QSP

What's in it for me

do more feel better live longer

Quantitative

Systems

Pharmacology

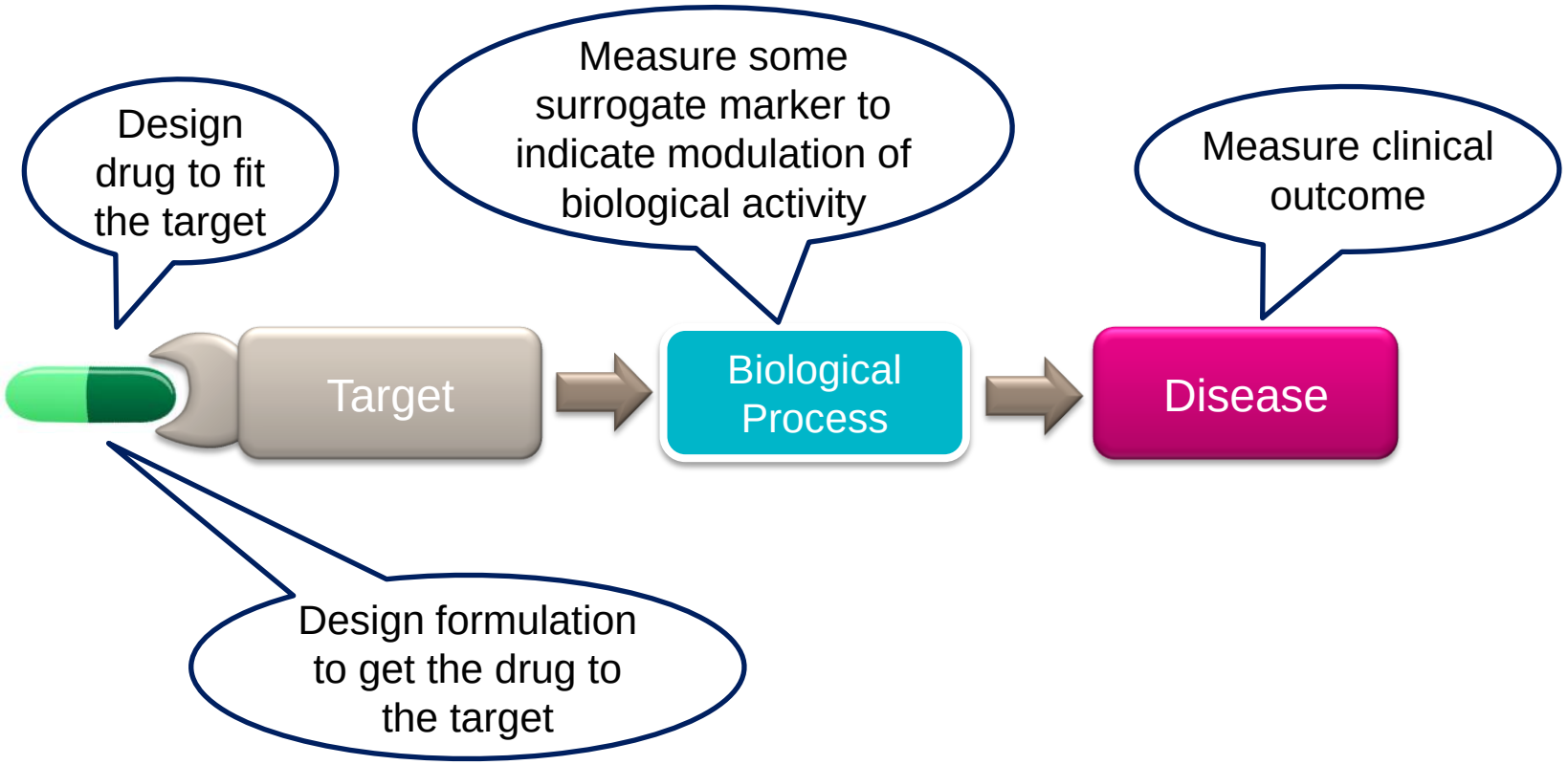
Rosa webinar
July 2017

Valeriu Damian

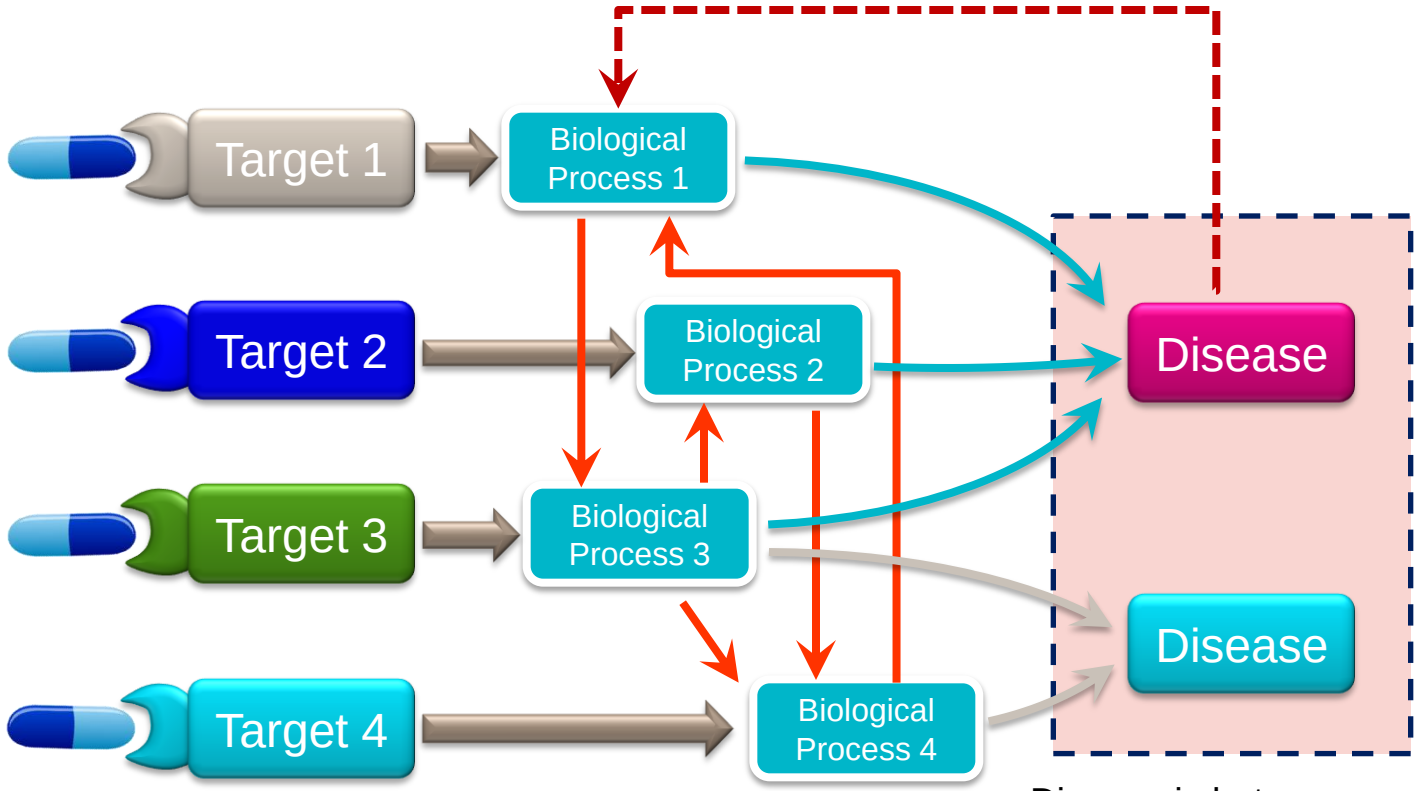
ISoP Special Interest Group

Quantitative Systems Pharmacology

One Drug-One Target-One Disease Philosophy



Unfortunately biology is a little more complicated than that . . . .

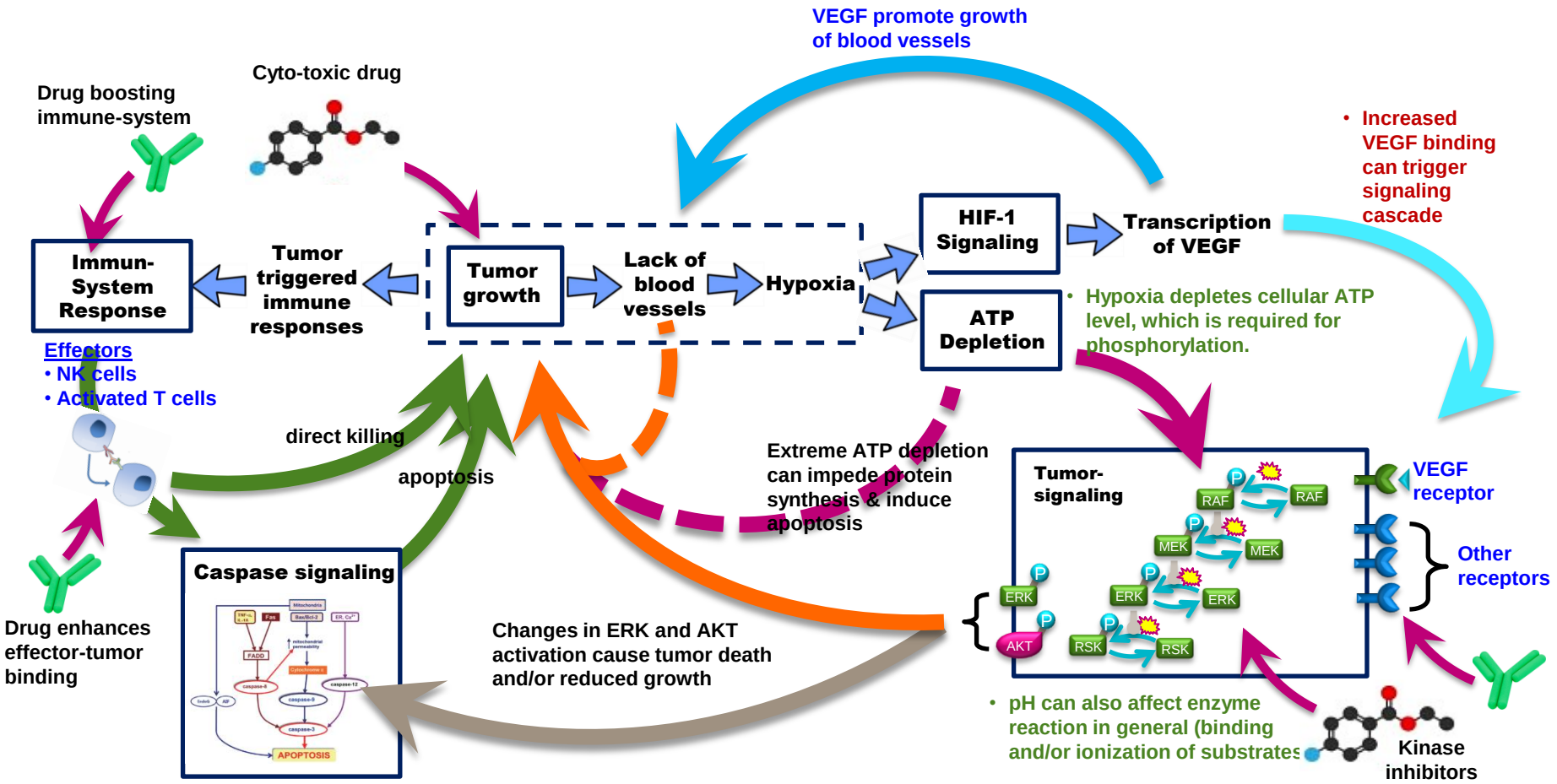


Disease is heterogeneous

Multiple interactive biological processes are in play:

- Redundancy
- Switching
- Feedback

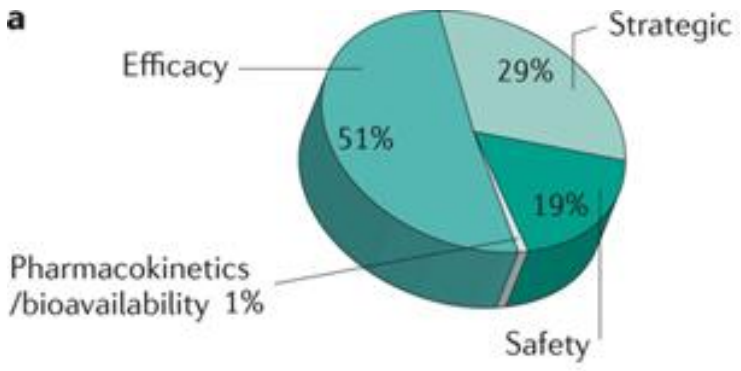
An example of complex disease biology



What happens when we ignore this complexity

Many drug candidate fail due to lack of efficacy

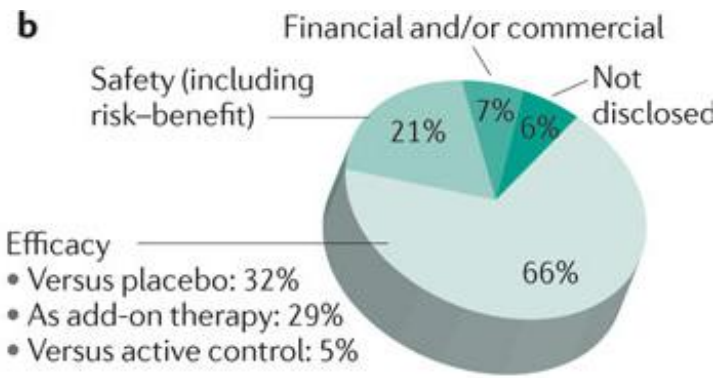
Phase II Failures 2008-2010



Total of 108 failures

Arrowsmith, John. *Nature Reviews Drug Discovery* 10.5 (2011): 328-329

Phase III Failures 2007-2010



Total of 83 failures

Arrowsmith, John. *Nature Reviews Drug Discovery* 10.2 (2011): 87-87.

Solution

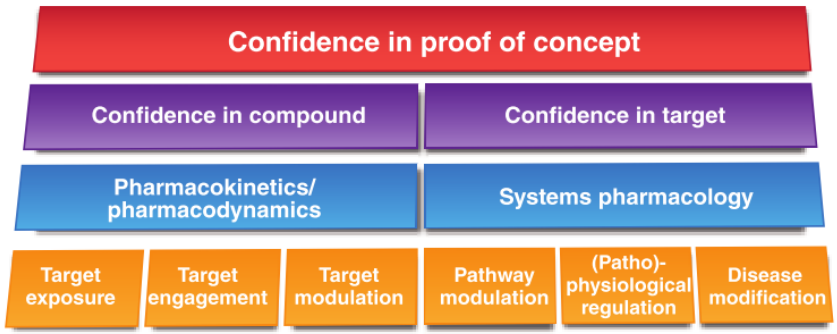


Figure 2 The relationship between pharmacokinetics/pharmacodynamics ("three pillars of survival"[11]) and systems pharmacology as parallel approaches to tackle attrition due to insufficient efficacy in proof-of-concept–phase II trials.

