Scaling New Heights

ACoP 11

AMERICAN CONFERENCE ON PHARMACOMETRICS

Session : Bridging from mechanistic QSP models to subjective or complex clinical outcomes: challenges and approaches

Chairs:
Michael C. Weis, PhD

Using mechanistic quantitative systems pharmacology (QSP) models to connect biomarkers to clinical disease activity scores – examples in dermatology and chronic inflammatory diseases areas

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ROSA™

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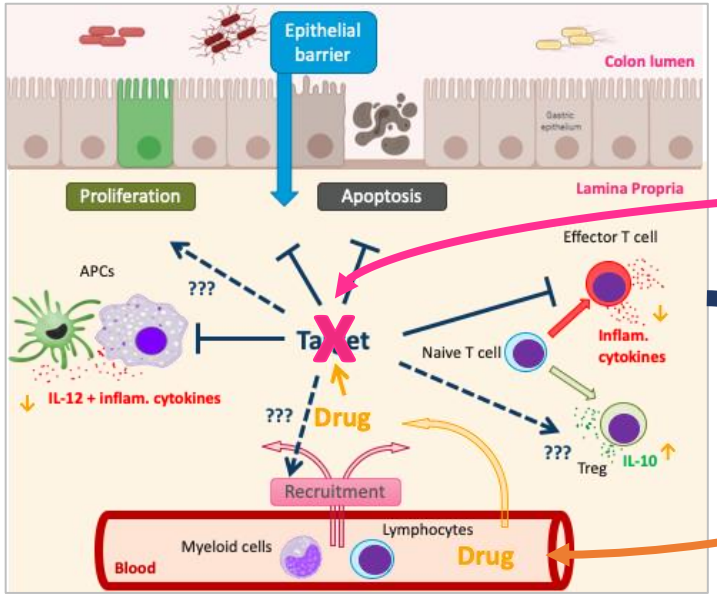
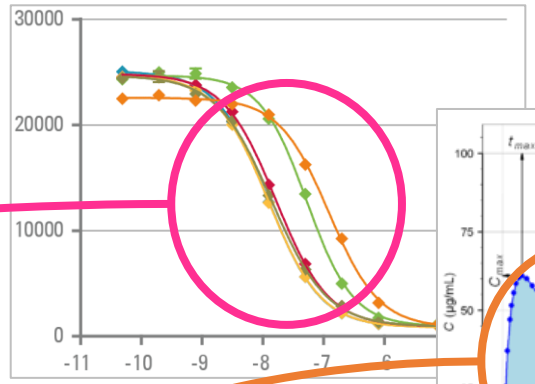
How to use QSP to bridge the gap between pre-clinical data, PKPD models and relevant clinical trials outcomes?

