THE POWERFUL MAST CELL

a promising target in treating allergic and inflammatory diseases

April 25, 2024

Today's agenda and speakers

WELCOME & INTRODUCTION

Fouad Namouni, MD
President, Research & Development

MAST CELLS: POWERFUL DRIVERS OF DISEASE

Becker Hewes, MD
Chief Medical Officer

Mariana Castells, MD, PhD
Brigham and Women's Hospital

A BLUEPRINT FOR TARGETING MAST CELLS

Percy H. Carter, PhD, MBA
Chief Scientific Officer

Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding plans, strategies, timelines and expectations for the company's future business growth, including the company's vision for mast cell driven diseases and the possibility of capturing multiple blockbuster opportunities; statements regarding whether any of the company's product candidates will successfully address medical needs; statements regarding the company's potential to drive innovation in allergic and inflammatory disease and its potential to revolutionize the allergy/inflammation space with BLU-808; statements regarding plans and expectations for the company's current or future approved drugs and drug candidates; the potential benefits of any of the company's current or future approved drugs or drug candidates in treating patients; and the company's strategy, goals, business plans and focus.

The words "aim," "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks and uncertainties related the company's ongoing and planned research and discovery activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; the company's ability and plans to continue to expand a commercial infrastructure, and successfully launch, market and sell current or future approved products; the company's ability to successfully expand the approved indications for AYVAKIT/AYVAKYT or obtain marketing approval for AYVAKIT/AYVAKYT in additional geographies in the future; the delay of any current or planned clinical trials or the development of the company's current or future drug candidates; the company's advancement of multiple early-stage efforts; the company's ability to successfully demonstrate the safety and efficacy of its drug candidates and gain approval of its drug candidates on a timely basis, if at all; the preclinical and clinical results for the company's drug candidates, which may not support further development of such drug candidates either as monotherapies or in combination with other agents or may impact the anticipated timing of data or regulatory submissions; the timing of the initiation of clinical trials and trial cohorts at clinical trial sites and patient enrollment rates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; the company's ability to obtain, maintain and enforce patent and other intellectual property protection for AYVAKIT/AYVAKYT or any drug candidates it is developing; the company's ability to successfully expand its operations, research platform and portfolio of therapeutic candidates, and the timing and costs thereof; and the success of the company's current and future collaborations, financing arrangements, partnerships or licensing arrangements. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the company's filings with the Securities and Exchange Commission (SEC), including the company's most recent Annual Report on Form 10-K, as supplemented by its most recent Quarterly Report on Form 10-Q and any other filings that the company has made or may make with the SEC in the future. The forward-looking statements in this presentation are made only as of the date hereof, and except as required by law, the company undertakes no obligation to update any forward-looking statements contained in this presentation as a result of new information, future events or otherwise. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

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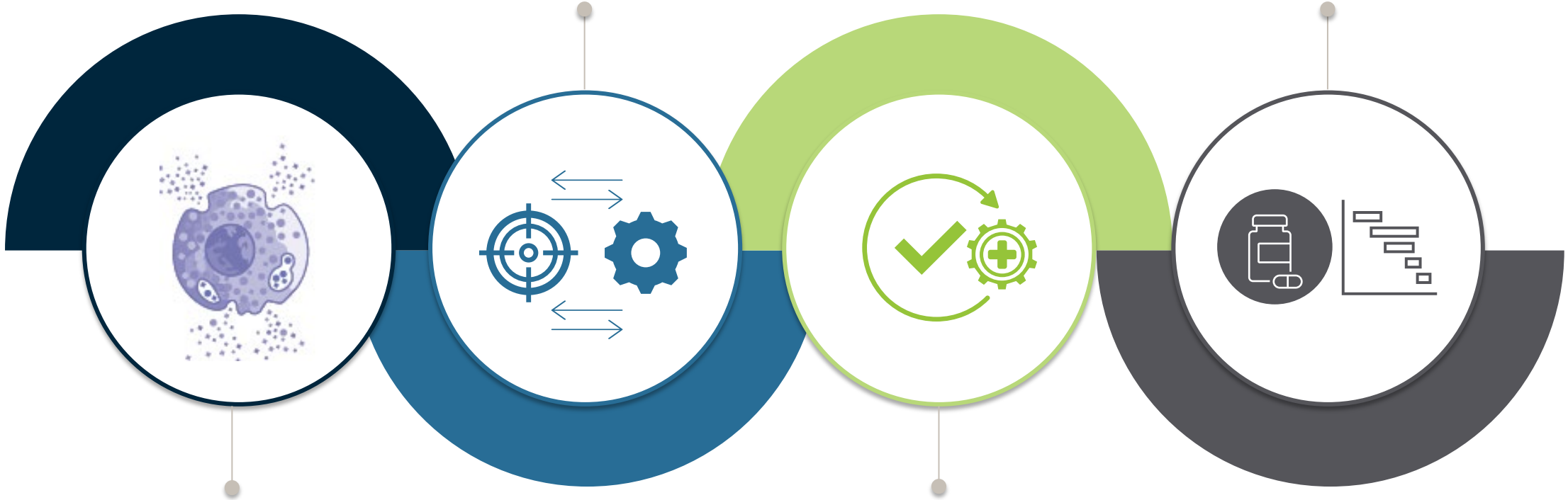
Blueprint's scientific vision for mast cell driven diseases

Optimize target and modality approach

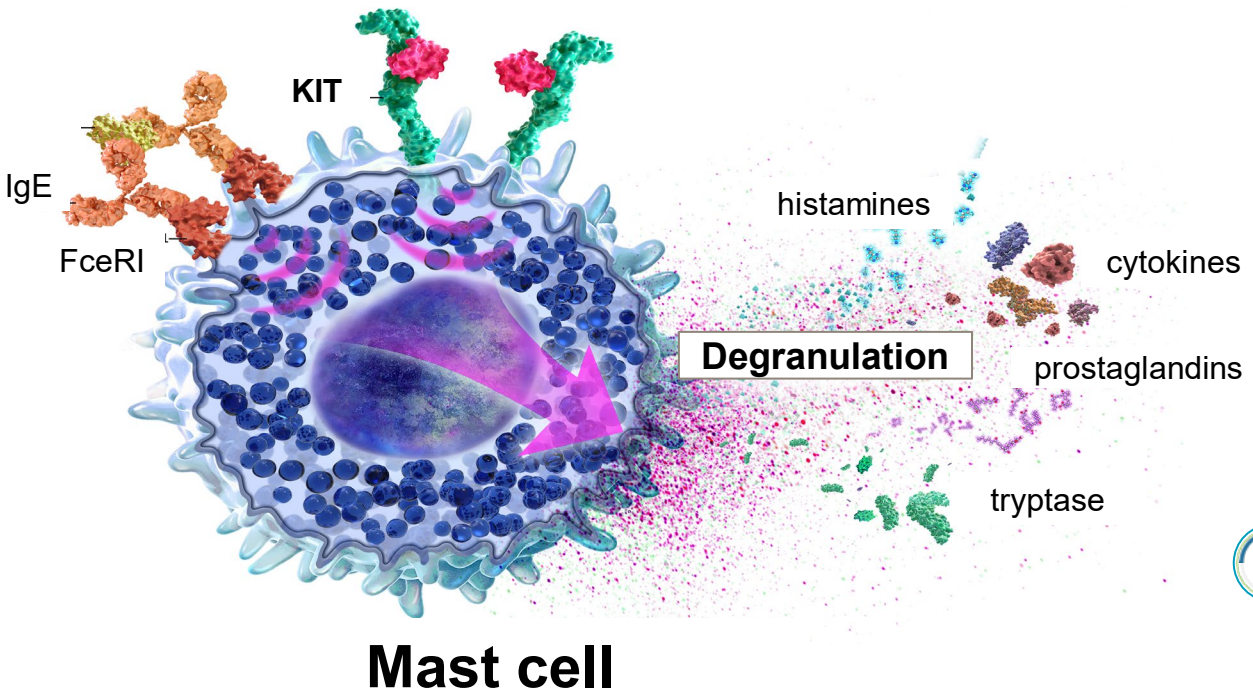
Pursue "pipeline in a pill" therapies to capture multiple blockbuster opportunities



