AB102 IS A POTENT AND ORALLY BIOAVAILABLE SMALL MOLECULE INHIBITOR OF MRGPRX2

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Abstract 1025

Disclosures

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I am an employee and shareholder of Arcus Biosciences, Inc.

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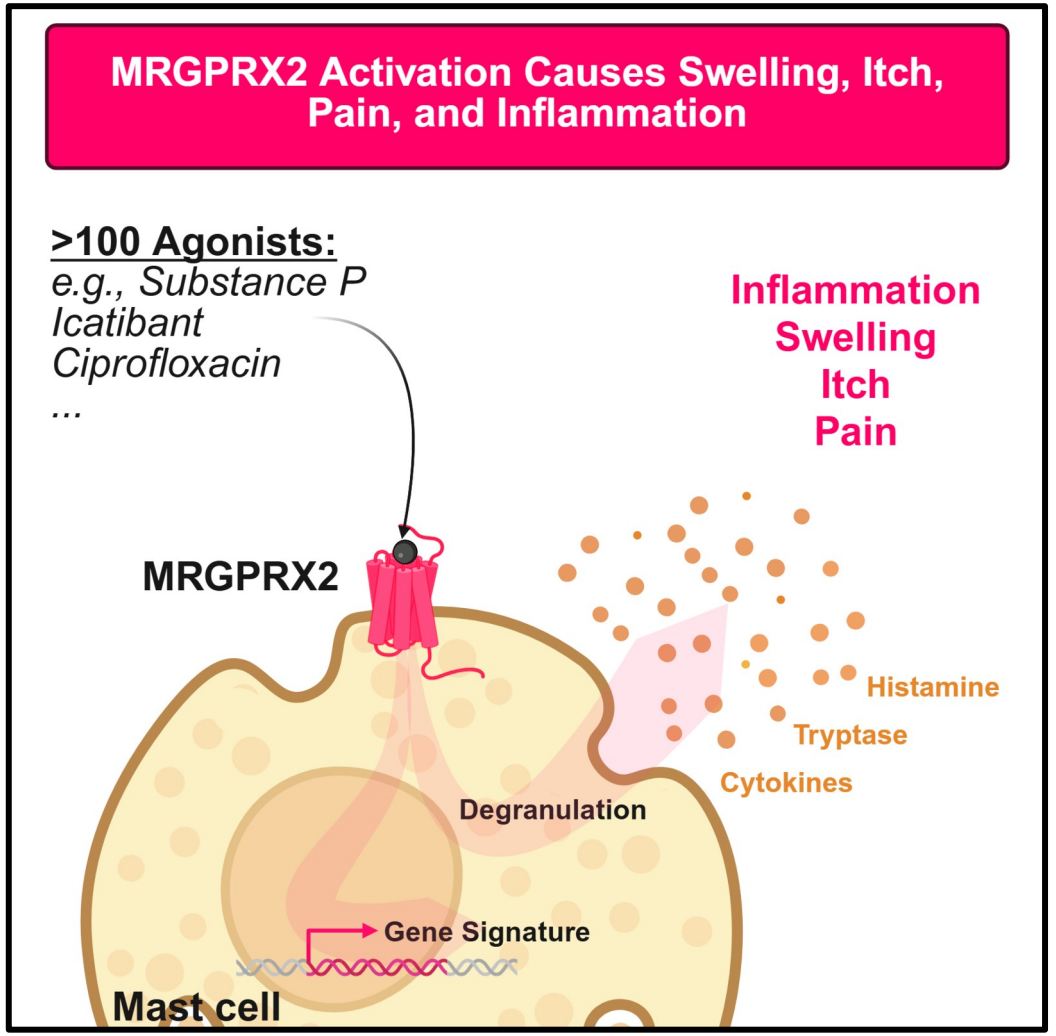
MRGPRX2 Triggers Mast Cell Degranulation and Transcriptional Responses

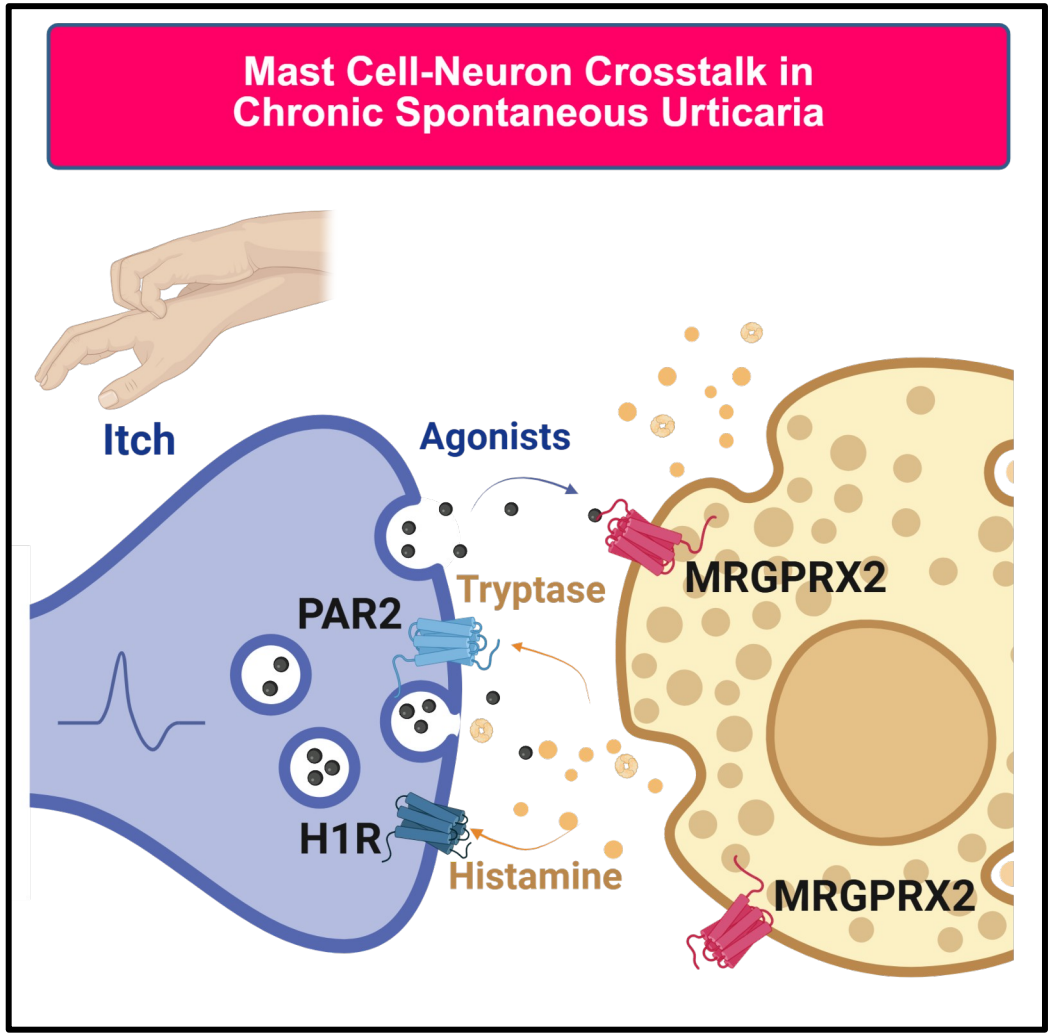
- MRGPRX2 is a mast cell-specific GPCR[1]
- MRGPRX2 is activated by multiple agonists driving IgE-independent degranulation[1]
- MRGPRX2-dependent mast cell activation leads to release of mediators driving pain, itch, swelling and inflammation[2]
- MRGPRX2 inhibition provides a mast cell-focused target for inflammatory dermal diseases



