Dalazatide, first-in-class Kv1.3 channel blocker, an immunomodulators journey from sea to clinic

Aurora Biomed Ion Channels Retreat 2015
Shawn Iadonato
Dalazatide: Potential Autoimmune Blockbuster

- Immune regulating therapy
- First in Class
- Novel Kv1.3 inhibitor

- Broad autoimmune indications
- Immune sparing
- No target organs of toxicity
- Well tolerated in clinical studies

- Expansive commercial opportunities
- Strong global patent estate

Phase 2 Ready
DALAZATIDE:
FIRST IN CLASS KV1.3 INHIBITOR
Kv1.3: A Novel Target for Autoimmune Disease

- Effector Memory T cells ($T_{EM}$) cause autoimmune disease
- $T_{EM}$ cells depend on the Kv1.3 channel for activation
- Blockade of Kv1.3 suppresses inflammation from $T_{EM}$ cells
- Kv1.3$^{HIGH}$ autoreactive $T_{EM}$ cells identified in multiple autoimmune diseases
Kv1.3\textsuperscript{HIGH} T cells Are Abundant in Atopic Dermatitis Lesional Skin

Most autoreactive, infiltrating Th1/2 cells in AD are Kv1.3\textsuperscript{HIGH}
Kv1.3: T Cells in Inflamed Mucosa of Ulcerative Colitis

23% of CD8$^+$ and 54% of CD4$^+$ T cells in UC biopsies are Kv1.3$^{HIGH}$

Large Number of Kv1.3 Channels Found Across Autoimmune T Cell Populations

Number of Kv1.3 channels on disease T cells 2 – 3 fold higher than control cells

Kv1.3 Expression Well-Established Across Autoimmune Space

*Kv1.3*<sup>HIGH</sup> Autoreactive T<sub>EM</sub> cells identified in:

- **CNS**
  - Multiple Sclerosis
- **Rheumatology**
  - Lupus (SLE)
  - Lupus Nephritis
  - Vasculitis
  - PsA
  - RA
- **GI**
  - Crohn’s Disease
  - Ulcerative Colitis
- **Ophthalmology**
  - Uveitis / Dry Eye
- **Dermatology**
  - Psoriasis
  - Atopic Dermatitis
- **Other**
  - Type 1 Diabetes
  - Asthma
  - GVHD
Dalazatide: Novel MOA Through Kv1.3 Blockade

- Highly specific and potent antagonist of Kv1.3 channel
- Blocks activation of autoreactive, Kv1.3\(^{\text{HIGH}}\), effector memory T cells (T\(_{\text{EM}}\))
- Does not block Naïve, Central Memory or Regulatory T cells
- Targeting of autoreactive T\(_{\text{EM}}\) reduces number of disease causing cells and proinflammatory mediators
- Blockade of Kv1.3 may lead to a remission by immunomodulation or induction of tolerance

Dalazatide is a first in class Kv1.3 inhibitor that targets a differentiated pathway
Dalazatide is Targeted and Immune Sparing

MoA Pathway

Kv1.3 Channel  KCa3.1 Channel

Kv1.3↑

KCa3.1↑

KCa3.1↑

Kv1.3↑

K Ca3.1

CD3  CTLA4  JAK  PDE4  Calcineurin

IL-12/23 integrin, S1PR

dalazatide

IL-1  IL-6  TNFα  IL17

Resting

Activated

Inflammatory Mediators

Inflammatory Mediators

Inflammatory Mediators

Autoimmunity

Naive CD4⁺ or CD8⁺ T Cells

Central Memory CD4⁺ or CD8⁺ T Cells

Effector Memory CD4⁺ or CD8⁺ T Cells

Th1/Th17
Dalazatide: Novel Kv1.3 Inhibitor

- 37 amino acid synthetic cyclic peptide
- Derived from the stichodactyla sea anemone
- Phase 1 clinical formulation: twice weekly subcutaneous injection to abdominal fat pad
- Phase 2: ready-to-use, pre-filled single use syringe
- Developmental formulations:
  - 8 – 12 week subcutaneous sustained release formulation
  - Eye drop
  - Topical cream

Dalazatide is a first in class Kv1.3 inhibitor that targets a differentiated pathway
DALAZATIDE: NON-CLINICAL PD, EFFICACY & TOXICOLOGY
Animal Models: Dalazatide Effective in Multiple Sclerosis

