

Uncovering the Potential Immunometabolic Impact of Tirzepatide Added to Ixekizumab in Patients With Psoriasis and Obesity or Overweight: Biomarker Insights From TOGETHER-PsO

James G. Krueger¹, Josh Poorbaugh², Veavi Ching-Yun Chang², David C. Gemperline², Christoph Preuss², Quy A. Ngo², Ernst R. Dow², Paul Faya², Robert Benschop², Francisco Ramírez-Valle², Kimberly Siu², Cianna Leatherwood², Najwa Somani², Diamant Thaçi³, Kristina Callis Duffin⁴, April W. Armstrong⁵, Johann E. Gudjonsson⁶

¹Laboratory for Investigative Dermatology, The Rockefeller University, New York, USA; ²Eli Lilly and Company, Indianapolis, USA; ³Institute for Inflammation Medicine, University of Lübeck, Germany; ⁴University of Utah, Salt Lake City, USA; ⁵Department of Dermatology, Keck School of Medicine of USC, Los Angeles, USA; ⁶Department of Dermatology, University of Michigan, Ann Arbor, USA

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OBJECTIVE

To explore biological pathways associated with the enhanced clinical response observed following the addition of TZP, a dual GIP/GLP-1 receptor agonist, to IXE in patients with PsO and overweight or obesity.

- The observed clinical benefit provided an opportunity to explore shared immunometabolic mechanisms linking obesity and PsO.

SUMMARY OF RESULTS

IXE+TZP Produced Proteomic and Transcriptomic Responses Associated with Enhanced Clinical Response

- Expected inflammatory and metabolic protein changes suggested engagement of both IXE and TZP.
- Co-administration of IXE+TZP was associated with broader proteomic and transcriptomic responses than IXE alone.
- Neutrophil-associated pathways of the whole blood transcriptome were associated with enhanced PASI clinical responses through mediation analyses.

CONCLUSION

- Obesity and psoriatic disease are linked through shared immunometabolic biology.
- Concomitant administration of IXE and TZP was associated with broader serum proteomic and blood transcriptomic responses than IXE alone.
- Neutrophil-associated expression signatures emerged as candidate biological pathways associated with enhanced clinical response.
- These findings support the concept that adding TZP, a dual GIP/GLP-1 receptor agonist, to IL-17A inhibition may influence shared immunometabolic pathways relevant to psoriatic disease.

Background

Targeting Obesity Alongside IL-17A Inhibition May Improve Outcomes in Psoriasis: Insights From TOGETHER-PsO

- 60–78% of people with psoriasis (PsO) have comorbid obesity or overweight.¹
- These diseases are linked through shared immunometabolic inflammatory pathways.²
- Weight reduction and treatment of obesity have been associated with improvements in PsO.¹
- In TOGETHER-PsO (NCT06588283):
 - 40.6% of participants who received concomitant ixekizumab and tirzepatide (IXE+TZP) achieved PASI 100 at Week 36, versus 29.0% with IXE alone.¹
 - 27.1% of participants who received IXE+TZP achieved both PASI 100 and ≥10% weight reduction at Week 36, versus 5.8% with IXE alone.¹

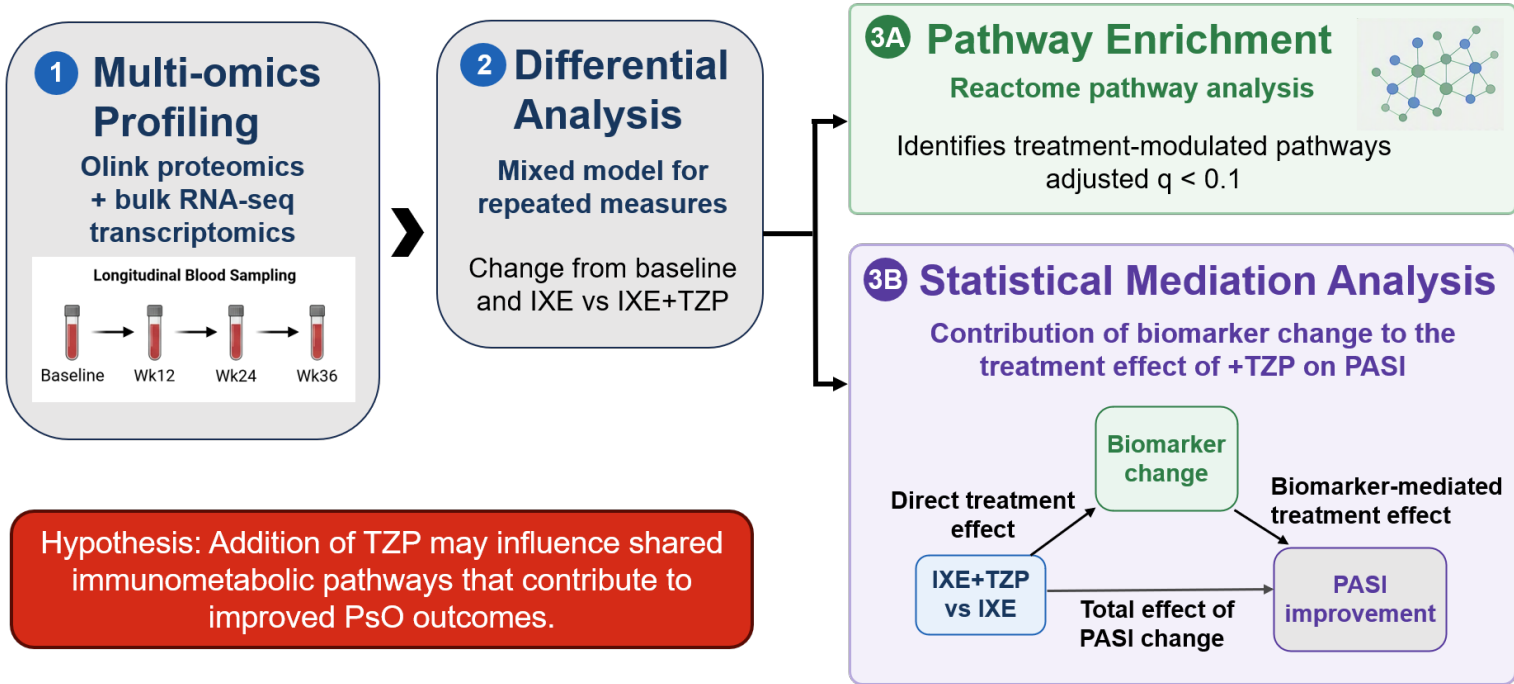
TOGETHER-PsO Enables Longitudinal Evaluation of Clinical and Biomarker Responses

- Adults with moderate-to-severe PsO and obesity (BMI ≥30 kg/m²) or overweight (BMI ≥27 to <30 kg/m² with ≥1 weight-related comorbidity*)
- Randomized 1:1 to IXE+TZP or IXE alone
- Individualized diet and exercise counseling in both treatment arms
- Primary endpoint at Week 36 (PASI 100 with ≥10% weight reduction)
- Biomarker sampling at baseline and Week (Wk) 12, 24, and 36
- Baseline biomarker comparisons between study population and healthy controls:
 - Age/sex-matched lean healthy controls
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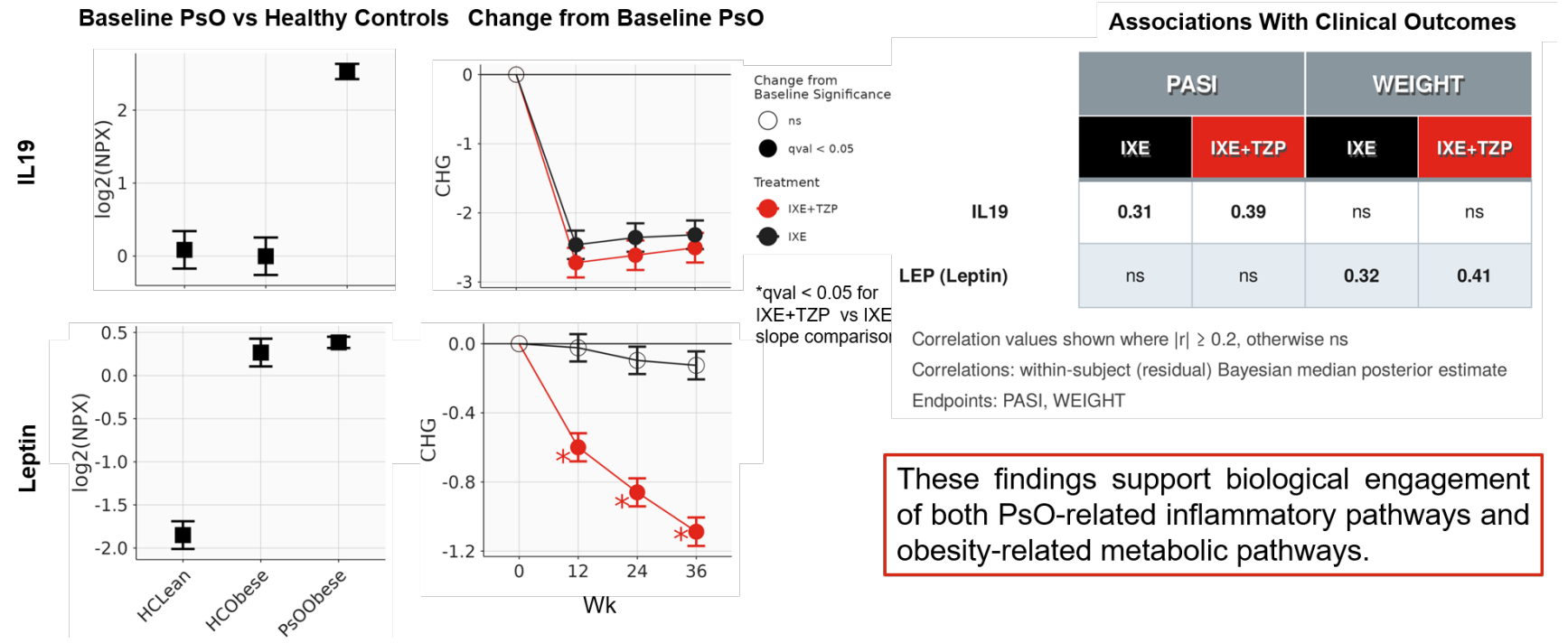
Methods