[1]McNeil et al, 2015; [2]Gour & Dong, 2024

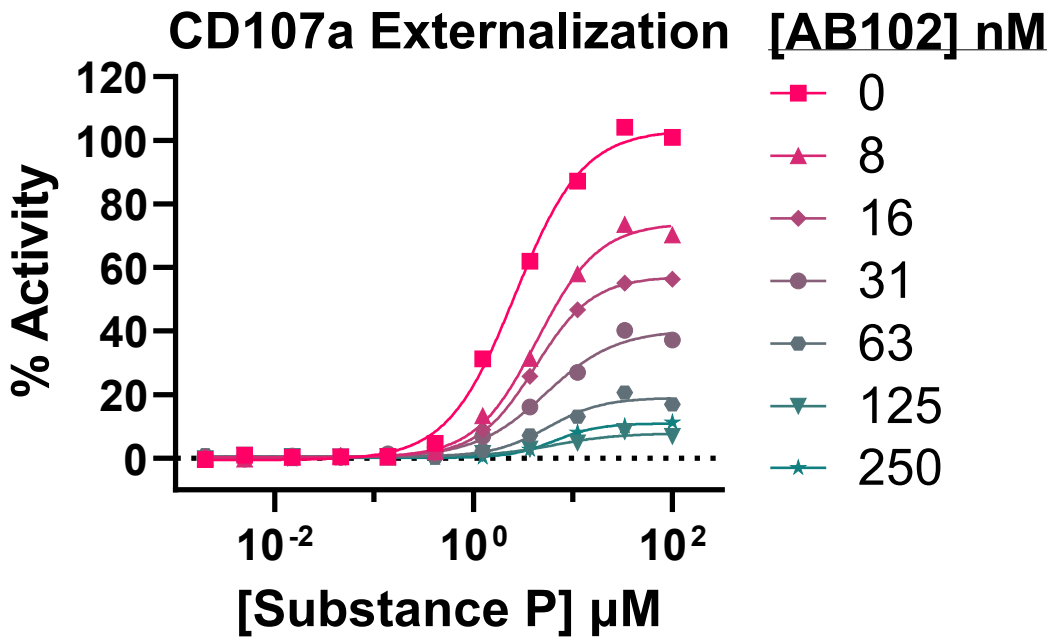
MRGPRX2 is Implicated in the Pathogenesis of Chronic Spontaneous Urticaria (CSU)

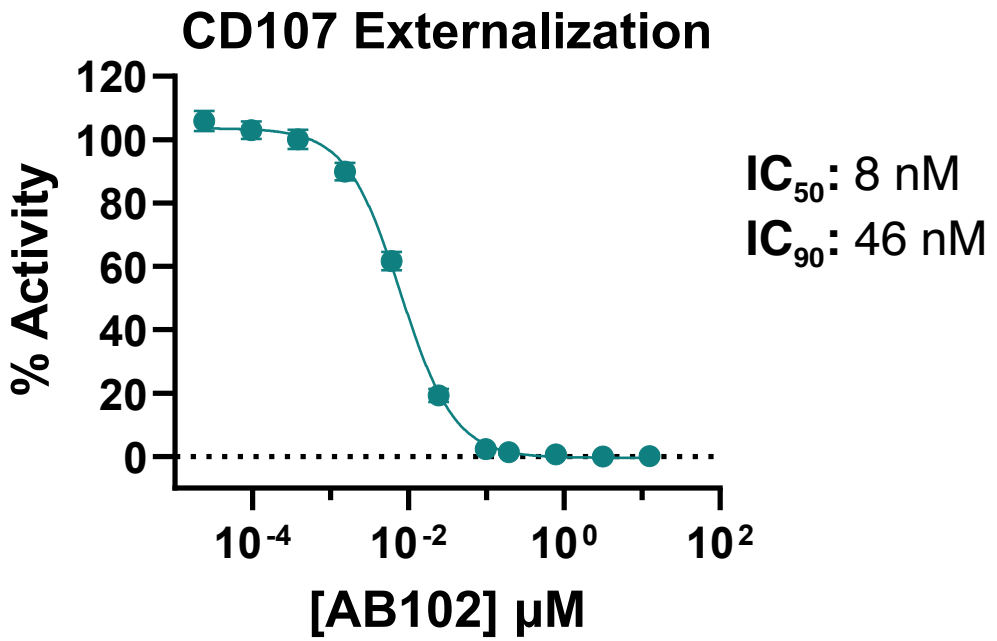
- CSU is characterized by recurrent, pruritic wheals and hives which resolve within 24 hours, but reoccur for 6 weeks or longer[1]
- MRGPRX2 agonists are elevated in serum of CSU patients and correlate with disease severity[2-5]
- Neuropeptide release from sensory neurons activates MRGPRX2 driving itch and wheal formation[6]
- Intradermal MRGPRX2 agonist provocation produces rapid wheal-and-flare responses in humans[7,8]



