

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

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Abstract 1025

Disclosures

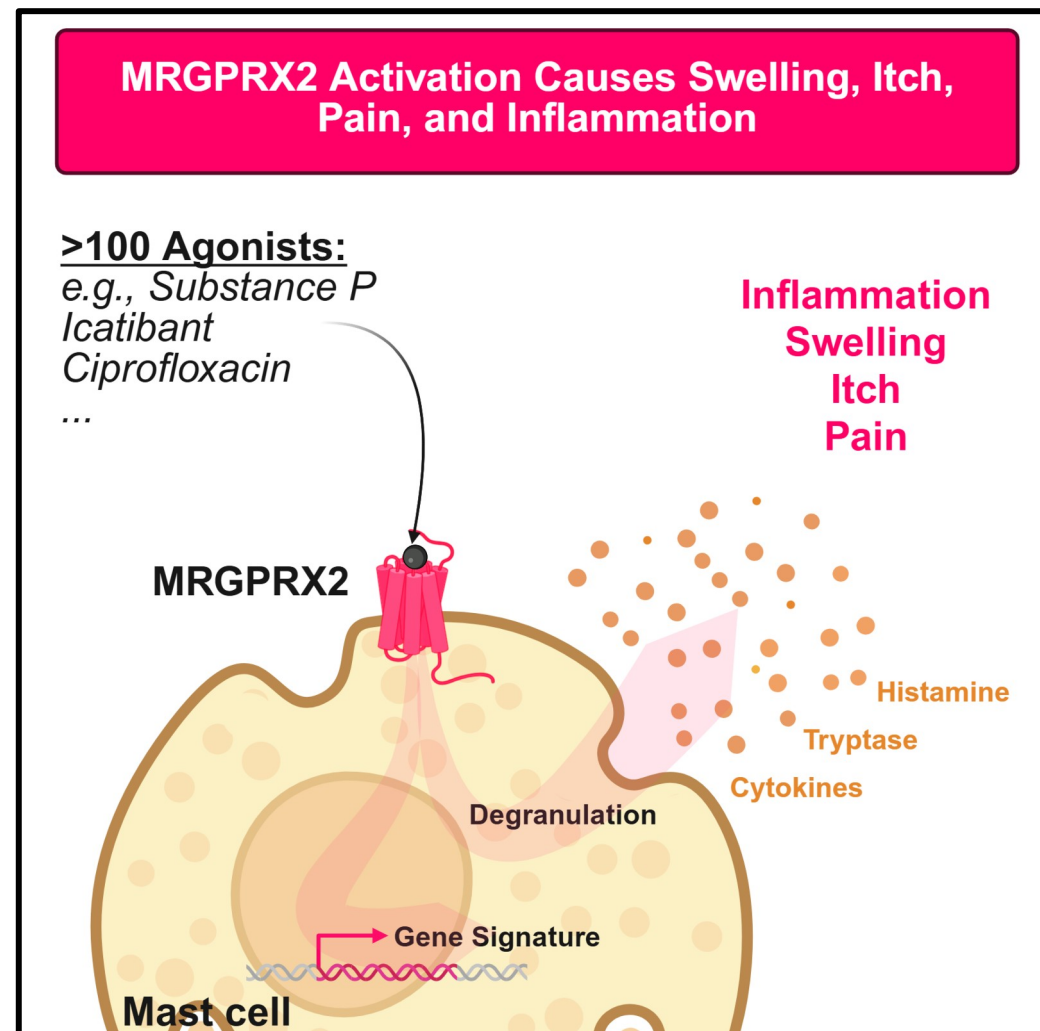


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I am an employee and shareholder of Arcus Biosciences, Inc.

