Dual targeting of Mast Cells and TSLP with the bispecific antibody CDX-622

Diego Alvarado, PhD

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Disclosures

- I am a full-time employee and stockowner of Celldex Therapeutics, Inc.

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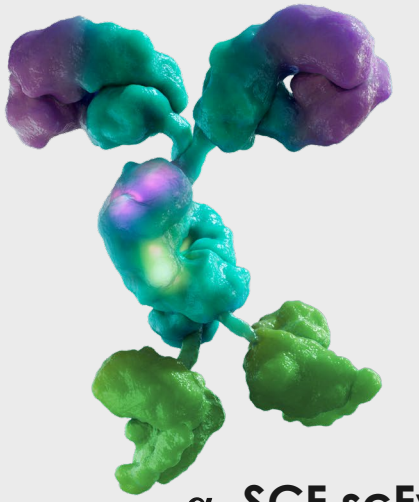
CDX-622: A Bispecific Antibody that Neutralizes TSLP and SCF

Designed to block TSLP-mediated inflammatory signals and inhibit/deplete mast cells

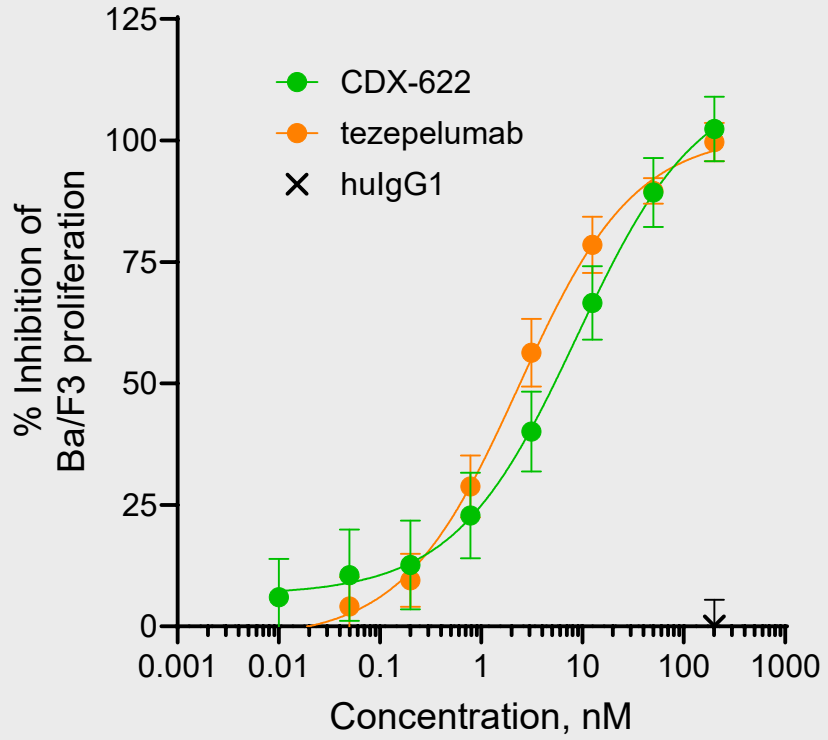
α–TSLP mAb



α–SCF scFv

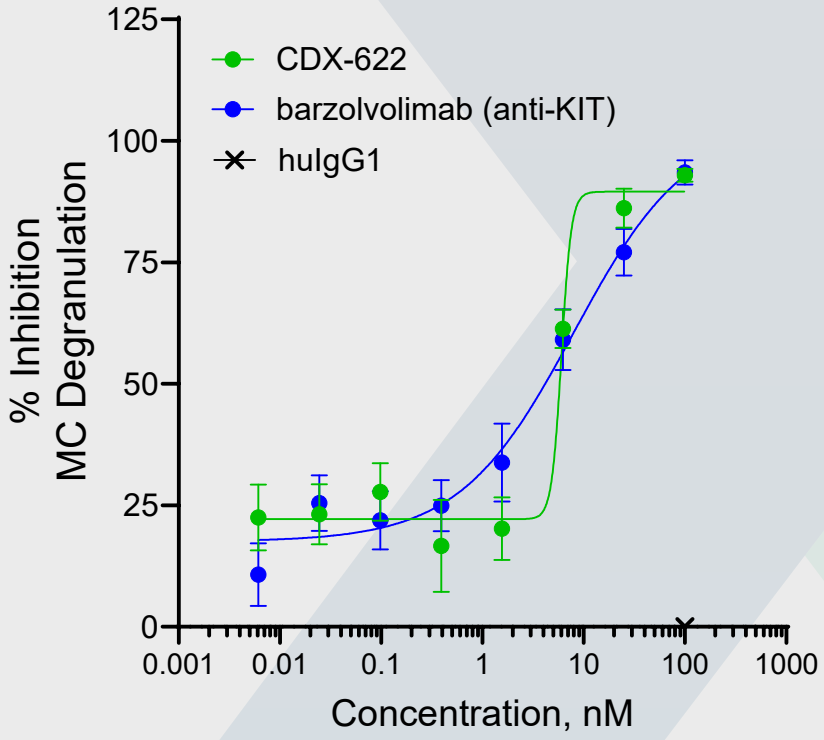
IgG1 engineered to disable effector function (AQQ) and reduce clearance (YTE)