[1]Kolkhir et al 2022, [2]Fujisawa et al 2014, [3]Metz et al 2014, [4]Tra Cao et al 2021, [5]Di Lorenzo et al 1996, [6]Elieh-Ali-Komi et al 2021, [7]Shtessel et al 2021, [8]Cohen et al 1986

AB102 is a Potent and Selective Small Molecule MRGPRX2 Antagonist

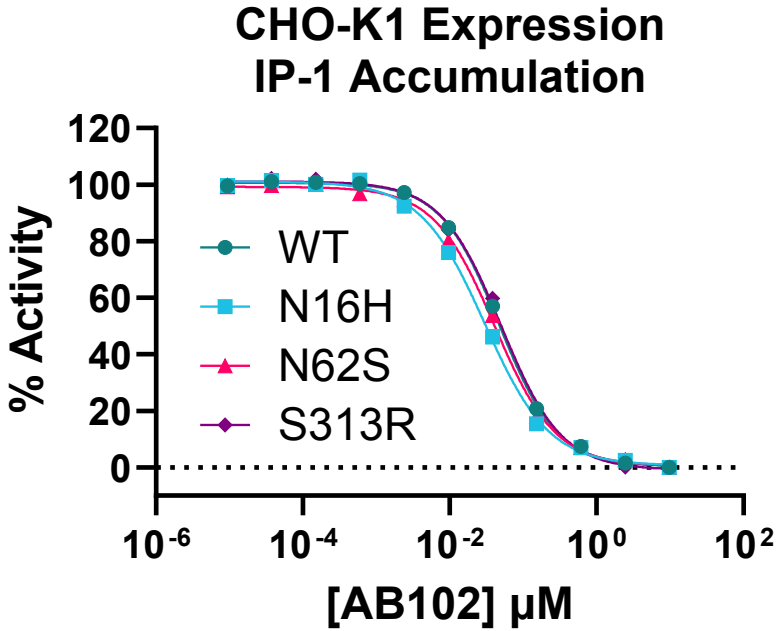


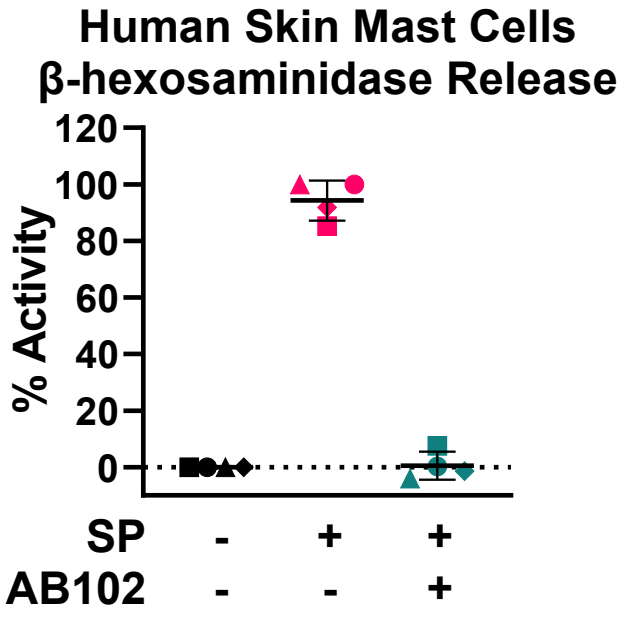


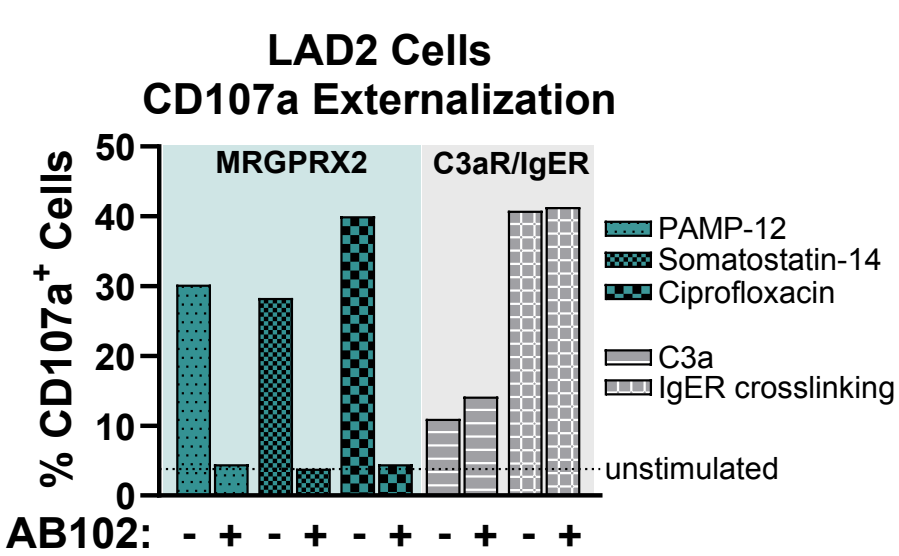
- AB102 binds MRGPRX2 in a reversible manner with an insurmountable inhibitory profile
- AB102 potently inhibits degranulation with an IC_{90} of 46 nM in 100% human serum

