What you need to know about BTK inhibitors in the treatment of allergic diseases

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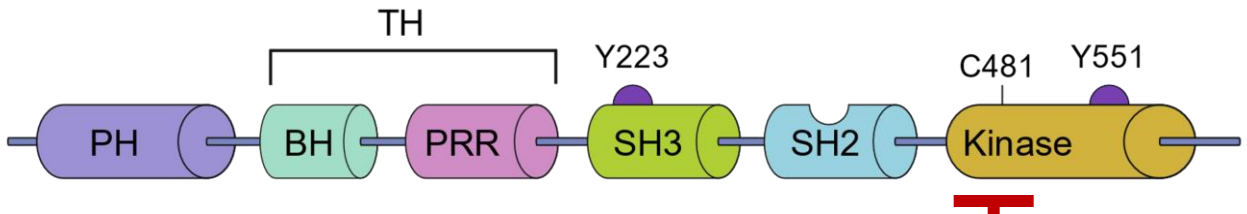
April 11, 2025

Learning objectives

- Upon completion of this learning activity, participants should be able to discuss recent efficacy data for the use of BTK inhibitors in preventing anaphylaxis and treating chronic urticaria.

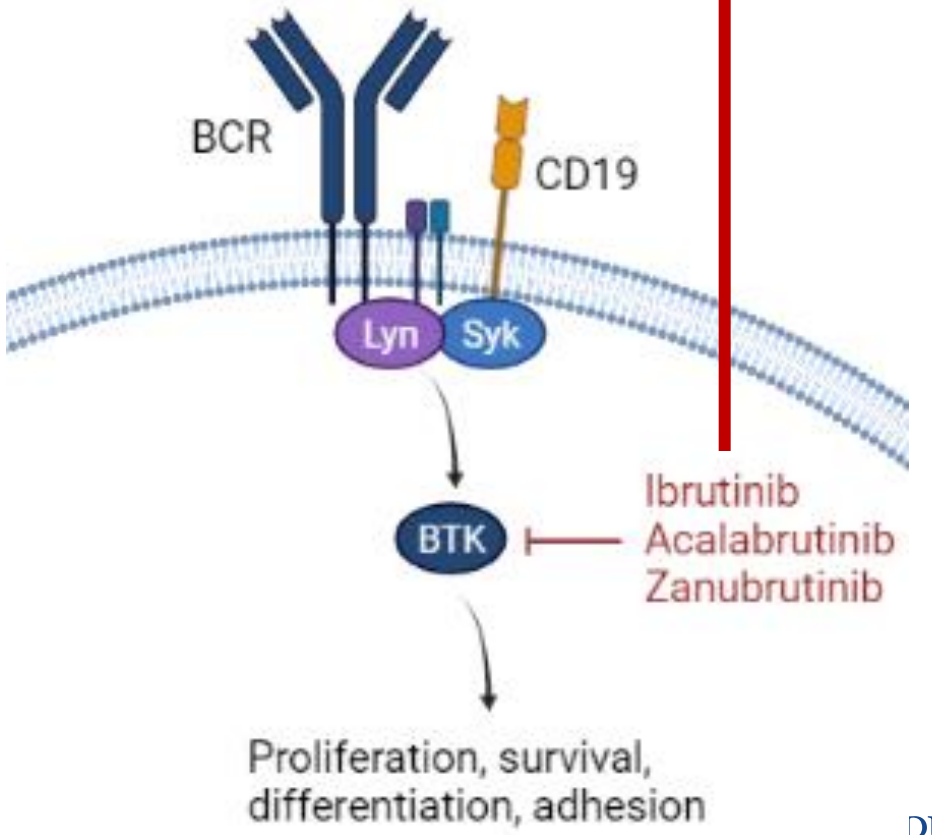
- Upon completion of this learning activity, participants should be able to compare safety data for BTK inhibitors.

Bruton's tyrosine kinase (BTK)



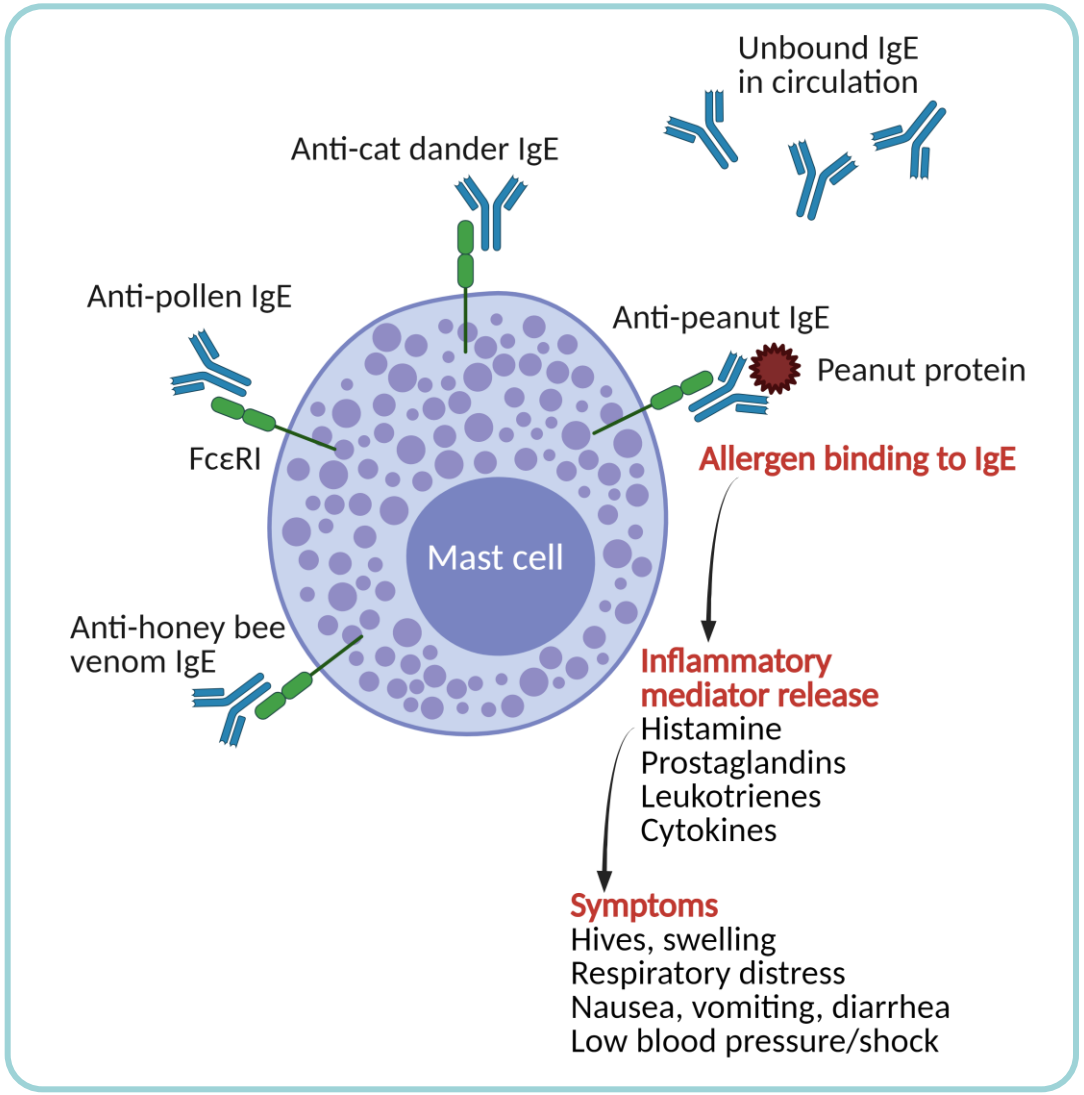
- Non-receptor tyrosine kinase in the TEC family
- Important for:
  - Fc signaling (BCR, TCR, Fcγ, Fcε)
  - TLR signaling
  - Inflammasome
- Congenital deficiency → Bruton's X-linked agammaglobulinemia (XLA)

