

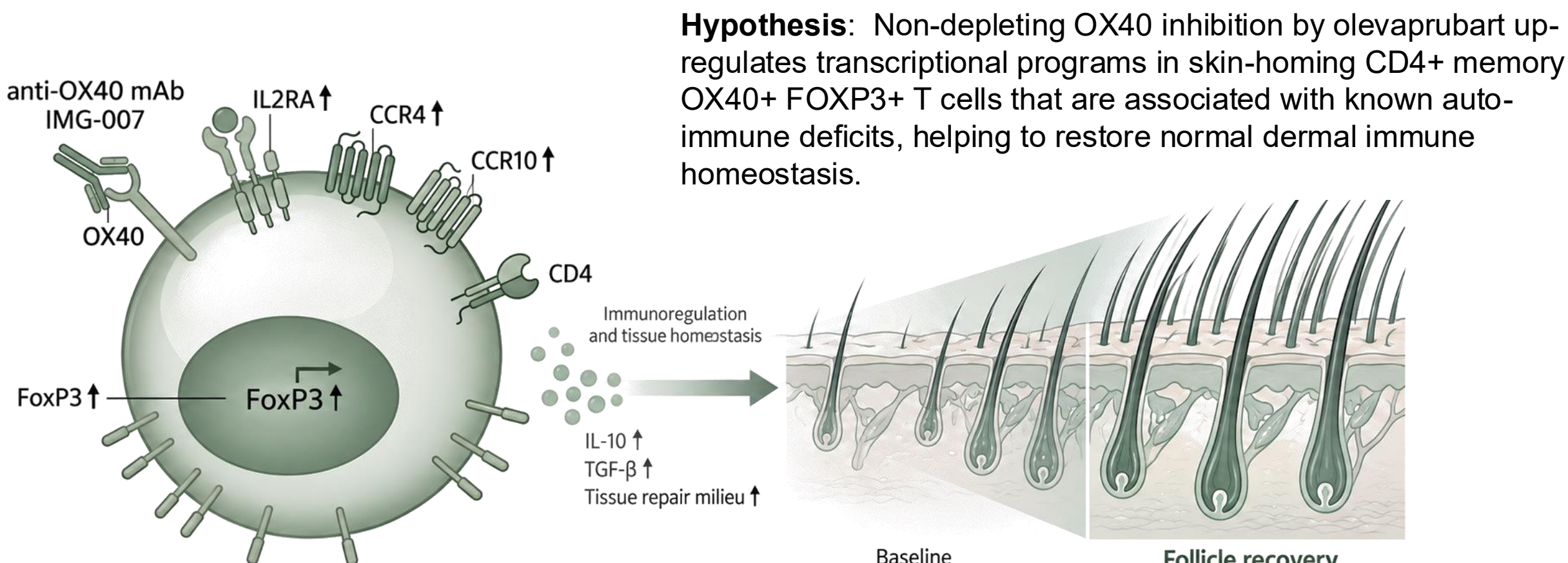
Olevaprubart (IMG-007), a non-depleting anti-OX40 mAb: Exploratory biomarker insights into T cell phenotypic modulation from a proof-of-concept study in alopecia areata