QSP

PBPK

PK/PD

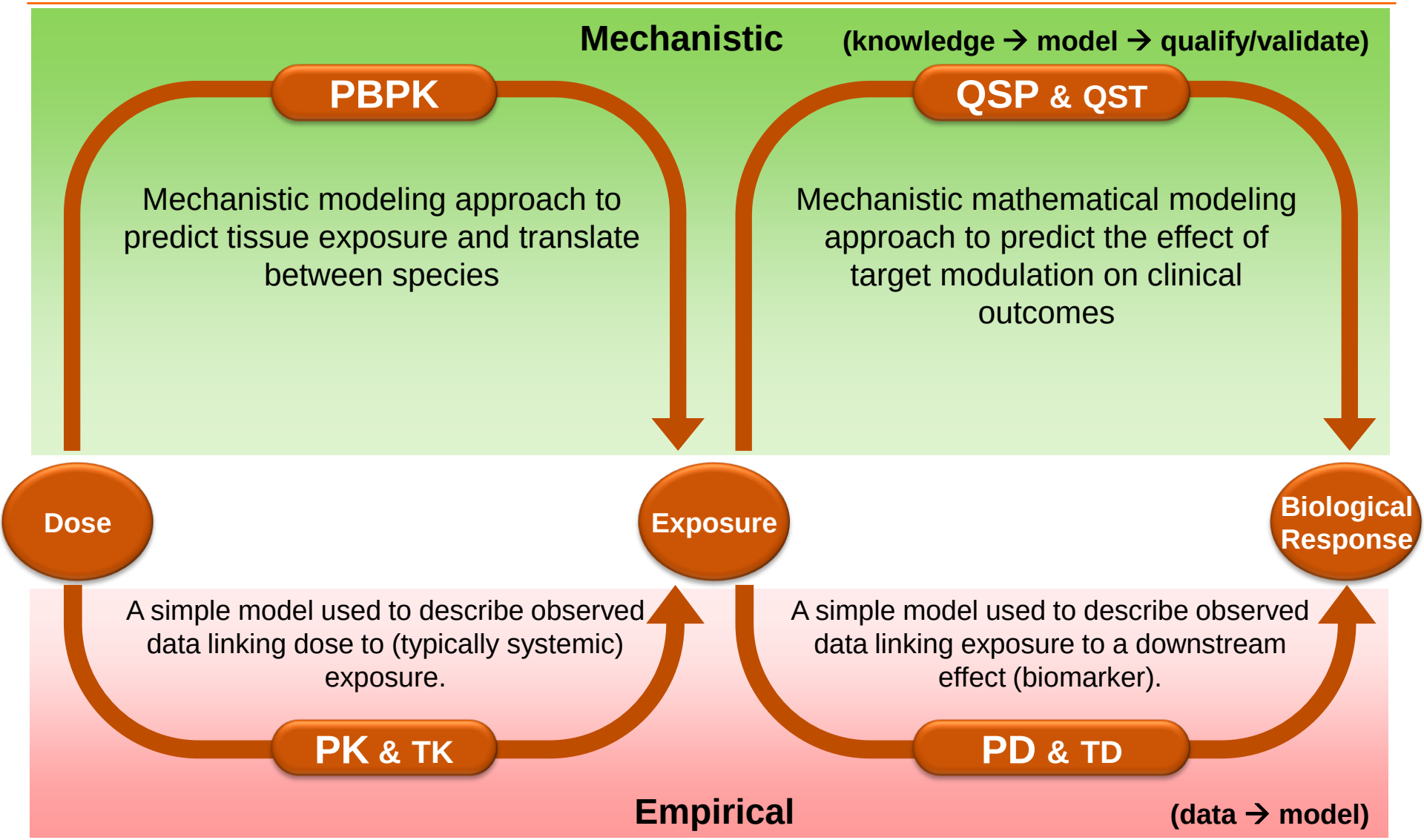
PBPK/PD

PK/QSP

PBPK/QSP

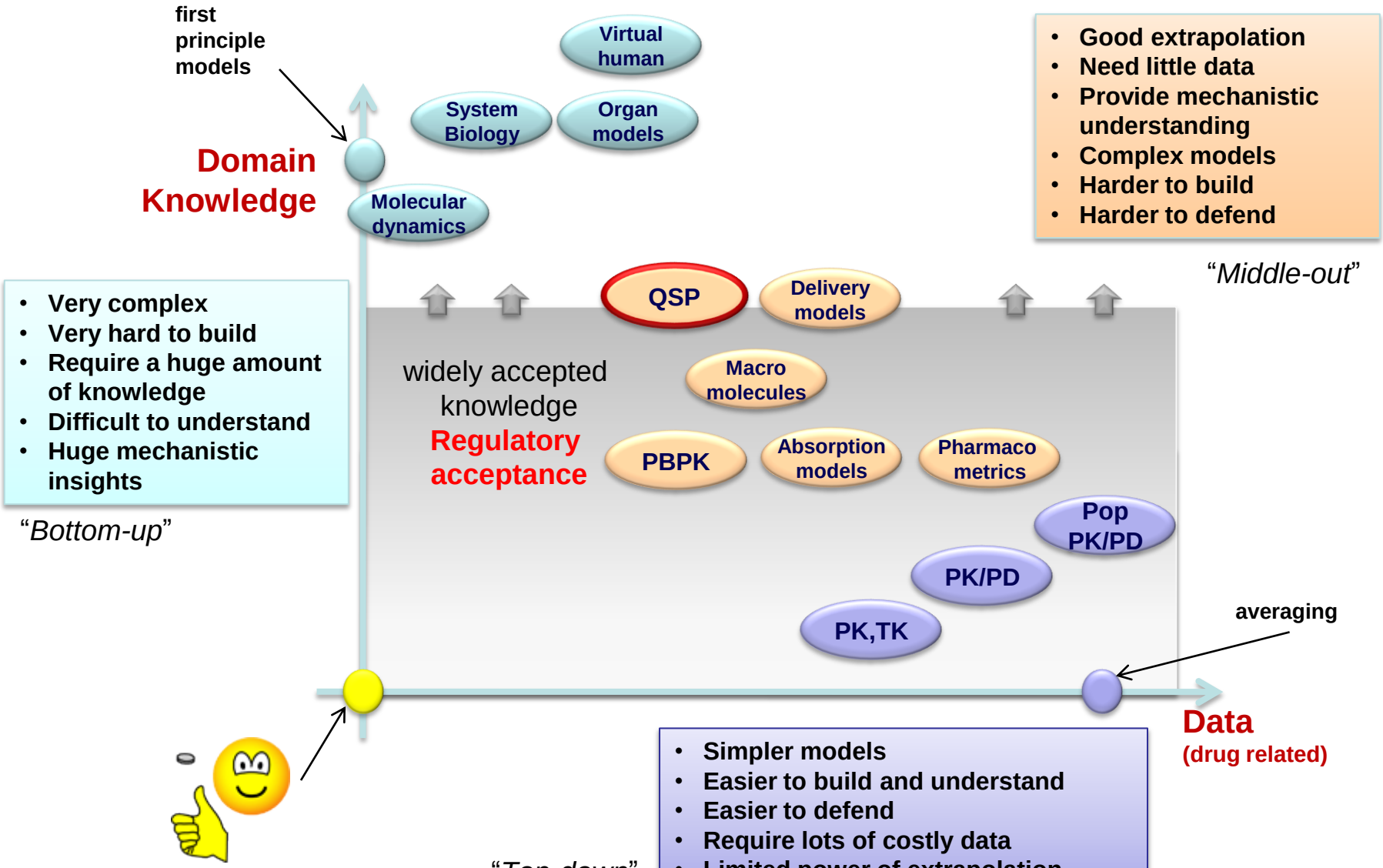
Vicini, P. and van der Graaf, P. H. (2013), Systems Pharmacology for Drug Discovery and Development: Paradigm Shift or Flash in the Pan?. Clinical Pharmacology & Therapeutics, 93: 379–381. doi:10.1038/clpt.2013.40

PBPK vs PK/PD vs QSP



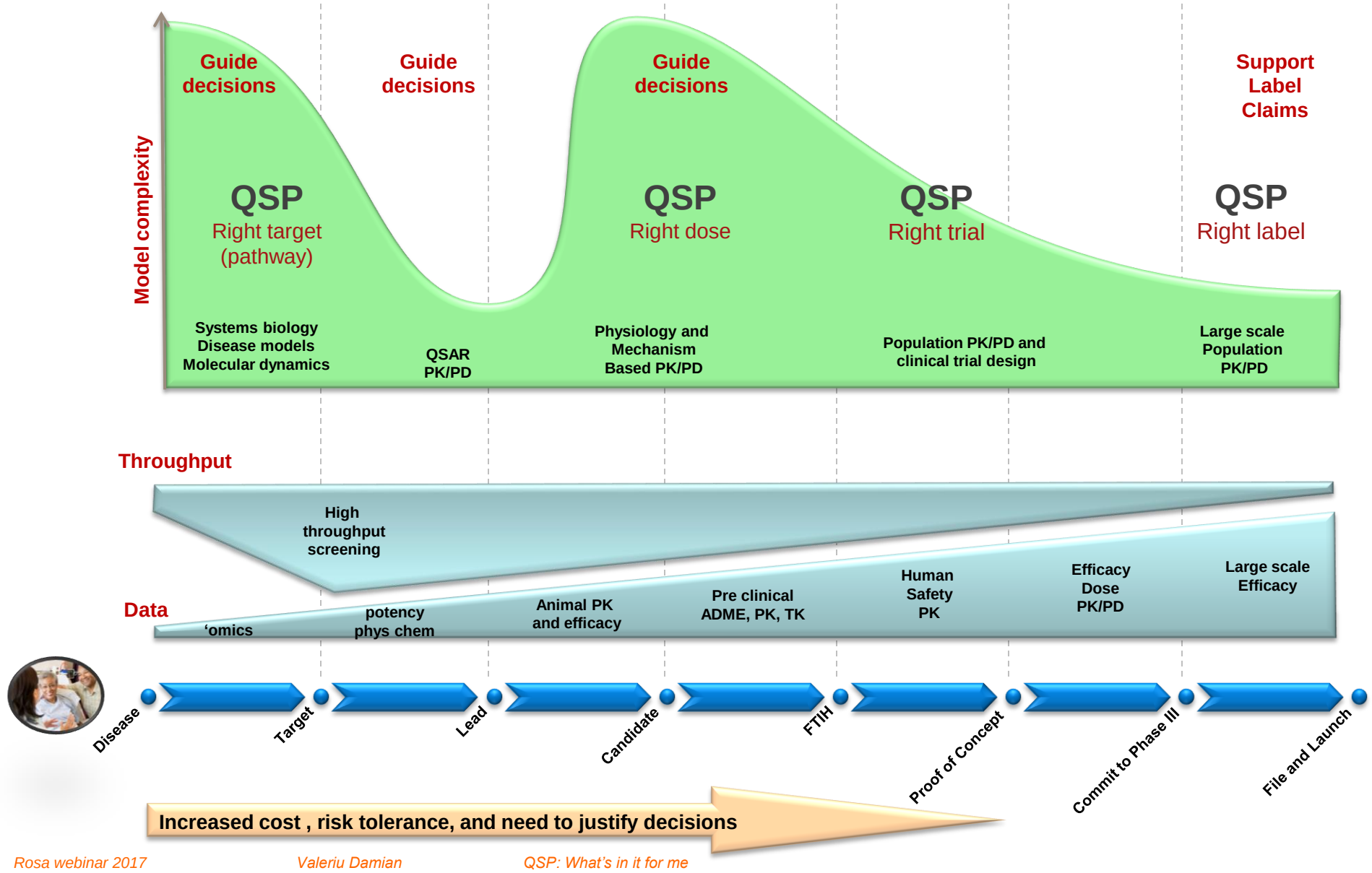
Data vs knowledge based models

Classification and regulatory acceptance



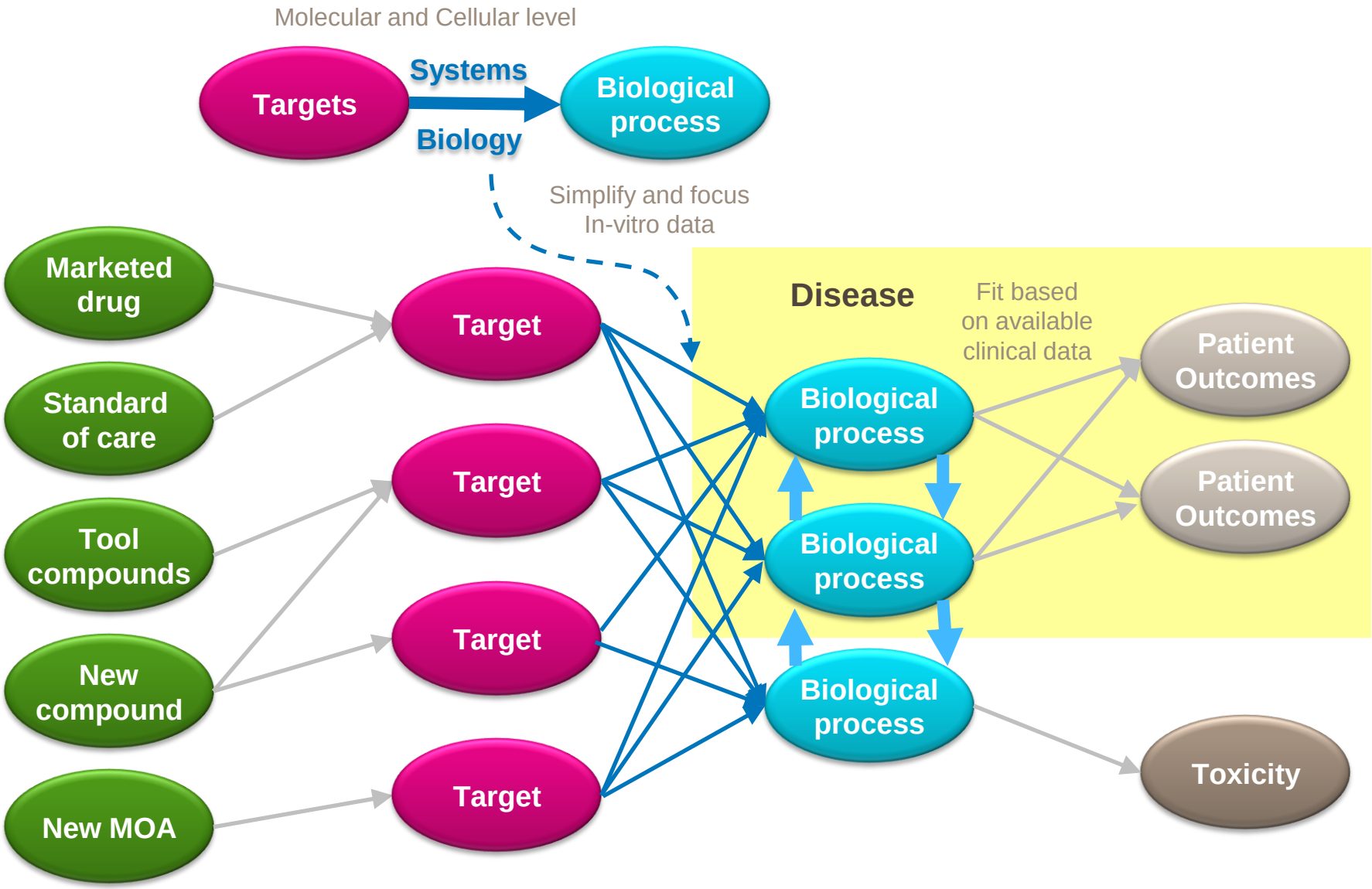
Data vs knowledge driven models

Model complexity in drug discovery and development



Quantitative System Pharmacology

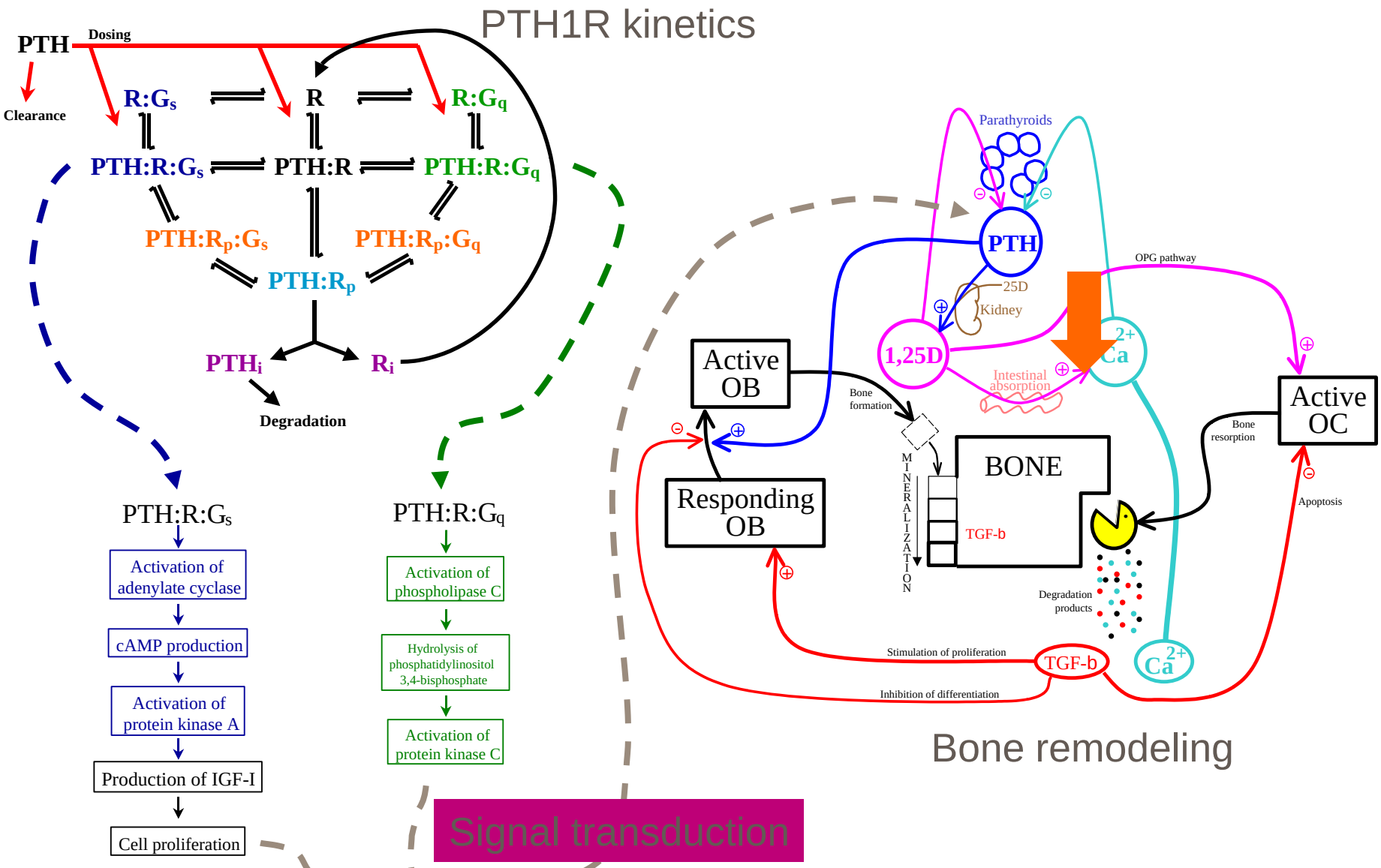
Lining drug action at target with clinical outcomes



QSP model for PTH-mediated effects on bone

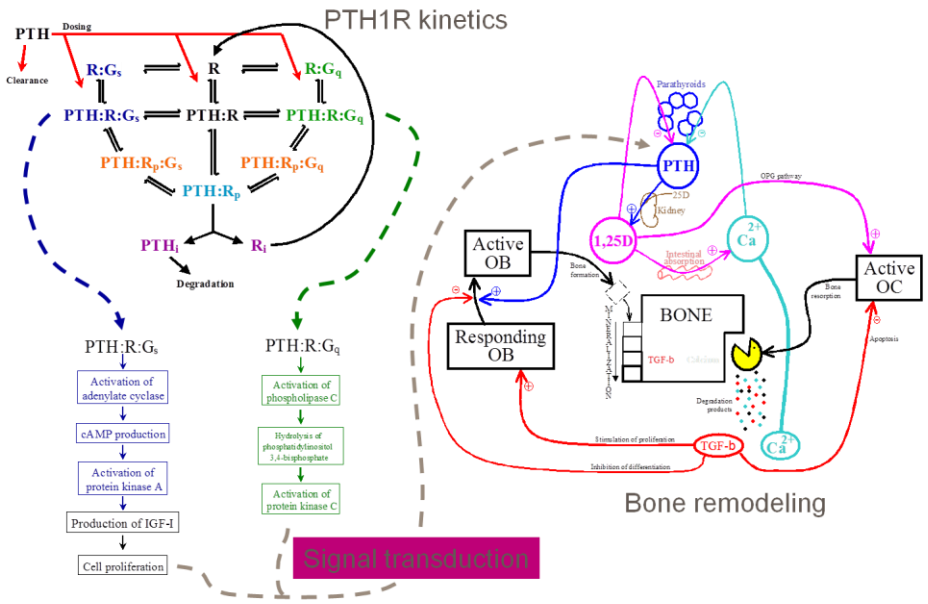
2003

Laura Potter and Vincent Lemaire



QSP model for PTH-mediated effects on bone 2003

Laura Potter and Vincent Lemaire



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Journal of Theoretical Biology 229 (2004) 293–309
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Modeling the interactions between osteoblast and osteoclast activities in bone remodeling

Vincent Lemaire[a,*], Frank L. Tobin[a,1], Larry D. Greller[a,2], Carolyn R. Cho[a,3], Larry J. Suva[b,4]

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Received 23 April 2003; received in revised form 27 January 2004; accepted 29 March 2004

Bone 46 (2010) 49–63
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Contents lists available at ScienceDirect
Bone
journal homepage: www.elsevier.com/locate/bone

A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling

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[b] Metrum Research Group LLC, 2 Tunxis Road, Suite 112, Tariffville, CT 06081, USA

