Bimekizumab treatment in psoriasis patients: A mechanistic understanding of the durable clinical response

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Objective

To understand the molecular mechanisms that lead to the durable and continuous complete skin clearance observed in bimekizumab (BKZ)-treated patients with psoriasis over 3 years.

Background

- Dual inhibition of interleukin (IL)-17F in addition to IL-17A with BKZ has been associated with superior clinical outcomes compared to inhibition of IL-17A alone.[1] BKZ treatment is associated with long-term skin clearance in patients with psoriasis, with more than 80% of patients who achieved complete skin clearance at Week 16 maintaining it through 3 years (**Summary**).[2]
- While IL-17A is more potent than IL-17F, IL-17F is more abundant in inflamed psoriatic tissue.[3,4] This suggests that, despite the overlapping biology of IL-17A and IL-17F, their production from IL-17-secreting cells is regulated differently; it was previously shown that chronic stimulation of these cells causes preferential IL-17F production.[5]
- Interest in tissue-resident memory T cells (Trm) has grown recently due to their implication in both psoriasis recurrence at the same location following treatment withdrawal and in disease perpetuation during treatment.[6] Trm cells have also been found in the joints and blood of psoriatic arthritis (PsA) patients,[7] and an increase in skin-derived Trms was observed in the circulation of these patients, which may contribute to the progression of psoriasis to PsA.[8]

Methods

- Three independent single-cell RNA sequencing (RNA-seq) datasets from lesional psoriatic biopsies (two external: Kim et al.[9] and Reynolds et al.;[10] one in-house[4]) were re-processed in a uniform manner and used to assess gene expression in specific cell types, such as Trm cells and IL17A/F-producing cells.
- Pre- and post-treatment bulk RNA-seq data from a phase 2a trial of BKZ in psoriasis (study design previously reported)[11] were used to evaluate the effect of BKZ on genes and gene signatures of interest.

Results

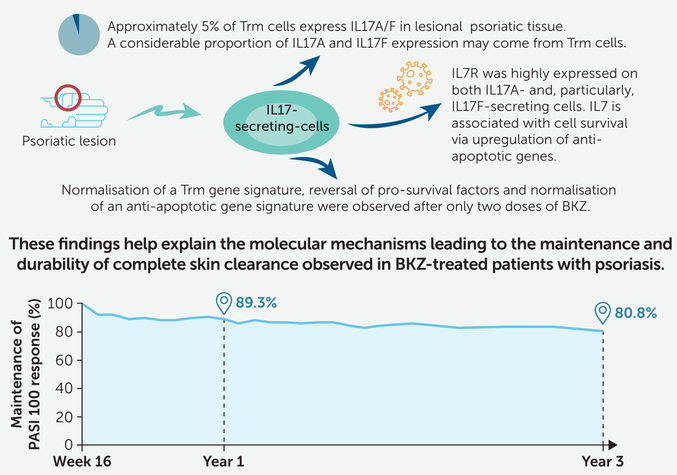
- Analysis of the three independent psoriasis single-cell datasets indicated that approximately 5% of Trm cells express IL17A/F in lesional psoriatic tissue (**Figure 1A**), and a considerable proportion of the IL17A and IL17F expression may come from these cells (**Figure 1B**).
- These single-cell datasets also consistently highlighted that, overall, IL17A- and IL17F-secreting cells have highly similar transcriptomes (**Figure 2**).
- Interestingly, IL7R was highly expressed on both IL17A- and, particularly, IL17F-secreting cells, with two out of the three datasets showing a significant upregulation in the IL17F-secreting cells (**Figure 3**). This may increase the survival of these pathogenic cells, as the IL7 pathway is associated with cell survival by upregulating anti-apoptotic genes, such as BCL2 and BCL2L1.[12]
- Additionally, several T cell pro-survival factors, including IL7R, and the more recently described IL32, were found to be expressed in Trm cells (median normalised expression >1.5, **Figure 4**).
- Bulk transcriptomic analysis showed normalisation of a Trm gene signature after only two doses of BKZ (median percentage improvement: 78.1% at Week 8, which increased to 87.7% at Week 28, following three doses; **Figure 5A**). Additionally, elevated expression of the pro-survival factors IL7R and IL32 was reversed (**Figure 5B**) and normalisation of an anti-apoptotic gene signature was also observed (median percentage improvement: 104.5% at Week 8; **Figure 5C**).

Conclusions

These mechanistic data from patient samples highlight the importance of IL-17F and IL-17A dual neutralisation in normalising both Trm biology and pro-survival factors.

Together with the previously shown normalisation of IL23 expression,[11] these observations have implications for disease modification and are important for the maintenance and durability of complete skin clearance during treatment in patients with psoriasis.

