# Normalization of molecular signatures associated with pruritis in plaque psoriasis correlate with itch resolution following bimekizumab treatment

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## OBJECTIVES:

- 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.

## Background:

- Substantial pruritis (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[a] with BKZ** at Week 16 versus active comparators and placebo in phase 3 trials.[2]

## Methods:

- An **itch signature** was defined based on a previous transcriptomic study, which identified psoriatic pruritis-associated genes by comparing lesional itchy skin with non-lesional, non-itchy skin.[3]
- **Single-cell RNA sequencing** (RNA-seq) data from lesional and non-lesional biopsies allowed assessment of cell type-specific itch mediator expression.[4]
- **Dysregulation of the itch signature** in psoriasis and its **normalization by BKZ** was then determined by **bulk RNA-seq** data from a phase 2a trial.[5]
  - 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.[6,7]

**[a]** As denoted by 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 P-SIM.

**1.** Blome C et al. Arch Dermatol Res 2016;308:69–78; **2.** Gottlieb AB et al. Presented at WCD 2023, P1607; **3.** Nattkemper LA et al. J Invest Dermatol 2018;138:1311–7; **4.** Reynolds G et al. Science 2021;371:eaba6500; **5.** Oliver R et al. Br J Dermatol 2022;186:652–63, NCT03025542; **6.** Hänzelmann S et al. BMC Bioinformatics 2013;14:7; **7.** Ritchie ME et al. Nucleic Acids Res 2015;43:e47. BKZ: bimekizumab; GSVA: Gene Set Variation Analysis; RNA-seq: RNA sequencing; P-SIM: Psoriasis Symptoms and Impacts Measure.

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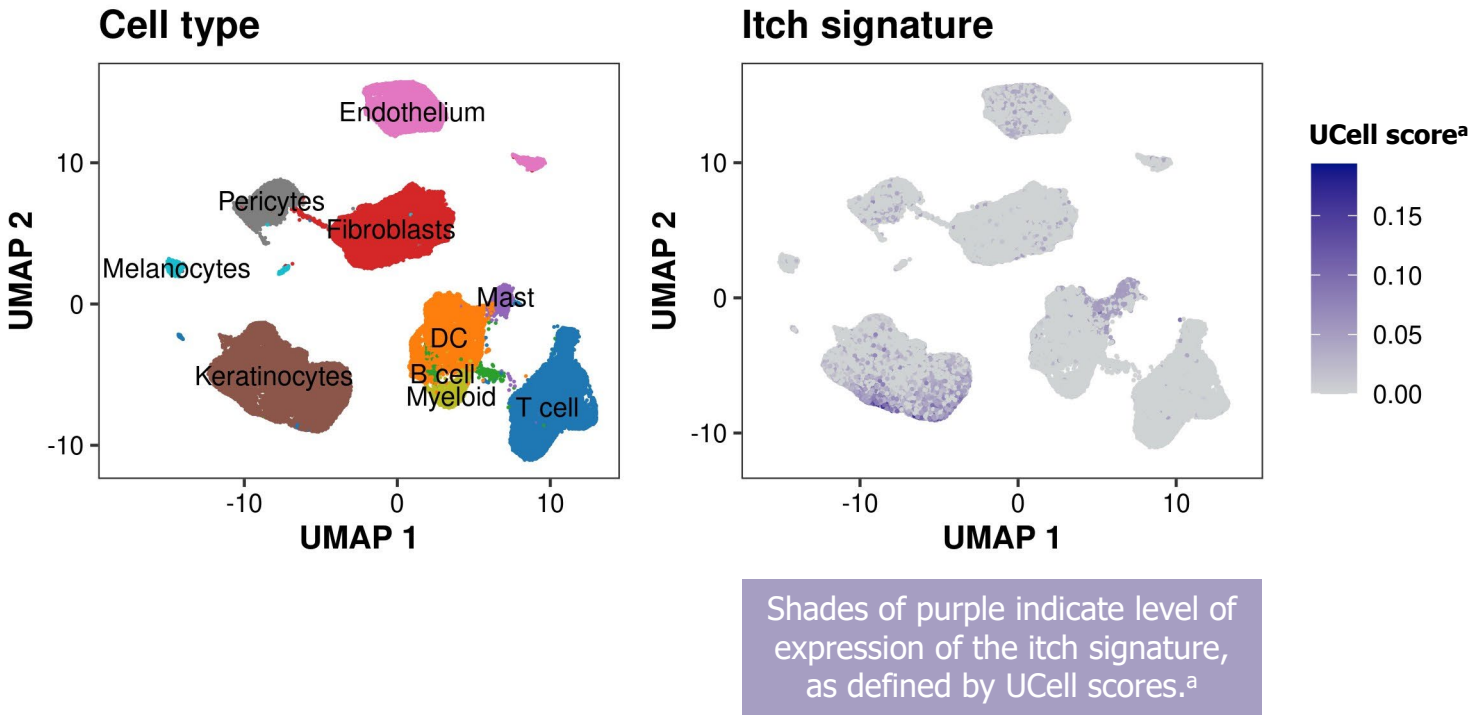
# Itch Signature Expression from Single-Cell Data