Dalazatide effective in animal model of relapsing MS over broad range of doses and dose frequencies

Animal Models: Dalazatide Effective in Arthritis Model

Dalazatide demonstrated efficacy in pristane-induced arthritis model

Animal Models: Dalazatide Effective in Autoimmune Glomerulonephritis

Dalazatide effective in glomerulonephritis model of SLE and preserved kidney function
Safety Established in Pre-clinical Toxicology Program

- Toxicology studies conducted in rat and cyno monkey
- Following ICH S6 guidance
- Six month chronic toxicology conducted in both species
  - Established safety margins range 17-25X
  - No target organs of toxicity identified
  - NOAEL was highest dose tested

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<tr>
<td>Clinical Chemistry/Hematology/Uricalysis</td>
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<td>Safety Pharmacology</td>
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<td>Cardiovascular</td>
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<td>Respiratory</td>
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<td>Neurological</td>
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No safety pharm concerns or target organs of toxicity identified
DALAZATIDE:
CLINICAL PROGRAM
Dalazatide Clinical Development Status

1A
• Single Ascending Dose Safety Study
• 32 Healthy Volunteers
• One Dose
• One site in Netherlands

1B
• Multiple Ascending Dose Safety Study
• 32 Healthy Volunteers
• Twice-weekly dosing for 4 weeks
• One site in the U.S.

1B
• Safety and Biomarker Study in Psoriasis
• 24 Mild-moderate active plaque psoriasis
• Twice-weekly dosing for 4 weeks
• Two sites in Canada

Phase 2 Ready Asset
Initial Phase 1 Studies Demonstrate Dalazatide Safety in Healthy Volunteers

- Open IND in Rheumatology Division of FDA
- 186-01 Single Ascending Dose Study (NL)
- 186-02 Multiple Ascending Dose 28-Day Study (USA)
- Subcutaneous administration to abdominal fat pad

Results
- Drug well tolerated in both studies
- No significant findings in labs, vitals, ECGs, physical exams, neurological exams
- AE’s were considered to be mild
- Maximum tolerated dose not determined
- No subject developed anti-drug antibody

Dalazatide is well tolerated in clinical studies
Dalazatide Demonstrates Clinical Proof-of-Concept in Phase 1b Psoriasis Trial

- 186-03 study of the safety, tolerability and pharmacodynamics of dalazatide in active plaque psoriasis.
- Active plaque psoriasis with 3% BSA and multiple target lesions
- Received twice-weekly injections at 2 dose levels (30 mcg or 60 mcg) for 4 weeks followed by 4-week follow-up

Safety & Tolerability
- Drug well tolerated; all subjects completed all scheduled doses
- Most AEs judged to be mild, consistent with previous trials
- No subjects withdrew, reduced dose or missed a dose

Dalazatide is well tolerated in active plaque psoriasis population
Dalazatide Demonstrates Clinical Proof-of-Concept in Phase 1b Psoriasis Trial

Clinical Activity
- Study not powered to evaluate clinical efficacy
- 50% of subjects in 60 mcg group achieved clinical improvement in target lesion
- Improvements observed as early as day 15 and for up to 4 weeks following last dose (end-of-study)
- 90% of subjects in 60 mcg group had reduction in PASI score
- Mean PASI score reduction reached statistical significance (p=.004) in 60 mcg group

Biomarker Studies
- Ongoing with James Krueger (Rockefeller U.)
- Gene expression and immunohistochemistry of biopsies
- Inflammatory mediators concentration in blood plasma
- T cell subsets/PD marker evaluation by flow cytometry

Dalazatide treatment results in improvements in validated psoriasis endpoints in up to 90% of subjects
Dalazatide Clinical Activity - 30µg Dose

Significant improvement in target lesions following 4 weeks of treatment.
Why Dalazatide?

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<th>dalazatide</th>
<th>CD3</th>
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<td>Tolerability in Clinical Trials</td>
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Dalazatide offers differentiation in indications and safety from competing therapies
Dalazatide Collaborators

**UC Irvine**
- George Chandy
- Michael Cahalan
- Many others

**Baylor College of Medicine**
- Christine Beeton

**Peptides International**
- Mike Pennington

**Monash University**
- Ray Norton

**UC Davis**
- Heike Wulff

**Kineta**
- Eric Tarcha
- Ernesto Munoz
- Kayla Norton
- David Peckham
- John Grigg
- Jose Mercado
- Many others
Thank You & Questions

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