AB102 is a Potent and Orally Bioavailable Small Molecule Inhibitor of MRGPRX2

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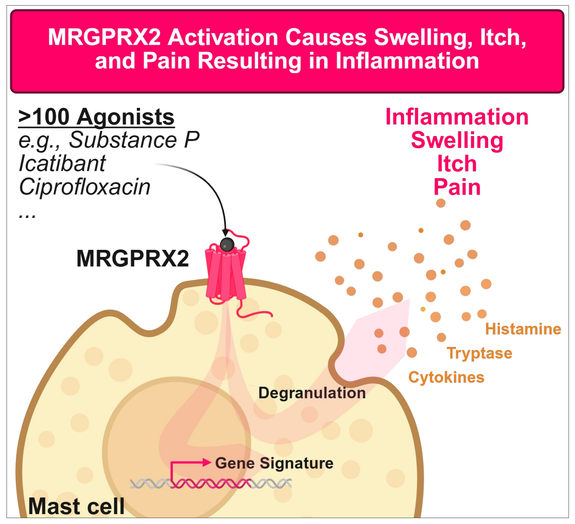
Background

MRGPRX2 Activation Causes Swelling, Itch, and Pain Resulting in Inflammation



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

Results

AB102 is Optimized for Physiological Relevance

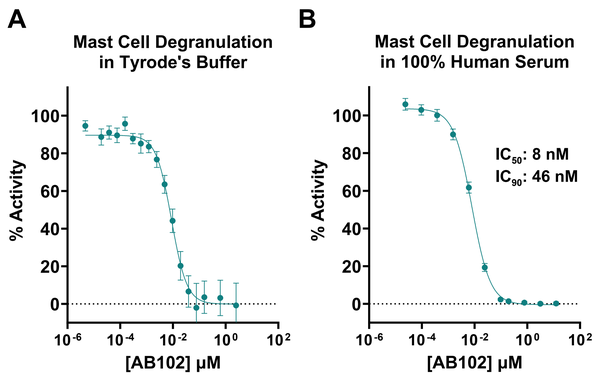


Figure 1 – AB102 potently inhibits LAD2 mast cell degranulation in Tyrode's buffer **(A)** and in 100% human serum **(B)**. AB102-treated cells were stimulated with substance P. Degranulation was assessed through β-hexosaminidase release **(A)** or CD107a externalization **(B)**.

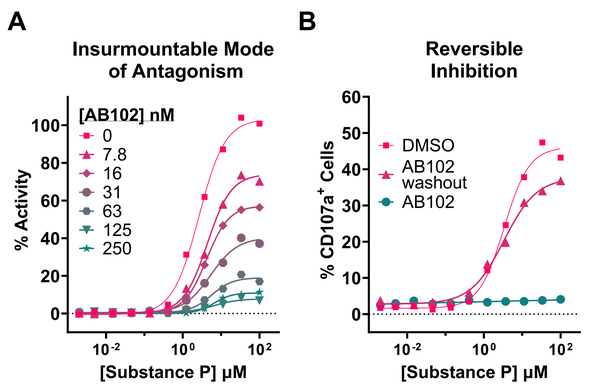


Figure 2 – **(A)** LAD2 cells were incubated with AB102 before stimulation with substance P in a Schild assay. **(B)** For washout analysis, LAD2 cells were incubated with 1 µM AB102 and washed before stimulation with substance P.

