Normalisation of molecular signatures associated with pruritus in plaque psoriasis correlates with itch resolution following bimekizumab treatment

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Objective

To demonstrate the dysregulation of itch-related genes in psoriatic plaques using transcriptomics data.

To elucidate the molecular mechanisms behind resolution of itch in patients with psoriasis upon bimekizumab (BKZ) treatment.

Introduction

- Substantial pruritus (itching) in moderate to severe plaque psoriasis can greatly impact patients' quality of life, with 84% of patients stating that itch reduction is a treatment goal.[1]
- Higher proportions of patients achieved resolution of itch with BKZ at Week 16 versus active comparators and placebo in phase 3 trials.[2]
  - Resolution of itch was defined as a score of 0 on a numeric rating scale from 0 (no symptom/impact) to 10 (very severe symptom/impact) in the itching item of the Psoriasis Symptoms and Impacts Measure.[3]

Methods

- An itch signature was defined based on a previous transcriptomic study, which identified psoriatic pruritus-associated genes by comparing lesional itchy skin with non-lesional, non-itchy skin.[4]
- Single-cell RNA sequencing (RNA-seq) data from lesional and non-lesional biopsies allowed assessment of cell type-specific itch mediator expression.[5]
- Dysregulation of the itch signature in psoriasis and its normalisation by BKZ was then determined by bulk RNA-seq data from a phase 2a trial.[6]
  - Patients received BKZ 320 mg at baseline and Week 4. Lesional and non-lesional skin biopsies were collected at baseline and Week 8
  - Gene Set Variation Analysis (GSVA) and *limma* statistical methods were used to assess gene- and pathway-level expression changes following BKZ treatment.[7,8]

Results

Expression of itch signature and itch mediators

- Single-cell RNA-seq data indicated that the itch signature was predominantly expressed in mast cells and keratinocytes (**Figure 1**), which is consistent with the known roles of these cell types in promoting itch.[9,10]
- Expression of the itch mediators kallikrein 8 (KLK8) and transient receptor potential (TRP) channels (TRPV3) was highly specific to keratinocytes (**Figure 2A**).
- RNAscope imaging showed increased expression of these mediators in areas associated with hyperkeratosis and increased interleukin (IL)17A+ and F+ cell infiltration in lesional tissue (**Figure 2B**).

Normalisation of itch signature following BKZ treatment

- Bulk RNA-seq following two BKZ doses (BKZ Week 8) indicated that individual mediators contributing to the overall itch signature, including KLK6/8/14, TRPV3, and histamine receptors (HRH2/3), were all normalised post-treatment (percentage improvement >75%) (**Figure 3A**).
- Bulk RNA-seq indicated that the overall itch signature was normalised to non-lesional levels post-BKZ treatment (**Figure 3B**), with a median percentage improvement of 98.5% at Week 8.

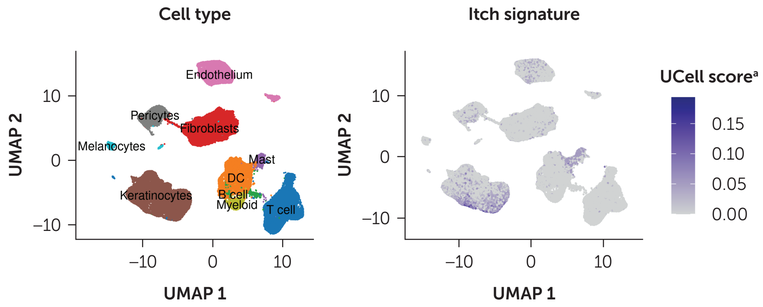
Conclusions

Dysregulation of several different types of itch mediators was observed in psoriatic lesional skin, with dysregulation of keratinocyte-specific itch mediators such as KLK8 and TRPV3 associated with increased areas of IL17A+ and IL17F+ cell infiltration.