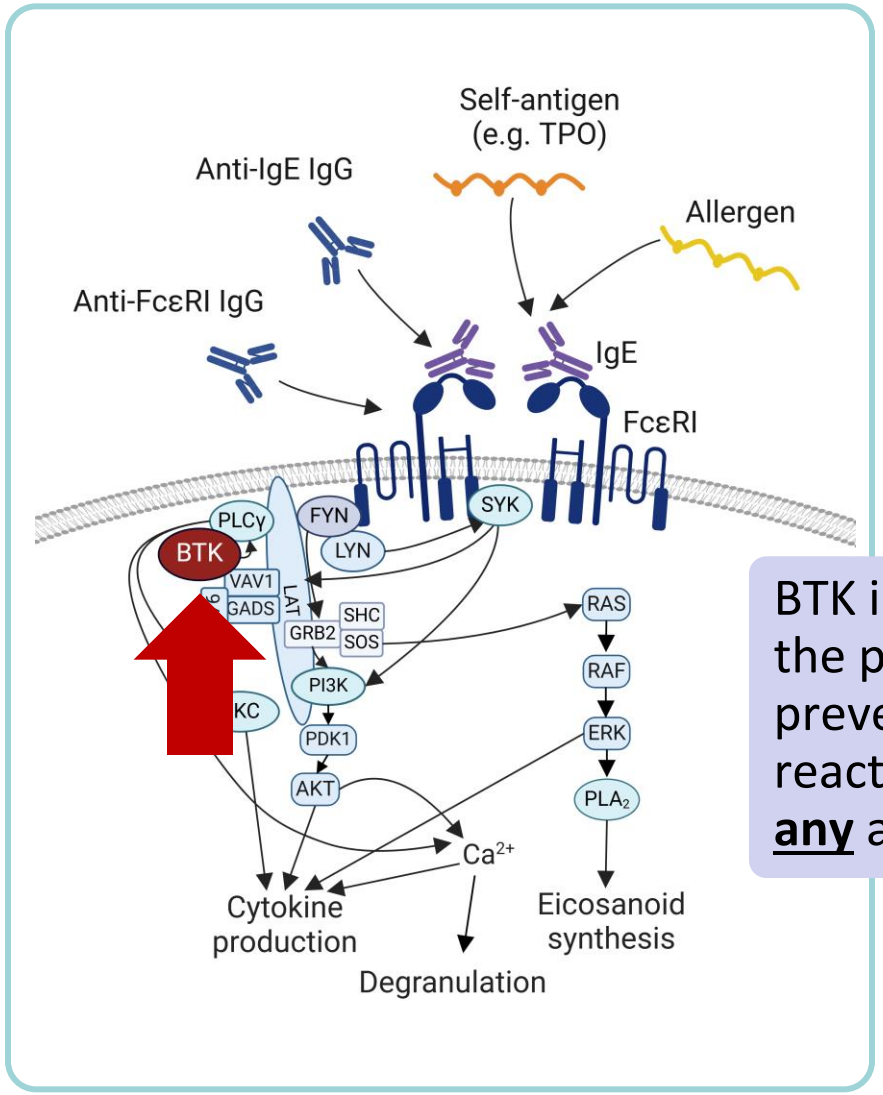
Importance in B cell maturation



Created with BioRender.

BTK is essential for activation of human mast cells and basophils through FcεRI





BTK inhibitors have the potential to prevent IgE-mediated reactions caused by **any** allergen

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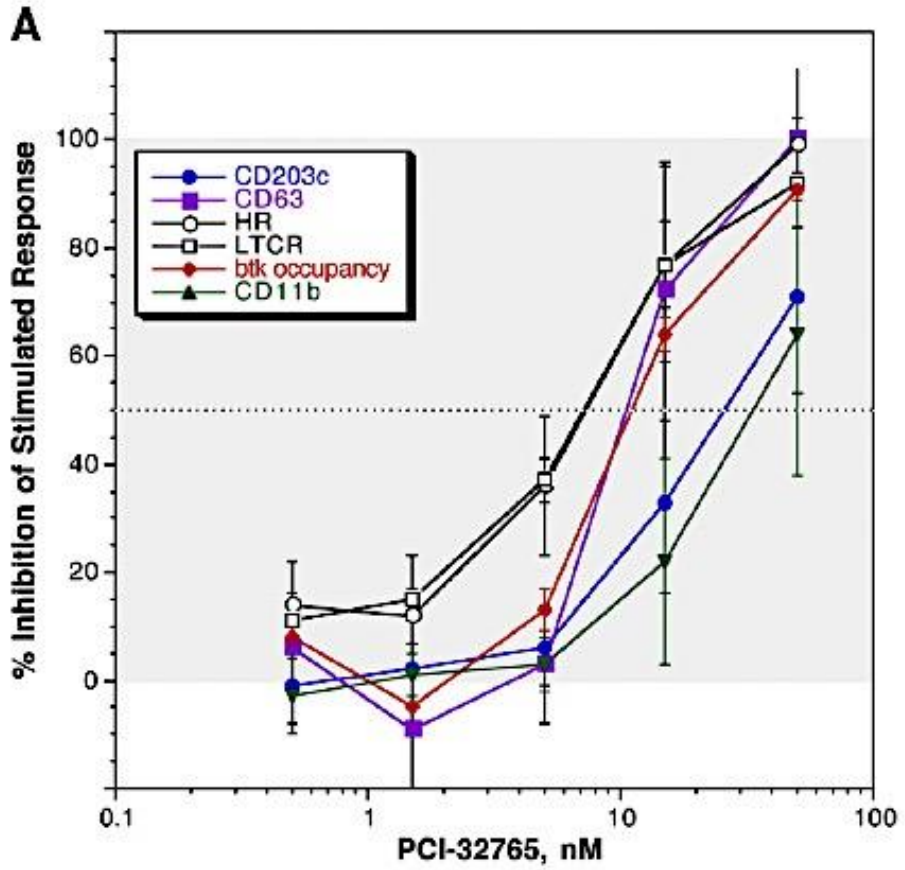
Ibrutinib (1st-generation BTKi) inhibits IgE-dependent basophil activation and secretion *in vitro*

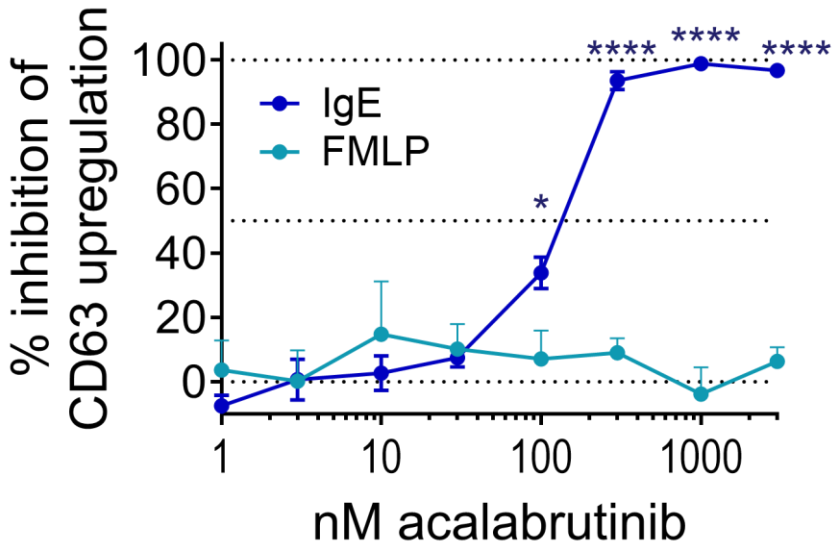


MacGlashan et al. *Int Immunopharmacol*. 2011

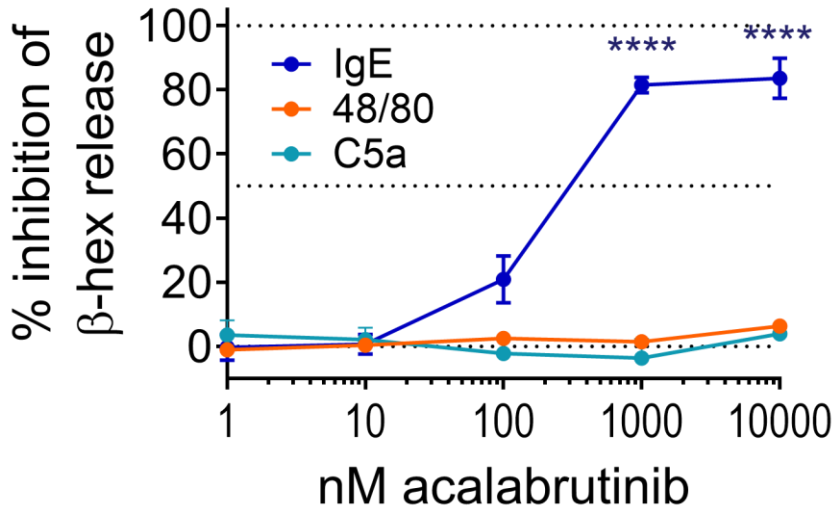
JOHNS HOPKINS MEDICINE

Acalabrutinib (2nd-gen BTKi) rapidly inhibits IgE-mediated degranulation of human mast cells and basophils *in vitro*

Basophils



Skin-derived mast cells



BTK inhibitors have identical IC_{50}s for inhibiting IgE-mediated activation of human mast cells and basophils