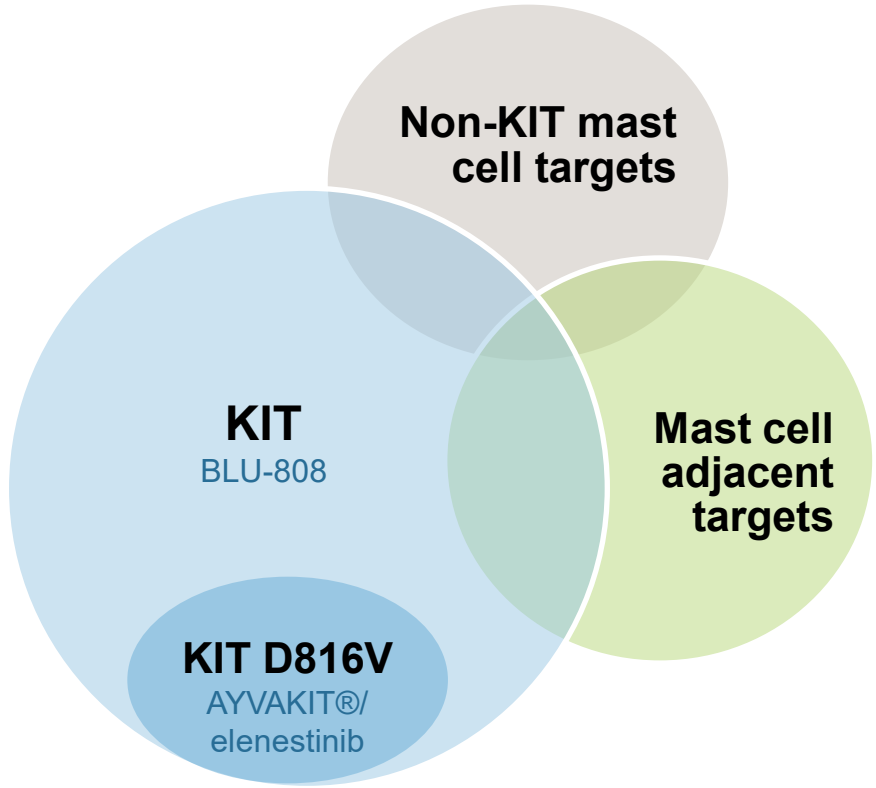
Leverage deep understanding of mast cell biology

Establish **strong POC and rapidly de-risk** development

Mast cells are core drivers in a range of inflammatory diseases



- **Central effector cell** in many inflammatory diseases
- Activation leads to release of multiple classes of inflammatory molecules with a broad range of physiological effects
- KIT is a clinically validated **master control switch** for mast cells



- Monotherapy opportunities to inhibit wtKIT, a primary mast cell target
- Opportunities for novel regimens of combination approaches at intersections between therapeutic targets

Proprietary image; AVYAKIT® avapritinib

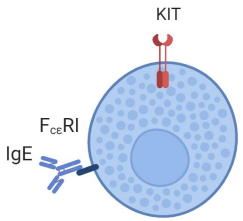
Blueprint is poised to drive a new wave of innovation in allergic and inflammatory disease

Mast cells are key drivers of inflammatory responses, yet therapeutic interventions have focused on the mediators not the source.

Directly inhibiting activation and degranulation of mast cells is an innovative approach to how we treat several allergic disorders.

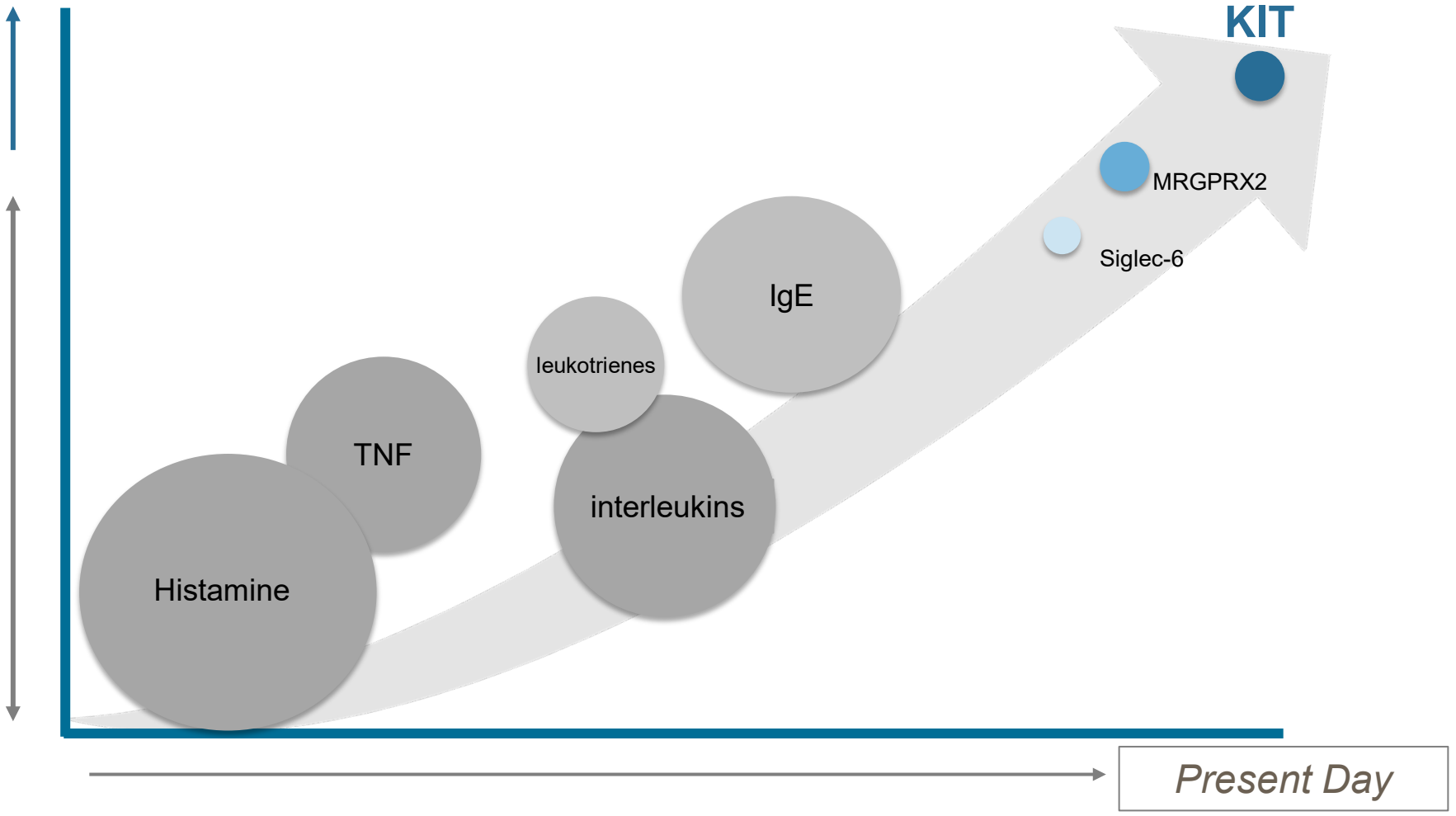
Blueprint is well positioned to succeed in large patient populations with significant medical need by delivering blockbuster medicines.

Directly targeting the mast cell stands out as an attractive opportunity in the allergy and inflammation space



Mast cell targeting

Mediator Targeting



Note: bubble size is illustrative of the competitive intensity directed at each target

Mast Cells: Powerful Drivers of Disease

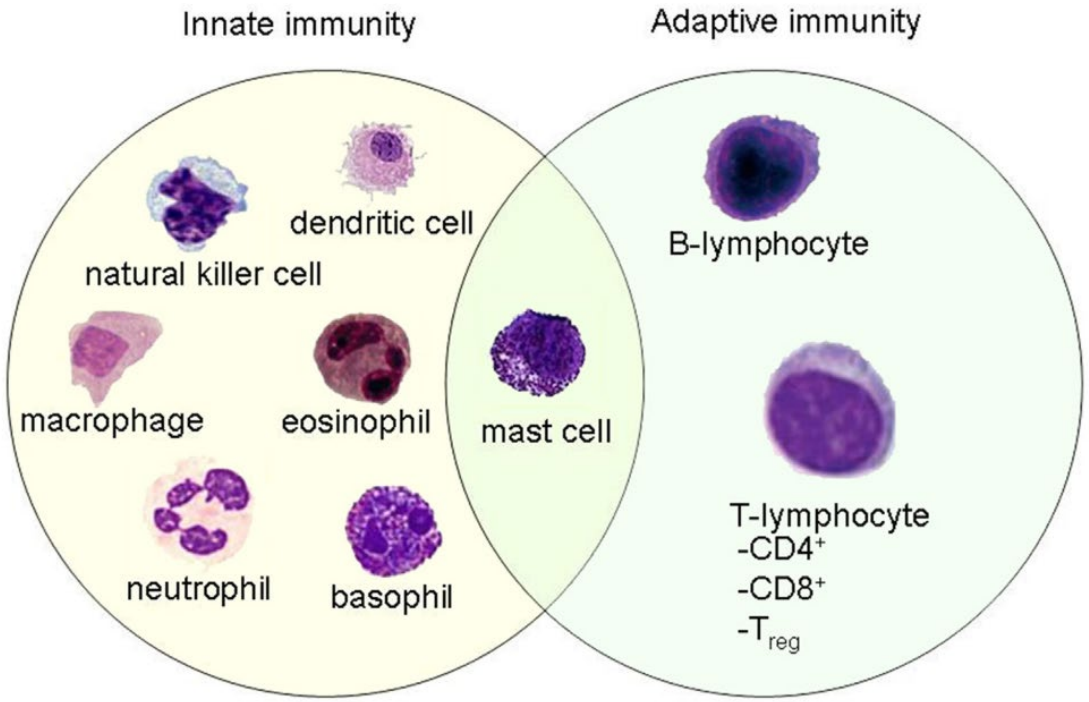
A Conversation with Dr. Becker Hewes and Dr. Mariana Castells

Mariana Castells, MD, PhD

- Brigham and Women's Hospital, Boston
  - Director, Mastocytosis Center
  - Director, Drug Hypersensitivity and Desensitization Center
- Professor, Harvard Medical School
- Board of Directors: AAAAI, ABAI
  - AAAAI Foundation Research Chair
- PIONEER trial investigator

AAAAI, American Academy of Allergy, Asthma & Immunology; ABAI, American Board of Allergy and Immunology.