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BACKGROUND

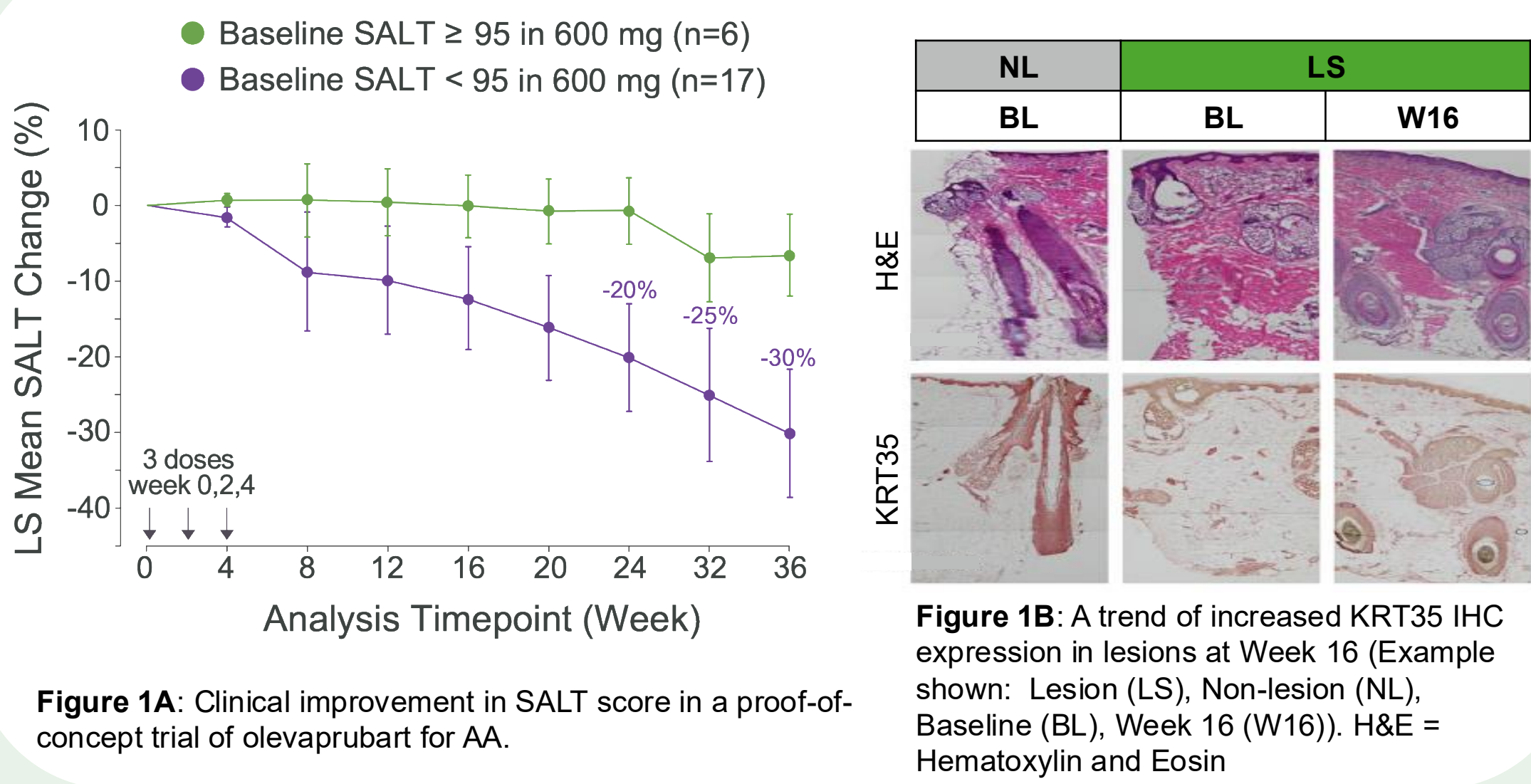
Olevaprubart (IMG-007) is an Fc-silenced (N297A) IgG1 antibody designed to block OX40–OX40L costimulation without FcγR-mediated depletion. OX40 signaling regulates T-cell activation, trafficking, and survival, processes implicated in alopecia areata (AA). OX40 blockade holds the promise of durable immune modulation (1-5), but clinical and translational data in AA are lacking. In the current study, we examined molecular responses to olevaprubart to generate hypotheses about its immunologic mechanism of action in AA. Data indicate robust molecular recovery of scalp keratin expression, with peripheral OX40+ T-cell levels and serum cytokines associated with antiviral and cell-mediated immune programs remaining stable during and after treatment. In addition, these preliminary findings suggest modulation of skin-homing CD4+ memory OX40+ FOXP3+ T cells, a subset implicated in dermal autoimmunity but not previously shown to be modulated by OX40-directed therapy in patients.



OX40 blockade with the non-depleting anti-OX40 mAb olevaprubart produced a durable clinical response in a proof-of-concept study in AA

The Clinical Study: In a proof-of-concept trial of olevaprubart (NCT06060977) in AA, patients received three IV doses of antibody at 600 mg/dose over 4 weeks (at weeks 0, 2 and 4).

Clinical Improvement: We previously reported progressive clinical improvement up to 8 months after cessation of olevaprubart administration (Fig. 1A), and a trend towards increased KRT35 expression as measured by scalp biopsy IHC (Fig. 1B) (6).



METHODS

In the current exploratory biomarker study, we seek to characterize the molecular pharmacology of olevaprubart and generate hypotheses through transcriptomic, proteomic and other studies of the broader cohort and additional PBMC scRNAseq of a 4-patient subset.

