Ph.D. at csteen@kineta.com

Abbreviations: APC: Antigen presenting cells; IL: Interleukin; bAbs: B cell antibodies; EM: Effector memory; SLE: Systemic Lupus Erythematosus; Tg: Transgenic cells; * = p value of 0.05; ** = p value of 0.01; *** = p value of 0.001

8. Current Status and Future Plans

- Grafting collection of patient samples for cytokine assays
- Developing new assays to study surface markers unique to lupus
- Immunofluorescence studies looking at multiple markers in urinary T cells
- Future Plans
- Proof of concept studies to work towards an adult and pediatric SLE clinical trial
- Kineta is currently seeking a partner(s) to maximize the potential of the dalazatide / ShK-186 franchise.