Mast cells are central to multiple components of immune response



Key roles impacting both innate and adaptive immunity

First line of defense against pathogens, and respond to other stimuli including allergens

Enriched in tissues that **interface with external environment**, including skin, lungs, GI system

Degranulation releases inflammatory modulators to protect the body

Downstream impact on multiple cell types of the **adaptive immune** system

Pathogenic behavior can cause **disruption across immune system**

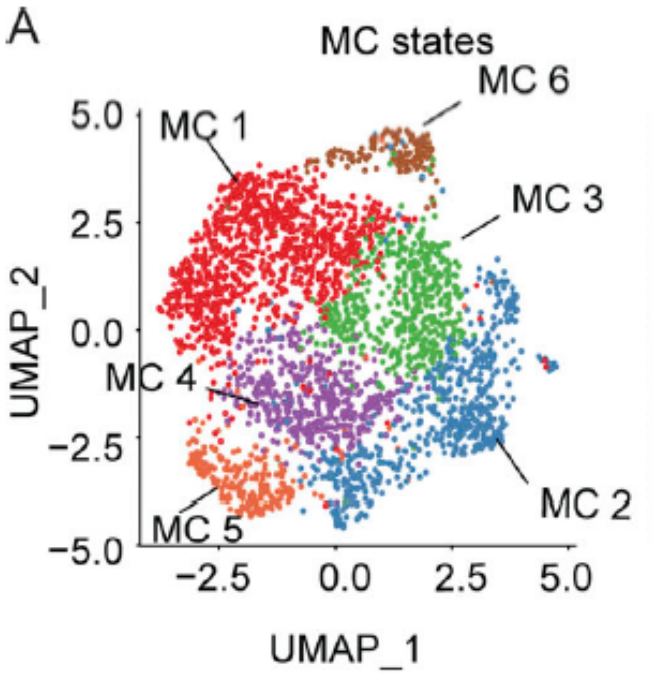
Molderings, G.J. et al, (2015) *Critical Reviews in Oncology/Hematology*

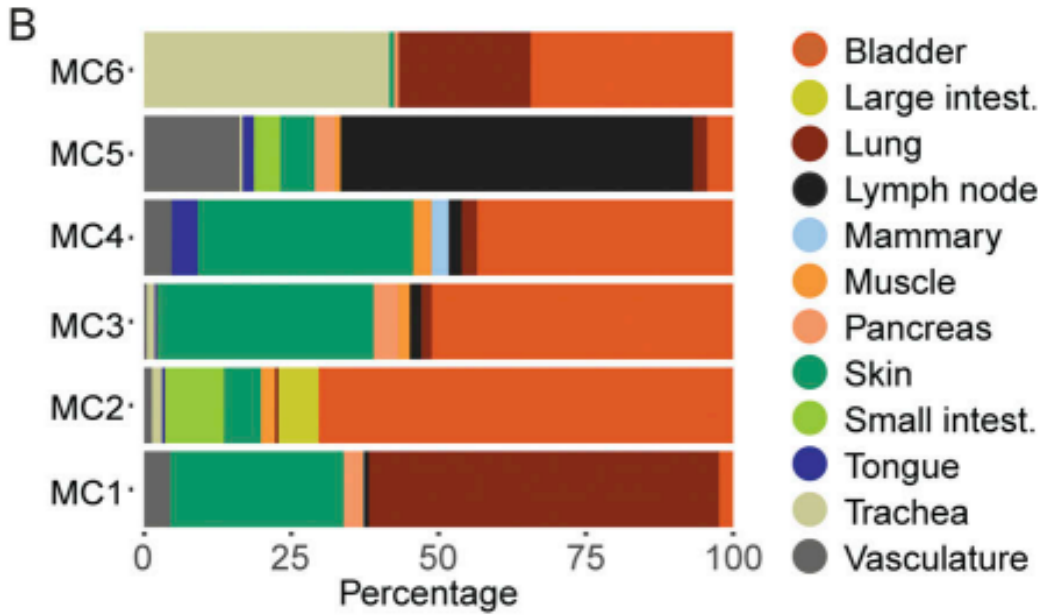
Does location of the mast cell drive differences in normal or pathologic biology?

Mast cell phenotype and tissue distribution vary widely

Genetic profiling reveal 6 distinct mast cell subsets all of which express KIT.

All tissues examined have unique mast cell repertoires.

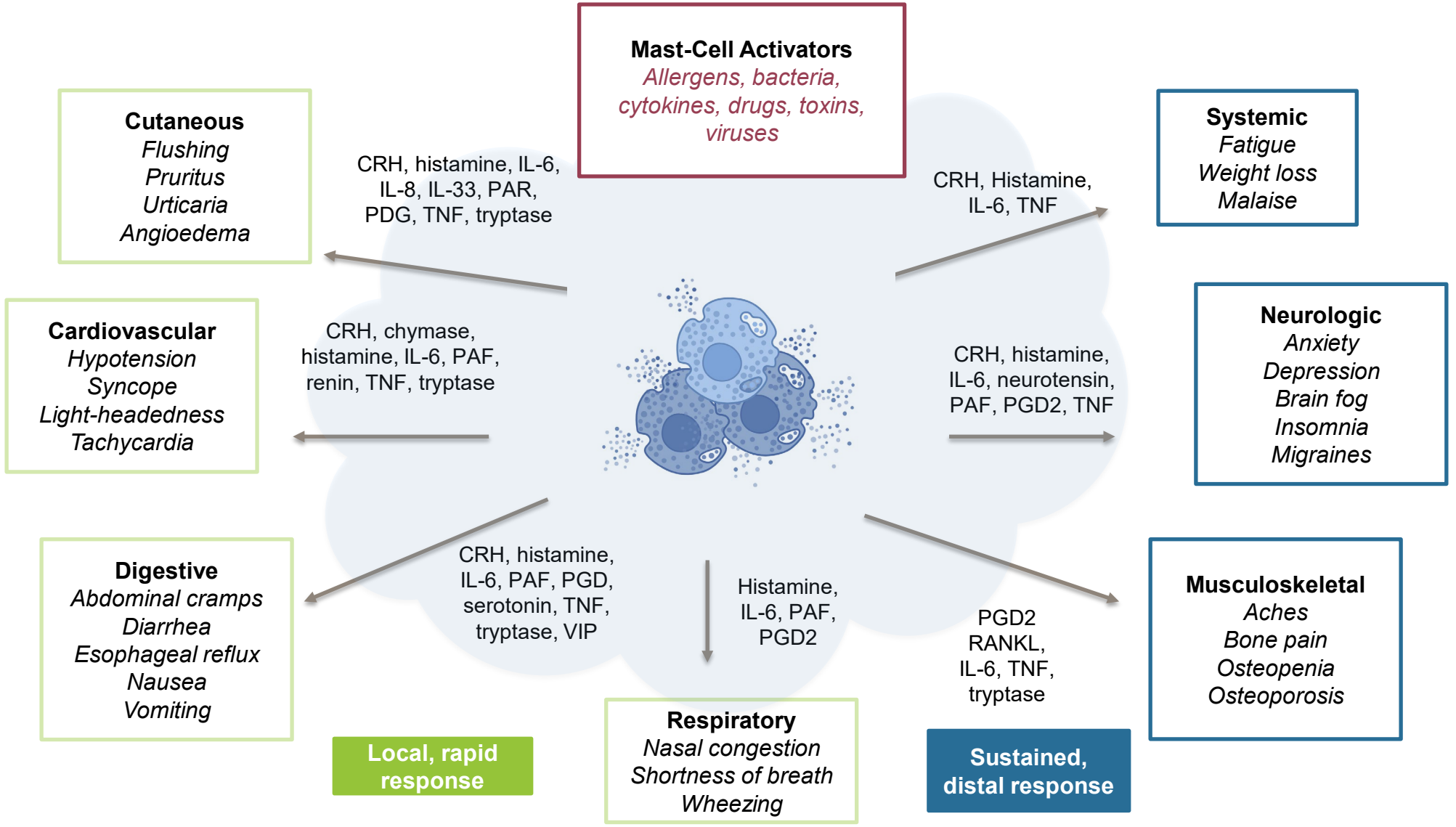




- Mast cell variation in location and phenotype may drive differential disease manifestations.
- Ideally therapy should be tailored to the desired effect in the target tissue.

Tauber, T et al. (2023) *J Exp Med*.

