MRPGRX2 Antagonist EP262 Prevents Inflammation and Disease in a Mouse Model of Atopic Dermatitis

Presented at the American Academy of Dermatology (AAD) 2023 Annual Meeting, March 17-21, 2023 in New Orleans, Louisiana

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Rationale: Mast cells are shown to play a role in multiple inflammatory diseases including atopic dermatitis. 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 and has been implicated in mast cell-mediated conditions. Our objective was to investigate whether small molecule MRGPRX2 antagonist EP262 could improve disease phenotype in the house dust mite (HDM)/ *Staphylococcus aureus* enterotoxin type B (SEB) mouse model of atopic dermatitis.

Methods: EP262 pharmacology was characterized *in vitro* in MRGPRX2-overexpressing cells, LAD2 cells, peripheral stem cell-derived mast cells, and primary human skin mast cells to evaluate degranulation inhibition potential, and *in vivo* in MRGPRX2 knock-in (KI) transgenic mice to characterize its efficacy. Vehicle or EP262 were orally dosed once daily for 4 weeks in MRGPRX2 KI mice sensitized to HDM/SEB.

Results: EP262 potently inhibited MRGPRX2 activation induced *in vitro* by a wide variety of agonists, and inhibited agonist-induced mast cell degranulation and accompanying release of inflammatory cytokines. Orally administered EP262 demonstrated excellent *in vivo* efficacy and significantly inhibited HDM/SEB-induced atopic dermatitis with improvements in skin thickness, transepidermal water loss, tissue weight, overall disease score and decreased inflammation. EP262 efficacy was comparable to the effect of anti-IL4Rα antibody in this chronic disease model.

Conclusions: EP262 is a MRGPRX2 antagonist that inhibits HDM/SEB-induced atopic dermatitis disease phenotype and inflammation. EP262 is a potential novel oral treatment for atopic dermatitis and other mast cell-mediated diseases.

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