Targeting MRGPRX2: A Transformative Approach to Inflammatory Skin Conditions

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Abstract

Mas-related G protein-coupled receptor X2 (MRGPRX2) has emerged as a potential transformative therapeutic target for inflammatory skin diseases, including chronic spontaneous urticaria (CSU) and atopic dermatitis (AD). Expressed on human skin mast cells and peripheral sensory neurons, MRGPRX2 drives neuroinflammation through activation by endogenous ligands, such as neuropeptides and antimicrobial peptides. Its synergistic interplay with FcεR and IL-33 pathways amplifies mast cell-driven inflammation, positioning it as a central player in disease pathology.

In Mrgprb2 knockout mice, the murine ortholog of MRGPRX2, mast cell activation and inflammatory itch were significantly reduced, underscoring the receptor's therapeutic relevance. EVO756, a novel and potent small-molecule antagonist of MRGPRX2, effectively blocked mast cell degranulation, cytokine release, and neuronal activation while disrupting the synergistic effects of MRGPRX2 with IgE and IL-33. Clinically, oral EVO756 suppressed icatibant-induced wheal formation in a phase 1 trial, confirming its ability to inhibit MRGPRX2-mediated responses in humans. A phase 2a study in Chronic Inducible Urticaria further validated its potential, demonstrating significant reductions in wheals and itch.

These findings establish MRGPRX2 as a master regulator of mast cell and sensory neuron activation, driving neurogenic inflammation in CSU, AD, and beyond. EVO756 offers a potential groundbreaking therapeutic strategy, delivering multipronged benefits by targeting key pathogenic pathways across inflammatory skin diseases and other chronic inflammatory conditions.