Dispenza et al, *J Clinical Investigation*, 2020

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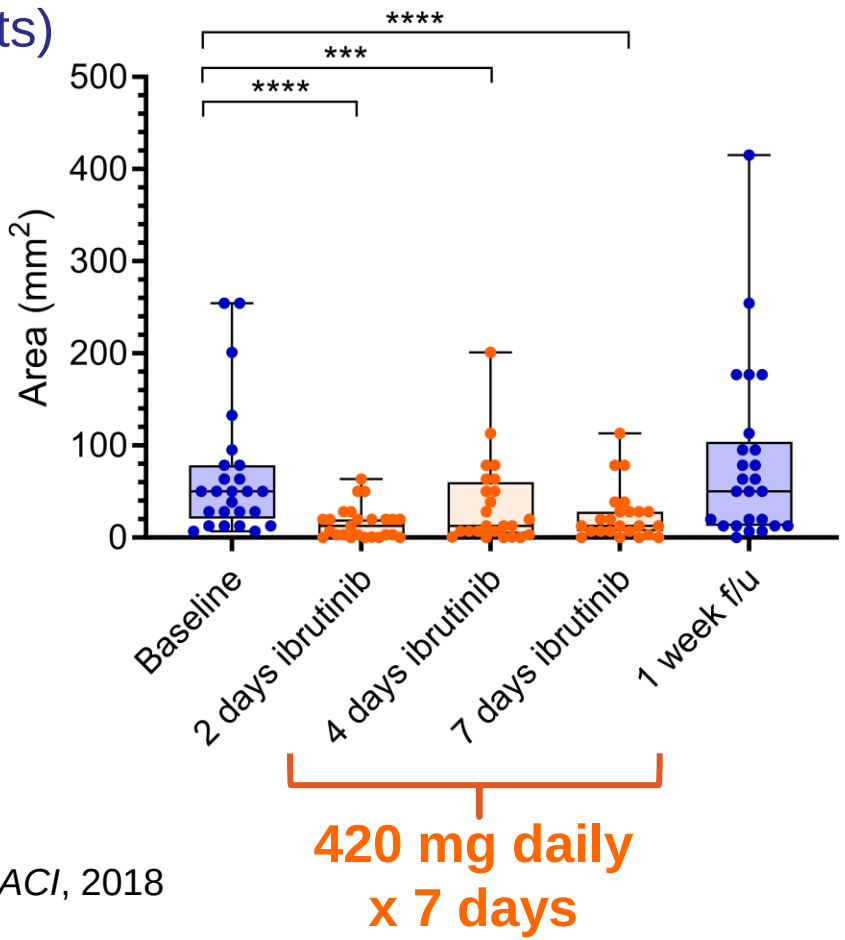
Q: Can BTK inhibitors suppress mast cell and basophil activation *in vivo*?

We designed an open-label clinical trial using ibrutinib to suppress skin test responses in peanuts with peanut or tree nut allergy

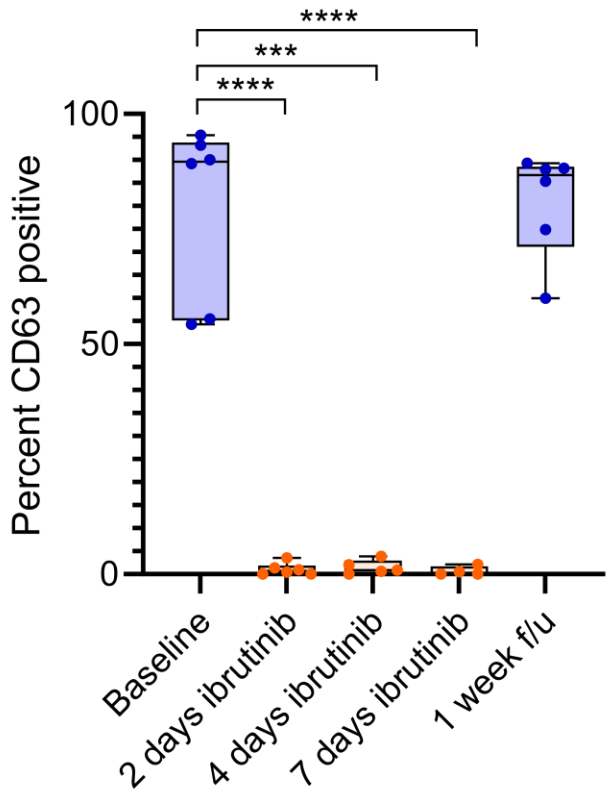
2 doses of **ibrutinib** reduces or eliminates skin test response to foods in peanut and tree nut allergic adults

N = 6 subjects
(25 skin tests)

Skin testing



Basophil activation testing



Dispenza et al, *JACI*, 2018

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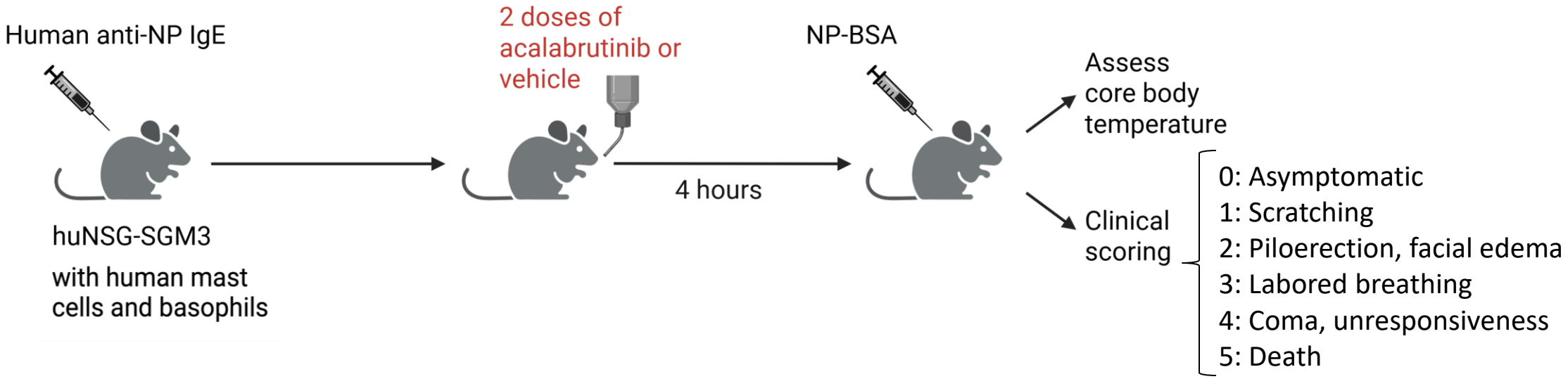
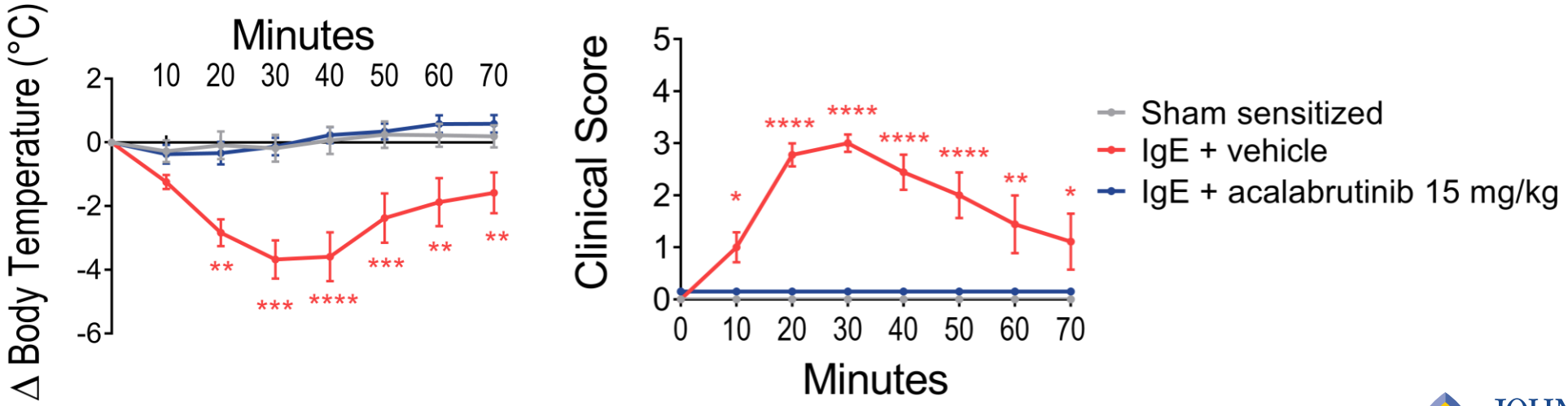
2 doses of **acalabrutinib** pretreatment prevents anaphylaxis responses to IV allergen in humanized mice





Dispenza et al, *J Clinical Investigation*, 2020

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Q: Can BTK inhibitors prevent anaphylaxis?

We designed an open-label, proof of concept clinical trial using acalabrutinib to prevent clinical reactivity to oral peanut challenge in peanut-allergic adults