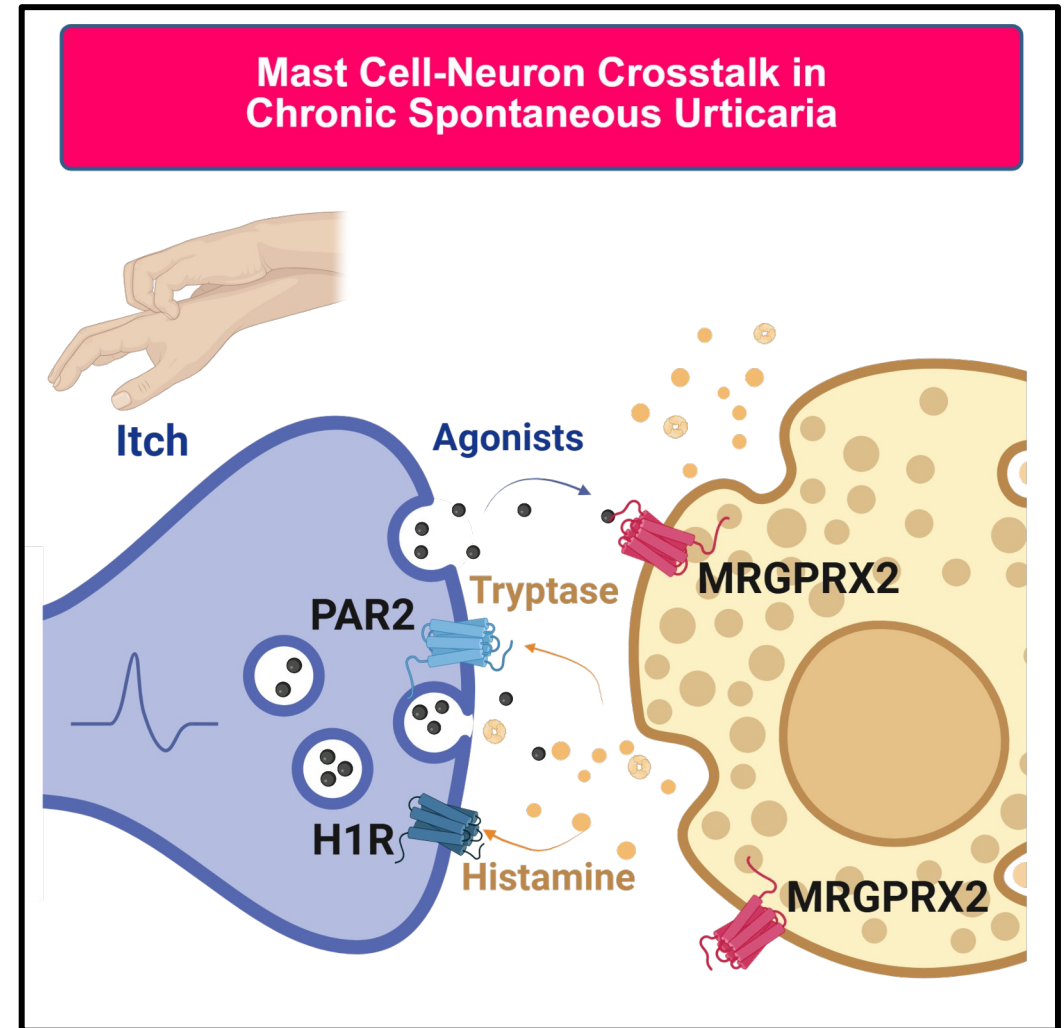
MRGPRX2 Triggers Mast Cell Degranulation and Transcriptional Responses

- MRGPRX2 is a mast cell-specific GPCR¹
- MRGPRX2 is activated by multiple agonists driving IgE-independent degranulation¹
- MRGPRX2-dependent mast cell activation leads to release of mediators driving pain, itch, swelling and inflammation²
- MRGPRX2 inhibition provides a mast cell-focused target for inflammatory dermal diseases

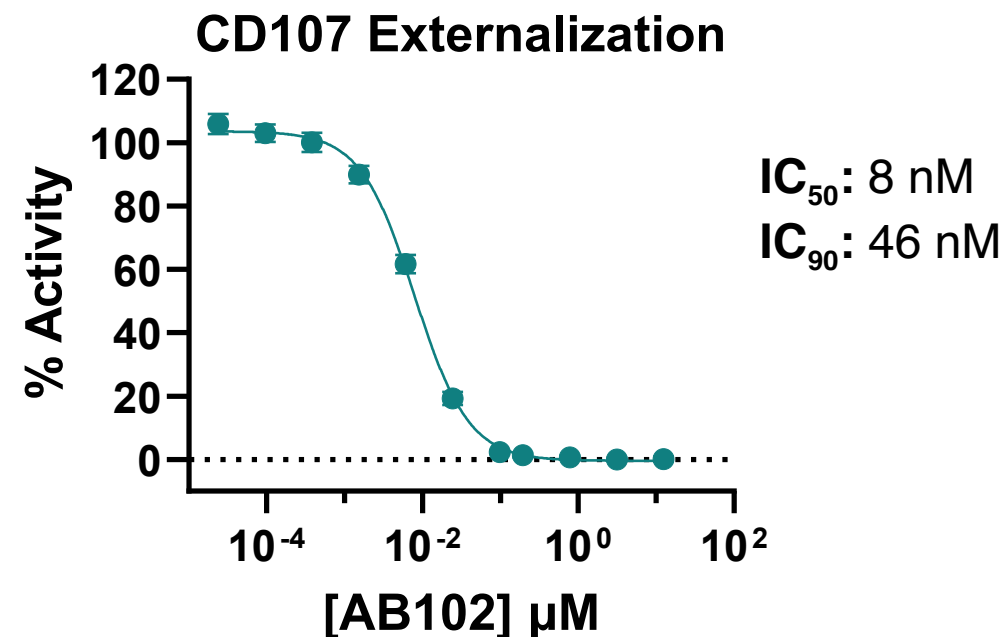
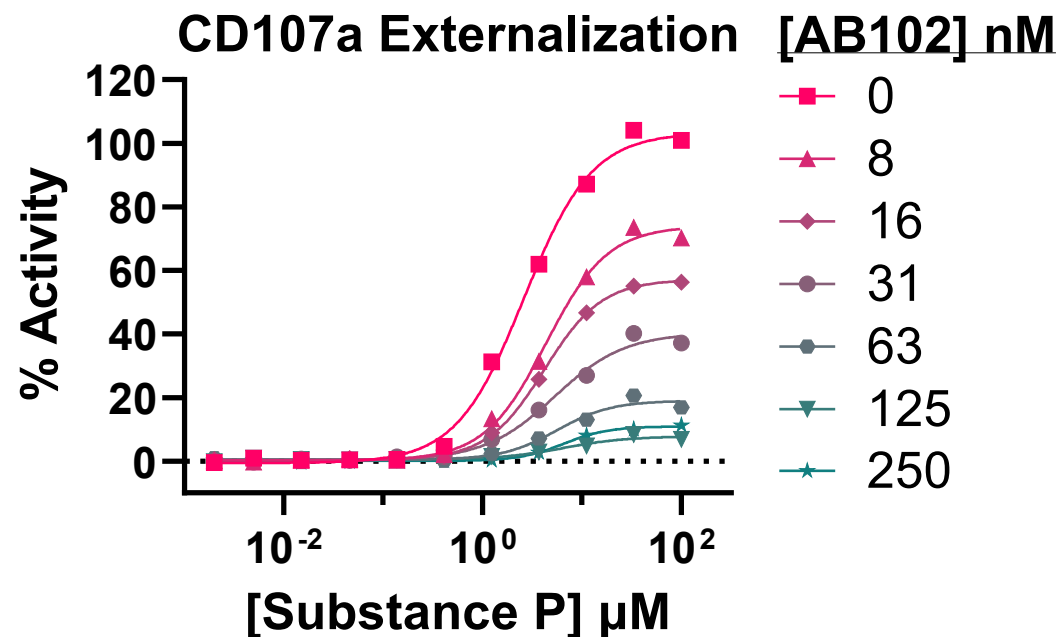