Background

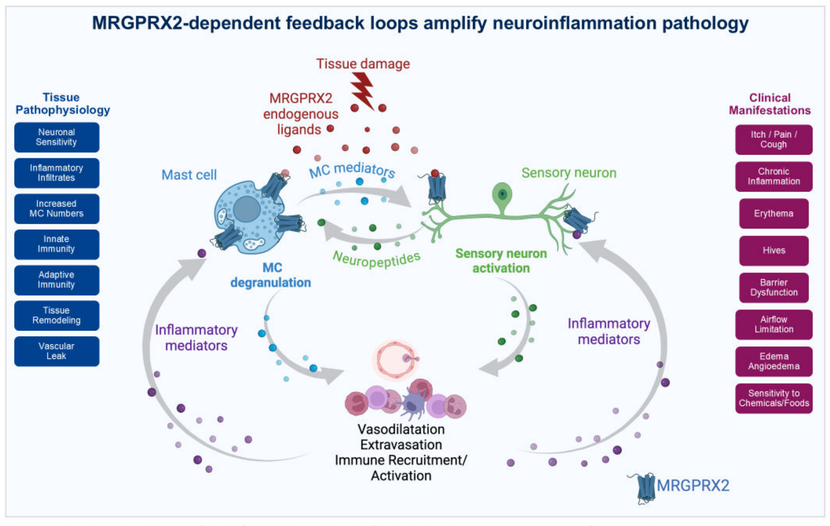

Figure 1. Pivotal Role of MRGPRX2 in Mast Cell Activation and Neuroinflammation

EVO756 prevents MRGPRX2-mediated mast cell degranulation *in vitro*

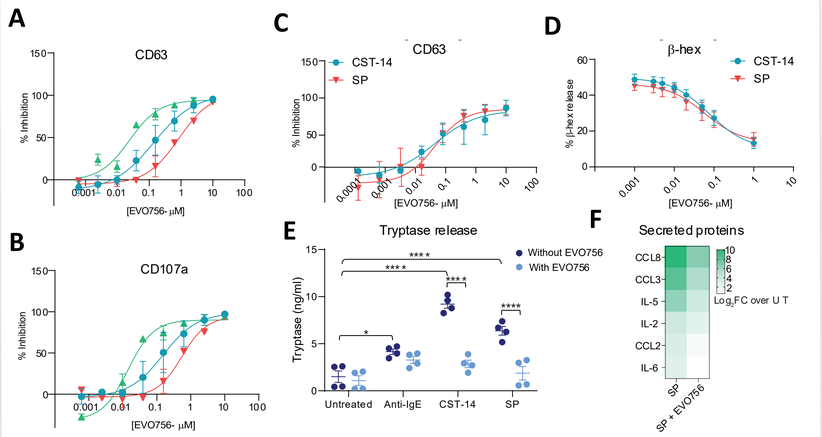

Figure 3. Inhibition of MRGPRX2-mediated mast cell degranulation by EVO756. EVO756 inhibition of MRGPRX2-mediated (A) CD63 and (B) CD107a surface expression by flow cytometry in LAD2 cells. EVO756 inhibition of MRGPRX2-mediated (C) CD63 surface expression by flow cytometry and (D) B-hexosaminidase release by hMCs. (E) Tryptase release by hMCs upon treatment with IgE overnight followed by treatment with anti-IgE, CST-14, and SP with and without EVO756 (1 uM). Tryptase was detected using an ELISA. (F) Cytokine and chemokine release (in the absence and presence of EVO756- 5 uM) was measured by MSD from LAD2 cells following stimulation with SP. Heatmap depicts the log2 fold change of cytokines and chemokines in SP-treated versus untreated cells.

EVO756 inhibits MRGPRX2 activation of human sensory neurons

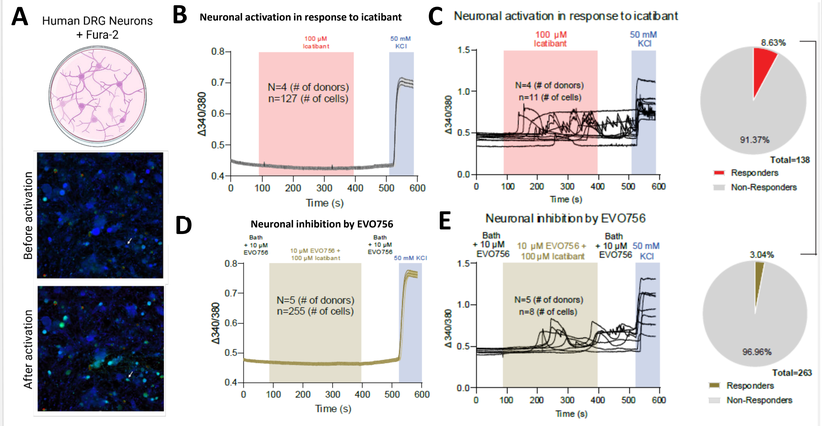

Figure 5. EVO756 inhibits functional MRGPRX2 activation of human sensory neurons. (A) Schematic of calcium imaging: cultured human DRG neurons were pre-loaded with Fura-2 prior to time-lapse fluorescent imaging. (B-E) Calcium imaging traces of human DRG neuron (B,D) non-responders and (C,E) responders after treatment with (B-C) icatibant alone (5 minutes, 100µM) (n=4 organ donors) and (D-E) inhibition in the presence of EVO756 (10µM) (n=5 organ donors) followed by treatment with KCl (50mM).