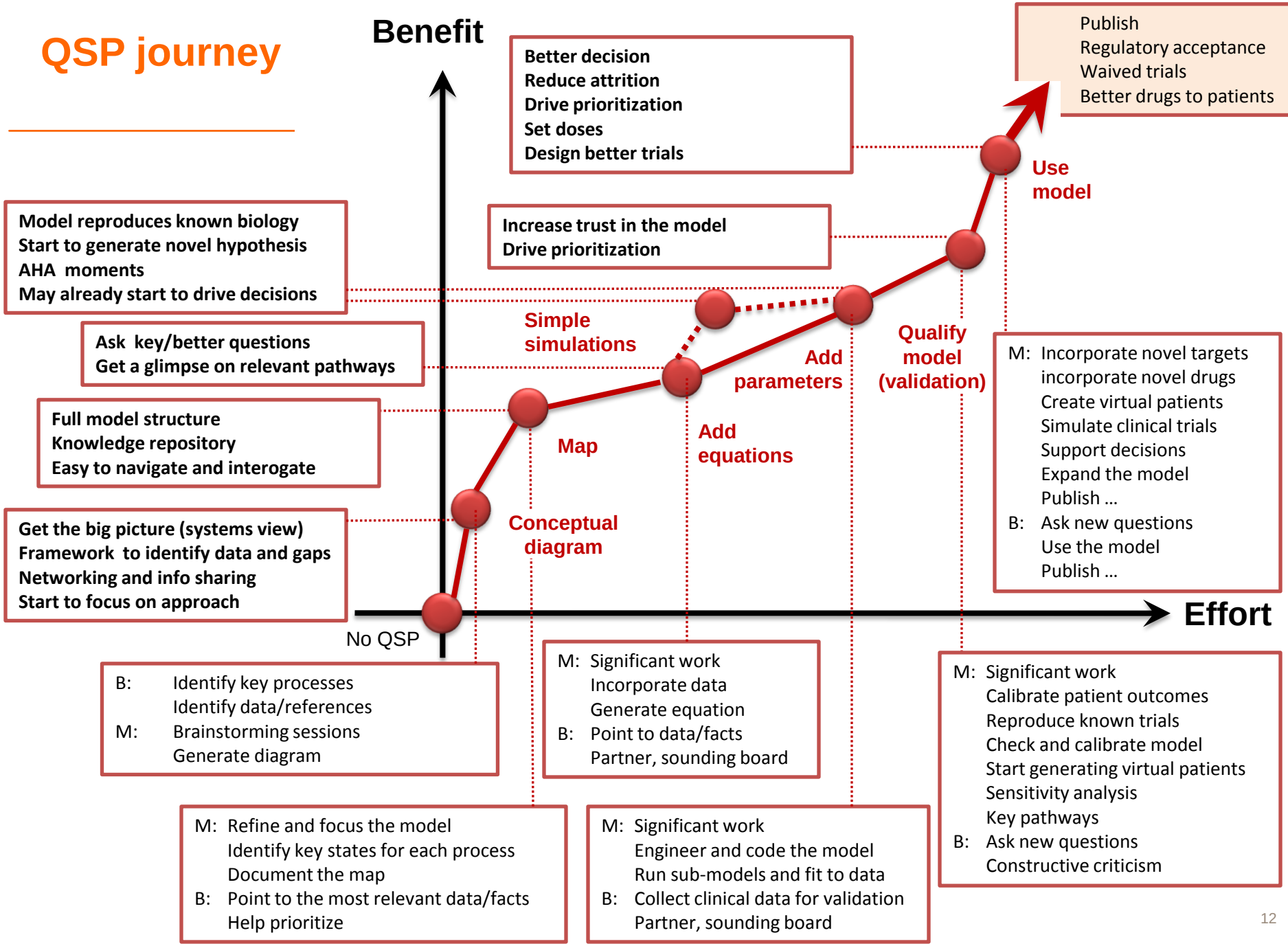
First FDA approval supported in part by QSP model

NPS Pharma
The Nexus of Patients and Science™

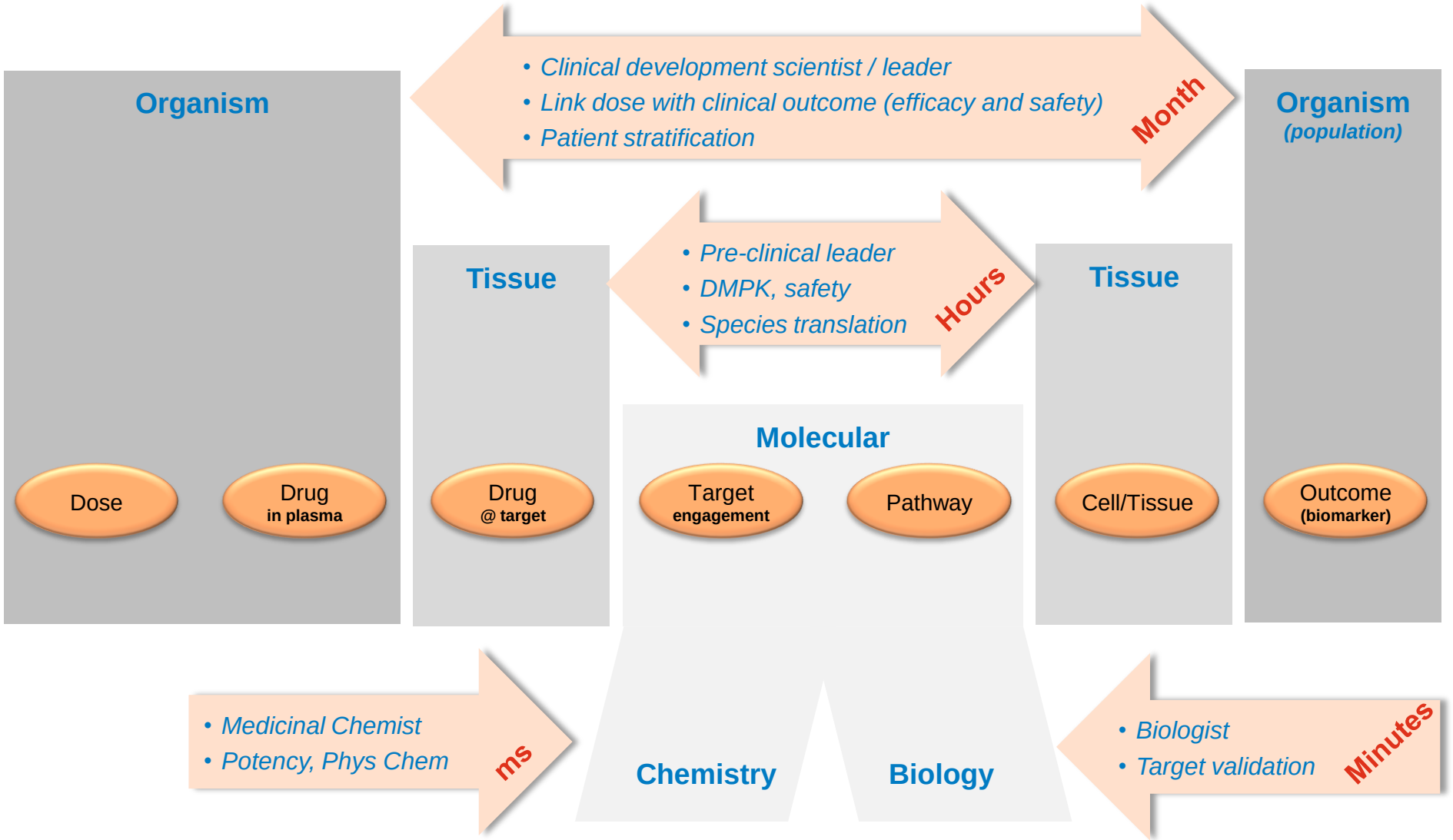
Jan 23, 2015

FDA Approves Natpara® (parathyroid hormone) for Injection as an Adjunct to Calcium and Vitamin D to Control Hypocalcemia in Patients with Hypoparathyroidism

QSP journey

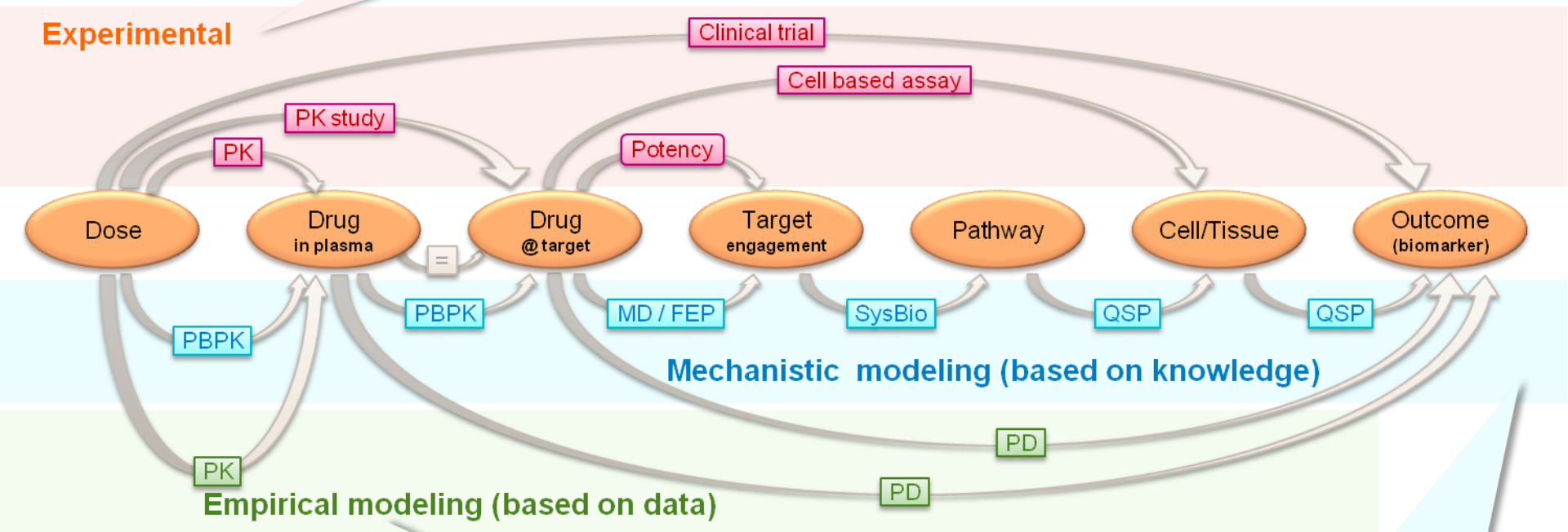

Benefit
Effort
No QSP
Conceptual diagram
Map
Add equations
Add parameters
Simple simulations
Qualify model (validation)
Use model
Better decision
Reduce attrition
Drive prioritization
Set doses
Design better trials
Publish
Regulatory acceptance
Waived trials
Better drugs to patients
Model reproduces known biology
Start to generate novel hypothesis
AHA moments
May already start to drive decisions
Increase trust in the model
Drive prioritization
Ask key/better questions
Get a glimpse on relevant pathways
Full model structure
Knowledge repository
Easy to navigate and interogate
Get the big picture (systems view)
Framework to identify data and gaps
Networking and info sharing
Start to focus on approach
M: Incorporate novel targets
incorporate novel drugs
Create virtual patients
Simulate clinical trials
Support decisions
Expand the model
Publish …
B: Ask new questions
Use the model
Publish …
B: Identify key processes
Identify data/references
M: Brainstorming sessions
Generate diagram
M: Significant work
Incorporate data
Generate equation
B: Point to data/facts
Partner, sounding board
M: Significant work
Calibrate patient outcomes
Reproduce known trials
Check and calibrate model
Start generating virtual patients
Sensitivity analysis
Key pathways
B: Ask new questions
Constructive criticism
M: Refine and focus the model
Identify key states for each process
Document the map
B: Point to the most relevant data/facts
Help prioritize
M: Significant work
Engineer and code the model
Run sub-models and fit to data
B: Collect clinical data for validation
Partner, sounding board

Multidisciplinary and multiscale nature of QSP models



Quantitative Pharmacology (QP) toolbox

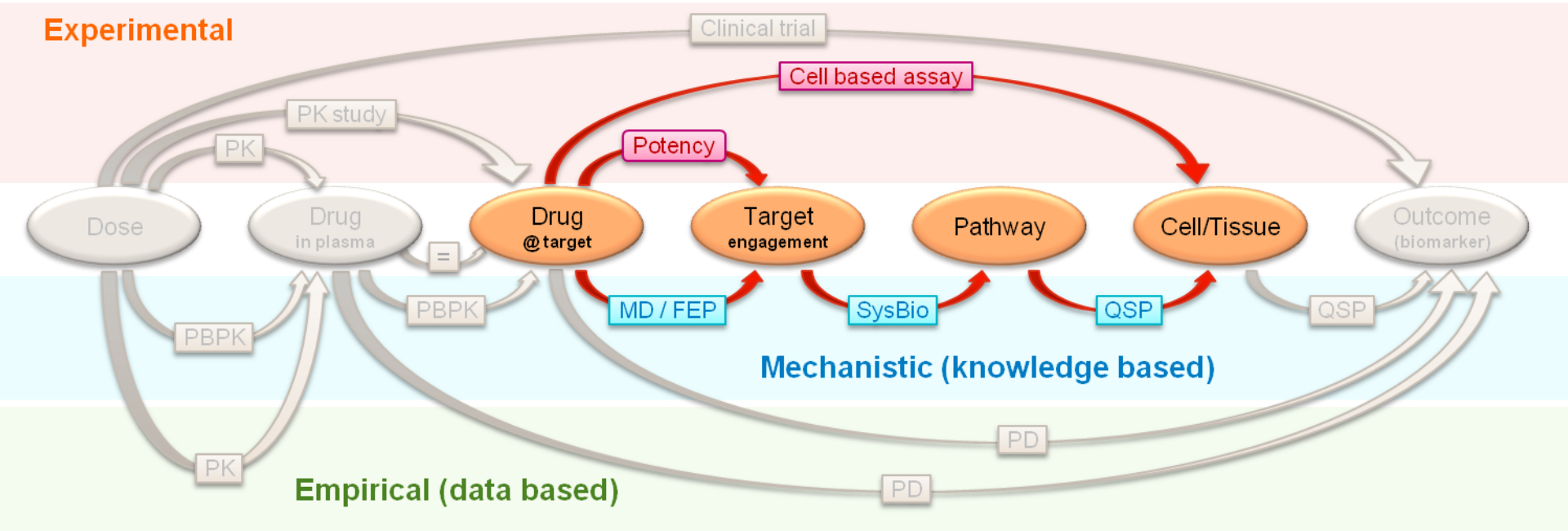
- *Costly to generate*
- *Expected in most cases*
- *Definitive answer*
- *… almost all the time*



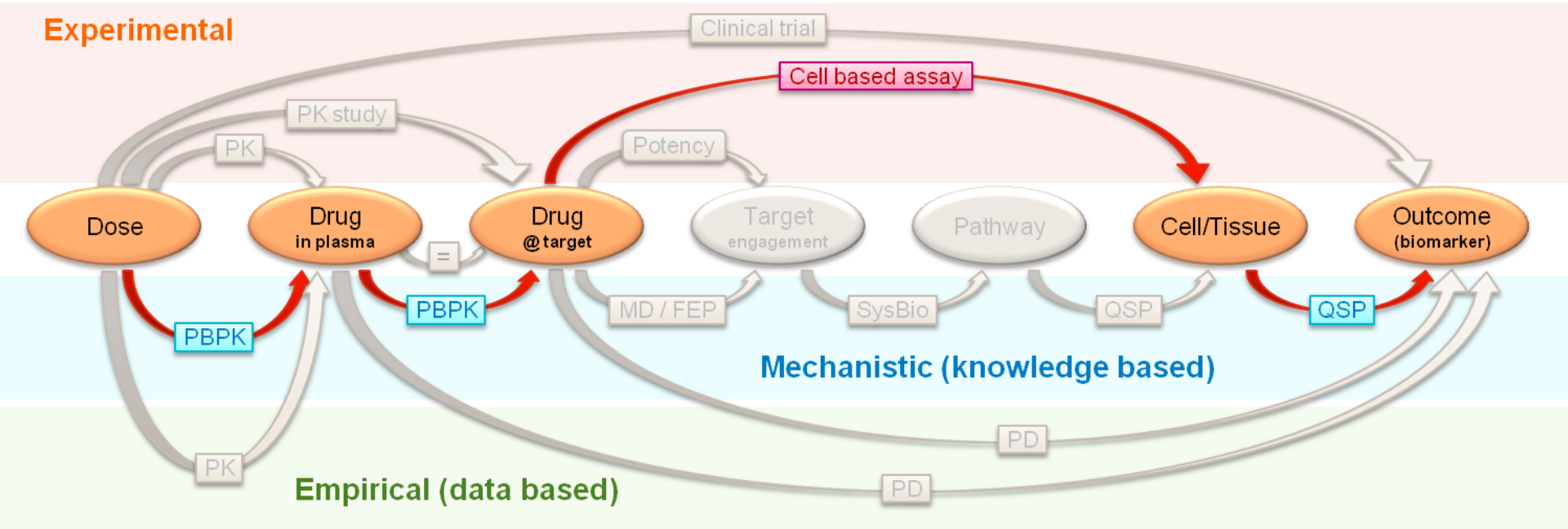
- *Easier to build the model*
- *Easier to defend*
- *Requires costly data*
- *Limited extrapolation*

- *Challenging to build*
- *Challenging to defend*
- *Mostly in-vitro data needed*
- *Understanding and extrapolation*

