

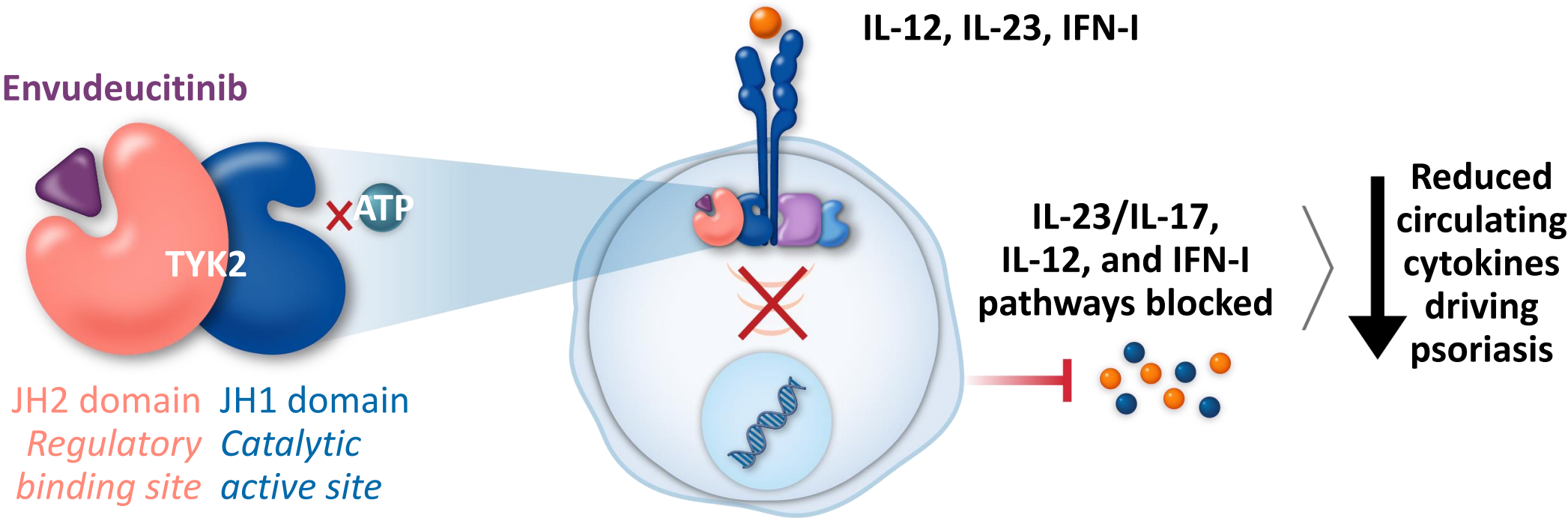
Nicole R. Narayan¹, Joshua D. Hoffman¹, Alex Tseng¹, Claire L. Langrish¹, Pedro R. Corpuz Jr¹, Mera K. Tilley¹
¹ Alumis Inc., South San Francisco, CA

mtilley@alumis.com

Background

Envudeucitinib (ESK-001) is an investigational*, next-generation, oral, highly selective allosteric inhibitor of tyrosine kinase 2 (TYK2) that provides maximal target inhibition over a 24-hour period in patients with psoriasis^{1,2}.

- TYK2 mediates signaling from key proinflammatory cytokines, including IL-12, IL-23, and IFN- γ .
- The STRIDE Phase 2 and its open-label extension results demonstrated the **favorable benefit/risk profile** of **envudeucitinib**, with **meaningful clinical efficacy** throughout 52 weeks, and **good tolerability**^{2,3}.
- Extensive biomarker profiling was performed to characterize impact of envudeucitinib on inflammatory cell states in the skin.



*Envudeucitinib is an investigational therapy not reviewed or approved by any regulatory agency.
ATP, adenosine triphosphate; IL-12/17/23, interleukin 12/17/23; IFN- γ , interferon type I; JH1/2, Janus kinase homology 1/2; TYK2, tyrosine kinase 2.