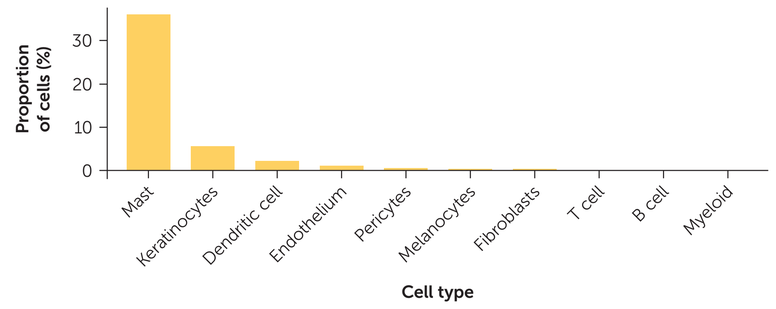
Normalisation of the itch signature post-bimekizumab treatment supports findings of substantial itch resolution observed in phase 3 trials;[2] this is the first analysis describing the mechanism behind itch resolution in psoriasis.

Figure 1 Itch signature expression from single-cell data

A) UMAP representation indicating which cell types expressed the itch signature



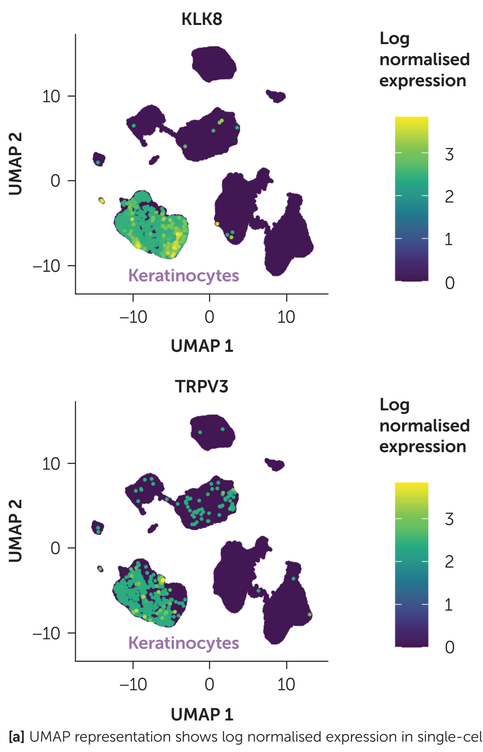
B) Proportion of cells for each cell type that showed an enriched itch signature[b]



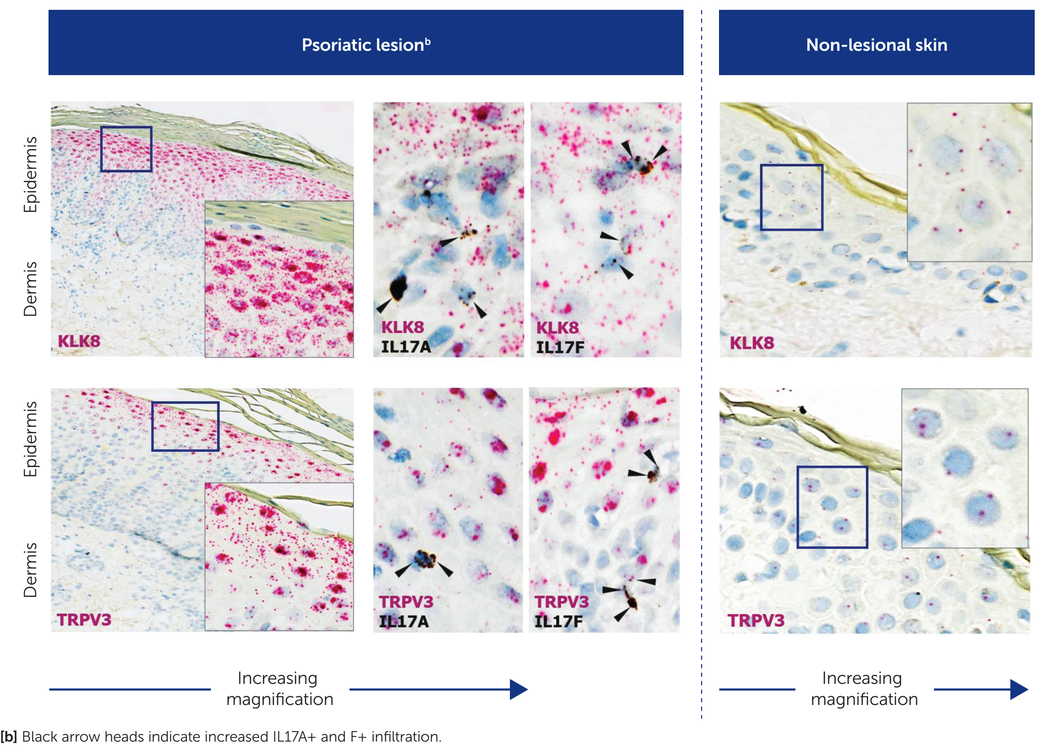
To make this signature more itch-specific, generic inflammation-related genes were removed and a total of 21 genes were kept: F2RL2, HRH2, HRH3, IL31, KLK6, KLK8, KLK14, MRGPRX2, MRGPRX3, PLA2G4B, PLA2G4D, PLA2G4E, SCN3A, SCN9A, SCN11A, TAC1, TACR1, TPSAB1, TRPM8, TRPV1, TRPV3. **[a]** Itch signature enrichment score, computed using the UCell R package.[11] Shades of purple indicate level of expression of the itch signature, as defined by UCell scores; **[b]** Enriched itch signature was defined as UCell score ≥0.05.

