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

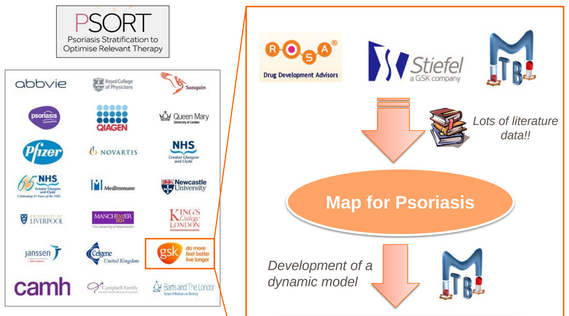
Loveleena Bansal[1], Tom Wilde[2], Grace Kang[1], Rebecca Baillie[3], Christina Friedrich[3], Valeriu Damian[2]

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

Introduction

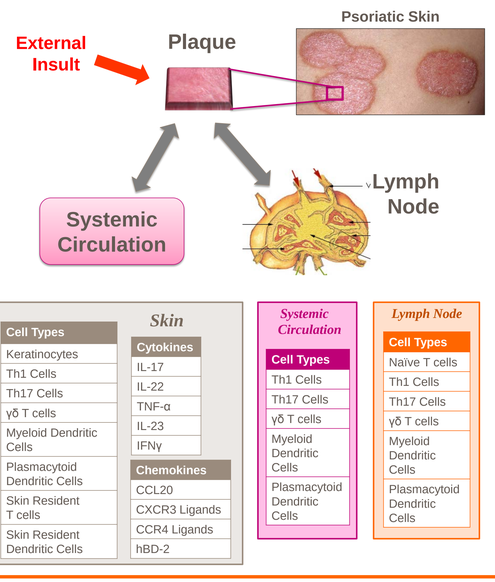
Psoriasis is a chronic inflammatory skin disease with a complex pathogenesis involving multiple tissues and immune response spanning a number of cell types. Thus, a QSP model of psoriasis is being developed to better understand its pathophysiology and to assess the drug targets and candidates in development 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.

Figure 1 Development of the QSP model of psoriasis and collaboration with PSORT consortium in UK



Conceptual Diagram

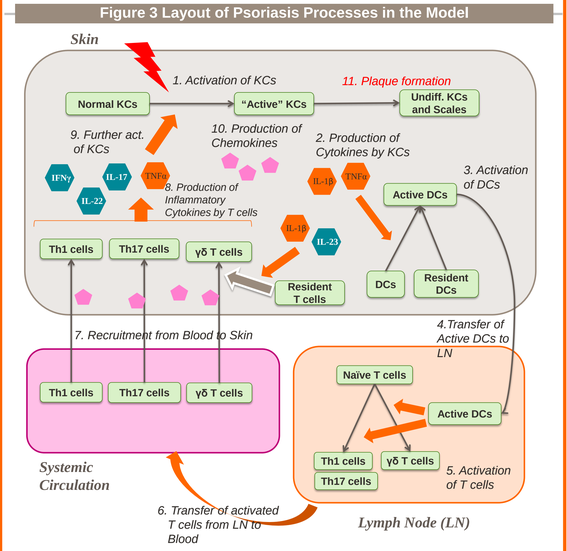
Figure 2 Components of the Psoriasis Model



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).

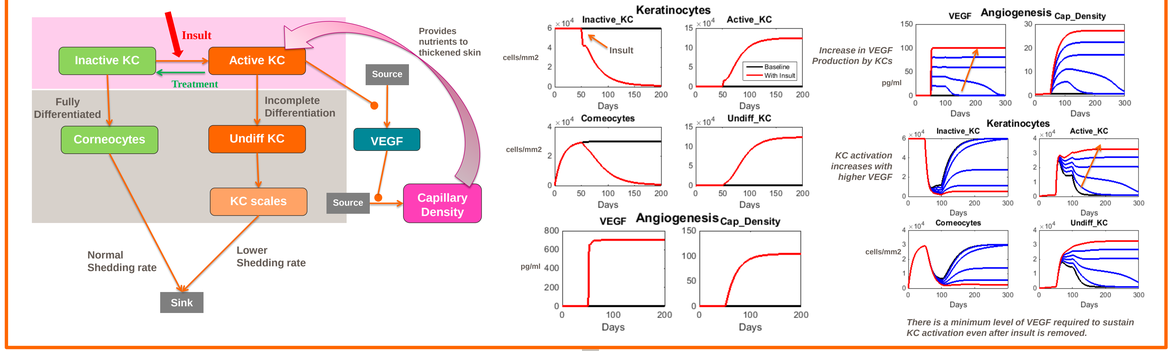
Figure 3 Layout of Psoriasis Processes in the Model