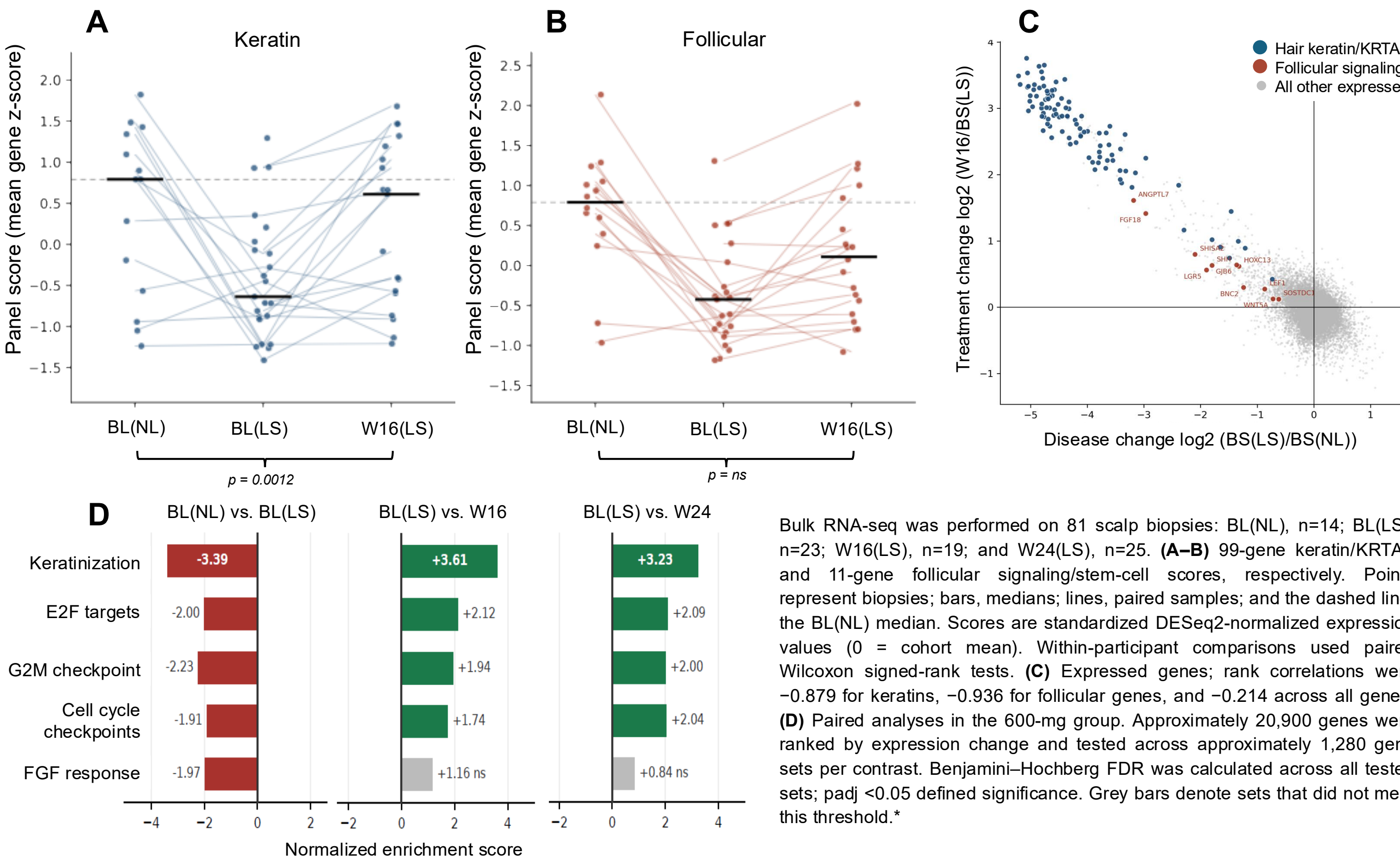
EXPLORATORY BIOMARKERS

- Scalp, blood and serum samples collected at baseline and available post-treatment visits (n=23 subjects).
- scRNAseq and TCR-seq (10X Genomics) assessed PBMC gene expression and TCR repertoire (n= 4 subjects).
- Flow cytometry was used to assess PBMC OX40.
- RNA-seq profiled gene expression in lesional (LS) and adjacent non-lesional (NL) scalp biopsies.
- Serum proteins were measured using the Olink Target 48 panel, while TARC (CCL17) was quantified by ELISA (data not shown)
- KRT35 and other proteins were measured by IHC

RESULTS

IMG-007 supports robust, stable molecular recovery of hair keratins and follicular gene expression, as measured by bulk RNA-Seq of scalp biopsy samples

Figure 2: Disease-associated expression changes in keratin (A) and follicular (B) genes are selectively reversed following olevaprubart treatment (C) and remain reversed through Week 24, including cellular-proliferation genes (D).



