FLX193: A Potent, Selective CCR4 Antagonist for Allergic Disorders

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1 Abstract

Type 2 helper T cells (Th2) cells have been shown to express CCR4 receptor, and play a critical role in driving the pathogenesis of asthma and atopic dermatitis. FLX193 is a best-in-class, highly-potent and selective small molecule CCR4 antagonist under investigation for the treatment of allergic disorders. FLX193 blocked migration of CCR4+ Th2 cells (human and mouse) towards CCL17 and CCL22 in an in vitro chemotaxis assay. FLX193 is well-tolerated in animals at efficacious doses.

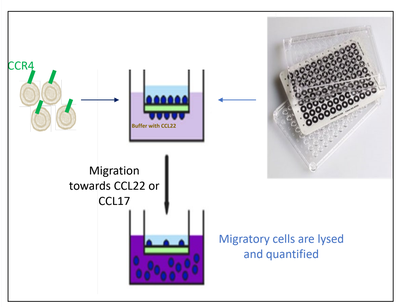
In an Ovalbumin (OVA)-induced asthma model, FLX193 significantly reduced lymphocyte and eosinophil counts in the Bronchoalveolar lavage (BAL) fluid and showed a reduction of the effector Th2-relevant cytokines IL-5 and IL-13. FLX193 treatment also reduced the levels of CCL17 and CCL22 in the BAL fluid, indicating an overall reduction of inflammation. In addition, we used an atopic dermatitis mouse model to demonstrate that treatment with FLX193 decreased CCR4+ T-cell mediated inflammation. Hence FLX193 shows promise in the treatment of atopic dermatitis and asthma.

2 Introduction

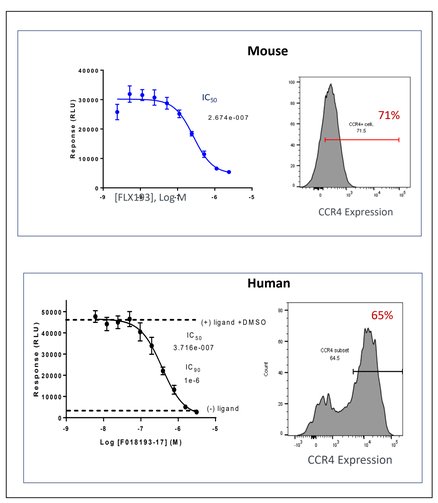
- Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease that causes dry skin, intense pruritus (itching), and a red, raised rash; the disease is categorized into mild, moderate, & severe
- AD affects ~19 Million (M) (~9M Diagnosed) people in the US and ~43.7M (~20.9M Diagnosed) in the major global markets. About 60% of patients have moderate to severe disease
- Pre-clinical and clinical data have shown a predominant role of Th2 cells allergic disorders
- Increased levels of CCL17 and CCL22 is detected in patients with atopic dermatitis in the skin as well as serum
- Human Th2 cells express CCR4 (70-80%) and migrate towards CCR4 ligands
- Hence, in this study we examine whether migration of Th2 cells into inflamed tissue and the increase disease severity is CCR4 dependent

3 Dose Dependent Inhibition of CCL22-Induced Migration

A) Chemotaxis Assay (CTX)



B) *In vitro* differentiated mouse and human Th2 cells

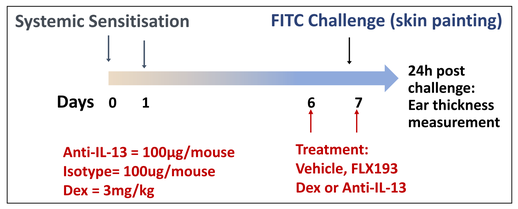


A) Chemotaxis assay for measurement of CCR4 antagonists potency in inhibition of CCL17 or CCL22 induced migration. The assay is carried out in 100% human serum; IC_{50} automatically takes protein binding into account

