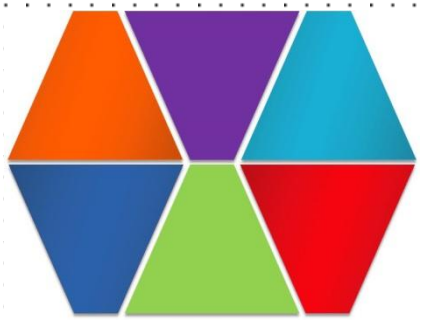
Dalazatide, first-in-class Kv1.3 channel blocker, an immunomodulators journey from sea to clinic

Aurora Biomed Ion Channels Retreat 2015

Shawn Iadonato



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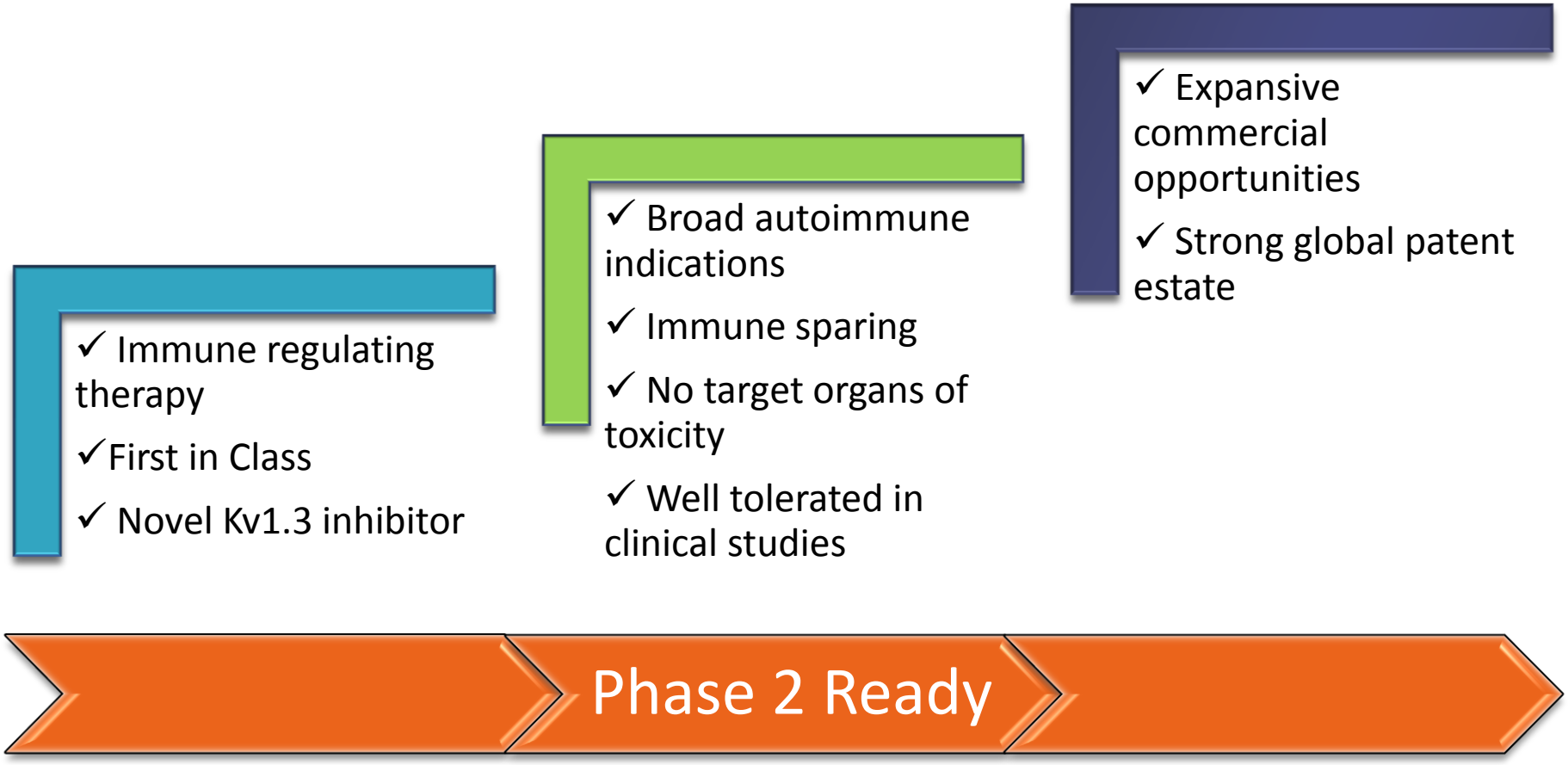
innovation from within™

Dalazatide:
Potential Autoimmune Blockbuster



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DALAZATIDE:
FIRST IN CLASS KV1.3 INHIBITOR