From Multi-omics Profiling to TZP Contribution to PASI Response



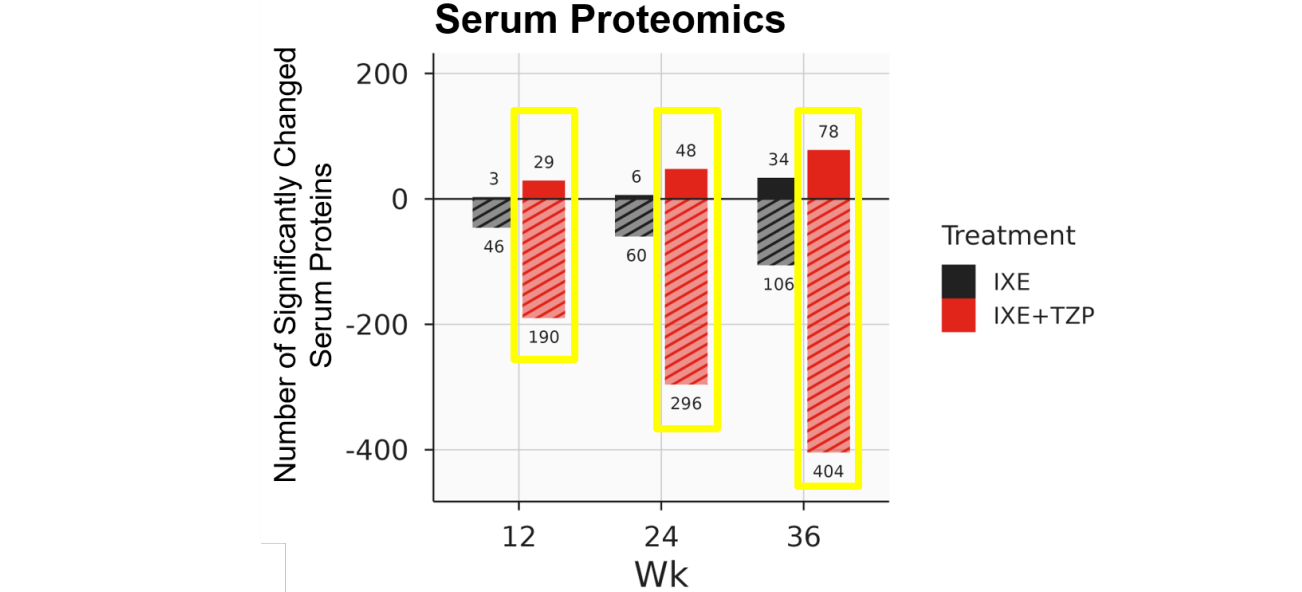
Results

Expected Inflammatory and Metabolic Biomarker Changes Indicate Activity of Both Treatment Components