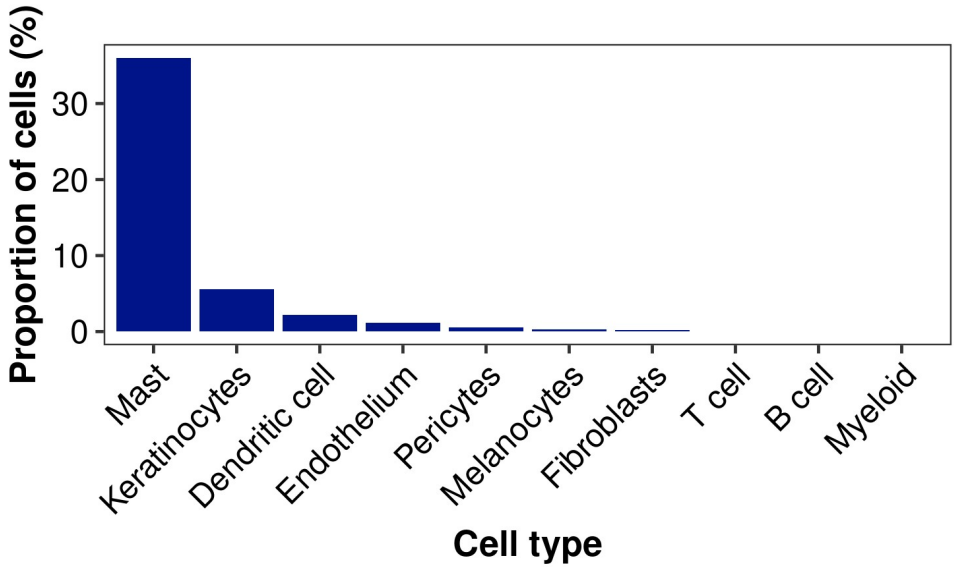
**Single-cell RNA-seq** data indicated that the **itch signature** was predominantly expressed in **mast cells** and **keratinocytes**, which is consistent with the known roles of these cell types in promoting itch.[1,2]

## UMAP representation indicating which cell types expressed the itch signature




Shades of purple indicate level of expression of the itch signature, as defined by UCell scores.[a]

