

CCR6 Inhibition as an Approach to Block Pathogenic Cell Trafficking in Inflammatory Diseases: Development of Novel, Potent, and Selective CCR6 Antagonists

SID Annual Meeting 2026
May 13-16th, Chicago, IL
Poster #1039

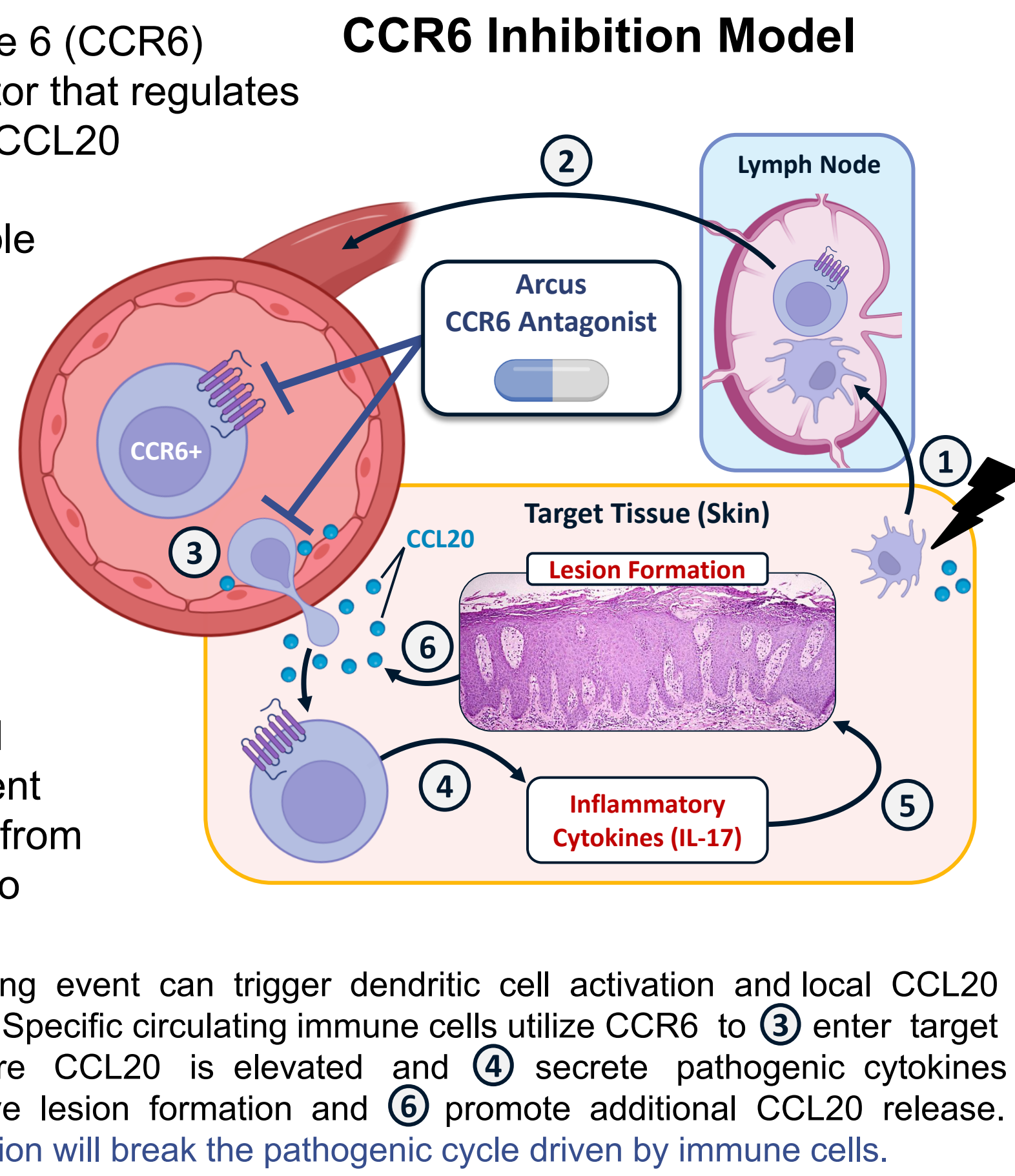
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Background