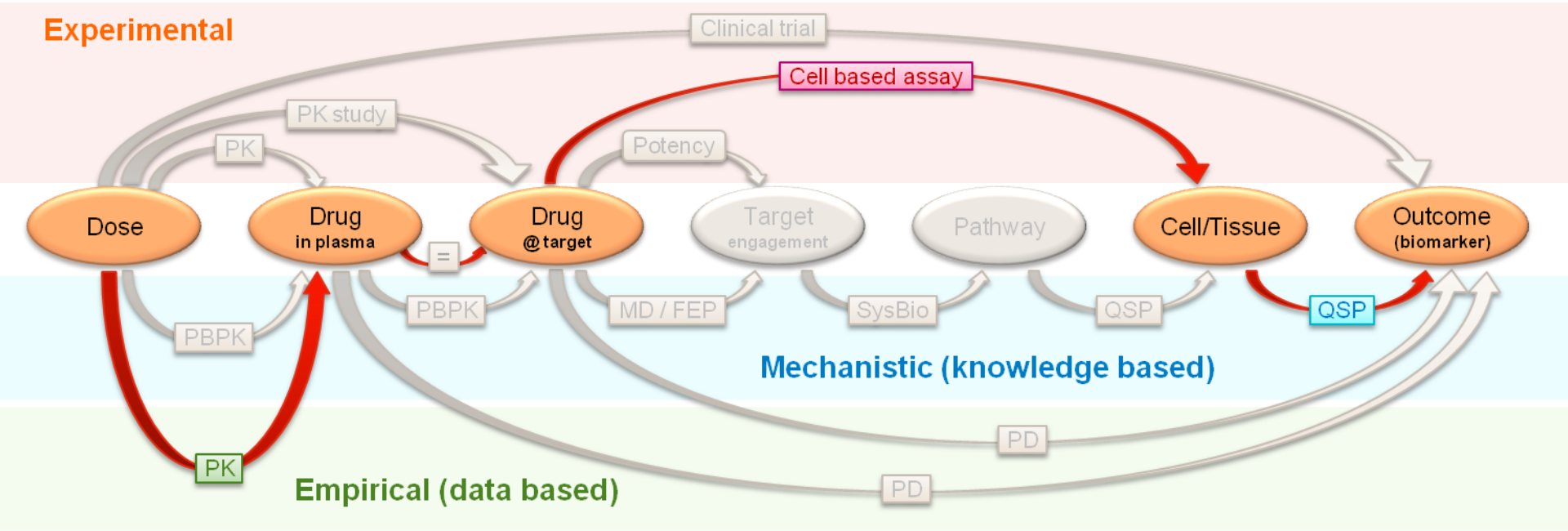
QSP during early discovery (target validation)



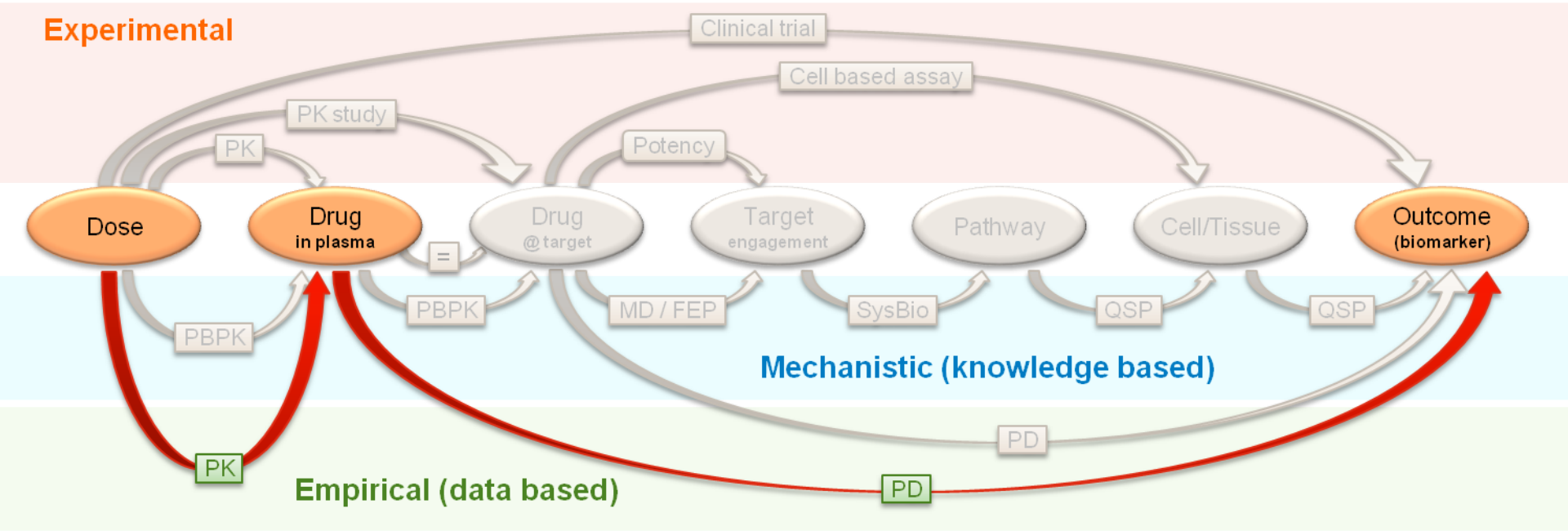
QSP early stage clinical development



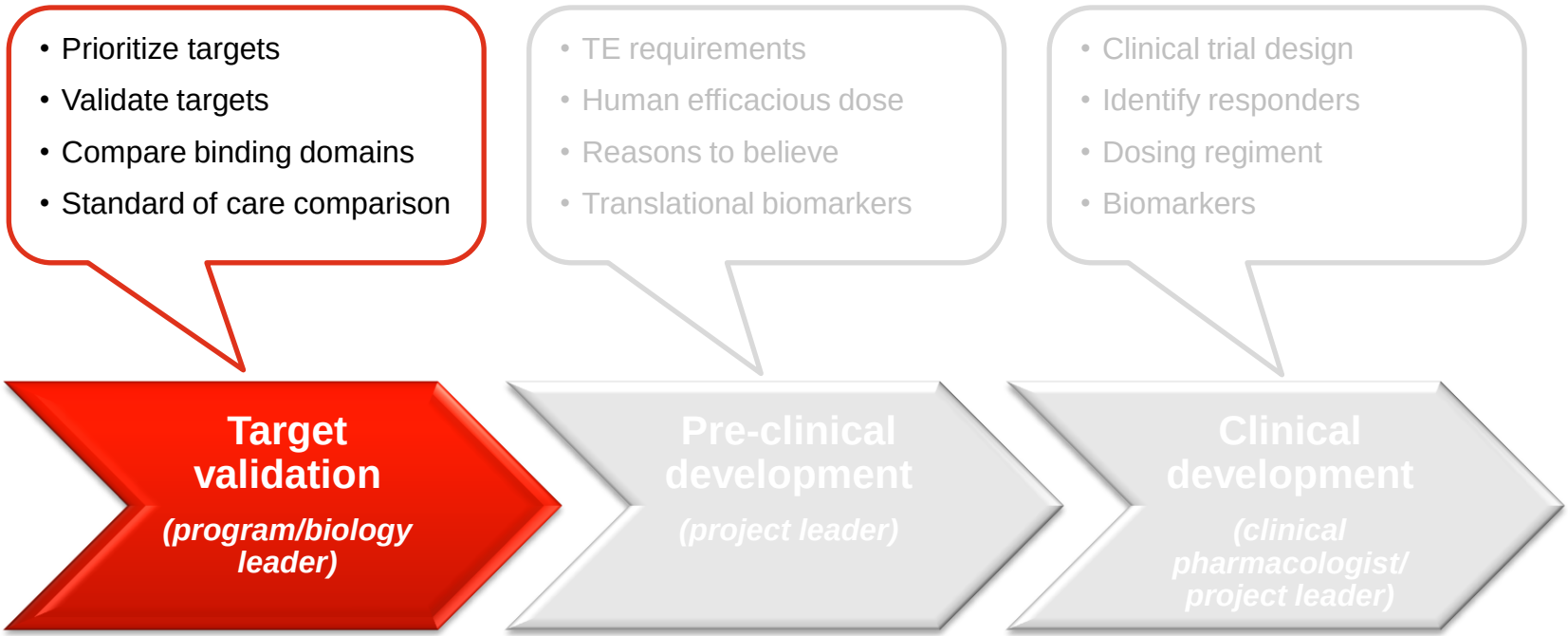
QSP – clinical development after FTIH

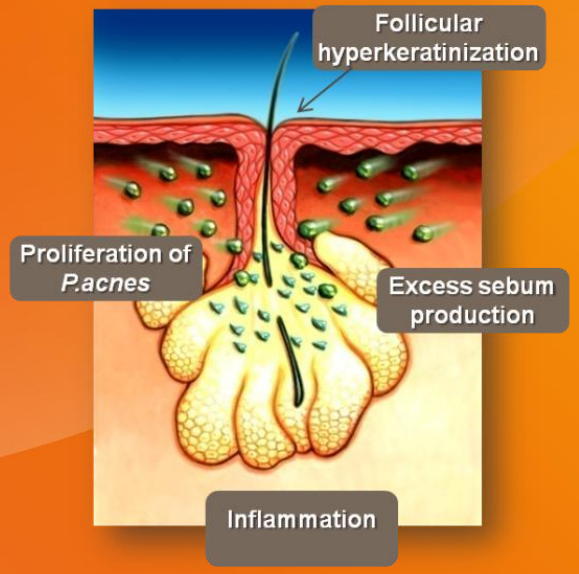


QSP – late stage clinical trial

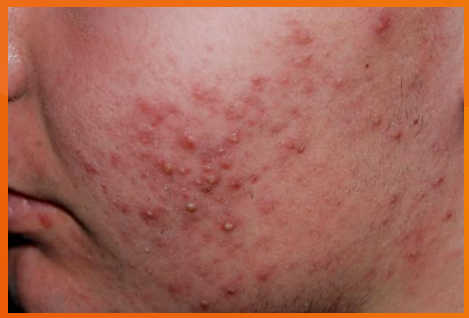


What's in it for me?





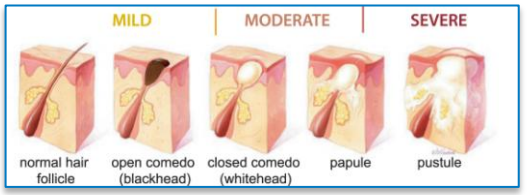
QSP Model for Acne



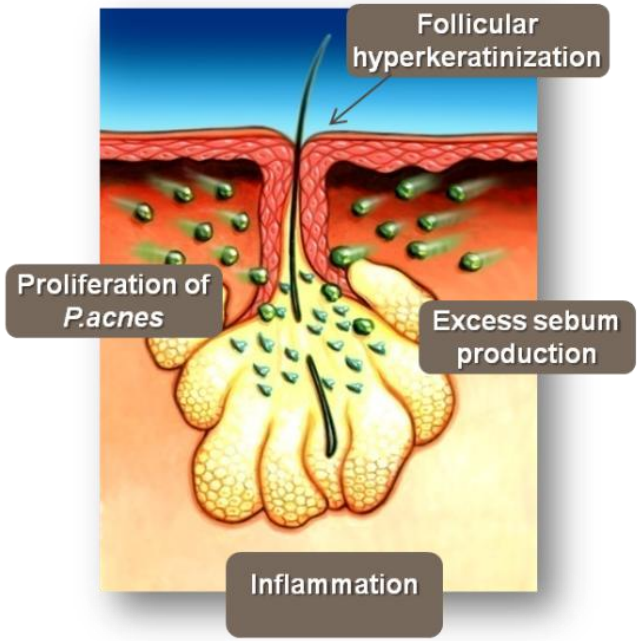
Modeling done by Loveleena Bansal (GSK)