MRGPRX2 is Implicated in the Pathogenesis of Chronic Spontaneous Urticaria (CSU)

- CSU is characterized by recurrent, pruritic wheals and hives which resolve within 24 hours, but reoccur for 6 weeks or longer¹
- MRGPRX2 agonists are elevated in serum of CSU patients and correlate with disease severity²⁻⁵
- Neuropeptide release from sensory neurons activates MRGPRX2 driving itch and wheal formation⁶
- Intradermal MRGPRX2 agonist provocation produces rapid wheal-and-flare responses in humans^{7,8}



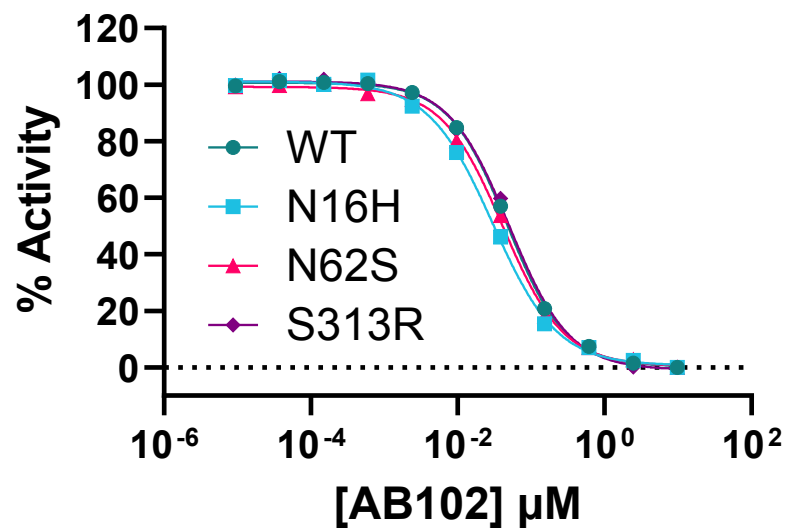
AB102 is a Potent and Selective Small Molecule MRGPRX2 Antagonist



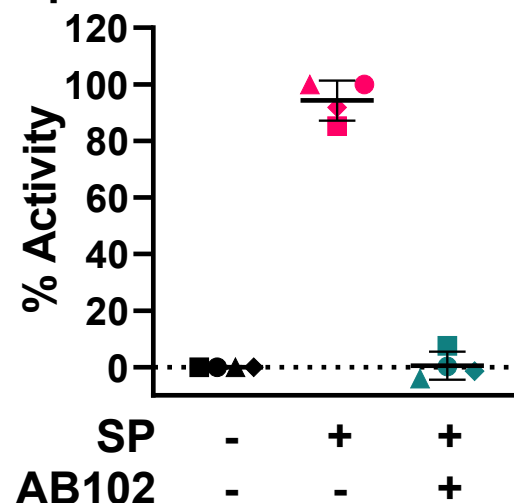
- AB102 binds MRGPRX2 in a reversible manner with an insurmountable inhibitory profile
- AB102 potently inhibits degranulation with an IC_{90} of 46 nM in 100% human serum