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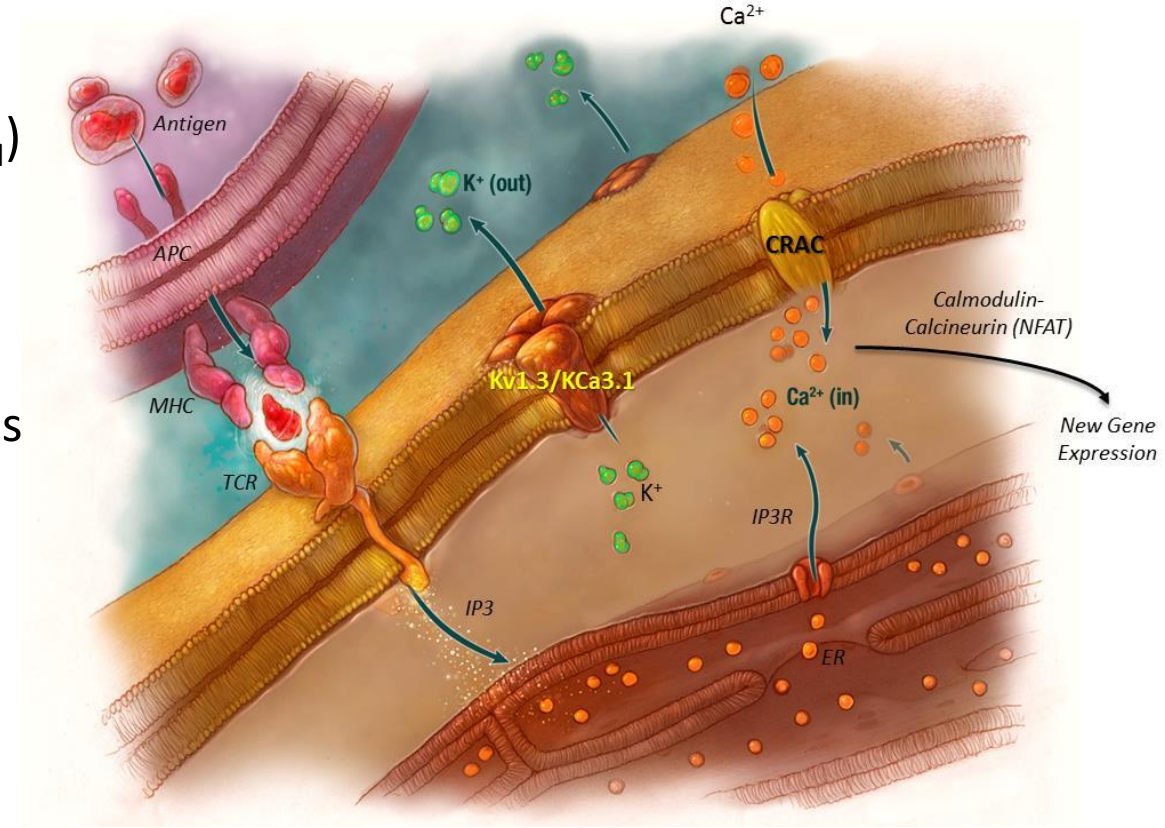
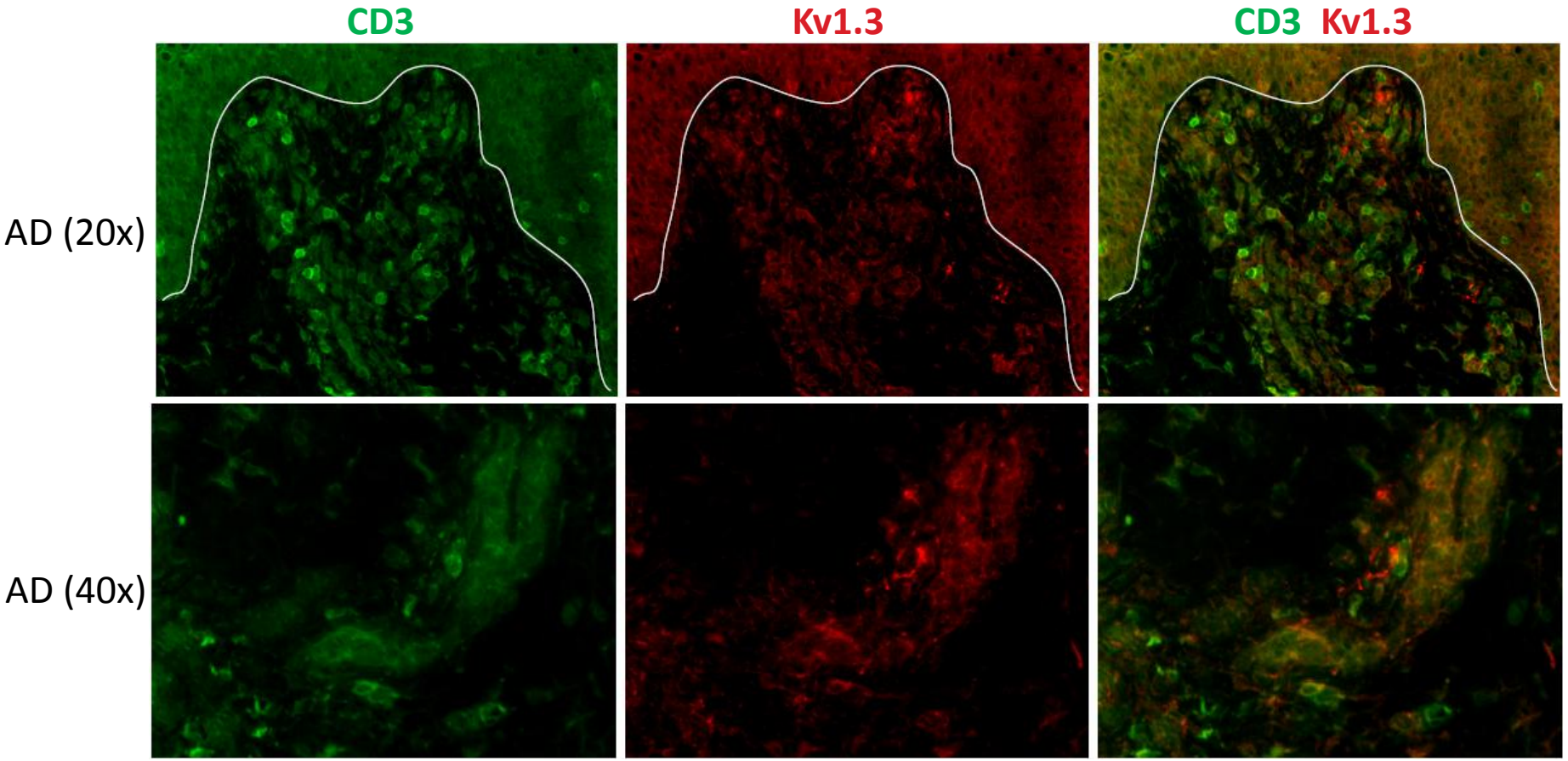
Kv1.3: A Novel Target for Autoimmune Disease

- 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^{HIGH} T cells Are Abundant in Atopic Dermatitis Lesional Skin