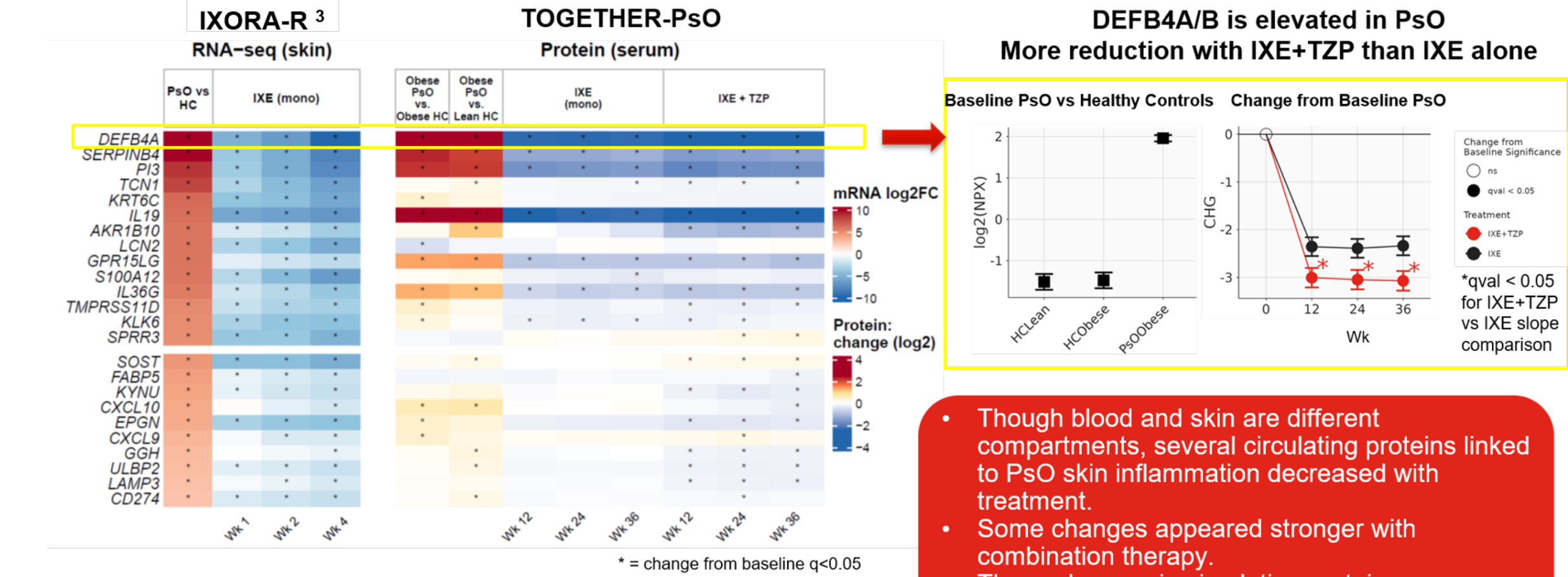


Results, continued

IXE+TZP Produced Earlier and Broader Serum Proteomic Changes Than IXE Alone

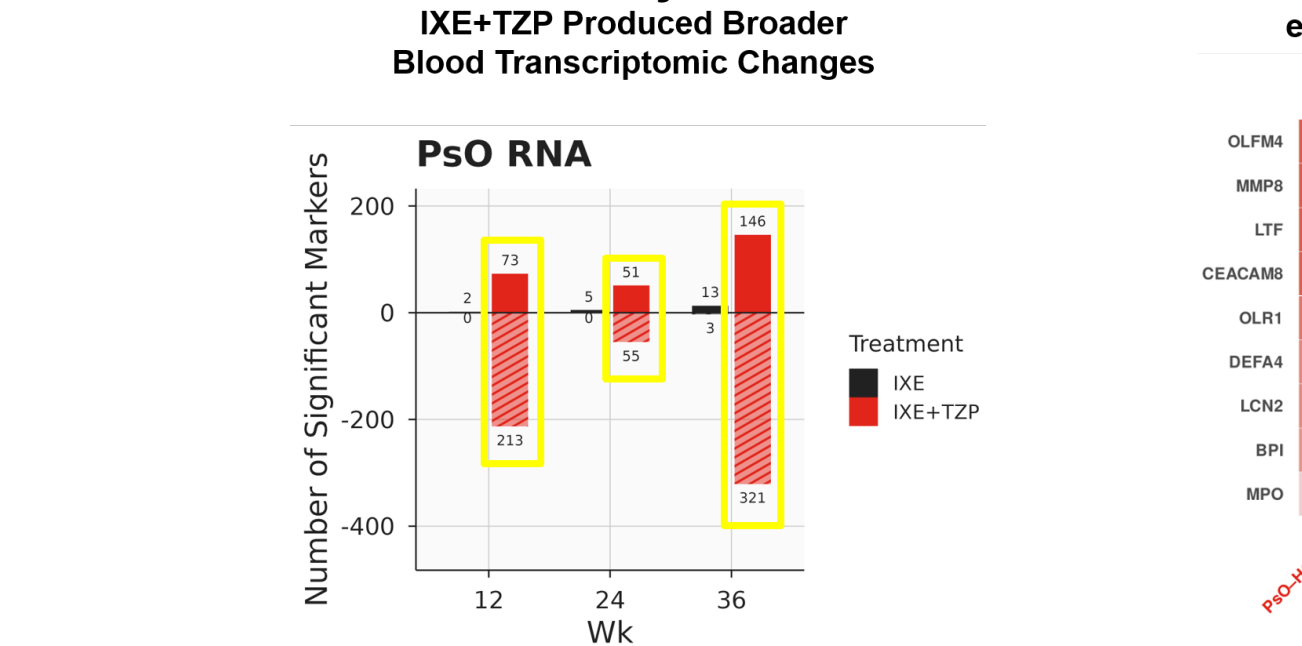


Circulating Proteins Linked to Lesional Psoriasis Biology Decline With Treatment

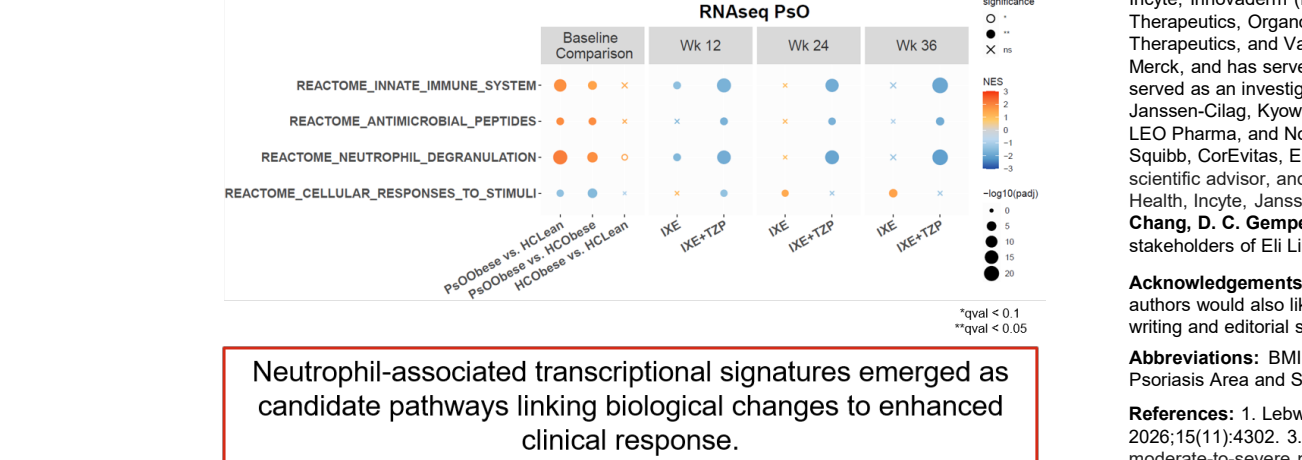


- Though blood and skin are different compartments, several circulating proteins linked to PsO skin inflammation decreased with treatment.
- Some changes appeared stronger with combination therapy.
- These changes in circulating proteins were consistent with improvement in PsO biology.

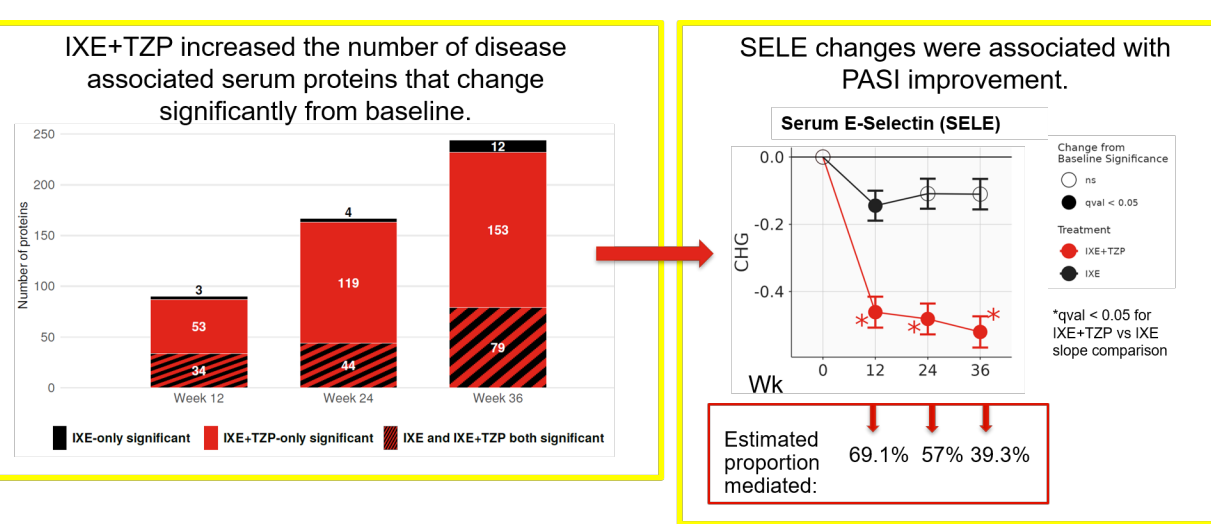
IXE+TZP Produced Broader Blood Transcriptomic Changes and Reduces Neutrophil-Associated Pathways



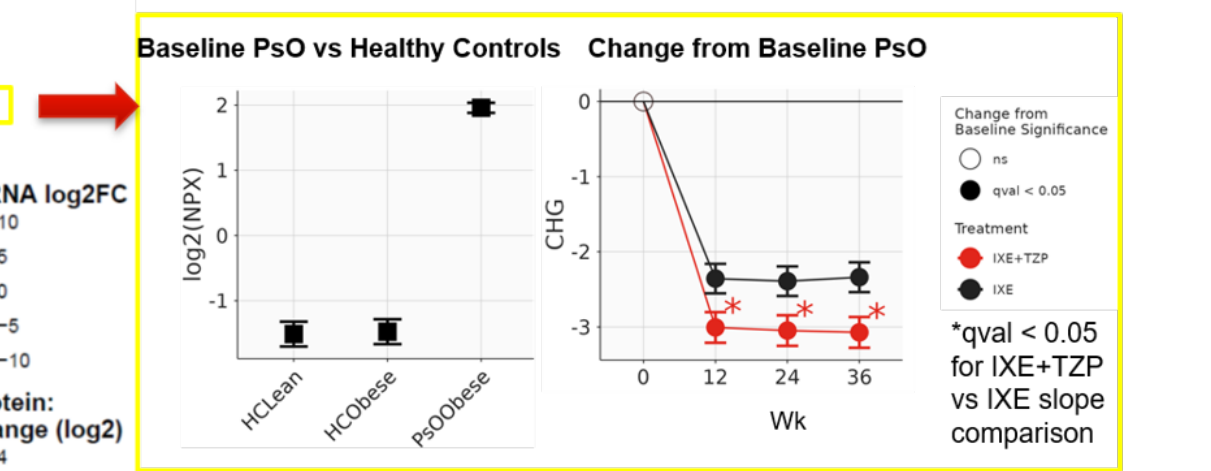
IXE+TZP Reduced Neutrophil-Associated Expression Signatures



IXE+TZP Modulated Additional Dysregulated Circulating Proteins in Serum Compared to IXE Alone

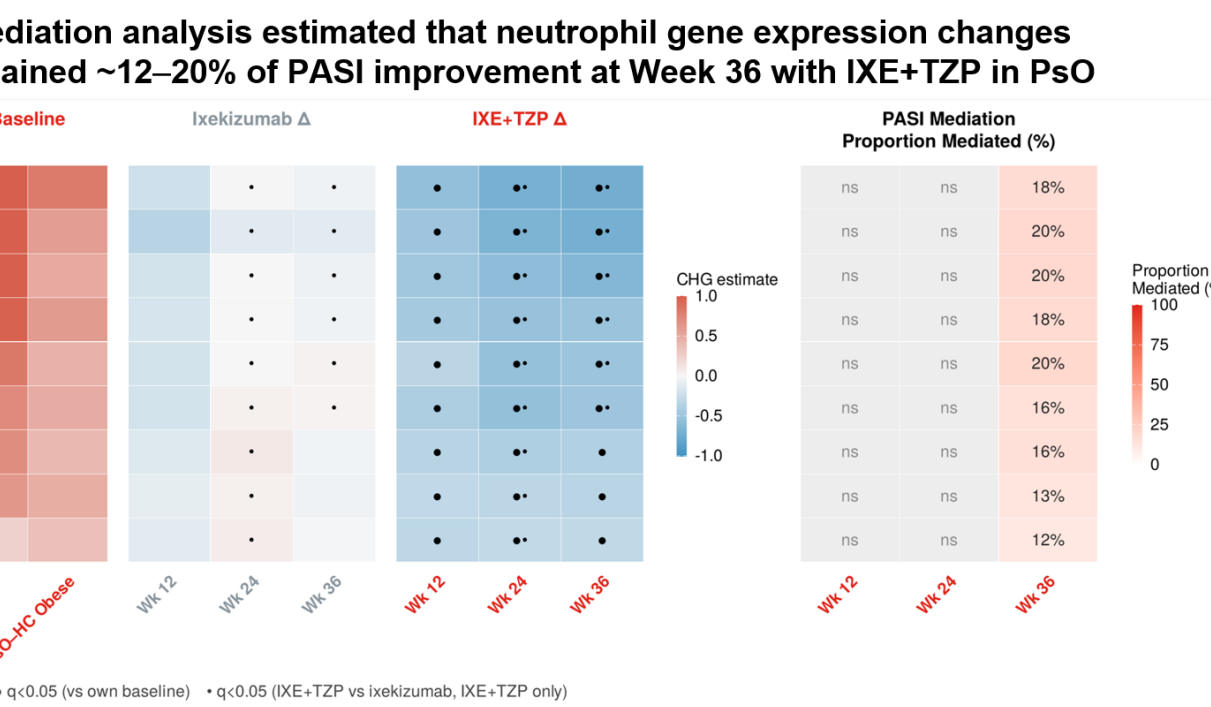


DEFB4A/B is elevated in PsO



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Neutrophil-Associated Expression Changes Were Estimated to Mediate Part of the Enhanced PASI Response