Objectives

Determine whether envudeucitinib selectively modulates pathologic keratinocyte differentiation states in human psoriasis skin using bulk and spatial transcriptomics of skin punch biopsies.

Methods

Study Design

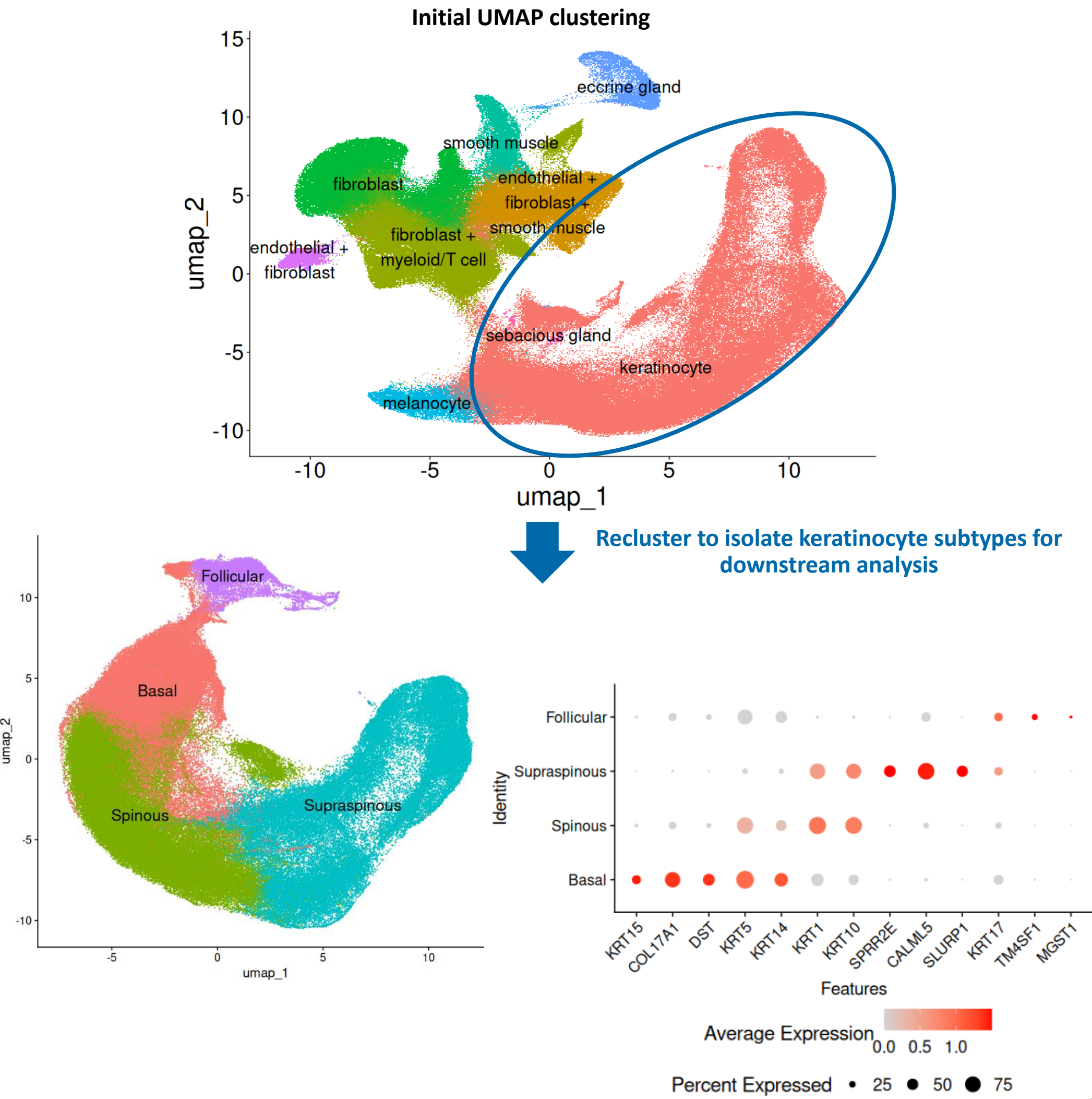
- STRIDE study** = a 12-week randomized, double-blinded, placebo-controlled Phase 2 study of envudeucitinib in adults with moderate-to-severe plaque psoriasis(NCT05600036).
 - A total of 228 subjects were 1:1:1:1:1 randomized to receive 1 of the 5 doses of envudeucitinib or placebo, given orally for 12 weeks.
 - Optional lesional and non-lesional 4 mm skin punches from subjects at baseline and Week 12.
 - Lesional = actively inflamed psoriatic plaque, not typically ultraviolet (UV) exposed.
 - Non-lesional = non-inflamed skin, taken 5 cm away from the margin of lesional skin.
 - Punch biopsy was cut in half, with one half submerged in preservative for **bulk transcriptomics** and the other embedded in paraffin for **spatial transcriptomics**.