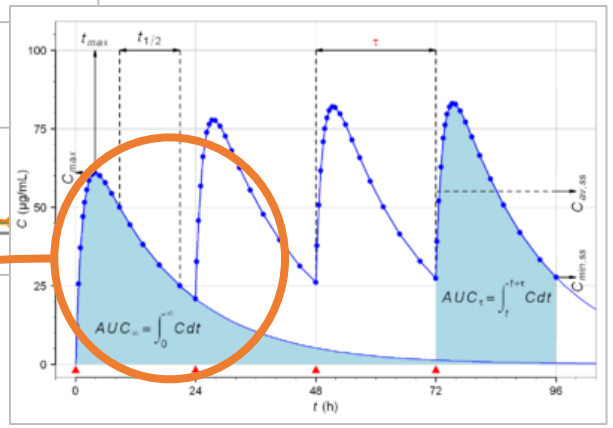
Mechanistic Understanding



Preclinical Evidence

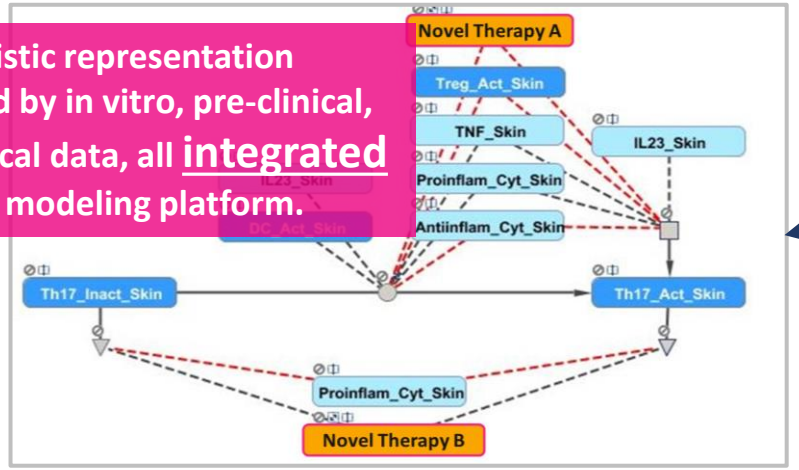


Drug PK



Alfie↑↓© (Helmut Schütz)

Mechanistic representation informed by in vitro, pre-clinical, and clinical data, all integrated into one modeling platform.



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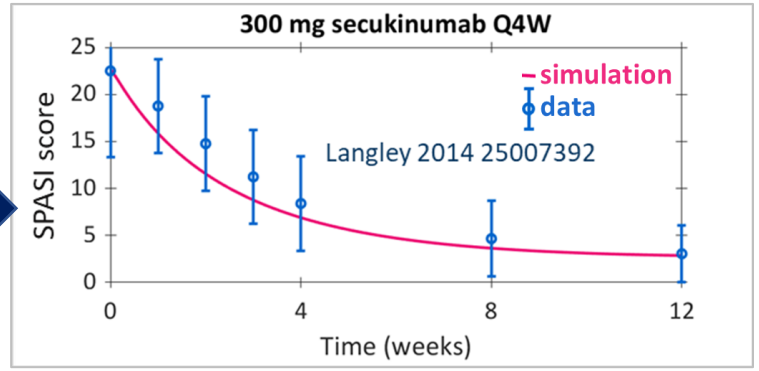
Clinical Outcomes



Disease scores are more or less complex, involving multiple objective and subjective measurements.

Robarts histopathology index (ulcerative colitis)

RHI = 1 × chronic inflammatory infiltrate level (4 levels)
+ 2 × lamina propria neutrophils (4 levels)
+ 3 × neutrophils in epithelium (4 levels)
+ 5 × erosion or ulceration (4 levels after combining Geboes 5.1 and 5.2).

EASI score (atopic dermatitis)

Table 1. Eczema area and severity index: calculation for patients 8 years of age and older[1]

Body region	EASI Score[2,3]
Head/Neck (H)	(E+I+Ex+L)×Area×0.1
Upper limbs (UL)	(E+I+Ex+L)×Area×0.2
Trunk (T)	(E+I+Ex+L)×Area×0.3
Lower limbs (LL)	(E+I+Ex+L)×Area×0.4
EASI =	*Sum of the above 4 body region scores*

[1]For children aged 0–7 years, proportionate areas were head/neck, 20%; upper limbs, 20%; trunk, 30%; and lower limbs, 30%.
[2]E=Erythema, I=induration/papulation, Ex=excoriation, L=lichenification.
[3]Where area is defined on a 7-point ordinal scale: 0=no eruption; 1=<10%; 2=<10%–29%; 3=<30%–49%; 4=<50%–69%; 5=<70%–89%; and 6=>90%–100%.