Disclosures: J. G. Krueger has received grant support (to The Rockefeller University) from: AbbVie, Amgen, Artax Biopharma, Avillion, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, ONO-Pharma, Ouka Therapeutics, Pfizer, Provetus, Regeneron, SUDO Bio, Takeda, UCB, Vitae, and Zoman. Consulting fees received from: AbbVie, Allergan, Almirall, Alumis, Amgen, Anstera, Artax Biopharma, Boehringer Ingelheim, Bristol Myers Squibb, Calildas, Cityll, CSL Behring, Eli Lilly and Company, Evmmune, Incyte, Inovavader (Indero), Janssen, Kymira Therapeutics, Kyowa Kirin, M22 Therapeutics, Merck, MoonLake Immunotherapeutics, Navigator Medicines, Novartis, Nuvig Therapeutics, Organon, Ortho Dermatologics, Ouka Therapeutics, Pfizer, Sanofi, Schrodinger, Sitlyx, Sun Pharma (SPARK), Takeda, Target-Derm, UCB, UNION Therapeutics, and Valeant. J. E. Gudjonsson has received research support from AbbVie, Almirall, Bristol Myers Squibb, Eli Lilly and Company, Johnson & Johnson, and Merck, and has served as an advisor to AbbVie, Almirall, Bristol Myers Squibb, Eli Lilly and Company, GSK, Incyte, Johnson & Johnson, Merck, and Sanofi. D. Thaçi has served as an investigator and/or consultant/advisor for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly and Company, Galderma, Janssen-Cilag, Kyowa Kirin, LEO Pharma, L'Oreal, New Bridge, Novartis, Pfizer, Regeneron, Samsung, Sanofi, Target RWE, and UCB, and has received grants from AbbVie, LEO Pharma, and Novartis. K. C. Duffin received research funds as salary or honoraria as a consultant from AbbVie, Alumis, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, CorEvitas, Eli Lilly and Company, Janssen, Novartis, Ouka Therapeutics, Pfizer, Takeda, and UCB. A. W. Armstrong has served as a research investigator, scientific advisor, and/or speaker for AbbVie, Almirall, Anoctis, Astan, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dermira, Eli Lilly and Company, EPI Health, Incyte, Janssen, LEO Pharma, Mendera Health, Nimbus, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB. J. Poorbaugh, V. C. Chang, D. C. Gemperline, C. Preuss, Q. A. Ngo, E. R. Dow, P. Faya, R. Benschop, F. Ramirez-Valle, K. Siu, C. Leatherwood, and N. Somani are employees and minor stakeholders of Eli Lilly and Company.

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Abbreviations: BMI, body mass index; HC, healthy control; IL, interleukin; ns, not significant; PASI, Psoriasis Area and Severity Index; RNA-seq, RNA sequencing; Wk, Week.

References: 1. Lebwohl M et al. JAMA Dermatol. 2026;162(7):709-19. 2. Almeida-Silva G et al. J Clin Med. 2026;15(11):4302. 3. Garrett et al. Comparative molecular analysis of IL-17A and IL-23 pathway inhibition in moderate-to-severe psoriasis: 4-week results from IXORA-R. J Invest Dermatol. 2026;146(3):669-77.e6.

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- **Purpose: To explore biological pathways associated with the enhanced clinical response observed following the addition of TZP, a dual GIP/GLP-1 receptor agonist, to IXE in patients with PsO and overweight or obesity.**
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Abbreviation: BMI, body mass index.

From Multi-omics Profiling to TZP Contribution to PASI Response

1

Multi-omics Profiling

Olink proteomics + bulk RNA-seq transcriptomics

Longitudinal Blood Sampling

BaselineWk12Wk24Wk36



2

Differential Analysis

Mixed model for repeated measures

Change from baseline and IXE vs IXE+TZP



3A

Pathway Enrichment

Reactome pathway analysis

Identifies treatment-modulated pathways adjusted $q < 0.1$

3B

Statistical Mediation Analysis

Contribution of biomarker change to the treatment effect of +TZP on PASI

Direct treatment effect

Biomarker change

Biomarker-mediated treatment effect

IXE+TZP vs IXE

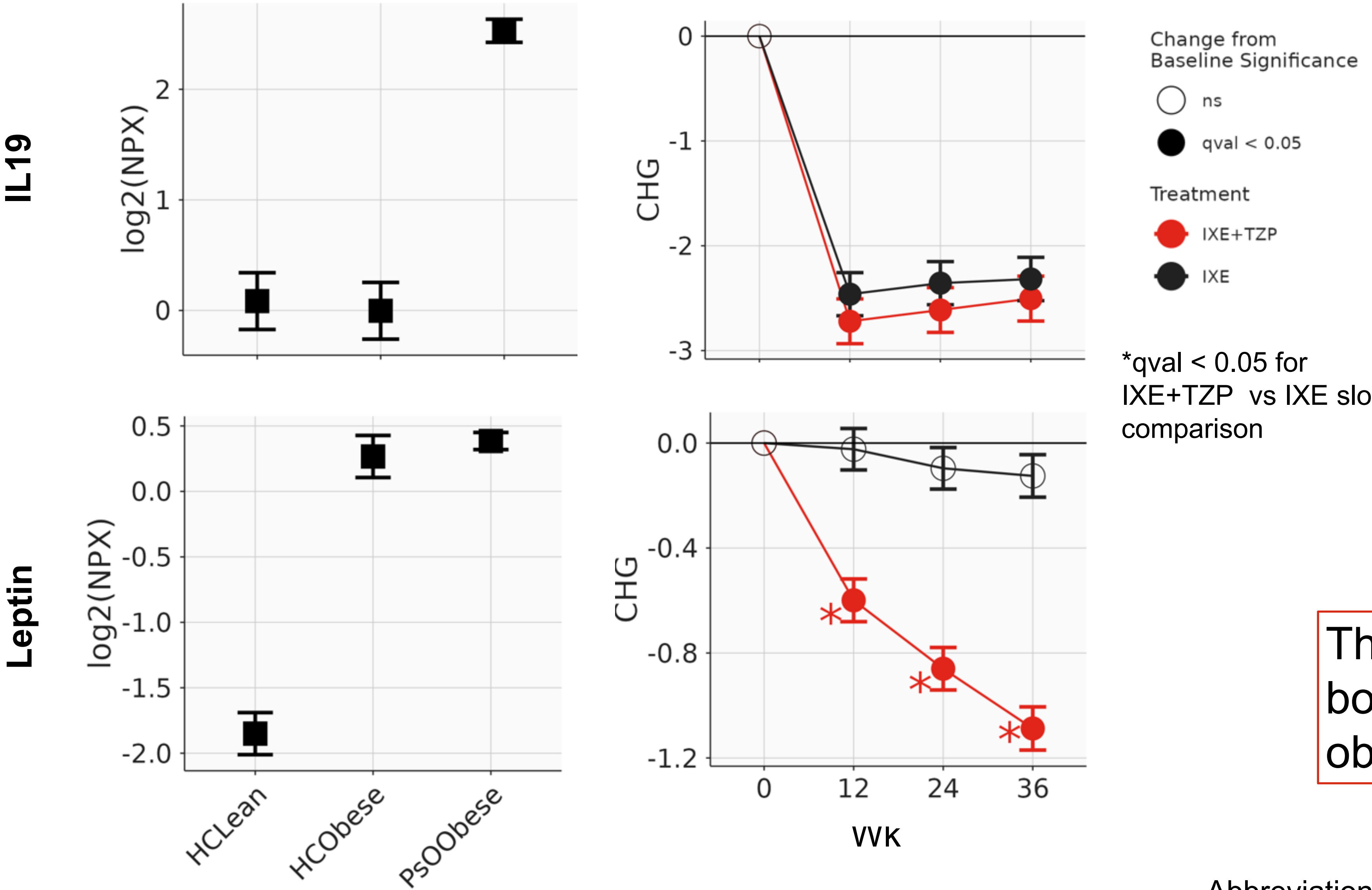
PASI improvement

Total effect of PASI change

Hypothesis: Addition of TZP may influence shared immunometabolic pathways that contribute to improved PsO outcomes.

Expected Inflammatory and Metabolic Biomarker Changes Indicate Activity of Both Treatment Components