Potent TSLP neutralizing activity



TSLP-dependent BaF3 Cell Proliferation

Potent SCF/KIT neutralizing activity



IgE+SCF-Dependent Mast Cell Degranulation

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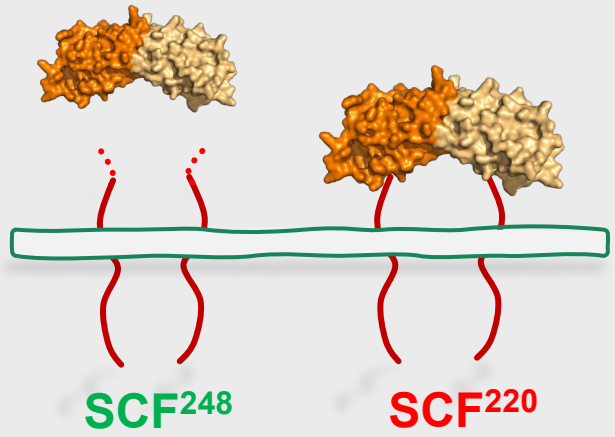
Two Isoforms of SCF with Independent and Overlapping Functions

Soluble SCF (derived predominantly from SCF^{248})

- Tissue homing
- Mast cell activity/survival
- Inflammation

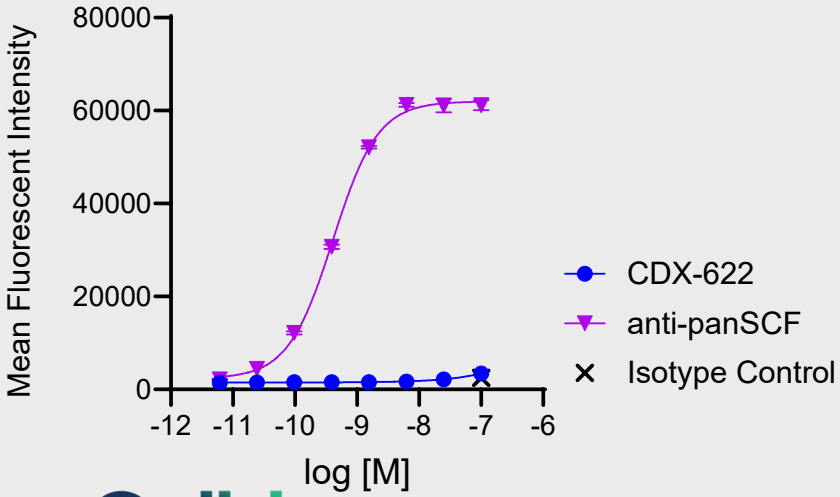


Membrane SCF (SCF^{220})

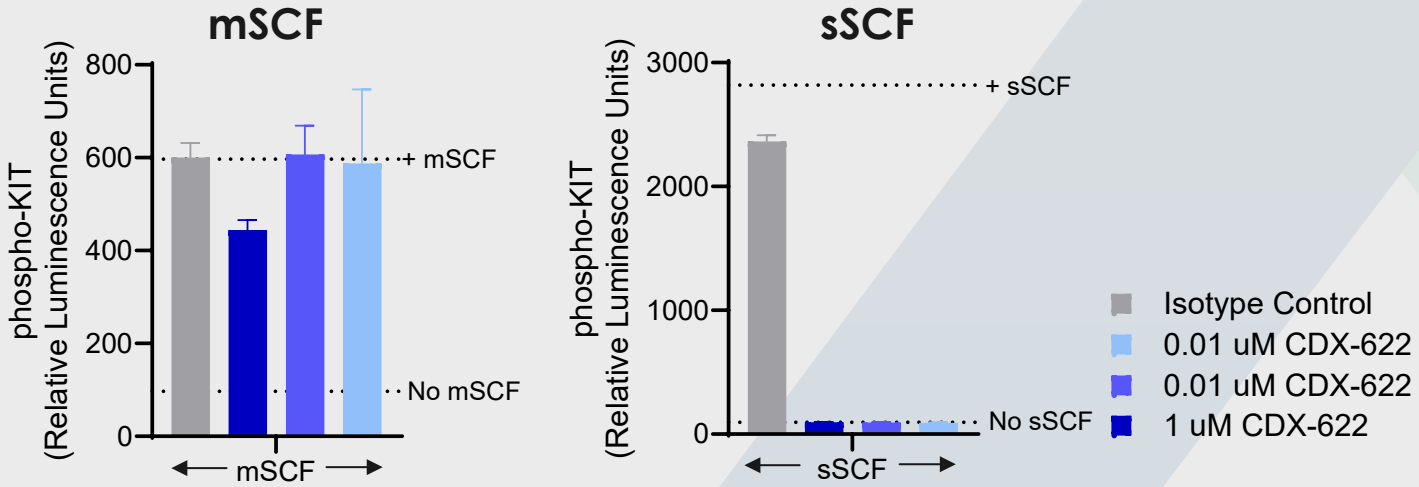
- Hematopoiesis
- Spermatogenesis
- Melanogenesis