AB102 Selectively Inhibits MRGPRX2 Activation in Human Relevant Systems

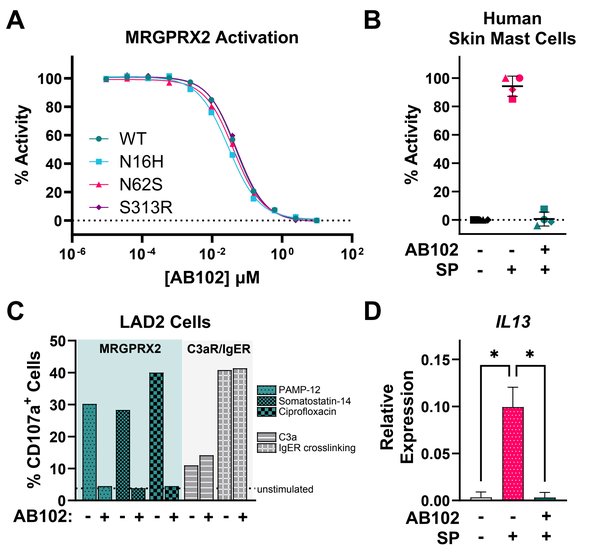
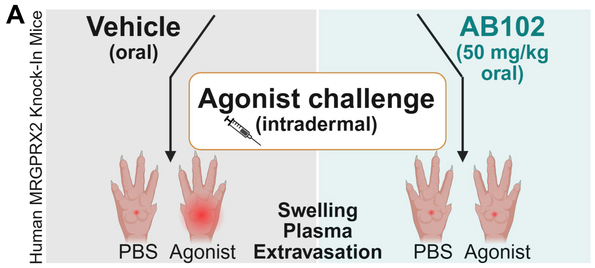


Figure 3 – **(A)** CHO-K1 cells overexpressing WT or variant MRGPRX2 were incubated with AB102 followed by stimulation with substance P (SP). Activity was determined through IP1 accumulation. **(B)** Primary human mast cells isolated from skin of 4 donors were incubated with AB102 before stimulation with substance P (SP). **(C)** LAD2 cells were preincubated with AB102 or DMSO before stimulation with MRGPRX2 agonists PAMP-12, somatostatin-14, ciprofloxacin, C3aR-activating C3a, or IgE receptor cross-linking agents. **(D)** *IL13* transcript upregulation following SP stimulation is shown. AB102 inhibits IL13 expression.

AB102 Inhibits Swelling Responses Triggered by Substance P



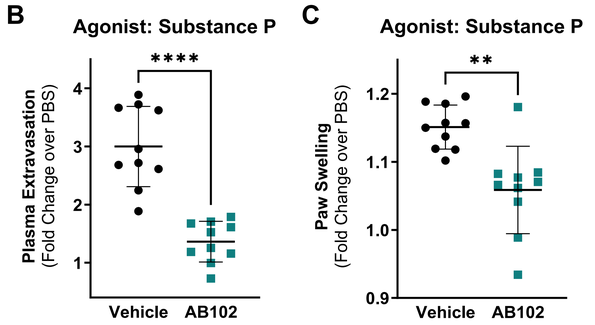


Figure 4 – (A) Human MRGPRX2 knock-in (KI) mice were treated orally with AB102 followed by intradermal injection of substance P or PBS. **(B)** Plasma extravasation was evaluated through Evans Blue dye accumulation. **(C)** Paw thickness was measured by caliper 30 min after injection.

AB102 Inhibits Swelling Responses Triggered by Icatibant

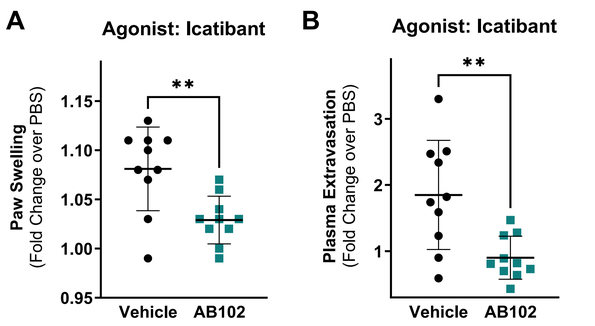
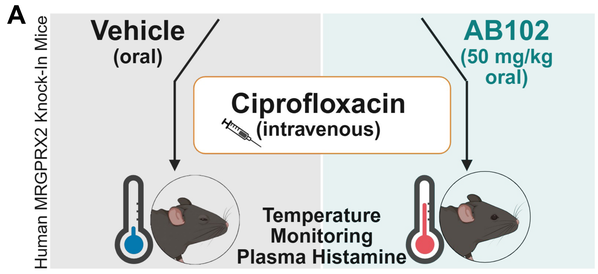


Figure 5 – Human MRGPRX2 KI mice were treated orally with AB102 followed by intradermal injection of icatibant or PBS as outlined in Figure 4A. Plasma extravasation **(A)** and paw thickness **(B)** were evaluated.