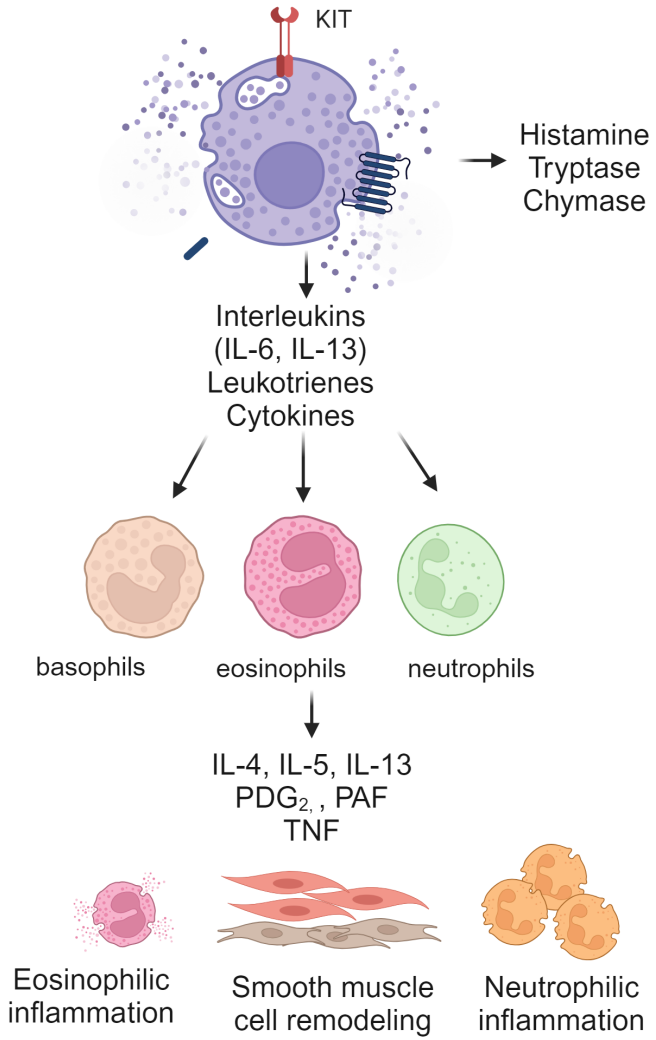
Mast cells impact behavior of cells throughout the body



Adapted from Theoharides, T. et al, (2015) *New England Journal of Medicine*

How do mast cells contribute to inflammation throughout the body?

Mast cell activation initiates a wide range of pathological effects



Rapid response
Blood pressure changes
Vasoconstriction/dilation
Bronchoconstriction

- Anaphylaxis
- Asthma

Early response
Hives
Flushing
Congestion

- Urticaria
- Allergic rhinitis

Chronic response
Smooth muscle remodeling
Bone changes
Fatigue

- SM
- Chronic GI disorders
- Osteopenia/ Osteoporosis

Mast cells are activated by various factors then…

…rapid release of preformed granules leads to immediate response…

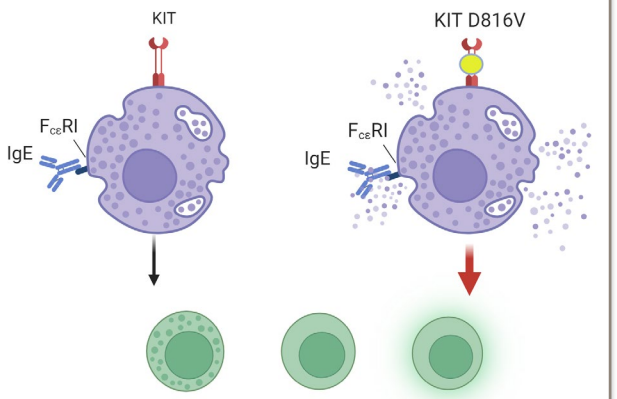
…plus, release of newly synthesized molecules activates other cells ….

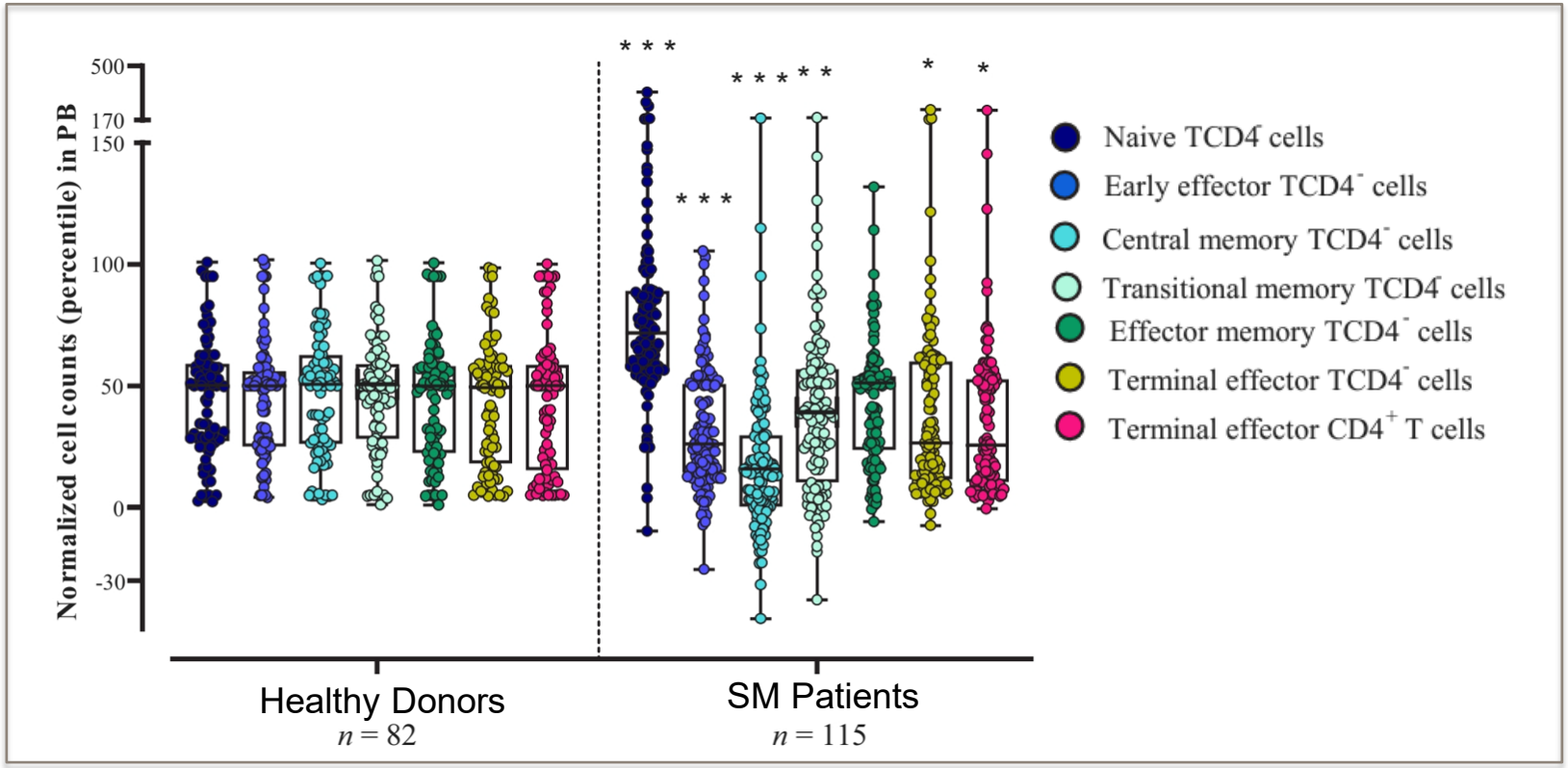
…resulting in both local and distant effects.

Created with Biorender.com

Insights from SM: mast cells influence the adaptive immune system

Experimental design





- KIT D816V mutant provides a system to study the interplay between mast cells and other components of the immune system
- Altered mast cell function results in changes across subtypes of T-cells
- Similar fingerprints of altered T-cell function are seen in other diseases

Perez-Pons, A et al., (2024) *Allergy*. Created with BioRender.com.

What role do mast cells play in disease pathogenesis?

