Investigating the mechanisms of short- and long-term responses to IL-23 inhibition using Tildrakizumab in moderate to severe plaque psoriasis using high-definition multiomics

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Protocol Synopsis

Study title	Investigating the mechanisms of short- and long-term responses to IL-23 inhibition using Tildrakizumab in moderate to severe plaque psoriasis using high-definition multiomics
Hypothesis	Define the mechanisms underlying the short- and the long-lasting effects of IL-23 targeting in plaque PsO, by characterizing the longitudinal effects of IL-23 inhibition on the ratio of Trm/Treg cells in the skin of moderate to severe plaque PsO patients.
Objectives	HDST (Visium HD) and HDSP (MICS) are used to characterize the early (2 weeks) and late (16 weeks) molecular effects of treatment with tildrakizumab on the skin of three patients with moderate to severe plaque psoriasis. Non-lesional and lesional skin samples taken at the start of treatment with tildrakizumab will be used, as well as healed skin adjacent to the original sampling sites at week 2 and week 16 after the start of treatment with tildrakizumab. The same samples will be examined using Visium HD and the MACSima imaging system.
Study design	This is a retrospective, exploratory study using material from our existing biobank (Excellence cluster, 'Clinical Demonstrator 1') in patients with moderate-to-severe plaque psoriasis who received Tildrakizumab treatment.
Sample size	3 patients
Study site location	The study will be conducted at the Institute for Inflammation Medicine at the University of Lübeck, Lübeck, Germany

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List of abbreviations

HDST	high-definition spatial transcriptomics
mDCs	myeloid dendritic cells
pDCs	plasmacytoid dendritic cells
PsO	Psoriasis
UKSH	University Medical Center Schleswig-Holstein

1. Background

Psoriasis (PsO), a chronic inflammatory skin disease that affects up to 2-3% of the western population (1) and ~125 million people worldwide (2). It is marked by the presence of red, scaly plaques that are commonly seen in its plaque-type form that accounts for over 80% of all PsO cases (3). Its development is driven by a complex interplay of genetic and environmental factors, and involves both keratinocytes, and innate and adaptive immune cells (4). Early activation of keratinocytes, leads to activation of plasmacytoid dendritic cells (pDCs), that in turn release IFN-α– and stimulate myeloid dendritic cells (mDCs) to produce interleukin (IL)-23 (5). The IL-23 cytokine, composed of the IL-12/23p40 subunit, which is shared with IL-12, and the IL-23p19 subunit, is crucial in sustaining the inflammatory response in plaque PsO by activating distinct subsets of IL-17-producing lymphoid cells such as CD4+ helper T cells (Th17), cytotoxic CD8+ T cells (Tc17), γδ T cells, and innate lymphoid cells (ILC3) (6). In the presence of IL-23, these IL-17 producing cells expand clonally and secrete large amounts of IL-17, in particular, the IL-17A and IL-17F cytokines that drive the key pathological features in plaque PsO (7). Elevated IL-17 levels promote keratinocyte proliferation, angiogenesis, upregulation of adhesion molecules on endothelial cells, and immune cell recruitment into the skin. This, in turn, leads to a feedforward inflammatory loop, amplifying keratinocyte hyperproliferation and sustaining the disease pathology (8). While mDCs are the main producers of IL-23, other cell types, such as, macrophages, also contribute to IL-23 production (9). These additional sources may play a role in the pathogenesis and persistence of psoriatic lesions, further highlighting the complexity of PsO-related inflammation.

Targeted therapies like ustekinumab, which inhibit the IL-12/23p40 subunit, have proven effective in treating plaque PsO. Furthermore, evidence from tissue expression and genetic studies indicates that the therapeutic impact of these agents is largely due to their ability to block IL-23, rather than IL-12 (10), underscoring the significance of the IL-23 pathway. Furthermore, a head to head comparison suggests that IL-23p19 inhibitors like guselkumab and risankizumab offer superior efficacy over TNF inhibitors such as adalimumab (11) and IL-17A inhibitors like secukinumab (12). Nevertheless, IL-17A inhibitors, including secukinumab and ixekizumab, exhibit a faster onset of action compared to IL-23p19 inhibitors in the treatment of plaque PsO (13).

Tildrakizumab is a high-affinity, humanized, IgG1/κ monoclonal antibody that selectively binds to the (IL)-23p19 subunit but does not bind to human IL-12 or the IL-12/23p40 subunit (18). Importantly, treatment effects that were achieved over the first 16 weeks of treatment were maintained through 52 weeks of treatment with doses of 100 and 200 mg Tildrakizumab (19). Upon cessation of treatment, the rate of relapse was low during a 20-week nontreatment period

(19), suggesting that Tildrakizumab might have beneficial effect in clearing Trm cells and expanding Treg cells in the skin in plaque PsO patients.

Global spatial transcriptomics (ST) revolutionized the study of drug effects within tissues by charting the spatial organization of cells while preserving their native cellular context (20). Furthermore, it permitted studying cell-cell interactions and eliminated the biases associated with cell dissociation and recovery, especially in extracellular matrix-rich tissues, like skin (21). Though conventional spatial profiling methods captured spatial data in intact tissues, they often relied on pre-selected markers and lacked adequate resolution (22). The recently established cutting edge high-definition spatial transcriptomics (HDST) approach (10x Genomics) overcomes these limitations by combining spatial barcoding with high-resolution RNA sequencing (23). Using this novel technology, we can now map precise localization of gene expression at every 2 µm achieving a single-cell resolution (22,23). In addition to HDST, spatial proteomics methods such as MICS also known as MACSima Imaging Cyclic Staining technology (Miltenyi Biotec) enabled the immunofluorescent imaging of hundreds of protein targets across a single specimen at subcellular resolution, and offered new insights into cellular complexity of the skin in response to treatment (24,25). By integrating data from these state-of-the-art technologies, we aim to study the short (2 weeks after initiation of treatment) and the long-term effects (16 weeks after initiation of treatment) of Tildrakizumab treatment on the cellular composition and activation in the skin of plaque PSO patients, especially of Trm and Treg cells.

2. Study Purpose

This study aims to define the mechanisms underlying both short- and long-term effects of IL-23 inhibition in patients with moderate-to-severe plaque psoriasis during treatment with Tildrakizumab. Specifically, the study will investigate longitudinal changes in the ratio of tissue-resident memory T cells (Trm) to regulatory T cells (Treg) in lesional, non-lesional, and resolved skin. In addition, the study will assess spatial and temporal alterations in IL-23 source and target cells using high-definition spatial transcriptomics (Visium HD) and high-dimensional spatial proteomics (MACSima MICS).

3. Study Methodology

The study will use HDST (Visium HD) and HDSP (MACSima Imaging Cyclic Staining – MICS) to analyze early (2 weeks) and late (16 weeks) molecular effects of Tildrakizumab treatment in the skin of three moderate-to-severe plaque psoriasis patients using previously collected

biopsies from our existing biobank. Sections will be subjected to spatial transcriptomic analysis using Visium HD and multiplex imaging with the MACSima system.

4. Biobank

The biological samples used in this project originate from the Clinical Demonstrator 1 Biobank, which is registered under file number 2023-800. It is confirmed that the patients, from whom the materials are derived, have consented to the use of their biological samples within the scope of project 2023-800. The use of the samples is carried out exclusively in accordance with the purposes described in the consent form and in compliance with applicable data protection regulations.

5. Signatures

6. References

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