Most autoreactive, infiltrating Th1/2 cells in AD are Kv1.3^{HIGH}

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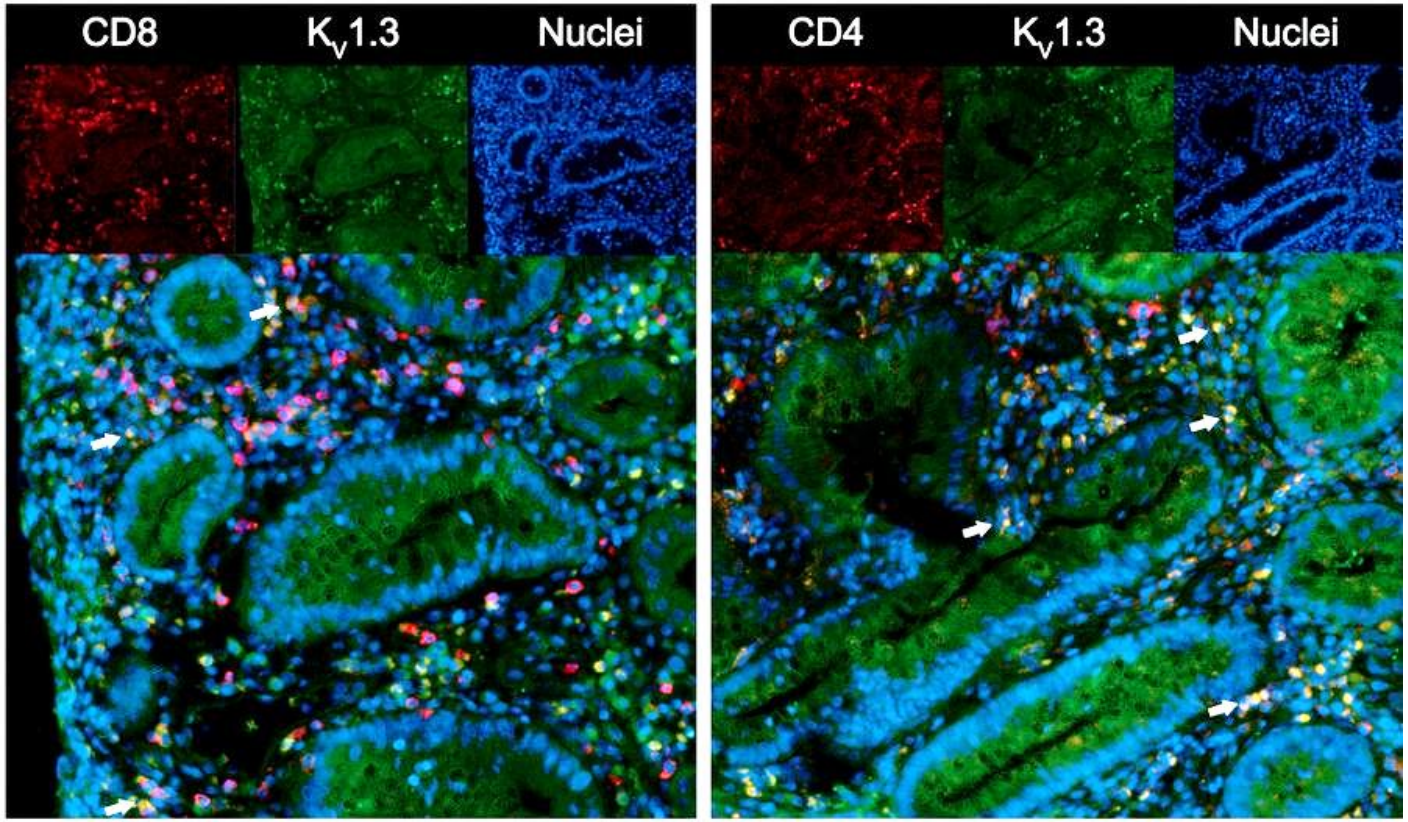
Kv1.3: T Cells in Inflamed Mucosa of Ulcerative Colitis



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

From Koch et al. J Crohns Colitis. 2014 Nov 1;8(11):1378-91.

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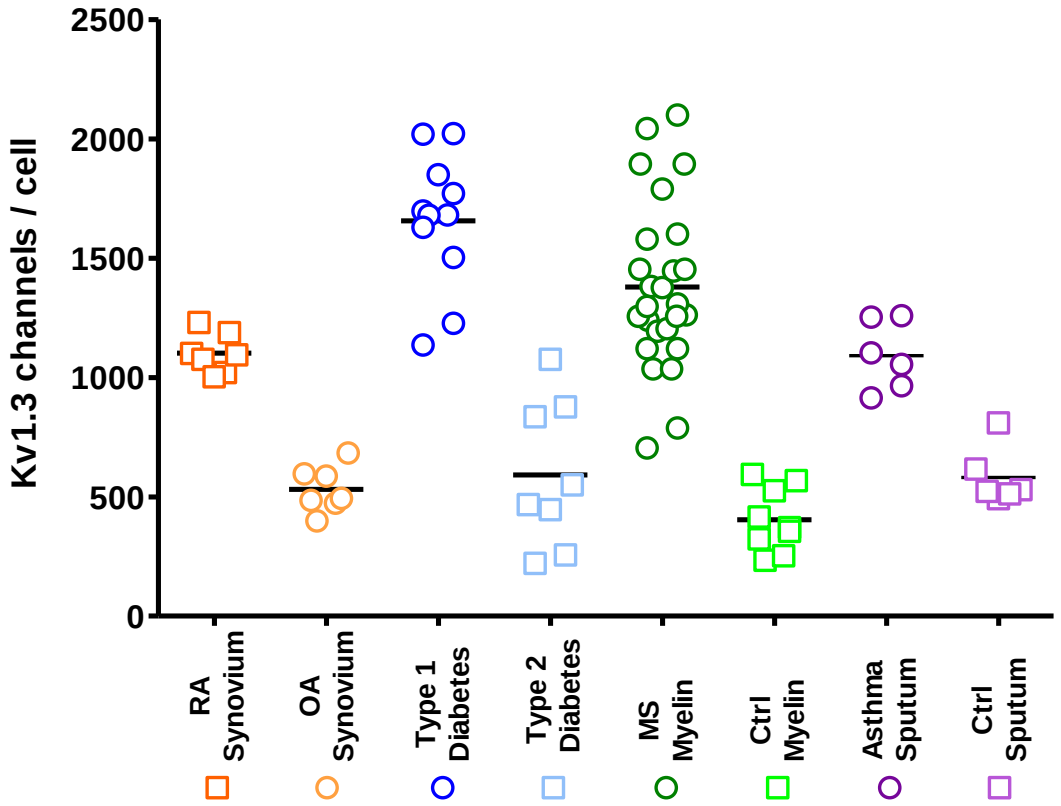
Large Number of Kv1.3 Channels Found Across Autoimmune T Cell Populations



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

From Koshy et al. J Biol Chem. 2014 May 2;289(18):12623-32 and Beeton et al. Proc Natl Acad Sci U S A. 2006 Nov 14;103(46):17414-9.