Hanifin 2001 PMID 11168575

DAS28, SDAI score (rheumatoid arthritis)

Formulae to calculate the different DAS and SDAI score

Score	Formula
DAS28	0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.70*ln(ESR) + 0.014*pt global VAS
DAS28-3	[0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.70*ln(ESR)]*1.08 + 0.16
DAS28-CRP	0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.36*ln(CRP+1) + 0.014* pt global VAS + 0.96
DAS28-CRP-3	[0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.36*ln(CRP+1)] * 1.10 + 1.15
SDAI	28TJC + 28SJC + CRP/10 + pt global VAS/10 + phys global VAS/10
CDAI	28TJC + 28SJC + pt global VAS/10 + phys global VAS/10

Quantitative biomarker (# of affected joints, CRP levels)

Subjective measurement

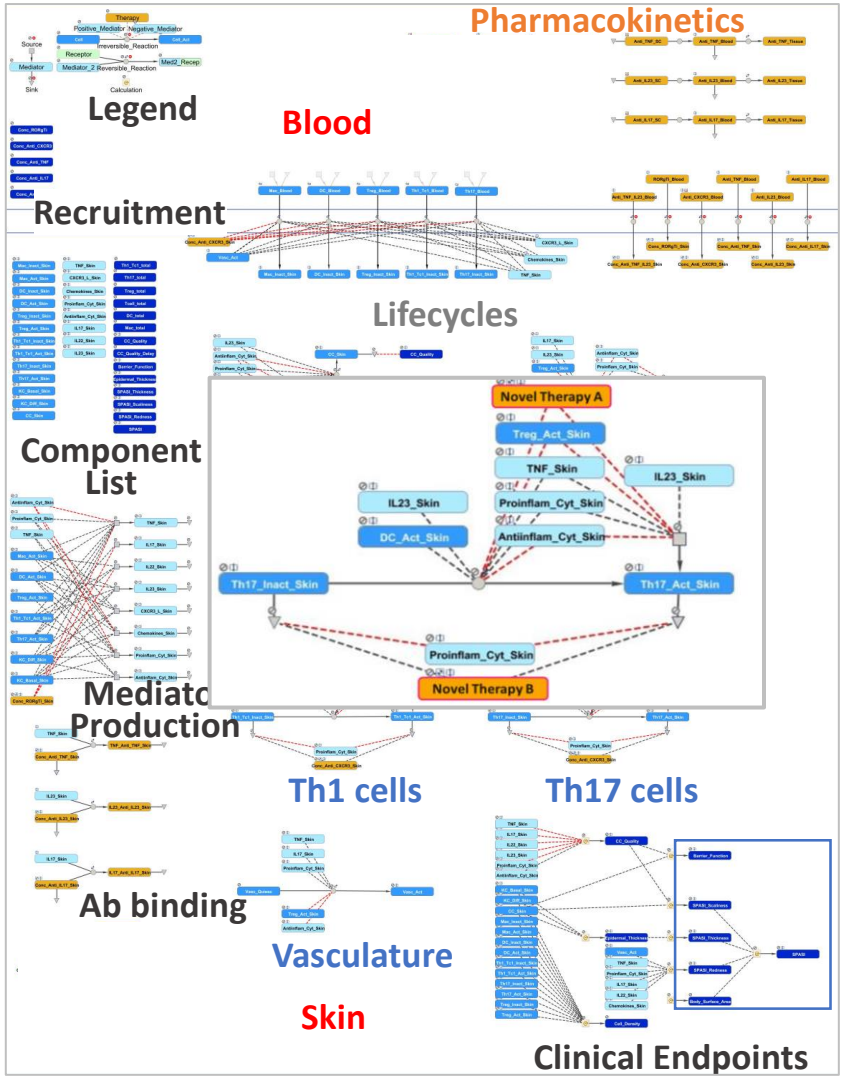
Vander Cruyssen 2005 PMID 16207323

Systematic Process Used by Rosa

1. Develop QSP model connecting mechanisms to measurable biomarkers

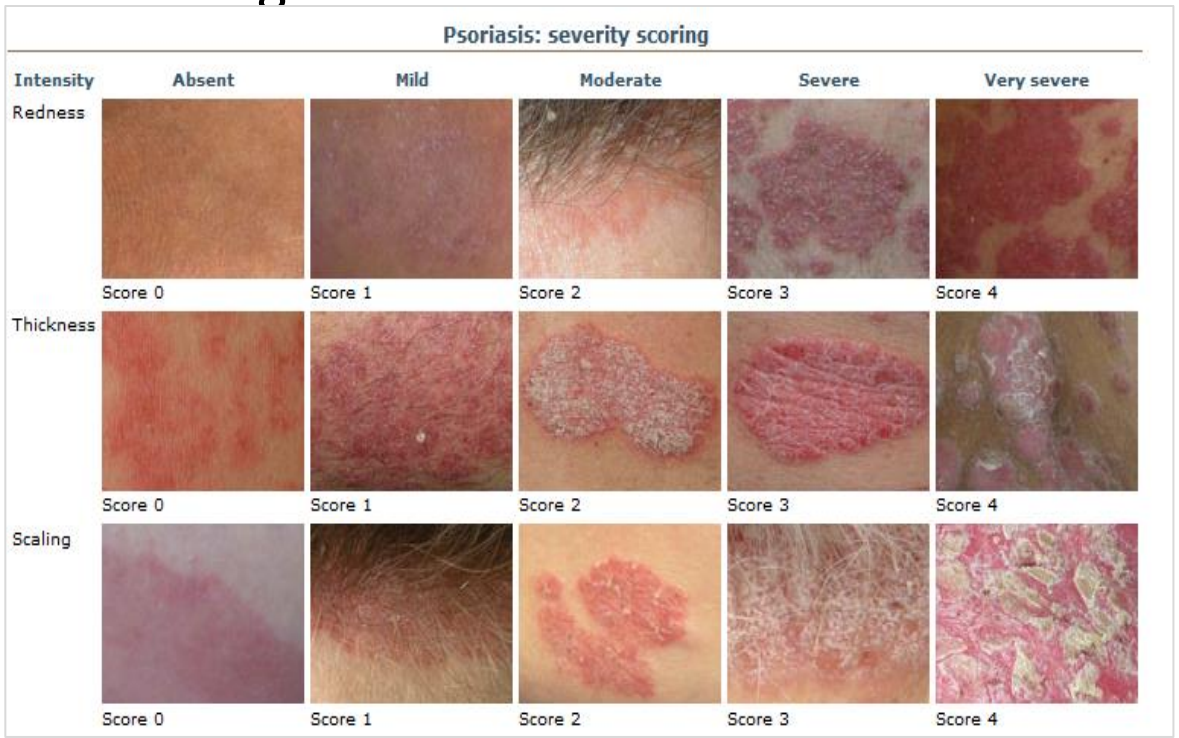
- The goal of the fit-for-purpose QSP model is to address a specific research question
- Model components necessary to represent target MOA and disease pathophysiology are prioritized
- Discussions with the scientific team inform inclusion of relevant biomarkers, therapies and calculations of defined endpoints