AB102 is a Potent and Selective Small Molecule MRGPRX2 Antagonist

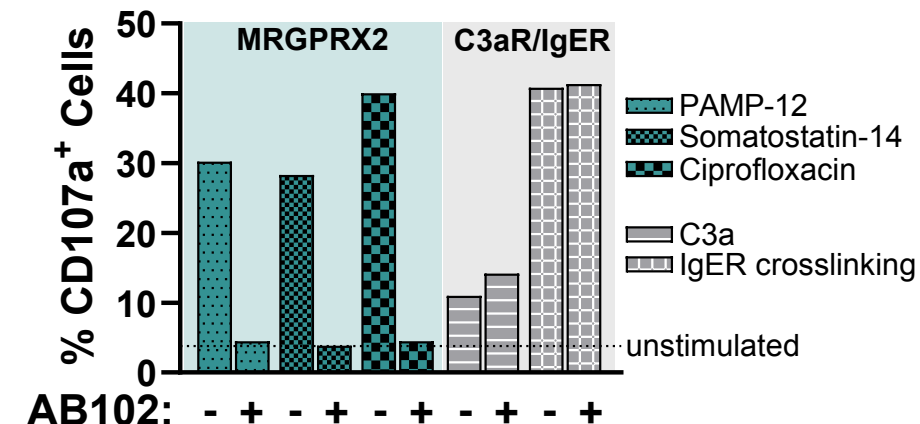
CHO-K1 Expression
IP-1 Accumulation



Human Skin Mast Cells
 β -hexosaminidase Release

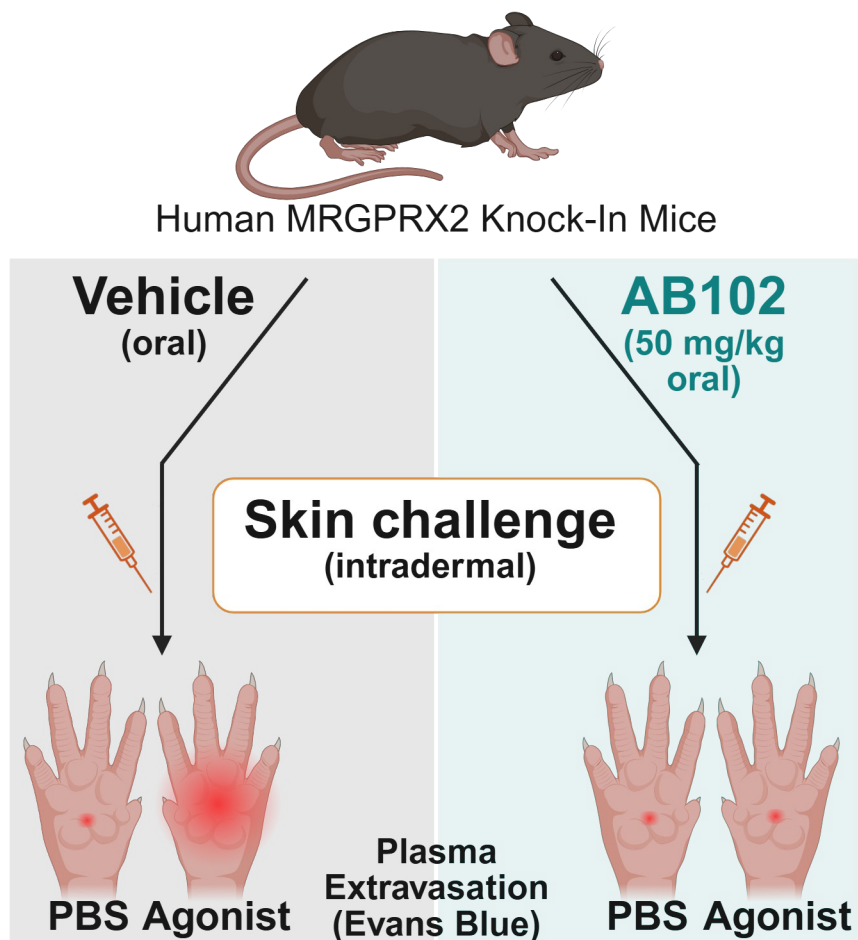


LAD2 Cells
CD107a Externalization

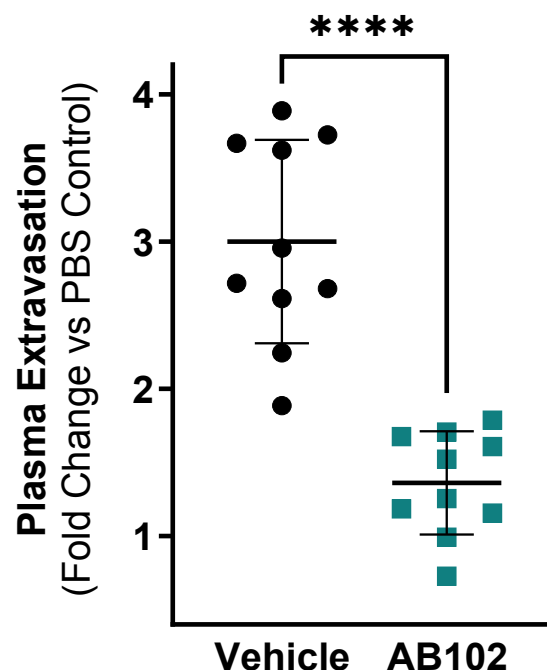


- AB102 maintains full activity against common MRGPRX2 variants
- AB102 inhibits MRGPRX2 activity in primary skin mast cells
- AB102 is selective for MRGPRX2 triggered by a variety of agonists