Baseline PsO vs Healthy Controls Change from Baseline PsO



Associations With Clinical Outcomes

PASI		WEIGHT	
IXE	IXE+TZP	IXE	IXE+TZP
0.31	0.39	ns	ns
ns	ns	0.32	0.41

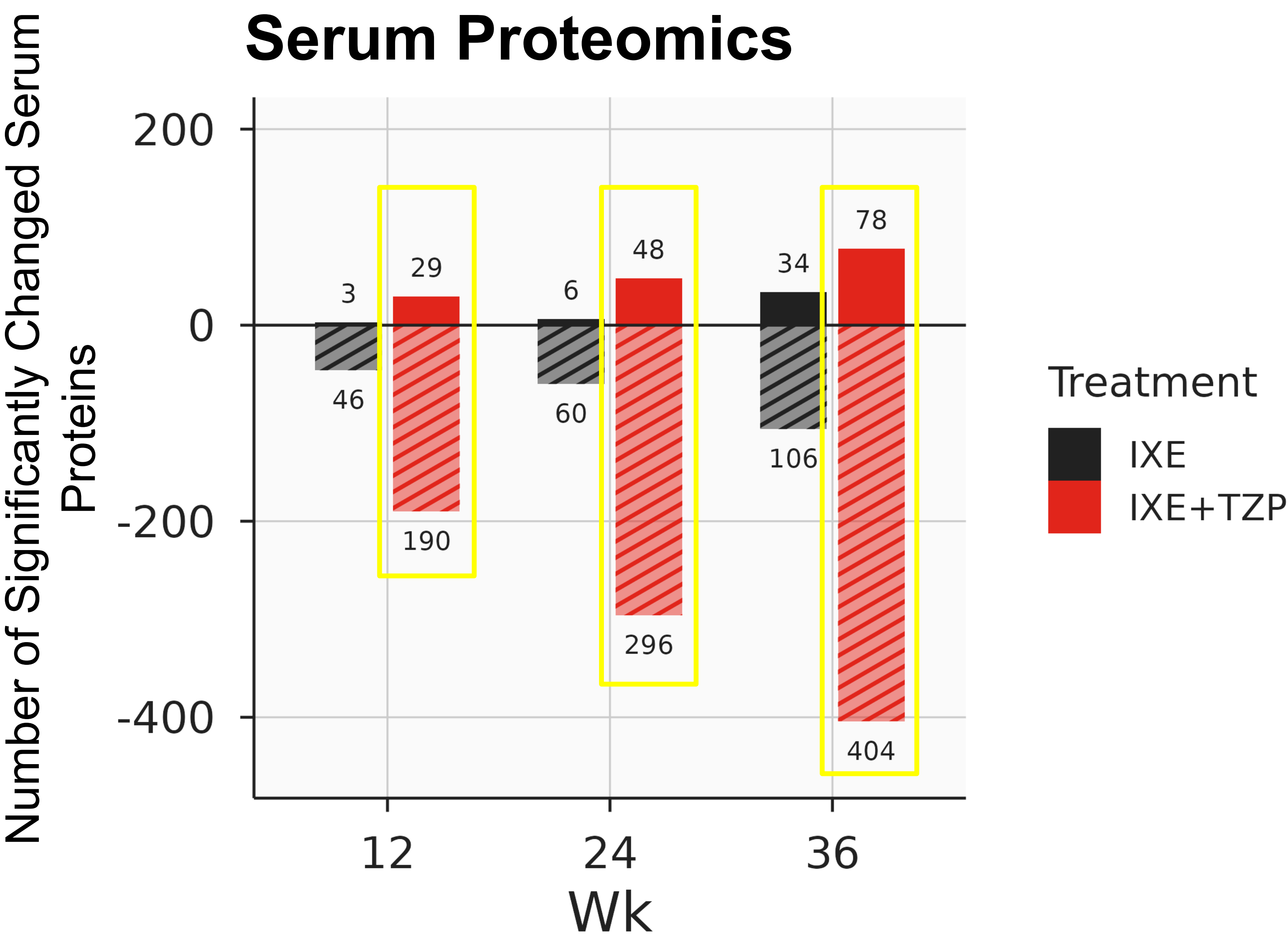
IL19

LEP (Leptin)

Correlation values shown where $|r| \geq 0.2$, otherwise ns
Correlations: within-subject (residual) Bayesian median posterior estimate
Endpoints: PASI, WEIGHT

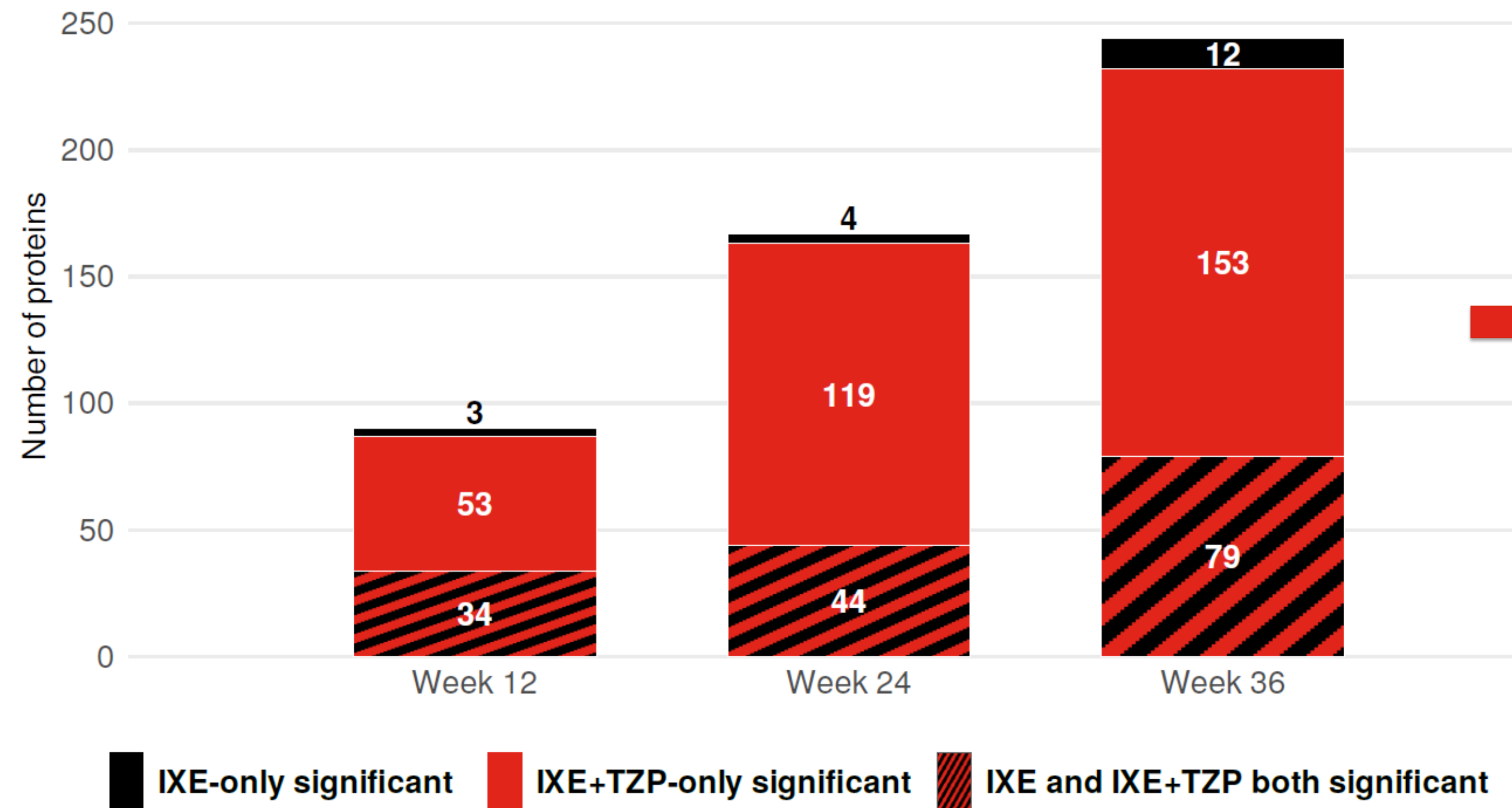
These findings support biological engagement of both PsO-related inflammatory pathways and obesity-related metabolic pathways.

IXE+TZP Produced Earlier and Broader Serum Proteomic Changes Than IXE Alone

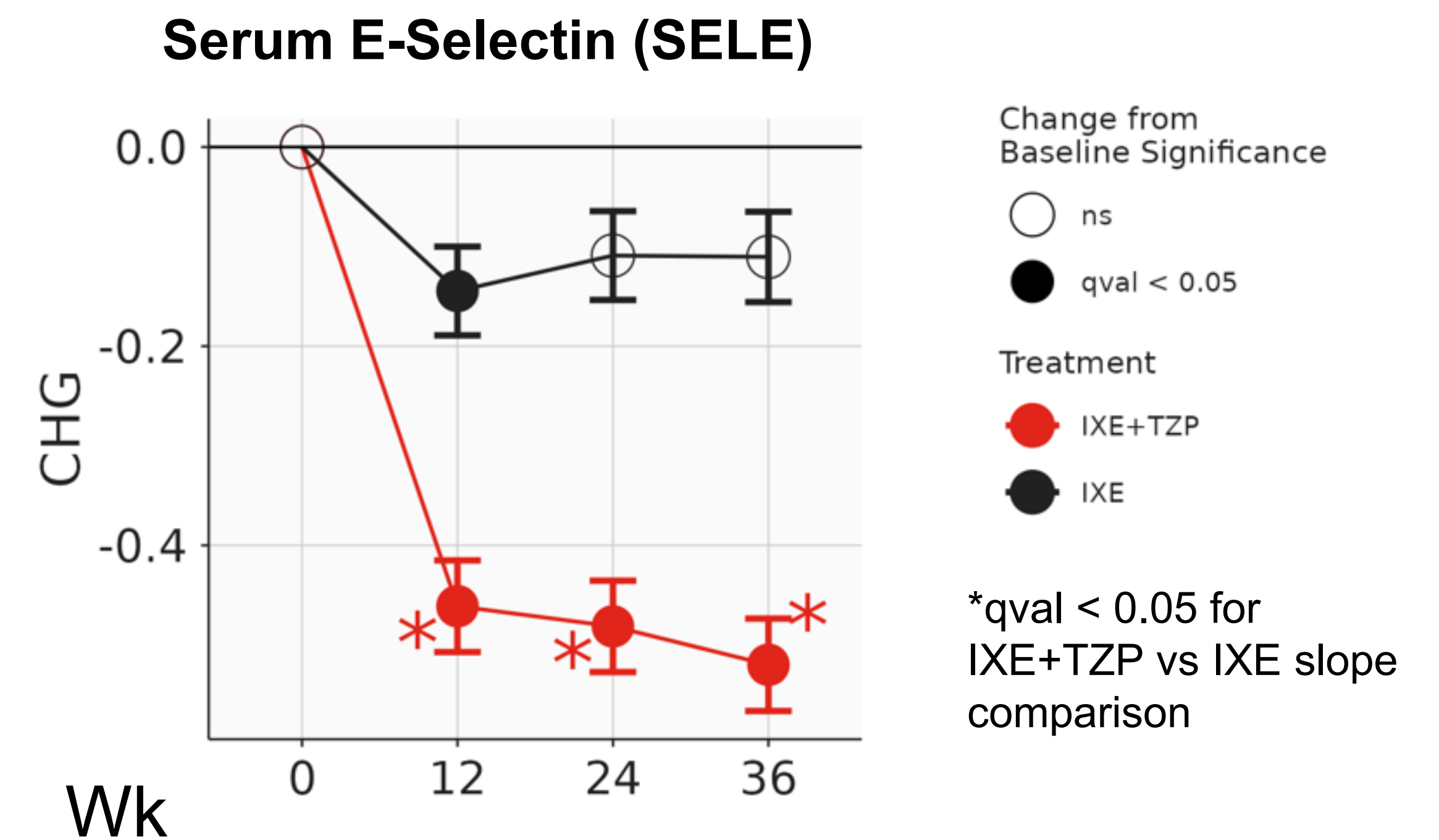


IXE+TZP Modulated Additional Dysregulated Circulating Proteins in Serum Compared to IXE Alone

IXE+TZP increased the number of disease associated serum proteins that change significantly from baseline.



