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Innovation Through Single-Cell Transcriptomics: New Pathways for Tackling Skin Inflammation and Aging

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1. Introduction

Inflammation is a central driver of many skin concerns, from age-related changes **[1]** to complex conditions like Psoriasis **[2].** Skin immune diseases are chronic inflammatory conditions that disrupt normal skin function, leading to lesions, discomfort, and a significant reduction in quality of life **[3].** Both aging and Psoriasis are linked to overlapping inflammatory pathways **[4]**, underscoring the need for innovative strategies to enhance skin health and longevity. Current treatments primarily focus on masking symptoms rather than addressing root causes , highlighting the need for more effective solutions .

Addressing these challenges in cosmetology requires a comprehensive understanding of the cellular and molecular mechanisms underlying skin inflammation **[5].** Advances in skin care offer the potential to improve efficacy by selectively acting on specific cell types or biological pathways involved in skin imbalance. Combining active ingredients that target multiple pathways could help restore skin health and resilience, presenting new opportunities for innovation in product development and ingredient repurposing.

Recent advances in omics technologies enables cell type-specific target prediction, facilitating the identification of active compounds that modulate dysregulated pathways in a more precise manner. Single-cell transcriptomics provides researchers with the opportunity to analyze gene activity and cellular composition at an unprecedented resolution **[6]** , paving the way for groundbreaking discoveries in complex biological systems like skin. In fact, the skin is a complex organ made up of many different cell types, including specialized cells like keratinocytes and melanocytes, as well as a variety of immune cells **[7].** This diversity makes single-cell technologies especially useful for understanding the functions of each cell type and designing cell-type-specific therapies, including combinatorial, tailored to the unique cellular landscape of interest. Leveraging this technology, DeepLife has developed a platform to construct a comprehensive single-cell transcriptomic atlas of the skin. This atlas aims to identify innovative solutions for skin rejuvenation and inflammation management by repurposing existing bioactive compounds.

2. Materials and Methods

2.1 Data foundation and atlas construction

The objective of the drug repurposing framework is to identify compounds that potentially modulate disease-related pathways in the context of a specific disorder, such as psoriasis or aging. The first step to construct high-resolution cell atlases that capture the complexity and diversity of skin is a robust data foundation. The data foundation was established by curating relevant datasets from an internal catalog, applying stringent inclusion criteria to ensure biological relevance and minimize technical variability for reliable integration (**Table 1**).

Table 1. Criteria for dataset selection.

Filtering criteria	***Accepted values***
Tissue type	*Primary skin tissue (excluding organoids, cell lines, or in vitro cultures)*
Disease context	*Healthy, autoimmune or inflammatory skin conditions*
Species	*Human*
Library preparation technology	*10x Genomics*
Sample processing	*Unsorted (excluding Smart-seq and Visium technologies)*
Modality	*scRNA-seq gene expression (GEX)*

These criteria were designed to mitigate batch effects arising from divergent experimental and technical protocols. Each sample in the selected datasets is annotated with controlled vocabulary, encompassing over 50 metadata fields such as patient demographics, disease state, tissue origin, and technical parameters. All sample annotations are first generated with an automated computational pipeline and then undergo expert validation to ensure high data quality and reliability for analyses.

The datasets are then processed using an internal proprietary single-cell RNA-seq pipeline, which aligns raw sequencing reads to a standardized reference transcriptome, conducts rigorous quality control, and applies foundation model-based cell type annotation to harmonize cell identity labels across datasets. To construct the scRNA-seq skin atlas, datasets are integrated in a manner that reduces confounding effects arising from variations in experimental design, sequencing platforms, and library preparation methods. An accurate integration ensures that biological differences, such as those related to disease, are not confounded by batch effects or dataset-specific artifacts. A combination of state-of-the-art integration techniques is employed, to allow for consistent cell type classification and comparison across samples, conditions, and tissues. Integration performance is evaluated using the scIB benchmarking **[8]** framework to identify the optimal method that preserves biological signal while minimizing batch effects. The initial atlas is filtered based on quality parameters such as : counts and features per cell, removing low expressed genes, percent of mitochondrial reads (sign of apoptosis), presence of technical batch effects. Additionally the atlas is manually curated to refine and harmonize parameters like metadata labels (tissues, diseases, treatments, etc.) and cell type annotation, keeping specific cell classes relevant for skin and skin conditions.