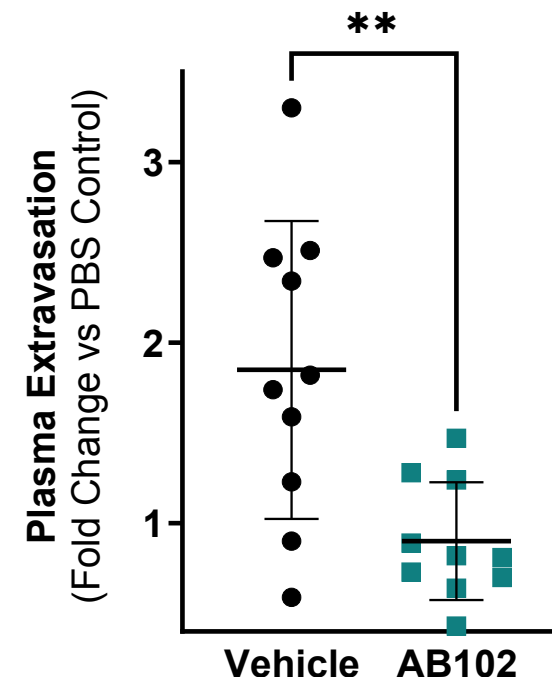
AB102 Suppresses Swelling and Acute Plasma Extravasation Triggered by MRGPRX2