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



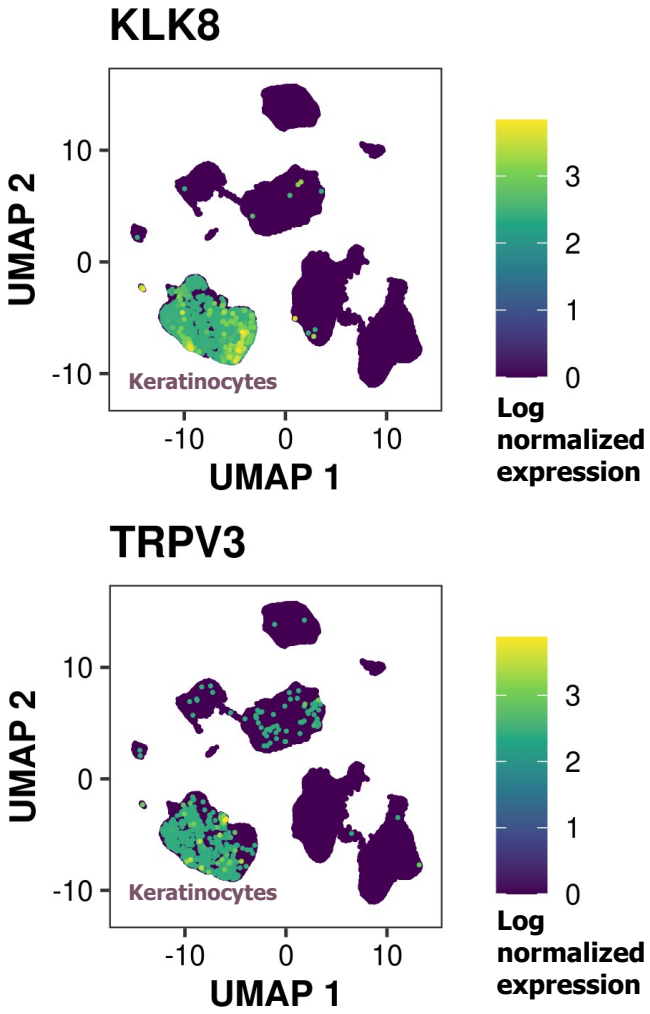

To make this signature more itch-specific, generic inflammation-related genes were removed, and a total of 21 genes were kept: F2RL2, HRH2, HRH3, IL31, KLK6, KLK8, KLK14, MRGPRX2, MRGPRX3, PLA2G4B, PLA2G4D, PLA2G4E, SCN3A, SCN9A, SCN11A, TAC1, TACR1, TPSAB1, TRPM8, TRPV1, TRPV3. **[a]** Itch signature enrichment score, computed using the UCell R package;[3] **[b]** Enriched itch signature was defined as UCell score ≥0.05.

**1.** Gupta K et al. Immunol Rev 2018;282:168–87; **2.** Schwendinger-Schreck J et al. Handb Exp Pharmacol 2015;226:177–90; **3.** Andreatta M et al. Comput Struct Biotechnol J 2021;19:3796–8. DC: dendritic cell; RNA-seq: RNA sequencing; UMAP: Uniform Manifold Approximation and Projection.

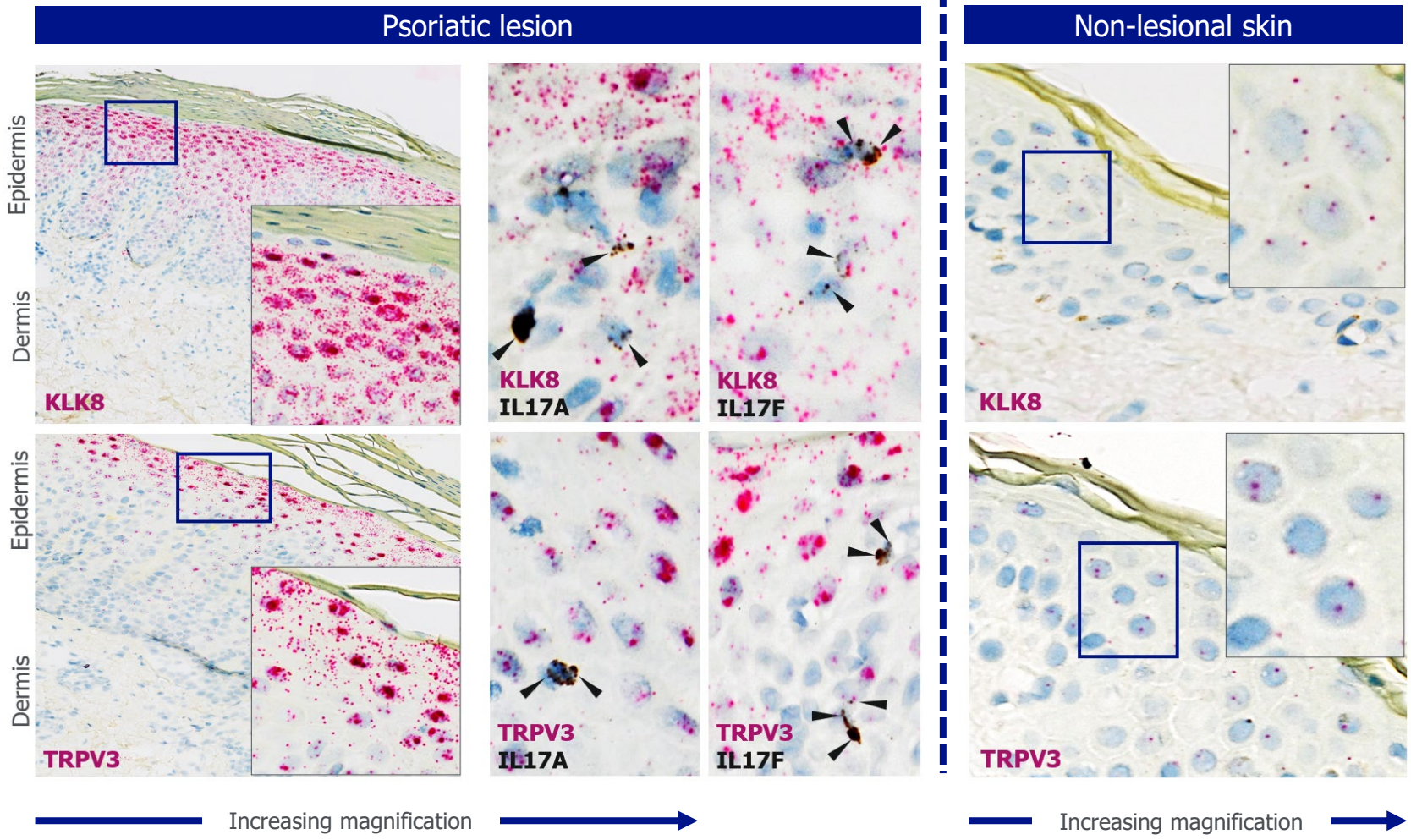
# Examples of Cell Type-Specific Expression of Itch Mediators (KLK8 and TRPV3)