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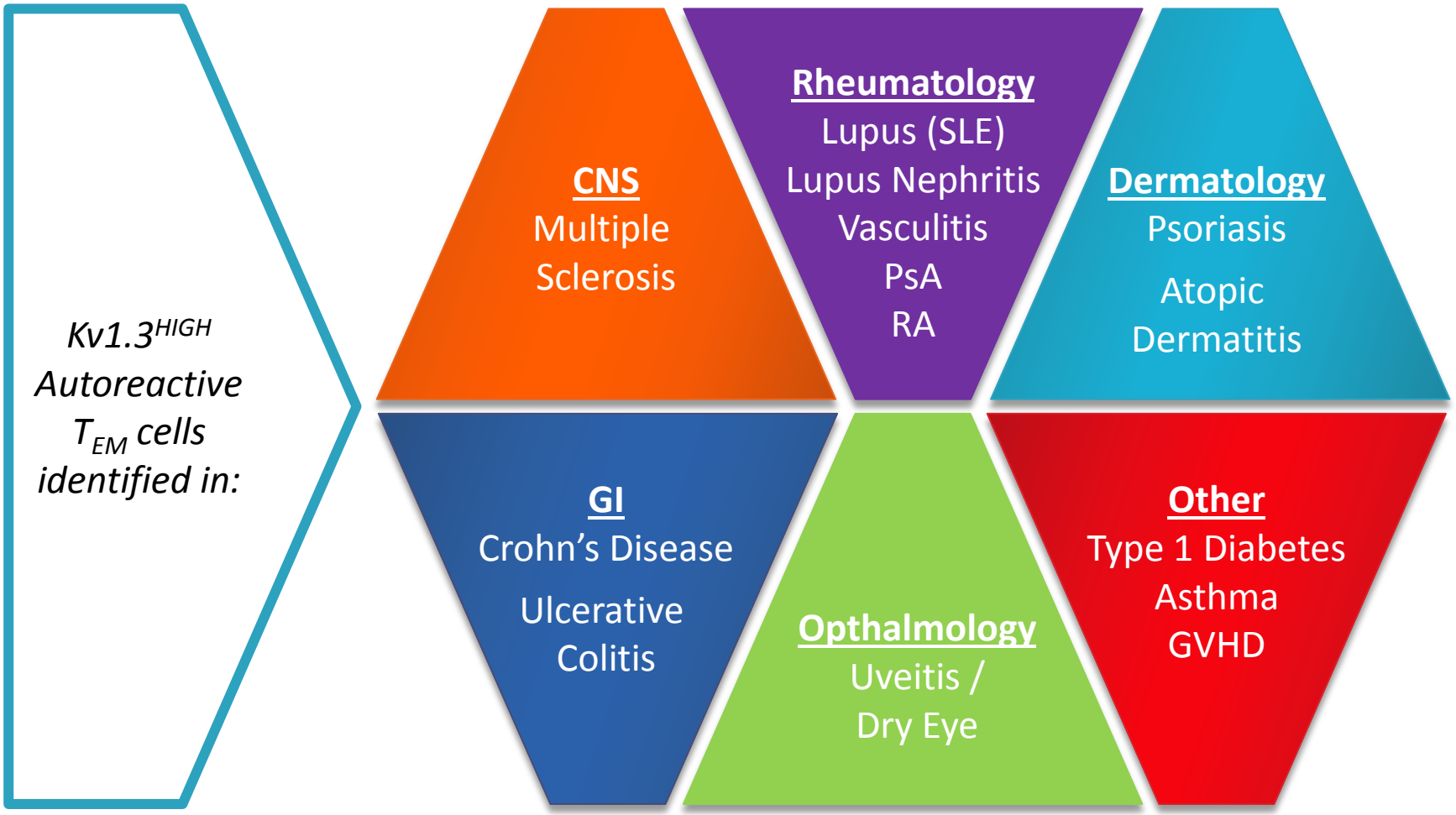
Kv1.3 Expression Well-Established Across Autoimmune Space



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Dalazatide: Novel MOA Through Kv1.3 Blockade

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

Dalazatide is a first in class Kv1.3 inhibitor that targets a differentiated pathway

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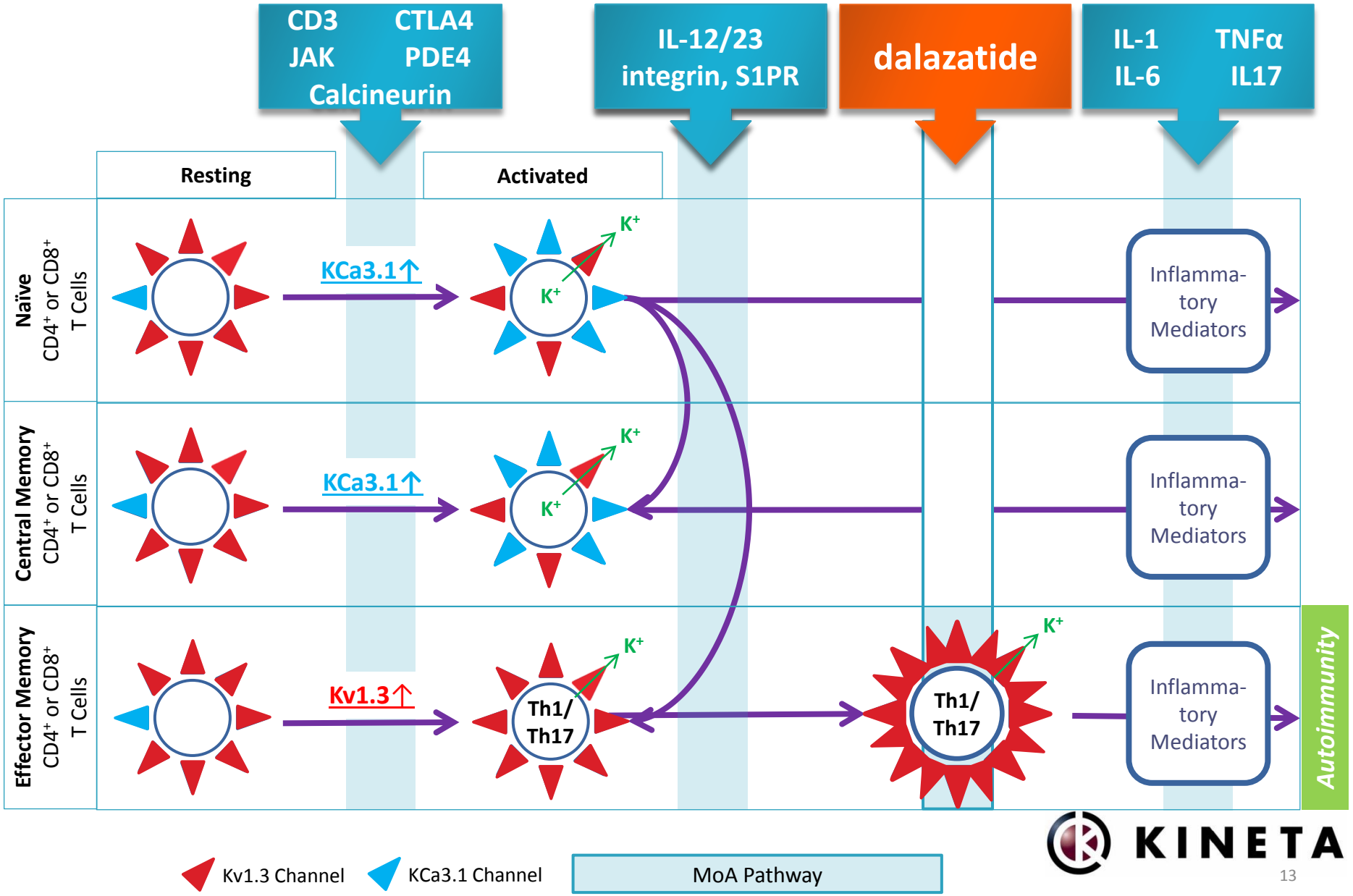
Dalazatide is Targeted and Immune Sparing