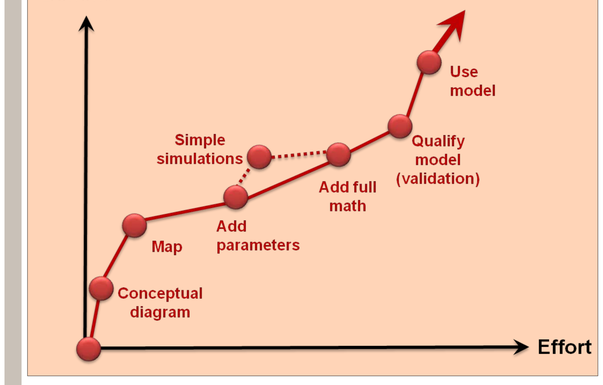
An external insult like skin injury, allergens or stress activates the keratinocytes (KCs) in the skin which start producing inflammatory cytokines. These cytokines activate the dendritic cells (DCs) which lead to priming of T cells in the LN. The activated T cells are recruited into the skin through chemokines and further activate KCs by producing inflammatory cytokines like IL-17, IL-22, TNFα etc. This eventually leads to skin scaling and plaque formation.

Simple Simulations

Simulation of Keratinocyte Differentiation, Scaling and Angiogenesis in Psoriasis



Benefit



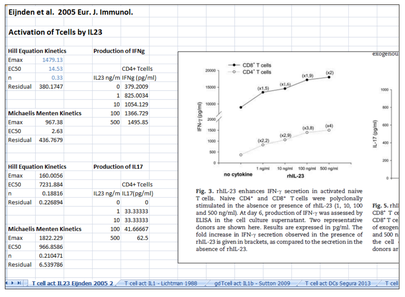
Parameter Estimation

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 Immune cells/ 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

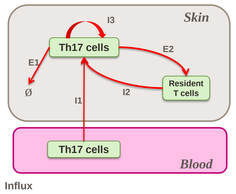
Description	Value	Units	Source1
Death Rate of Th17 cells in Skin	0.013888	1/hr	Palsson 2013 BMCSB, Table S5 - eta26
Death Rate of Th1 cells in Skin	0.013888	1/hr	Palsson 2013 BMCSB, Table S5 - eta26
Death Rate of γδ Tcells in Skin	0.013888	1/hr	Palsson 2013 BMCSB, Table S5 - eta26
Death Rate of Inactive TIP- DCs in Skin	4.17E-05	1/hr	Lee 2009 J Virol, Table 2, deltaD
Death Rate of Active TIP- DCs in Skin	0.020833	1/hr	Palsson 2013 BMCSB, Table S5 - eta18
Death Rate of Macs in Skin	0.000417	1/hr	Palsson 2013 BMCSB, Table S5 - eta13
Death Rate of Macs in Blood	0.000417	1/hr	Palsson 2013 BMCSB, Table S5 - eta13
Death of Inactive TIP- DCs in Blood	0.000417	1/hr	Palsson 2013 BMCSB, Table S5 - eta16
Death Rate of Naïve Tcells in Skin	0.0005	1/hr	Palsson 2013 BMCSB, Table S5 - eta20
Death Rate of Inactive γδ Tcells in Lymph	0.0005	1/hr	Palsson 2013 BMCSB, Table S5 - eta20
Degradation rate of hBD2 inSkin	4.158883	1/hr	Assuming 10 min half life in skin (approx)
Degradation rate of IFNγ inSkin	4.158883	1/hr	Assuming 10 min half life in skin (approx)
Degradation rate of CCL8 inSkin	4.158883	1/hr	Assuming 10 min half life in skin (approx)