Mast cells range from primary disease driver to a secondary response resulting from inflammation

MAST CELL-DEPENDENT
Proliferation and activation drives disease

Mutated mast cell activation
- Systemic mastocytosis
- monoclonal MCAS

Non-mutated mast cell hyperactivation
- Idiopathic MCAS
- Hereditary alpha tryptasemia

Allergic diseases
- Chronic urticaria
- Nasal polyps
- Insect sting
- Food allergy
- Allergic rhinitis

MAST CELL-ASSOCIATED
Implicated in disease but do not drive pathogenesis

Gastrointestinal
- Irritable bowel syndrome
- Eosinophilic GI disorders

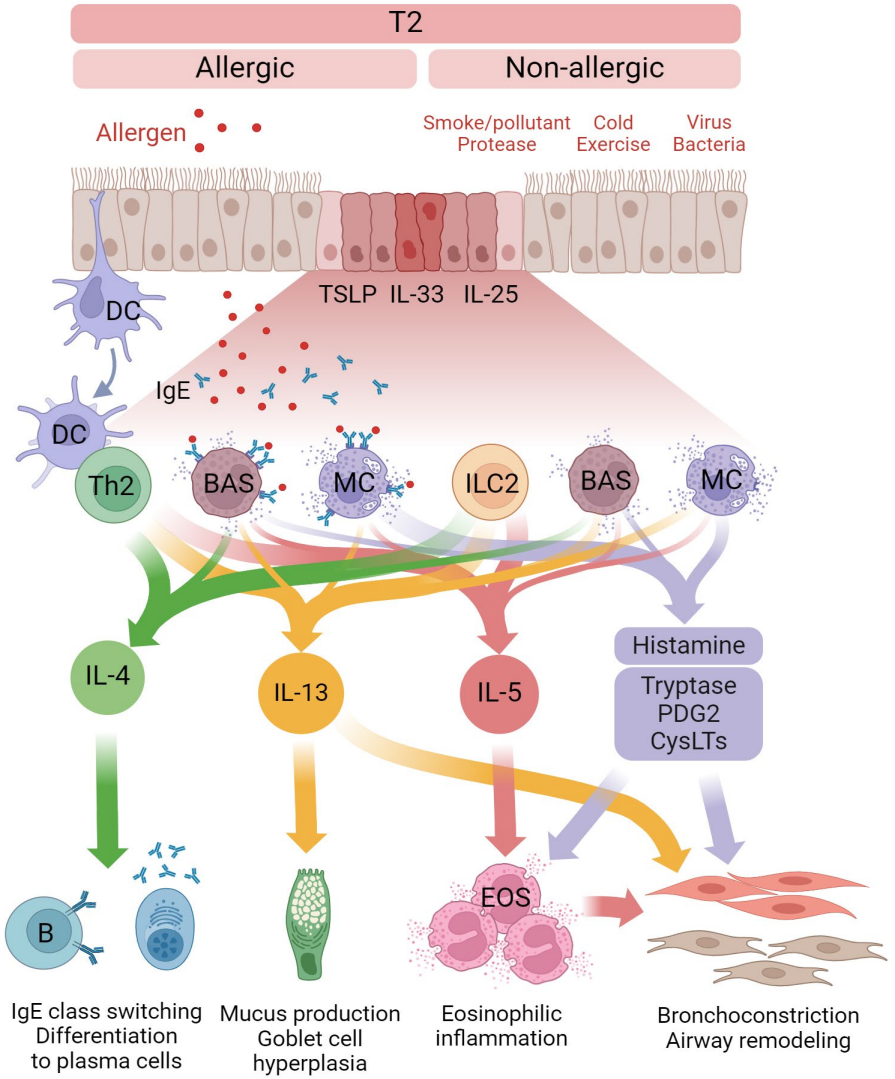
Respiratory
- Idiopathic pulmonary fibrosis
- COPD

Skin
- Psoriasis
- Atopic dermatitis
- Chronic prurigo nodularis

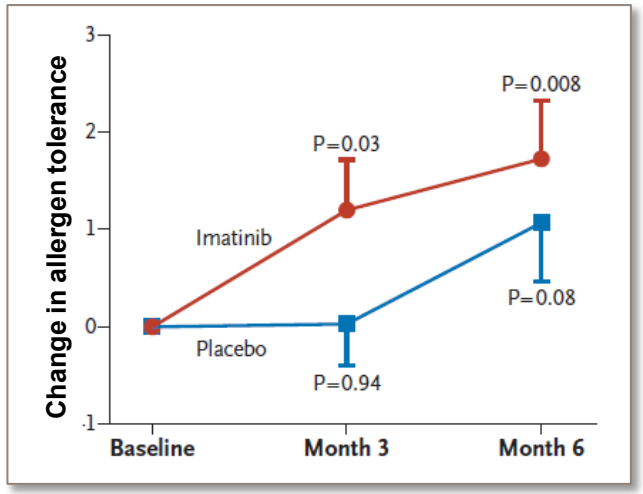
Type 2 Asthma

Adapted from Metz, M et al, (2023) Allergy

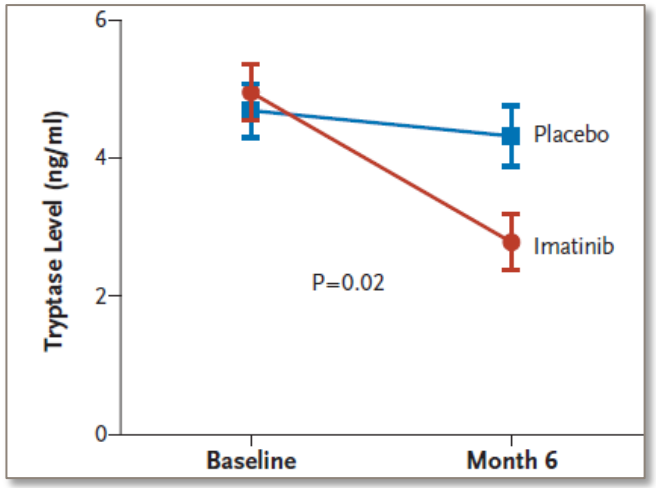
Disease state: mast cells play a role in pathophysiology of T2 asthma



Imatinib, a TKI with KIT activity, reduces disease markers in asthma



Mast cell inhibition increases the amount of allergen tolerated in asthma patients.[1]



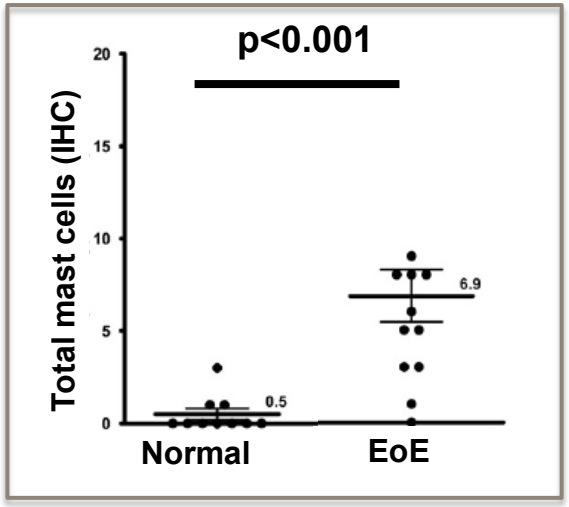
Mast cell inhibition improves asthma biomarkers of disease.[1]

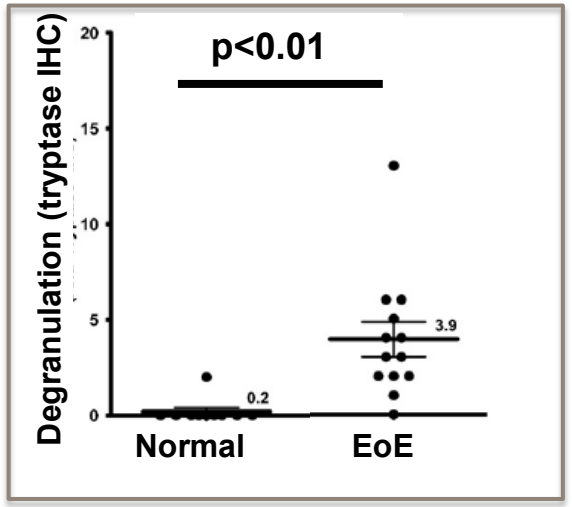
Therapeutic opportunity to address underlying drivers of disease by:

- Inhibiting IgE-mediated mast cell degranulation
- Depleting mast cell numbers
- Utilizing combination therapies to target both mast cells and other immune cells chronically activated in disease

[1]Cahill, K.N. et al, (2017) *New England Journal of Medicine*; [2]Created with BioRender.com

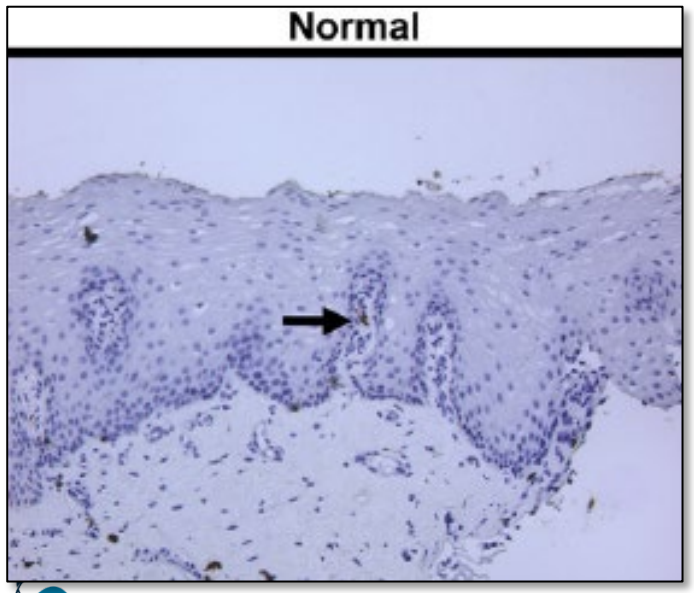
Disease state: mast cells are present and activated in eosinophilic esophagitis patient samples