Bulk transcriptomic analysis

- Placebo (n=7) and envudeucitinib 40 mg twice daily (BID) (n=5)
- Bulk RNA-sequencing (RNAseq)**: reads were aligned to the genome and transcriptome using STAR. Transcripts were quantified with Salmon.

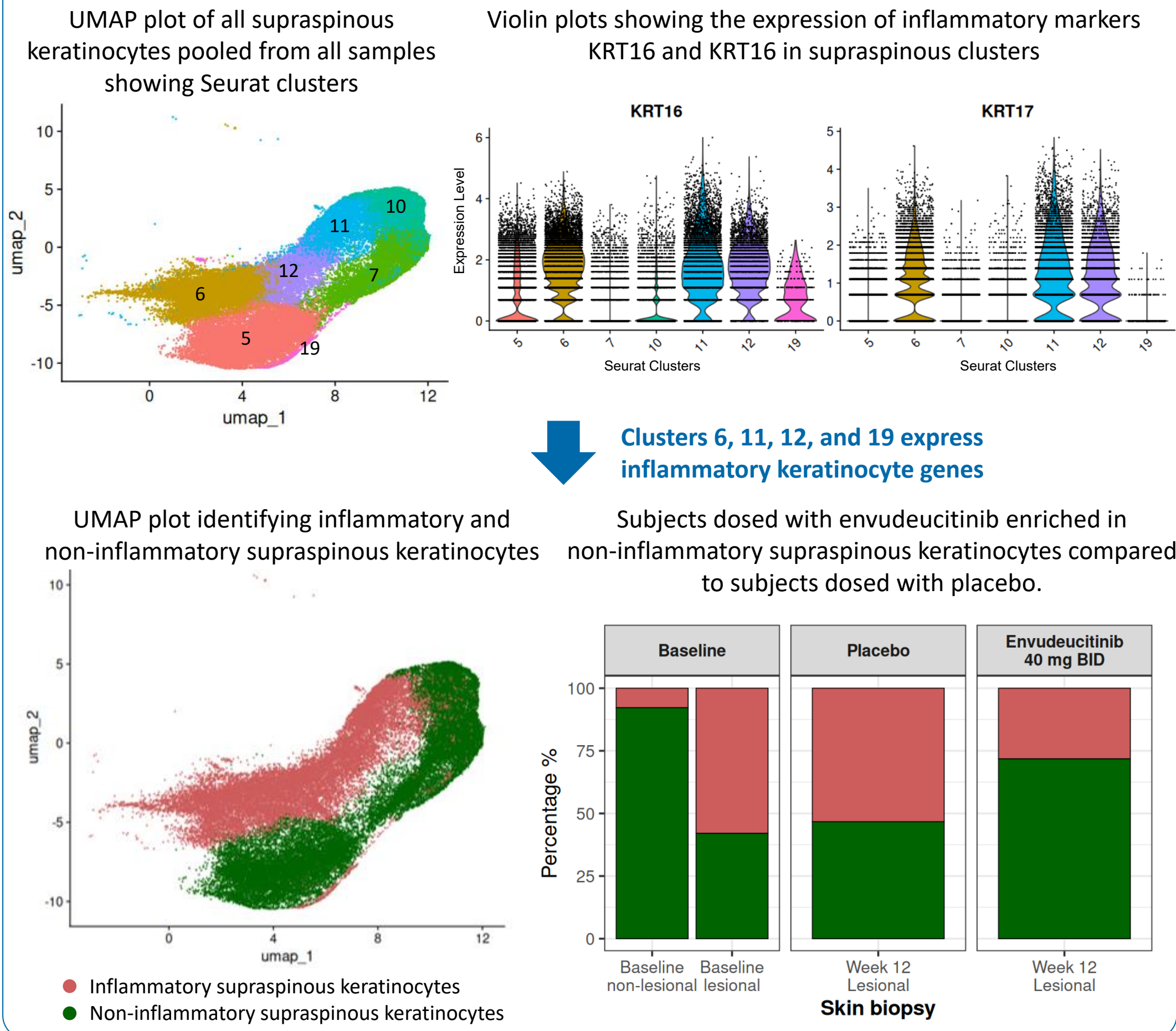
Spatial transcriptomic analysis

- Placebo (n=4) and envudeucitinib 40 mg BID (n=5)
- Spatial transcriptomics was performed on formalin-fixed paraffin-embedded tissues using the **10X Genomics Visium HD** platform. Sequencing-reads were processed with Space Ranger 4.0 with nuclei segmentation. Analysis was performed with **Seurat** package in R. After quality control and filtering, samples were normalized and harmony-based sample integration was performed.
- Using all samples, spatial clusters were identified and visualized with **UMAP** (Uniform Manifold Approximation and Projection). Clusters were manually annotated based on expression of marker genes for skin cell types established in Ma et al⁴.
 - FindAllMarkers() in Seurat was used to identify differentially expressed genes between inflammatory and non-inflammatory supraspinous keratinocytes.