Drug Development Advisors

Conceptual QSP model for ACNE



Lesion severity



Isotretinoin

Clindamycin

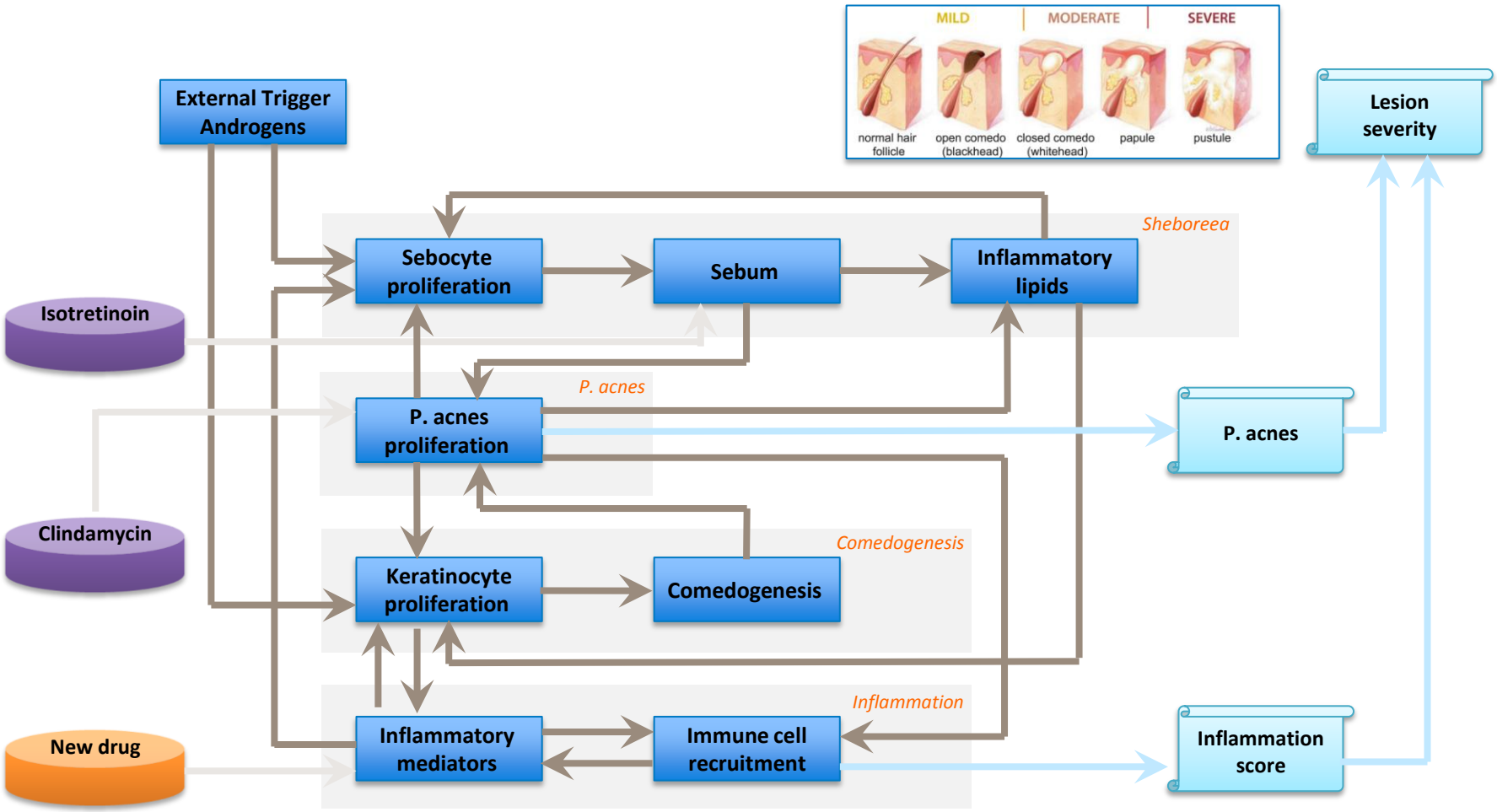
New drug

P. acnes

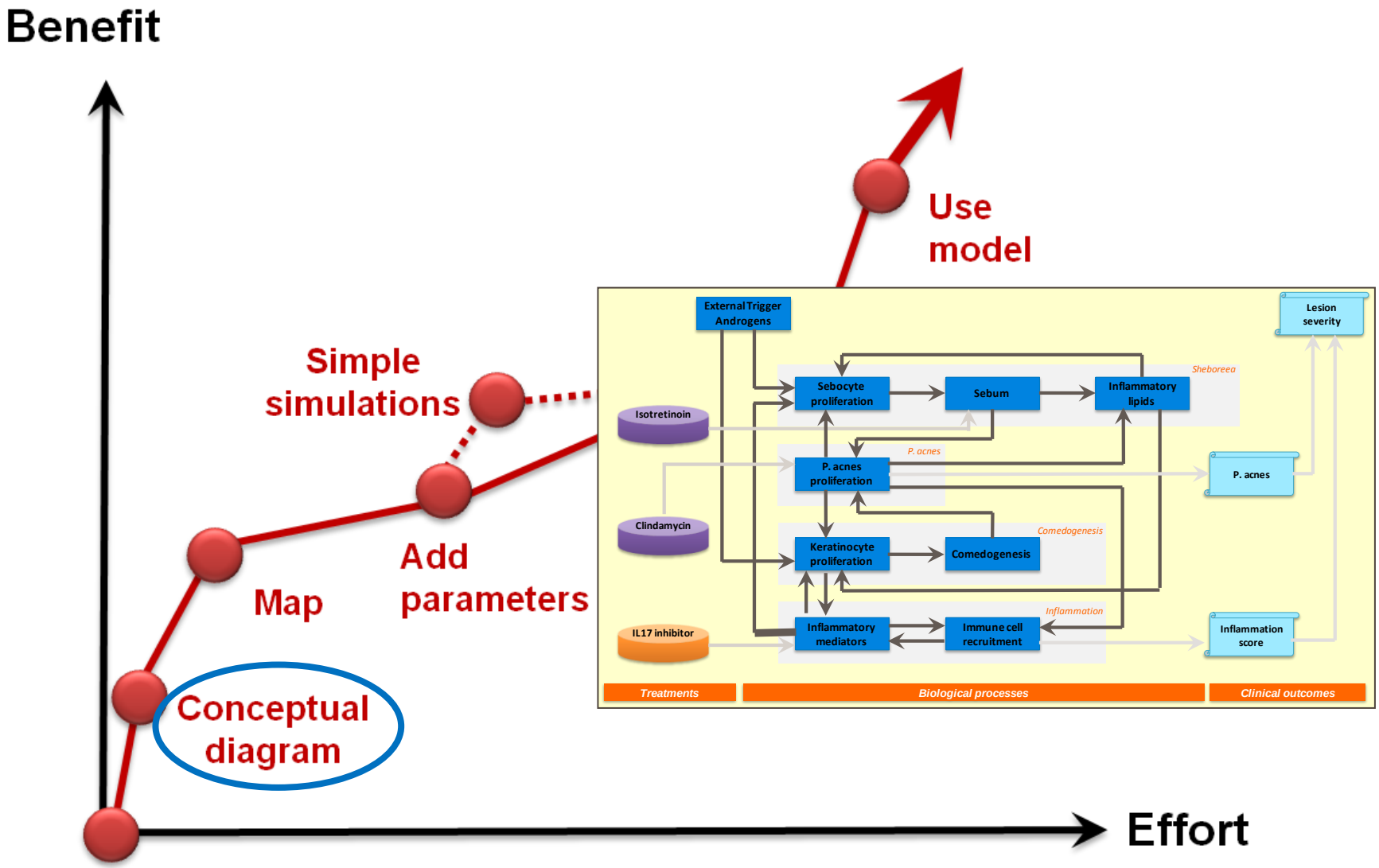
Inflammation score

Treatments	*Biological processes*	*Clinical outcomes*

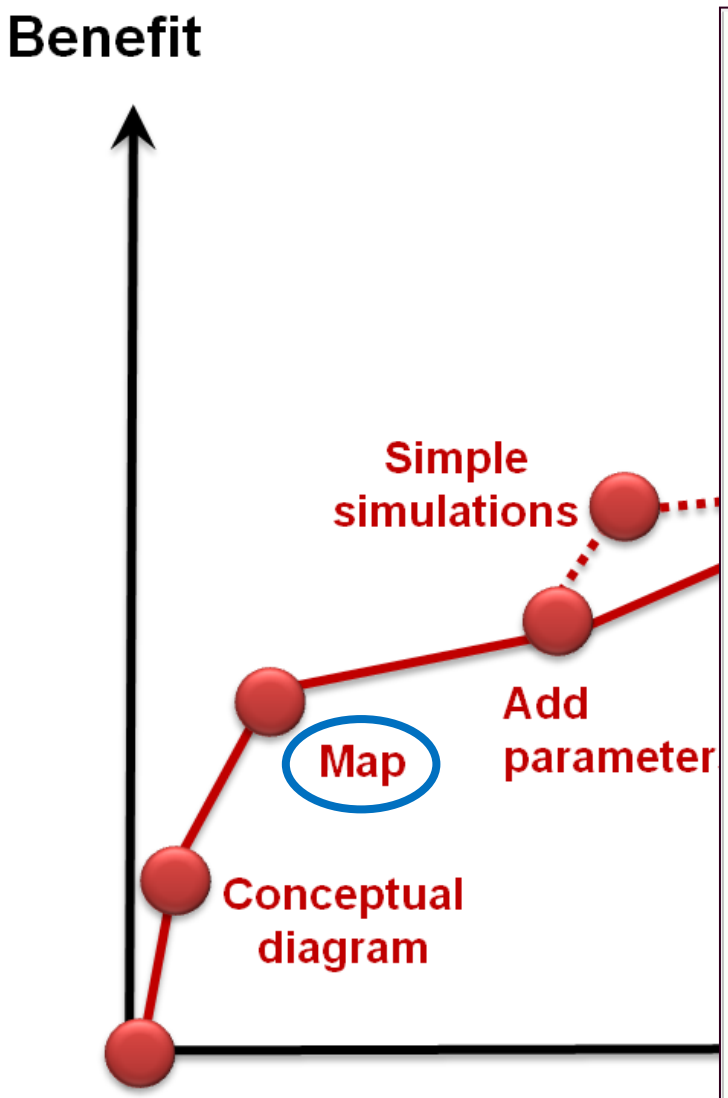
Conceptual QSP model for ACNE

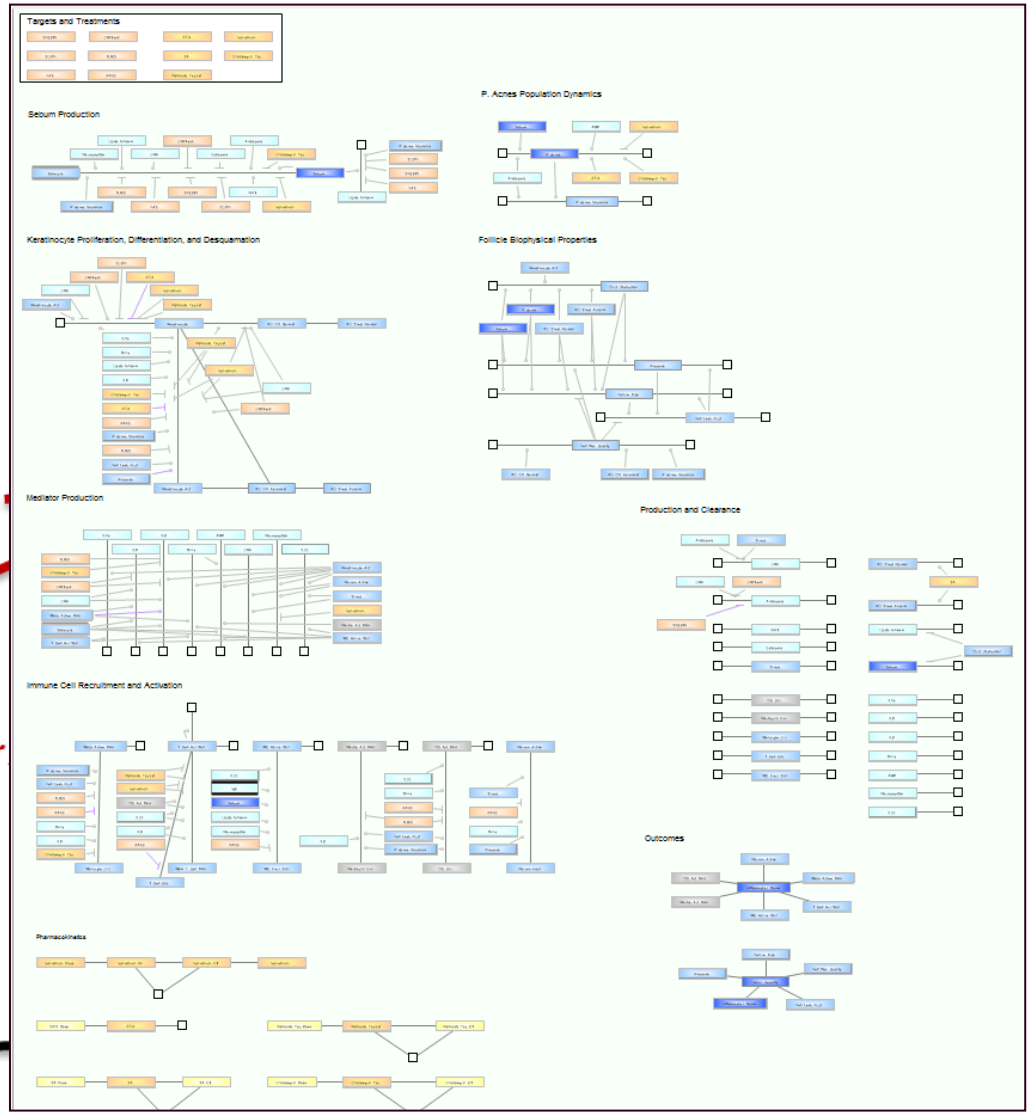


Acne QSP Model Building Process

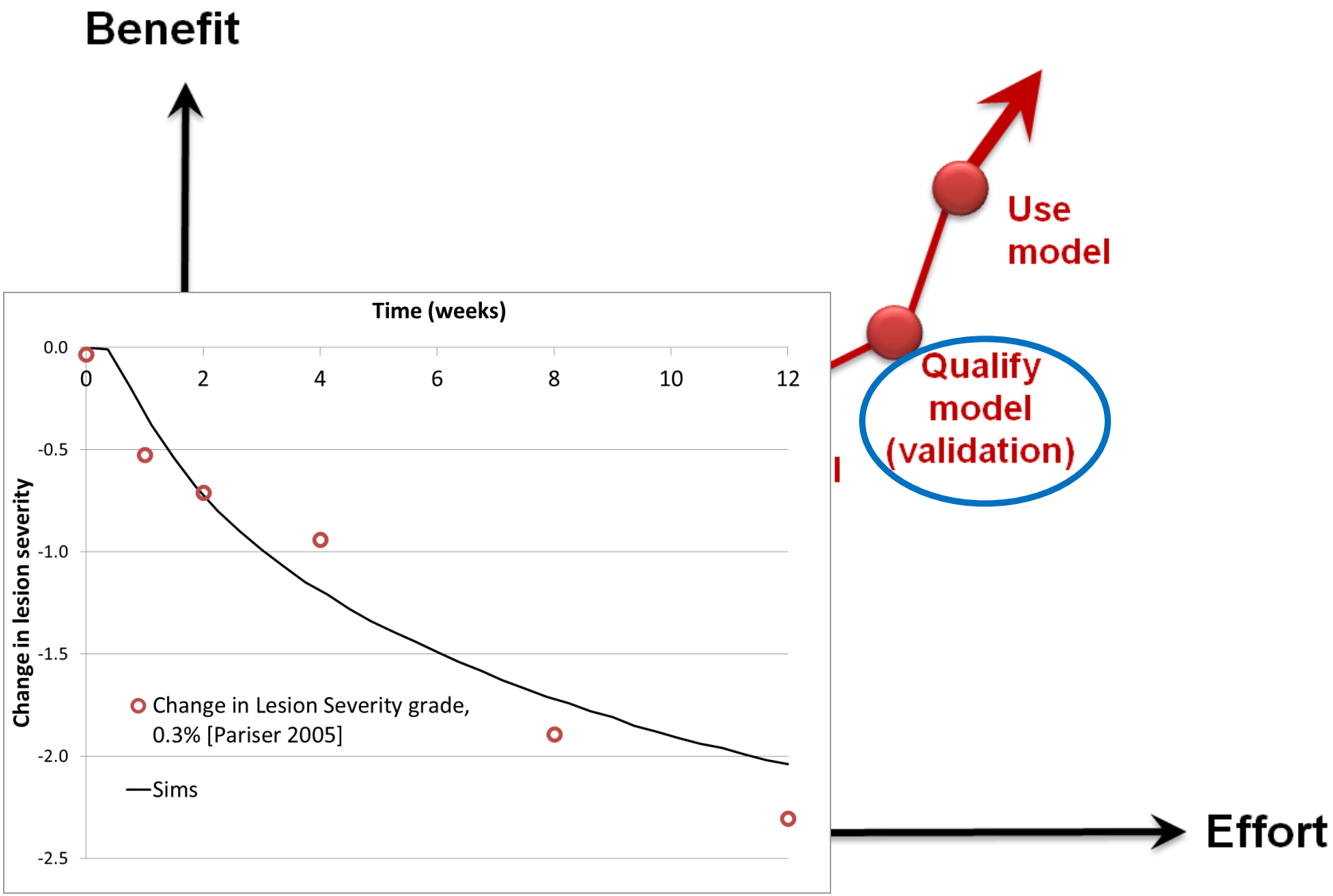


Acne QSP Model Building Process

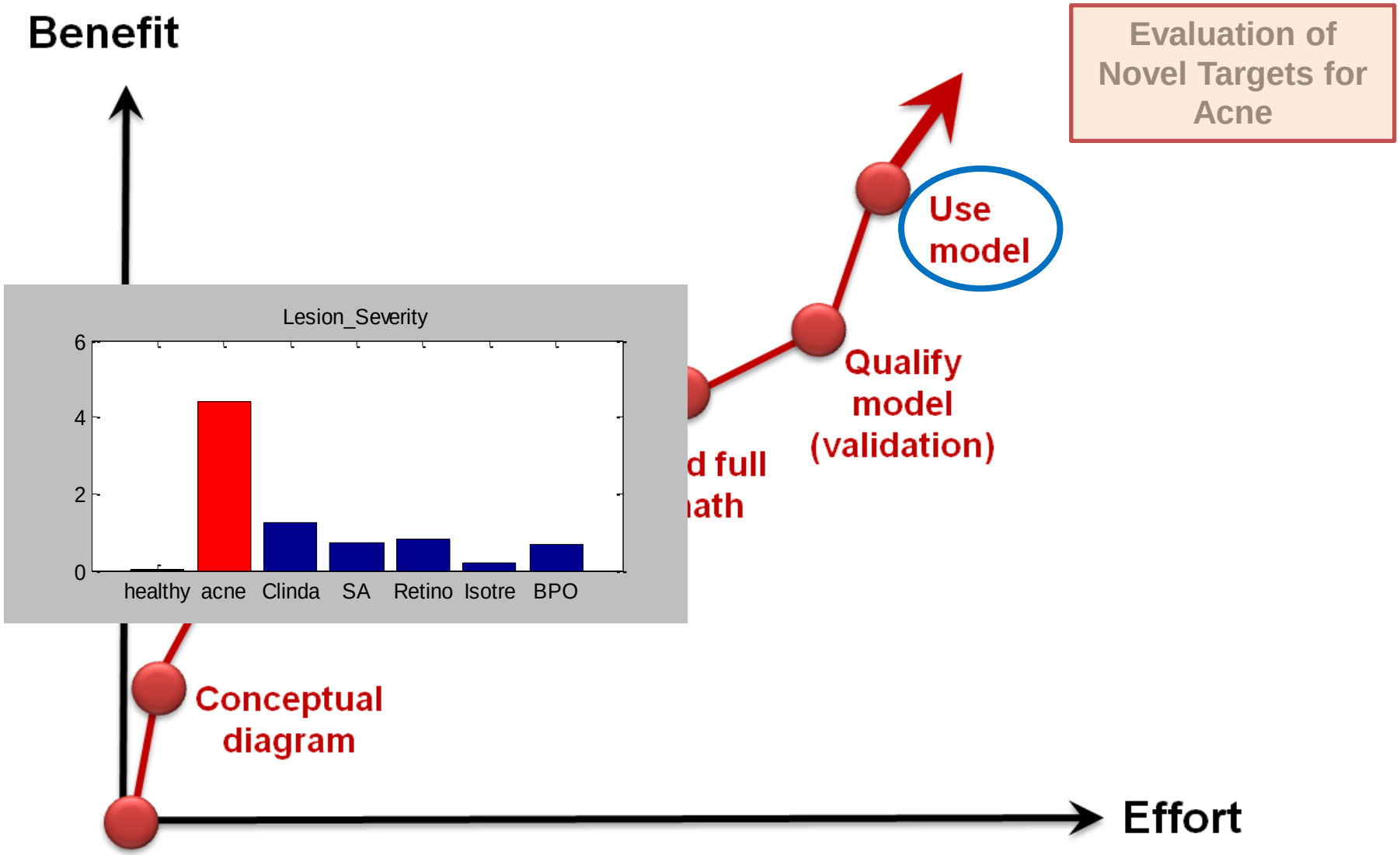




Acne QSP Model Building Process

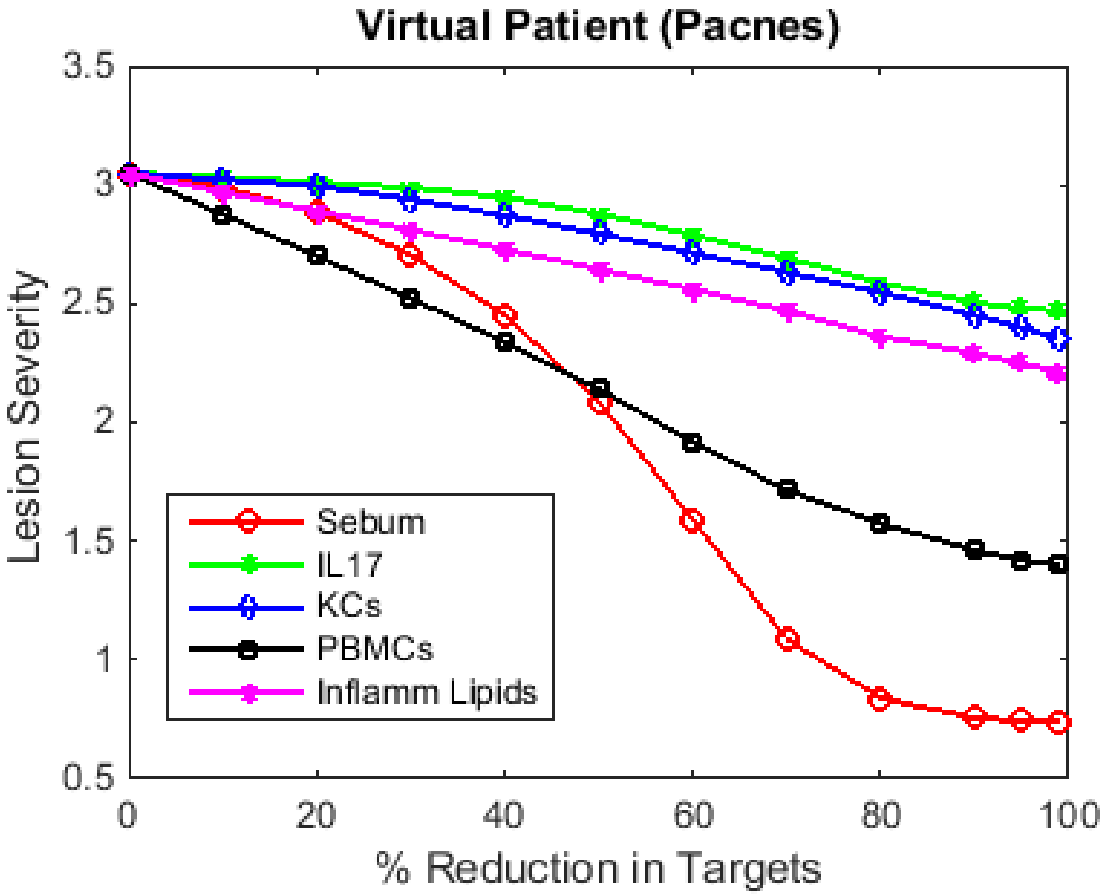


Acne QSP Model Building Process



Evaluation of Acne Targets

- Sebum reduction has the most significant effect in reducing Lesion Severity
- 80-90% reduction in Sebum is required for maximum efficacy
- Complete inhibition of IL17 or Keratinocyte activation provide only a moderate reduction in Lesion Severity