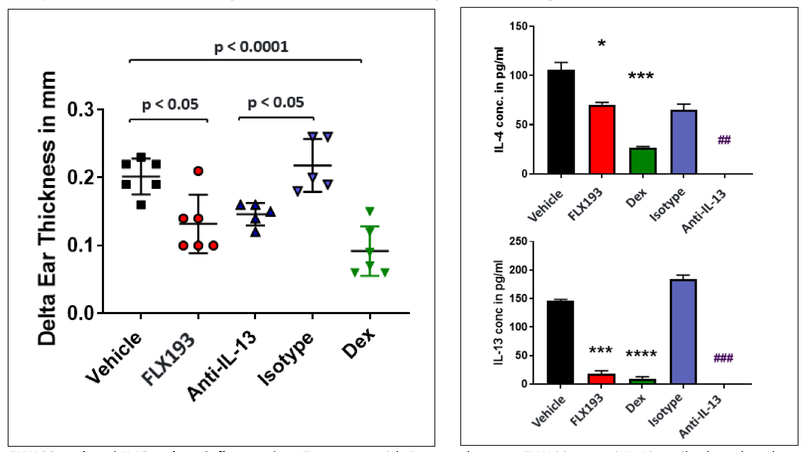
B) Inhibition of CCR4$^+$ Th2 migration in presence of FLX193 in mouse with an IC_{50} of 267nM and 372nM in human Th2 cells. The percent of CCR4+ mouse and human Th2 cells were similar (71% and 65% respectively), but human Th2 cells expressed overall higher levels of CCR4.

4 FLX193 Reduces Ear Thickness in FITC-Induced Skin Inflammation Model

A) FITC-induced skin inflammation model



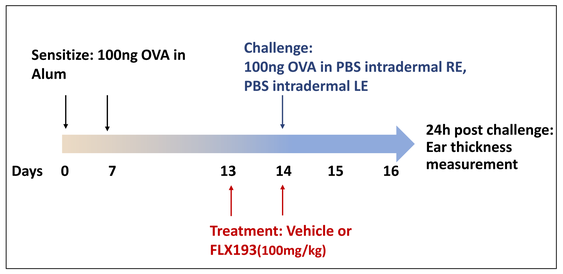
B) Ear thickness and cytokine data 24 hours post challenge



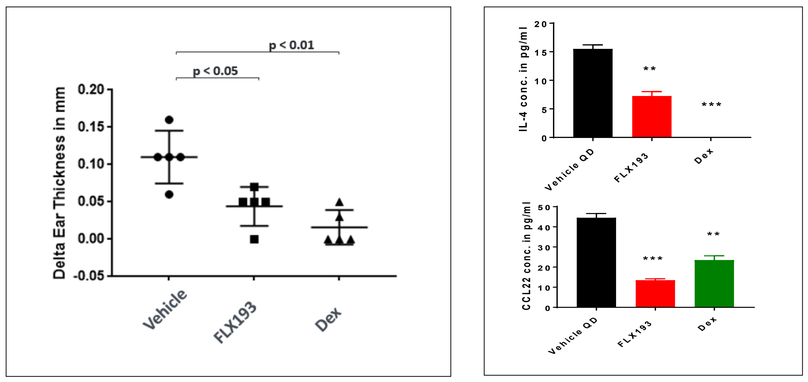
FLX193 and anti-IL13 reduce inflammation. Treatment with Dexamethasone, FLX193 or anti-IL-13 antibody reduced ear inflammation compared to the vehicle group. The efficacy of reduction of ear inflammation was comparable between FLX193 and anti-IL-13 antibody, which targets an inflammatory cytokine IL-4, IL-13 produced by Th2 cells. (* p<0.05 vs vehicle; *** p<0.001 vs vehicle; ## p<0.01 vs Isotype for IL-4 and (*** p<0.001 vs vehicle; **** p<0.0001 vs vehicle; ## p<0.001 vs Isotype; ### p<0.0001 vs Isotype)

5 FLX193 Reduces Ear Thickness in OVA-Induced Skin Inflammation Model

A) OVA-induced skin inflammation model



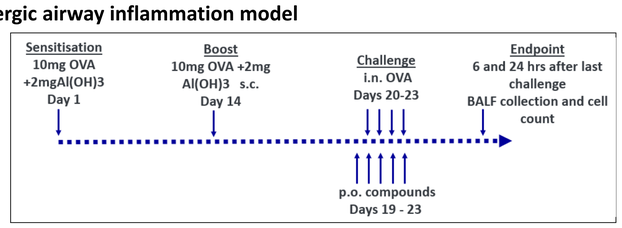
B) Ear thickness and cytokine data 24 hours post challenge