Figure 2 Examples of cell type-specific expression of itch mediators KLK8 and TRPV3

A) UMAP representation of KLK8 and TRPV3 expression[a]



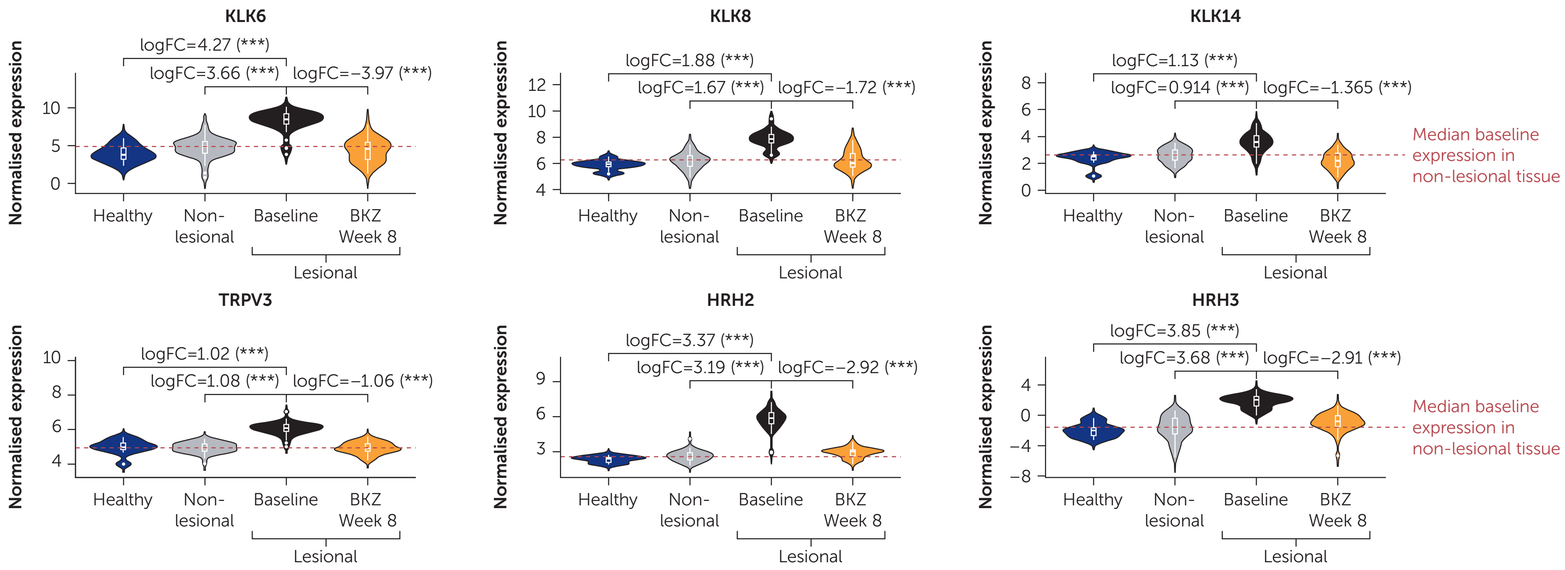
B) RNAscope imaging showing differential expression of KLK8, TRPV3 and IL17A and IL17F in psoriatic lesional versus non-lesional skin