Substance P

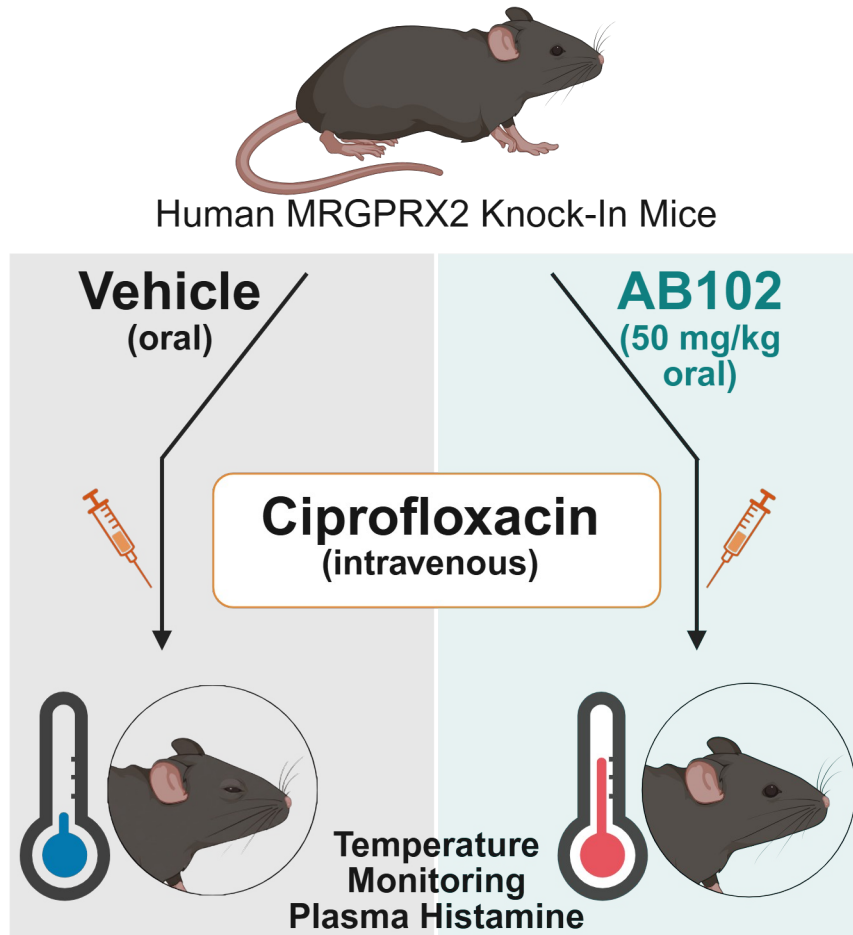


Icatibant

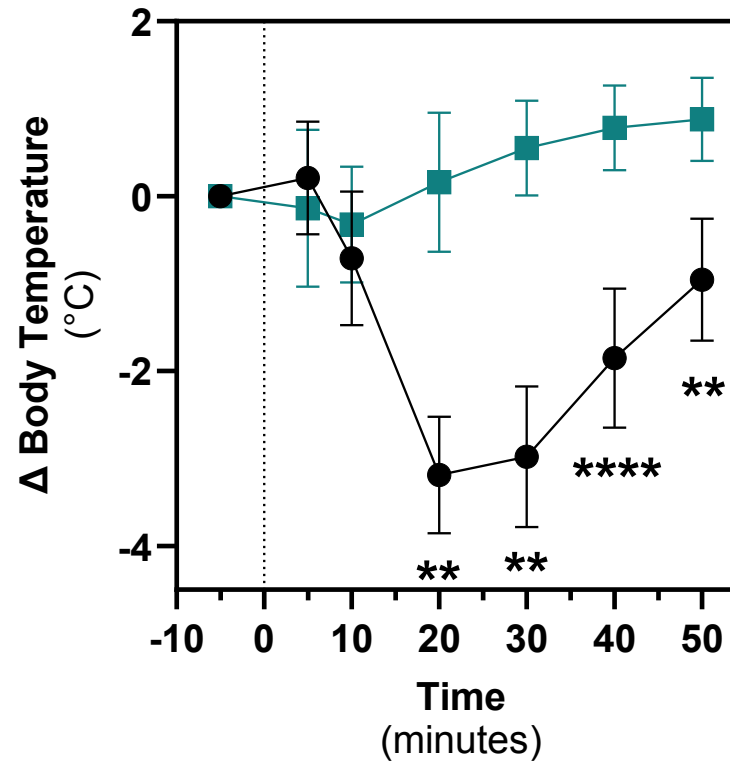


✓ *In vivo* inhibition across two distinct agonists

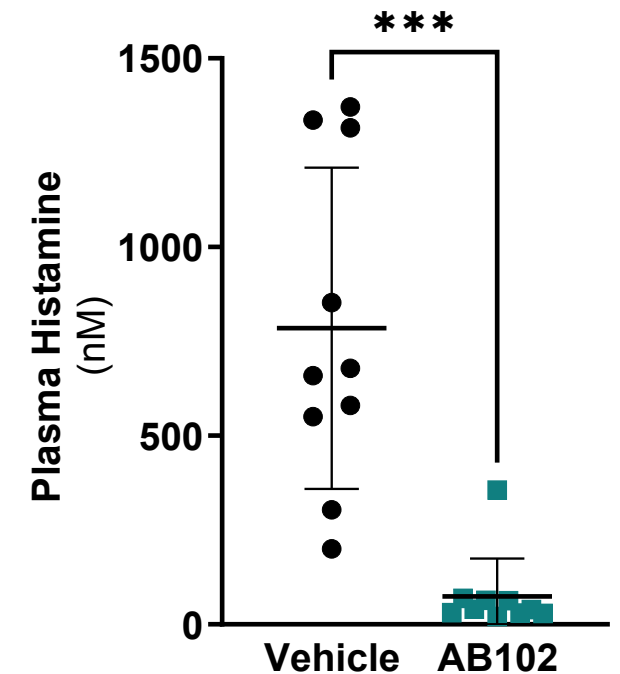
AB102 Prevents Systemic Mast Cell-Driven Anaphylaxis



Temperature Drop



Histamine Levels

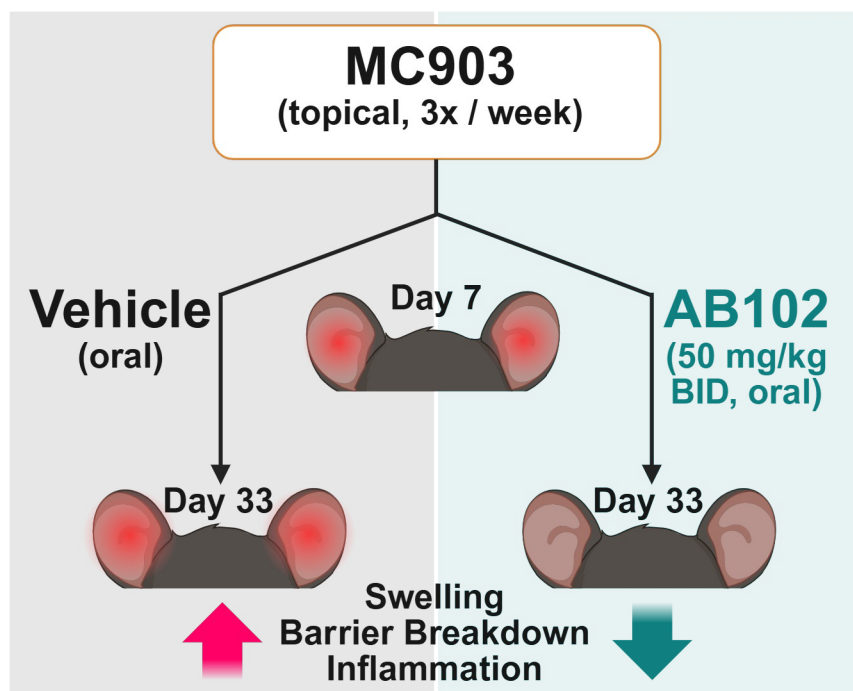


✓ Activity of AB102 confirmed outside dermal setting

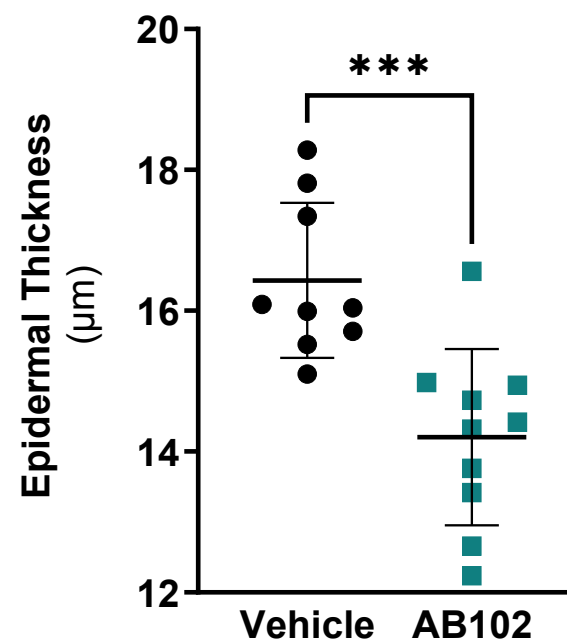
Therapeutic AB102 Reduces Inflammation in Atopic Dermatitis Model