Skin-homing CD4+ memory FOXP3+ T cells, a population implicated in dermal autoimmunity, identified in AA PBMC as measured by single-cell RNA-Seq

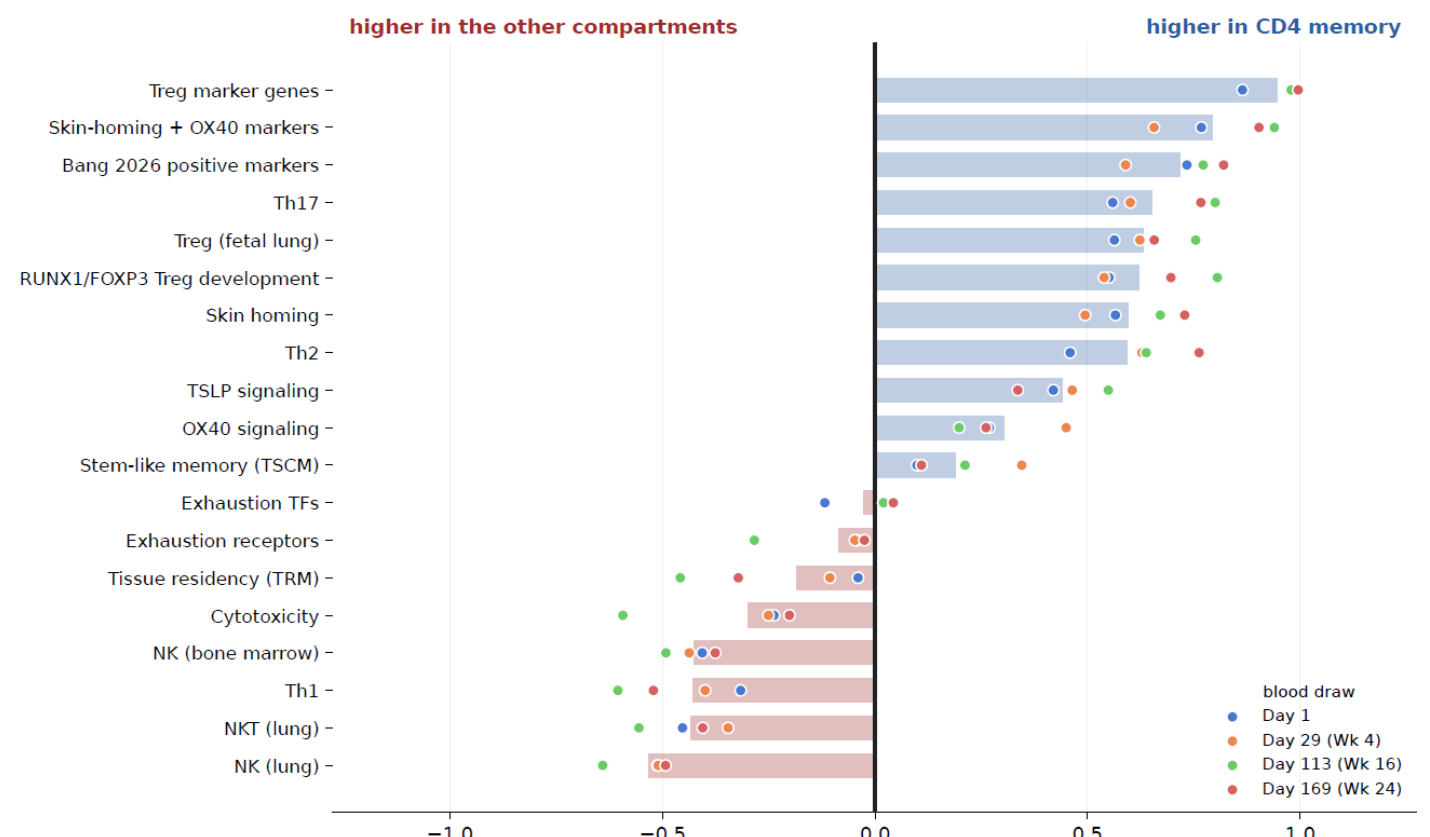


Figure 4: Peripheral memory (CCR7-low CD4 T cells) express trafficking and homing gene programs and are consistent between patients and timepoints. Skin-homing CD4 and Treg in AD have elevated OX40, and suppressed Treg function (7-8).