2.2 Causal pathway and drug identification

To identify promising active ingredients for skin-related applications, we employed a proprietary computational workflow that utilizes gene expression profiles derived from carefully selected skin cell models. Skin condition–associated genes are identified as differentially expressed genes between disease and healthy skin cell populations in the atlas. A proprietary causal inference framework is then applied to the differentially expressed genes in a cell type-specific manner to identify transcription factors and upstream regulators driving

skin condition–related changes. This approach leverages cell type-specific gene regulatory networks, cell type specific proprietary interactomes, and a network propagation algorithm to select regulators most likely to influence skin perturbations within each cellular context.

A network-based approach is then used to prioritize active compounds by evaluating the network proximity between their known targets and skin condition–associated genes within cell type-specific interactomes. Compounds are then ranked after a normalized score that enables comparison across cell types. The predictive performance of the approach is benchmarked using a reference set of approved and failed compounds for skin immune disease. Discriminatory power is quantified by using the Area Under the Receiver Operating Characteristic Curve (ROC AUC) , a method to rate the performance of a classifier, based on a trade off between sensitivity and specificity parameters **[9]**. In the case of drug repurposing, it evaluates the ability to differentiate effective compounds from ineffective ones. The analysis also highlights the specific cell types that confer the highest predictive accuracy for efficacy. Using the most predictive cell types, the trained skin model is applied to evaluate compounds that have not previously been tested in the context of skin diseases. Top-ranked candidates are prioritized based on their predicted capacity to modulate key disease-driving pathways.

3. Results

The atlas integrates data from 5 independent datasets **[10-14]**, encompassing 133 samples collected from 89 distinct donors (**Table 2**). After integration and quality control, 230,000 high quality cells were retained and classified into 26 distinct cell classes, in which related subtypes were grouped together to facilitate the understanding of the cellular landscape.

Table 2. Summary of Atlas Composition and Dataset Characteristics

Atlas characteristics	
Number of datasets	***5***
Number of samples	***133***
Number of donors	***89***
Number of high quality cells	***230000***
Number of cell classes	***26***
Number of conditions/diseases	***4***
Number of tissues	***4***

The skin atlas comprises 26 distinct cell classes grouped into five major categories: immune cells, epithelial and support cells, mesenchymal cells, muscle cells, and specialized cells such as specific subtypes of keratinocytes (**Figure 1. d,e**). Immune cells include various T cell subsets like CD4+ and CD8+ αβ T cells **(Figure 1. b,c**), B cells, macrophages, monocytes, and dendritic cells, reflecting the complex immune landscape of the skin.