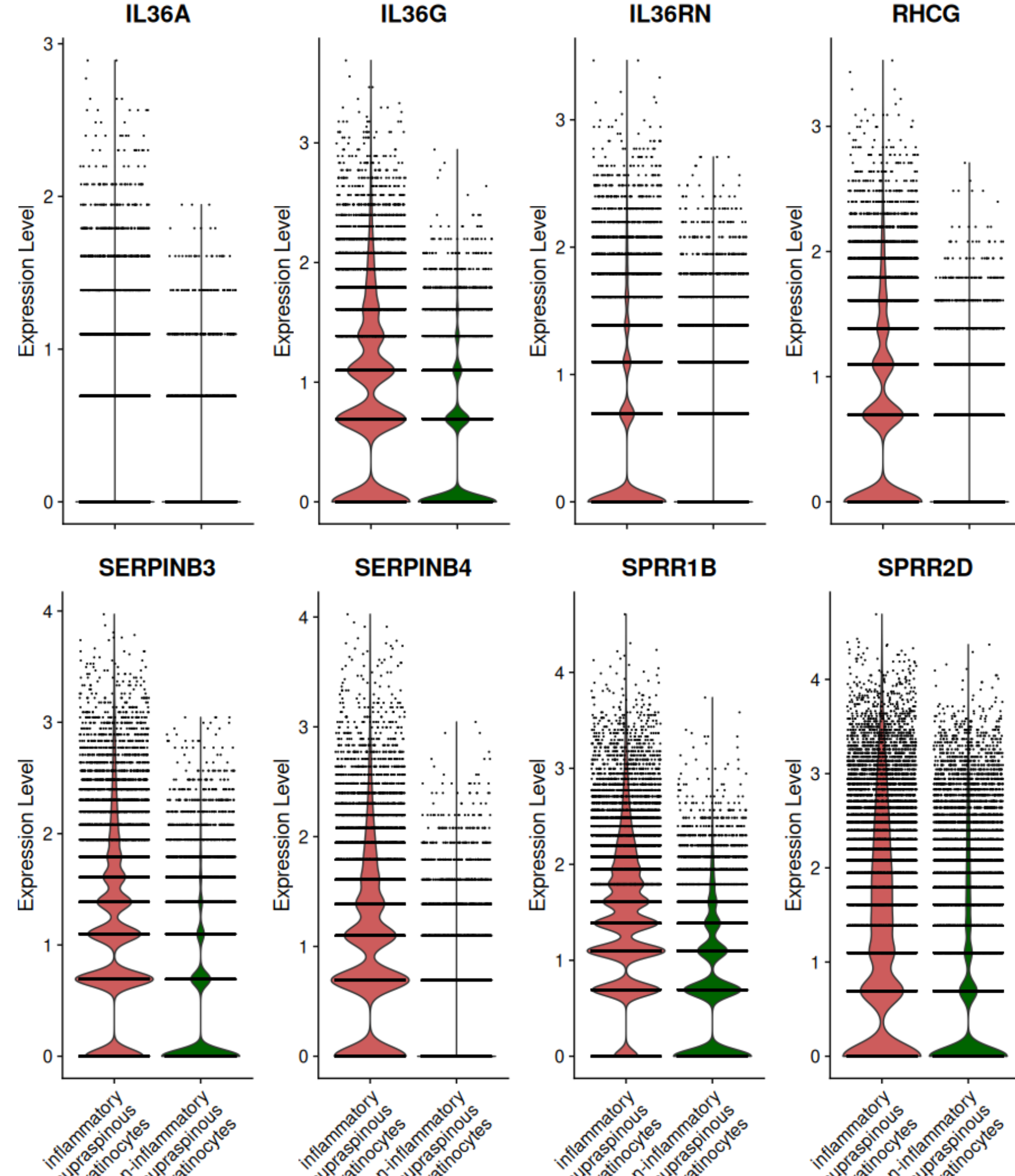
Spatial transcriptomics identifies inflammatory populations of supraspinous keratinocytes in the skin

- Spatial transcriptomic data from all samples used to characterize supraspinous keratinocytes.
 - Supraspinous keratinocytes are located in the upper spinous layer of the epidermis and amplify inflammation in inflammatory skin conditions such as psoriasis.