Bars show the mean across 11 libraries; points show draw-specific means. Profiles were highly concordant across draws (rank correlations, 0.96–0.98). Days 113 and 169 each include two libraries from different patients; differences in magnitude should not be interpreted as longitudinal change.

X-axis denotes module score difference (CCR7-low CD4 memory minus other compartments).

OX40 expression is enriched in skin-homing CD4+ memory FOXP3+ T cells

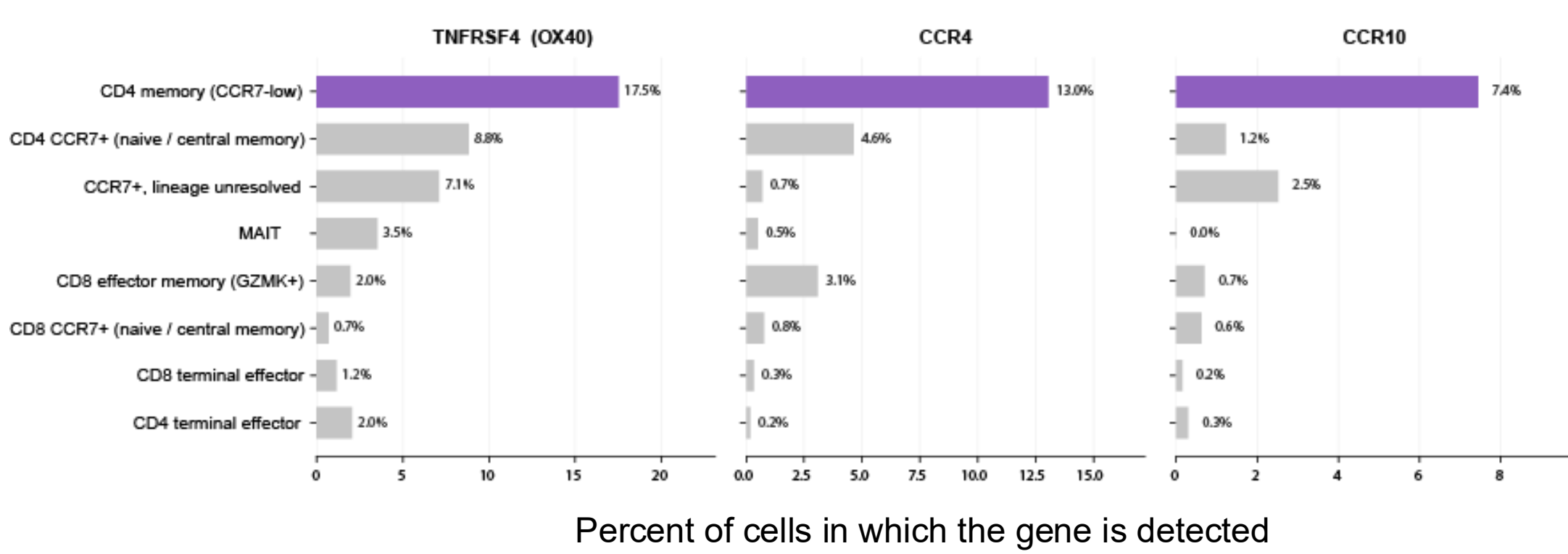


Figure 5: OX40 is enriched in CD4 memory T cells and memory Treg expressing CCR4 and CCR10 receptors for the skin-associated chemokines CCL17/TARC and CCL27, respectively.

Detection represents the fraction of cells with ≥1 transcript detected and may underestimate expression at this sequencing depth. CD4 memory CCR7-low cells showed the highest OX40 (17.5%), CCR4 (13.0%), and CCR10 (7.4%) detection. CCR4 and CCR10 mediate skin homing; SELPLG and FUT7 serve as transcriptional proxies for CLA.

Measured maintenance of CD4+ cells in PBMC, OX40 expression in scalp, and stable serum cytokines are consistent with non-depleting mechanism of olevaprubart