**KLK8** and **TRPV3** expression was highly specific to keratinocytes; **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.

## UMAP representation
of KLK8 and TRPV3 expression



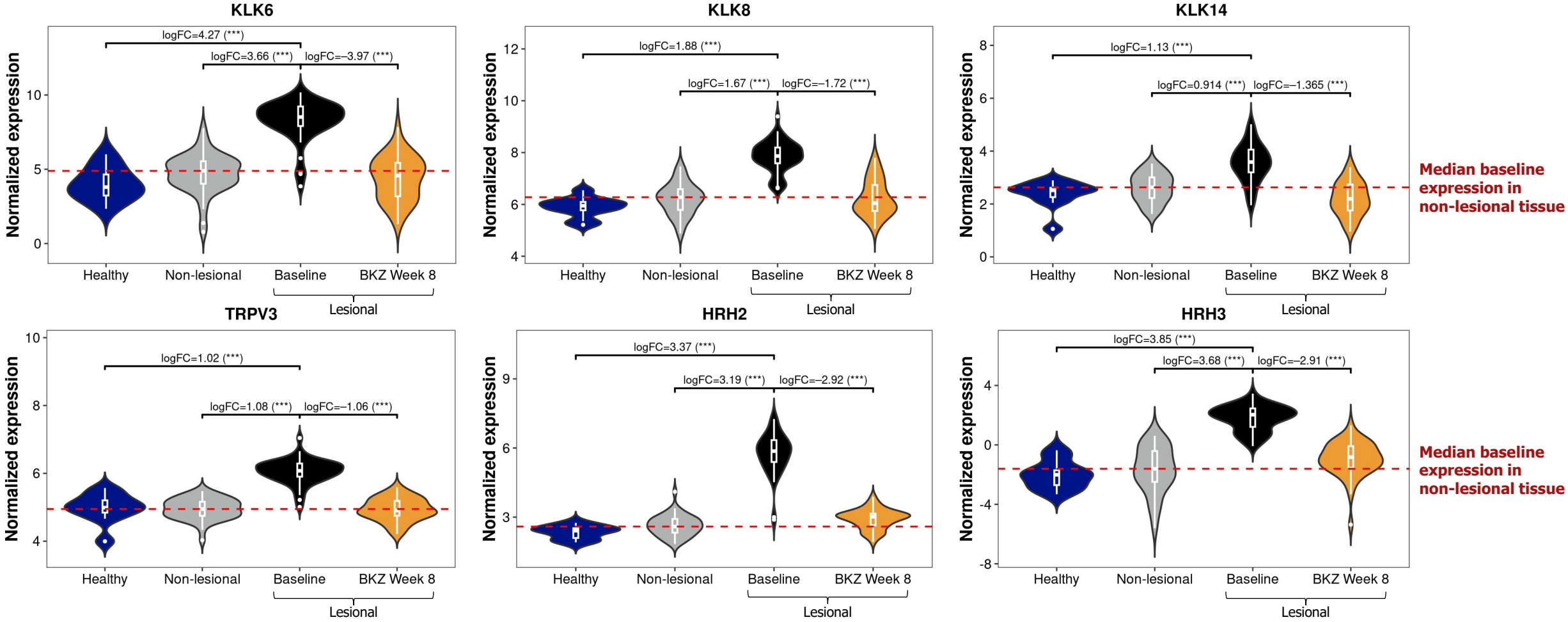

## RNAscope imaging showing differential expression
of KLK8, TRPV3, and IL17A and F in psoriatic lesional versus non-lesional skin




UMAP representation shows log normalized expression in single-cell data. Black arrow heads in RNAscope images indicate increased IL17A+ and F+ infiltration. IL: interleukin; KLK8: kallikrein 8; TRPV3: transient receptor potential vanilloid 3; UMAP: Uniform Manifold Approximation and Projection.