Summary



These findings help explain the molecular mechanisms leading to the maintenance and durability of complete skin clearance observed in BKZ-treated patients with psoriasis.

Response maintenance in BKZ-treated patients reported by Strober et al.[2]

Figure 1 IL17 expression in Trm (CD103+) cells across three single-cell datasets

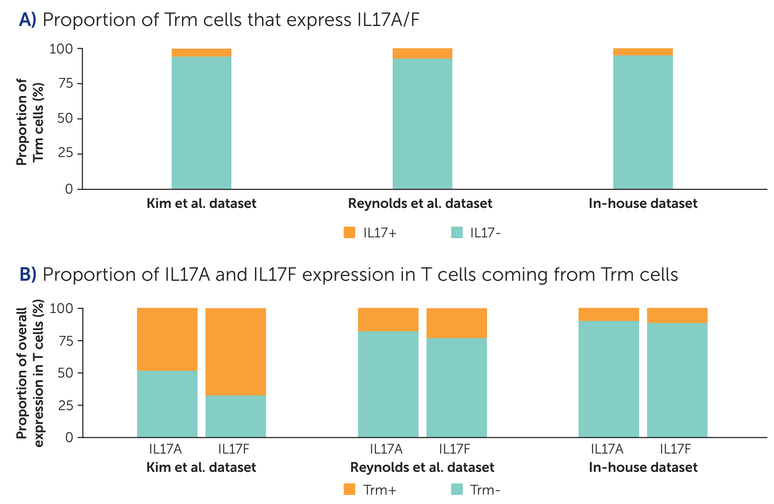
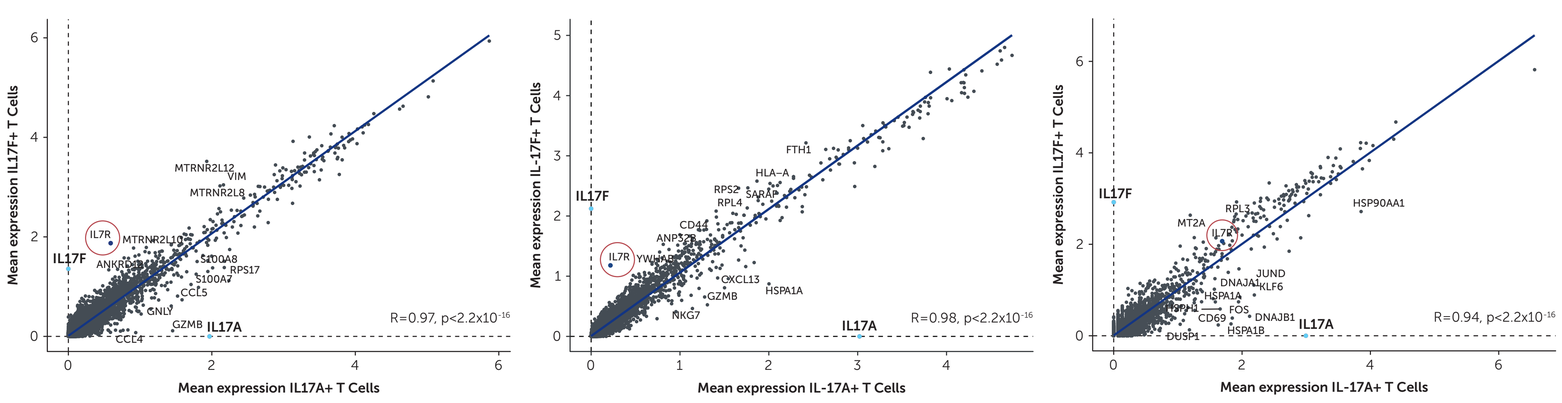
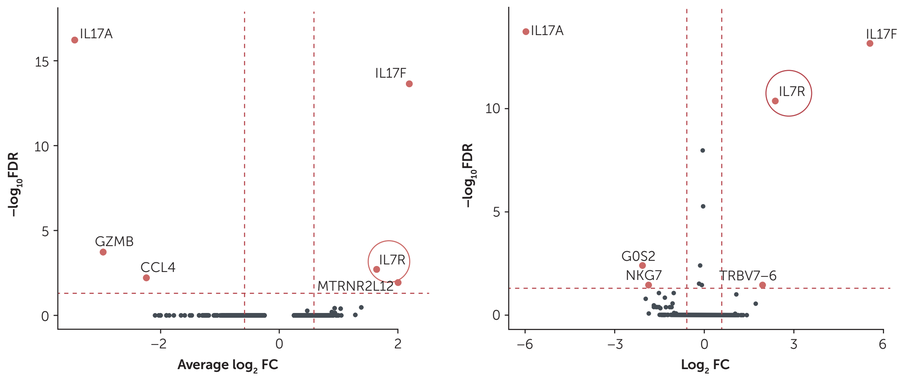


Figure 2 Correlation of average gene expression profiles for IL17A+ and IL17F+ T cells in three single-cell datasets



The top 15 genes with largest mean expression differences are labelled. R is the Pearson correlation coefficient.