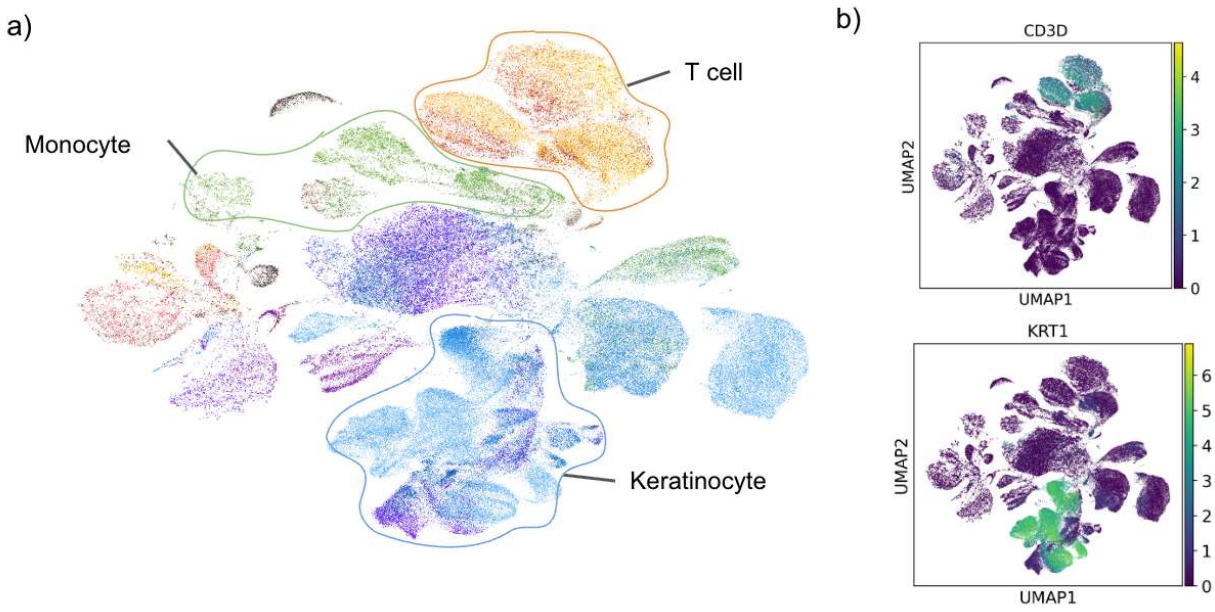

Figure 1. *Representation of the human skin atlas and specific cell-type populations. a) Uniform manifold approximation and projection (UMAP) plot depicting the full integrated human skin atlas. Each point is a cell, the color palette depicting different cell classes. b) Average expression of known cell type markers projected on the UMAP plot. Yellow indicates maximum gene expression, while dark blue indicates low expression of the gene in log-normalized UMI counts. The following cell-types are identified with marker CD3D : T cell, with marker KRT1 : Keratinocyte (spinous).*

The samples originate from 4 different skin tissue types, enabling to distinguish how disease affects the different layers of the skin, or between exposed and non exposed skin. From the datasets, 4 disease or condition states (**Figure 2**) were identified, psoriasis, atopic dermatitis, hidradenitis suppurativa and healthy controls, providing a comprehensive overview of cellular heterogeneity across healthy and diseased skin.

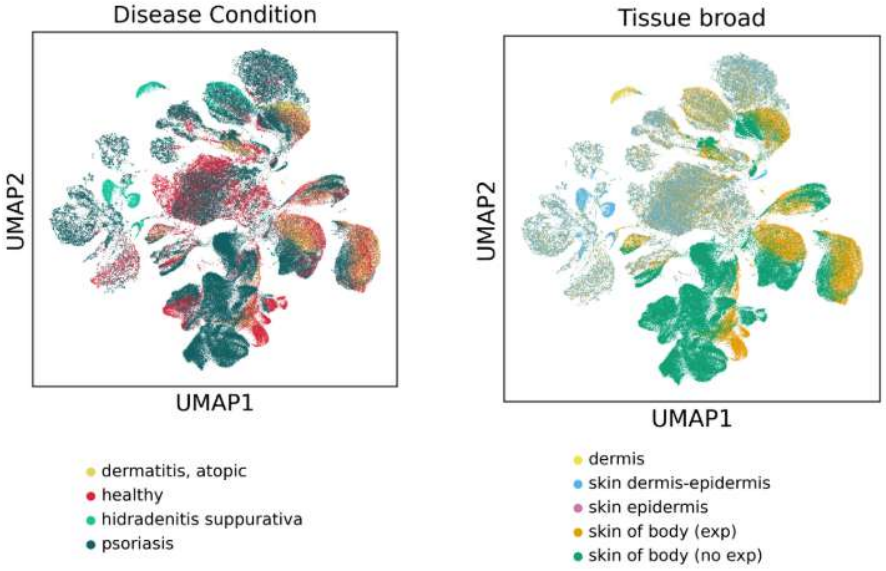

Figure 2. *UMAP representation of the skin atlas per tissue et per disease.*

Following the construction of the atlas and the subsequent identification and curation of distinct cell classes, cell class–specific interactomes were generated. These interactomes capture the gene and protein interaction networks unique to each cell class, enabling the identification of disease-associated pathway alterations in a cell type–specific manner (Figure 3). The interactomes reveal distinct clusters in which genes and proteins with related biological functions are grouped together. Notably, one such cluster is associated with cytokine and interferon signaling modulation, where TNF (Tumor Necrosis Factor) emerges as an important node. TNF is a pro-inflammatory cytokine known to play a pivotal role in the pathogenesis of inflammatory diseases, including psoriasis **[15]**.