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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

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DALAZATIDE:
NON-CLINICAL PD, EFFICACY & TOXICOLOGY

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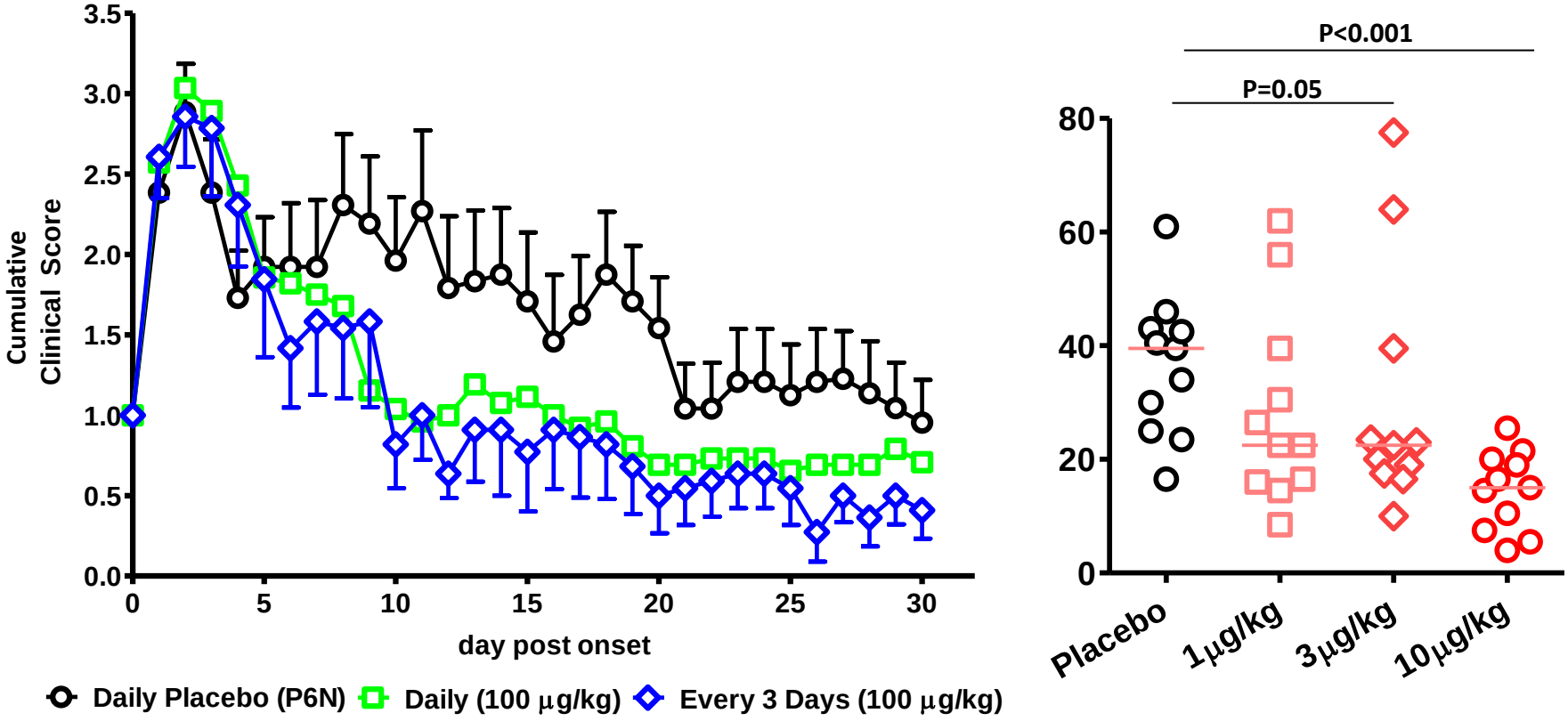
Animal Models: Dalazatide Effective in Multiple Sclerosis



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

From Tarcha et al. J Pharmacol Exp Ther. 2012 Sep;342(3):642-53.

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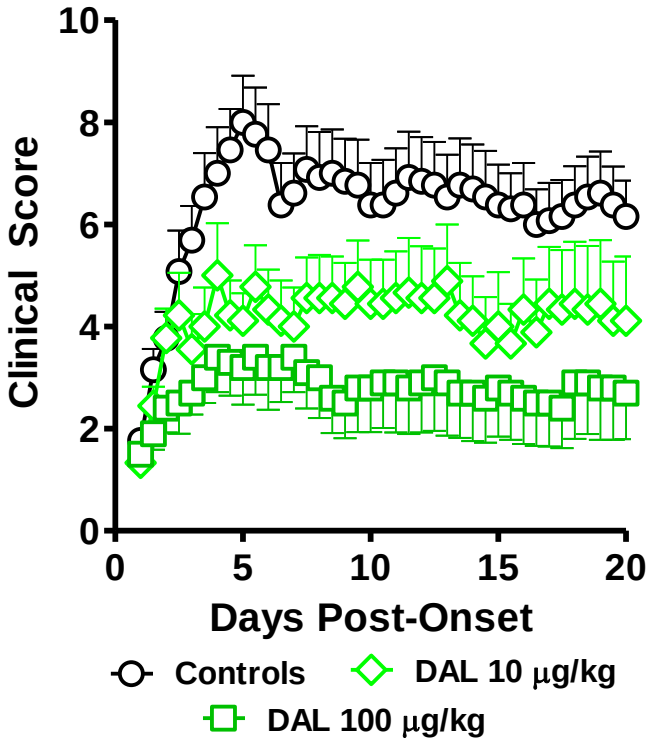
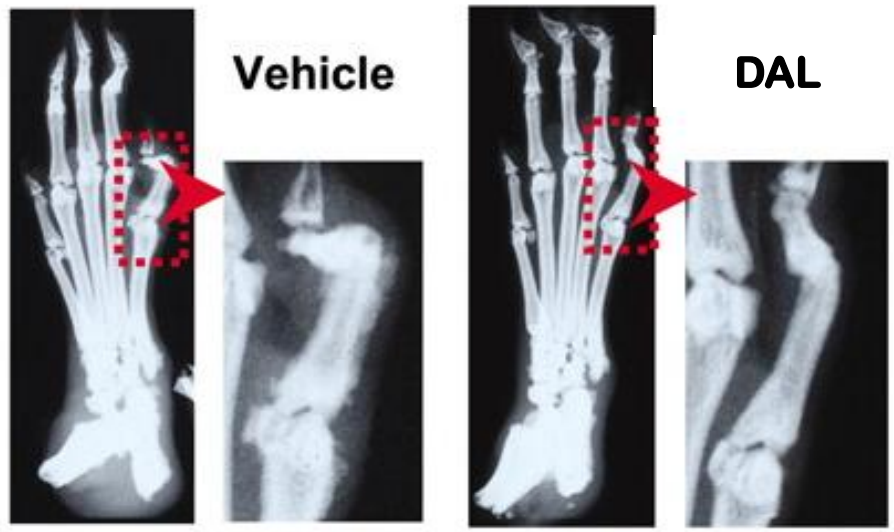
Animal Models: Dalazatide Effective in Arthritis Model