AB102 Inhibits Ciprofloxacin-Induced Systemic Anaphylaxis



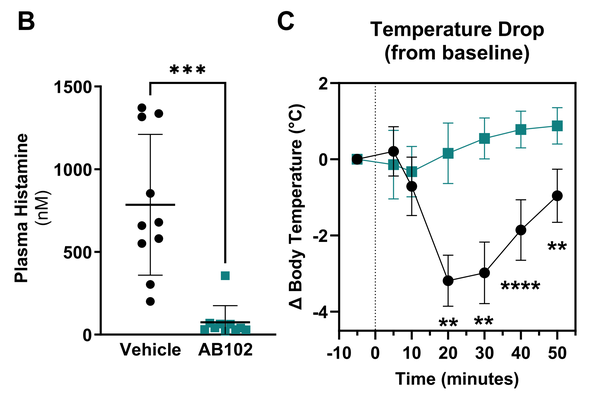
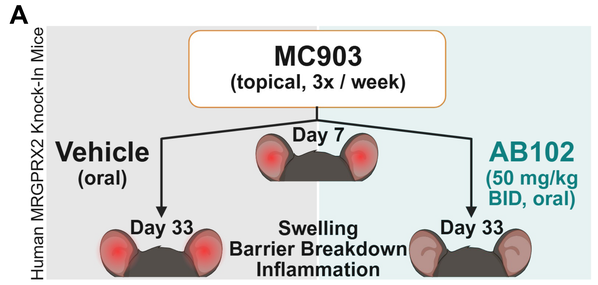


Figure 6 – **(A)** Human MRGPRX2 KI mice were treated with 50 mg/kg AB102 or vehicle followed by intravenous injection of ciprofloxacin. **(B)** Plasma was harvested 1 hour after ciprofloxacin injection and analyzed for histamine. **(C)** Body temperature was measured with transponders.

AB102 Inhibits MC903-Driven Chronic Inflammation



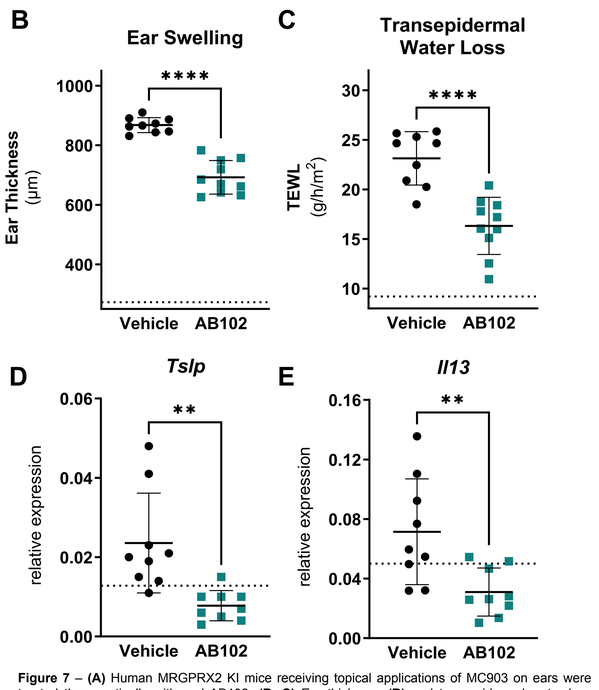


Figure 7 – **(A)** Human MRGPRX2 KI mice receiving topical applications of MC903 on ears were treated therapeutically with oral AB102. **(B, C)** Ear thickness **(B)** and transepidermal water loss (TEWL) **(C)** were measured on study day 33. **(D, E)** Terminal transcript analysis of *Tslp* **(D)** and *Il13* **(E)** expression in the ears of human MRGPRX2 KI mice treated for 33 days with topical MC903. Dotted lines indicate mean values of ethanol treated control mice.