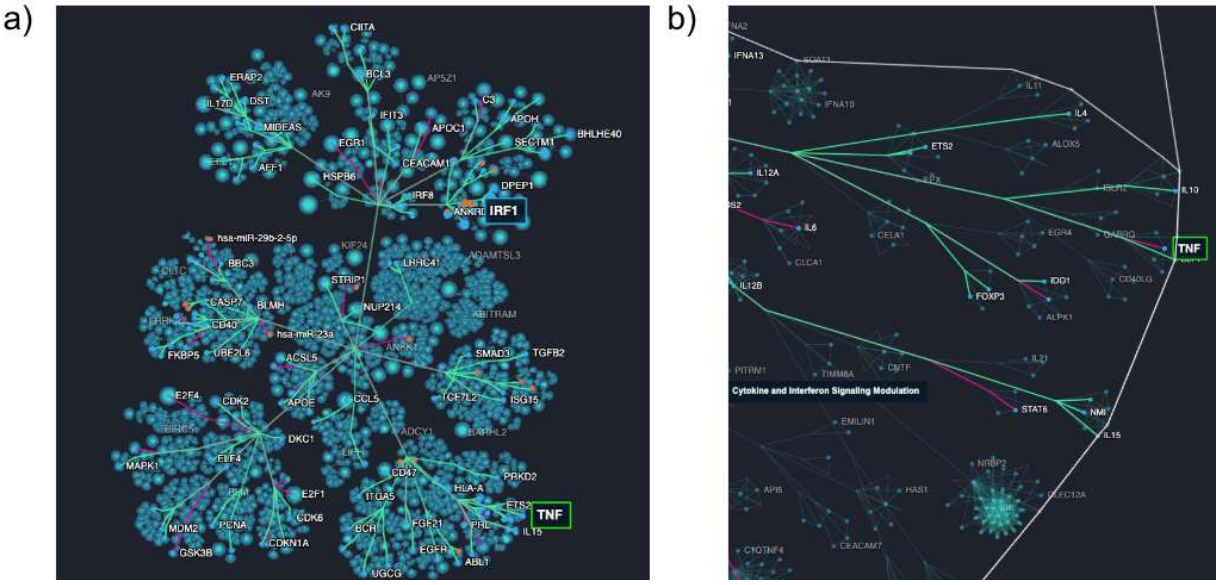

Figure 3. *Visualization of gene/protein network as interactome a) Interactome network displaying gene/protein interactions of interest. Nodes represent individual genes/proteins, and edges denote known or predicted interactions.* ***b)*** *Zoomed-in view of a), highlighting the upstream (red) and downstream (green) nodes of the gene TNF.*

As an illustrative example of the drug repurposing pipeline's output, we focused on the γδ T cell state group. These T cells are highly enriched in the skin and play a pivotal role in skin immune surveillance, making them a compelling target for immune-mediated skin disorders such as psoriasis **[16]**. Differential gene expression analysis within this cell class revealed key transcription factors and upstream regulators, we identified IF16 as a key differentially expressed gene, and by using our approach, lead to the identification of STAT1, STAT2 and IRF1 as important transcription factors in γδ T cells (**Figure 4**). In addition, causal network analysis identified TNF as a central regulatory node in these cells, in line with its established role in inflammatory signaling and as a validated drug target in psoriasis therapy **[23]**. These regulatory genes, which play a central role in the dysregulated pathways associated with psoriasis **[17]**, were subsequently prioritized as potential targets for therapeutic intervention. Each compound in the drug catalog is assigned a relevance score reflecting its network-based proximity to these disease driver genes, with higher scores indicating greater potential for successful repurposing.