Virtual Patients for Acne

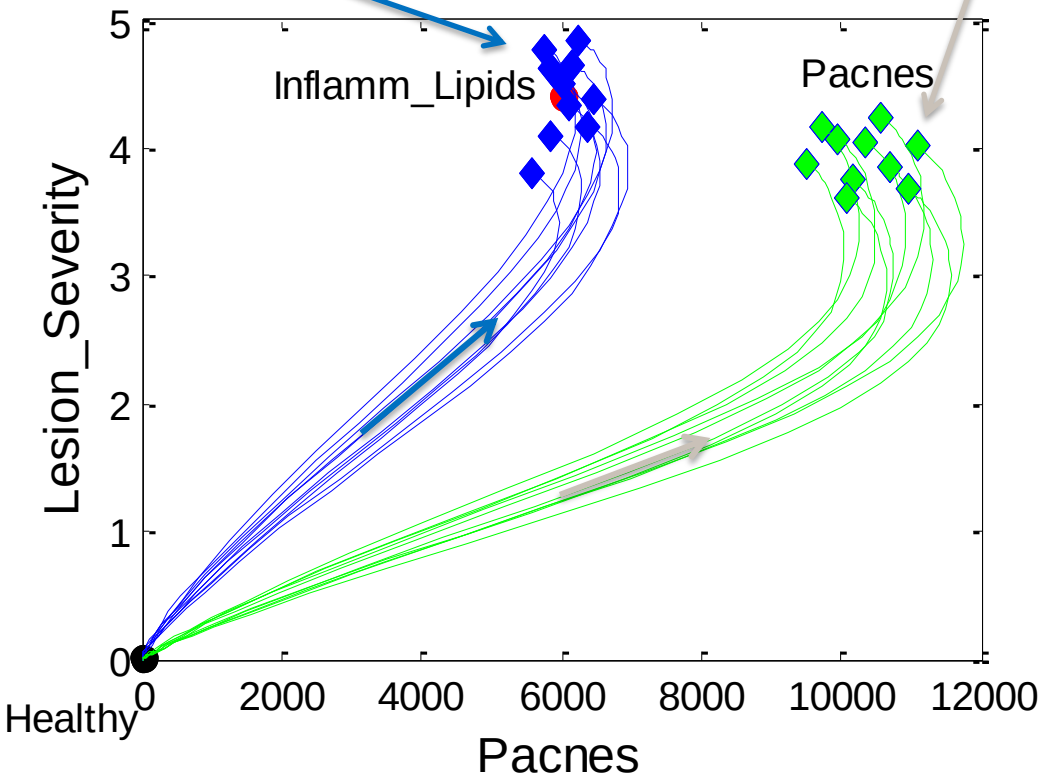
Two sets of Virtual Patients

High Inflammatory Lipids

Patients with increased inflammatory lipid production

High P. acnes

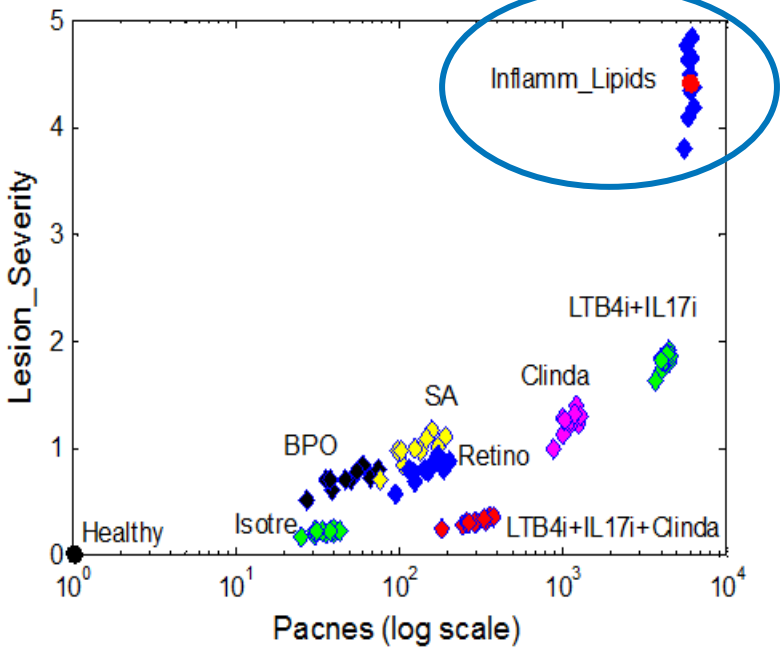
Patients with increased P. acnes proliferation and macrophages in the skin



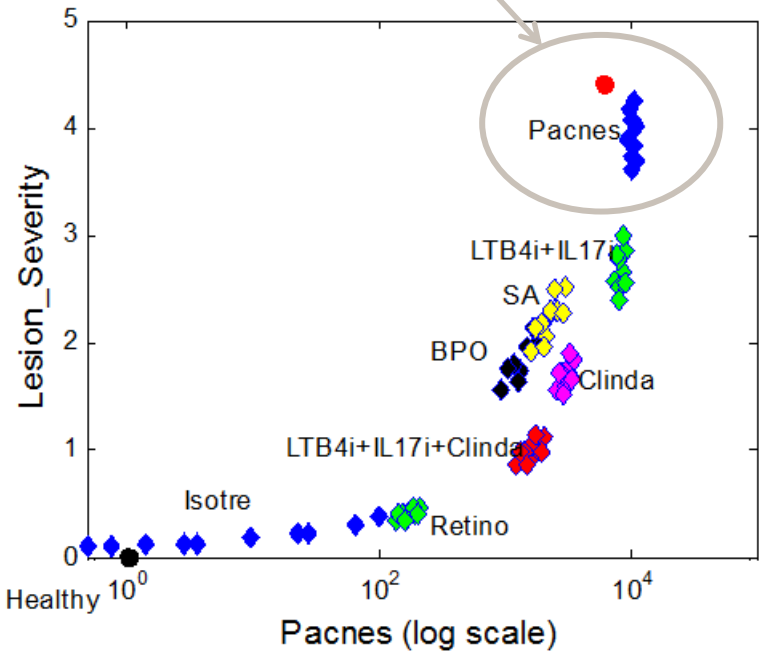
Effect of Treatments

Accounting for patient and disease heterogeneity

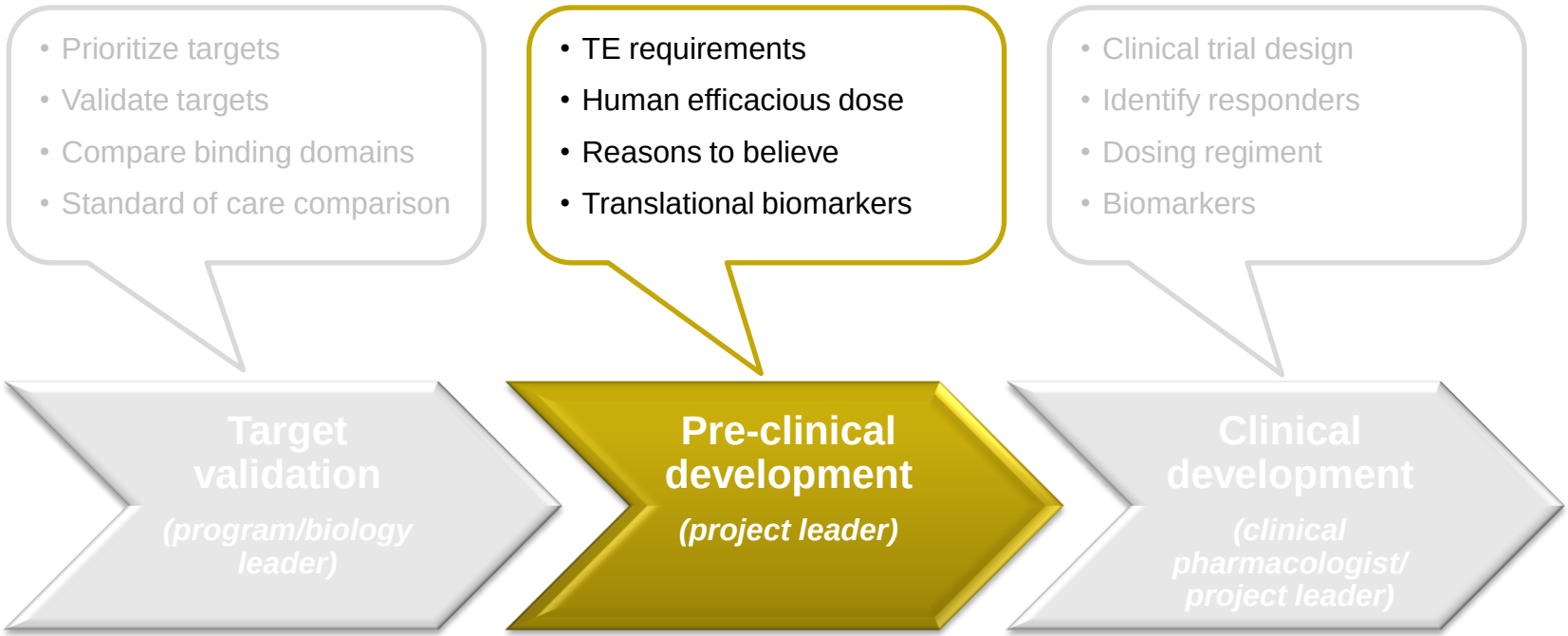
Patients with high Inflammatory Lipids



Patients with high P. acnes



What's in it for me?

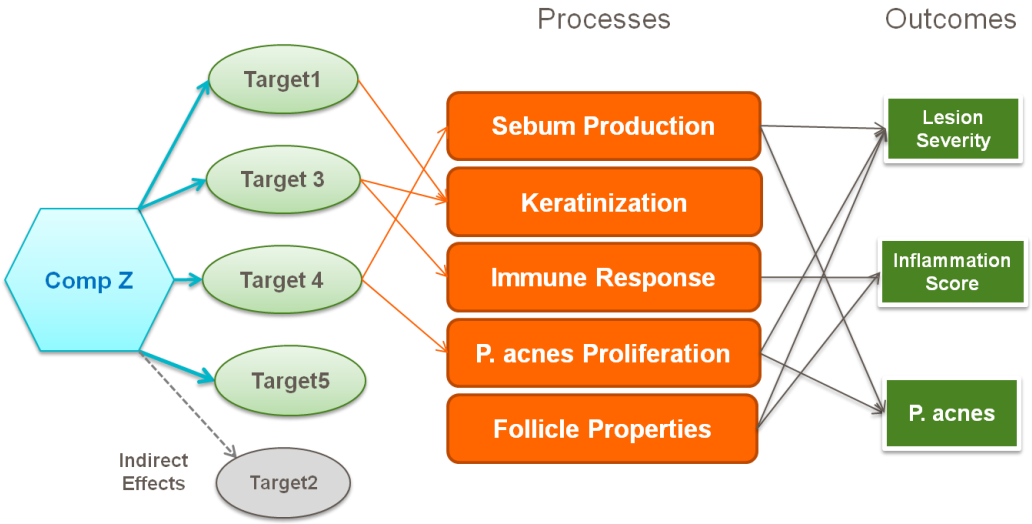


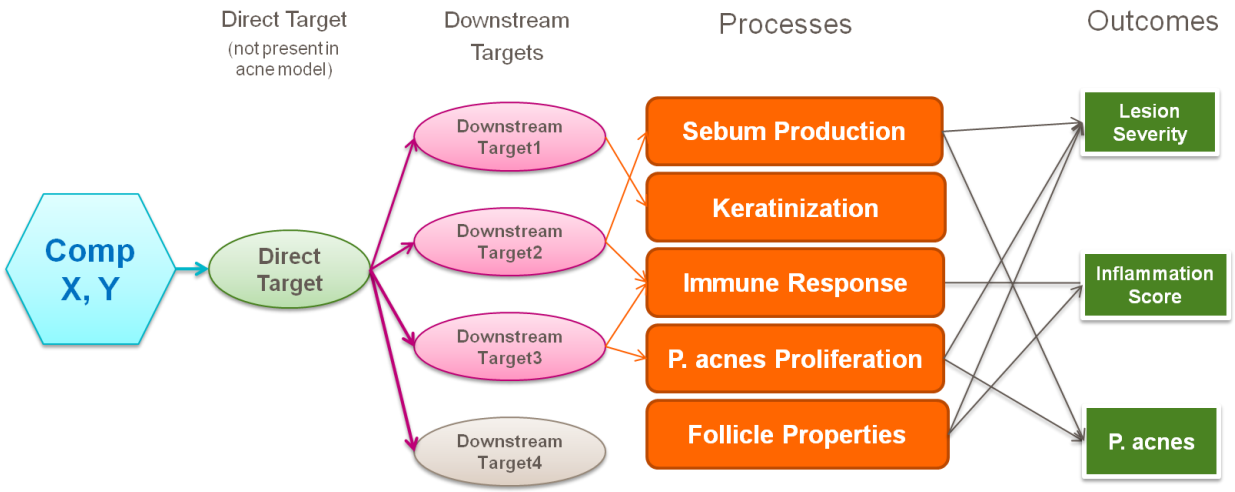
Treatment Simulations

Effect of compounds **X,Y** and **Z** modeled based mainly on in-vitro data

TARGET(s) already in the model

- Compounds **Z** has:
  - several of anti-inflammatory effects
- Modeled using measured inhibition against its targets

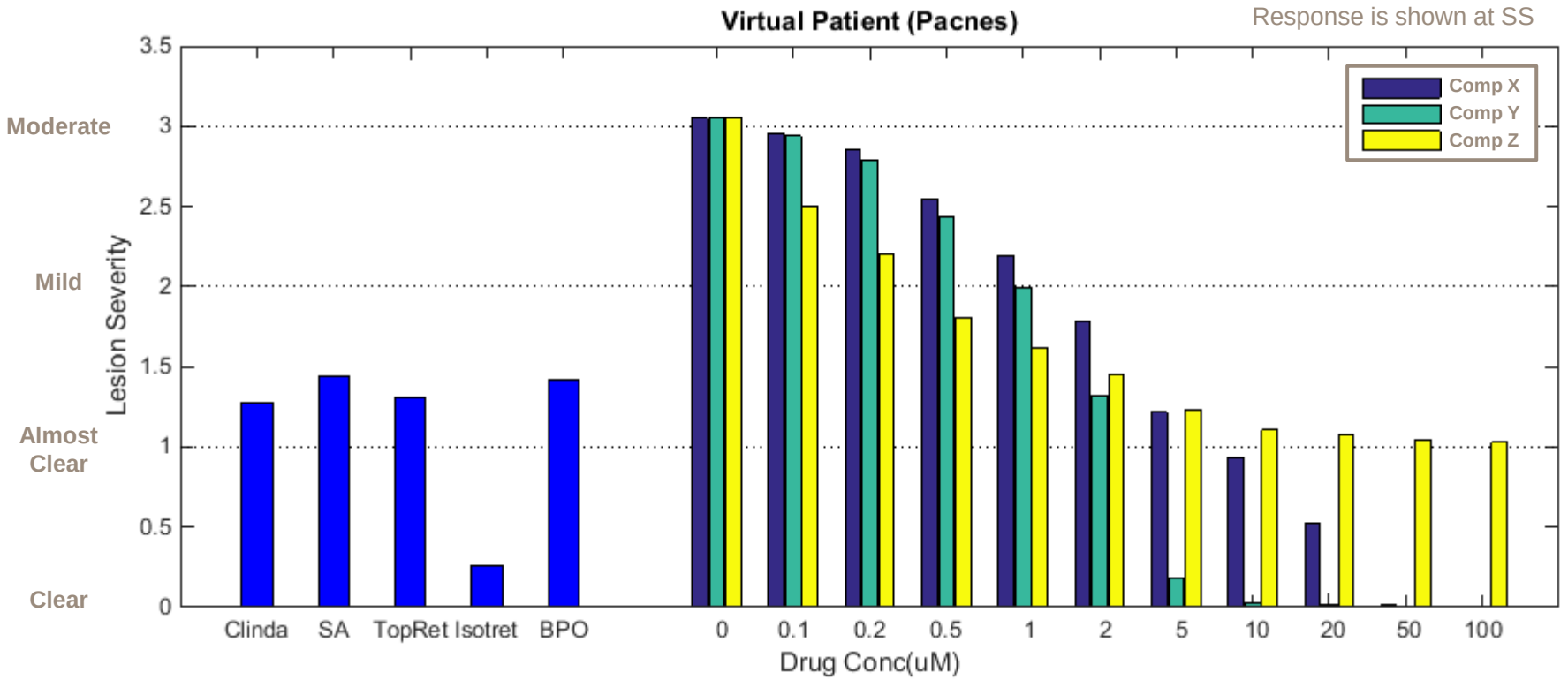




New TARGET

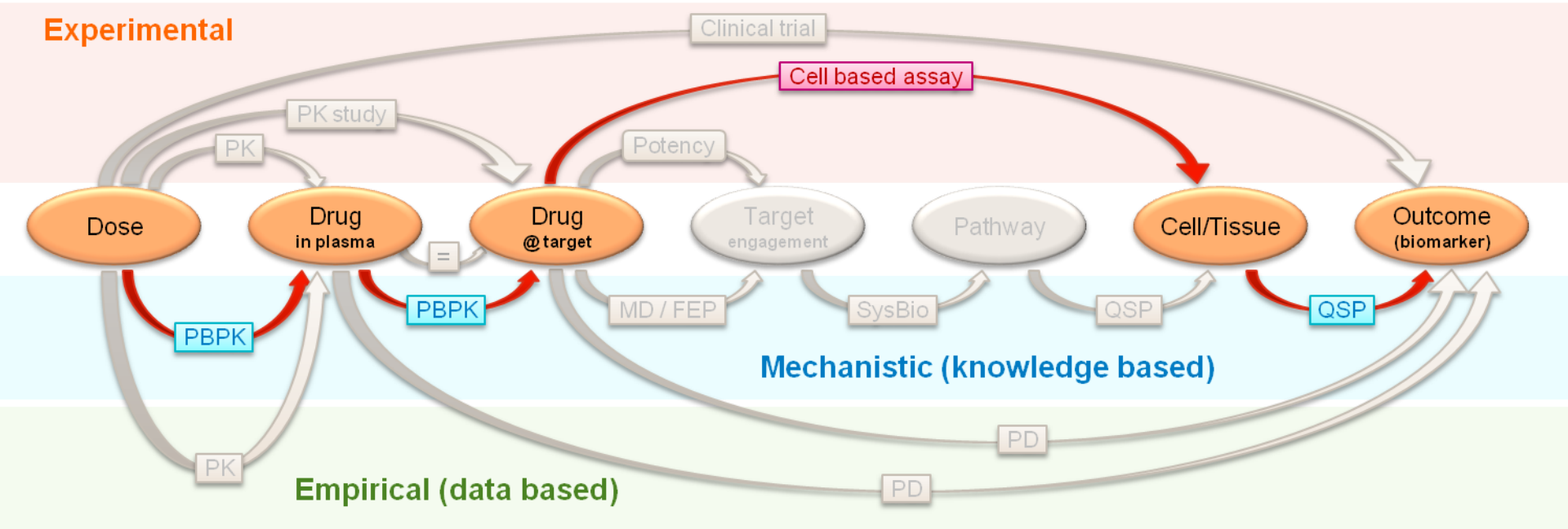
- Compounds **X & Y** have:
  - anti-inflammatory
  - anti-lipogenic activity
- Modeled using measured effect on downstream targets

