MRGPRX2 Small Molecule Antagonists Potently Inhibit Agonist-Induced Skin Mast Cell Degranulation

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Rationale: Mas-Related G-Protein Coupled Receptor X2 (MRGPRX2) is a promiscuous receptor on mast cells that mediates IgE-independent mast cell degranulation in response to a wide variety of structurally diverse compounds and has been implicated in the pathogenesis of multiple mast cell-mediated disorders, including chronic urticaria and atopic dermatitis. Our objective was to investigate whether small molecule MRGPRX2 antagonists could inhibit mast cell degranulation and wheal/flare response in skin both in vivo and ex vivo across multiple species, providing a novel therapeutic approach for mast cell-mediated diseases.

Methods: MRGPRX2 antagonist pharmacology was characterized in vitro using cell lines overexpressing human MRGPRX2 as well as mouse and canine orthologs, LAD2 mast cells, peripheral stem cell-derived mast cells, and primary human skin mast cells to evaluate potential to inhibit MRGPRX2 activity and mast cell degranulation. Inhibition of in vivo skin mast cell degranulation was evaluated using MRGPRX2 knock-in (KI) transgenic mice by assessment of agonist-induced skin vascular permeability, and in beagle dogs by assessment of skin wheal/flare reactions. The ability of antagonists to inhibit ex vivo skin mast cell degranulation was evaluated by microdialysis and assessment of histamine release in human skin samples.

Results: MRGPRX2 antagonists potently inhibited MRGPRX2 activation induced in vitro by a wide variety of agonists across species, and inhibited agonist-induced mast cell degranulation in all mast cell types tested including isolated human skin mast cells. Orally administered antagonists demonstrated excellent in vivo efficacy in both MRGPRX2 KI mice and dogs, inhibiting agonist-induced degranulation and wheal/flare response, respectively. In addition, MRGPRX2 antagonists potently inhibited agonist-induced degranulation in ex vivo human skin as evidenced by a dose-dependent reduction of histamine levels in skin microdialysis samples.

Conclusions: MRGPRX2 small molecule antagonists potently inhibit agonist-induced skin mast cell degranulation in vitro and in vivo in multiple species as well as in ex vivo human skin, supporting their potential therapeutic utility as a novel treatment for a broad range of mast cell-mediated diseases.

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