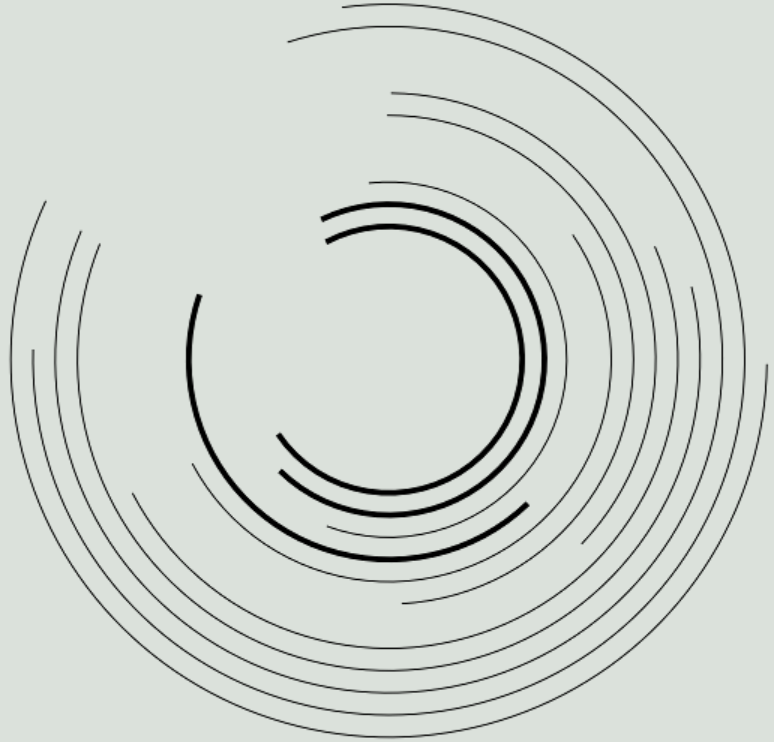
Modeling Subcutaneous Absorption & Immunogenicity of Large Molecules

Erik Sjögren and Salih Benamara

OSP Community Conference 2024

Modeling Subcutaneous Absorption and Local/Systemic Immunogenicity



Erik Sjögren

Pharmetheus

OSP Community Conference 2024

Subcutaneous drug administration

Subcutaneous (SC) drug administration is becoming increasingly popular

- Increasing number of large and/or sensitive molecules not suitable for oral administration
- SC route is more convenient/flexible than intravenous administration

Local dependencies

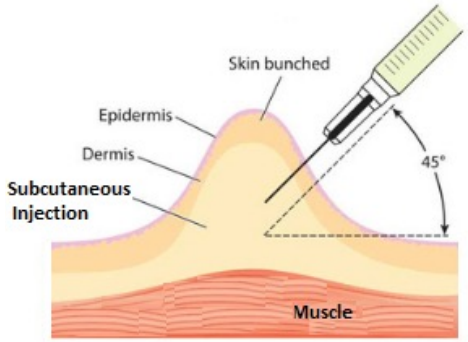
- Processes specific for SC administration
- Drug, Formulation, Physiology

Bioavailability - The fraction of the dose reaching the system

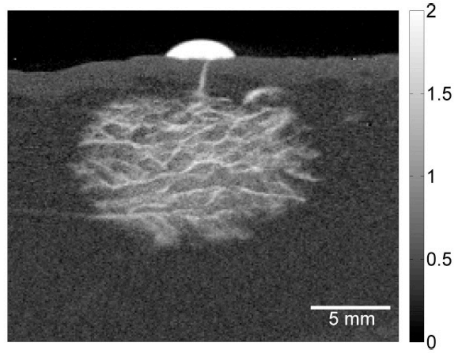
- Determines the effective dose
- Absorption and presystemic degradation

Immunogenicity –To provoke an immune response

- Desired - vaccines
- Unwanted – other therapeutics



https://www.medilogbiohealth.com



Thomsen et al. 2012

Bioavailability of therapeutic proteins after subcutaneous administrations is relevant

Differences in bioavailability after SC administration has been observed.