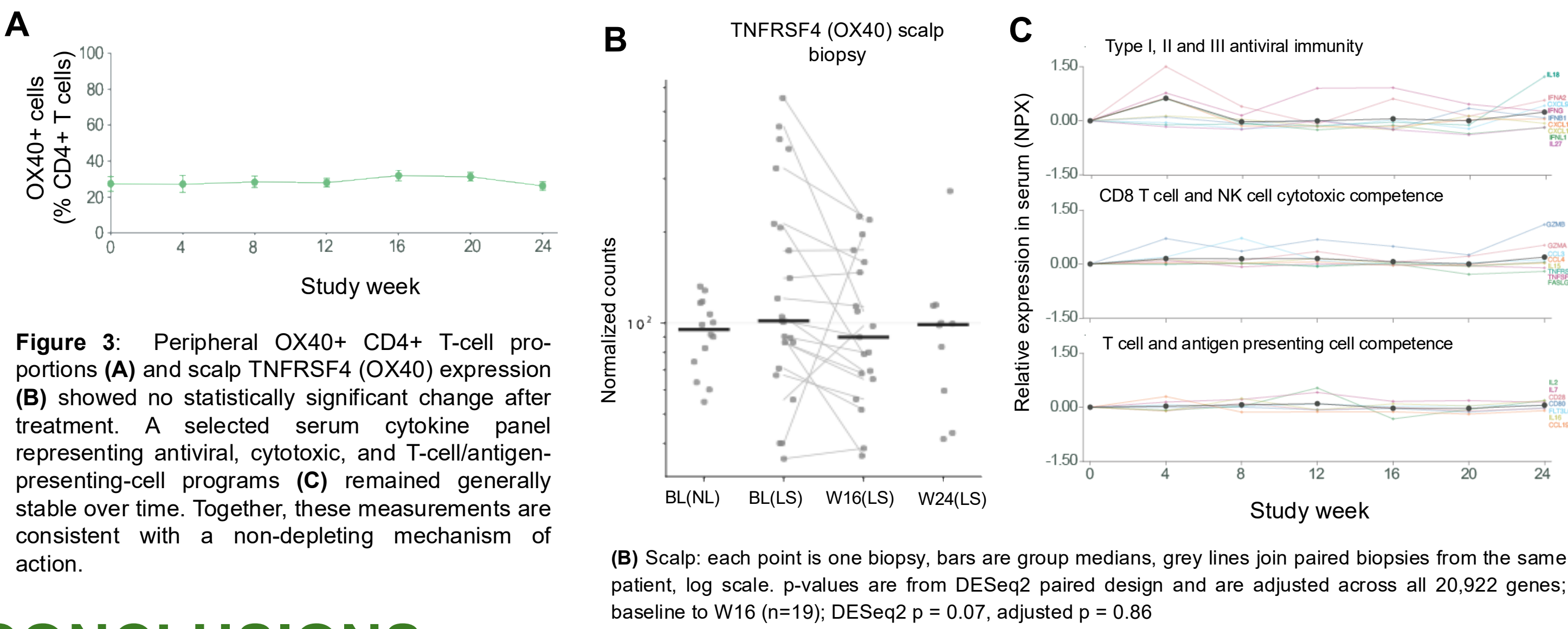


Figure 3: Peripheral OX40+ CD4+ T-cell proportions (A) and scalp TNFRSF4 (OX40) expression (B) showed no statistically significant change after treatment. A selected serum cytokine panel representing antiviral, cytotoxic, and T-cell/antigen-presenting-cell programs (C) remained generally stable over time. Together, these measurements are consistent with a non-depleting mechanism of action.