SELE changes were associated with PASI improvement.



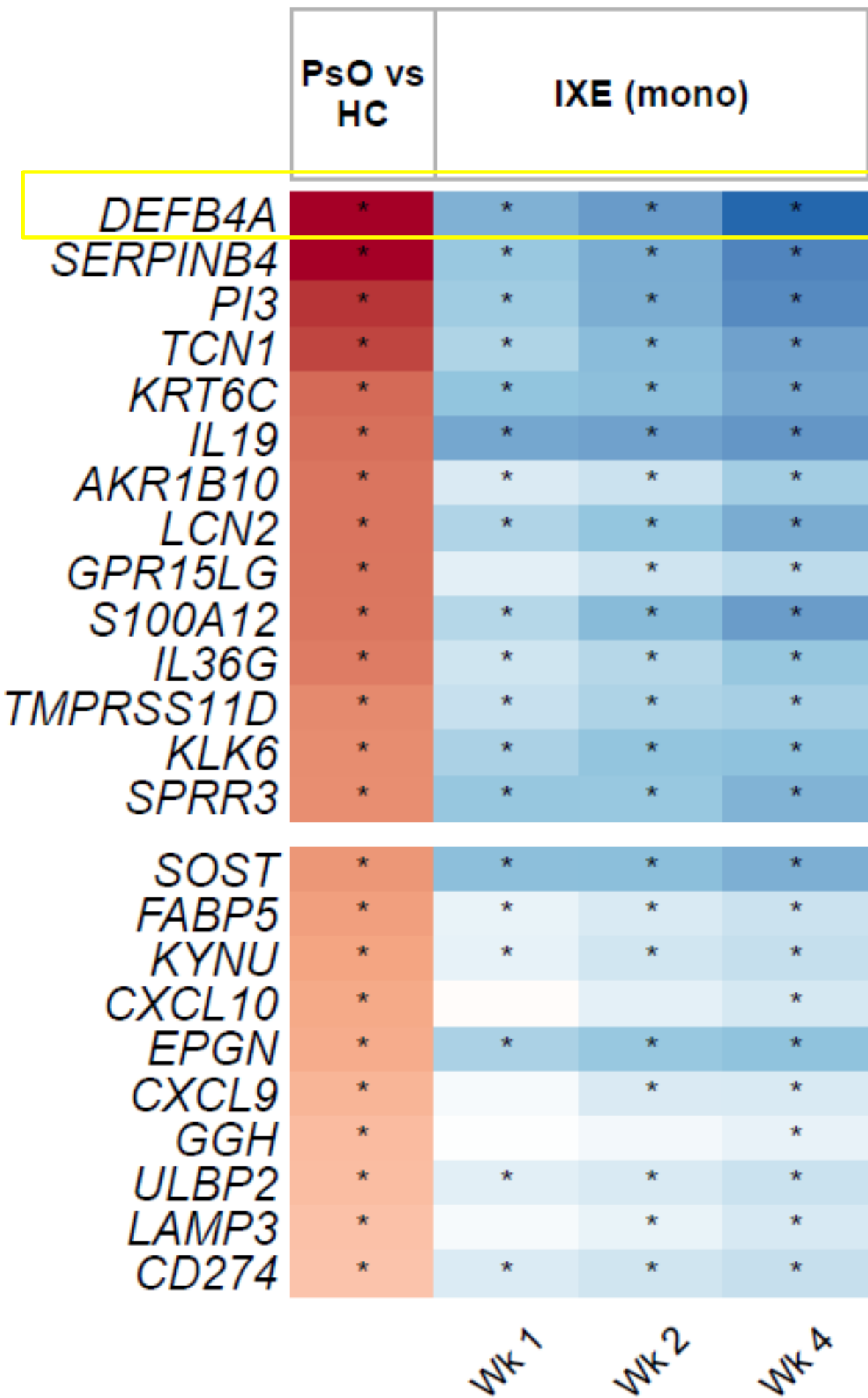
Estimated proportion mediated: 69.1% 57% 39.3%

Circulating Proteins Linked to Lesional Psoriasis Biology

Decline With Treatment

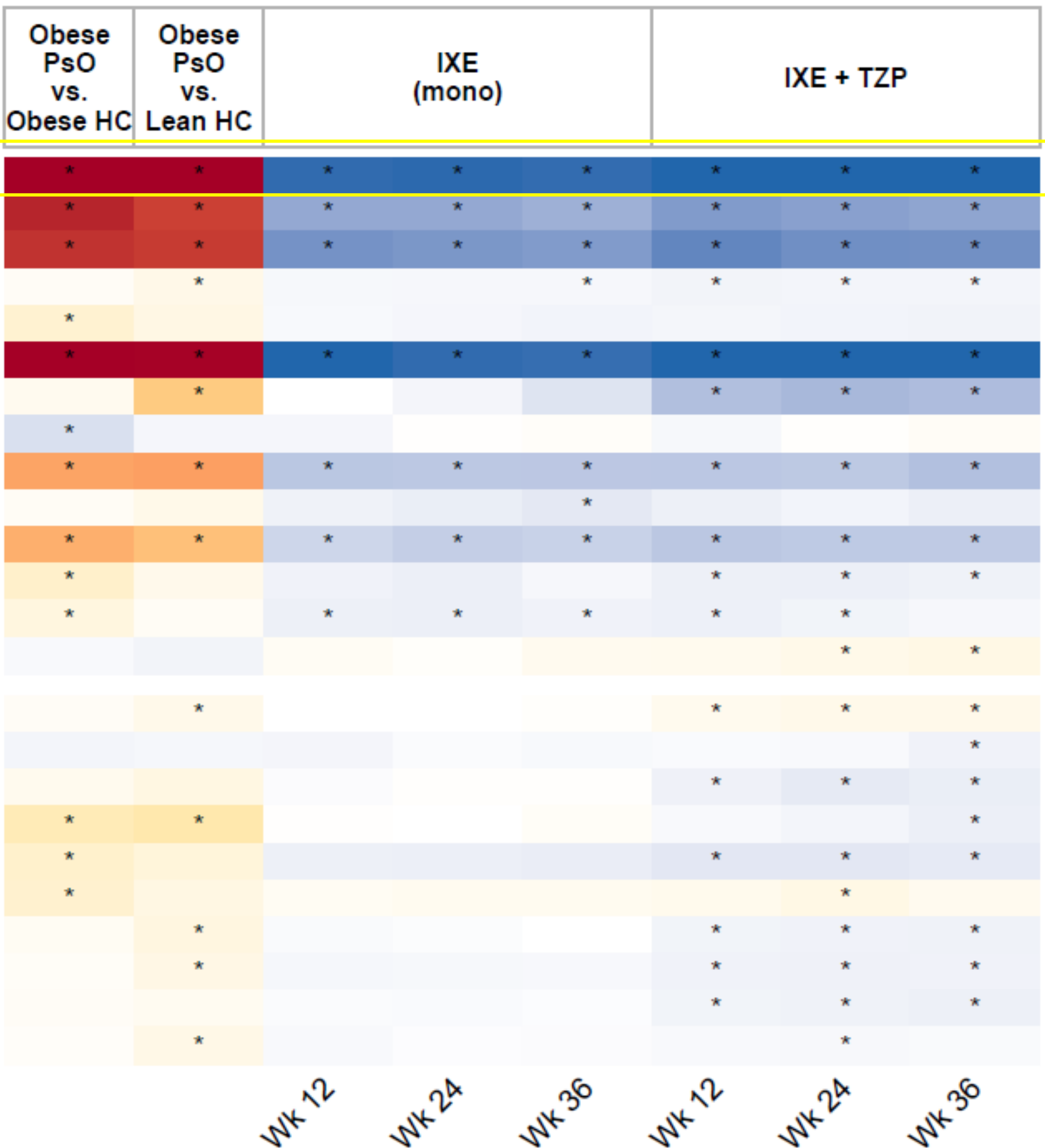
IXORA-R¹

RNA-seq (skin)



TOGETHER-PsO

Protein (serum)