Dalazatide demonstrated efficacy in pristane-induced arthritis model

Beeton et al. Proc Natl Acad Sci U S A. 2006 Nov 14;103(46):17414-9.

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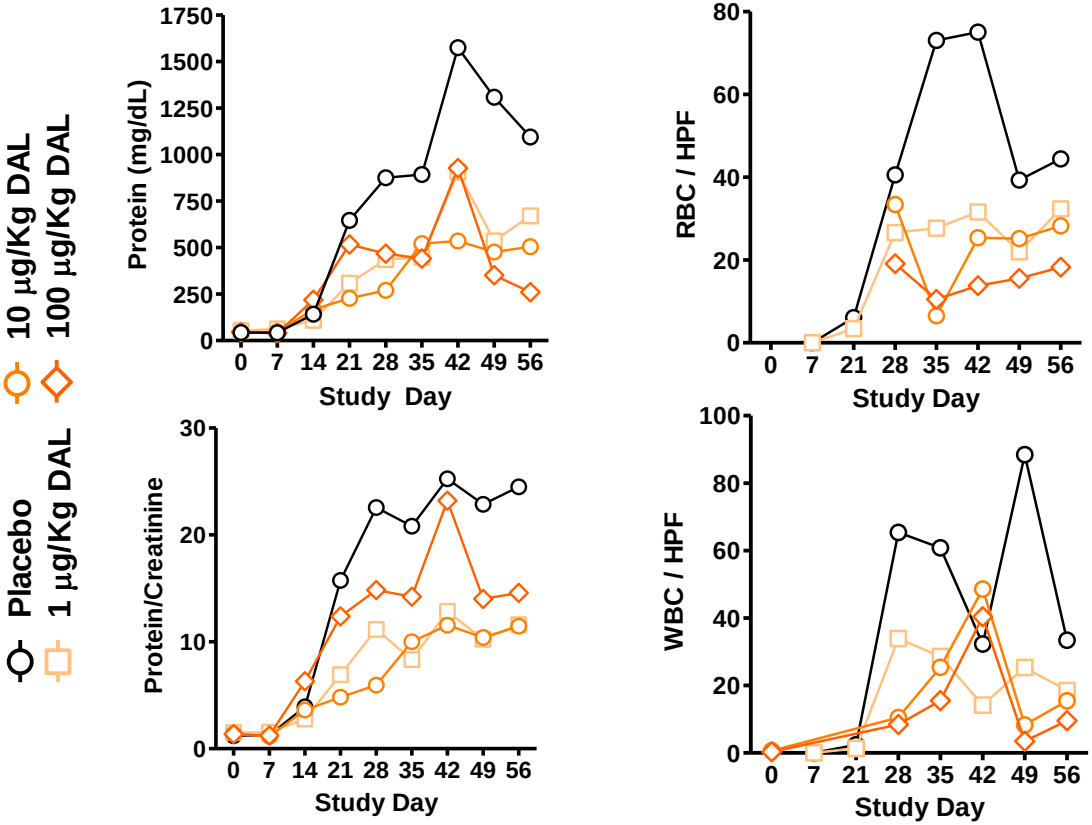
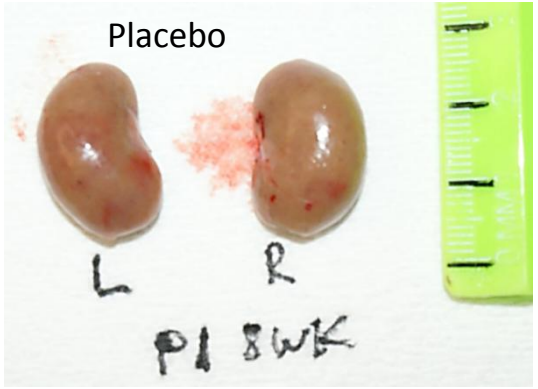
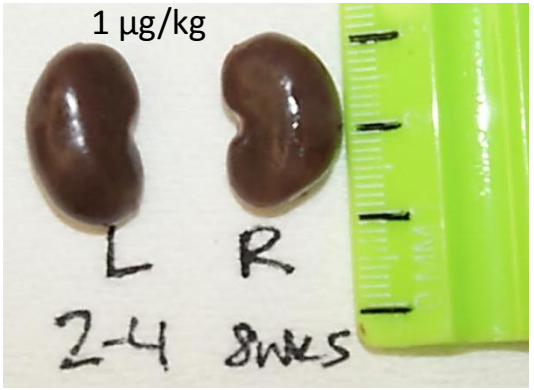
Animal Models: Dalazatide Effective in Autoimmune Glomerulonephritis







Dalazatide effective in glomerulonephritis model of SLE and preserved kidney function

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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

Evaluation	Toxicity
Histopathology	No
Clinical Chemistry/Hematology/Urinalysis	No
Safety Pharmacology	
Cardiovascular	No
Respiratory	No
Neurological	No