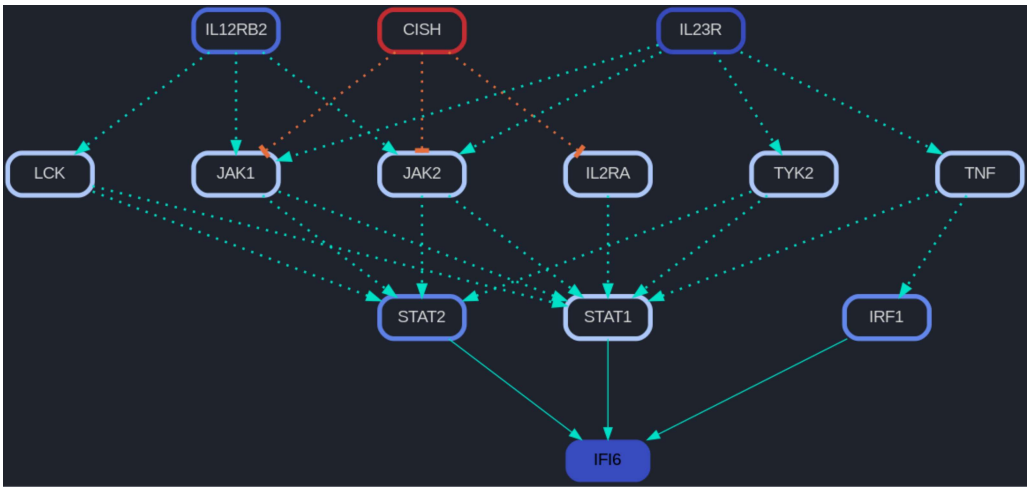

Figure 4. *Causal network highlighting transcription factors and upstream regulators dysregulated between psoriasis and healthy in gamma delta T cells.*

To evaluate the predictive power of the scoring system, we selected known drugs previously repurposed for psoriasis and currently in clinical use or late-stage trials, as well as compounds that failed in clinical trials for psoriasis. Among approximately 1200 evaluated compounds, the score distribution revealed that drugs associated with failed repurposing efforts received lower scores than successfully repurposed agents (**Figure 5**). For instance, Adalimumab, a TNF-alpha inhibitor initially used in rheumatoid arthritis, has been successfully used for psoriasis treatment **[18]**, and shows a high score for repurposing in psoriasis treatment, based on the model built on γδ T cell data. Other drug compounds actually ranked higher based on their repurposed score, highlighting potential drug candidates for psoriasis treatment.

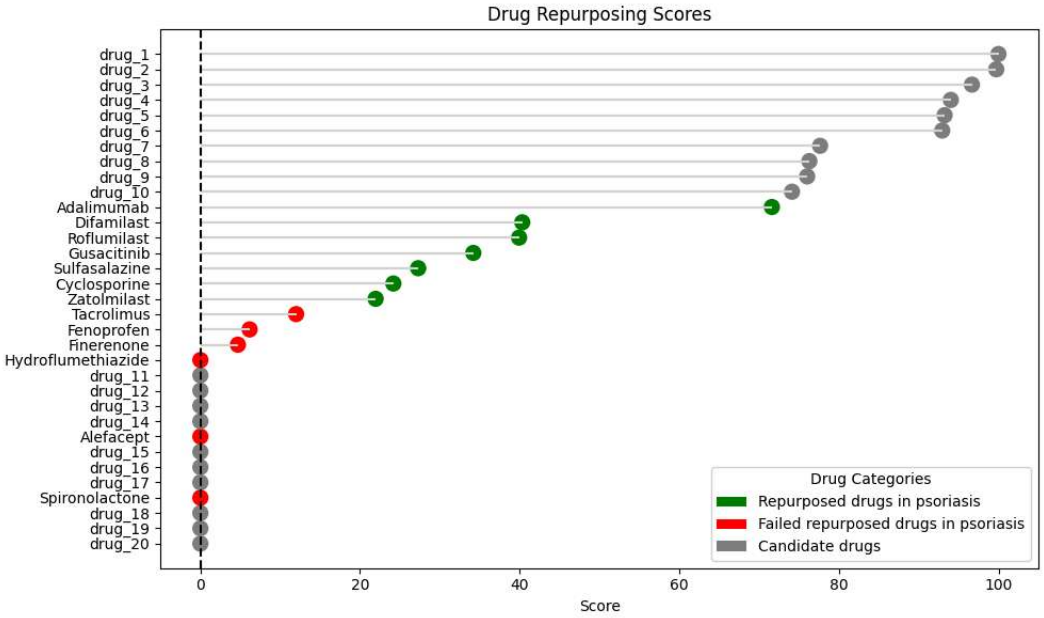

Figure 5. *Normalised drug repurposing scores of combined top 10, bottom 10 drugs and known drugs repurposed in psoriasis. Scores are normalized to 100. Green dots indicate the scores of known drugs*

that successfully were repurposed in psoriasis, while red dots indicate the scores of known failed drugs.

