MRGPRX2 Antagonist EP262 Potently Inhibits Agonist-Induced Mast Cell Degranulation *In Vitro* and *In Vivo*

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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 activation and degranulation in response to a wide variety of structurally diverse compounds including neuropeptides and host defense peptides and has been implicated in inflammatory conditions involving mast cell activation. Our objective was to develop and characterize a small molecule antagonist that potently inhibits MRGPRX2-mediated mast cell degranulation as a novel therapeutic approach for mast cell-mediated diseases.

Methods: Antagonist pharmacology was characterized *in vitro* and *in vivo* in MRGPRX2-overexpressing cell lines, LAD2 mast cells, peripheral stem cell-derived mast cells (PSCMCs), primary human skin mast cells and human MRGPRX2 knock-in (KI) transgenic mice to evaluate degranulation inhibition potential and characterize PK/PD.

Results: EP262, the MRGPRX2 antagonist development candidate selected, potently inhibited MRGPRX2 activation induced by a wide variety of agonists and functions as a non-competitive inverse agonist. EP262 was also able to inhibit agonist-induced mast cell degranulation in LAD2 mast cells, PSCMCs and human skin mast cells with high potency. EP262 effectively blocked the release of tryptase and inflammatory cytokines in human mast cells and demonstrated excellent ADME/PK properties. Orally administered EP262 potently inhibited agonist-induced mast cell degranulation and vascular permeability in a dose-dependent manner in MRGPRX2 KI mice and demonstrated excellent *in vivo* potency.

Conclusions: EP262 is a potent MRGPRX2 inverse agonist which inhibits agonist-induced mast cell degranulation both *in vitro* and *in vivo,* supporting potential utility as a therapeutic treatment for a broad range of mast cell mediated diseases.

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