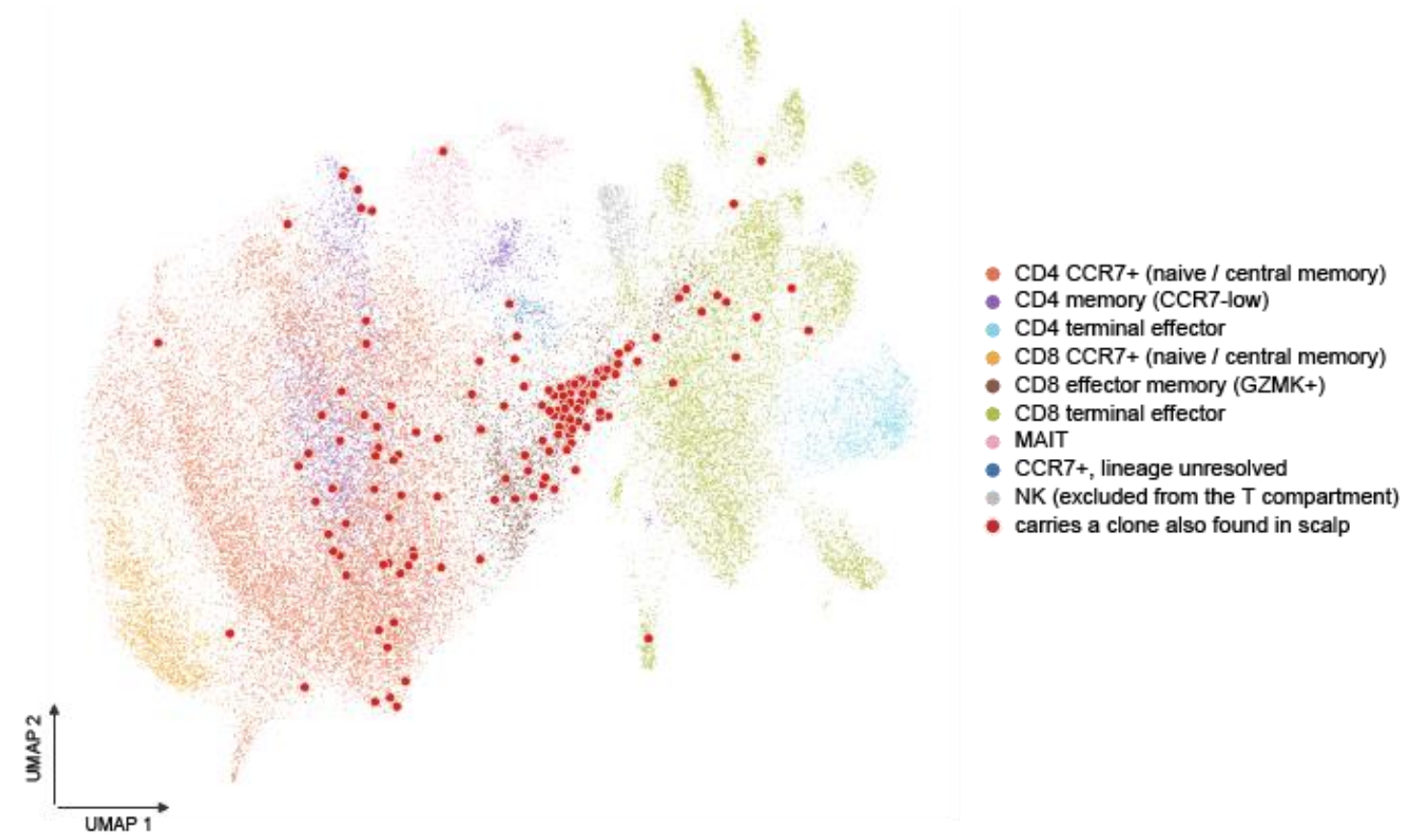
(B) Scalp: each point is one biopsy, bars are group medians, grey lines join paired biopsies from the same patient, log scale. p-values are from DESeq2 paired design and are adjusted across all 20,922 genes; baseline to W16 (n=19); DESeq2 p = 0.07, adjusted p = 0.86

Skin-homing CD4+ memory OX40+ FOXP3+ T cells and CD8 TEM contain clonotypes of T cells also found in scalp lesions, suggesting link between PBMC and scalp

Figure 6: Shared T cell clonotypes (nucleotide identity at TCRB V/J junction) are clustered in PBMC CD4+ memory and CD8 TEM populations.

A total of 152 of 48,469 cells across all PBMC scRNAseq libraries carry a TCR clone also found in that patient's scalp. The 152 highlighted cells carry 52 distinct clonotypes.

Blood T cell population	Share of matched scalp / PBMC TCR clonotype
CD8 effector memory (GZMK+)	54.6%
CD4 memory, CCR7-low	21.1%
CD4 CCR7+ (naive / central memory)	15.1%
CD8 terminal effector	7.9%
CD8 CCR7+ (naive / central memory)	0.7%
MAIT	0.7%
CD4 terminal effector	0.0%



The Hypothesis: Olevaprubart may promote transcriptional programs in skin-homing CD4+ memory OX40+ FOXP3+ T cells that support immune regulation, potentially helping to restore dermal immune homeostasis