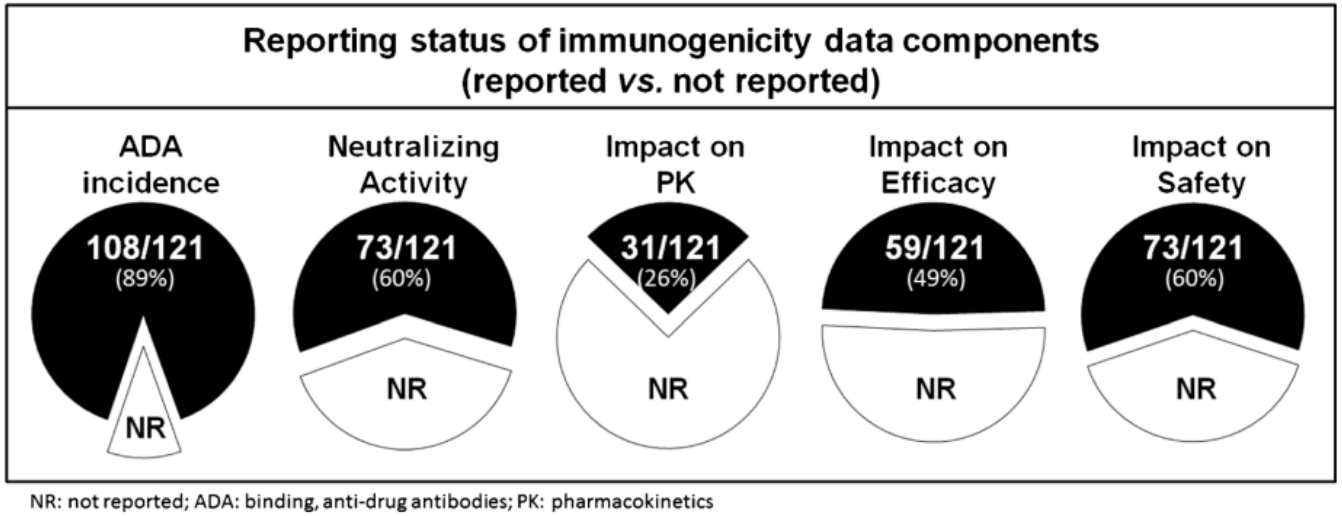
Drug	Description	Bioavailability (%)	Reference
Adalimumab	Human IgG1	64	FDA-Product Approval Information
Rituximab	Chimeric IgG1	65	FDA-Product Approval Information
Trastuzumab	Humanized IgG1	82-99	EMA-CHMP assessment report
Interferon β	rProtein	27-50	PRISMS (1998)
Darbepoetin α	Cytokine	30-50	FDA-Product Approval Information
Factor VIIa	rProtein	20-30	Tiede et al. (2011)
rHuman Insulin	Peptide Hormone	40-100	Soeberg et al. (2012)

Many potential mechanisms of presystemic degradation (loss of active drug)

- Means for predictions are still limited

Immunogenicity may negatively impact drug pharmacokinetics, efficacy, and safety

Particularly via the induction of antidrug antibodies (ADA)



NR: not reported; ADA: binding, anti-drug antibodies; PK: pharmacokinetics

Wang et al. AAPS Journal, Vol. 18, No. 2, March 2016

SC administration involves additional elements of concern related to localization and residence time in SC tissue as well as API and formulation characteristics

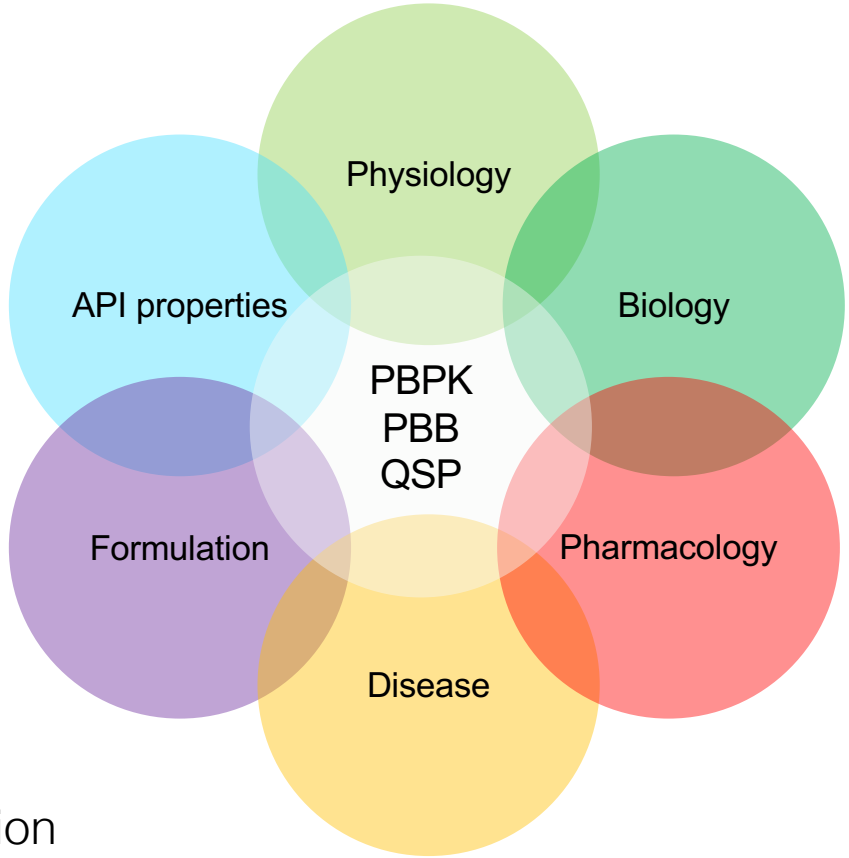
- Current means for predictions are limited