LEFT and RIGHT: LAD2 cells in 100% human serum

AB102 is a Potent and Selective Small Molecule MRGPRX2 Antagonist

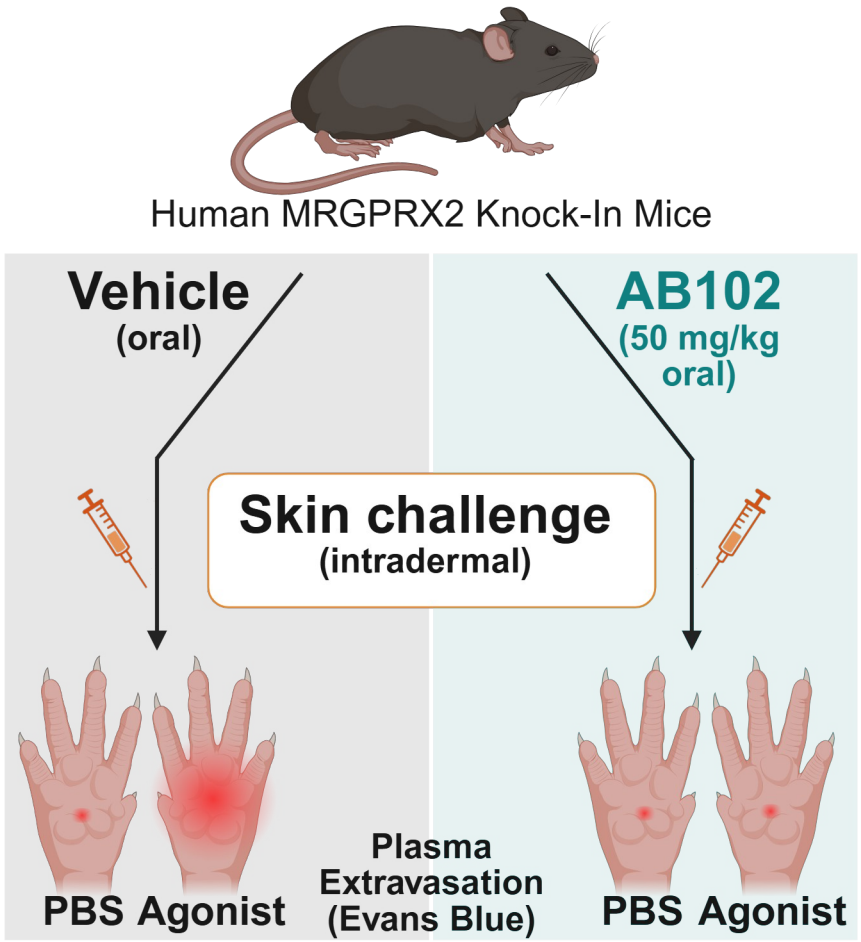




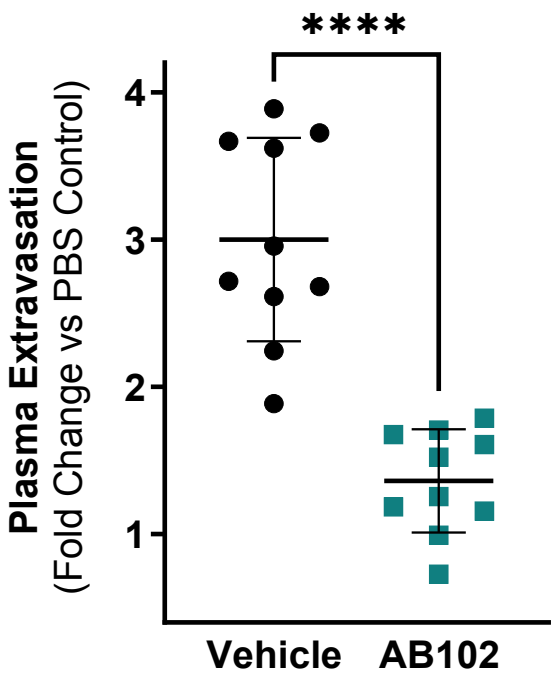


- AB102 maintains full activity against common MRGPRX2 variants
- AB102 inhibits MRGPRX2 activity in primary skin mast cells
- AB102 is selective for MRGPRX2 triggered by a variety of agonists