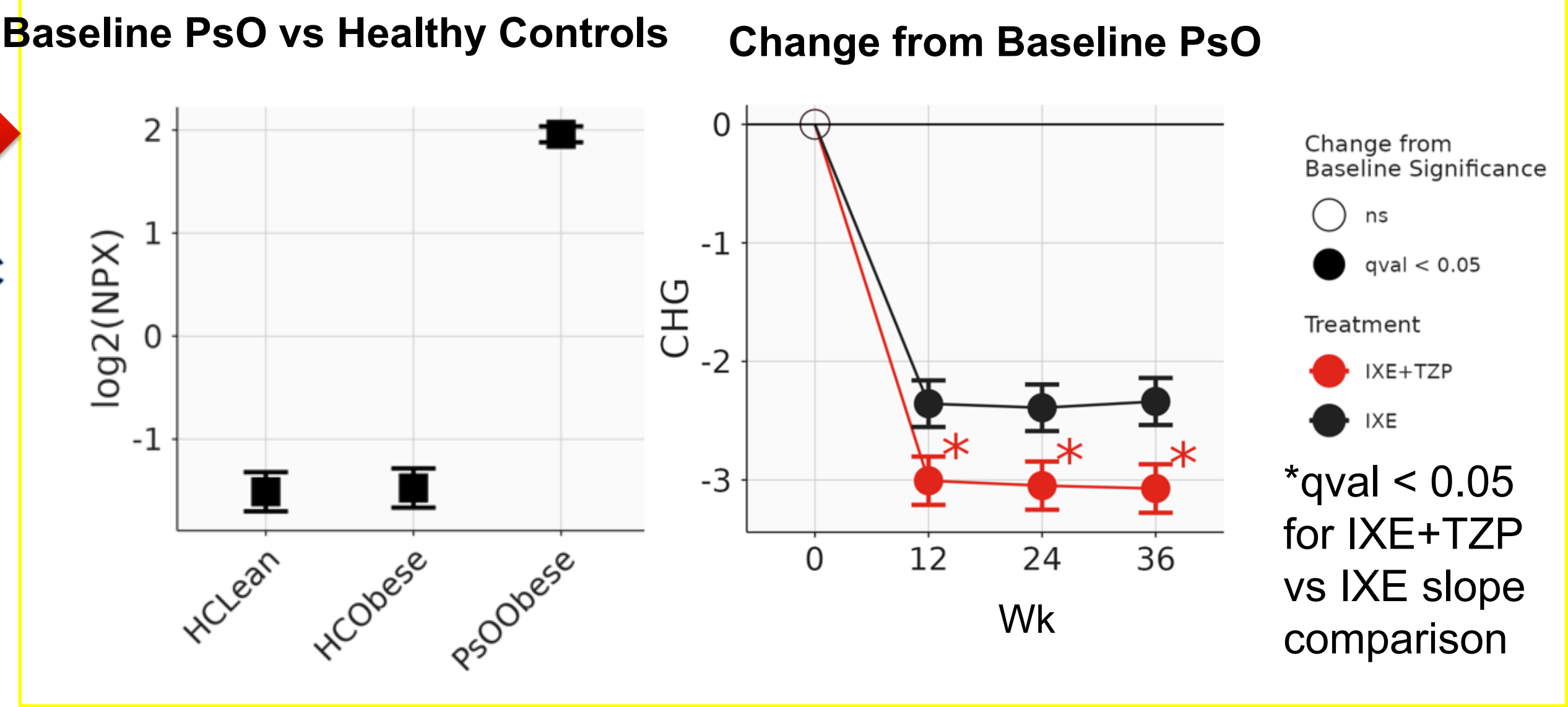
mRNA log2FC

Protein: change (log2)

* = change from baseline q<0.05

DEFB4A/B is elevated in PsO

More reduction with IXE+TZP than IXE alone

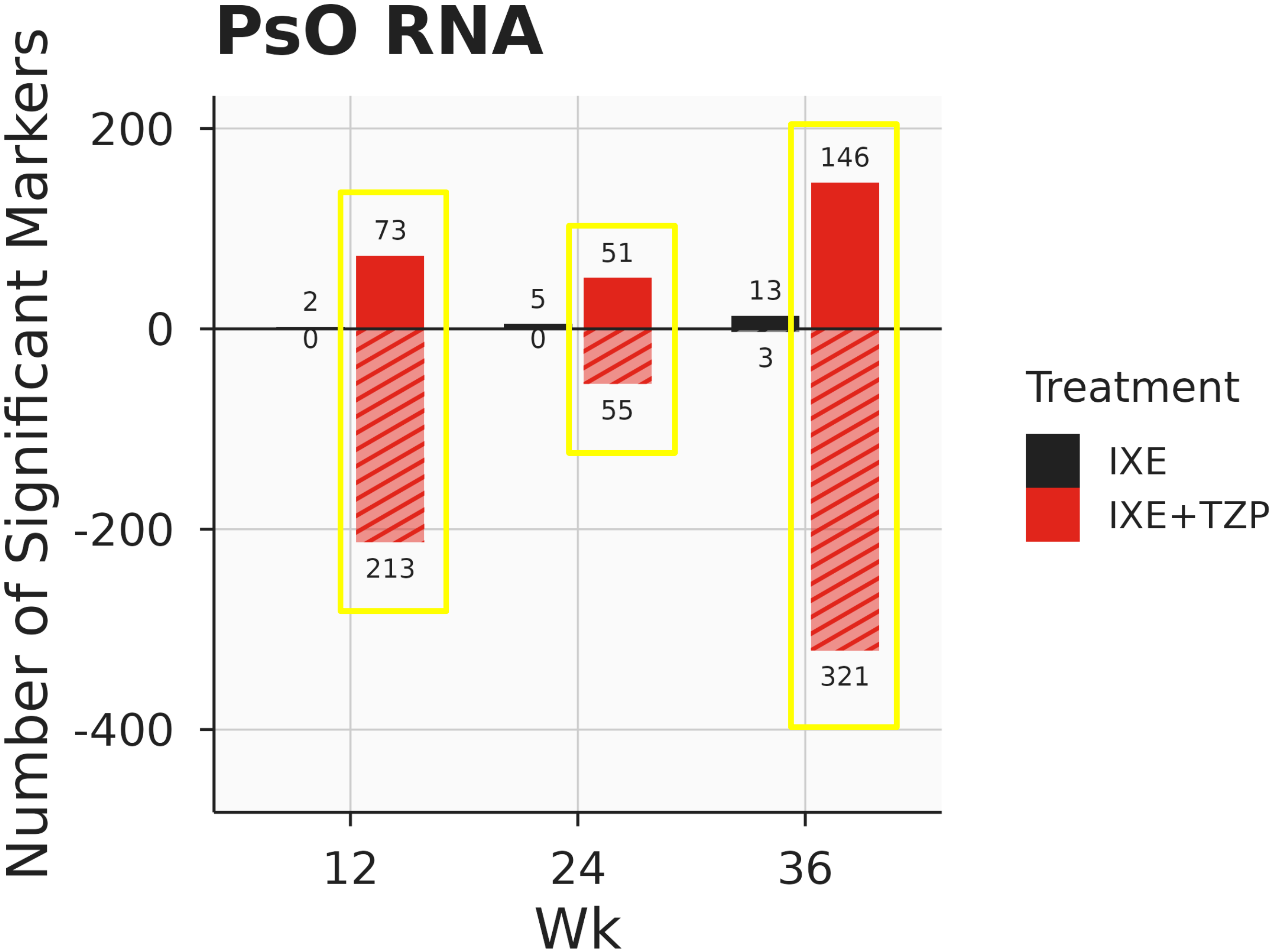


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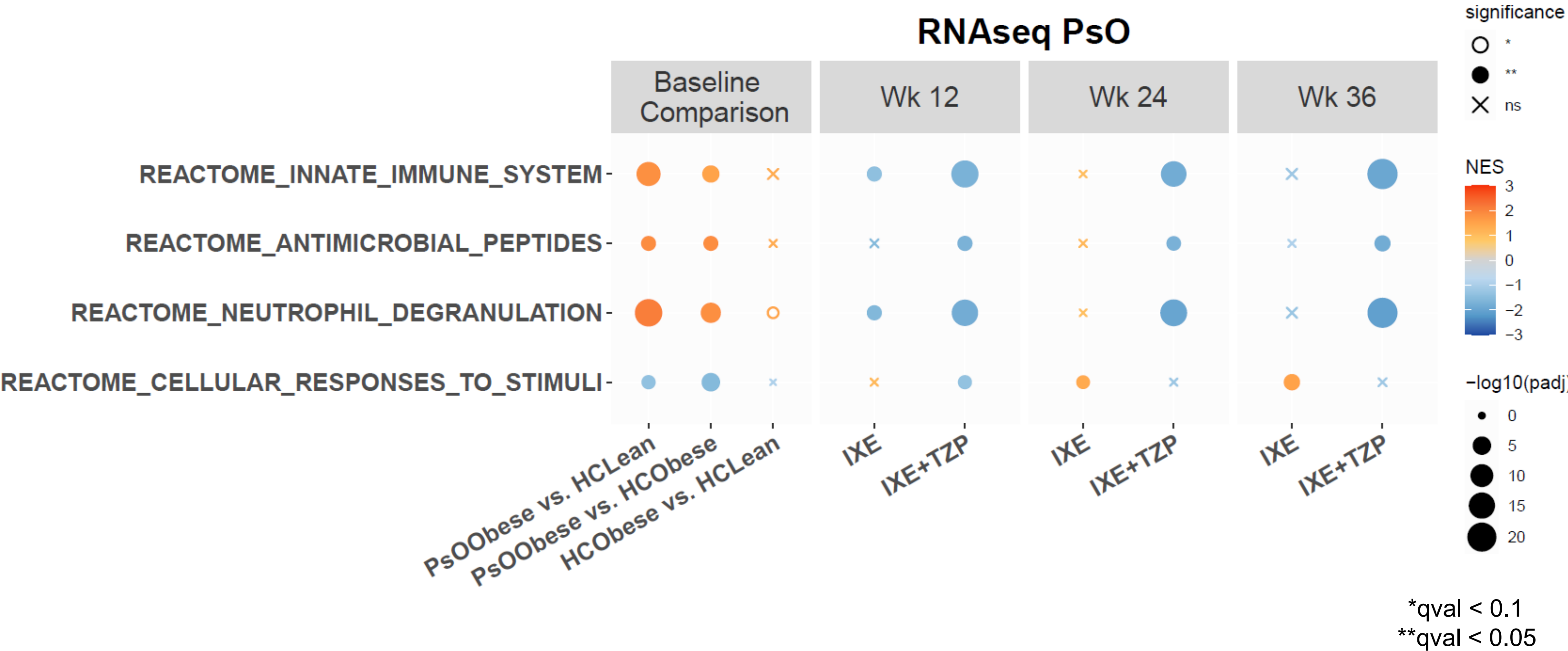
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IXE+TZP Produced Broader Blood Transcriptomic Changes



