

Using Mechanistic Quantitative Systems Pharmacology (QSP) Models To Connect Biomarkers To Clinical Disease Activity Scores – Examples In Atopic Dermatitis (AD) And Psoriasis (Pso)

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Problem Statement

- Many clinical trials use **complex disease activity scores** to assess patient response
- QSP modeling elucidates **mechanistic connections** between **biological pathways** and **objectively measurable outcomes or biomarkers**
- The relationship between objectively measurable markers and disease activity scores is often unclear
- QSP prediction of clinical response to novel protocols requires **extrapolation** from biomarkers to disease scores

Example: Atopic Dermatitis EASI Score

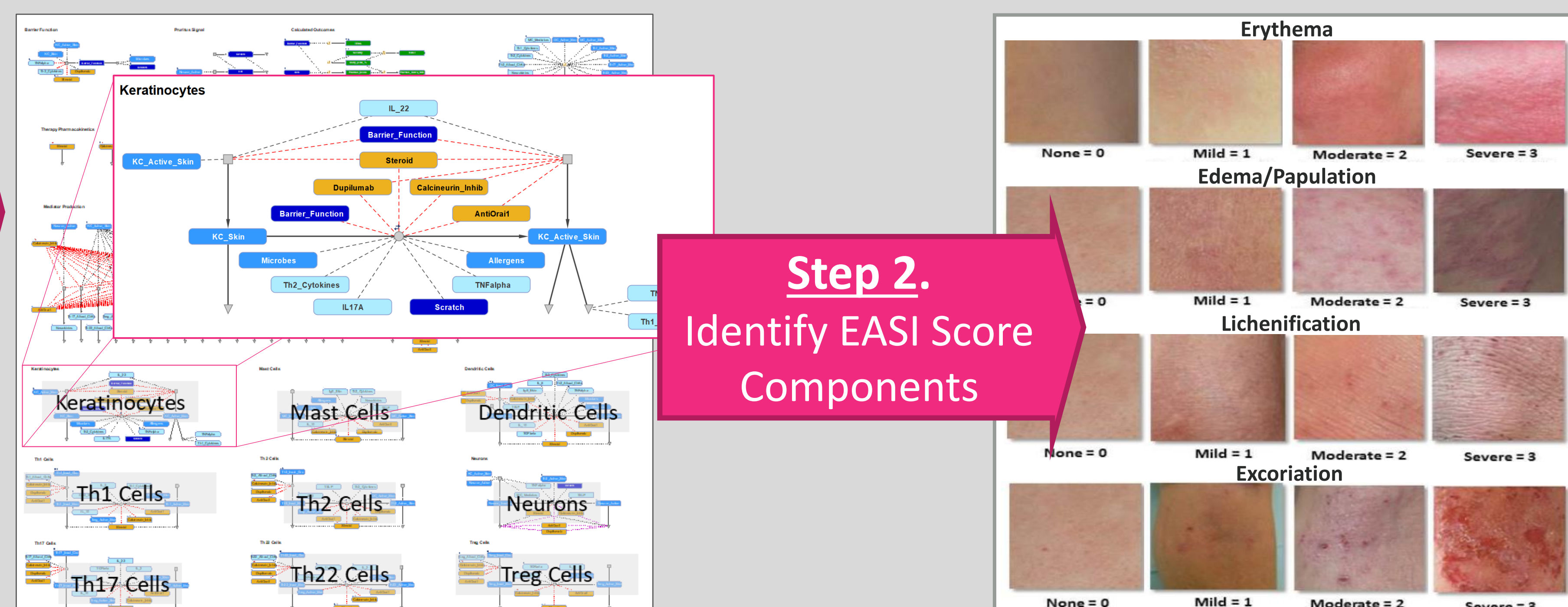


Figure 1. AD QSP model developed in MATLAB SimBiology².



Figure 2. EASI component scoring³. EASI score considers the four symptoms multiplied by affected body area.