AB102 Suppresses Swelling and Acute Plasma Extravasation Triggered by MRGPRX2



Substance P



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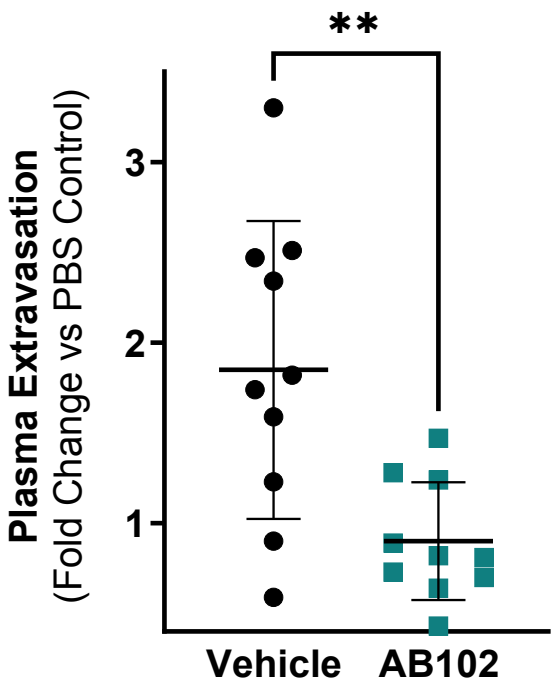
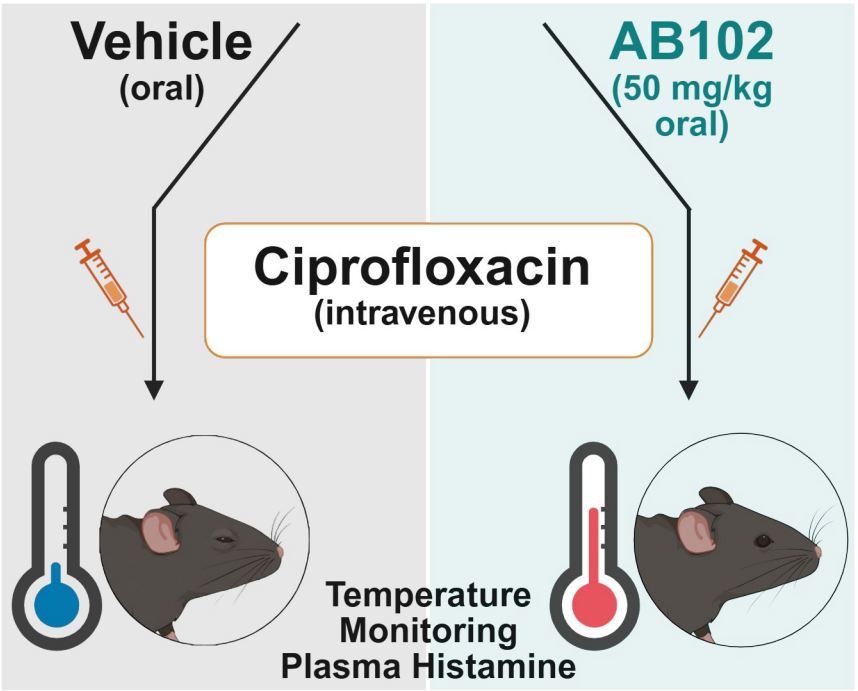


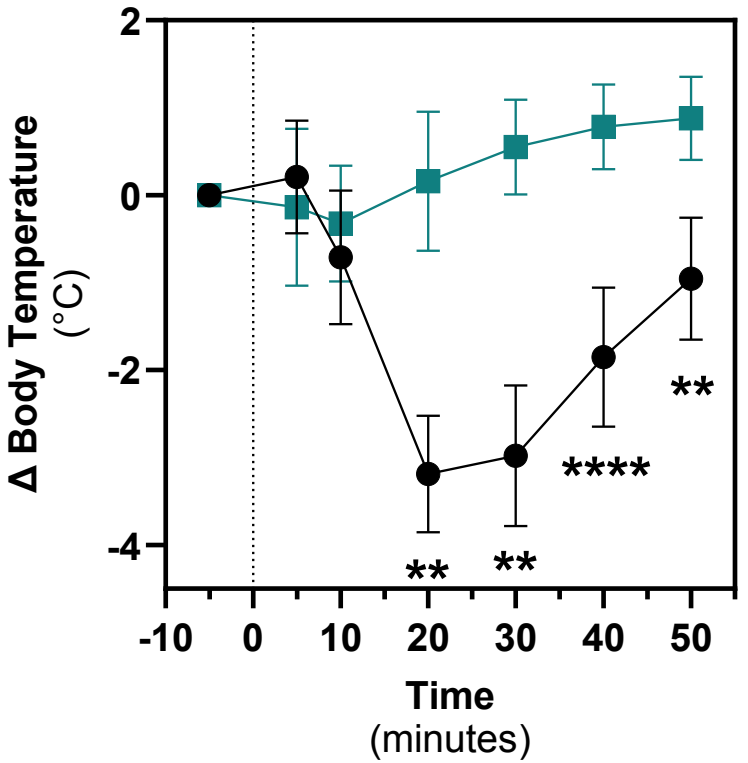
✓ ***In vivo*** **inhibition across two distinct agonists**