3. Levels of Cells and Cytokines in Disease and Healthy State

Compartment	Species	Initial Amount	Units	Source1
Lymph_Node	Th1_Active_LN	2.77E+07	cells/ml	Calc from various sources (see Psor_Params_ImmuneCells.xlsx)
Lymph_Node	Th17_Active_LN	5.55E+06	cells/ml	Calc from various sources (see Psor_Params_ImmuneCells.xlsx)
Lymph_Node	gd_Tcells_Inact_LN	3.47E+07	cells/ml	Calc from various sources (see Psor_Params_ImmuneCells.xlsx)
Lymph_Node	gd_Tcells_Active_LN	3.47E+07	cells/ml	Calc from various sources (see Psor_Params_ImmuneCells.xlsx)
Lymph_Node	TIP_DC_Active_LN	7.91E+03	cells/ml	calc using FB = TIP_DC_Act _Skin*skin_vol/LN_vol
Lymph_Node	Source_LN	1		
Circ	gd_Tcells_Act_Circ	8.80E+04	cells/ml	Calc based on 5% of total lymphocytes (see excel Psor_Params_Im
Circ	Th17_Active_Circ	1.73E+04	cells/ml	Calc based on data in Baker 1984 and Kagami 2010 (see excel Psor
Circ	Th1_Active_Circ	8.66E+04	cells/ml	Calc based on data in Baker 1984 and Kagami 2010 (see excel Psor
Circ	pDC_Inactive_Circ	1.88E+02	cells/ml	Calculated (see Psor_Params_ImmuneCells_DCs.xlsx, Sheet - mD
Circ	TIP_DC_Inact_Circ	1.01E+03	cells/ml	Calculated (see Psor_Params_ImmuneCells_DCs.xlsx, Sheet - mD
Circ	Source_Circ	1		
Skin	pDC_Inactive_Skin	1.00E+03	cells/ml	low level in psoriasis
Skin	DC_Active_Skin	1.48E+06	cells/ml	Calculated (see Psor_Params_ImmuneCells_DCs.xlsx, Sheet - mD
Skin	Th1_Active_Skin	4.83E+06	cells/ml	Calc based on data in Lowes 2008 and Bos et al 1989 (see excel Ps
Skin	KCs_Inactive_Skin	1.00E+03	cells/ml	Hoath and Leahy 2003 JID, average from various sources
Skin	Th17_Active_Skin	1.71E+06	cells/ml	Calc based on data in Lowes 2008 and Bos et al 1989 (see excel Ps

4. Influx/Efflux Balance

Some of the unknown parameters are estimated by balancing the fluxes in/out of different cell types, e.g.



Influx

1. Recruitment of Th17 cells from blood to skin (**I1**)
2. Activation of skin resident T cells to Th17 cells (**I2**)
3. Proliferation of Th17 cells (**I3**)

Efflux

1. Degradation of Th17 cells (**E1**)
2. Deactivation of Th17 cells (**E2**)

In homeostasis

I1+I2+I3 – E1 – E2 = 0

The activation rate of Th17 cells from Resident T cells has been obtained using the above flux balance.

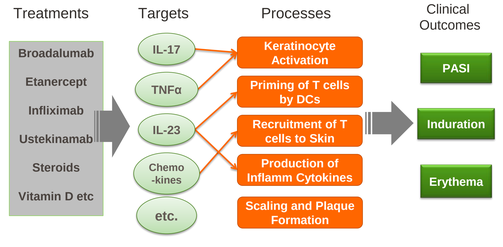
Model Validation and Challenges

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 case.
- 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 transcriptomics 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 compounded 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.



Acknowledgements

We would like to thank current and former colleagues in Stiefel for their contributions to developing this model – Betty Hussey, Javier Cote-Sierra, Susan Smith, Steve Frey and Akanksha Gupta.

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