CDX-622 preferentially inhibits soluble SCF mediated KIT signaling

Binds poorly to membrane SCF



Weakly inhibits KIT phosphorylation by membrane SCF



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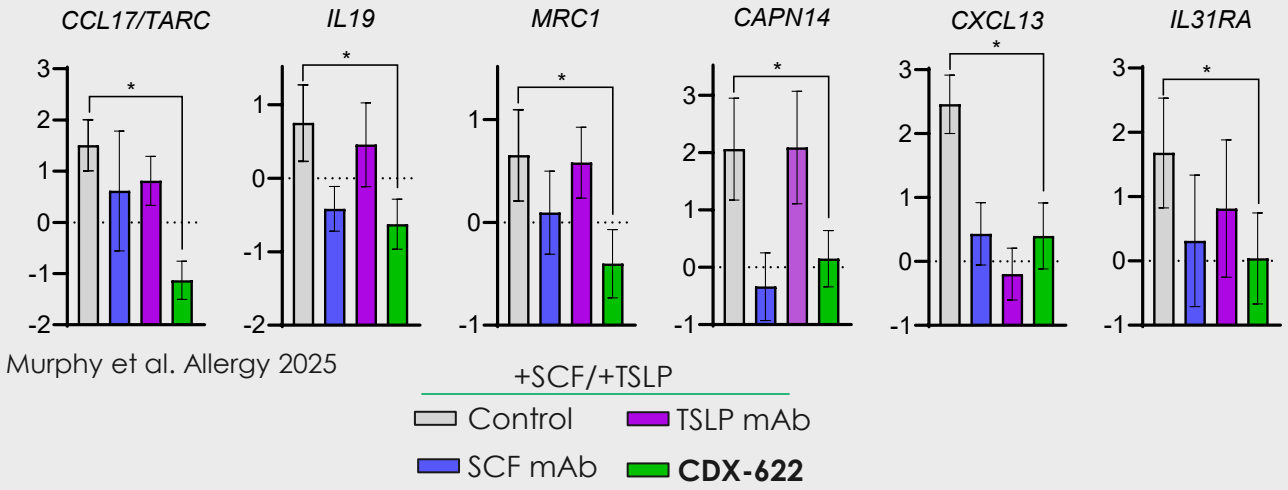
CDX-622 Preclinical Characterization

Ex vivo human skin slices treated with TSLP+SCF

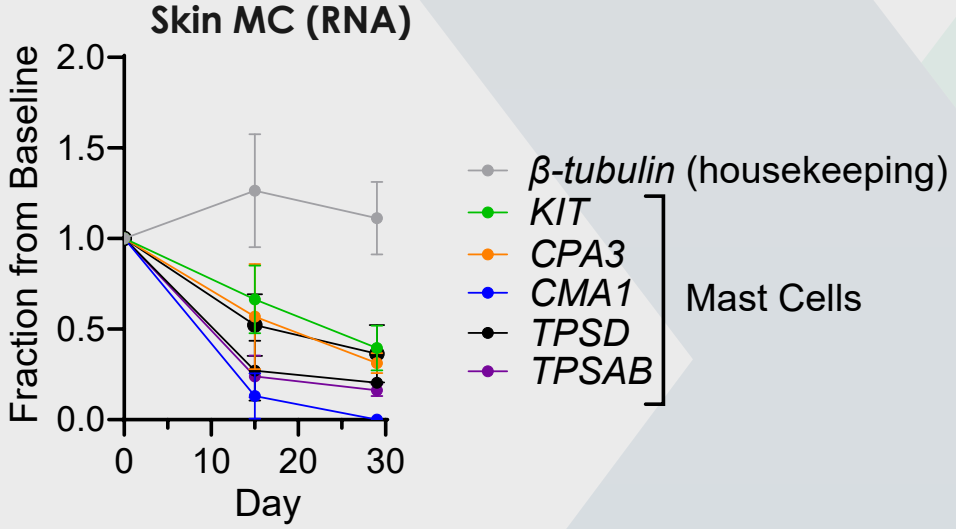
- CDX-622 inhibition of TSLP and SCF-dependent signatures