# Normalization of Itch Mediator Expression following Bimekizumab Treatment

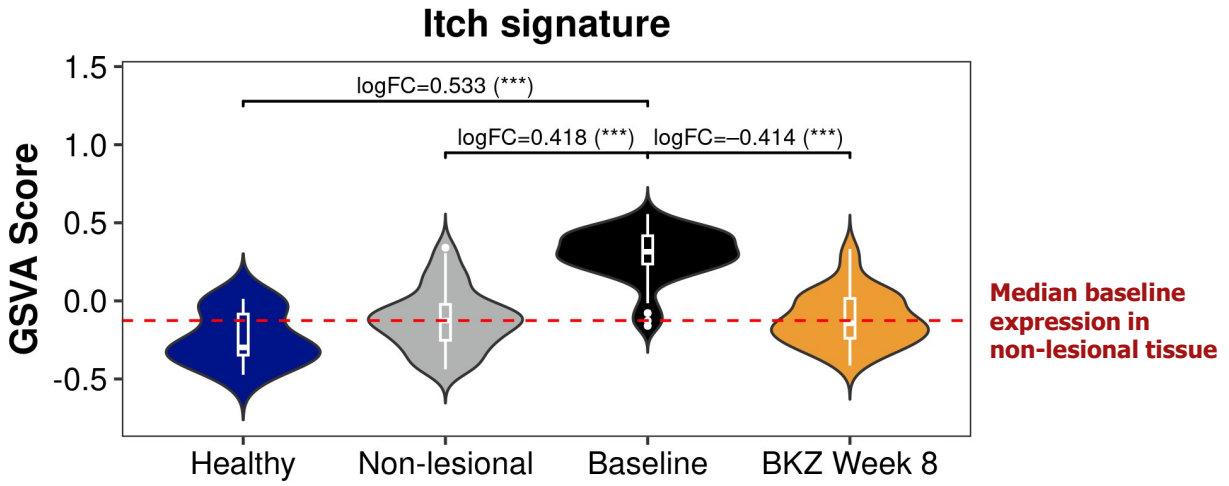
**Bulk RNA-seq following two BKZ doses** (BKZ Week 8) indicated that individual mediators contributing to the overall itch signature, including kallikreins (KLK6/8/14), TRP channels (TRPV3), and histamine receptors (HRH2/3), were **all normalized post-treatment** (percentage improvement >75%).




Violin plots show log normalized expression of key itch mediators 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 normalized expression. LogFC and FDR-adjusted p-values were calculated using the *limma* moderated t-test.[1] ***FDR<0.001. **1.** Ritchie ME et al. Nucleic Acids Res 2015;43:e47. BKZ: bimekizumab; FC: fold change; FDR: false discovery rate; HRH2/3: histamine receptor H2/3; IQR: interquartile range; KLK6/8/14: kallikrein 6/8/14; TRPV3: transient receptor potential vanilloid 3.

# Normalization of Overall Itch Signature Expression following Bimekizumab Treatment

**Bulk RNA-seq** indicated that the **overall itch signature was normalized to non-lesional levels** post-BKZ treatment, 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 F+ cell infiltration.
- Normalization of the itch signature post-bimekizumab treatment supports findings of substantial itch resolution observed in phase 3 trials;[3] this is the first analysis describing the mechanism behind itch resolution in psoriasis.

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Violin plot shows expression of the itch signature, using GSVA to estimate gene set level expression,[1] 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 normalized expression. LogFC and FDR-adjusted p-values were calculated using the *limma* moderated t-test.[2] ***FDR<0.001. **1.** Hänzelmann S et al. BMC Bioinformatics 2013;14:7; **2.** Ritchie ME et al. Nucleic Acids Res 2015;43:e47; **3.** Gottlieb AB et al. Presented at WCD 2023, P1607. BKZ: bimekizumab; FC: fold change; FDR: false discovery rate; GSVA: Gene Set Variation Analysis; IL: interleukin; IQR: interquartile range; KLK8: kallikrein 8; RNA-seq: RNA sequencing; TRPV3: transient receptor potential vanilloid 3.