4. Discussion

In this study, we described the construction of a single-cell atlas of human skin, with a particular focus on inflammatory skin diseases such as psoriasis. By integrating five publicly available single-cell RNA-sequencing datasets, we demonstrated the feasibility of harmonizing heterogeneous studies while effectively correcting for batch effects. Importantly, this integration preserved key biological signals, including disease state, tissue origin, and cell class identity. Through manual curation and expert annotation, we defined robust cell classes such as epithelial and endothelial cells as structural subtypes, or mesenchymal cells including fibroblasts and progenitors involved in tissue maintenance and repair, but also important specific sub-types of T cells or keratinocytes, which have specific roles in psoriasis **[19-20]**. This enabled the comparison of specific cell states across different conditions and facilitated the identification of cell populations with disease-specific roles.

Building upon this refined cell-type classification, we constructed cell class–specific interactomes to model gene and protein interaction networks tailored to each population. Coupled with differential gene expression analysis, this approach allowed the identification of key transcription factors and upstream regulators driving pathway dysregulation in psoriasis. Leveraging these regulatory nodes, we applied a network-based scoring method to prioritize drug compounds with potential efficacy in modulating the disease-relevant interactome. Our results showed that repurposed drugs with known efficacy in psoriasis ranked higher than those that failed in clinical or preclinical settings, based on literature-derived drug lists. As an example, we focused on immune cell populations as they are critical in psoriasis pathogenesis, especially T cells and antigen-presenting cells such as dendritic cells and macrophages mediate inflammatory responses that drive keratinocyte hyperproliferation and lesion formation **[21]**, highlighting their importance as therapeutic targets. We explore the γδ T cells population known to be implicated in psoriasis pathogenesis **[22]** , yet representing only 5% of the peripheral lymphocyte population, an even smaller fraction of the T cell compartment in the skin. Despite their low abundance, our integrated single-cell approach enabled the identification of key regulatory mechanisms within this rare population. Such insights would likely have been obscured in bulk transcriptomic analyses or in studies limited to smaller datasets, highlighting the strength of combining single-cell resolution with multi-dataset integration. From the causal analysis and drug repurposing computational results, adalimumab—an anti-TNF biologic with proven success in treating psoriasis—received a high score, aligning with the predictions of our causal inference analysis. Interestingly, some drugs outperformed Adalimumab in the scoring metric. Looking at the top five scoring candidate drugs, it includes inhibitors targeting vascular endothelial growth factor A (VEGFA), interleukin-2 receptor (IL-2R), and T-cell surface antigen CD4. These mechanisms are relevant in the context of skin immune diseases characterized by aberrant T cell activation, angiogenesis, and cytokine dysregulation. VEGFA inhibitors may reduce pathological neovascularization observed in psoriatic lesions **[24]**, while IL-2R inhibitors can dampen overactive immune responses **[25]**, and CD4 inhibitors may modulate the activity of helper T cells implicated in disease pathogenesis **[26]**.

This proof-of-concept illustrates the utility of integrating single-cell transcriptomic data, regulatory network inference, and drug repurposing strategies to uncover cell-type-specific therapeutic targets. Our approach can be further expanded by incorporating additional datasets encompassing other conditions such as photoaging, sun-exposed versus non-exposed skin, or other inflammatory dermatoses. Such comparisons may reveal shared

and unique pathogenic pathways and guide the identification of novel therapeutic candidates across dermatological indications.

5. Conclusion

Our high resolution approach, using comprehensive skin cell atlas and cell-specific interactomes, captures the complexity and diversity of skin as a tissue. **Our case study demonstrates the discovery of causal genes linked to key inflammatory pathways responsible for skin irritation and damage in Psoriasis. By mapping these genes to our curated catalog of active compounds, we identified several promising molecules able to tune down inflammation.** We can identify and prioritize novel bioactive compounds and combinations that target specific cell types and pathways. The integration of detailed biological insights with advanced computational approaches, combining Single-cell transcriptomics and interactomes, gives a powerful framework for innovation in cosmetology, enabling the design of next-generation products that precisely modulate skin biology to enhance skin health, reduce inflammation, and delay signs of aging.

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