Step 1.
Develop AD QSP Model Connecting Mechanisms to Measurable Biomarkers

- AD (Figure 1) QSP models were developed and qualified¹

Step 3.
Map Score Components to Biomarkers in QSP Model

- Use biological reasoning supported by literature
 - E.g., neuronal activation was reasoned to be related to pruritus and scratching (Figure 3)

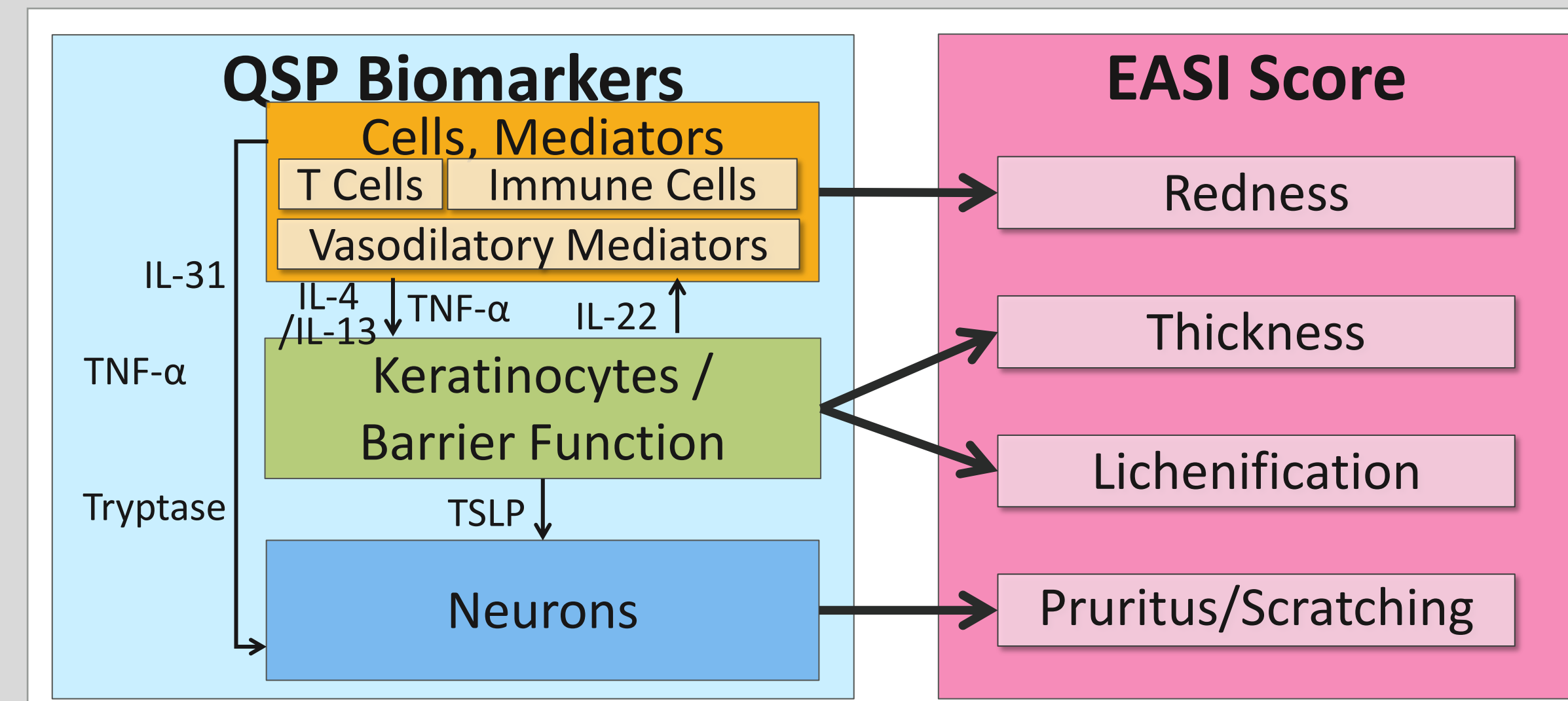


Figure 3. EASI score components linked to selected key biomarkers in an AD QSP model.