Murphy et al. Allergy 2025

In vivo pilot study in cynomolgus macaques

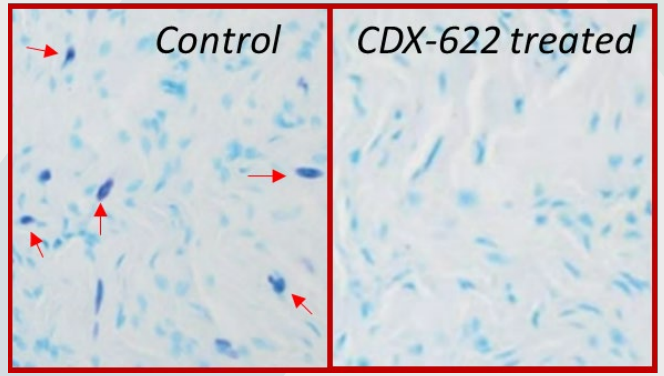
- CDX-622 binds to macaque TSLP and SCF
- Single dose of 10 mg/kg- reduction on mast cell genes



CDX-622 GLP toxicology study in NHPs - 3, 20, & 75 mg/kg Weekly x 9

- No observed adverse effect level (NOAEL) was 75 mg/kg/dose, the highest dose tested
- Mast cell depletion observed
- Notable KIT-related findings not seen
  - No fur discoloration
  - No change in bone marrow (M:E ratio)

Mast Cells (Toluidine Blue)



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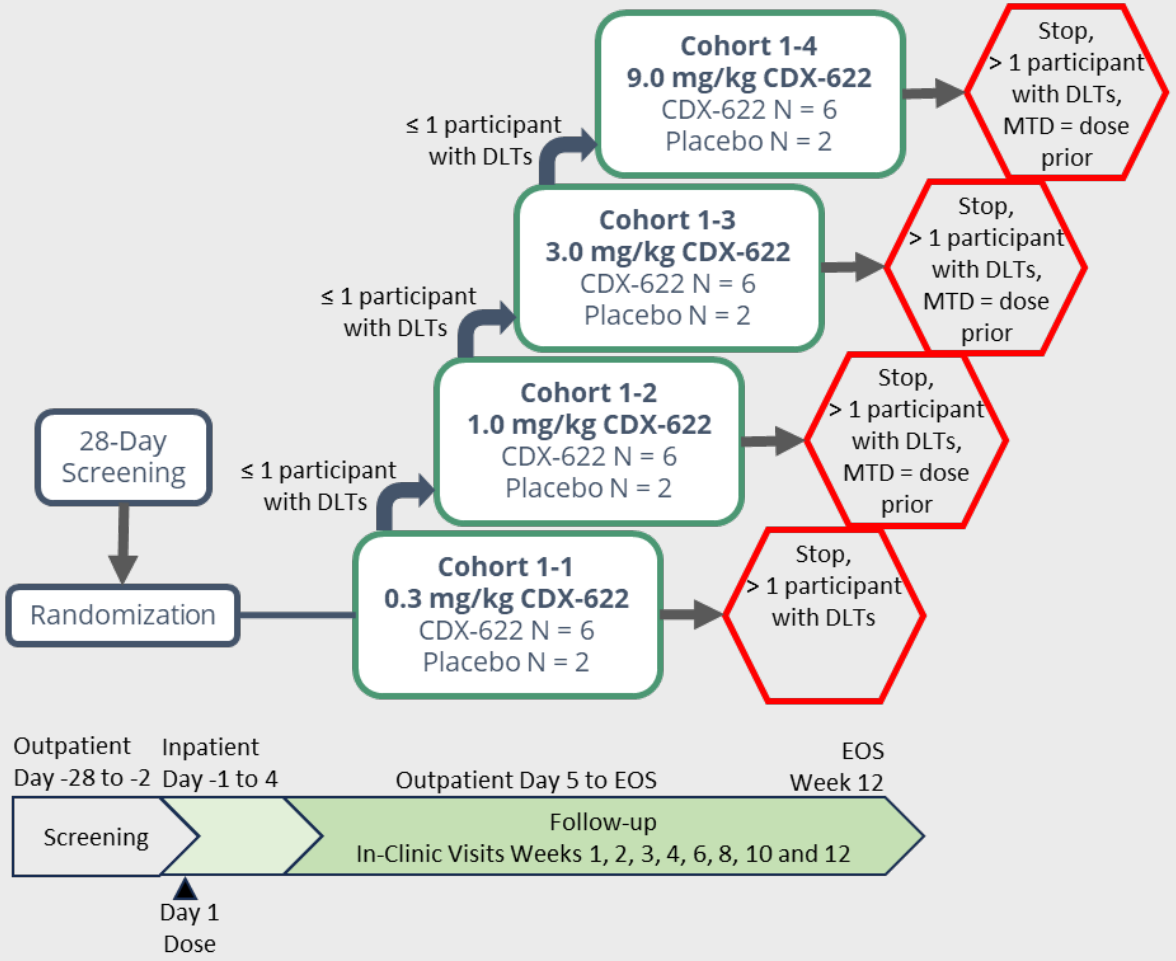
Phase 1 Healthy Volunteer Studies