Exposure required at target for efficacy

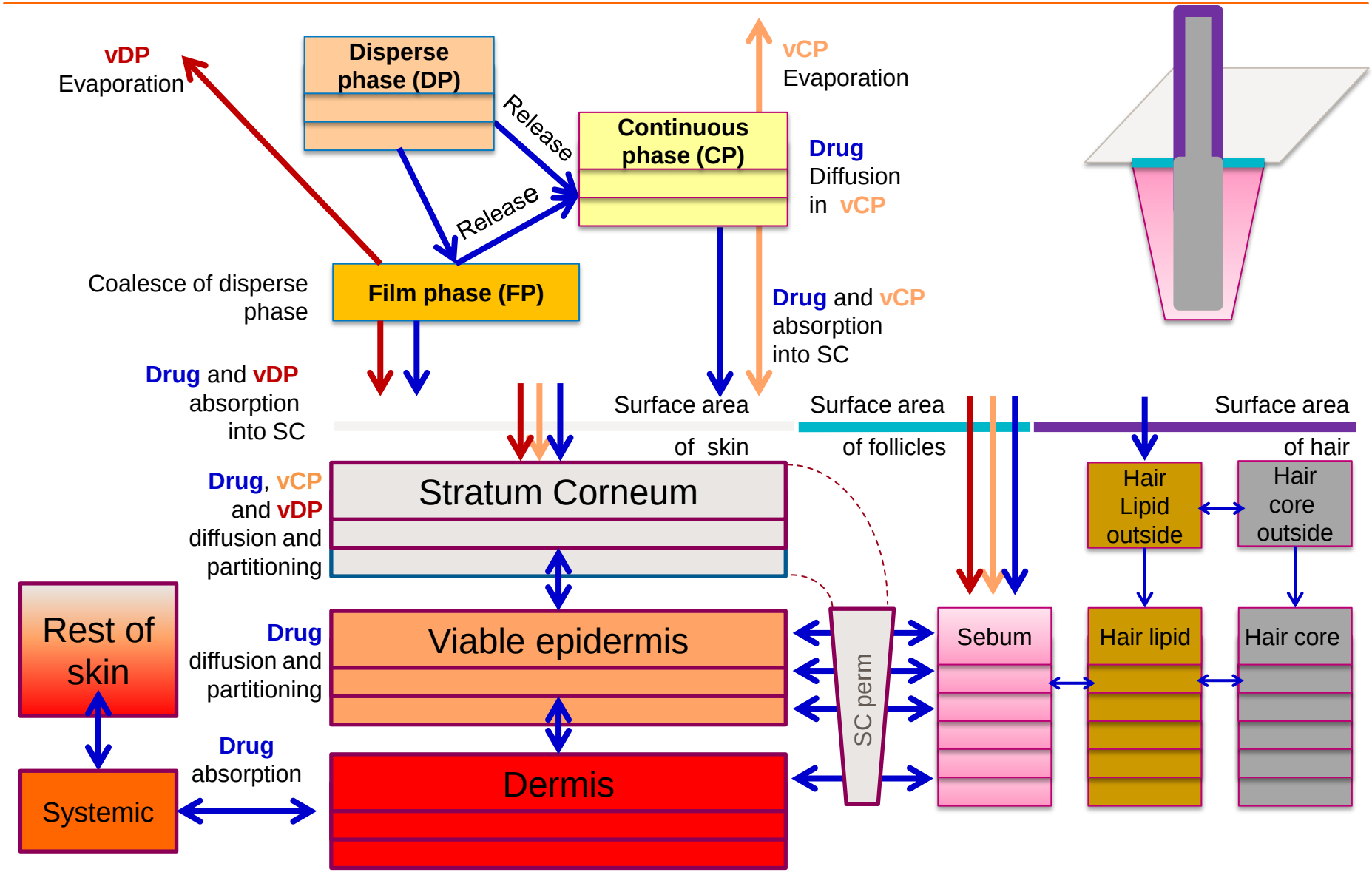


- **Comp Z** leads to reduction in lesion severity even at lower skin concentrations, however the effect saturates and cannot be reduced to <1 even at very high skin concentrations.
- **Comp X** can reduce lesion severity to 0 but high concentrations in the skin are required.
- **Comp Y** is most "potent" and efficacious at even lower skin concentrations. Lesion Severity is reduced to the level of SoC at free concentration of about 5 µM.
- Isotretinoin, which is most effective treatment for acne, is a systemic treatment with a number of side effects.

QSP early stage clinical development

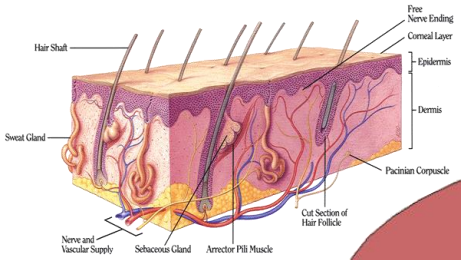


Modeling dermal formulations

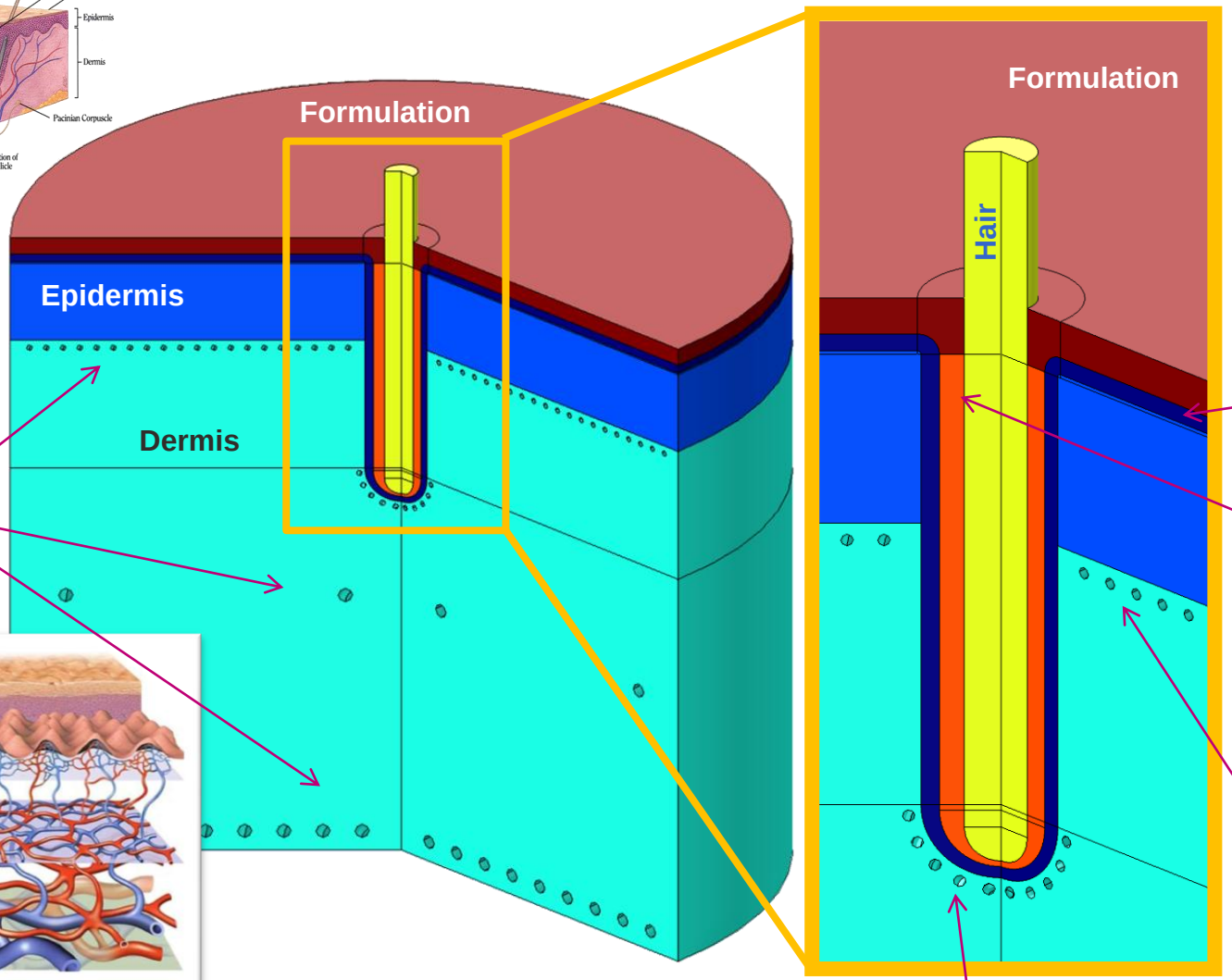


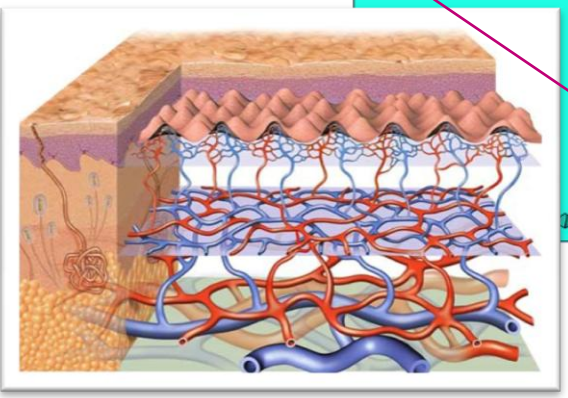
Three dimensional finite element skin model

Attempting to model the 3D skin complex structure



thanks Sumeet Thete





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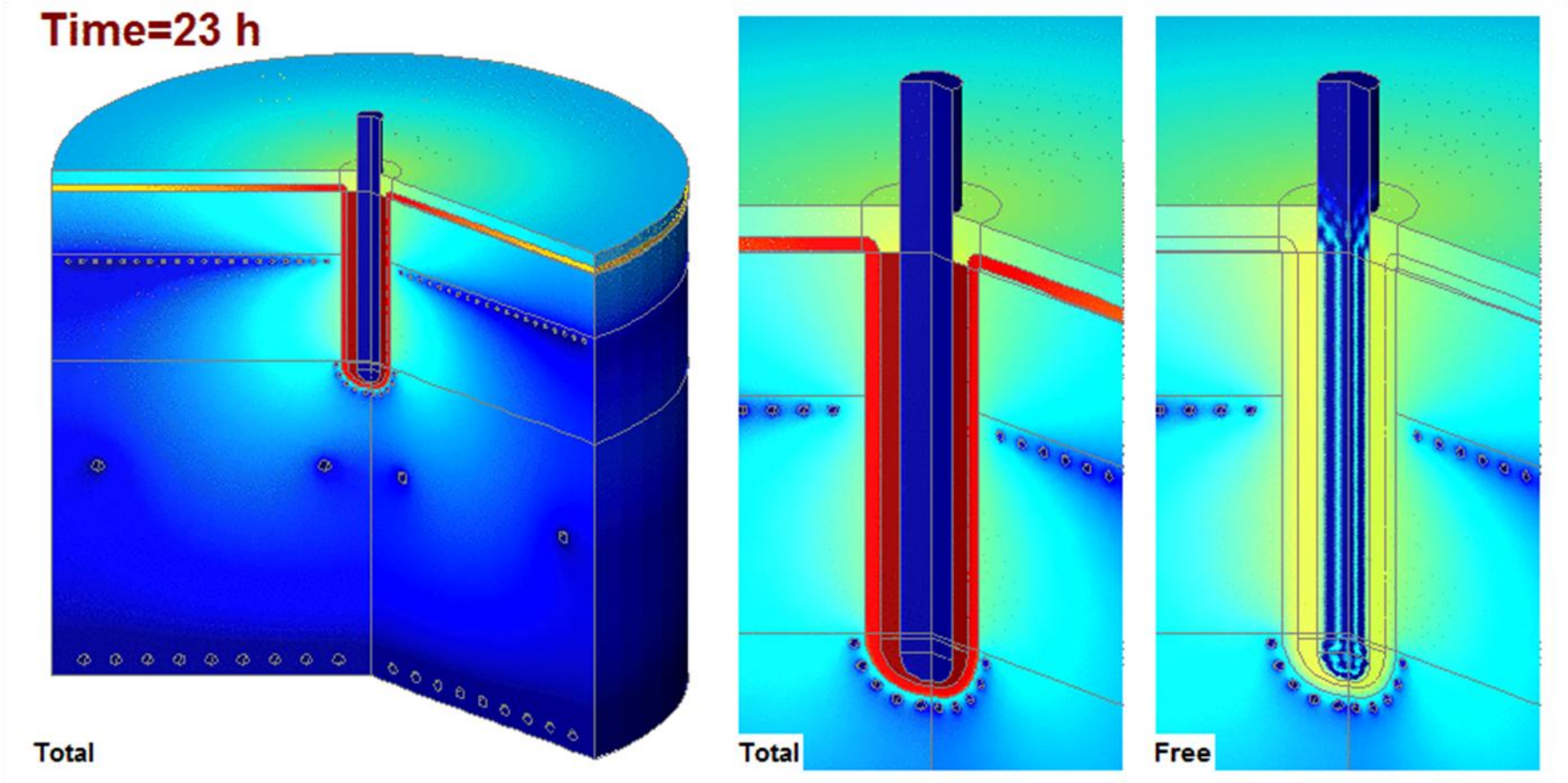
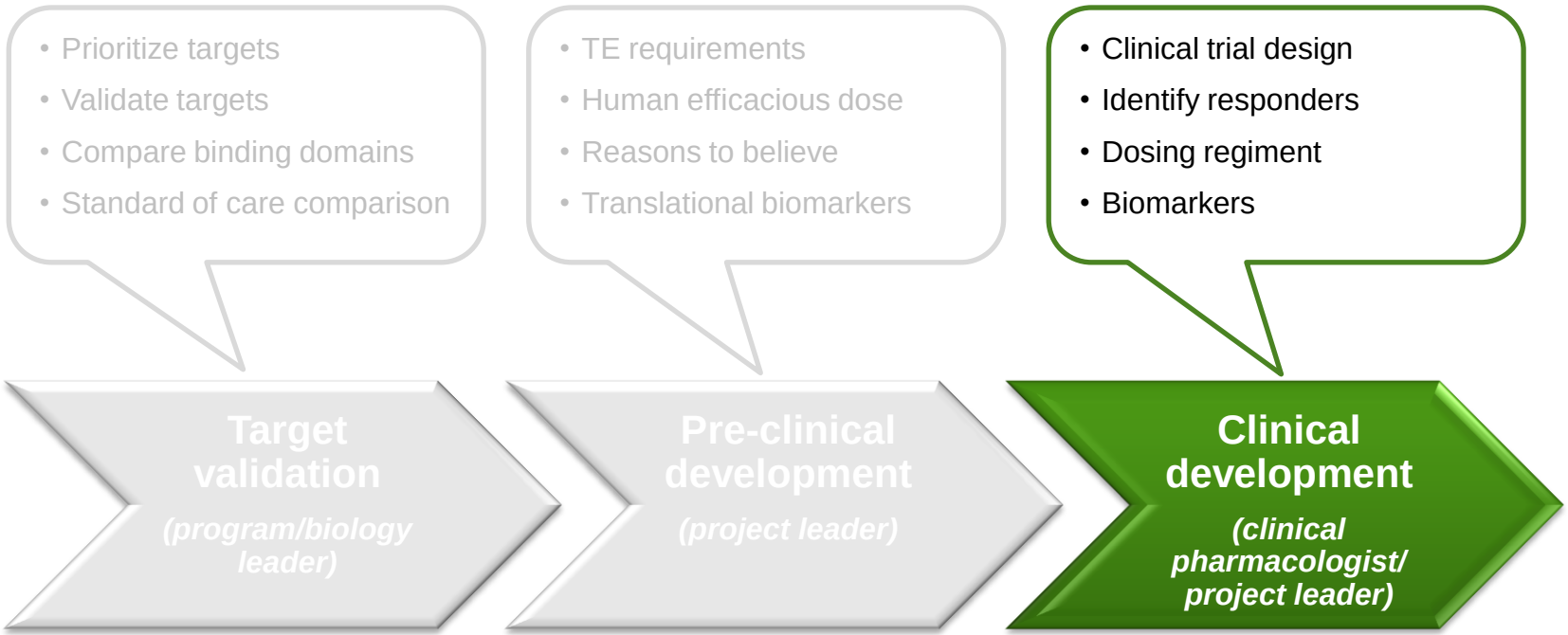
Sample simulation

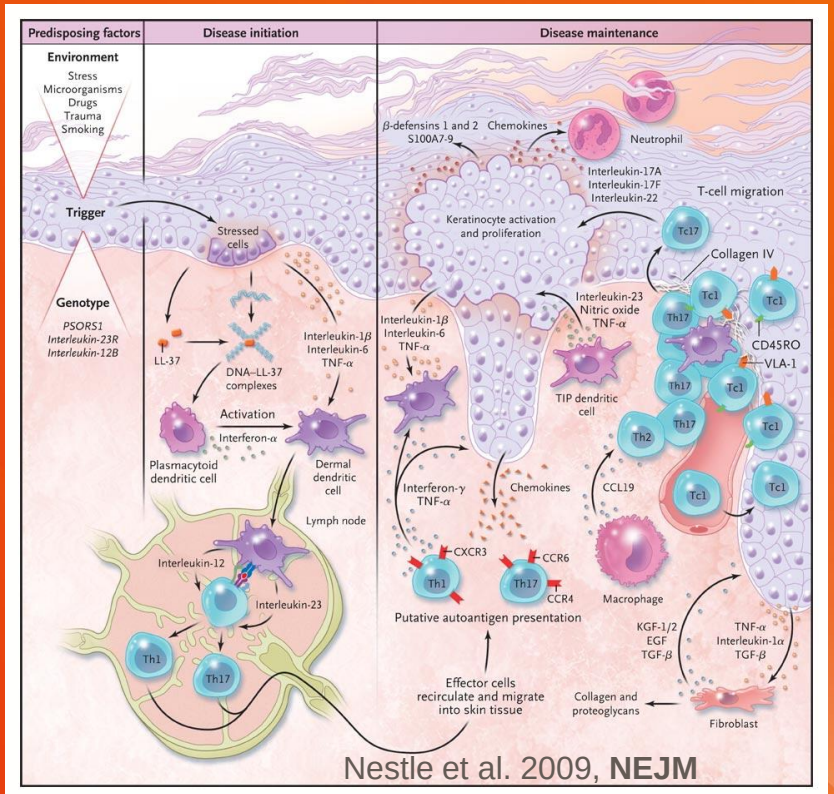
3D finite element model *(2D axial symmetry)*

MW = 250, logP = 5, no vehicle partitioning, high systemic absorption



What's in it for me?





