Development of a Mechanistic Model of Keratinocyte Dynamics and Skin Barrier Function for Psoriasis Research

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Problem Statement

Introduction

- Keratinocytes (KCs) have a **central role** in psoriasis
  - **Cytokine and chemokine** produced by KCs contribute to inflammation
  - KCs undergo **hyperproliferation**, resulting in thickened skin
  - **Abnormal desquamation** of corneocytes (CCs) causes scales and itching
- Understanding KC behavior and response to interventions is critical to the development of new psoriasis therapies

Objectives

- Develop a focused QSP model of KC dynamics and skin barrier function that can be integrated within larger models of inflammatory skin disorders

Conclusion

- A focused model of keratinocyte differentiation was able to reproduce healthy and psoriatic skin dynamics
- This model can be integrated within comprehensive QSP models of skin disorders
- Pharmaceutical clients were able to accelerate development programs for novel psoriasis therapies using our research with this model

Design and Qualification

- Model includes **three states of KC differentiation** representing the functional phenotypes present in normal and psoriatic skin (**Figure 1**):
  - **Basal, proliferating KCs**
  - Non-proliferative, **differentiating KCs**
  - **Corneocytes (CC)**, i.e., terminally differentiated keratinocytes
- KC proliferation, differentiation, and cornification rates are regulated by cytokines
- Hyperactivation of differentiation and cornification inhibits the quality of the resulting corneocytes and barrier function
- CC quality regulates their shedding, barrier function, and scaliness
- Reduced barrier function stimulates KC proliferation

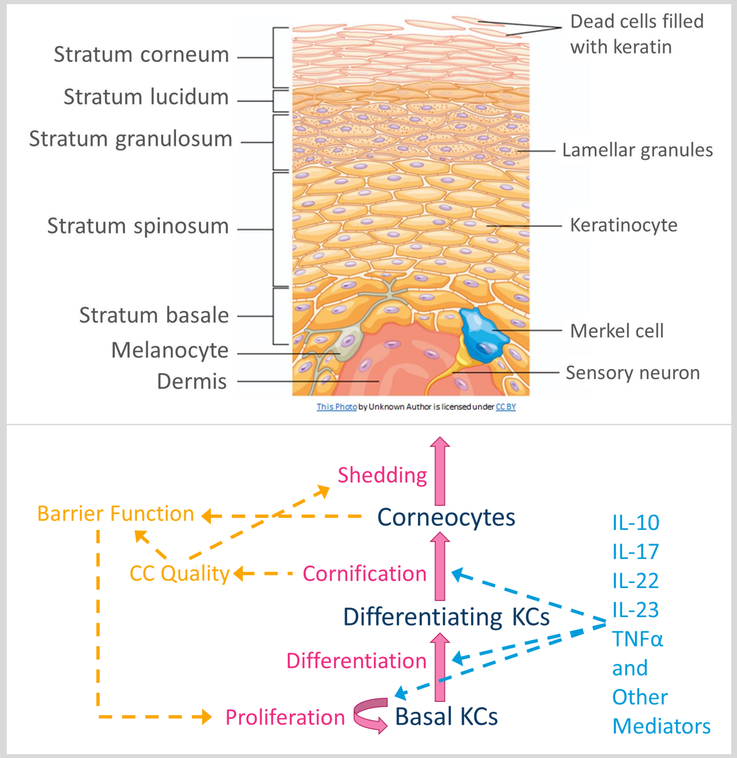

Figure 1: Structure of the epidermis (top) and QSP model (bottom)

Literature data informed the parameterization of the model, e.g.:

- **Densities** of KCs and CCs in healthy skin and psoriasis plaques
- **Turnover rates** of basal, differentiated KC, and CC in healthy skin
- **Fold change** in proliferation, differentiation, cornification, and desquamation rates in psoriasis plaques
- **Apoptotic index** in healthy and psoriatic skin
- **Effects of mediators** on proliferation, differentiation, and cornification
- Trans-epidermal water loss (**TEWL**) measurements of barrier function in healthy and psoriasis subjects

Table 1: Example data constraints used for model calibration

Cell type	Healthy Skin	Psoriatic Plaque	Units
Keratinocytes	50,000 (10,000-100,000)	110,000 (2.2x healthy)	Cells/mm^2 skin surface
Basal KCs	13 – 61	20	%
Differentiated KCs	39 – 60	45	%
Corneocytes (CCs)	19 – 27	35	%
Basal KC turnover	22	4	Days
KC differentiation	12	2	Days
CC desquamation	14	3	Days
Apoptotic index	0.12	0.035	%
TEWL	25	12	g/m^2/h

*References available upon request

Example Simulation (Figure 2)

- **Protocol**: Decrease all inflammatory mediators by 90% at the start of the simulation ("Treated") versus untreated baseline conditions
- **Result**: Cell numbers and turnover rates return to healthy equilibrium
- **Significance**: This is one example demonstrating that the model dynamics are consistent with expected KC responses to maximal inhibition of pro-inflammatory mediators

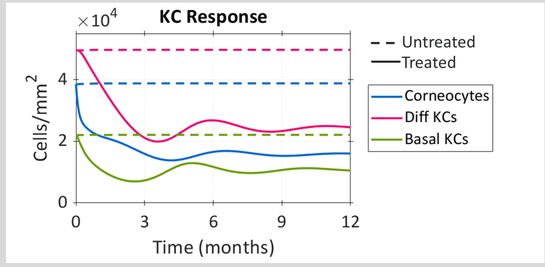

Figure 2: Simulated KC responses to inhibiting pro-inflammatory mediators ("Treated")

Example Application

- KC number and activation status are key contributors to clinically assessed disease activity scores, such as the Simplified Psoriasis Area and Severity Index (SPASI)
- This model has been integrated into larger psoriasis models, to predict the **SPASI response to existing and novel therapies**
- Components of the QSP model were mapped to components of the SPASI score (as shown in **Figure 3**)

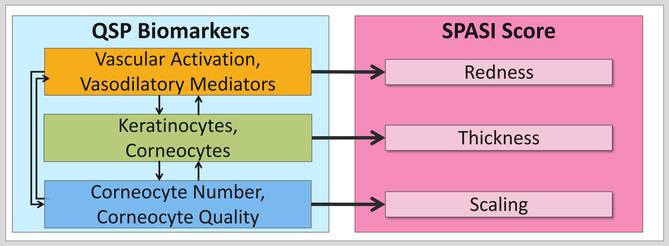

Figure 3: Mapping of QSP model components to SPASI sub-scores

- SPASI calculation parameters were fit to clinical data for **anti-TNFα, anti-IL-23, anti-IL-17 (secukinumab, Figure 4) and methotrexate**

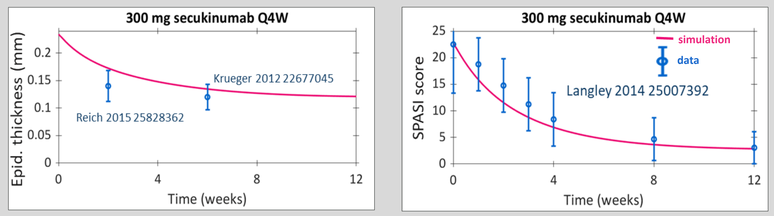

Figure 4: Model simulations (pink line) match clinical data (blue bars) for reduction in epidermal thickness and SPASI score following anti-IL-17 secukinumab administration

- The QSP model was then used to predict the SPASI response to novel therapies and address specific drug development questions

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