No safety pharm concerns or target organs of toxicity identified

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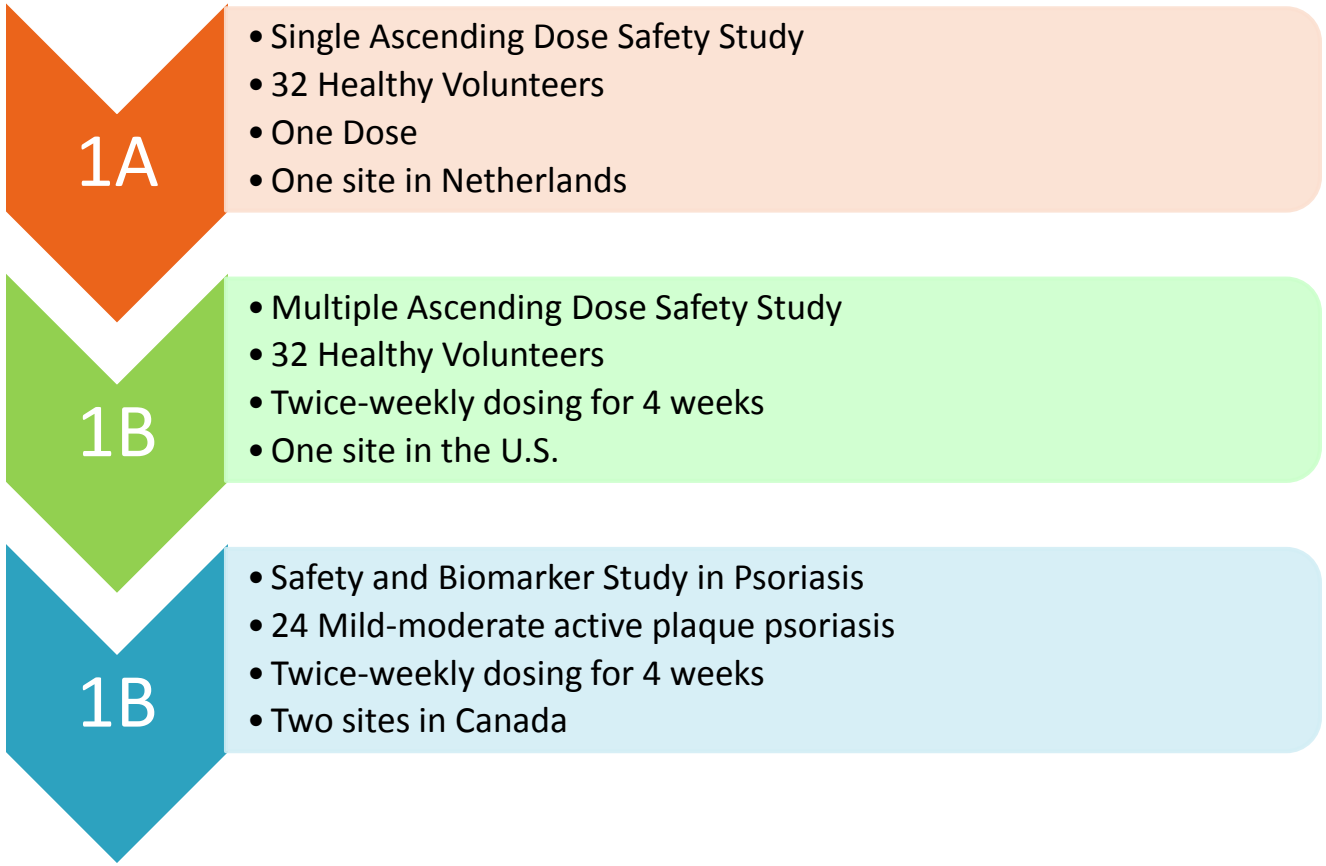
DALAZATIDE:
CLINICAL PROGRAM

Dalazatide Clinical Development Status



Phase 2 Ready Asset

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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

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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

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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

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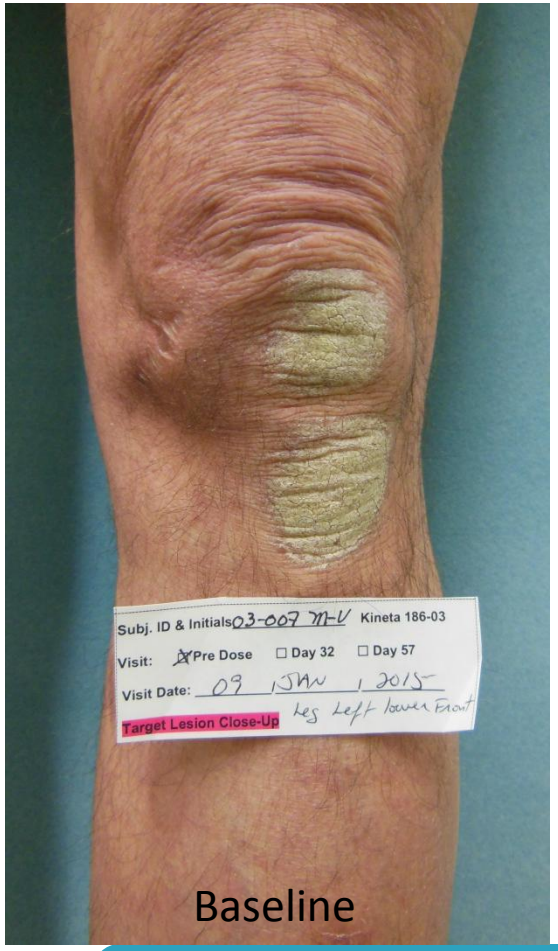
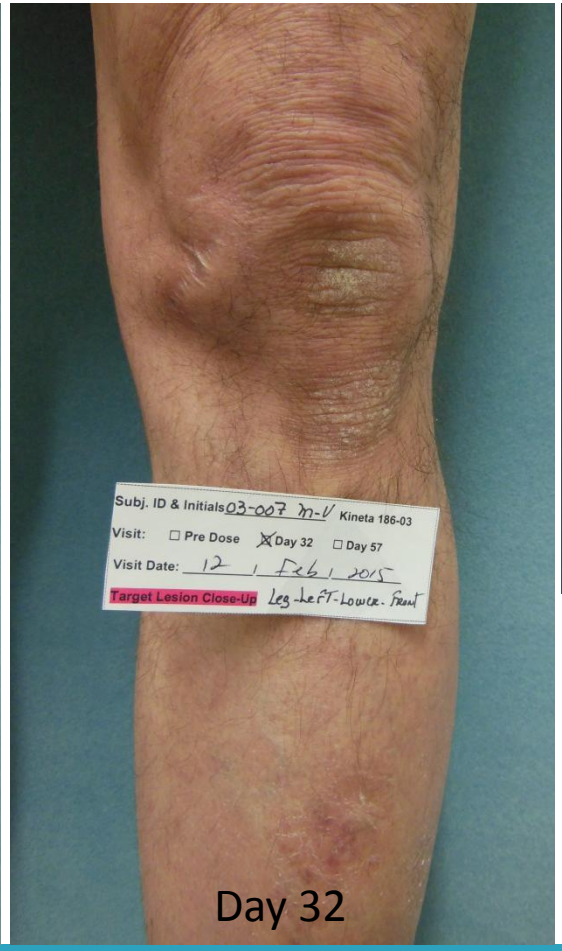
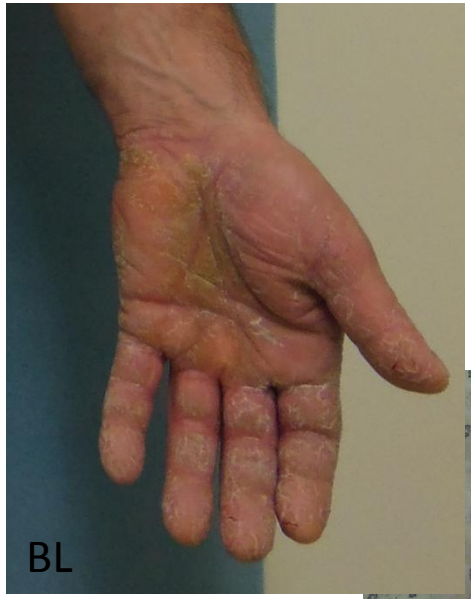
Dalazatide Clinical Activity - 30µg Dose