Nestle et al. 2009, **NEJM**

QSP Model for Psoriasis

Work in progress

within PSORT consortium

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

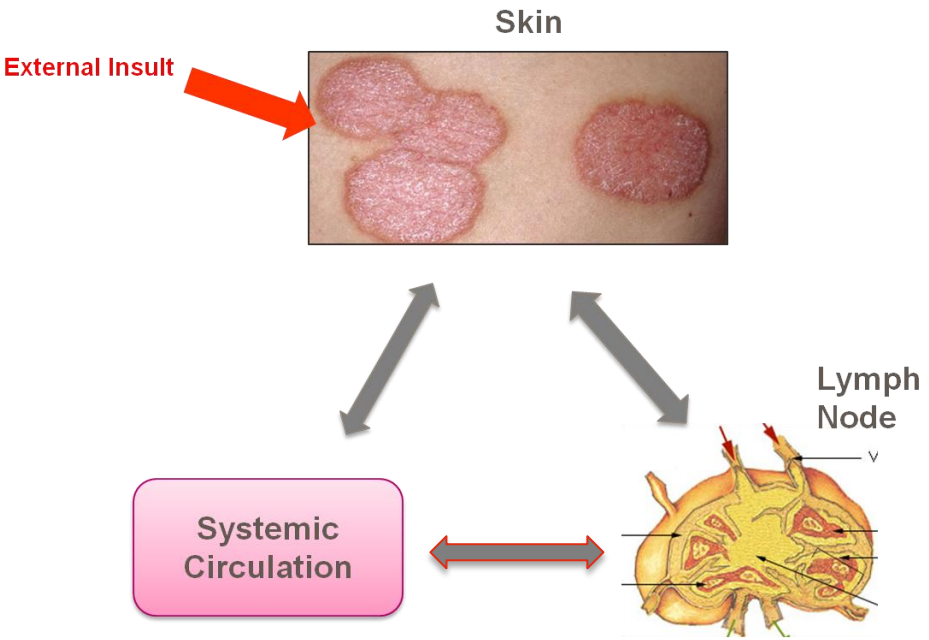
abbvie · Royal College of Physicians · Sanquin · psoriasis · QIAGEN · Queen Mary University of London · Pfizer · NOVARTIS · NHS Greater Glasgow and Clyde · 65 NHS Greater Glasgow and Clyde Celebrating 65 Years of the NHS · MedImmune · Newcastle University · University of Liverpool · Manchester 1824 The University of Manchester · King's College London · janssen · Celgene United Kingdom · gsk do more feel better live longer · camh · Campbell Family Mental Health Research Institute · Barts and The London School of Medicine and Dentistry

Modeling done by Loveleena Bansal (GSK)

ROSA® Drug Development Advisors

Layout of the Model

Cell Types and Other Components



Skin

Cell Types
Keratinocytes
Th1 Cells
Th17 Cells
γδ T cells
Myeloid Dendritic Cells
Plasmacytoid Dendritic Cells

Skin Resident T cells
Skin Resident Dendritic Cells

Chemokines & AMPs
CCL20
CXCR3 Ligands
CCR4 Ligands
hBD-2

Cytokines
IL-17
IL-22
TNF-α
IL23
IFNγ
IL-1β

Systemic Circulation

Cell Types
Th1 Cells
Th17 Cells
γδ T cells

Cell Types
Myeloid Dendritic Cells
Plasmacytoid Dendritic Cells

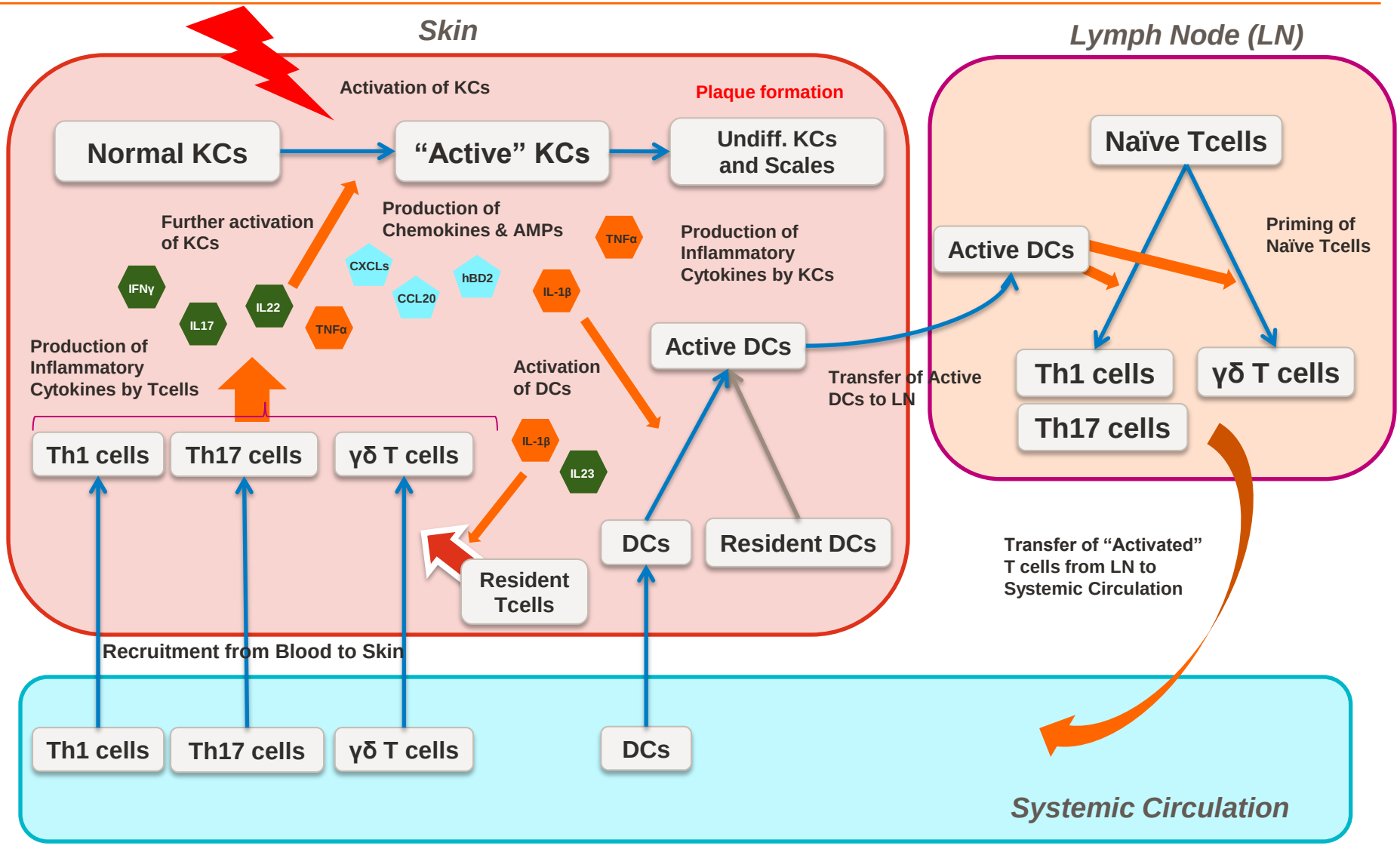
Lymph Node

Cell Types
Naïve T cells
Th1 Cells
Th17 Cells
γδ T cells

Cell Types
Myeloid Dendritic Cells
Plasmacytoid Dendritic Cells

Layout of the Model

Disease Mechanisms in Psoriasis

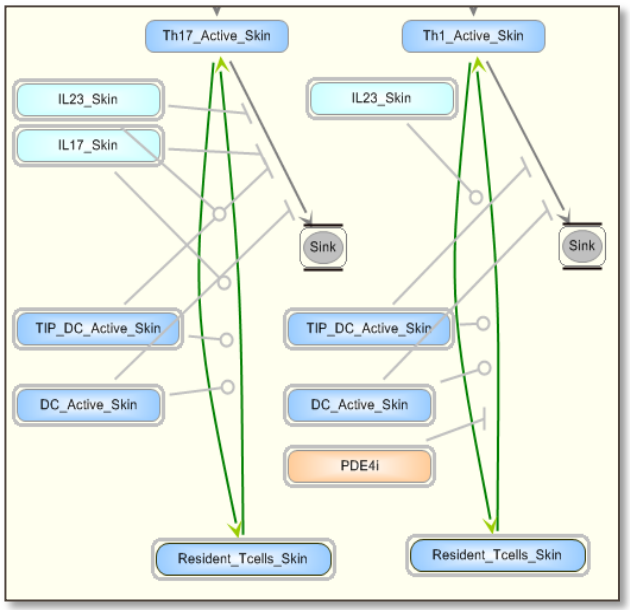


Parameter Estimation

"Activation/ Upregulation" Parameters

Over 200 literature references have been reviewed to obtain or estimate the parameters for the Psoriasis model

Activation/ Upregulation Parameters for
- Activation of Immune cells/ Keratinocytes by Cytokines
- Recruitment of Immune cells into the skin etc.



Eijnden et al. 2005 Eur. J. Immunol.

Activation of Tcells by IL23

Hill Equation Kinetics	
Emax	1479.13
EC50	14.53
n	0.33
Residual	380.1747

Production of IFNg	
	CD4+ Tcells
IL23 ng/m	IFNg (pg/ml)
0	379.2009
1	825.0034
10	1054.129
100	1366.729
500	1495.85

Michaelis Menten Kinetics	
Emax	967.38
EC50	2.63
Residual	436.7679

Hill Equation Kinetics	
Emax	160.0056
EC50	7231.884
n	0.18816
Residual	0.226894

Production of IL17	
	CD4+ Tcells
IL23 ng/m	IL17(pg/ml)
0	0
1	33.33333
10	33.33333
100	41.66667
500	62.5

Michaelis Menten Kinetics	
Emax	1822.229
EC50	966.8586
n	0.210471
Residual	6.539786

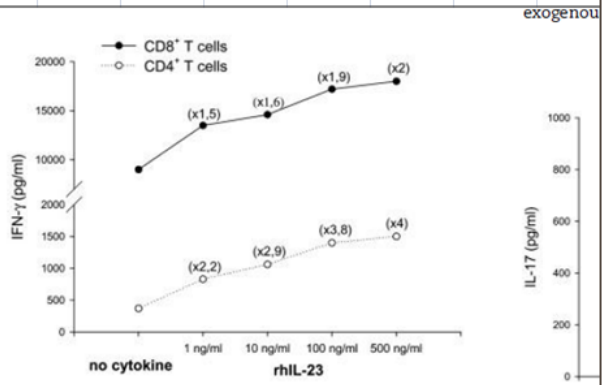
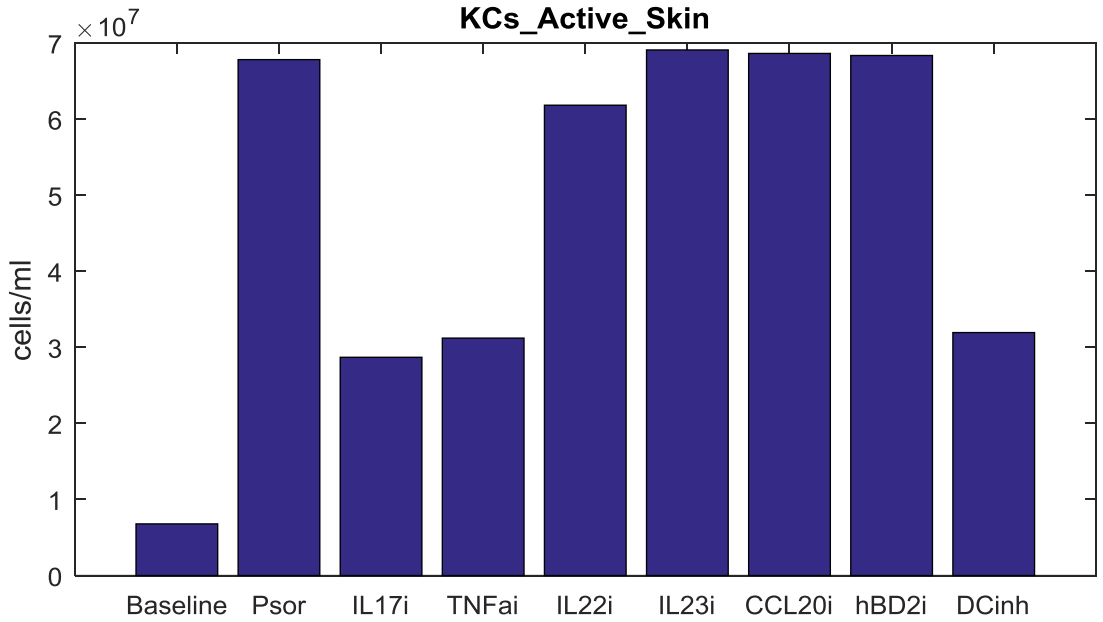


Fig. 3. rhIL-23 enhances IFN-γ secretion in activated naive T cells. Naive $CD4^+$ and $CD8^+$ T cells were polyclonally stimulated in the absence or presence of rhIL-23 (1, 10, 100 and 500 ng/ml). At day 6, production of IFN-γ was assessed by ELISA in the cell culture supernatant. Two representative donors are shown here. Results are expressed in pg/ml. The fold increase in IFN-γ secretion observed in the presence of rhIL-23 is given in brackets, as compared to the secretion in the absence of rhIL-23.

T cell act IL23 Eijnden 2005 2 | T cell act IL1 - Lichtman 1988 | gdTcell act IL1b - Sutton 2009 | T cell act DCs Segura 2013 | T cell

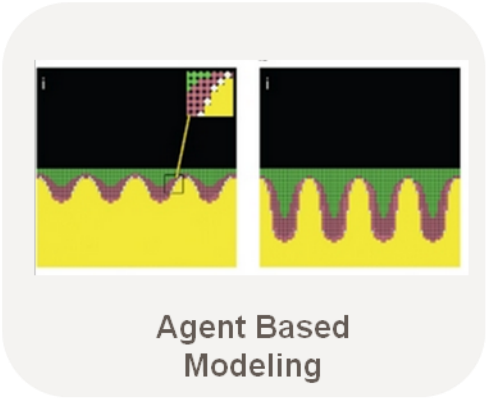
Cytokine Inhibition

Partial validation - Model development in progress

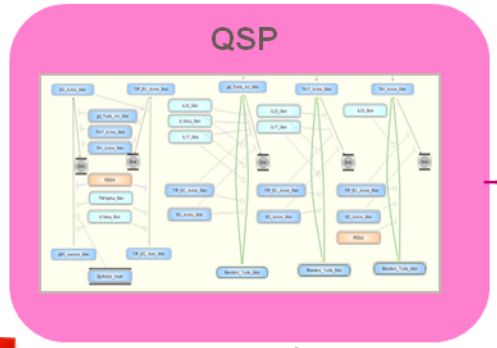


Model Predictions	Clinical Evidence	Comments
Inhibition of IL17 and TNFa leads to a significant reduction in active KCs	Anti-IL7 and anti-TNFa treatments have been extremely effective: secukinumab, Etanercept etc.	
Reduction in IL22 has some effect on reducing active KCs.		
Inhibition of IL23 does not have a significant effect on reducing active KCs	Anti IL23 treatments have been shown to be effective: Ustekinumab, Tildrakizumab etc.	The effect of IL23 is mediated by DCs in number of reactions
Inhibition of chemokines like CCL20 and hBD2 does not reduce active KCs.		

Multiscale Model and Data Integration in PSORT



- Dynamics of increase in plaque area and skin thickness
- Dynamics of cytokine regulation that activates epidermal proliferation



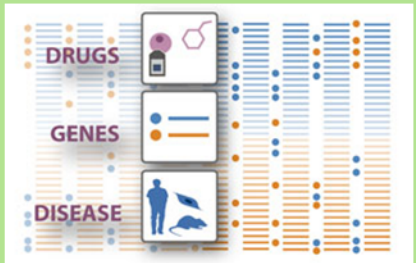
- Evaluation of novel targets for drug development
- Simulation of virtual patients and differences in effect of treatments
- Understanding of the dynamics of disease progression etc.

- Identification of important processes contributing to disease for further evaluation.

- Data for Model Calibration
- Building of pathway networks

Literature Data

- Information about disease and drug endotypes
- Information about patient stratification to help simulate variability.

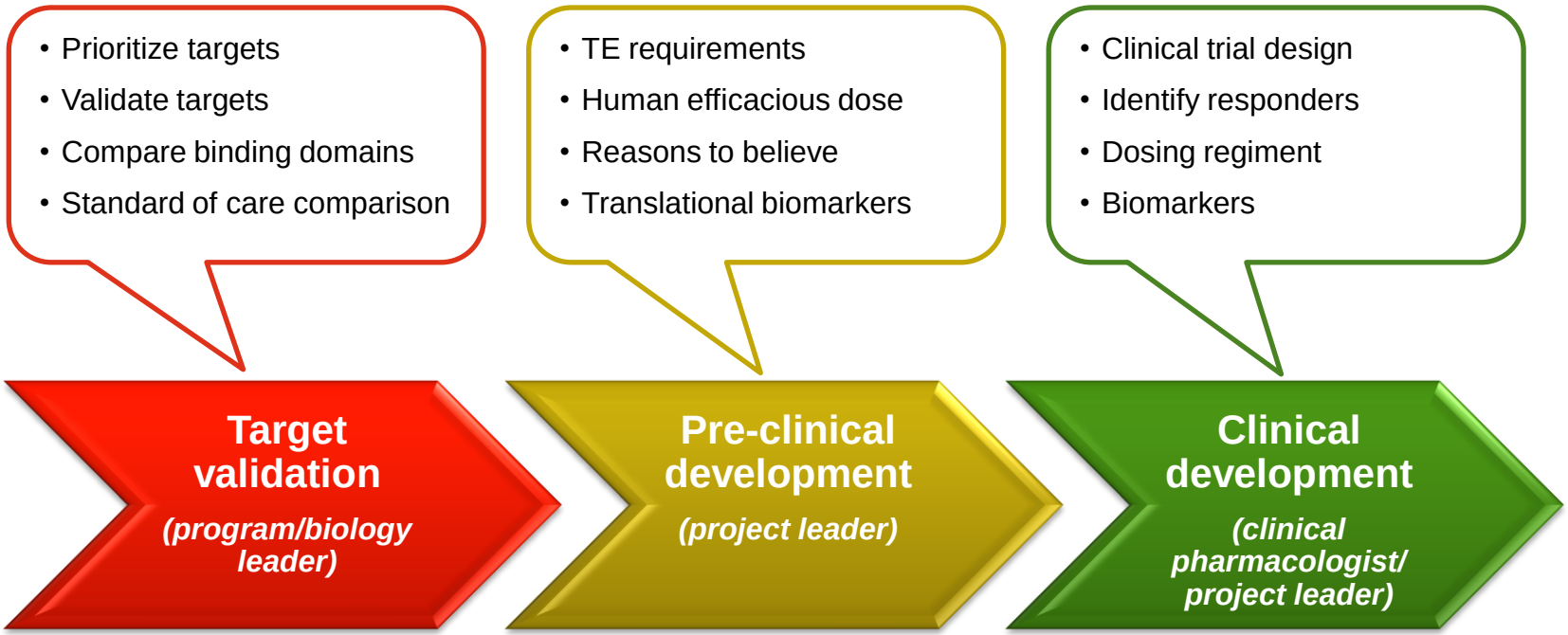


Bioinformatics Chemogenomics

- Identification of important pathway nodes which can be included in the QSP models.

PSORT Data

What's in it for me?



Acknowledgements

GSK: Systems Modeling and Translational Biology

- Loveleena Bansal
- Emile Chen
- Tom Wilde *(now at J&J)*

Rosa and Co.

GSK: Dermatology

- Betty Hussey
- Steve Frey
- Akanksha Gupta
- Javier Cote-Sierra
- Grace Kang
- … and many more!