Step 4.
Fit EASI Calculation Parameters to Clinical Data for Existing Drugs

- Fit parameters for new EASI calculations to clinical data for tacrolimus, steroids, and dupilumab (shown)
 - Use of drugs with different mechanisms of action (MOAs) increases robustness
 - Multiple solutions may be possibly

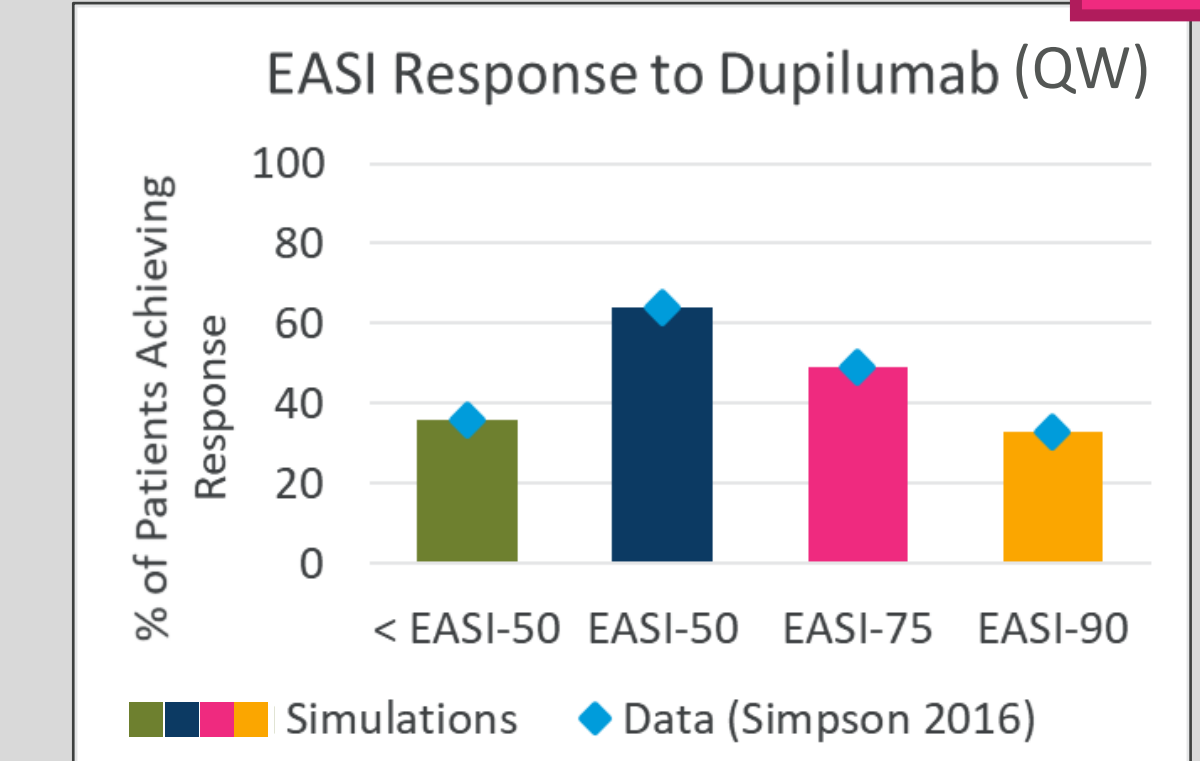
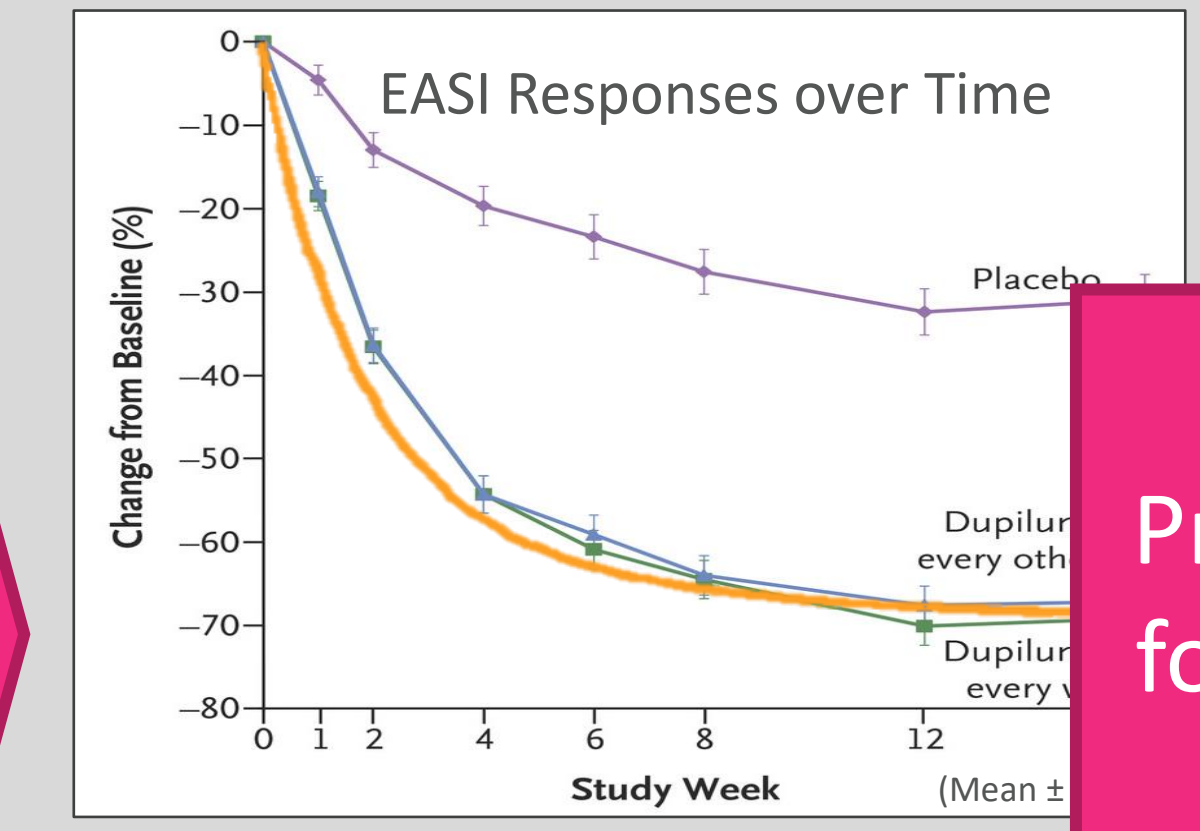


