Development of a Quantitative Systems Pharmacology (QSP) Model of Psoriasis: Overview and Challenges

Loveleena Bansal1, Tom Wilde2, Grace Kang1, Rebecca Baillie3, Christina Friedrich1, Valeriu Damian2

1Stiefel Discovery and Preclinical Development, GSK, 2Modeling and Translation Biology, DMPK, GSK, 3Rosa & Co.

**Introduction**

Psoriasis is a chronic inflammatory skin disease with a complex pathogenesis involving multiple tissues and immune response. Thus, a QSP model of psoriasis is being developed to better understand its pathophysiology and to assess the drug targets and candidates in development within GSK for the treatment of this disease (Figure 1). There is also an ongoing collaboration with PSORT consortium in UK to obtain data for model validation. This poster outlines the steps in development of the QSP model of psoriasis.

**Map of Psoriasis Processes**

A detailed map of psoriasis describing its processes and the crosstalk between these processes has been developed. A representative diagram of this map is shown below (Figure 3).

**Parameter Estimation**

Over 200 literature references have been reviewed to obtain or estimate the different kinds of parameters for the psoriasis model.

1. Activation/ Upregulation Parameters, e.g.
   - Activation of keratinocytes by cytokines
   - Recruitment of immune cells into the skin etc.
   In-vitro data from literature has been used for estimation of upregulation parameters.

2. Turnover rates

3. Levels of Cells or cytokines in Healthy and Disease State

4. Influx/Efflux Balance

Some of the unknown parameters are obtained by balancing the influx of different cell types, e.g.

- Recruitment of T cells from peripheral blood
- Recruitment of keratinocytes by cytokines

**Model Validation and Challenges**

Challenges in Psoriasis Model Development

- The upregulation parameters are estimated from in-vitro data in literature which may not be directly translatable to in-vivo cases.
- The levels of cells, cytokines or chemokines are usually not quantitatively measured in healthy or disease states and thus reasonable approximations are made based on imaging or transcriptional data.
- The systemic levels of proteins, which are most commonly measured, are not always good indicators of disease state. Skin biopsy or lymph node samples are rarely obtained.
- The clinical measures commonly used for psoriasis – like the psoriasis area and severity index (PASI) – are compound effects of a number of processes like skin thickness, redness, scaling and plaque area. These measures are challenging to translate to individual disease processes to use for model calibration.

**Model Validation**

The model will be validated by simulating the response of currently available psoriasis treatments and comparing them against available clinical data. Thus, the clinical outcomes like the PASI score will also be implemented in the model. Also, the academic collaborators in PSORT have collected patient data (skin biopsies, systemic levels of cytokines, metabolites etc.) with and without treatments which will be useful for validating or updating the model.

**Treatment**

- Broadalumab
- Ustekinumab
- Etanercept
- Steroids
- Digital Media

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