AB102 Prevents Systemic Mast Cell-Driven Anaphylaxis

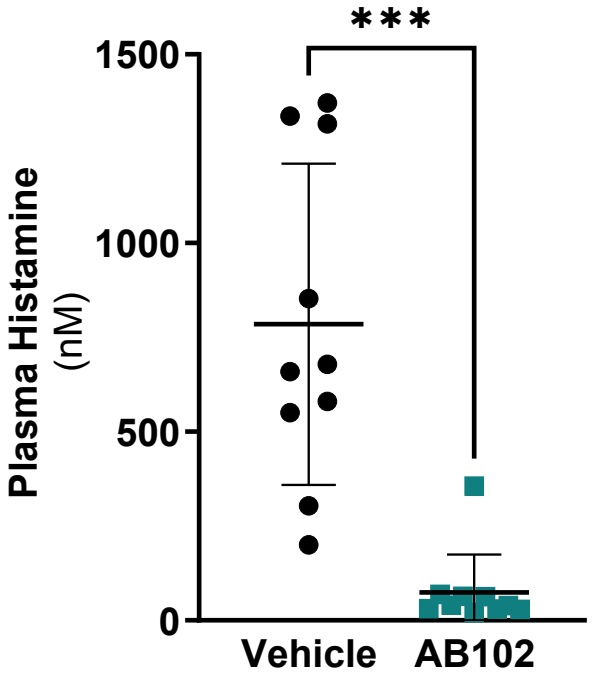
Human MRGPRX2 Knock-In Mice



Temperature Drop



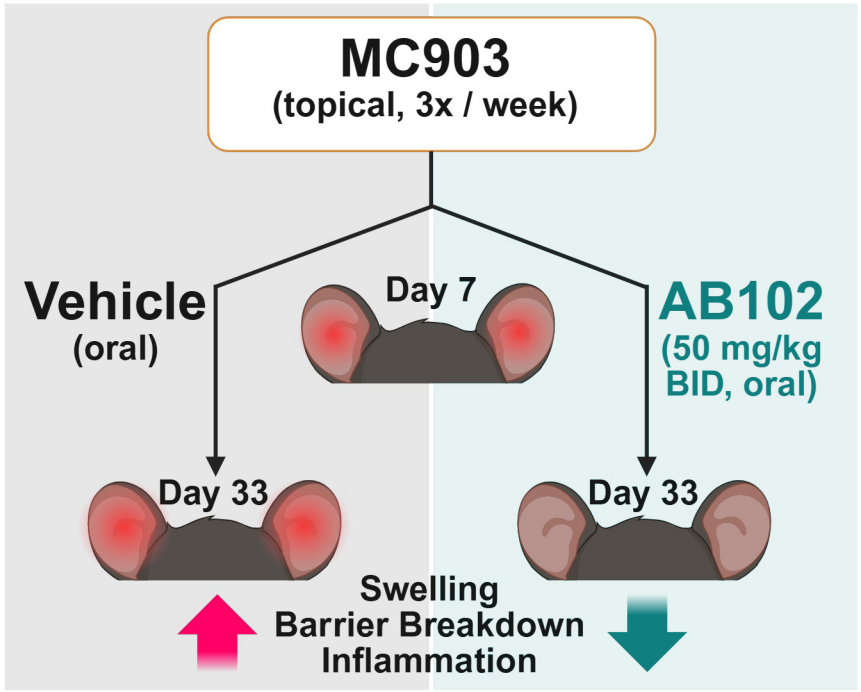
Histamine Levels



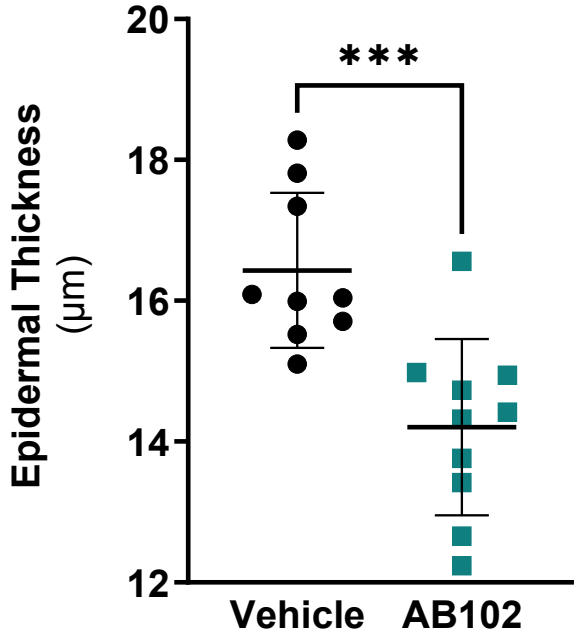
✓ **Activity of AB102 confirmed outside dermal setting**

Therapeutic AB102 Reduces Inflammation in Atopic Dermatitis Model

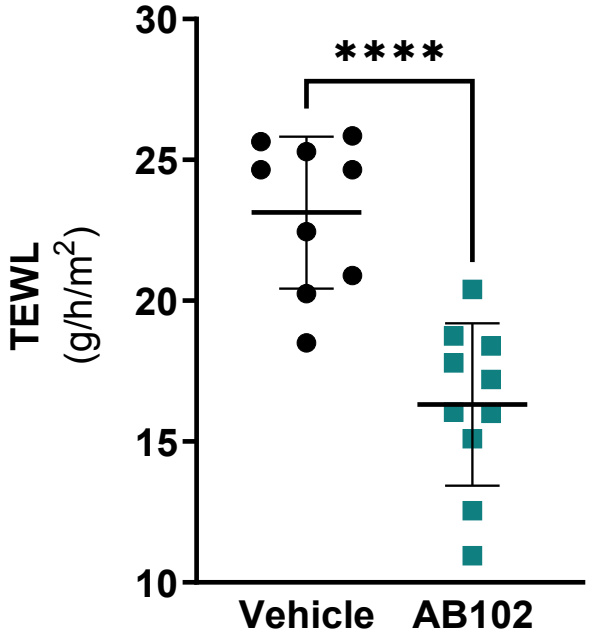
Human MRGPRX2 Knock-In Mice



Swelling



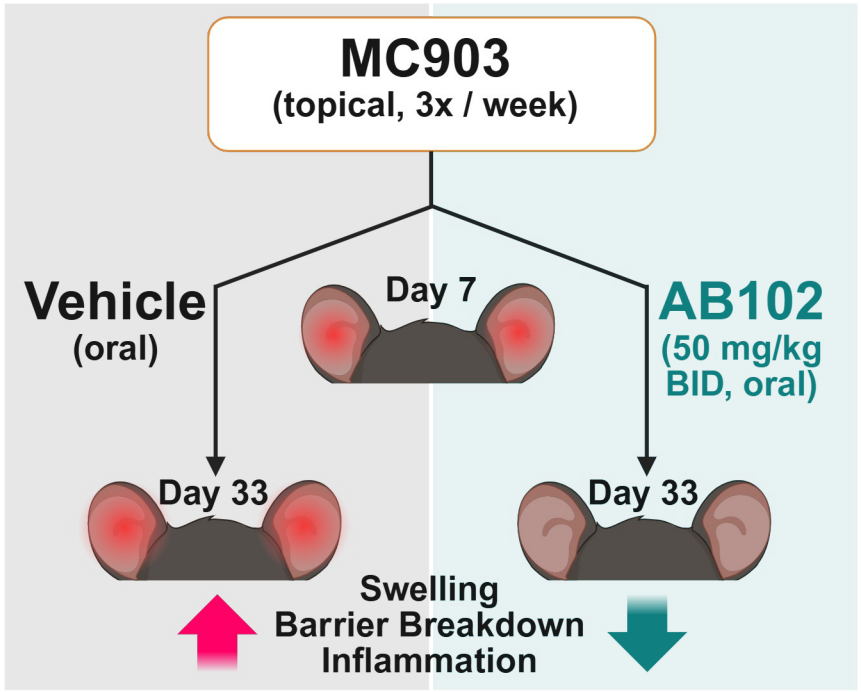
Transepidermal Water Loss (TEWL)