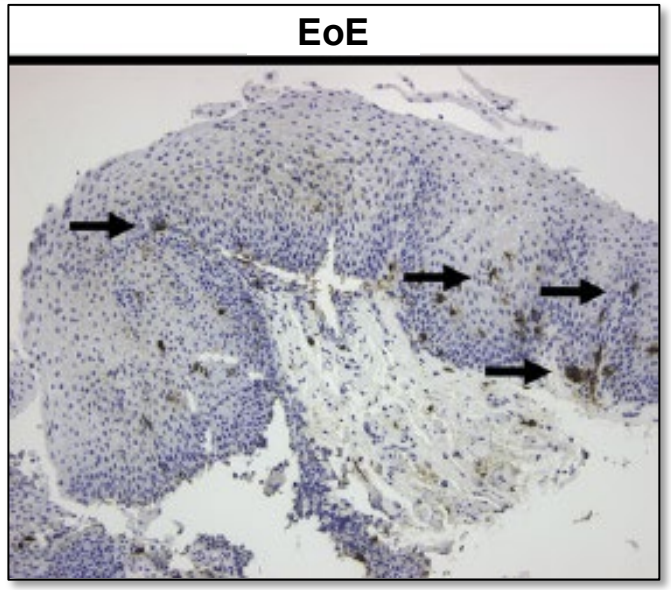




Left: Mast cell numbers are significantly increased in patients with eosinophilic esophagitis (EoE), relative to normal samples.

Right: Degranulation of mast cells, as measured by tryptase, is also increased in EoE.





Degranulation of mast cells is ~20-fold higher in patients with EoE relative to normal samples.

Abonia, J.P et al (2010) *Journal of Allergy and Clinical Immunology*

A Blueprint for Targeting Mast Cells

Percy H. Carter

We are achieving R&D scale by leveraging our strengths

PROVEN TRACK RECORD OF SUCCESS

2 approved medicines

~80% success rate from IND to POC

17 development candidates nominated

SCIENTIFIC EXPERTISE IN A/I & ONCOLOGY

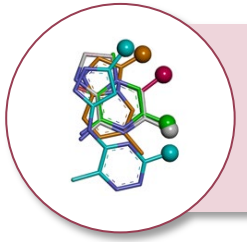
AYVAKIT® (avapritinib) and **elenestinib** for systemic mastocytosis

BLU-808 for mast cell diseases

BLU-222 and **BLU-956** for CDK2 vulnerable breast cancer

Multiple research programs

MODALITY AGNOSTIC DRUG DISCOVERY

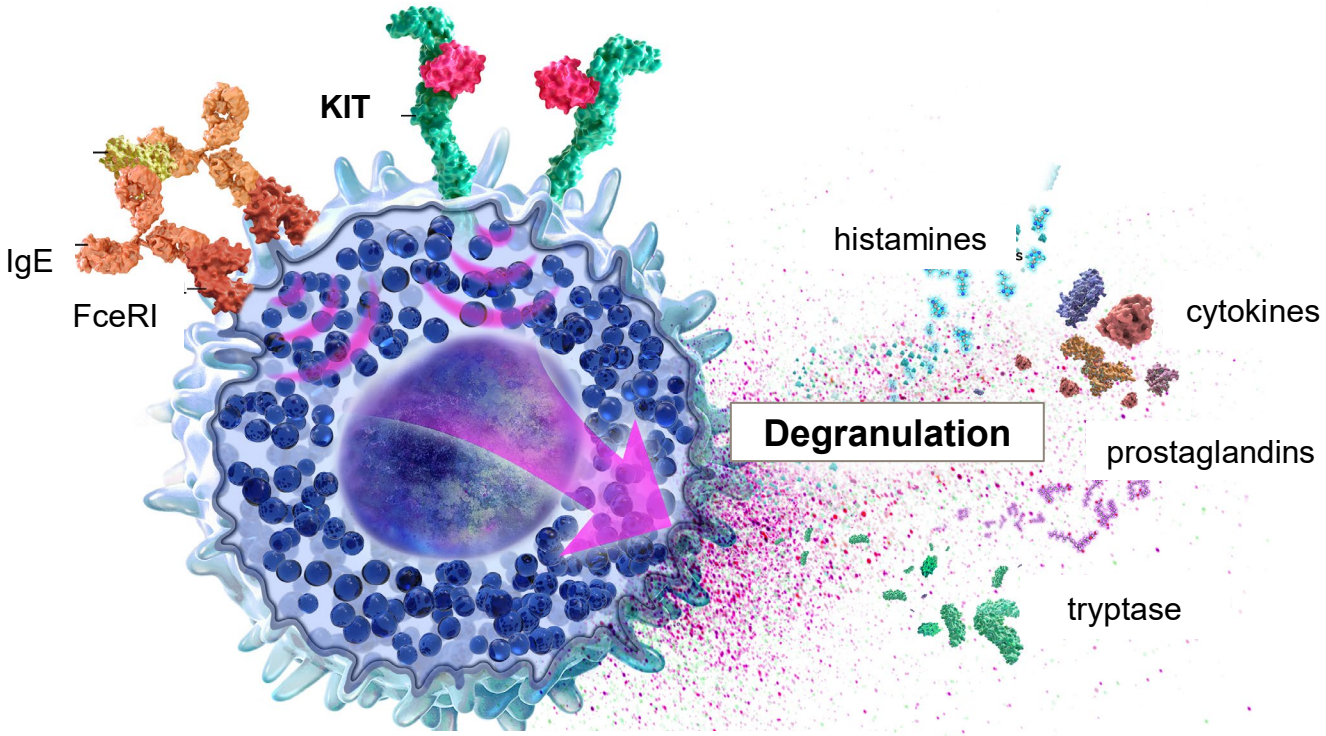


Kinase inhibitor platform

Targeted protein degrader platform

Additional exploratory research

KIT is a key regulator of mast cell activation and proliferation



Mast cell

- Mast cells drive disease and exacerbate inflammation
- KIT regulates mast cell survival
- Blueprint track record of success in mast cell drug development
- Combination approaches may broaden opportunities within and beyond KIT

Scientific leadership in KIT biology

MUTATED KIT

AYVAKIT® avapritinib | tablets

KIT D816V inhibitor
(Systemic mastocytosis)

IDRX-73*

KIT exon 13 inhibitor
(Gastrointestinal stromal tumor)

WILD-TYPE KIT

Elenestinib

Next-generation
KIT D816V inhibitor
(Systemic mastocytosis)

BLU-808

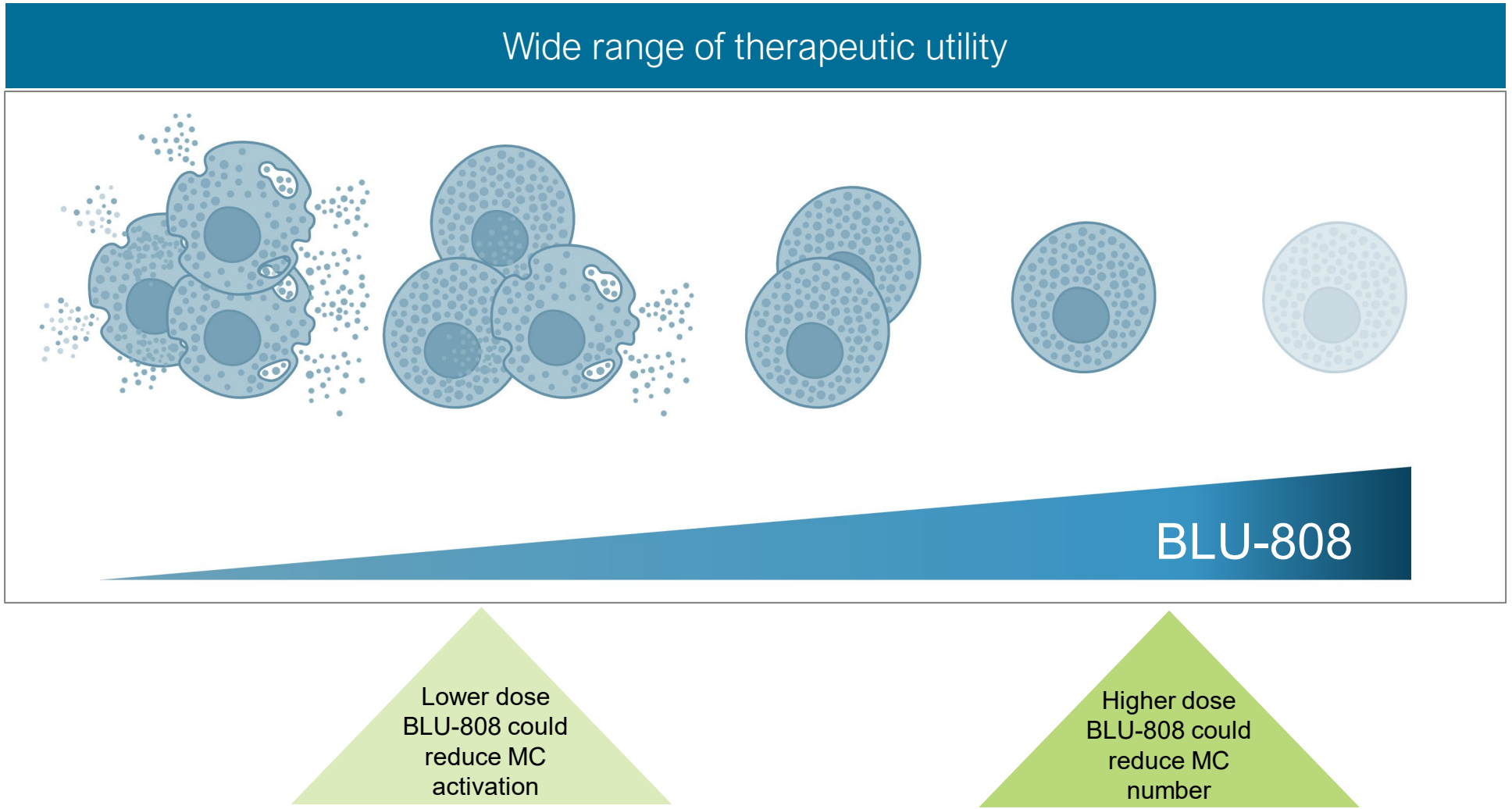
Wild-type KIT inhibitor
(Mast cell-mediated diseases)