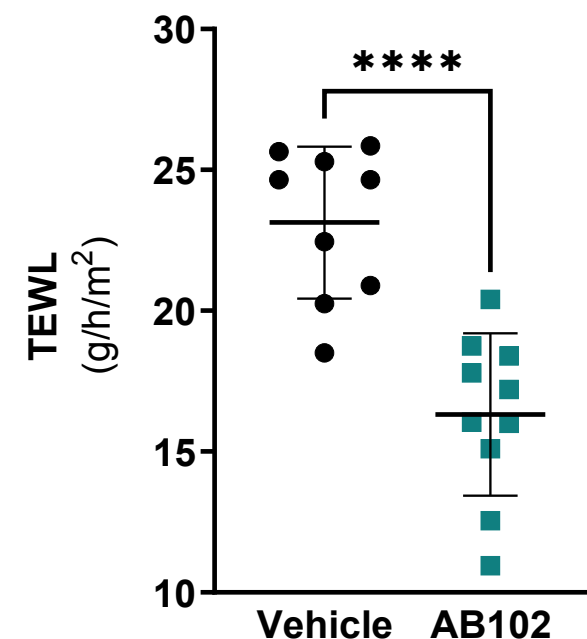
Human MRGPRX2 Knock-In Mice



Swelling

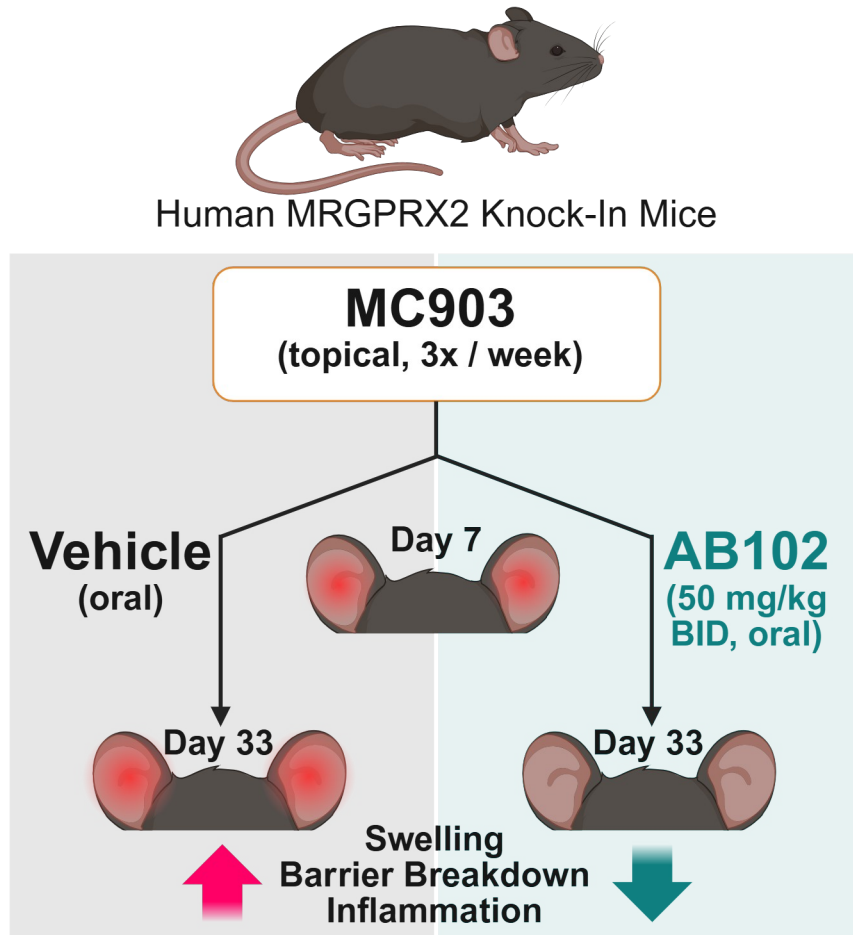


Transepidermal Water Loss (TEWL)