Figure 4. Simulations (300 mg QW) vs. clinical data⁴ for dupilumab. Top: EASI response over time. Bottom: % of VPs reaching EASI-50, -75, and -90 at 16 weeks.

Step 5.
Predict EASI Score for Novel Therapy or Protocol

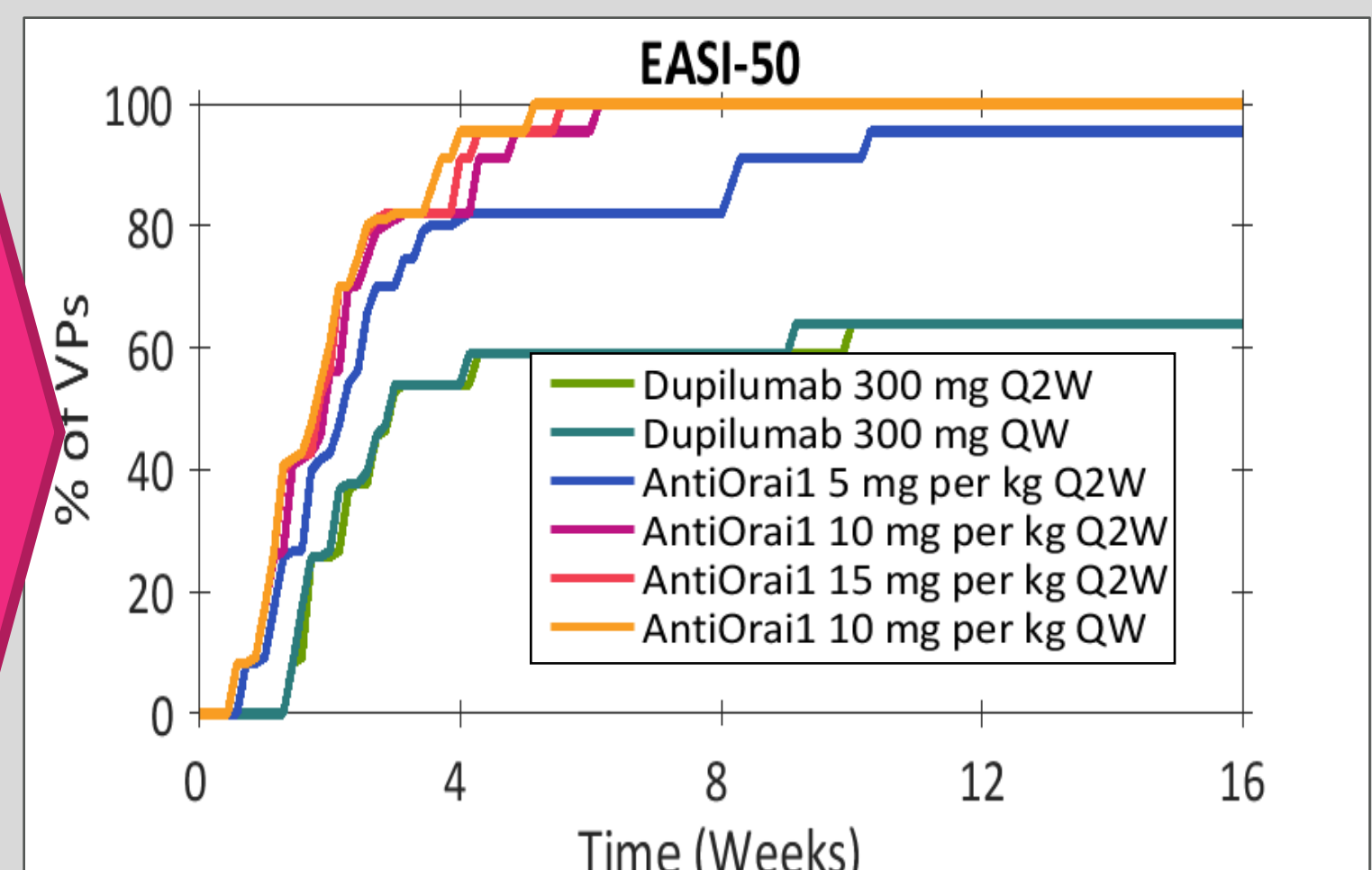
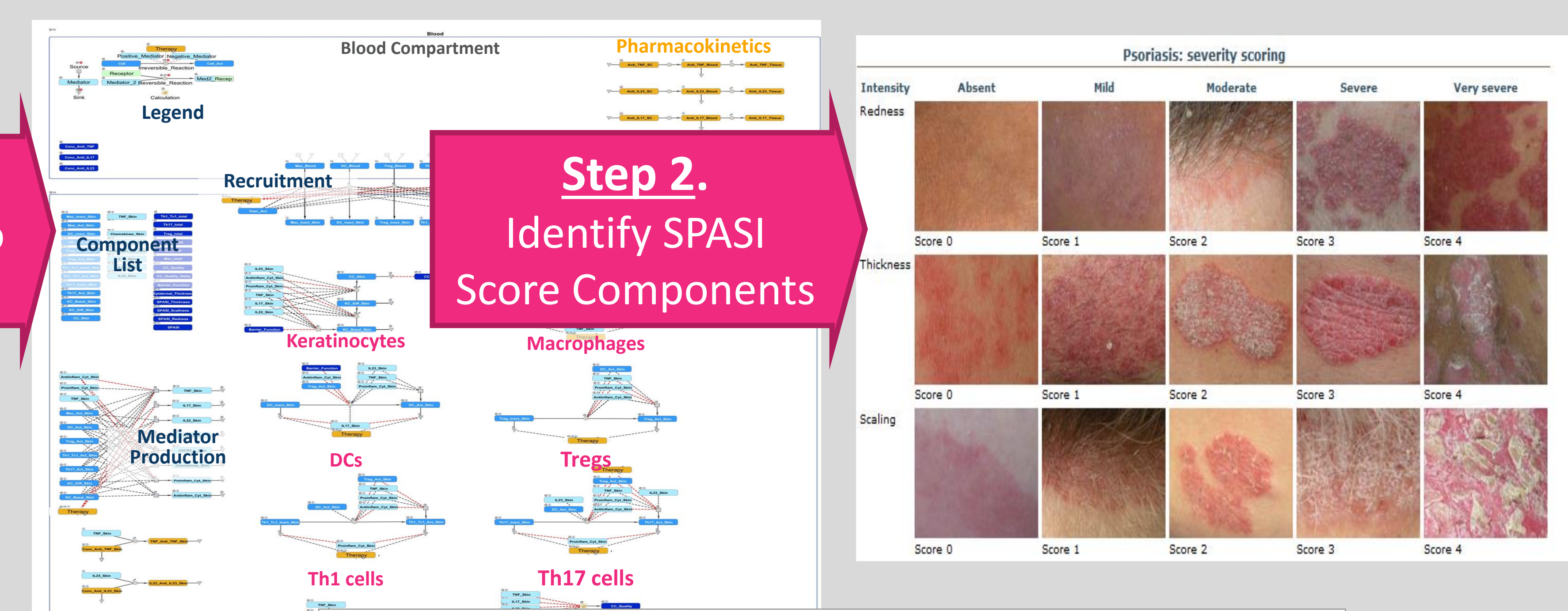