Independent representation of model elements unlocks possibilities for M&S beyond observations

- Mechanistic representation of processes relevant for pharmacokinetics, biopharmaceutics and pharmacology in a physiological and biological system

- Translation and prediction
- Investigations of causality and dependency
- Knowledge accumulation & integration allowing for discipline/competence synergies
- Learn & confirm strategies

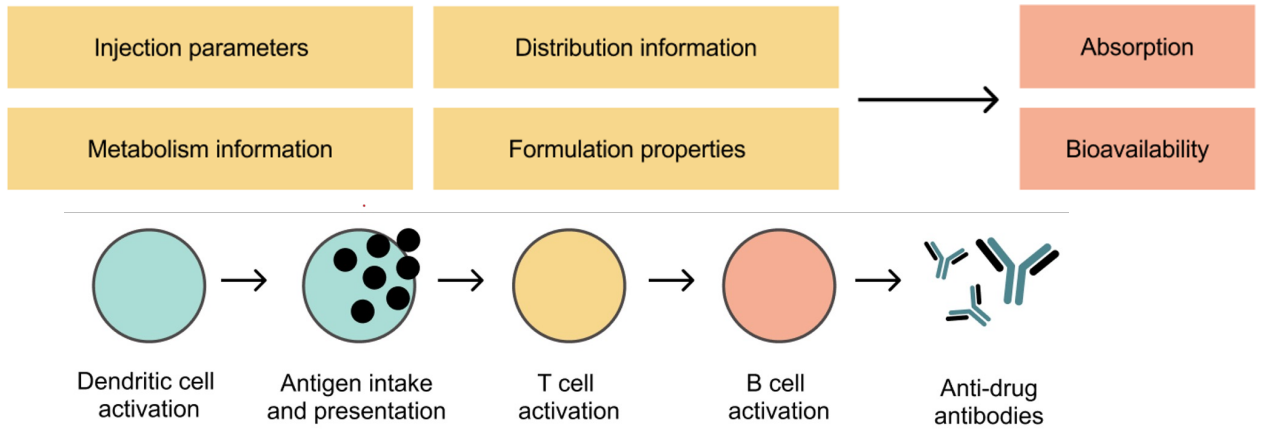
With standardized structure and generic parameterization such model can be repeatedly utilized
- Not specific to drug class, TA or drug development phase



Subcutaneous Platform

A generic *in-silico* model for translations and predictions of therapeutic proteins administered subcutaneously with focus on drug absorption and immune response, including drug deliver-related factors.

Address bioavailability and immunogenicity questions in the context of injectable vaccines, biologics and conventional small molecules



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A generic *in-silico* model for translations and predictions of therapeutic proteins administered subcutaneously with focus on drug absorption and immune response, including drug deliver-related factors.

Address bioavailability and immunogenicity questions in the context of injectable vaccines, biologics and conventional small molecules

<u>User perspective</u>

Provides a mechanistic model backbone for tailor made applications

- Translations and extrapolations in a clinical context
- Continuously leverage internal knowledge, data and experimental capabilities
- Accommodate for specific characteristics of entities in pipeline
- Linked to full functionalities of Open Systems Pharmacology Suite (WB-PBPK, R)
- Gain from continuous developments performed in the open science space
- Transparent, modifiable and free