IXE+TZP Reduced Neutrophil-Associated Expression Signatures



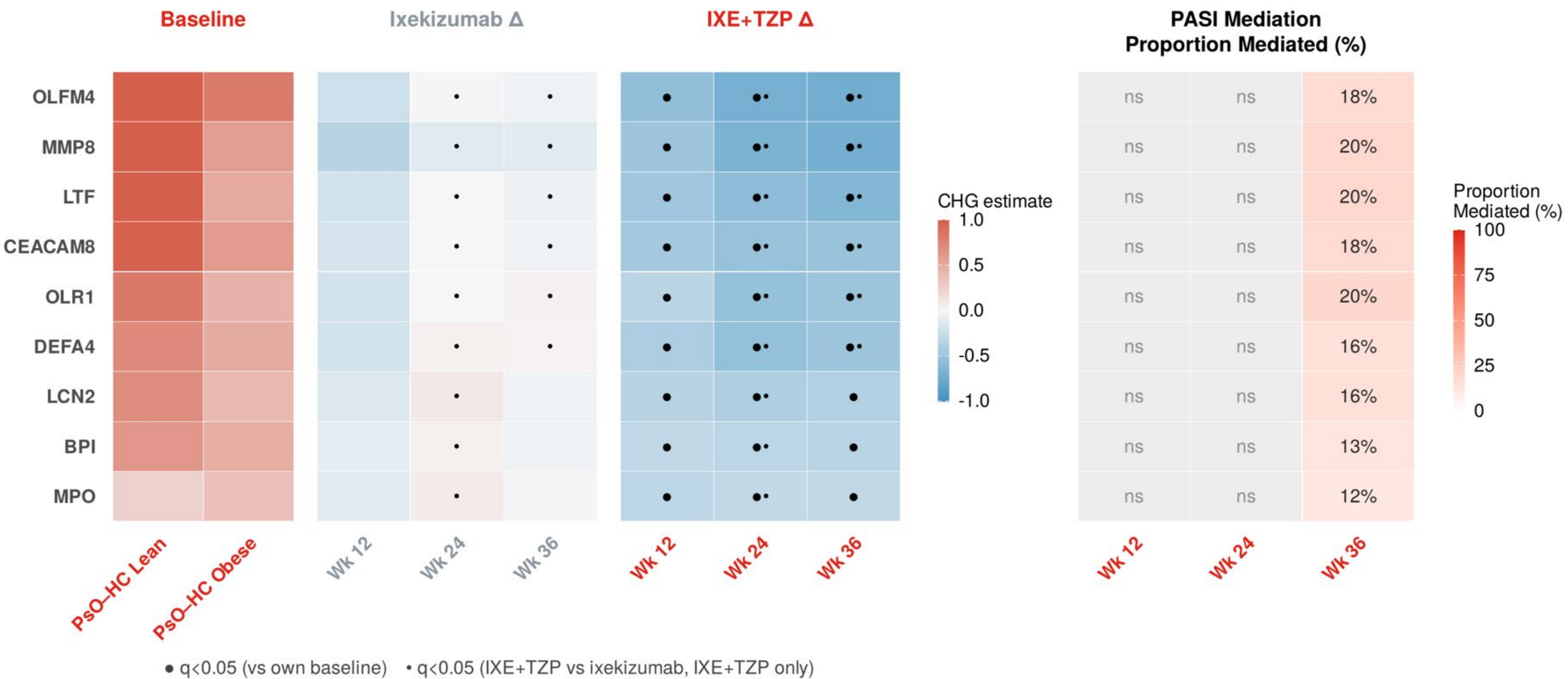
Neutrophil-associated transcriptional signatures emerged as candidate pathways linking biological changes to enhanced clinical response.

Abbreviations: HC, healthy control; NES, normalised enrichment score; ns, not significant.

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Neutrophil-Associated Expression Changes Were Estimated to Mediate Part of the Enhanced PASI Response

Mediation analysis estimated that neutrophil gene expression changes explained ~12–20% of PASI improvement at Week 36 with IXE+TZP in PsO



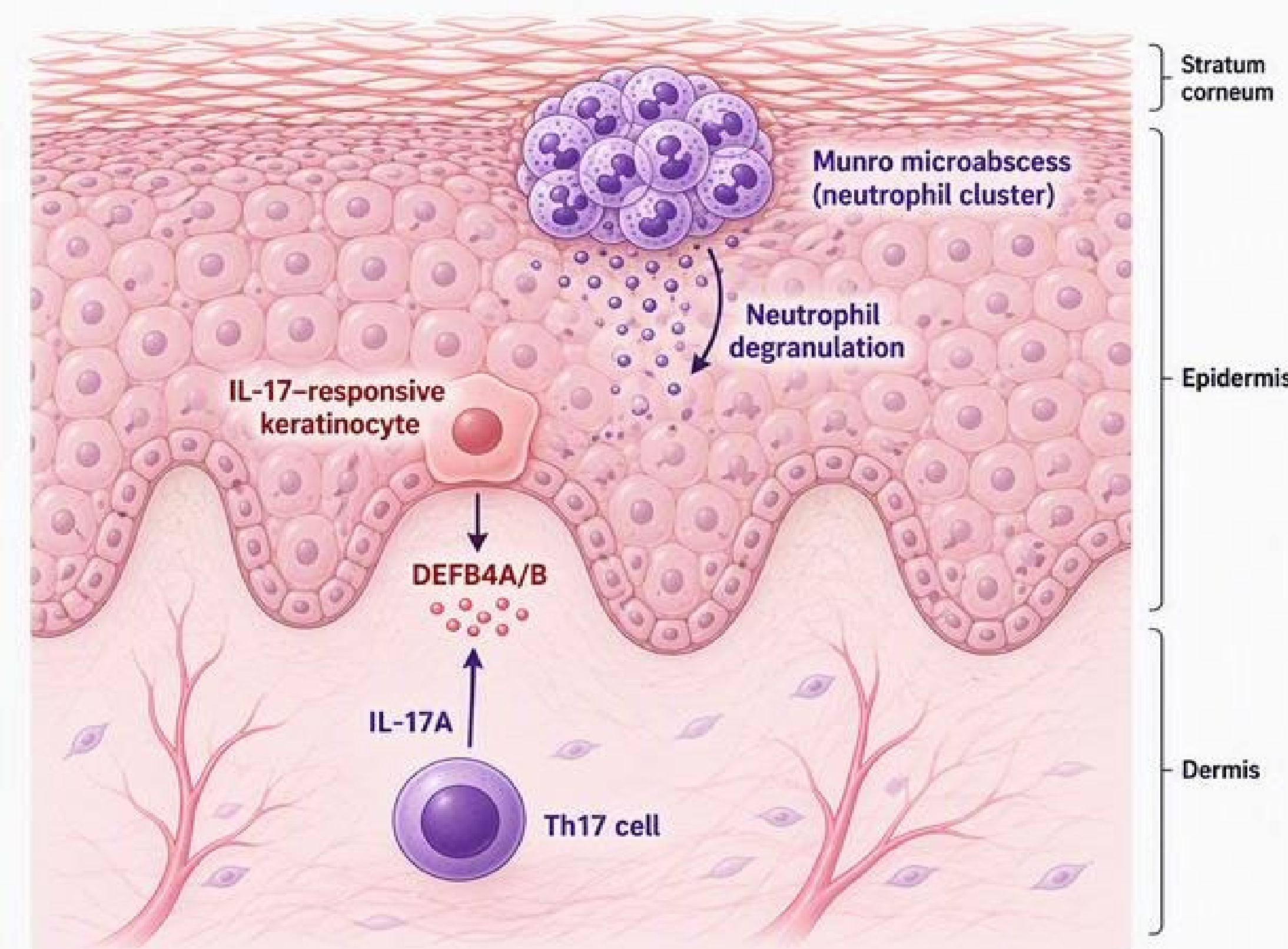
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IXE+TZP Broadened Biomarker Responses in Psoriasis

- Obesity and psoriatic disease are linked through shared immunometabolic biology.
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- Neutrophil-associated expression signatures emerged as candidate biological pathways associated with enhanced clinical response.
- These findings support the concept that adding TZP, a dual GIP/GLP-1 receptor agonist, to IL-17A inhibition may influence shared immunometabolic pathways relevant to psoriatic disease.

Psoriasis is a chronic inflammatory skin disease driven by interactions between keratinocytes and innate and adaptive immune cells.



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DISCLOSURES

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