Ragha Suresh, MD

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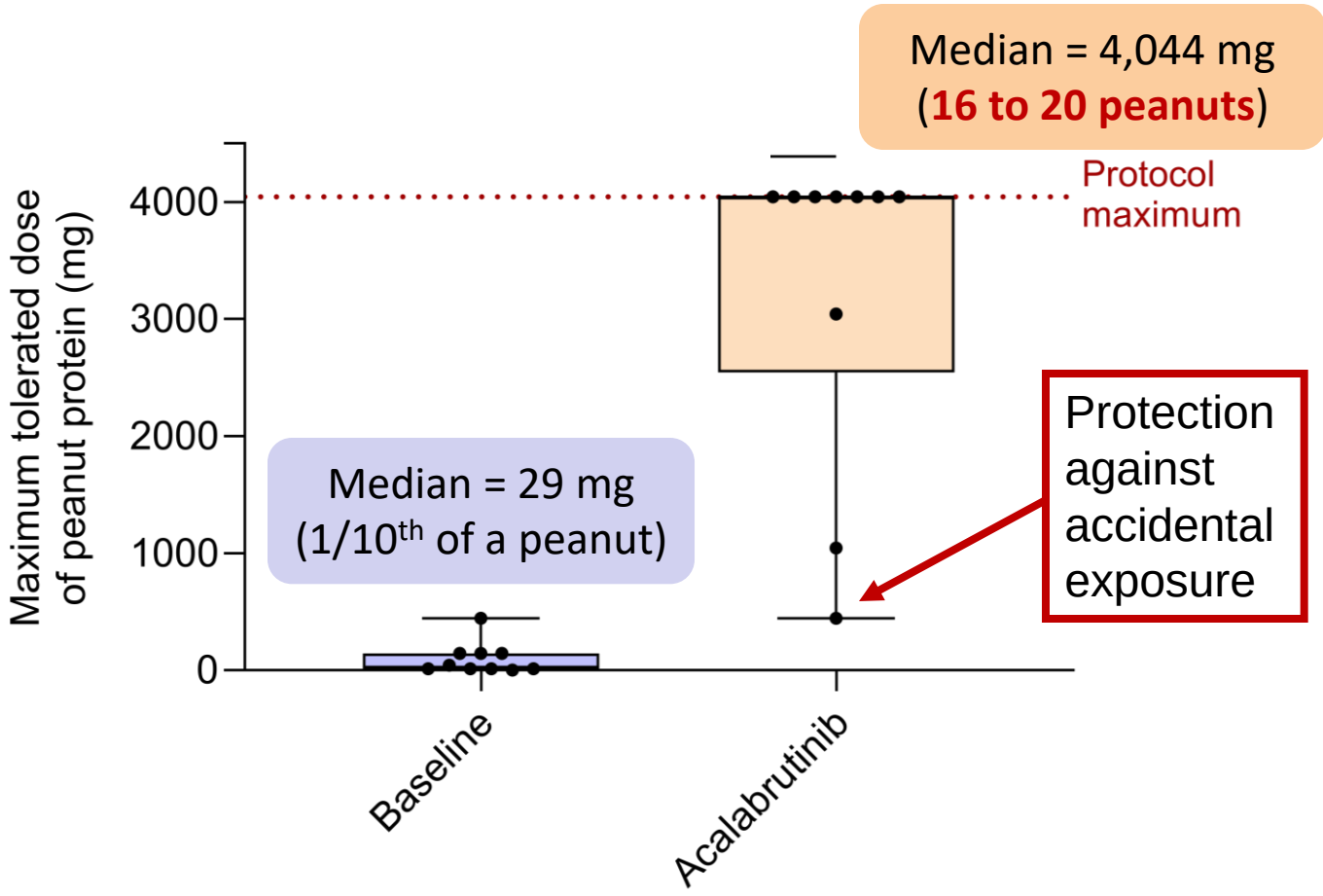
Pretreatment with the acalabrutinib prevents clinical reactivity to peanut ingestion in allergic adults

- We enrolled 10 patients with severe peanut allergy
- We performed placebo-controlled, graded challenges to peanut to determine patients' tolerance at baseline
- Every patient received 4 doses of acalabrutinib (100 mg orally twice daily) and underwent repeated peanut challenge



Suresh et al, *J Clinical Investigation*, 2023

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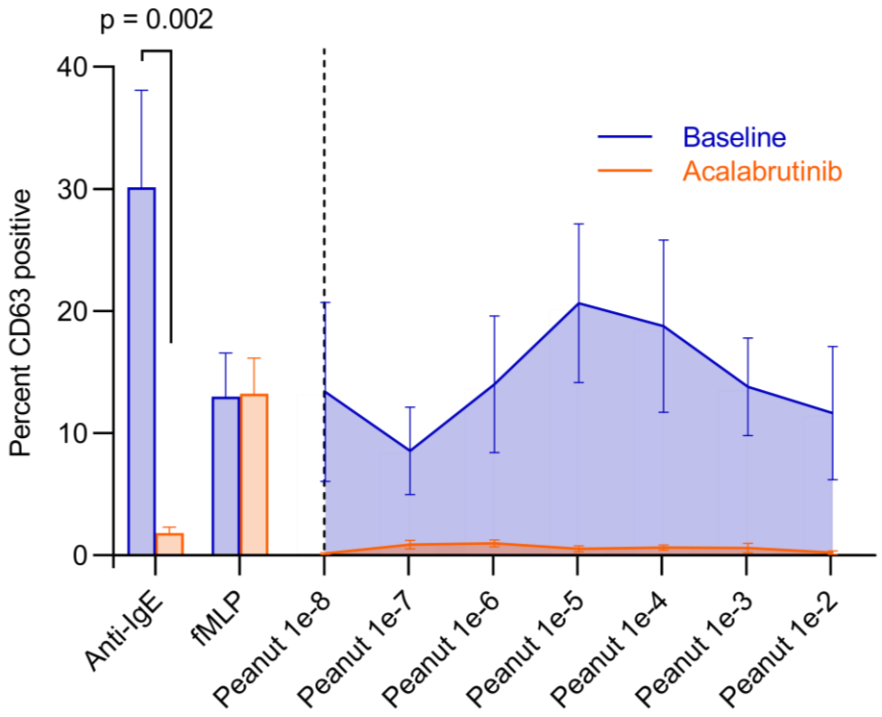
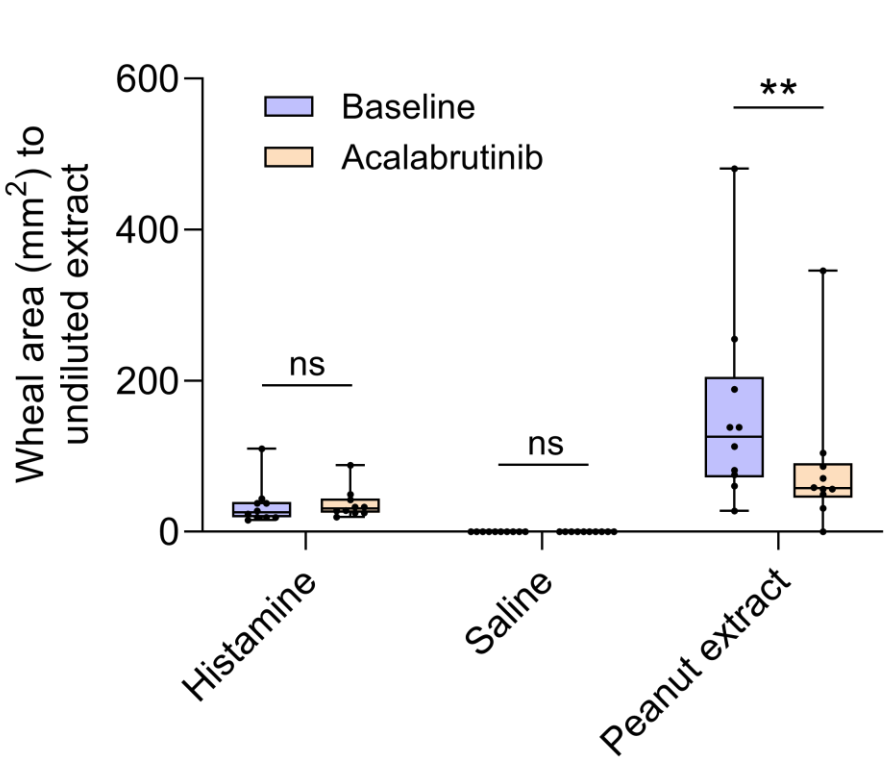
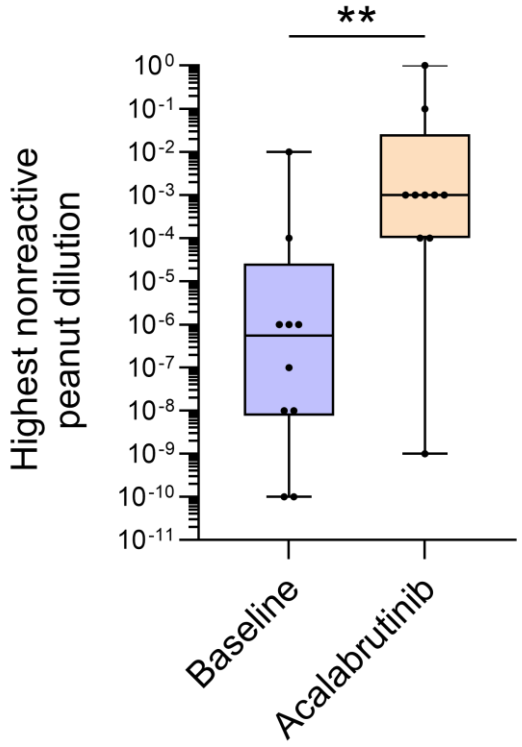
Acalabrutinib reduces peanut SPT size and abolishes IgE-mediated basophil activation in peanut allergic adults

Basophil activation testing



Skin testing





Suresh et al, *J Clinical Investigation*, 2023

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In the pipeline: remibrutinib

ClinicalTrials.gov BETA

Menu

Previous Study from Search Return to Search Next Study from Search →

Record 1 of 8

Home Search Results Study Record

RECRUITING

Study of Efficacy, Safety and Tolerability of Remibrutinib in Adult Participants With an Allergy to Peanuts

Information provided by Novartis Pharmaceuticals (Responsible Party)

Last Updated: November 2, 2022

ClinicalTrials.gov Identifier: NCT05432388

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BTK inhibitors could facilitate drug desensitizations: 2 case reports

Clinical Communications

Pretreatment with ibrutinib facilitates rapid drug desensitization in a difficult case of brentuximab vedotin–induced anaphylaxis

Pongsawat Rodsaward, MD[a,b],
Supranee Buranapraditkun, PhD[c], and
Jettanong Klaewsongkram, MD[a,b]

JACI In Pract 2023; 11:642-4.