Baseline



Day 32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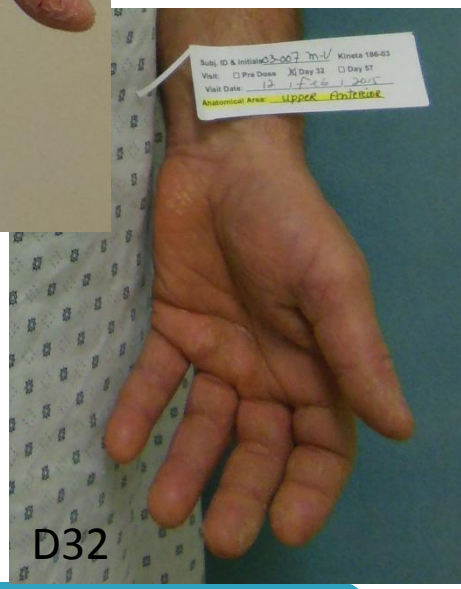
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Significant improvement in target lesions following 4 weeks of treatment.

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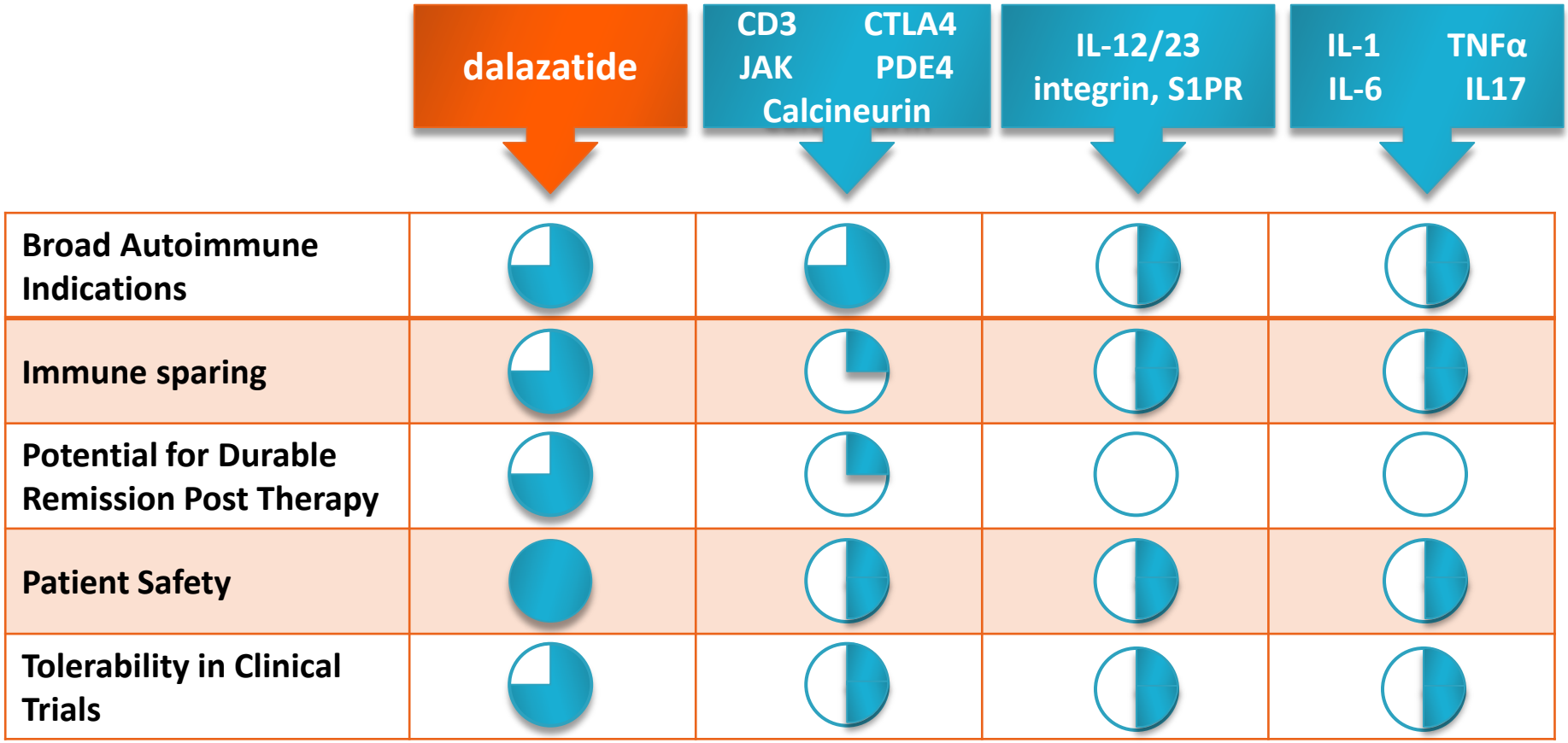
Why Dalazatide?



Dalazatide offers differentiation in indications and safety from competing therapies

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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

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Thank You & Questions

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