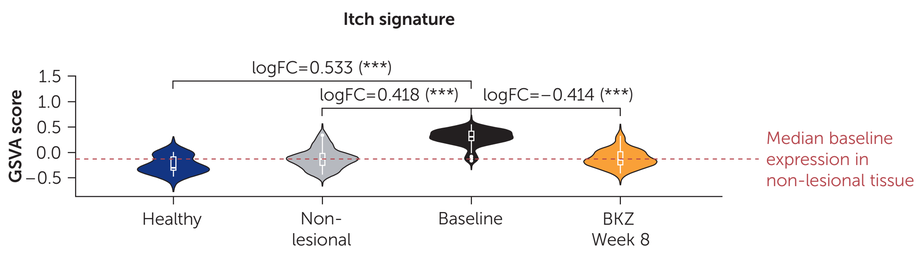
[a] UMAP representation shows log normalised expression in single-cell data; **[b]** Black arrow heads indicate increased IL17A+ and F+ infiltration.

Figure 3 Normalisation of individual itch mediator and overall itch signature expression following BKZ treatment

A) Individual itch mediator expression



B) Overall itch signature expression



Violin plots show log normalised expression of (A) key itch mediators and (B) the itch signature (using GSVA to estimate gene set level expression[7]) in healthy tissue (patients without psoriasis; blue), baseline non-lesional (clear skin in patients with psoriasis; grey), baseline lesional (baseline; black), and treated lesional tissue at Week 8 (BKZ Week 8; yellow). Wider sections of the violin plot indicate higher density of data at the respective y-axis value. White box plots show median and IQR normalised expression. LogFC and FDR-adjusted p-values were calculated using the *limma* moderated t-test.[8] ***FDR<0.001.

BKZ: bimekizumab; **DC:** dendritic cell; **FC:** fold change; **FDR:** false discovery rate; **GSVA:** Gene Set Variation Analysis; **HRH2/3:** histamine receptor H2/3; **IL:** interleukin; **IQR:** interquartile range; **KLK6/8/14:** kallikrein 6/8/14; **RNA-seq:** ribonucleic acid sequencing; **TRP:** transient receptor potential; **TRPV3:** transient receptor potential vanilloid 3; **UMAP:** Uniform Manifold Approximation and Projection.

References: [1]Blome C et al. Arch Dermatol Res 2016;308:69–78; [2]Gottlieb AB et al. WCD 2023. Poster Presentation 1607; [3]Warren RB et al. Dermatol Ther (Heidelb) 2021;11:1551–69; [4]Nattkemper LA et al. J Invest Dermatol 2018;138:1311–7; [5]Reynolds G et al. Science 2021;371:eaba6500; [6]Oliver R et al. Br J Dermatol 2022;186:652–63, NCT03025542; [7]Hänzelmann S et al. BMC Bioinformatics 2013;14:7; [8]Ritchie ME et al. Nucleic Acids Res 2015;43:e47; [9]Gupta K et al. Immunol Rev 2018;282:168–87; [10]Schwendinger-Schreck J et al. Handb Exp Pharmacol 2015;226:177–90; [11]Andreatta M et al. Comput Struct Biotechnol J 2021;19:3796–8. **Author Contributions:** Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **IC**, **JR**, **AF**, **MP**, **SSh**. Drafting of the publication, or reviewing it critically for important intellectual content: **IC**, **JR**, **AF**, **MP**, **SSh**. Final approval of the publication: **IC**, **JR**, **AF**, **MP**, **SSh**. **Author Disclosures:** **IC**, **JR**, **AF**, **SSh:** Employees and shareholders of UCB. **MP:** Employee and shareholder of UCB at the time the work was conducted; current employee of Relation Therapeutics. **Acknowledgements:** This study was funded by UCB. We would like to thank the patients and their caregivers in addition to all the investigators and their teams who contributed to this study. The authors acknowledge Inés Dueñas Pousa, UCB, Madrid, Spain for publication coordination, Sana Yaar, PhD and Alexa Holland, MSc, Costello Medical, Manchester, UK, for medical writing support and editorial assistance, Claire Osgood, MSc, Costello Medical, London, UK for editorial assistance and the Creative Team at Costello Medical Creative Team for design support. All costs associated with development of this poster were funded by UCB.

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Link expiration: 2 October 2025

Presented at the International Conference of the Skin Inflammation & Psoriasis International Network | 2–4 July 2025 | Paris, France

Previously presented at AAD 2024