Skin challenge test: Phase 1 proof of concept and target engagement

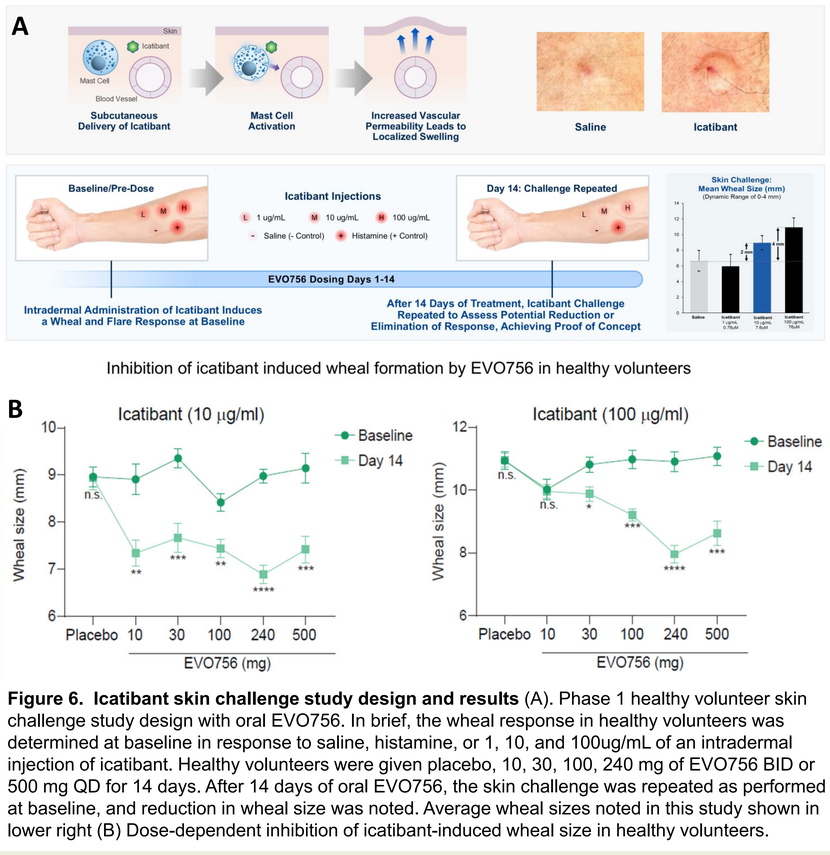

Figure 6. Icatibant skin challenge study design and results (A). Phase 1 healthy volunteer skin challenge study design with oral EVO756. In brief, the wheal response in healthy volunteers was determined at baseline in response to saline, histamine, or 1, 10, and 100ug/mL of an intradermal injection of icatibant. Healthy volunteers were given placebo, 10, 30, 100, 240 mg of EVO756 BID or 500 mg QD for 14 days. After 14 days of oral EVO756, the skin challenge was repeated as performed at baseline, and reduction in wheal size was noted. Average wheal sizes noted in this study shown in lower right (B) Dose-dependent inhibition of icatibant-induced wheal size in healthy volunteers.

Chronic Inducible Urticaria Phase 2a Results

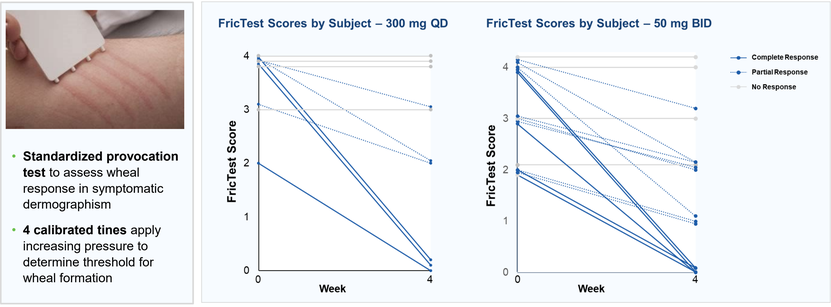

Figure 7. Phase 2a Results in Chronic Inducible Urticaria (NCT06603220). An open-label Phase 2a study in adults with chronic inducible urticaria (symptomatic dermographism) (n=30) received either 300 mg QD or 50 mg BID for 4 weeks. Fric scores were determined at baseline and at week 4. 28/30 subjects completed the study. The primary endpoint was safety as assessed by incidence of TEAEs. Efficacy measures included complete response, change from baseline in provocation test, change from baseline in pruritus NRS at provocation site. There were no serious adverse events, no treatment discontinuations due to adverse events and EVO756 was generally well-tolerated