Psoriasis Platform



2. Identify relevant and practical disease scores and their critical clinical subscores components

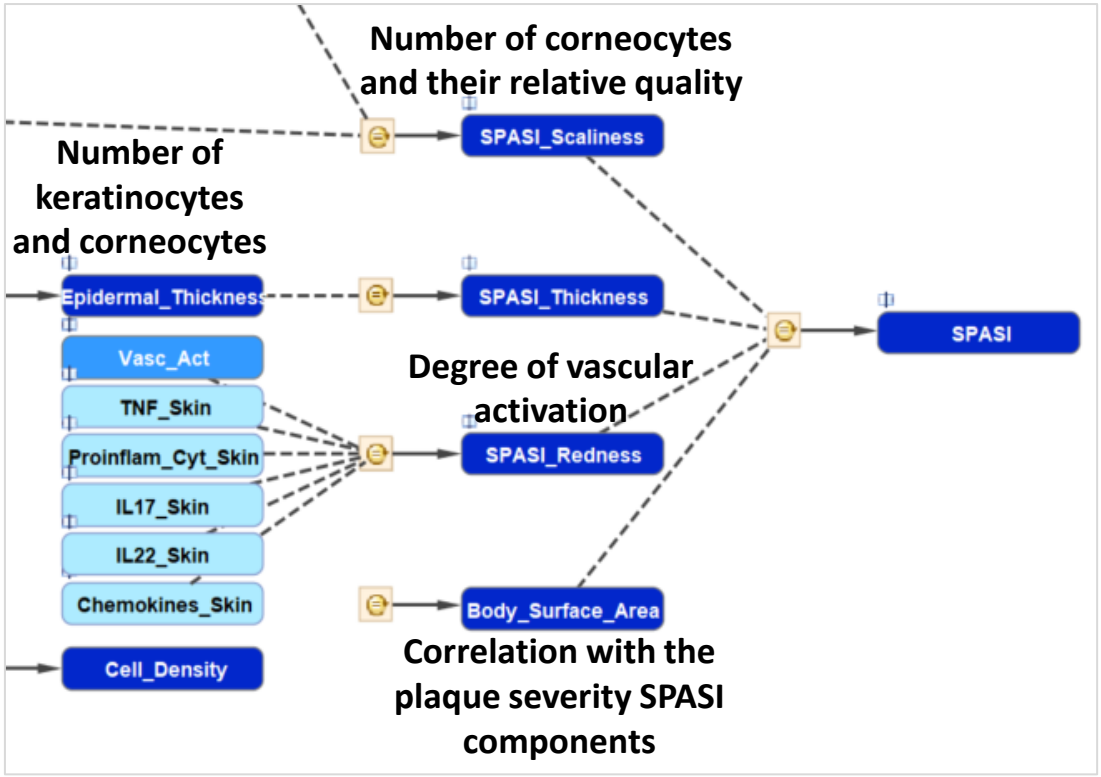
- PASI score $PASI = 0.1\cdot(E_H+I_H+D_H)\cdot A_H+0.2\cdot(E_A+I_A+D_A)\cdot A_A+0.3\cdot(E_T+I_T+D_T)\cdot A_T+0.4\cdot(E_L+I_L+D_L)\cdot A_L$
  - Body divided into four sections (**H**ead, **A**rms, **T**runk, **L**ower)
    - percent of body surface area (% BSA) involved estimated (A_H, A_A, A_T, A_L)
  - Severity estimated by three clinical signs measured on a scale from 0 to 4
    - **E**rythema (redness)
    - **I**nduration (thickness)
    - **D**esquamation (scaling)