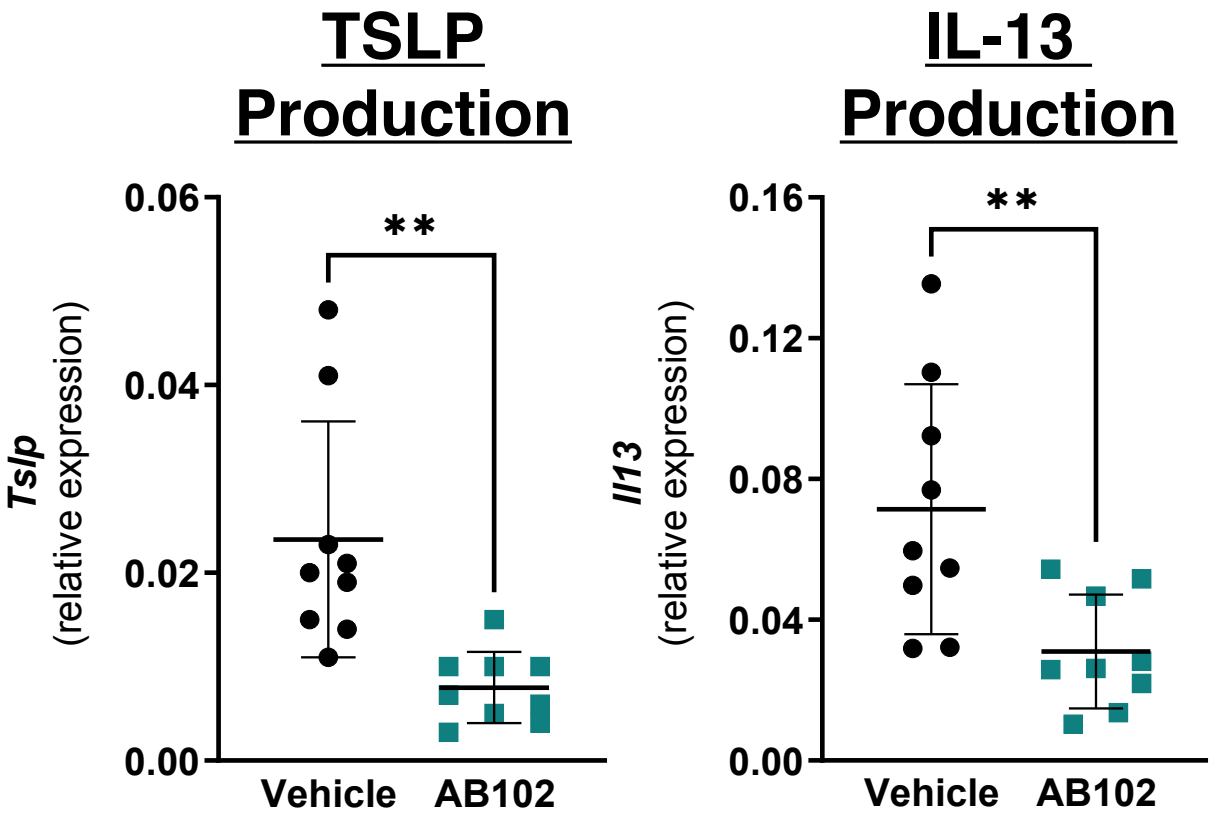


✓ **Therapeutic AB102 reduces TEWL in AD Model**

AB102 Markedly Reduces Markers of Type 2 Immunity in Inflamed Tissue

Human MRGPRX2 Knock-In Mice

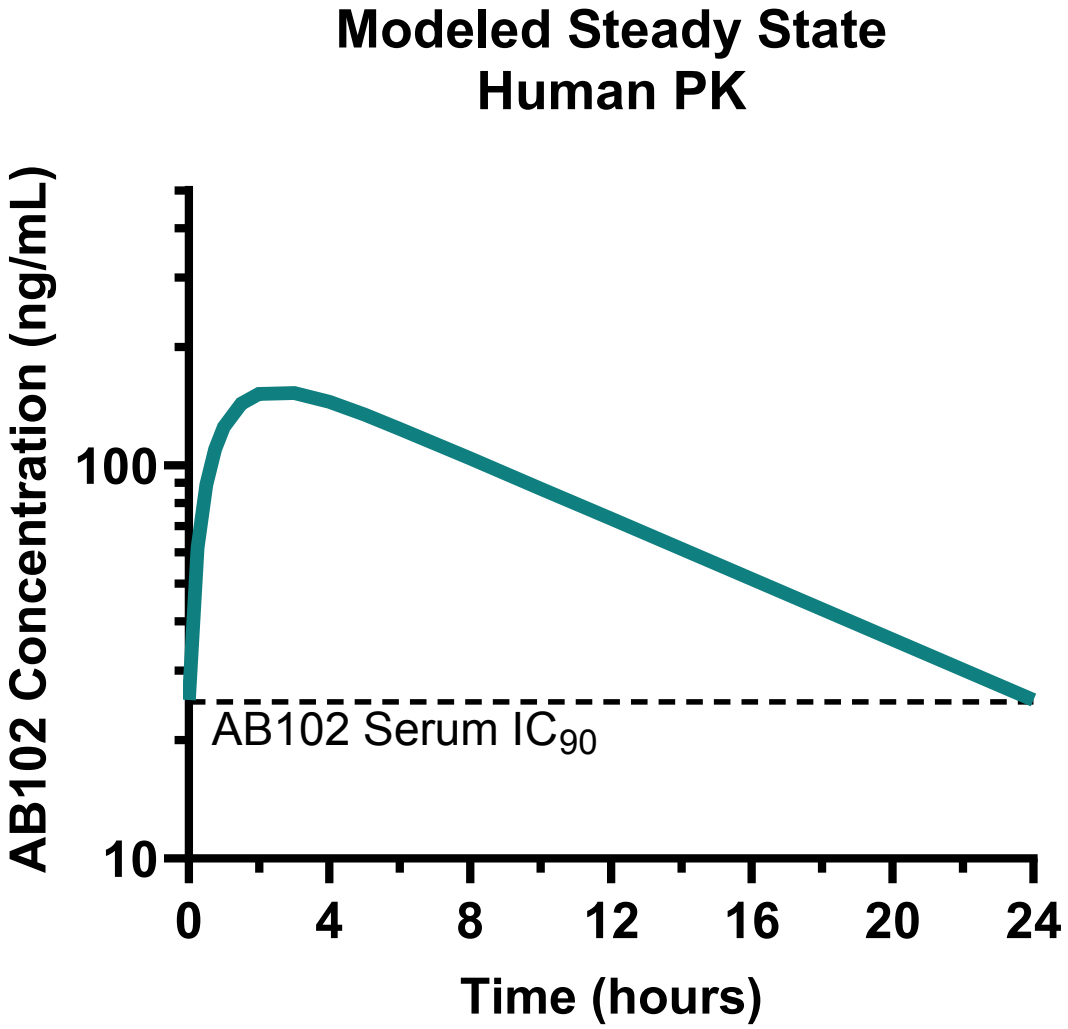




✓ **AB102 reduces disease-relevant type 2 cytokines**

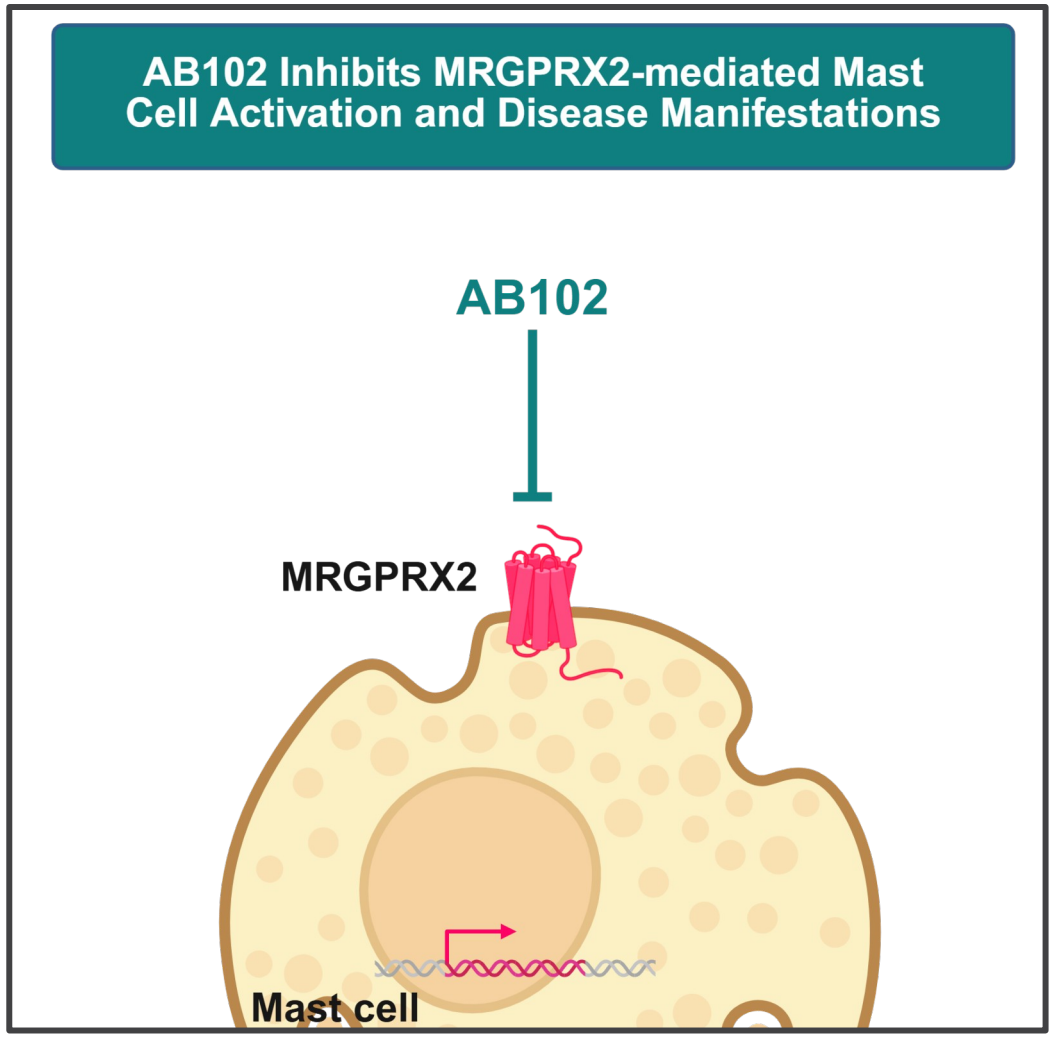
AB102 Predicted Human PK Supports MRGPRX2 Inhibition at Low Exposure

- ✓AB102 potently inhibits MRGPRX2 activity under physiologically relevant conditions
- ✓Due to this potency, we expect maximal pharmacological activity at relatively low plasma levels of compound
- ✓The totality of preclinical data indicate AB102 is suitable for once-daily oral dosing in chronic mast cell-driven diseases



AB102 is a Potent MRGPRX2 Antagonist for the Treatment of Inflammatory Skin Diseases

- ✓AB102 is an insurmountable, non-competitive antagonist of MRGPRX2 with activity in primary skin mast cells
- ✓AB102 attenuates disease onset and/or severity across multiple mouse models
- ✓Preclinical pharmacokinetic parameters predict that AB102 is suitable for once-daily oral dosing
- ✓AB102 is advancing through preclinical development activities to support clinical entry

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