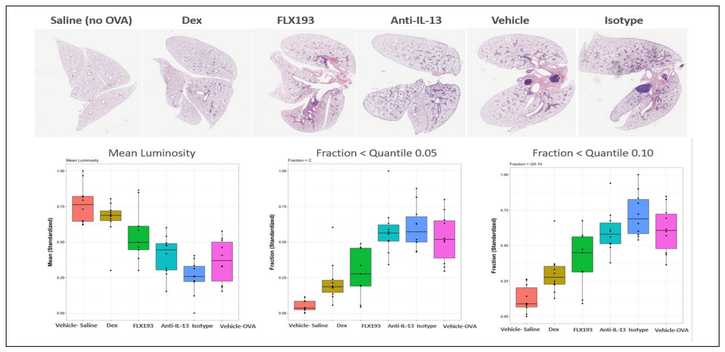
FLX193 reduced OVA-induced inflammation:. Treatment with Dexamethasone (Dex), FLX193 reduced ear inflammation compared to the vehicle group. The efficacy of reduction of ear inflammation was reflected in decrease in inflammatory cytokine IL-4 and chemokine CCL22 .(** p<0.001 vs. vehicle; *** p<0.0001 vs. vehicle)

6 FLX193 Is Efficacious in a Model of Allergic Asthma

A) Allergic airway inflammation model



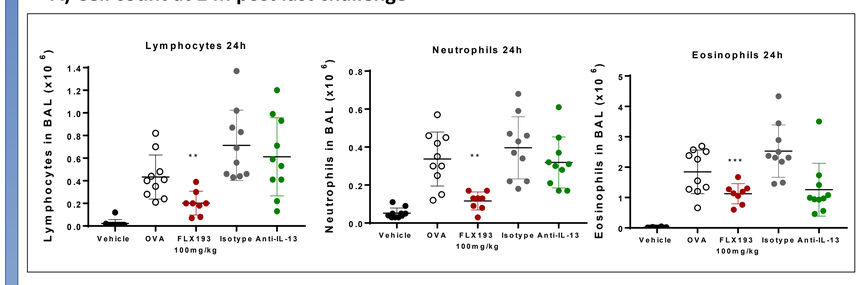
B) Asthma model lung H&E analysis



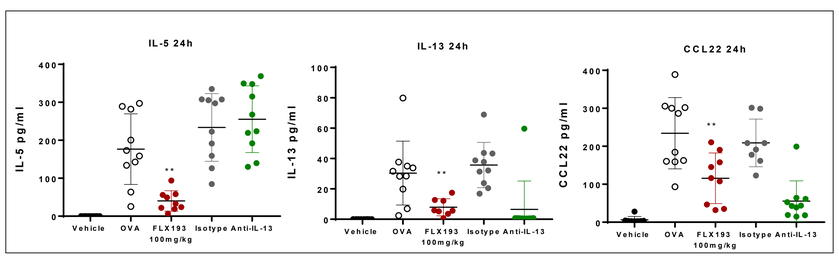
FLX193 reduces Lung immune inflammation in asthma model: Treatment with Dexamethasone, FLX193 or anti-IL-13 antibody reduced Lung immune infiltration compared to the vehicle group. The efficacy of the treatment was measured using H&E analysis- the decrease in immune infiltration is reflected by the decrease of Luminosity. The decrease was comparable between FLX193 and anti-IL-13 antibody

7 FLX193 Effectively Reduces the cell count and cytokine levels in the BALF

A) Cell count at 24h post last challenge



B) Cytokine and chemokine level at 24h post last challenge



FLX193 reduces cytokine and chemokine in asthma model:. Experimental design was similar to panel 6 BALF was obtained at 24 hours following the final challenge and analyzed for cell count (by flow cytometry or cytokine/chemokine levels by ELISA) FLX193 demonstrated a reduction in the BALF lymphocytes, Neutrophils and eosinophil number at 24hr timepoint. FLX193 showed a significant inhibition of IL-5, IL-13, MDC/CCL22 release at the 24 hour timepoints. (** p<0.001 vs. vehicle OVA)

8 Summary and Conclusion

- FLX193 is a highly potent CCR4 oral antagonist for allergic disorders
- FLX193 prevents migration of CCR4$^+$ Th2 cells towards CCL17 and CCL22 in vitro
- In preclinical mouse models of atopic dermatitis and asthma, FLX193 demonstrated anti- inflammatory efficacy comparable to an anti-IL-13 antibody
- Our studies suggest a potential role for FLX193 in treatment of patients with allergic disorders and other inflammatory diseases
- As an orally bioavailable small molecule inhibitor, FLX193 presents a potentially attractive alternative to treatment with injectable biologics or topical corticosteroids

References

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3. Blockade of CCR4 in a humanized model of asthma reveals a critical role for DC-derived CCL17 and CCL22 in attracting Th2 cells and inducing airway inflammation H Hammad et al. Allergy 2009 DOI: 10.1111/j.1398-9995.2009.02095.x