Figure 5. % of Virtual Patients achieving EASI-50 scores in simulated treatment with dupilumab and DS-2741a (AntiOrai1) over 16 weeks.

Conclusion

We have developed a general workflow for using QSP models to map biomarkers to complex disease scores. This enables the prediction of complex clinical outcomes of novel interventions.

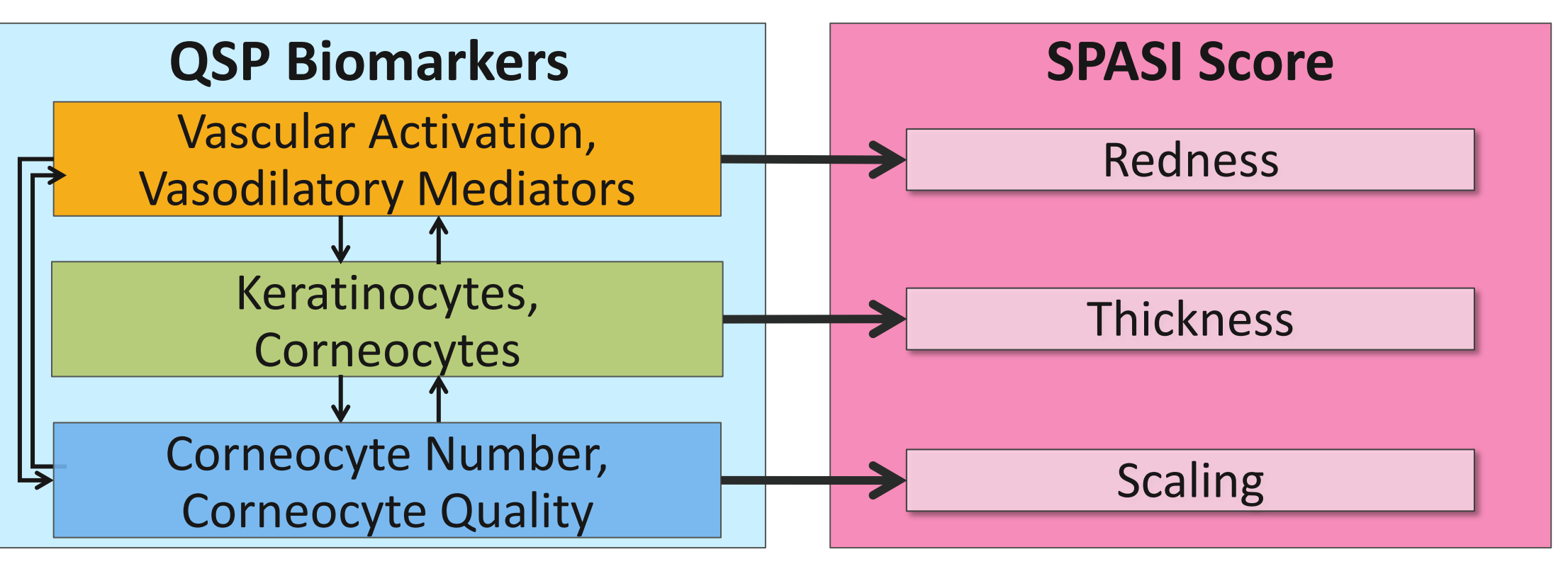
Example: Psoriasis SPASI Score



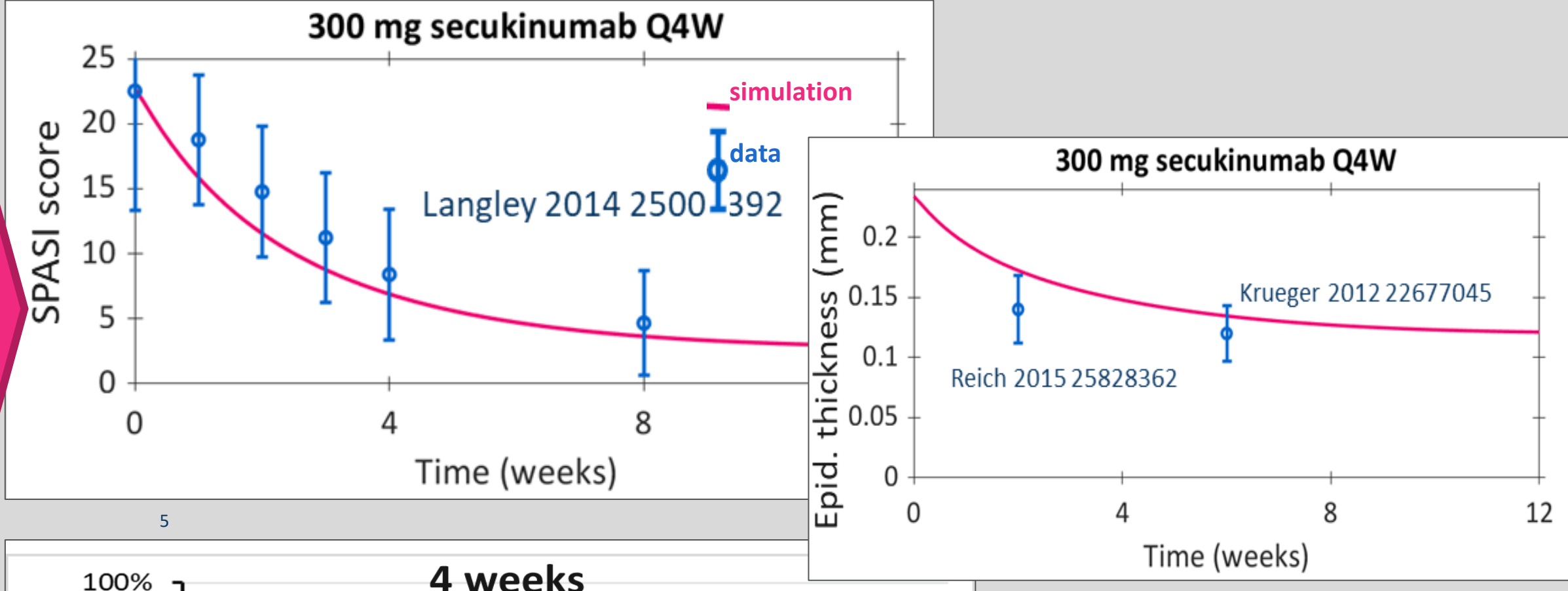
Step 1.
Develop Pso QSP Model

Step 2.
Identify SPASI Score Components

Step 3.
Map QSP model biomarkers SPASI score components



Step 4.
Fit SPASI Calculation Parameters to Clinical Data for anti-TNFα, anti-IL-23, anti-IL-17, and methotrexate