Brief reports

Prevention of allergic reactions during oxaliplatin desensitization through inhibition of Bruton tyrosine kinase

Kristin A. Erickson,[a] James E. Norton, MS,[a] Jennifer Law, PharmD,[b] Nicole Soriano, PharmD,[b] Malgorzata Strojny, PharmD,[b] Nicole Gentry, PA,[c] Morgan Fried, APRN,[c] Bruce S. Bochner, MD,[a] Sheetal Kircher, MD,[c] and Whitney W. Stevens, MD, PhD[a] *Chicago, Ill*

JACI 2024;154:222-8.

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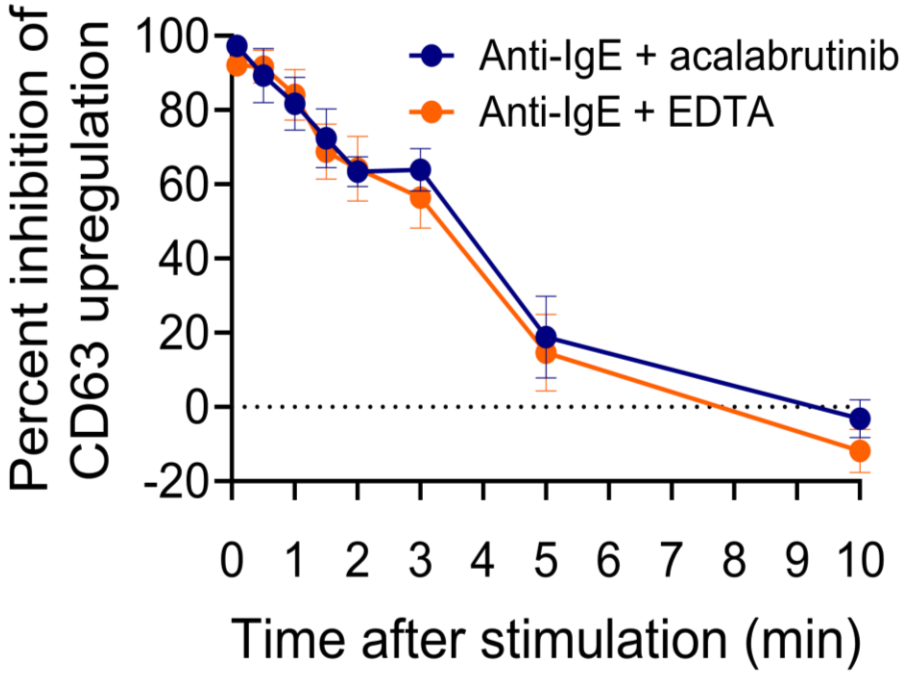
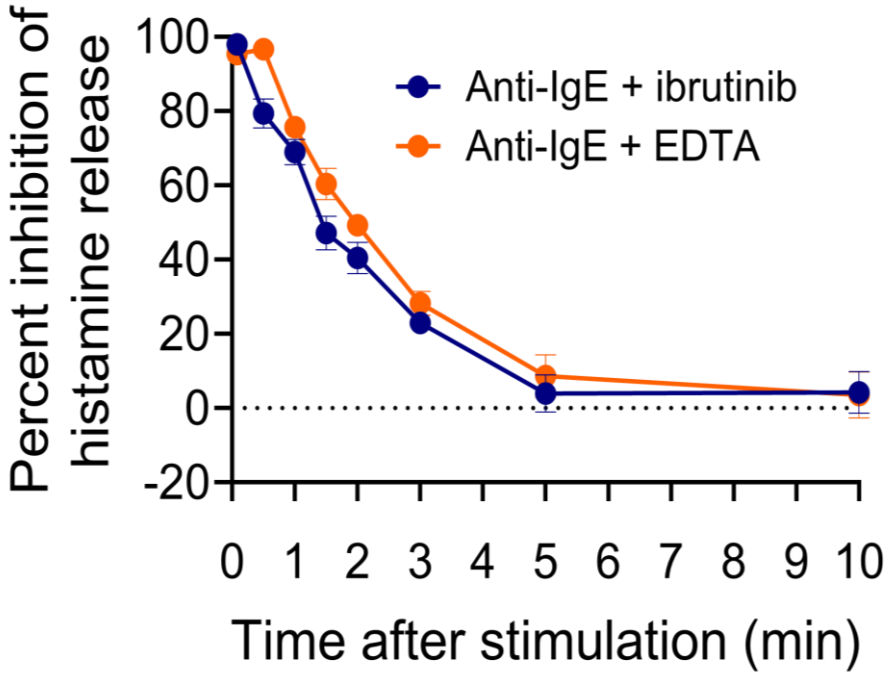
Q: Can BTK inhibitors also abort ongoing anaphylaxis?

Acalabrutinib stops ongoing basophil activation when added *after* IgE stimulation *in vitro*

Natalia Vilela





Arce et al, unpublished

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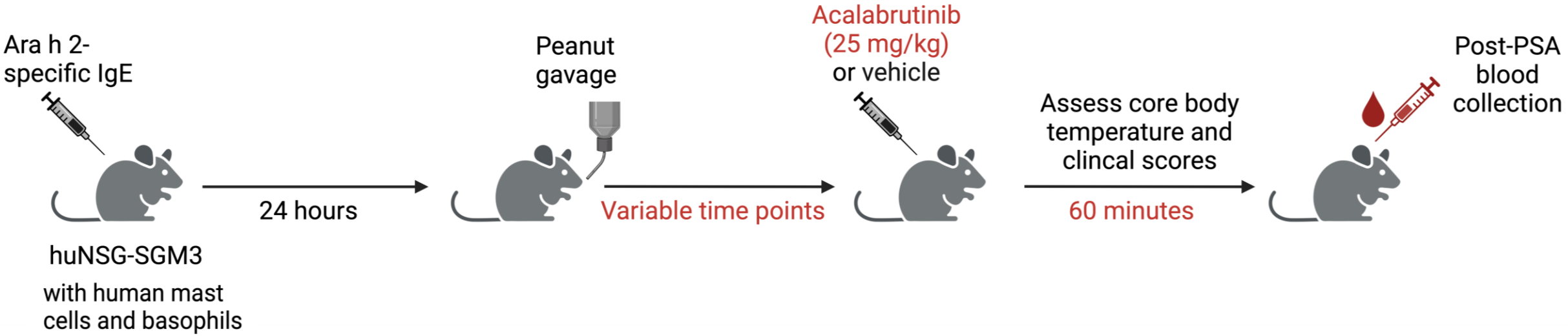
Food-induced anaphylaxis model in NSG-SGM3 humanized mice