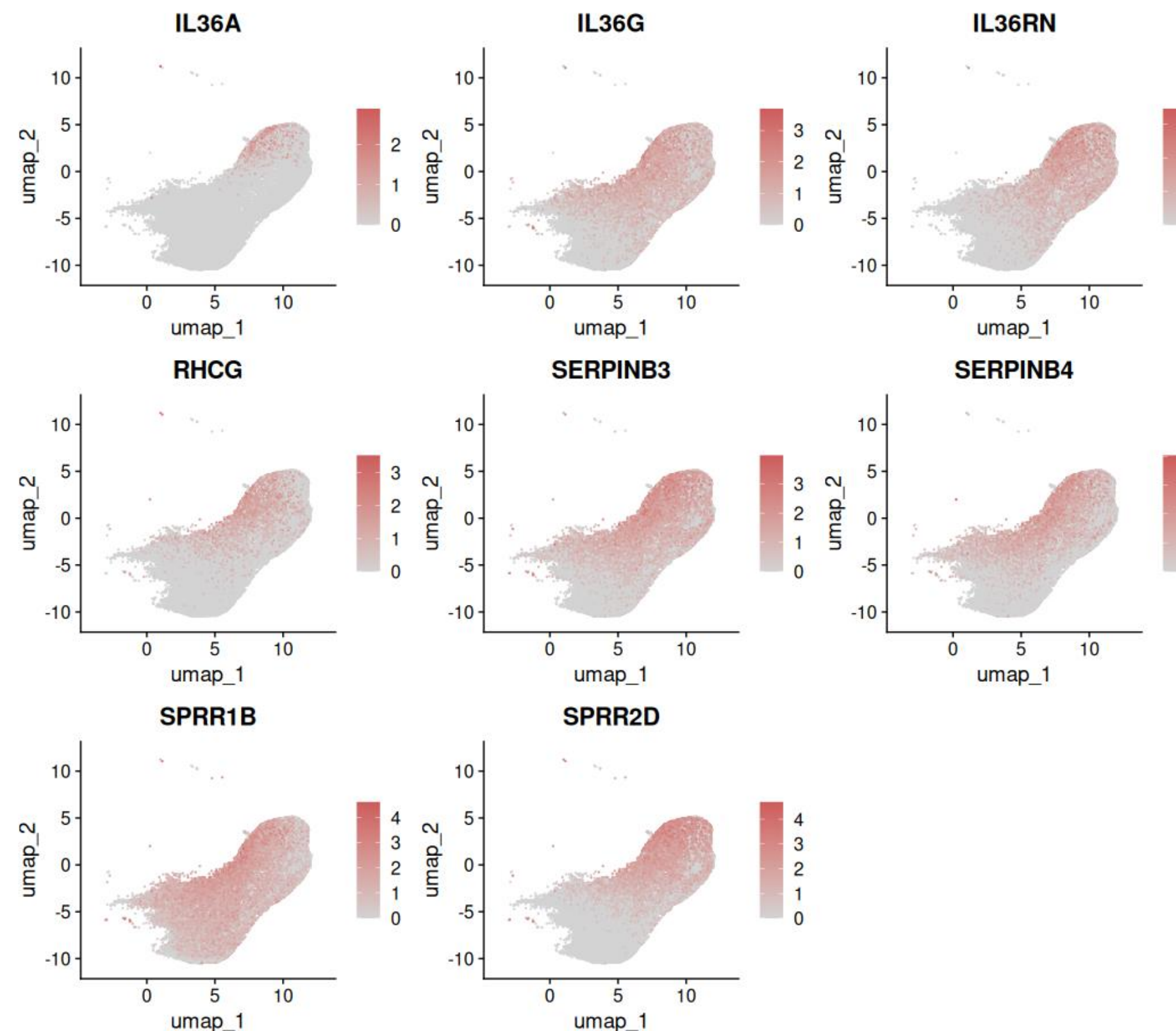


Inflammatory supraspinous keratinocytes show enriched expression of key psoriasis-related keratinocyte genes

- Gene-level characterization of inflammatory and non-inflammatory supraspinous keratinocytes in all samples.
- Inflammatory supraspinous keratinocytes characterized by high expression of psoriasis-related genes.



- UMAP of all supraspinous keratinocytes showing expression of psoriasis-related biomarkers in inflammatory supraspinous keratinocytes.