- ❖ C-C Chemokine receptor type 6 (CCR6) is a G protein-coupled receptor that regulates chemotaxis to a sole ligand, CCL20
- ❖ CCR6 is expressed by multiple immune cell types, including IL-17 producing T cells
- ❖ CCL20 is elevated in conditions where IL-17 producing cells accumulate and are pathogenic, such as psoriasis
- ❖ CCR6 inhibition offers a novel therapeutic approach to prevent disease-driving immune cells from reaching susceptible tissues to instigate and exacerbate inflammatory conditions



Results

CCR6 and CCL20 are Upregulated in Psoriatic Lesions and CCR6 Expressing Cells Make IL-17 and Other Inflammatory Cytokines

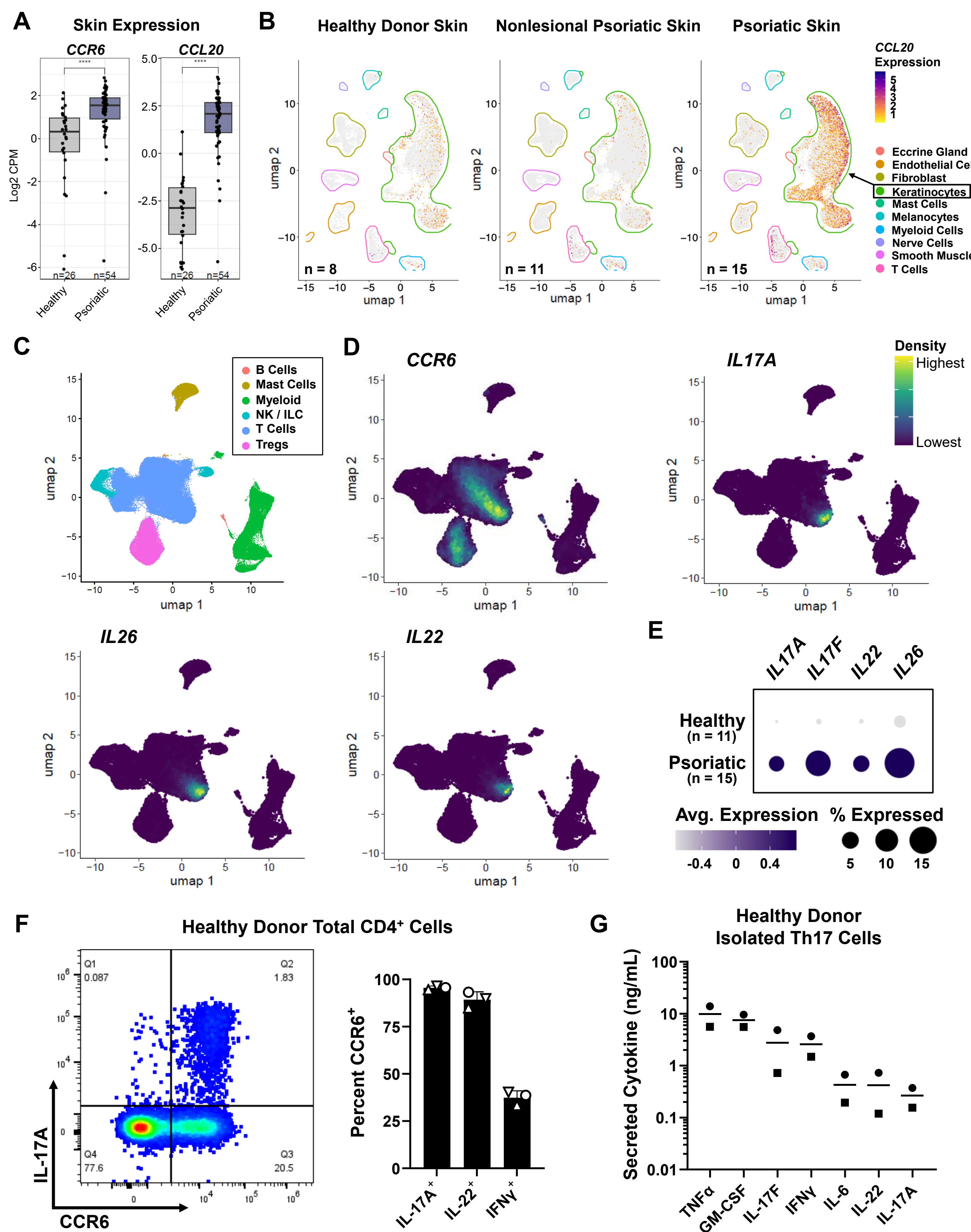


Figure 1. Bioinformatics analysis of RNA sequencing from psoriatic patient skin and evaluation of Th17 cell cytokine production. (A) CCR6 and CCL20 were significantly elevated in psoriatic skin based on bulk RNA-Seq (GSE212836). (B) Uniform Manifold Approximation and Projections (UMAPs) indicate CCL20 expression was elevated in keratinocytes within psoriatic lesions, based on single-cell RNA-Seq (GSE173706). (C) UMAP visualization of clustering by cell type of psoriatic skin samples sorted to enrich for immune cells and analyzed in (D-E) (dataset from Ref 1). (D) Density plots show areas of expression within psoriatic patient samples for given cytokines, revealing that CCR6 expression within the T cell subset overlaps with certain cytokines, including IL17A. (E) Comparison of cytokine gene expression in CCR6-expressing T cells (excluding Tregs) from healthy and psoriatic skin. (F) The percent of CCR6+ cells within cytokine expressing subsets of CD4+ cells was determined from ex vivo stimulated healthy donor samples. (G) Isolated and expanded healthy donor Th17 cells were stimulated with anti-CD3/CD28 and secreted cytokines were assessed after 72 hours in culture. For F-G each symbol represents a unique donor.