Step 5.
Predict SPASI Score Reduction for Novel Therapy or Protocol

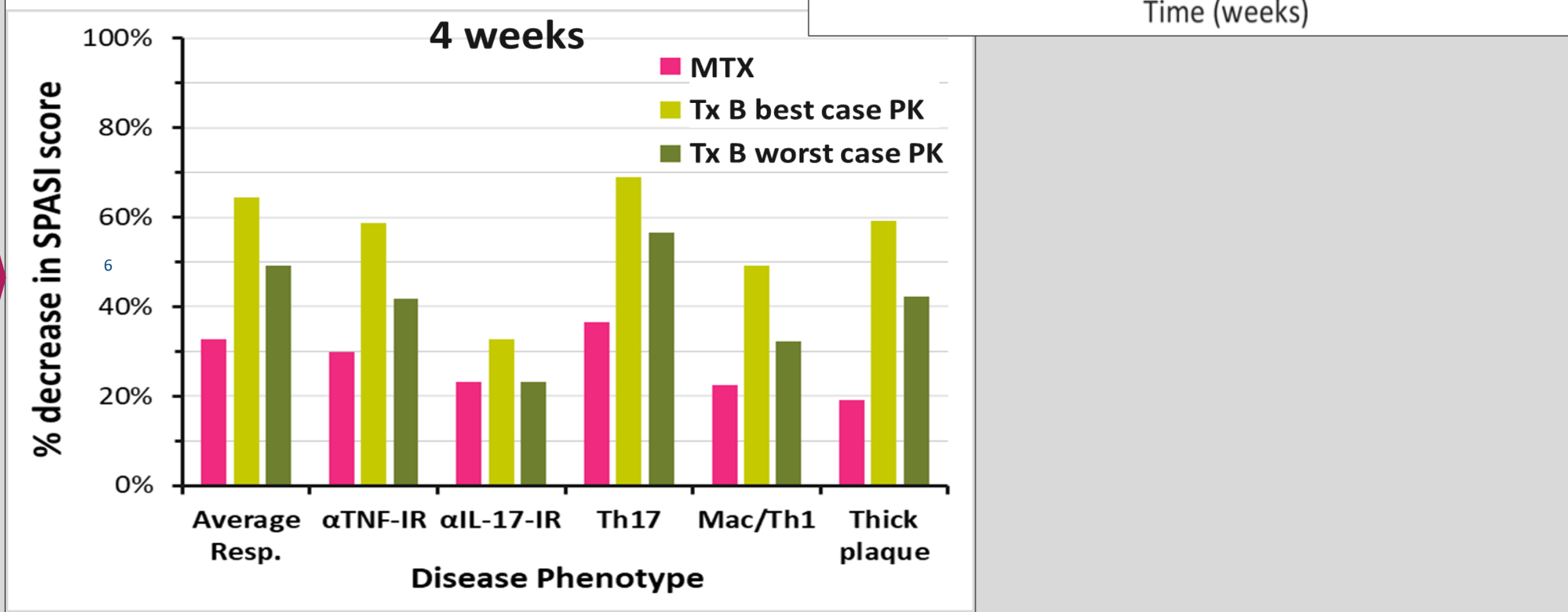


Figure 6. Application of the general workflow to derive a SPASI score calculation and predict SPASI response to a novel intervention in psoriasis.

References

1. Friedrich, CM. (2016) CPT: Pharmacometrics & Syst Pharmacol 5(2), 43-53.
2. <https://www.mathworks.com/products/simbiology.html>
3. <http://www.homeforeczema.org/research/easi-for-clinical-signs.aspx>
4. Simpson, EL, et al. N Engl J Med. 2016 Dec 15;375(24):2335-2348.
5. Langley, RG, et al. N Engl J Med. 2014 Jul 24;371(4):326-38.
6. Krueger, JG, et al. J Allergy Clin Immunol. 2012 Jul;130(1):145-54.e9.
7. Reich, K, et al. Exp Dermatol. 2015 Jul;24(7):529-35.