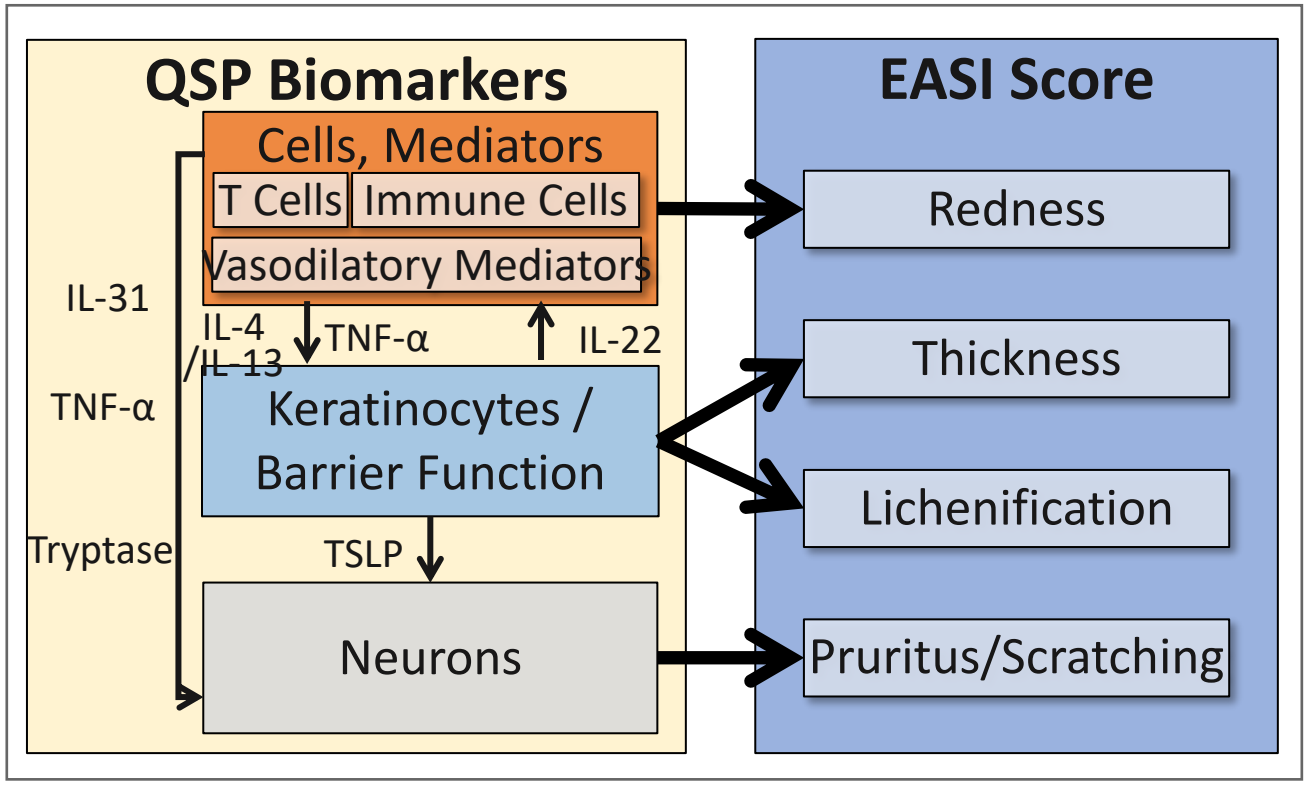
Examples of redness, thickness, and scaling used in a PASI score. (http://www.dermnetnz.org/scaly/pasi.html)