Endpoints: Safety, PK, ADA, PD

Single Ascending Intravenous Dose (N=32) - Complete



Multiple Ascending dose study- ongoing

- 1, 3 and 9 mg/kg Q2W

CDX-622 subcutaneous single ascending dose

- Planned to initiate in 2025
- Support subQ dosing in Phase 2 studies

CDX-622 PoM study in asthma patients

- Demonstrate effects on TSLP and SCF biomarkers
  - Impact on FeNO, Eos, and IL-5
  - Impact on lung mast cells
- Planned to initiate in 2026

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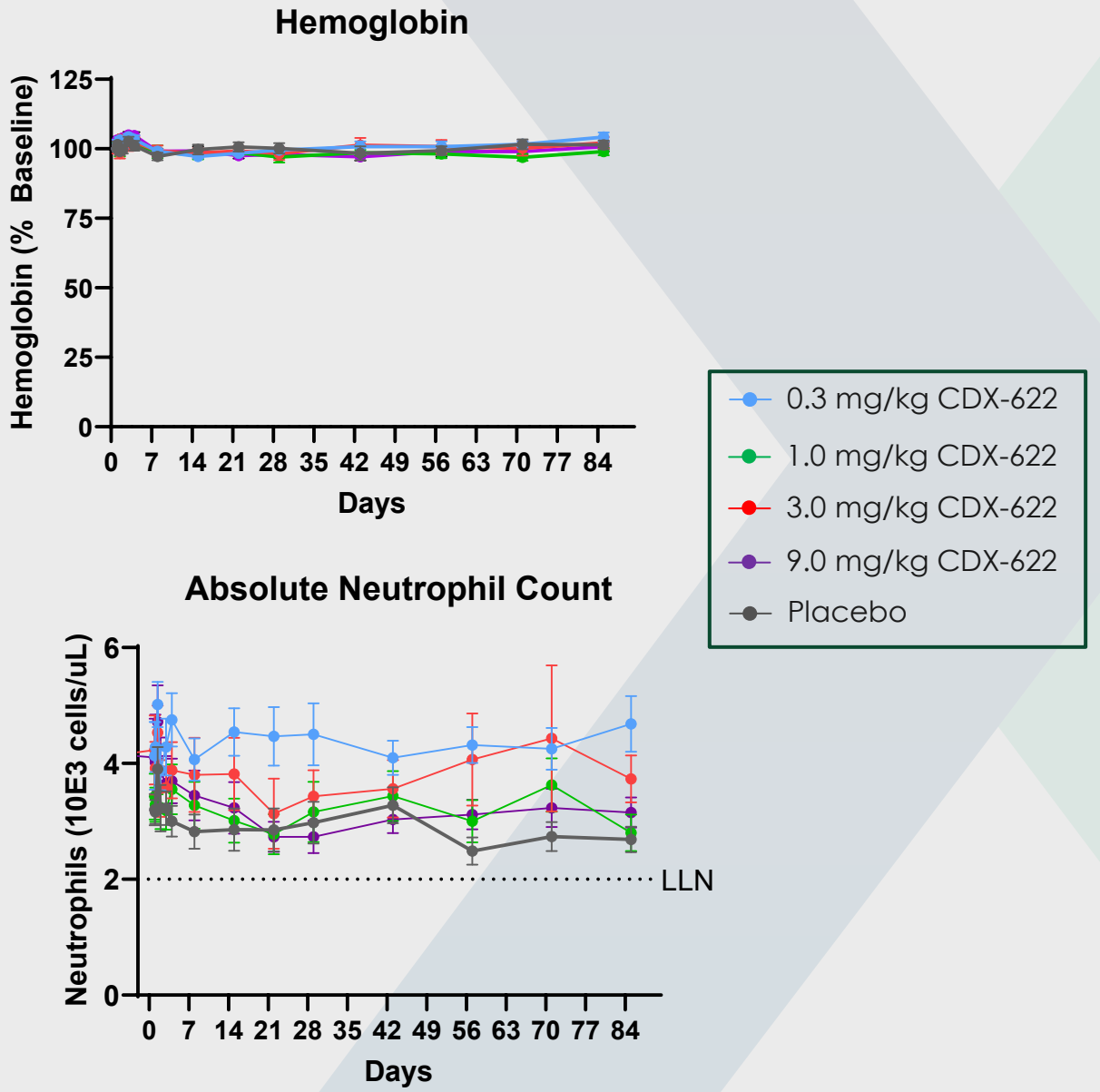
CDX-622 Was Well Tolerated