EVO756 is a novel and potent small-molecule antagonist of MRPGRX2

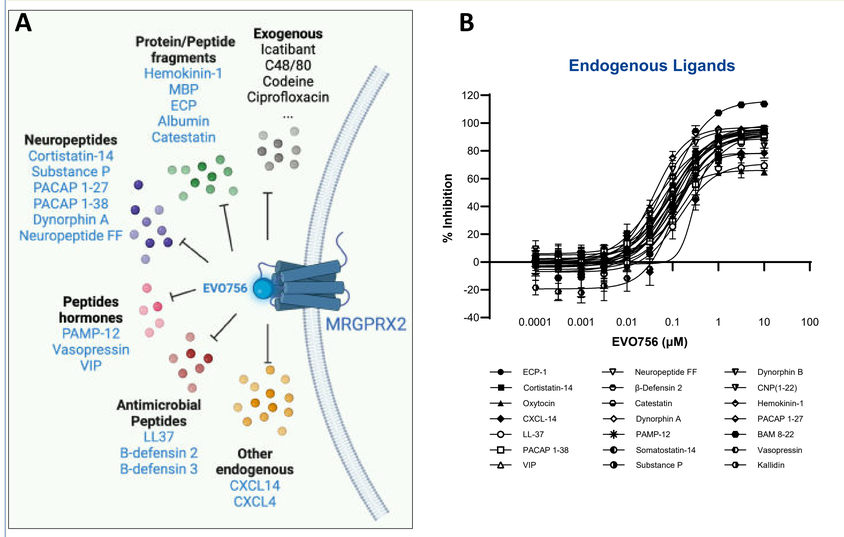

Figure 2. MRGPRX2 ligands and concentration-dependent inhibition of MRGPRX2 signaling by EVO756 in CHO-MRGPRX2 transfectants. (A) Ligands that activate MRGPRX2 (B) CHO cells expressing MRGPRX2 were loaded with the FLIPR calcium dye and incubated for 30 min with EVO756 at varying doses. Subsequently, various endogenous and exogenous (*not shown*) agonists were added by the FLIPR Penta instrument and calcium flux measured over time. Percent inhibition was calculated based on CHO-MRGPRX2 cells treated with only EVO756 or only agonist.

EVO756 inhibits synergistic effects of MRGPRX2 with IgE

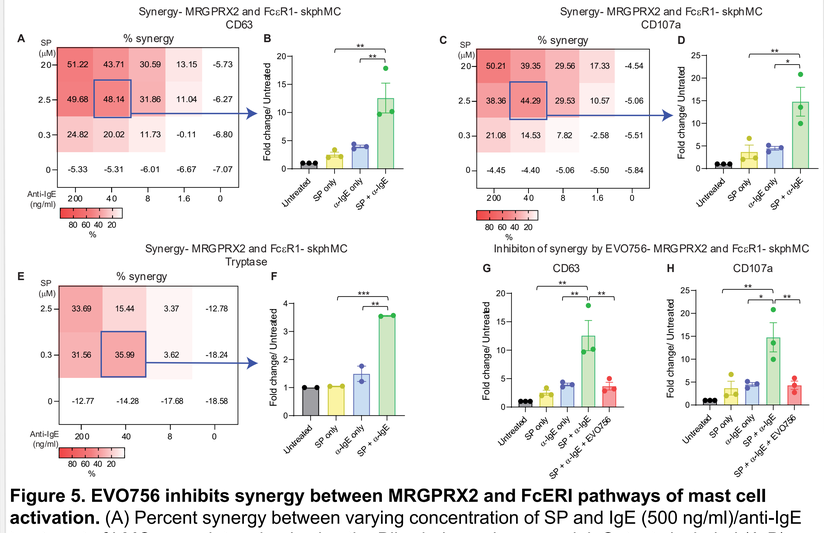

Figure 5. EVO756 inhibits synergy between MRGPRX2 and FcERI pathways of mast cell activation. (A) Percent synergy between varying concentration of SP and IgE (500 ng/ml)/anti-IgE treatment of hMCs was determined using the Bliss independence model. Outputs included (A-B) CD63 or (C-D) CD107a surface expression via flow cytometry, and (E-F) tryptase release (measured via ELISA) (G-H) SP/IgE synergy (as determined by CD63 and CD107a in hMCs) was inhibited by EVO756 (5 µM). n= 2-3 for all panels. Statistical significance was calculated using 1-Way ANOVA with Tukey's post-test. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001. Error bars = the standard error of the mean. .

Conclusions

- EVO756 is a novel, oral, small molecule inhibitor of MRGPRX2
- EVO756 inhibits MRGPRX2 activation in mast cells and peripheral sensory neurons involved in itch, pain and inflammation
- EVO756 inhibited icatibant-induced wheals in a dose-dependent manner
- EVO756 demonstrated positive results in a Phase 2a trial in Chronic Inducible Urticaria patients
- EVO756 is a potential therapeutic for the treatment of diseases caused by overactivation of mast cells and neuroinflammation mediated by MRGPRX2, such as chronic urticarias and atopic dermatitis

Acknowledgements and Disclosures

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