Betania Arce



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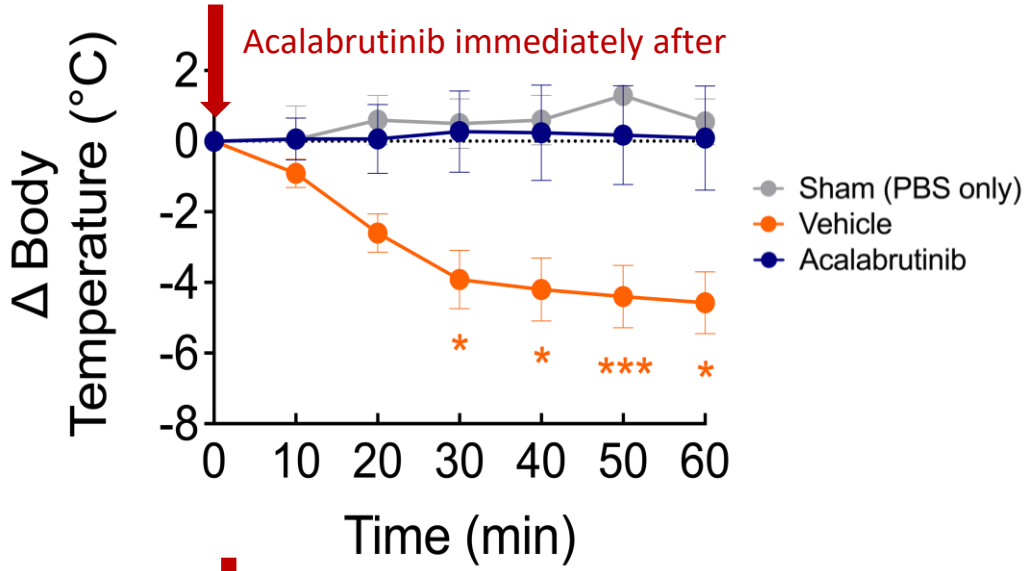
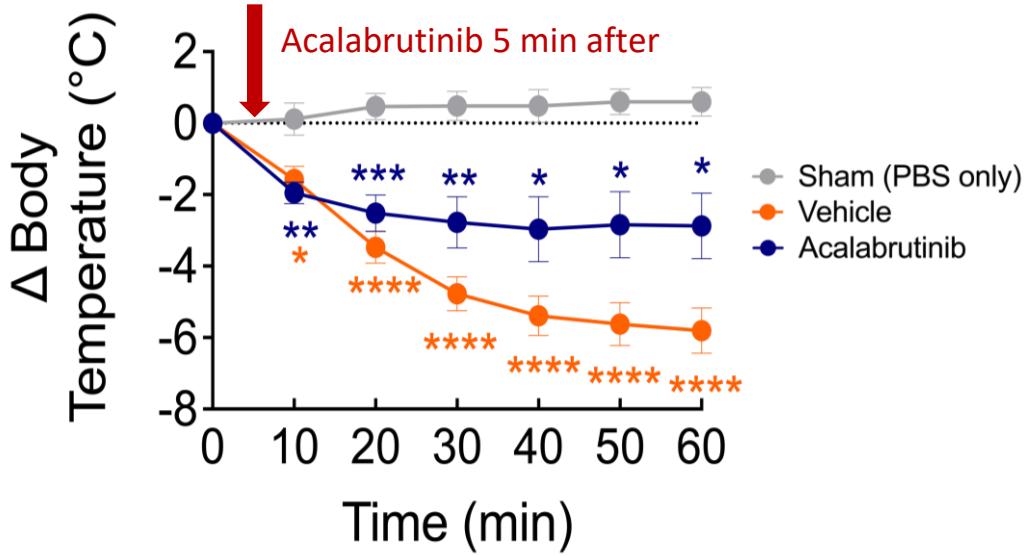
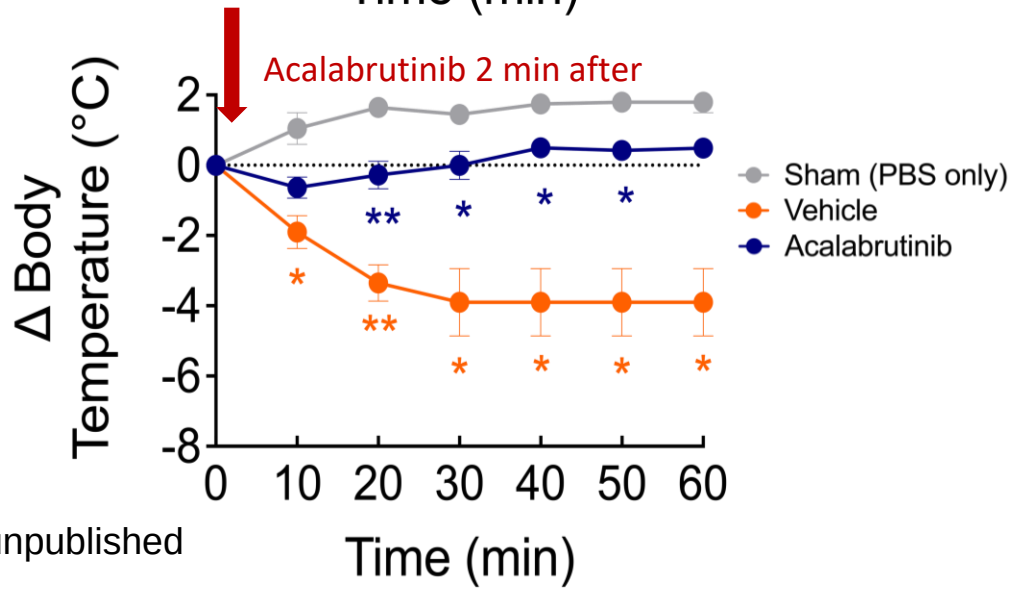
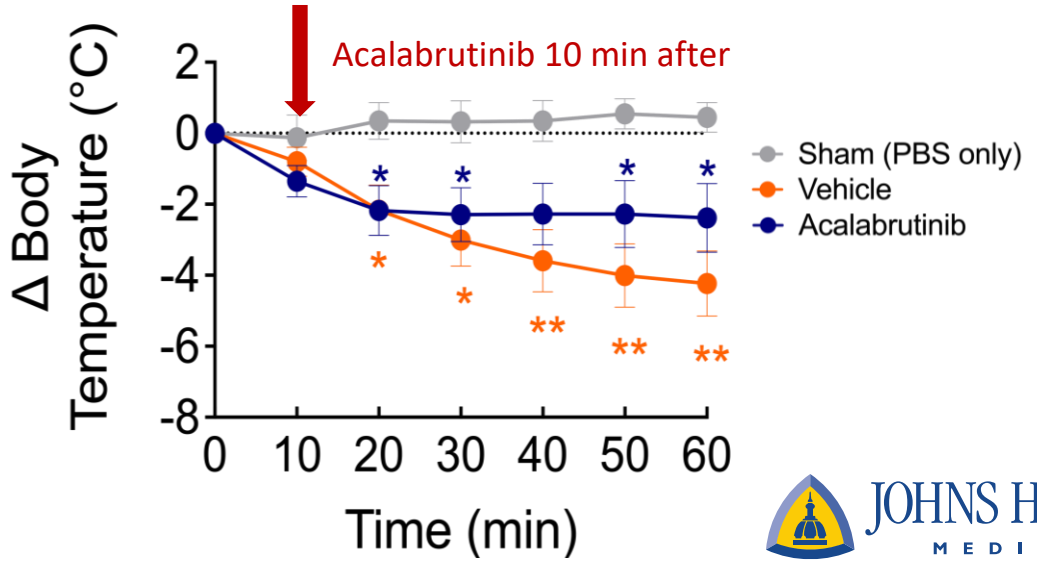
Acalabrutinib monotherapy aborts ongoing anaphylaxis when given within 5 minutes after allergen exposure









Arce et al, unpublished

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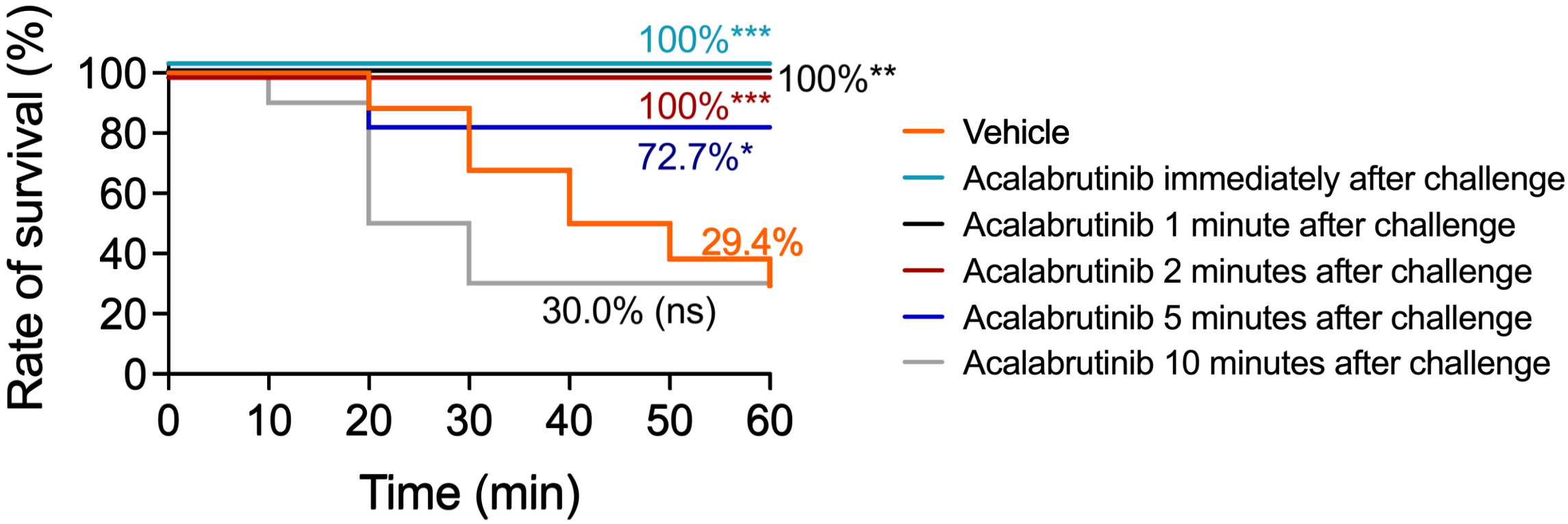
Acalabrutinib monotherapy reduces mortality from anaphylaxis when given after peanut exposure