Subcutaneous absorption model

Subcutaneous absorption model

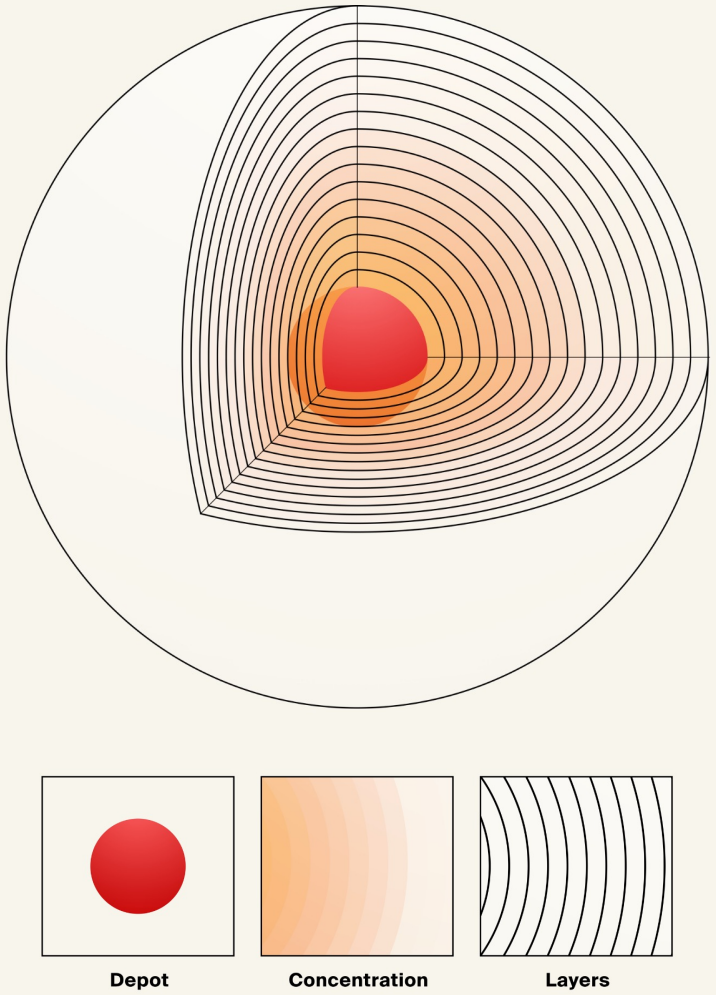
- Background to model structure

Physiologically based model structure and biopharmaceutics

- Describe the spatial-temporal drug disposition in the SC tissue (3D)

Model elements

- Depot = Injection
  - Injection volume
  - Injection rate
  - Undissolved drug – particles
- Layers = representing the tissue surrounding the depot
  - Dynamic layer sizing to allow for sufficient space
  - Geometry: sphere or cylinder
- Dispersion in tissue
  - Defined by user
  - 1/3 shells may be filled at administration
- Alignment to OSP PBPK structure
  - Parameterization and structure
  - 2-pore theory for extravasation
  - Endosomal clearance/FcRn-binding