Clean Safety Profile

- 32 participants were enrolled:
  - 24 received CDX-622, 8 received placebo.
- There were no dose limiting toxicities, serious adverse events, or infusion reactions
- No significant changes in hematology values relative to placebo-treated participants
- No reported hair/skin pigment changes in any participant



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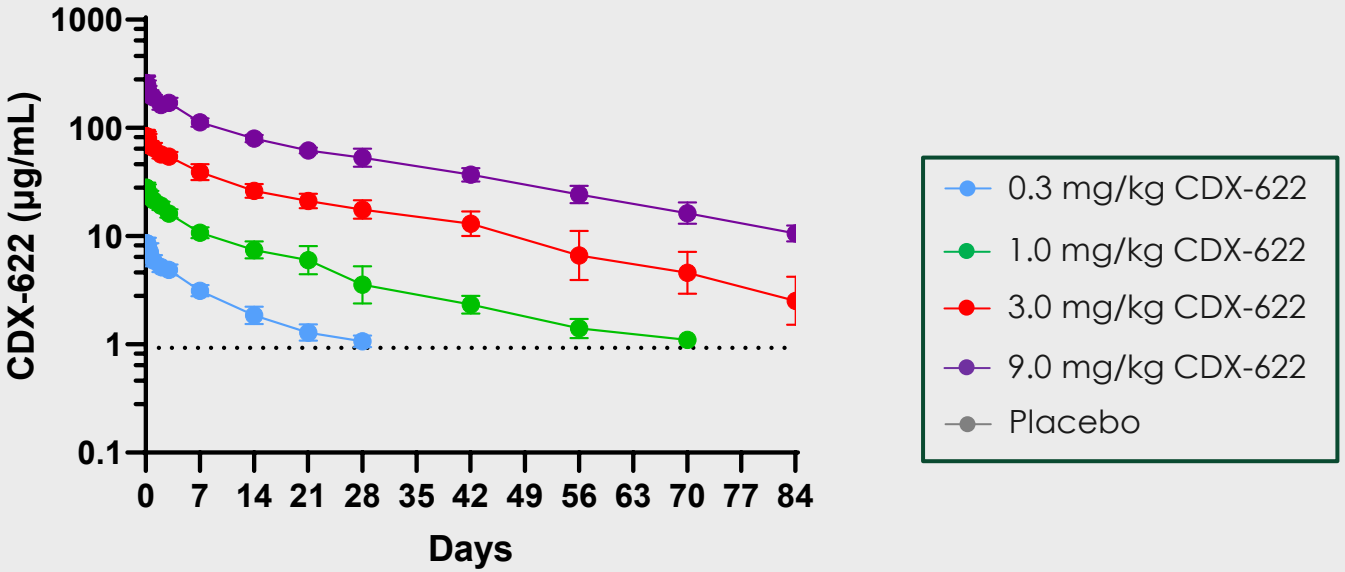
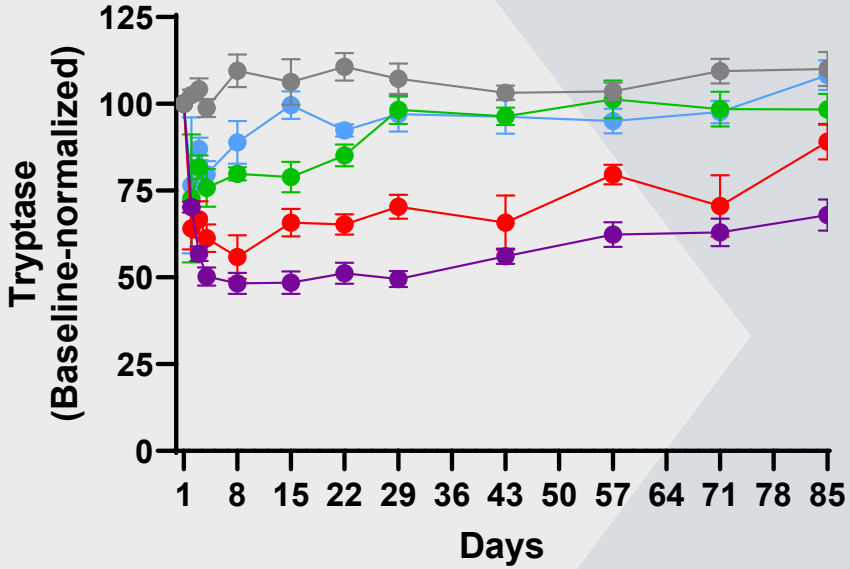
CDX-622 Exhibits mAb-Like Pharmacokinetics and Significantly Reduces Serum Tryptase