Results

CCR6 Inhibition Blocks Th17 Cell Chemotaxis Towards CCL20 *In Vitro*

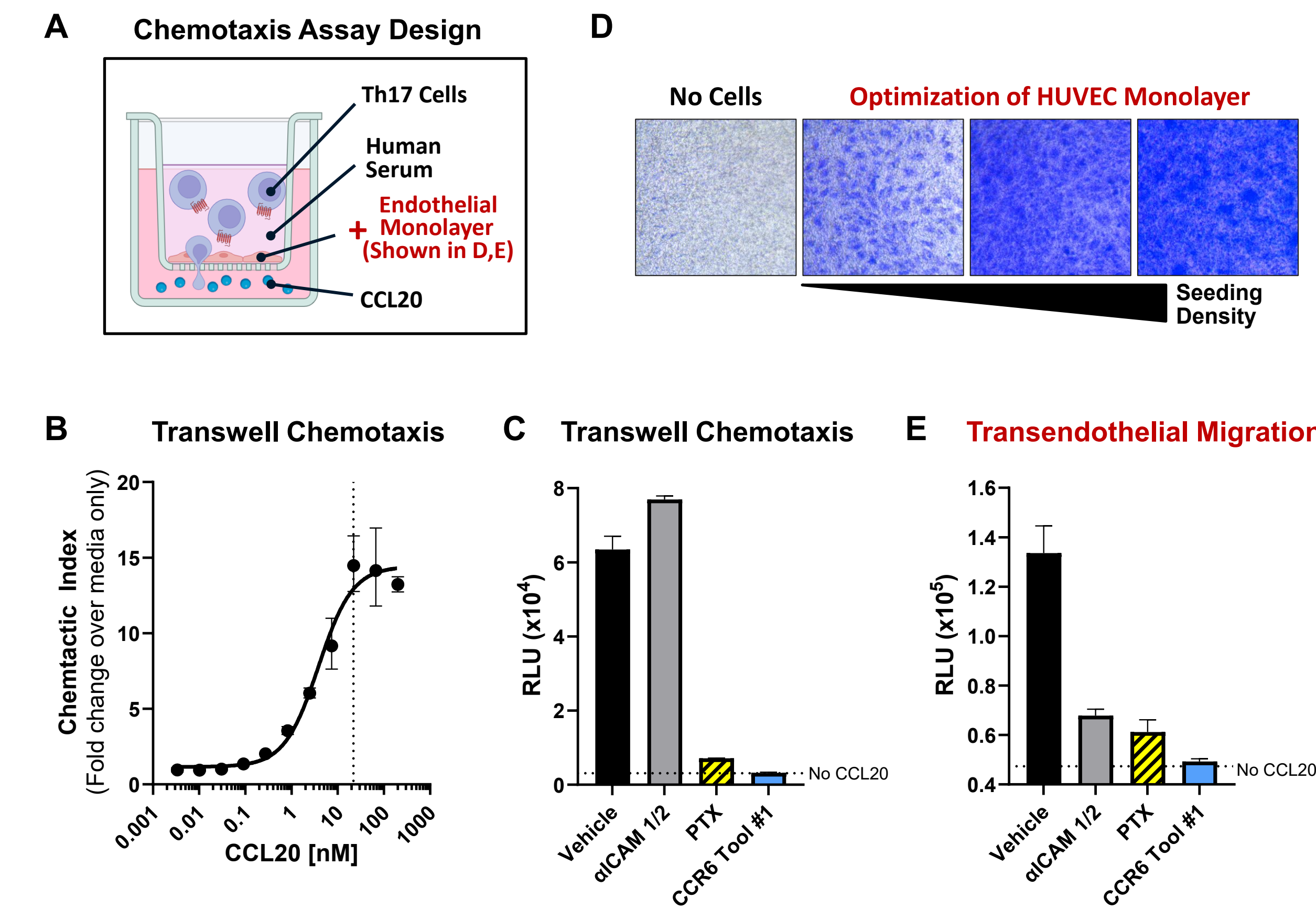


Figure 2. Evaluation of the impact of CCR6 inhibition on Th17 cell *in vitro* chemotaxis. (A) *In vitro* chemotaxis assay schematic. (B) Human Th17 cell chemotaxis to CCL20 in human serum. Dotted line at 22 nM of CCL20. (C) Th17 cells were suspended in human serum and treated with either vehicle (0.1% DMSO), anti-ICAM1/2, pertussis toxin (PTX), or 1 μM of a tool CCR6 inhibitor (CCR6 Tool #1) in an upper Transwell® chamber. Cell migration through 3 μm pores to a lower chamber, containing CCL20 (22 nM), was assessed by CellTiter-Glo® after 5-hours. (D-E) To evaluate transendothelial migration, a monolayer of human umbilical vein endothelial cells (HUVEC) was plated on the upper Transwell® chamber and chemotaxis was assessed as in (C).

CCR6 Inhibition is Effective in Preclinical Models of Skin Inflammation and Blocks IL-17+ Immune Cell Trafficking