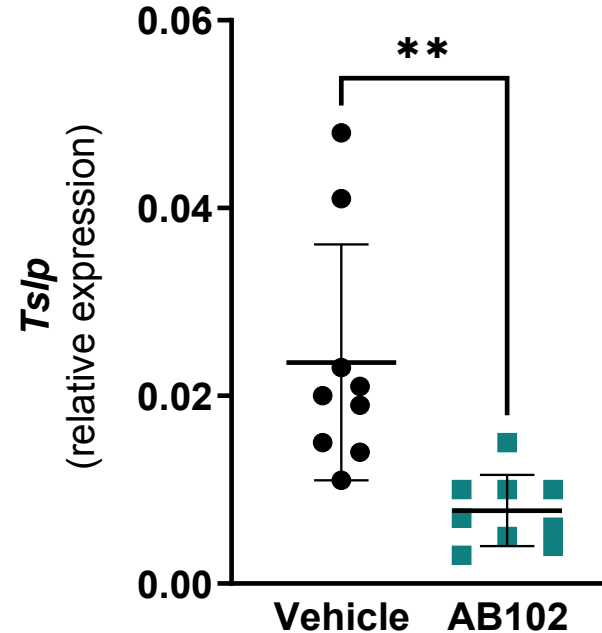


✓ Therapeutic AB102 reduces TEWL in AD Model

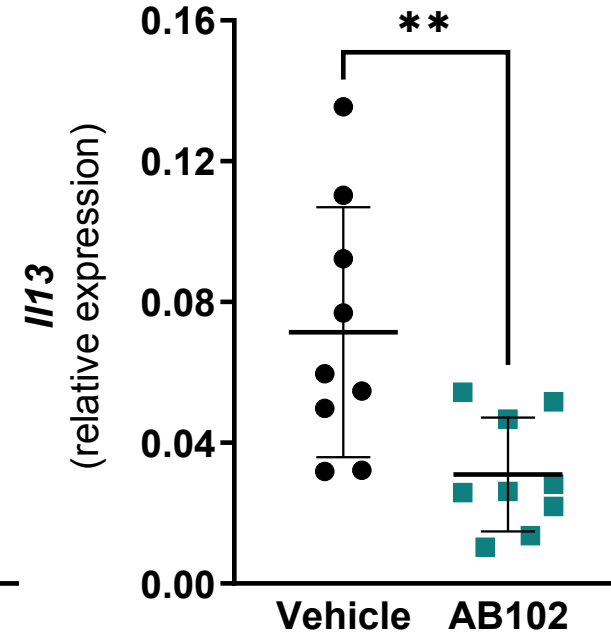
AB102 Markedly Reduces Markers of Type 2 Immunity in Inflamed Tissue



TSLP Production



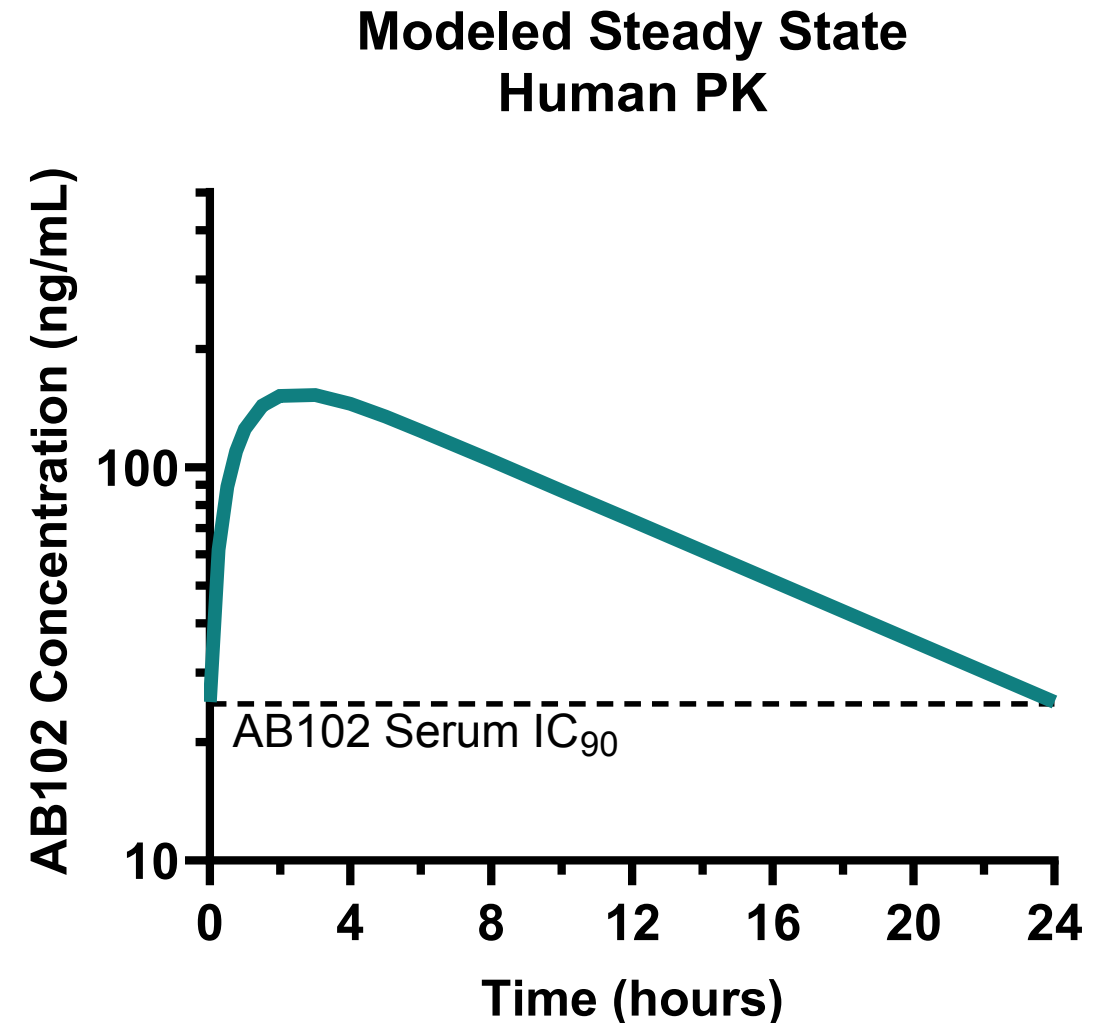
IL-13 Production



✓ 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