Pharmacokinetics



Serum Tryptase



- Good serum half life (~18 days at 9 mg/kg) and decreased clearance consistent with engineered Fc mutations that enhance FcRn binding
- No evidence of anti-drug antibodies

- Dose-dependent, rapid and sustained decrease in circulating tryptase consistent with systemic mast cell inhibition

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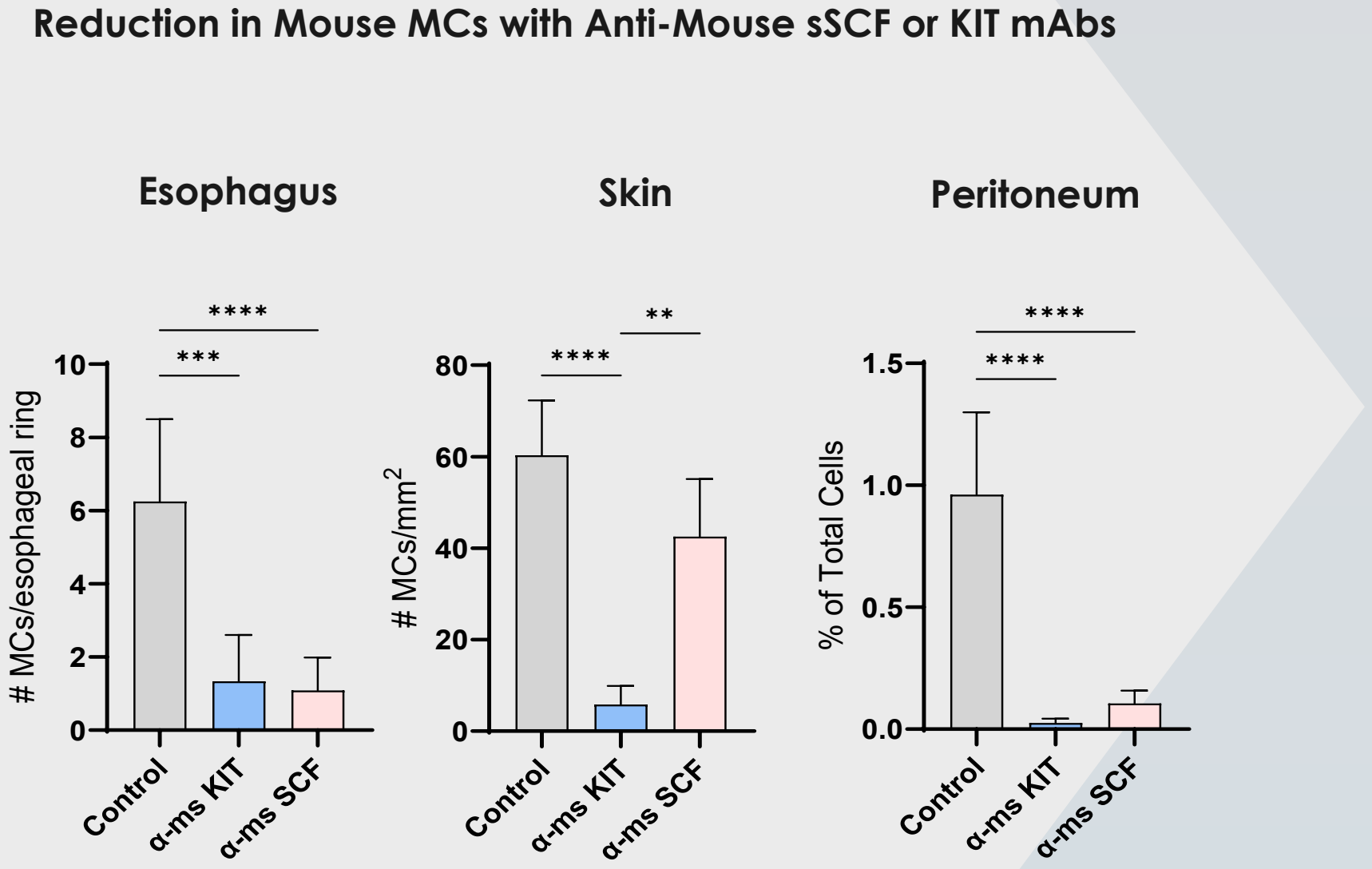
Mast Cell Populations May Respond Differently to Inhibition of Soluble SCF