The MRGPRX2 Signature is Enriched in Chronic Spontaneous Urticaria and Atopic Dermatitis

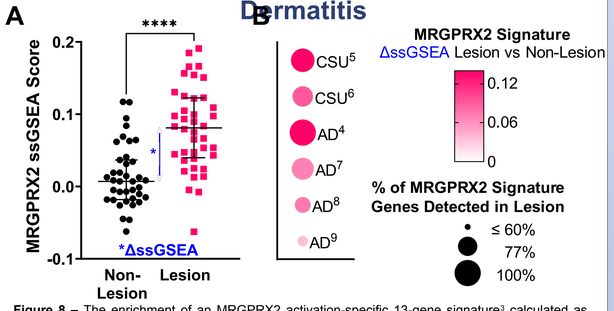


Figure 8 – The enrichment of an MRGPRX2 activation-specific 13-gene signature[3] calculated as single sample gene signature enrichment (ssGSEA) scores was evaluated in chronic spontaneous urticaria (CSU)[5-6] and atopic dermatitis (AD)[4,7-9] patient samples. **(A)** Example data of a training dataset[4] defining how ΔssGSEA of the MRGPRX2 signature in lesional versus non-lesional was calculated. **(B)** Evaluation of ΔssGSEA in CSU and AD dataset with color decoding ΔssGSEA and circle size indicating the percent of MRGPRX2 signature genes detected in lesional skin.

AB102 Supports Pharmacologic Inhibition at Low Exposure with Once Daily Dosing

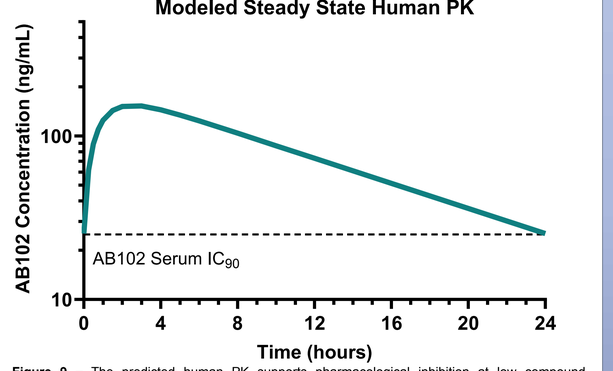
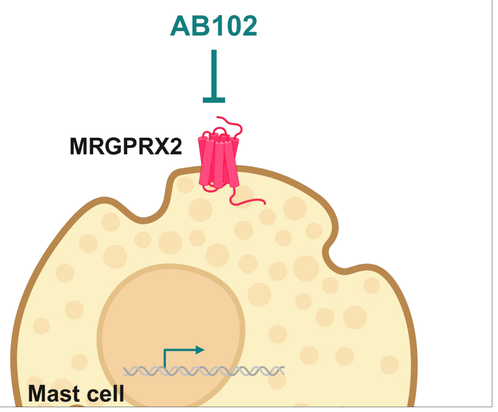


Figure 9 – The predicted human PK supports pharmacological inhibition at low compound exposures. Collectively, preclinical data support compatibility of AB102 with once-daily oral dosing in mast cell-driven diseases.

Summary

AB102 Inhibits MRGPRX2-mediated Mast Cell Activation, Swelling, and Inflammation



- AB102 is an **insurmountable**, **non-competitive antagonist** of **MRGPRX2** with activity in primary skin mast cells (Figures 1 - 3)
- AB102 **inhibits** pathology in multiple disease-relevant mouse models and **reduces type 2 inflammation** (Figures 4 - 8)
- AB102 is expected to achieve **robust pharmacological activity** at **low plasma levels** with **once-daily dosing**, supported by its **optimized potency** in 100% human serum (Figure 9)

References: [1]McNeil et al (2015) *Nature*; [2]Gour & Dong (2024) *Immunity;* [3]Brown et al, (2025) *EAACI Congress Poster Board # D3.412*; [4]Möbus (2021) *J Allergy Clin Immunol* GSE157194; [5]Gimenez-Arnau (2017) *Allergy* GSE72542; [6]Patel (2015) *Allergy and Rhinol* GSE57178; [7]Ungar (2021) *J Allergy Clin Immunol* GSE137430; [8]Tsoi (2019) *J Invest Dermatol* GSE121212; [9]Guttman-Yassky (2019) *J Allergy Clin Immunol* GSE130588; Some images made with BioRender. LAD2 human mast cells were provided by A. Kirshenbaum and D. Metcalfe (NIH, USA).

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