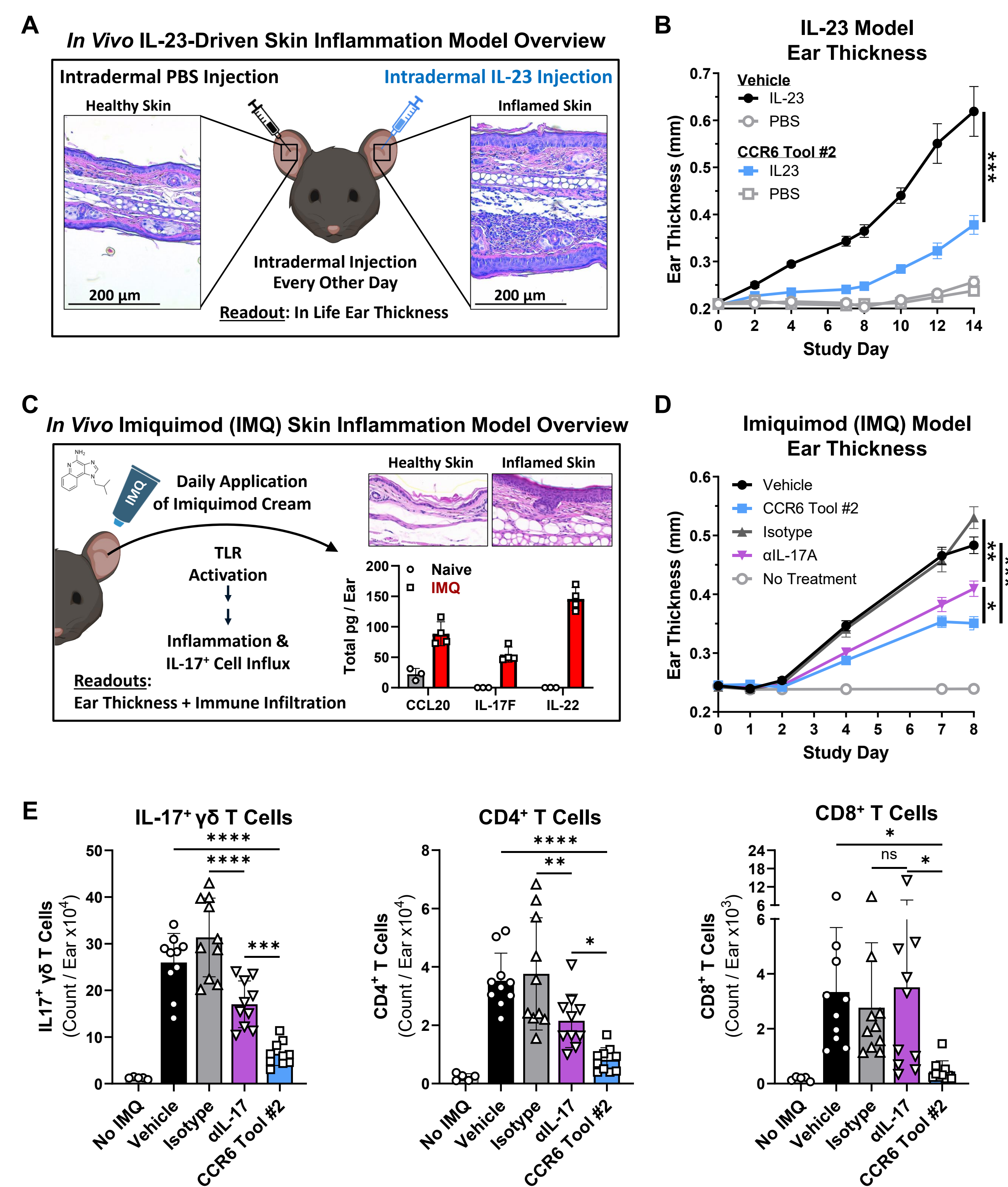


Figure 3. Evaluation of CCR6 inhibition in IL-23 and imiquimod (IMQ) induced skin inflammation mouse models. (A) Overview of the IL-23 injection ear inflammation model. (B) CCR6 inhibition *in vivo* using a tool compound (CCR6 Tool #2) significantly blocked IL-23-dependent ear thickening. (C) Overview of the imiquimod ear inflammation model, and (D) ear thickness measurements over time showing that inhibition of CCR6 or blockade of IL-17A significantly prevented thickening. (E) Flow cytometry-based analysis of immune cell infiltrates within ears from the imiquimod study endpoint. CCR6 inhibition significantly blocked the influx of IL-17+ producing γδ cells as well as the infiltration of CD4+ and CD8+ T cells. For all models, CCR6 tool antagonist or antibody dosing was started on day 0.

Results

Arcus Biosciences has Created Novel, Potent, and Selective Small Molecule CCR6 Antagonists