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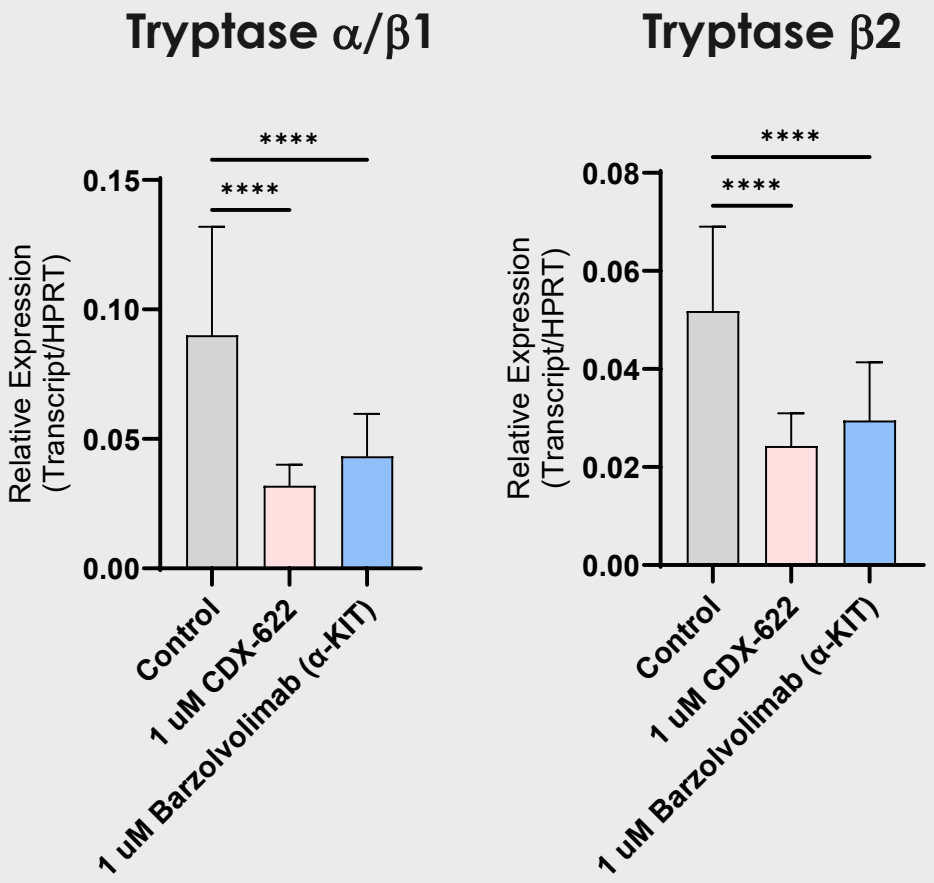
Evidence of Potent Impact on Human Lung Mast Cells

Reduction in MC Transcripts in Human Lung Explants (N=8 Donors)



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Summary

- Dual neutralization of TSLP and SCF (mast cells) may lead to improved efficacy in disorders where both pathways are implicated including asthma, allergic and fibrotic conditions
- CDX-622 potently neutralizes TSLP and soluble SCF and leads to mast cell reduction in preclinical models.
- CDX-622 was well tolerated with no emergent adverse events related to systemic KIT inhibition in a single ascending dose healthy volunteer study
- CDX-622 exhibits mAb-like pharmacokinetics and leads to dose-dependent reductions in serum tryptase, indicative of mast cell depletion
- Preferential inhibition of soluble over membrane SCF may lead to profound depletion of certain MC populations, while sparing other KIT-dependent functions.

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Acknowledgements

- We would like to thank our study participants, clinical staff, and our colleagues at Celldex.

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