Arce et al, unpublished

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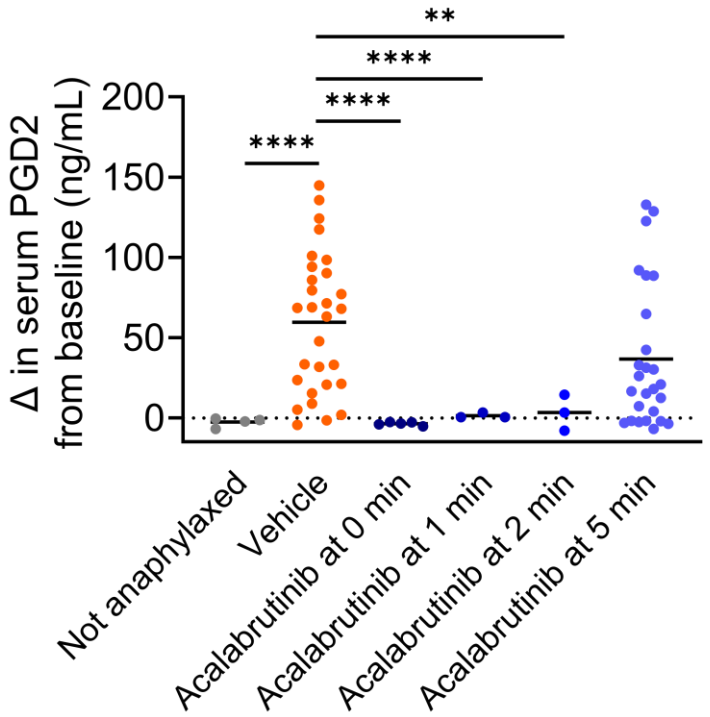
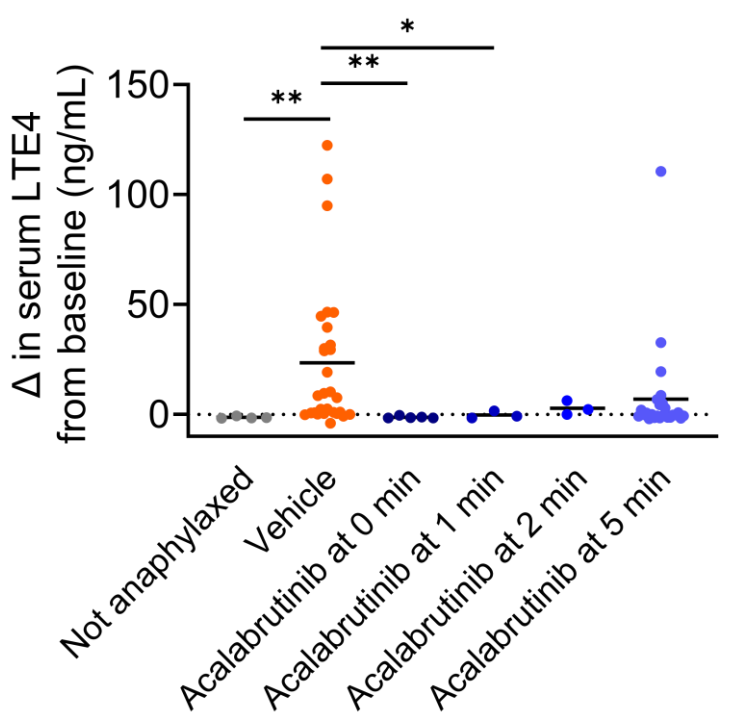
Acalabrutinib stops ongoing mediator release when given after allergen exposure

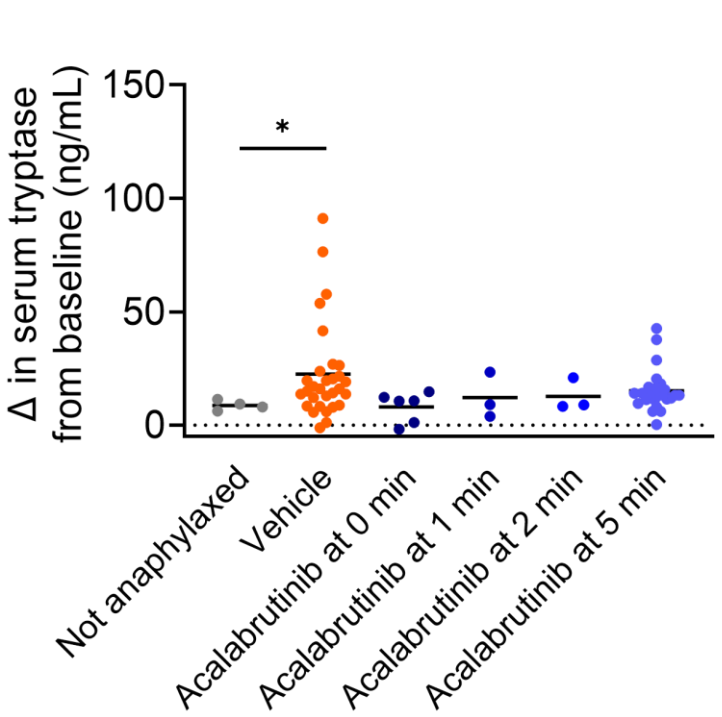
PGD2



LTE4



Tryptase



Arce et al, unpublished

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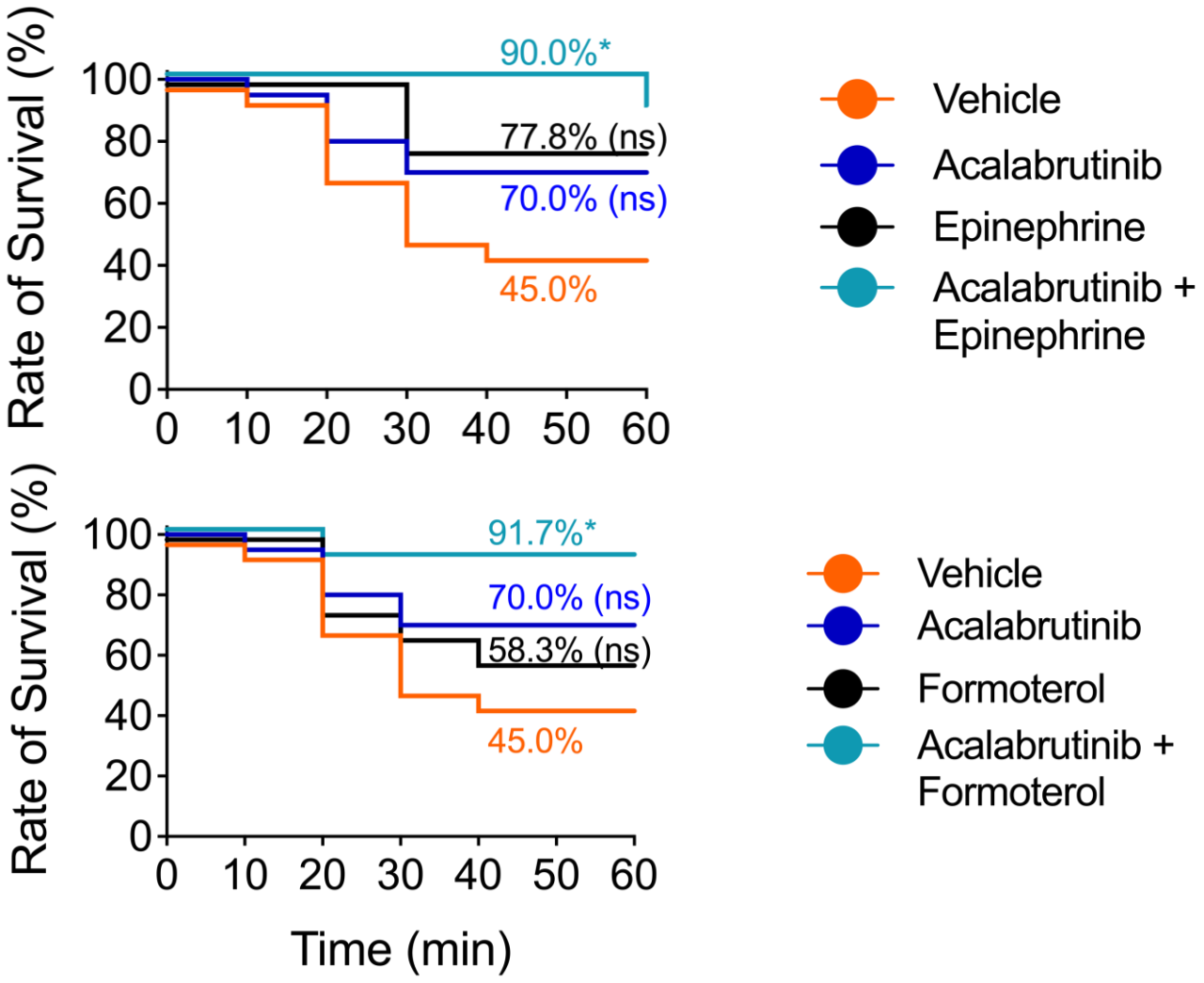
Acalabrutinib and epinephrine synergistically abort ongoing anaphylaxis when given 5 minutes after allergen exposure



Arce et al, unpublished

Summary

- Short exposures of BTK inhibitors prevent mast cell and basophil activation *in vitro*, and anaphylaxis in humanized mice
- Pretreatment with 2 days of acalabrutinib prevents clinical reactivity to peanut ingestion in the majority of peanut allergic adults
- When used as a rescue treatment within 5 minutes after food allergen ingestion, a single dose of acalabrutinib reduces mortality from anaphylaxis in humanized mice