Figure 3 Volcano plots showing significant upregulation of IL7R in IL17F-producing T cells in two single-cell datasets



Genes with FDR <0.05 and |FC| ≥1.5 are labelled.

Figure 4 Violin plots of IL7R and IL32 normalised expression in Trm cells (CD103+) across three single-cell datasets

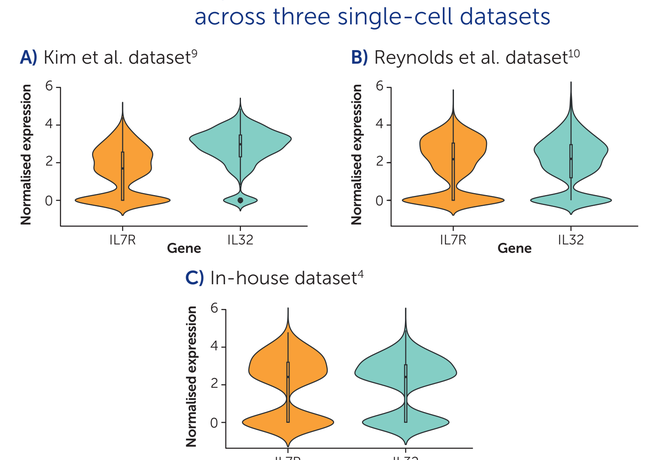
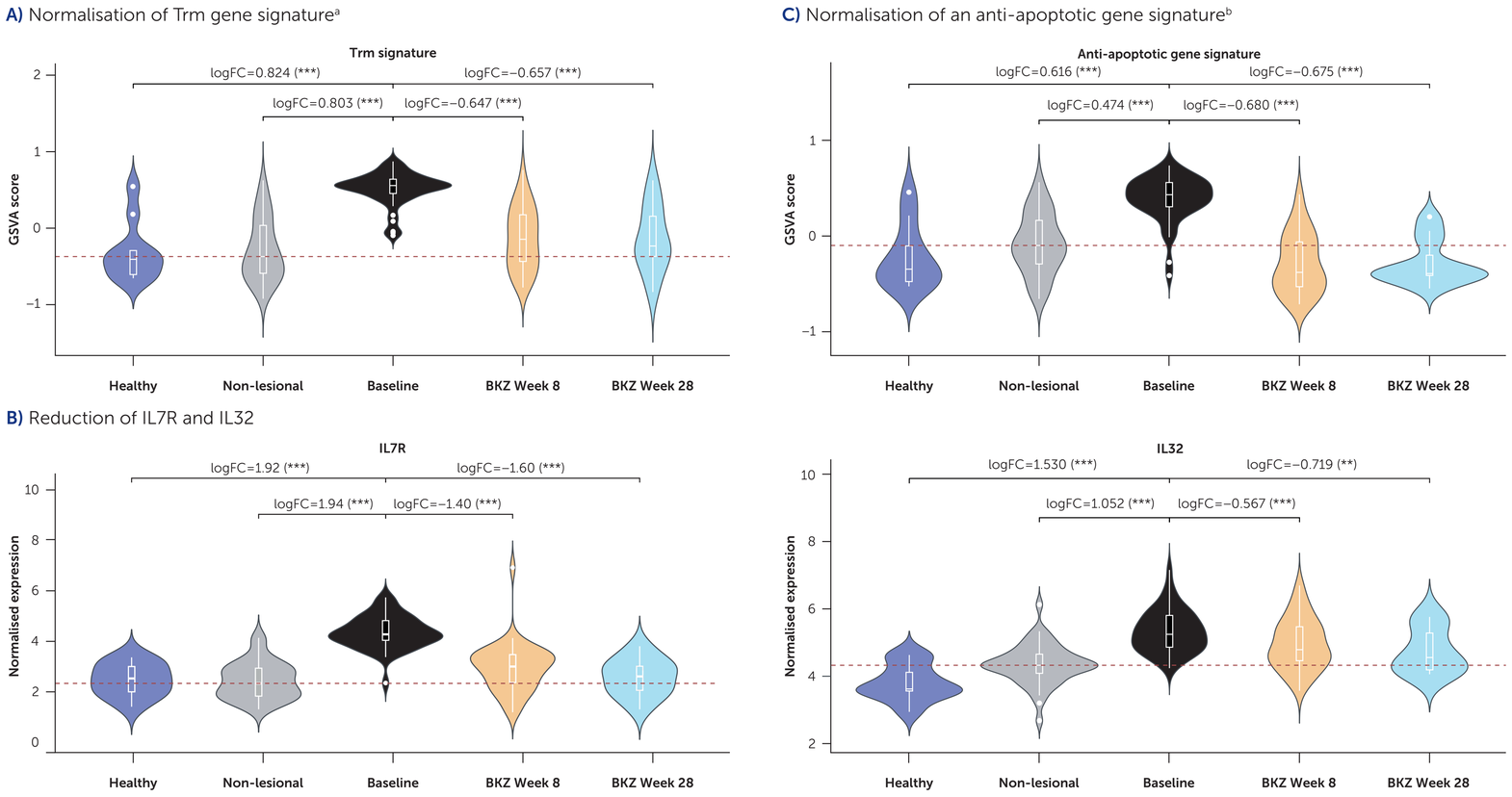