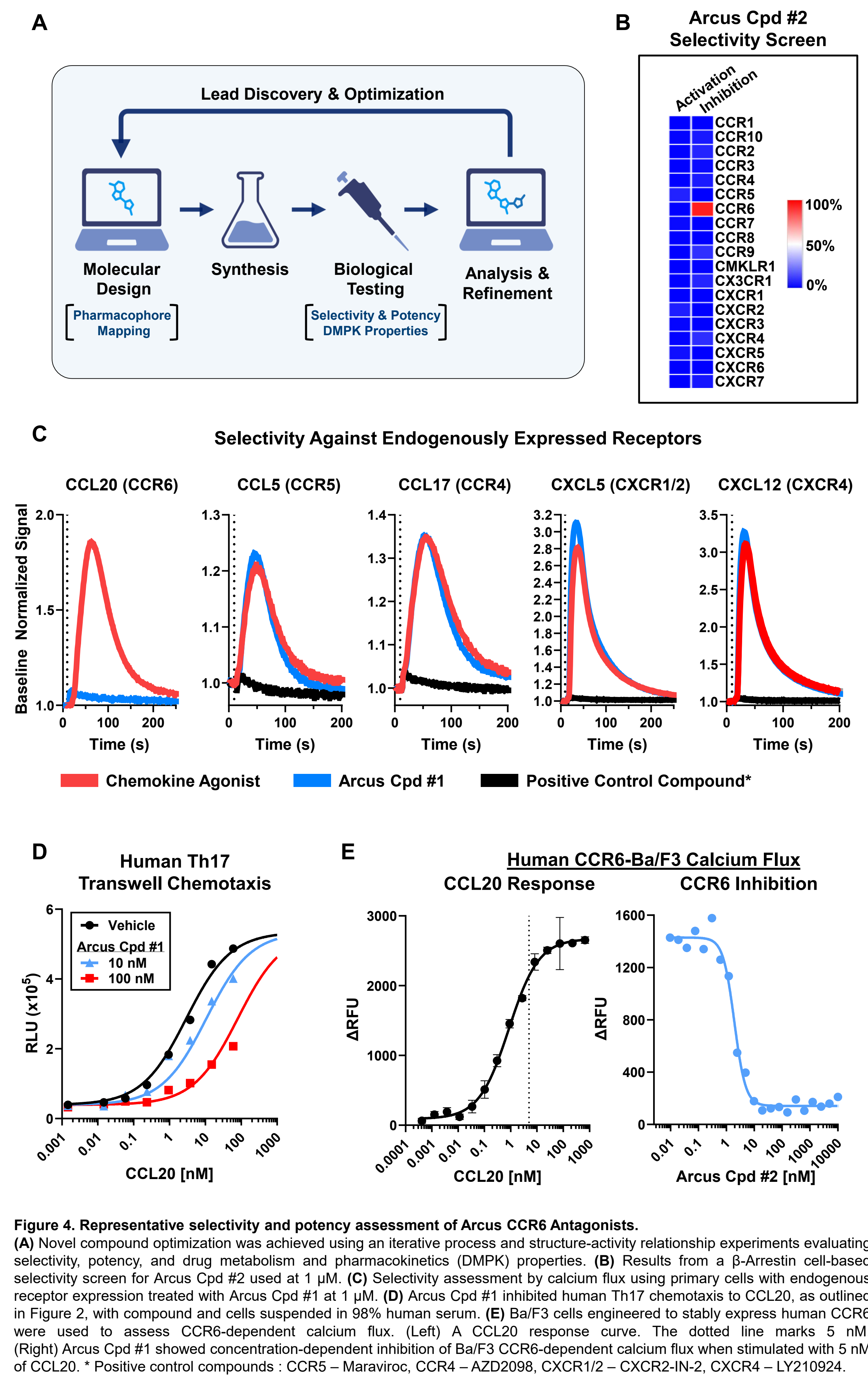


Figure 4. Representative selectivity and potency assessment of Arcus CCR6 Antagonists. (A) Novel compound optimization was achieved using an iterative process and structure-activity relationship experiments evaluating selectivity, potency, and drug metabolism and pharmacokinetics (DMPK) properties. (B) Results from a β-Arrestin cell-based selectivity screen for Arcus Cpd #2 used at 1 μM. (C) Selectivity assessment by calcium flux using primary cells with endogenous receptor expression treated with Arcus Cpd #1 at 1 μM. (D) Arcus Cpd #1 inhibited human Th17 chemotaxis to CCL20, as outlined in Figure 2, with compound and cells suspended in 98% human serum. (E) Ba/F3 cells engineered to stably express human CCR6 were used to assess CCR6-dependent calcium flux. (Left) A CCL20 response curve. The dotted line marks 5 nM. (Right) Arcus Cpd #1 showed concentration-dependent inhibition of Ba/F3 CCR6-dependent calcium flux when stimulated with 5 nM of CCL20. * Positive control compounds: CCR5 – Maraviroc, CCR4 – AZD2098, CXCR1/2 – CXCR2-IN-2, CXCR4 – LY210924.

Summary

- ❖ CCL20 and CCR6 are elevated in psoriatic lesional skin
- ❖ CCR6+ cells produce IL-17 and additional cytokines that can drive pathogenesis of inflammatory diseases
- ❖ *In vitro* and *in vivo* models demonstrate that CCR6 inhibition is effective at blocking CCL20-dependent cell chemotaxis and immune cell homing to inflamed tissue
- ❖ CCR6 inhibition was effective in both the IL-23-injection and IL-17-dependent imiquimod skin inflammation models
- ❖ Arcus Biosciences' advanced drug discovery program has identified novel, potent, and selective CCR6 antagonists

All work funded by Arcus Biosciences, Inc.
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