1 approved and 3 clinical-stage highly selective and potent KIT inhibitors designed by Blueprint scientists

blueprint™ MEDICINES

* IDRX-73, formerly known as BLU-654, was out-licensed to IDRx in 2022.

With BLU-808, tunable dosing could enable controlled reduction of mast cell number and activity



Created with BioRender.com

Wild-type KIT inhibitor BLU-808 has first- and best-in-class potential

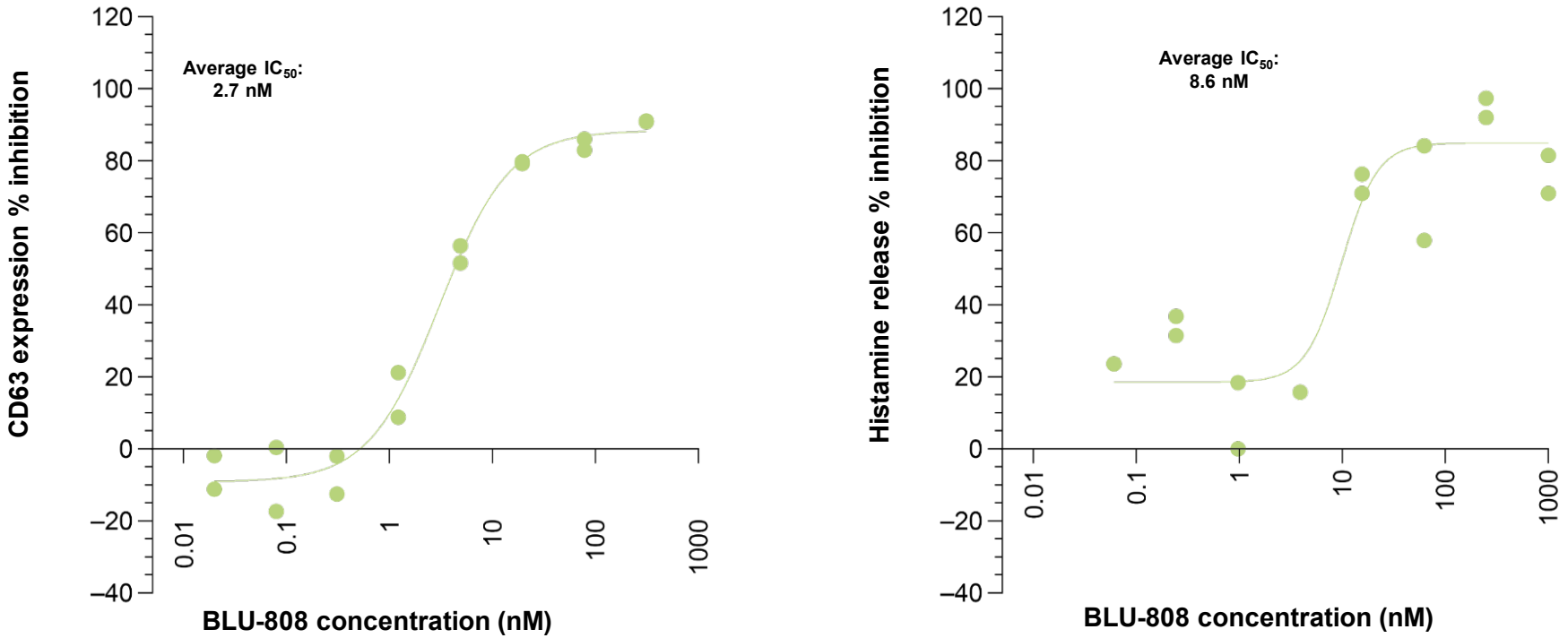
	BLU-808
Potency	
pKIT cellular IC_{50} (nM)	0.37
WT KIT-dependent proliferation IC_{50} (nM)	1.3
Human-derived $CD34^+$ mast cells: inhibition of CD63 extracellular expression IC_{50} (nM)	2.7
Human-derived $CD34^+$ mast cells: inhibition of histamine degranulation IC_{50} (nM)	8.6
Selectivity	
S(10) @ 3 µM	0.042
PDGFRA / PDGFRB / FLT3 cellular selectivity[a]	>300x/>400x/>9600x
CSF1R Kd selectivity	>800x
Brain penetrance ($Kp_{u,u}$)	0.021
Preclinical PK supports once daily oral dosing	

IND submission on-track for Q2 2024, then plan to initiate HV study

[a]Determined in a cellular assay. CSF1R, colony stimulating factor 1 receptor; FLT3, FMS-like tyrosine kinase 3; IC_{50}, half-maximal inhibitory concentration; PDGFRA/B, platelet-derived growth factor receptor alpha/beta; pKIT, phosphorylated KIT; S(10) @ 3 µM, selectivity score at a concentration of 3 µM; $Kp_{u,u}$, unbound brain to plasma partition

BLU-808 inhibits activation of human-derived CD34+ mast cells

Decreased CD63 expression and histamine release in treated human-derived CD34+ mast cells stimulated with IgE and anti-IgE

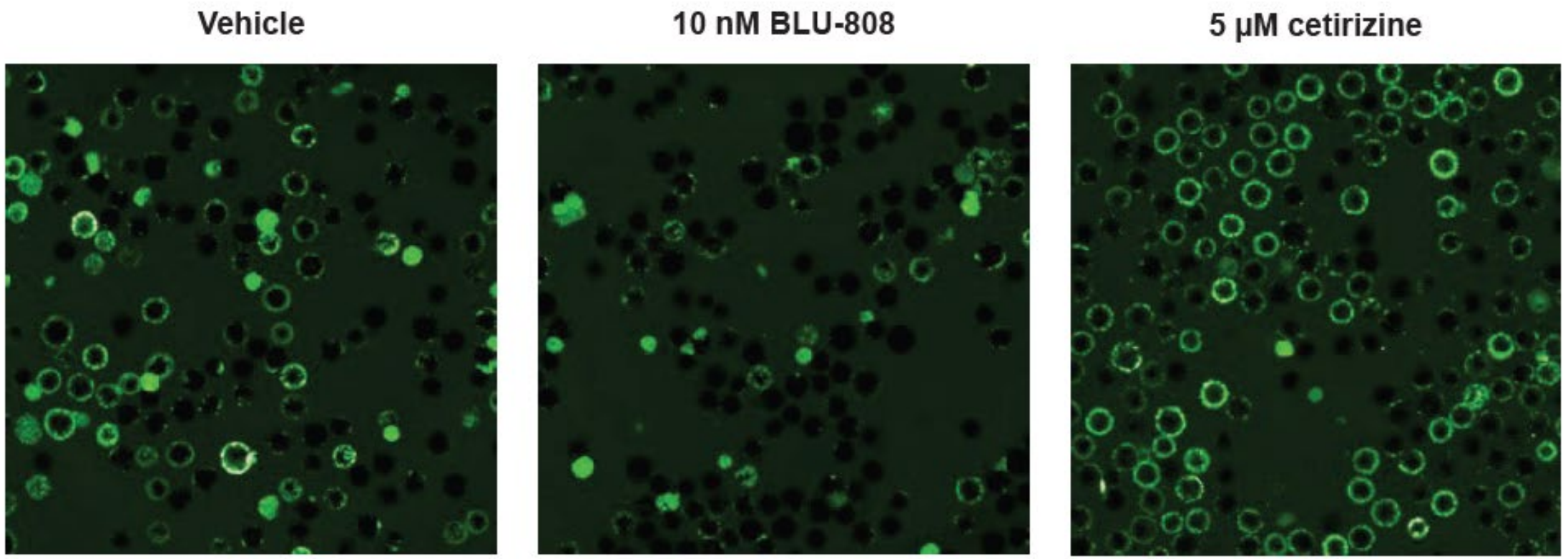


BLU-808 is potent in two human-derived CD34⁺ mast cell assays

- BLU-808 inhibits the expression of CD63 at the cell surface, which is a marker of mast cell degranulation
- Inhibition of histamine release shows that BLU-808 can reduce degranulation and subsequent release of inflammatory molecules