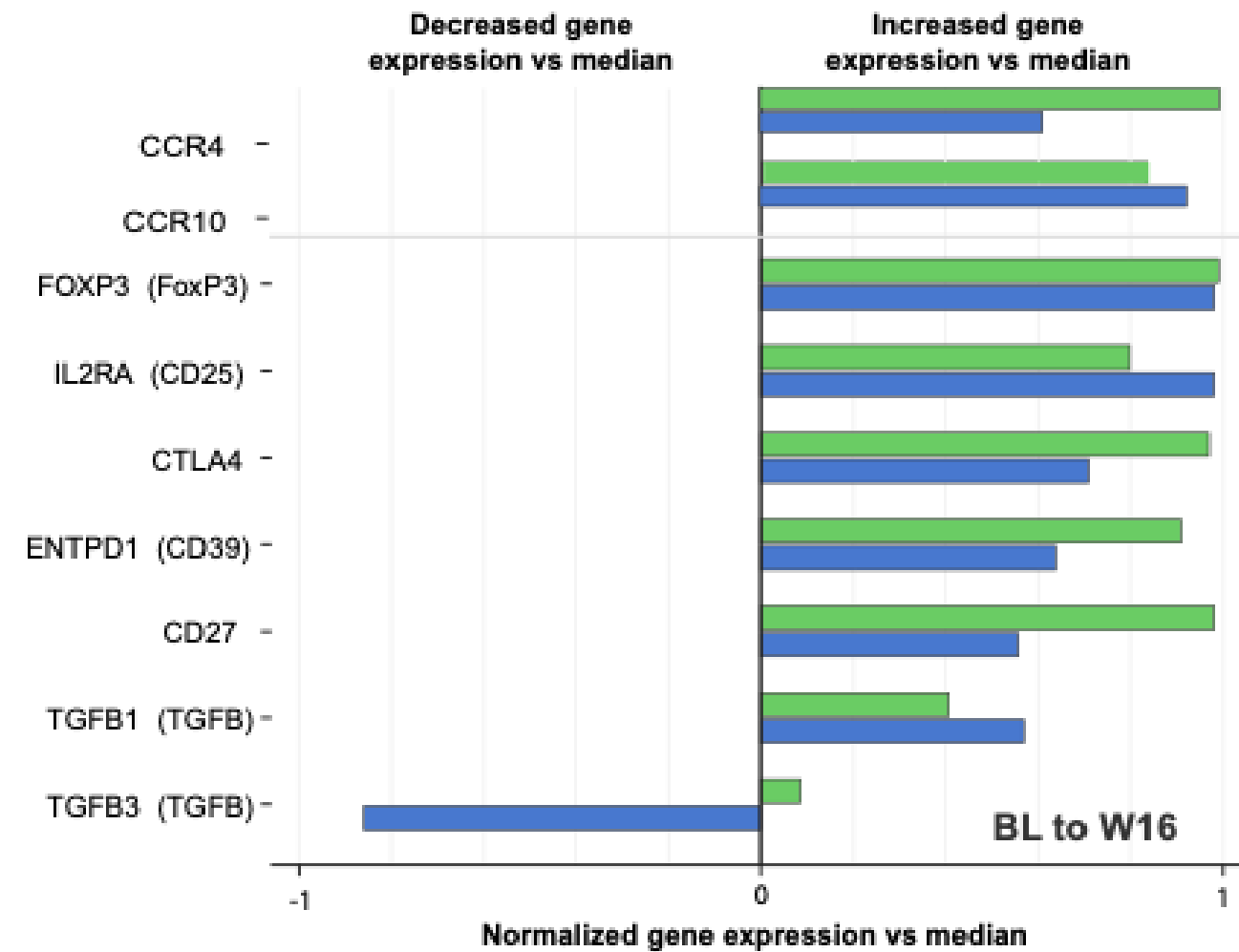


Figure 7: Exploratory within-participant shifts were observed upon treatment with olevaprubart, consistent with published data indicating OX40 suppression of FOXP3 and Treg function (9-11) and reports of defective Treg trafficking in dermal autoimmunity (12-13).

Each bar represents one gene in one patient. No statistical testing was performed or implied. Genes shown were from a pre-specified GSEA panel, and expression was normalized against 200 abundance-matched genes. A normalized value of 1 indicates expression at the 99th percentile relative to abundance-matched genes.

References: (1) Croft, Annu Rev Immunol. 2010;28:57-78; (2) Saghari, Clin Pharmacol Ther. 2022;111:1121-1132; (3) Rewerska, J Allergy Clin Immunol Glob. 2024;3:100195; (4) Sethi, J Allergy Clin Immunol. 2025 155(6):1993-2008; (5) Weidinger Immunotherapy. 2025 Aug;17(11):753-765; (6) ISDS 2025 abs#260; (7) Yamamura, Allergy. 2026 Mar. ; (8) Bang 2026 Allergol Int 2026 Jul;75(3):488-499; (9) Zhang Cell Rep. 2018 Jul 17;24(3):607-618; (10) Barbi 2014; (11) Kwiatek 2023; (12) Lee 2024, EBioMedicine; (13) Zhang 2010, Clin Immunol. 135:108-17. **Disclosures:** Jonatan Tuncel, Kurinji Pandiyan, and Kristin Yarema are employees of ImageneBio and may hold equity interests. No other relevant financial relationships to disclose.