3. Map disease score components to QSP model species or biomarkers

SPASI Score Component Mapping

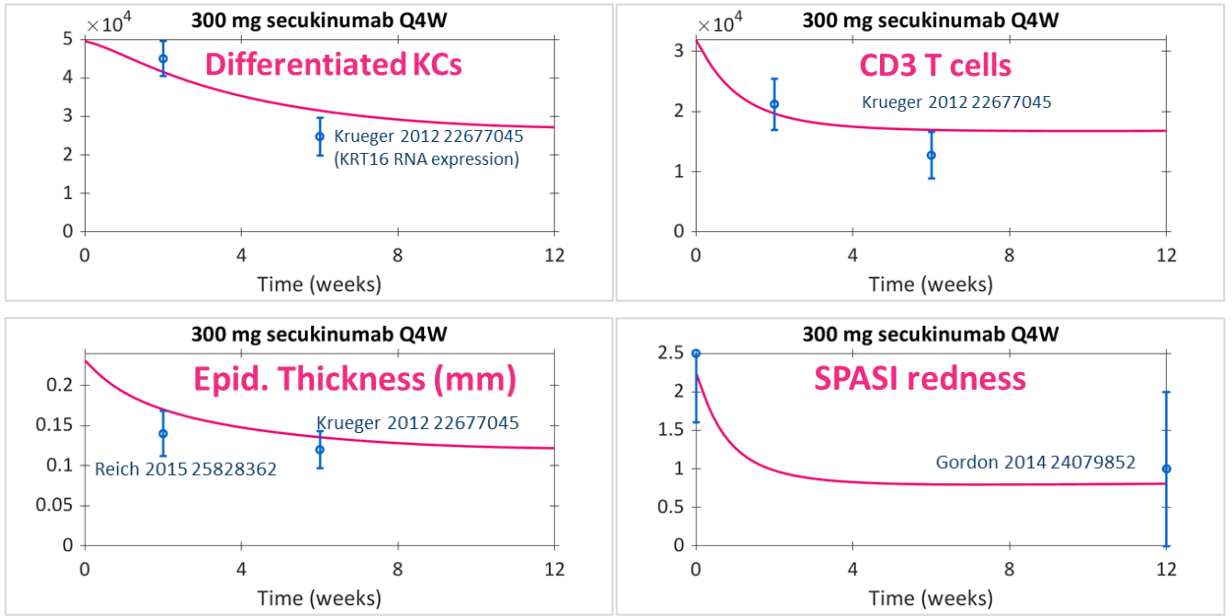


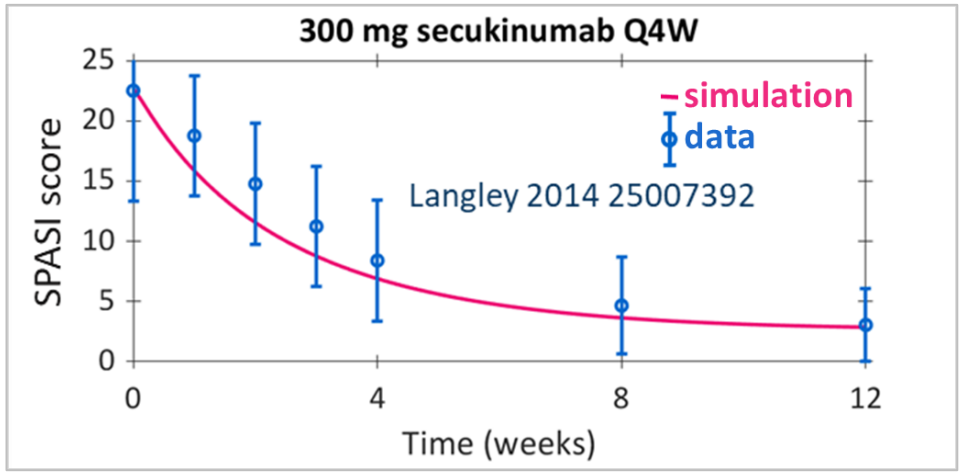
EASI Score Component Mapping



4 . Fit parameters for outcome calculations to match published/proprietary clinical data

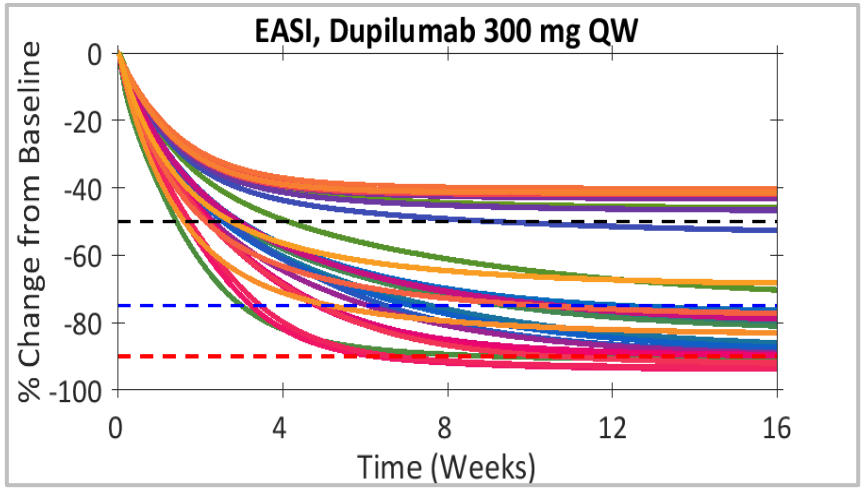
- Calibrate QSP model parameters to match changes in mediators and cell numbers with therapies
- Calculate disease score components parameters to match changes in disease subscores
- Integrate disease subscore components into overall clinical score, adjusting parameters if necessary, to match clinical data