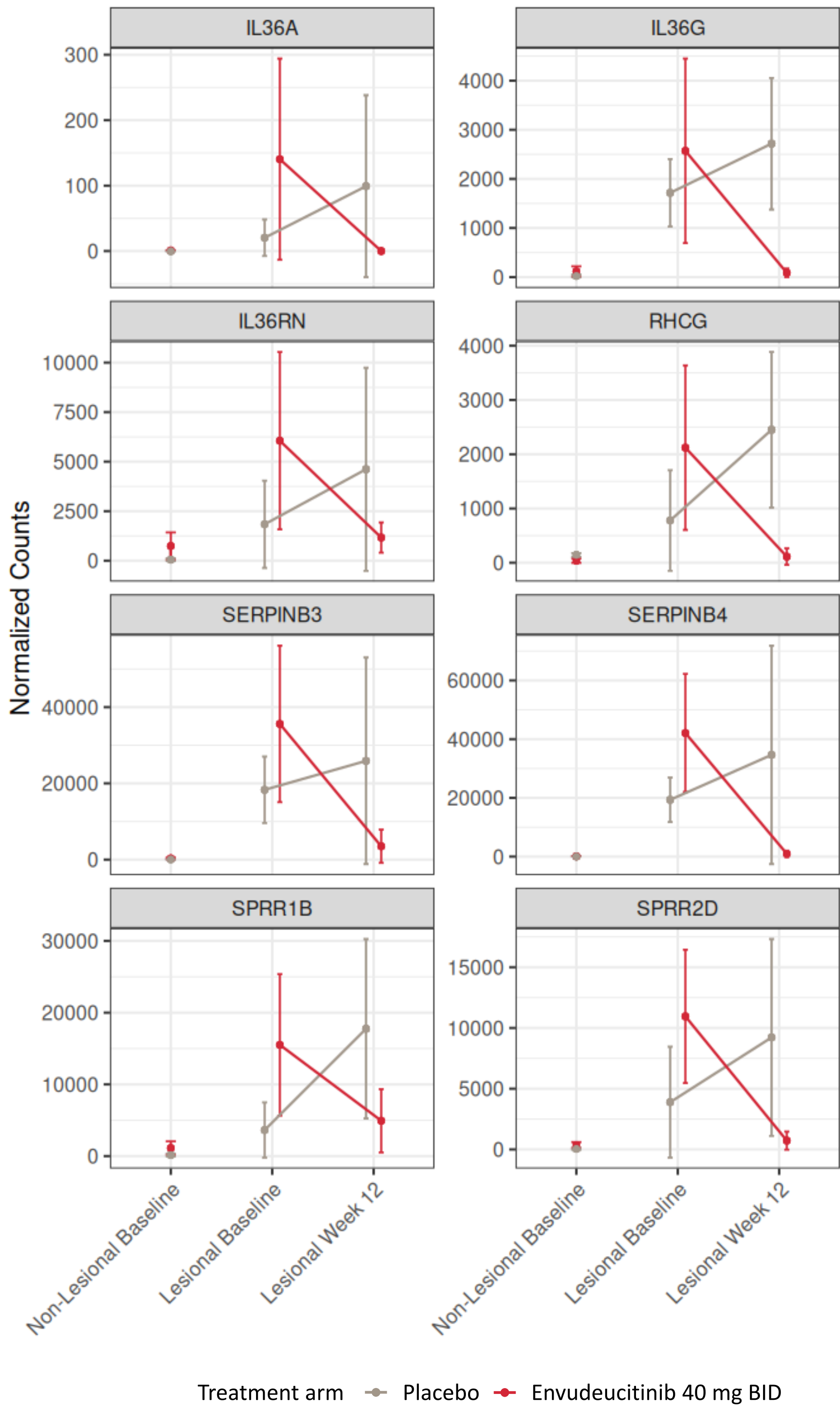


Conclusions

- Envudeucitinib suppressed a pathologic inflammatory supraspinous keratinocyte state associated with aberrant differentiation in psoriasis skin.
- These spatially resolved findings provide mechanistic insight into how allosteric TYK2 inhibition normalizes epidermal pathology and highlight keratinocyte cell-state modulation as a key component of therapeutic response in psoriasis.