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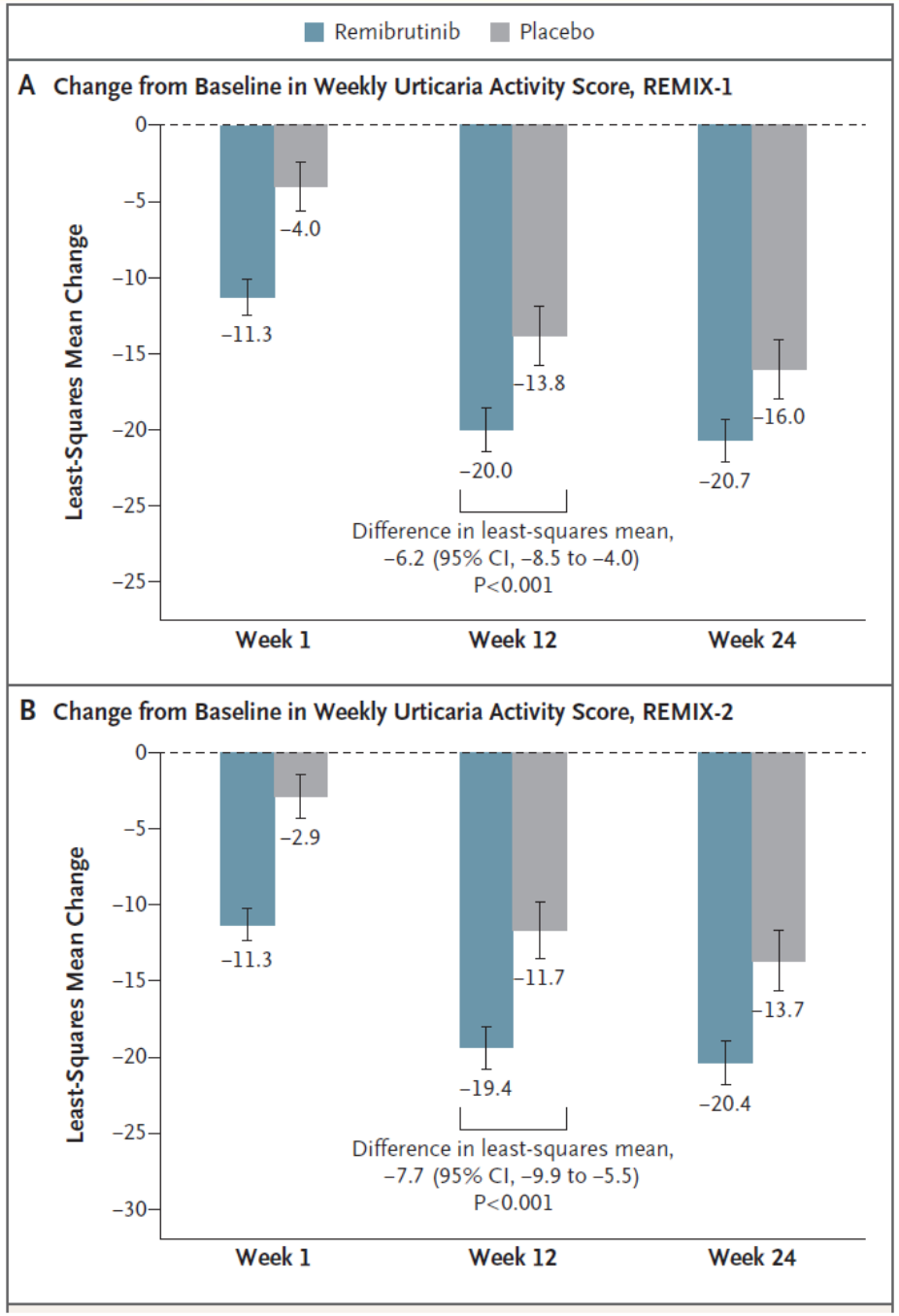
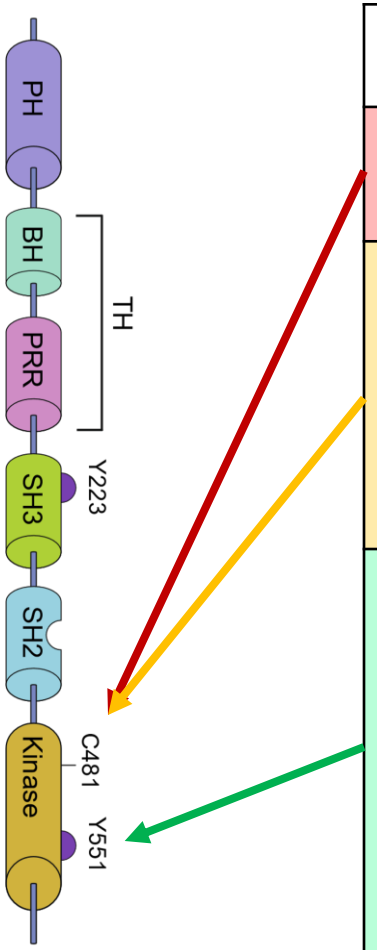
Remibrutinib shows efficacy in Phase 3 REMIX trials

- 925 patients in total
- Randomized to placebo or remibrutinib 25 mg bid
- At week 12:
  - UAS7 change = -19.7 for remi vs -12.75 for placebo
  - UAS7 = 0 for 29.5% for remi vs 8.5% for placebo
- No difference in serious adverse events between groups
- Most notable side effect was petechiae (3.8% in remibrutinib group vs 0.3% in placebo)

Metz, NEJM, 2025



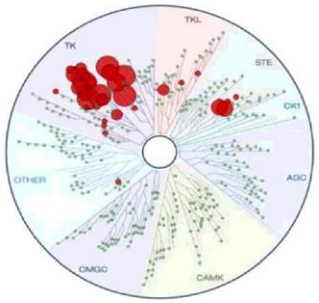
Side effect profiles of BTKis vary by target binding site



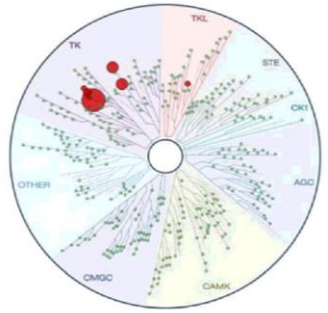
Generation	Drug	Potentially severe side effects
1st	Ibrutinib	Bleeding, infection, cytopenias, arrhythmias, hypertension
2nd	Acalabrutinib	Bleeding, infection, cytopenias, arrhythmias
	Zanubrutinib	Bleeding, infection, cytopenias, arrhythmias
	Pirtobrutinib	Bleeding, infection, cytopenias, arrhythmias
Next-gen	Remibrutinib	Bleeding (petechiae only)
	Rilzabrutinib	None
	Fenebrutinib	Elevated LFTs, nasopharyngitis
	Evobrutinib	Elevated LFTs, nasopharyngitis

Kinomes

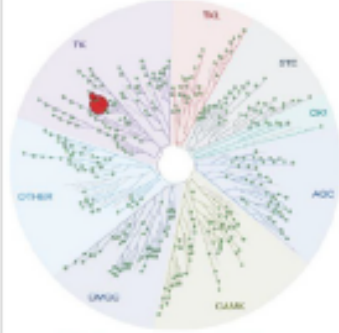
Ibrutinib



Acalabrutinib



Remibrutinib



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BTKi effects on immunoglobulins

Immunoglobulins in remibrutinib Phase 2 extension		
	Baseline	Change at 52 weeks tx
IgG	11.043 g/L	- 0.534 g/L
IgM	1.047 g/L	- 0.13 g/L
IgA	2.266 g/L	Unchanged
IgE	839.47 µg/L	- 140.22 µg/L

Jain et al, JACI, 2023

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BTKi effects on vaccines

Vaccine data from trials		
Drug	**Patient population**	**Outcome**
Ibrutinib	CLL patients (n = 81)	Seroconversion to COVID vaccine in 53% on BTKi, 43% other chemo, 75% treatment-naïve patients
Evobrutinib	MS patients	No effect of BTKi on COVID vaccine responses
Remibrutinib	107 healthy volunteers	Interrupted BTKi for (3 weeks) had comparable vaccine responses as placebo to influenza, PPV-23, KLH vaccines Continuous BTKi lowered response to PPV-23 but had not effect on other vaccines

Tomasulo et al, Leuk Lymphoma, 2023
Bar-Or et al, Mult Scler, 2023
Tillmann et al, Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) 2025 meeting

Current unknowns

Knowledge Gap	Implication
Incomplete understanding of pharmacodynamics on human mast cells and basophils in vivo	Currently approved doses of BTKis do not fully suppress tissue-resident mast cells, which may be required for certain applications (e.g. the prevention of anaphylaxis).
Unknown BTK turnover rates in mast cells and basophils in vivo	The minimum required dosing frequencies for inhibition of both cell types may differ, and likely differ from the frequency needed to target malignant B cells. These parameters will determine the duration of action of BTKis in vivo, which may be critical for certain applications (e.g. protection from anaphylaxis).
Incomplete understanding of anaphylaxis mechanisms in vivo	It is unknown if full inhibition of all mast cells is necessary for the prevention morbidity/mortality from anaphylaxis, or if only some compartments (e.g. the lung) are critical.
Long-term safety data of newer BTKi compounds	Though safety data has been favorable for next-generation compounds, the consequences of long-term immune dysregulation by BTKis is unknown.
Effects of chronic BTKi use on immune modulation	Given their effects on B cell physiology, it is still unknown whether or not BTKis would prevent the induction of tolerance to allergens (either natural tolerance or tolerance induced by immunotherapy).

EV Lin et al, JACI, *in press*

Conclusions

- BTK inhibitors may effectively:
  - Treat chronic urticaria
  - Prevent IgE-mediated anaphylaxis
- Safety profiles of newer BTK inhibitors appear favorable
- Further work is needed
  - Reformulation of oral drugs would be necessary for using as IM rescue medications
  - Pharmacodynamic studies in humans are critical

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Acknowledgements

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- Yun Cao
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