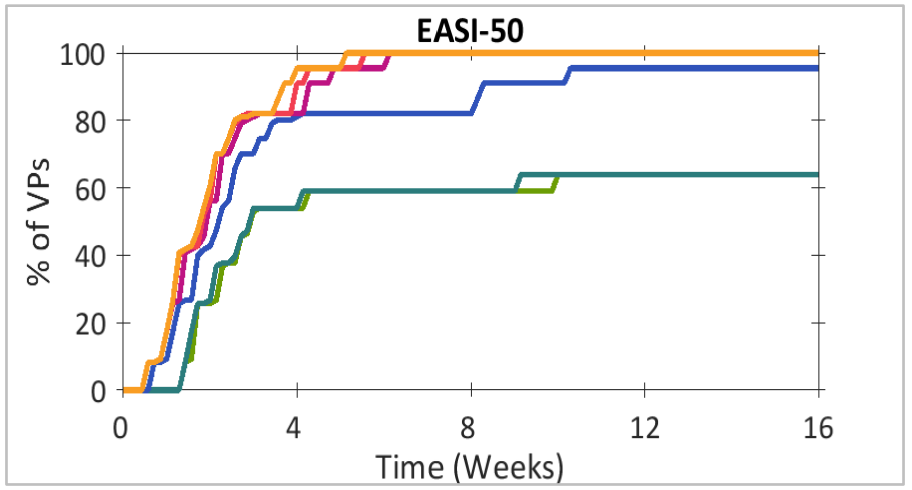




5. Use simulated clinical score outcomes to compare efficacy of new drugs to SOC therapies in virtual patients

EASI score (atopic dermatitis)



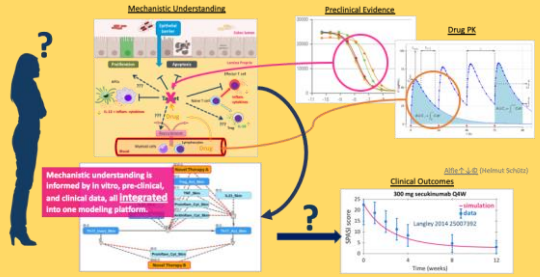


Dupilumab 300 mg Q2W
Dupilumab 300 mg QW
DS-2741a 5 mg per kg Q2W
DS-2741a 10 mg per kg Q2W
DS-2741a 15 mg per kg Q2W
DS-2741a 10 mg per kg QW

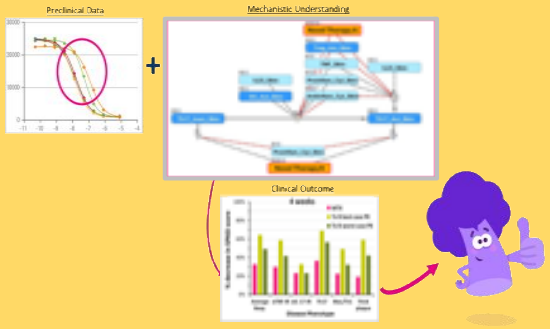
Remaining challenges and limitations

Challenging Clinical Endpoints for QSP	Solution Used in QSP Projects
• Trial results expressed as % of patients reaching a specific clinical response criteria (ACR20, EASI-50, RECIST,…)	➔ Build a prevalence weighted virtual patient cohort using detailed individual patient data from existing clinical trial
• Discrete events (flares, nausea, asthma attacks,…)	➔ Use a statistical threshold model based on correlation with a continuous outcome
• Progression-free survival in oncology • Cognitive outcomes in neurological disease	➔ Identify, with clinicians' help, alternate endpoints that can help answering the specific research question

Key Take Home Messages



Complex scores can be simulated in QSP models, if a link between model biomarkers and the disease subscores can be established and calibrated with clinical data.



The capacity of a QSP Platform to report clinically relevant disease scores allows broader adoption of QSP modeling throughout clinical organizations.

Acknowledgments

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