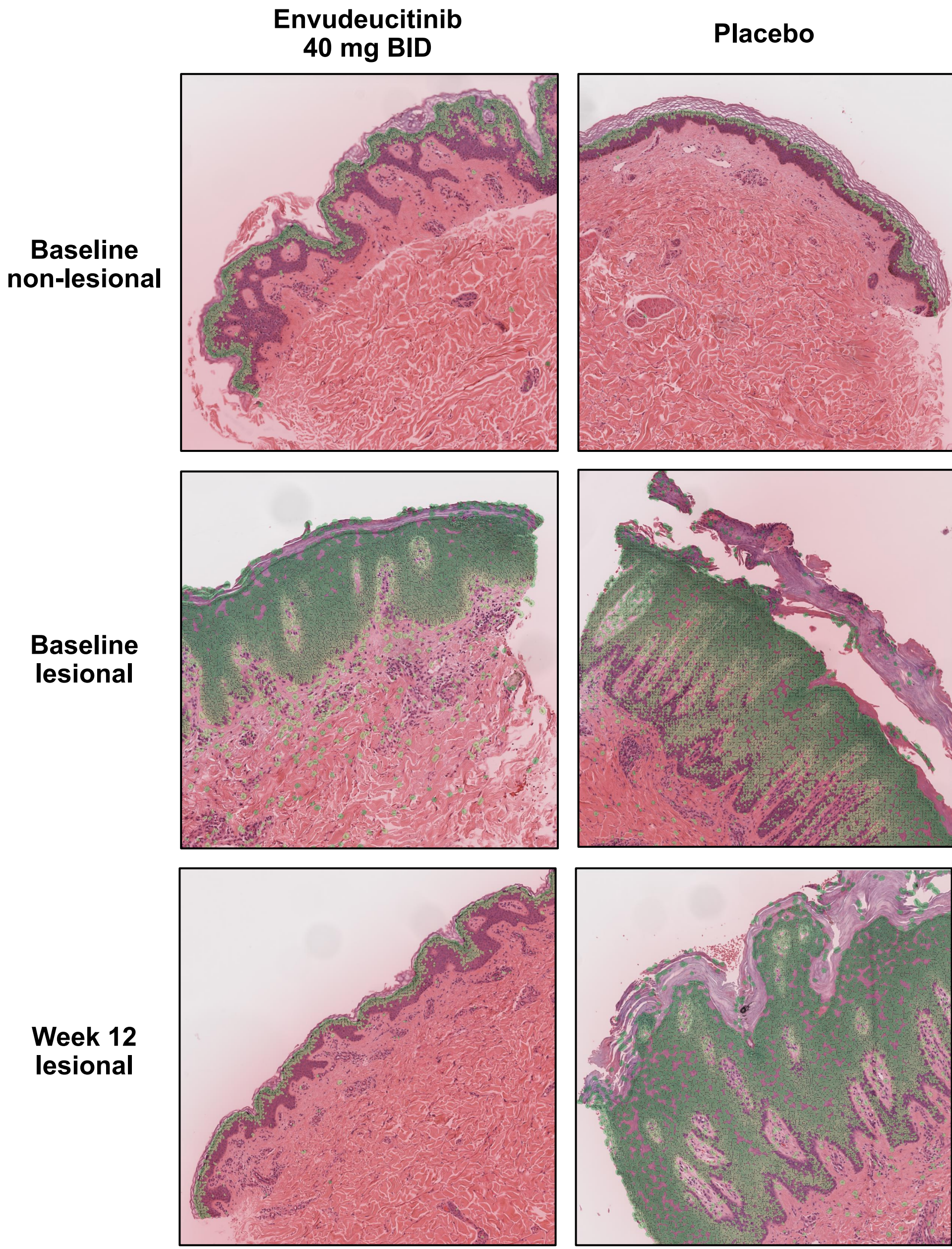
Results

Concordant suppression of keratinocyte inflammatory gene markers in bulk transcriptomics of punch biopsy after envudeucitinib treatment



All available samples with high-quality RNAseq data were included in the analysis. Median $\pm$ MAD is displayed. BID, twice daily; MAD, median absolute deviation.

Markers of inflammatory supraspinous keratinocytes returned to non-lesional profile with envudeucitinib treatment



Aggregated expression of inflammatory lesional supraspinous keratinocyte genes (green) visualized using Loupe Browser. Inflammatory lesional supraspinous keratinocyte genes: IL36A, IL36G, IL36RN, RHCG, SERPINB3, SERPINB4, SPRR1B, SPRR2D. Representative samples from one subject receiving envudeucitinib 40 mg BID and one receiving placebo are shown above.

Disclosures

This study was funded by Alumis Inc. All authors are employees and shareholders of Alumis Inc. The authors have no other relationships or conflicts of interest to disclose.

References

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