Grassian, A et al, AAAAI 2024

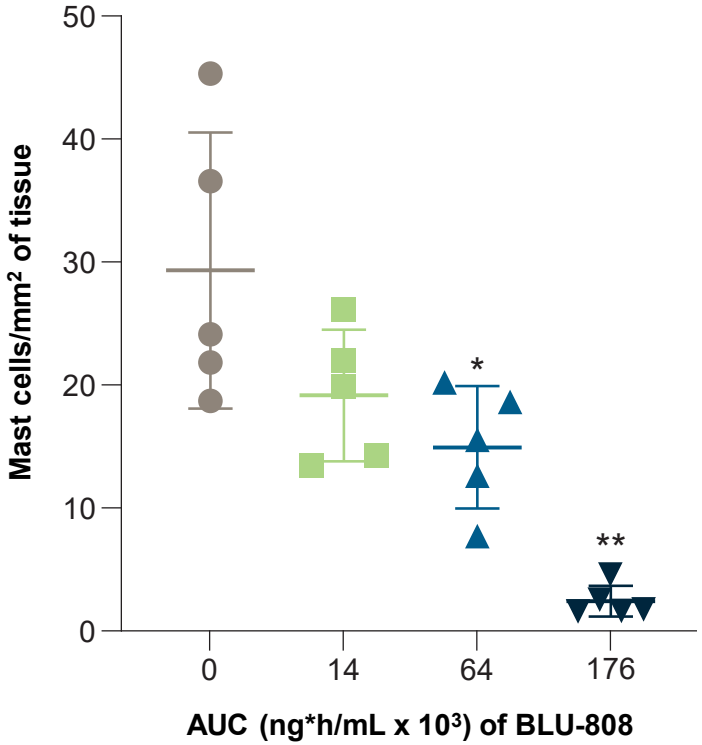
BLU-808 inhibits degranulation of human-derived CD34+ mast cells



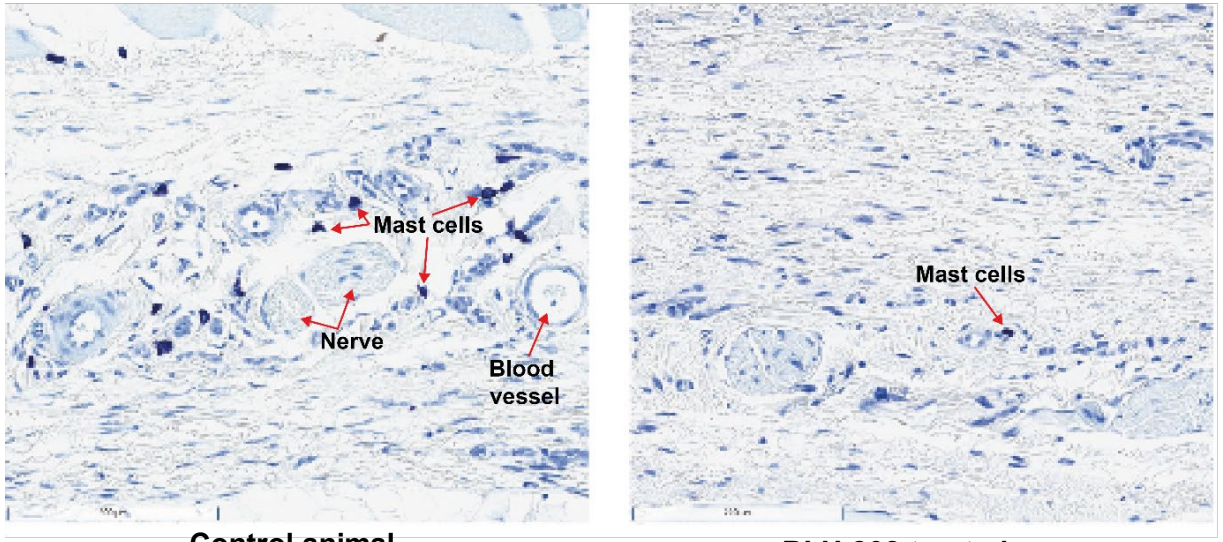
- **BLU-808 targets the source of histamine and other mediators by preventing mast cell degranulation**
  - Mast cells were labeled in green to visualize degranulation. Following stimulation, the increase in green fluorescence indicated that degranulation occurred in mast cells treated with vehicle and 5 µM cetirizine, however BLU-808 inhibited degranulation, as shown by reduced fluorescence intensity.
  - Cetirizine, a control here, is an antihistamine that does not affect degranulation in mast cells at lower concentrations[1,2]

Grassian, A et al, AAAAI 2024; IgE, immunoglobulin E. 1. Church DS et al. *World Allergy Organ J*. 2011;4:S22–S27; 2. Fujimura R et al. *Drug Discov Ther*. 2022;16:245–250.

BLU-808 can decrease mast cells in an exposure-dependent manner



Total mast cell % reduction from control:	--	35%	49%	92%



Control animal | BLU-808 treated

Haired skin: Subcutis at high magnification, toluidine blue staining

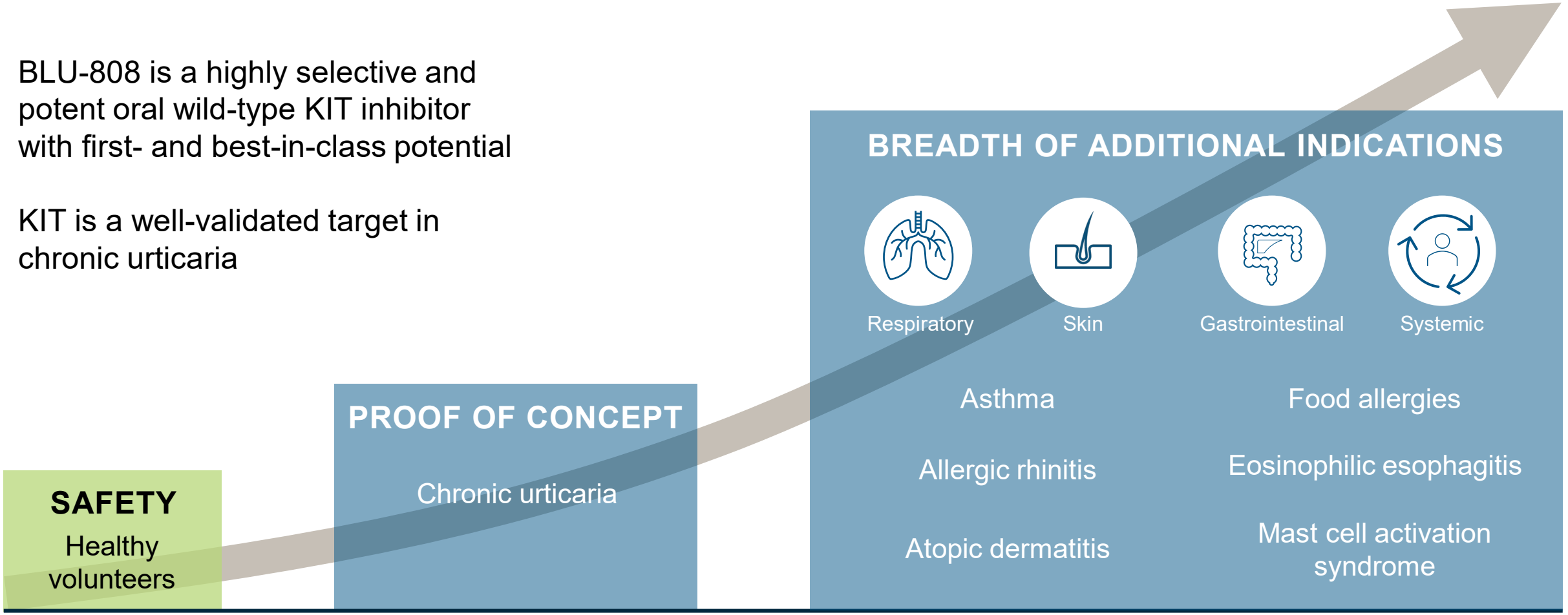
- BLU-808 was administered for 7 days at different specific doses in rats
- Mast cells were quantified by toluidine blue staining and showed a dose-dependent reduction
- *In vivo* data in mouse model of asthma also support dose-dependent response

Grassian, A et al, AAAAI 2024; AUC, area under curve. *, P<0.05; **, P<0.005; all per two-way analysis of variance with Tukey's correction for multiple comparisons. Horizontal lines represent mean and standard deviation.

Potential to revolutionize the allergy/inflammation space with BLU-808

BLU-808 is a highly selective and potent oral wild-type KIT inhibitor with first- and best-in-class potential

KIT is a well-validated target in chronic urticaria



Phase 1 healthy volunteer safety, pharmacokinetic and pharmacodynamic data represent key de-risking event

Thank you!