Figure 5 Expression of key genes and gene sets in baseline healthy, non-lesional and lesional tissue versus treated lesional tissue at Weeks 8/28



Gene Set Variation Analysis[13] was used to estimate gene set level of expression. Red horizontal lines correspond to the median baseline expression in non-lesional tissue. LogFC and FDR-adjusted p-values were calculated using the limma moderated t-test. ***FDR<0.001; **FDR<0.01. [a]CD103, CD69, CD44; [b]BCL2, BCL2L1, MCL1, BIRC5, CFLAR, BCL2A1, BIRC3, PEA15.

BKZ: bimekizumab; **FC:** fold change; **FDR:** false discovery rate; **GSVA:** Gene Set Variation Analysis; **IL:** interleukin; **PASI:** Psoriasis Area and Severity Index; **PsA:** psoriatic arthritis; **RNA-seq:** RNA sequencing; **Trm:** tissue-resident memory T cells.

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References: [1]Reich K et al. N Engl J Med 2021;385:142–52, NCT03536884; [2]Strober B et al. Br J Dermatol 2023;188(6):749–59, NCT03536884; [3]Kolbinger F et al. J Allergy Clin Immunol 2017;139(3):923–32; [4]Skelton A et al. Poster presented at SID 2022, P038; [5]Cole S et al. J Allergy Clin Immunol 2023;152(3):783–98; [6]Puig L et al. Br J Dermatol 2022;186(5):773–81; [7]Steel KJA et al. Arthritis Rheumatol 2020;72(3):435–47; [8]Leijten EF et al. Arthritis Rheumatol 2021;73(7):1220–32; [9]Kim J et al. J Allergy Clin Immunol 2021;148(5):1281–92; [10]Reynolds G et al. Science 2021;371(6527):eaba6500; [11]Oliver R et al. Br J Dermatol 2022;186(4):652–63, NCT03025542; [12]Chetoui N et al. Immunology 2010;130(3):418–26; [13]Hänzelmann S et al. BMC Bioinformatics 2013;14(7):1–15. **Author Contributions:** Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **IC**, **AS**, **AK**, **JR**, **JGK**, **MP**, **SS**; Drafting of the publication, or reviewing it critically for important intellectual content: **IC**, **AS**, **AK**, **JR**, **JGK**, **MP**, **SS**; Final approval of the publication: **IC**, **AS**, **AK**, **JR**, **JGK**, **MP**, **SS**. **Author Disclosures:** **IC**, **AS**, **AK**, **JR**, **MP**, **SS**: Employees and shareholders of UCB Pharma. **JGK:** Grants paid to institution from AbbVie, Amgen, Akros, Allergan, Avillion, Biogen MA, Boehringer Ingelheim, Botanix, Bristol Myers Squibb, Celgene, Eli Lilly, Exicure, Incyte, Innovaderm, Janssen, LEO Pharma, Novan, Novartis, Parexel, Pfizer, Regeneron, Sienna, UCB Pharma, and Vitae. Personal fees from AbbVie, Aclaris, Allergan, Almirall, Amgen, Arena, Aristea, Asana, Aurigne, BiogenIdec, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Escalier, Galapagos, LEO Pharma, Menlo, Nimbus, Novartis, Pfizer, Sanofi, Sienna, Sun Pharma, UCB Pharma, Valeant, and Ventyx. **Acknowledgements:** This study was funded by UCB Pharma. We thank the patients and their caregivers in addition to the investigators and their teams who contributed to this study. The authors acknowledge Susanne Wiegratz, MSc, UCB Pharma, Monheim am Rhein, Germany, and Inés Dueñas Pousa, PhD, UCB Pharma, Madrid, Spain for publication coordination, Isabel Raynaud, MBBS, Costello Medical, Cambridge, UK for medical writing and editorial assistance, and the Costello Medical Creative team for design support. All costs associated with development of this poster were funded by UCB Pharma.

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