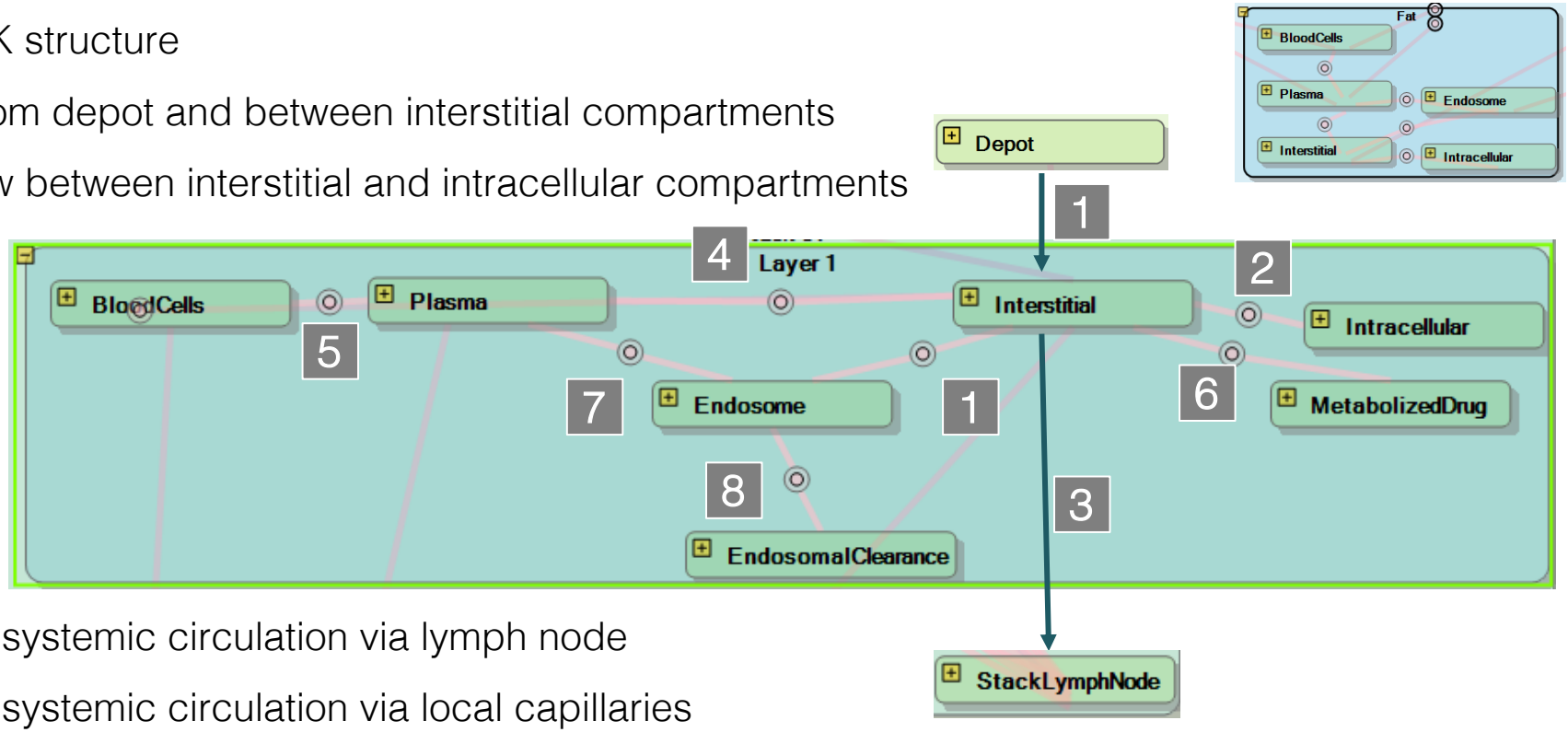


Subcutaneous absorption model

- Implementation in MoBi - 1

Alignment to generic OSP PBPK structure

1. Diffusion dependent flow from depot and between interstitial compartments
2. Permeability dependent flow between interstitial and intracellular compartments

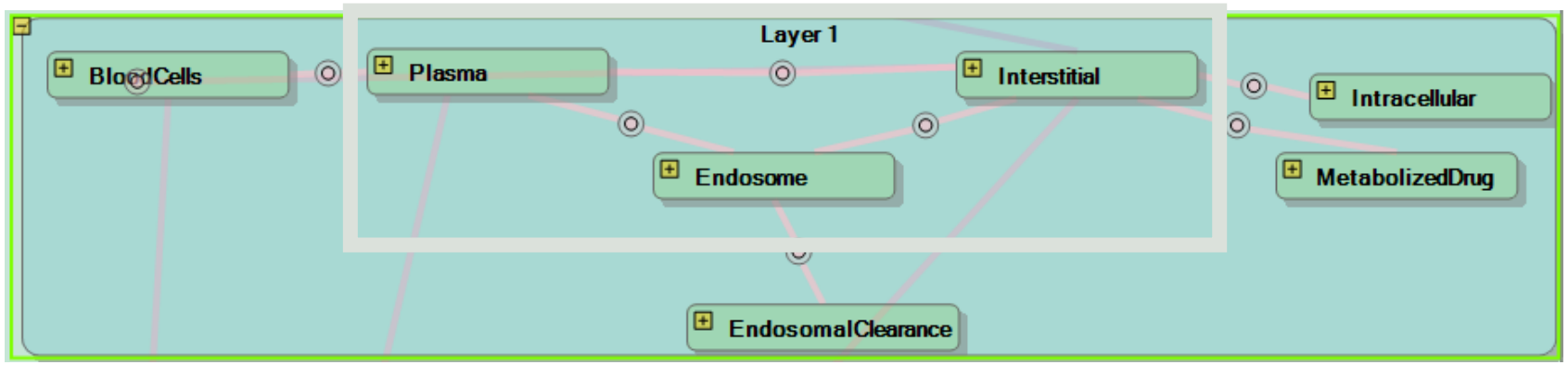


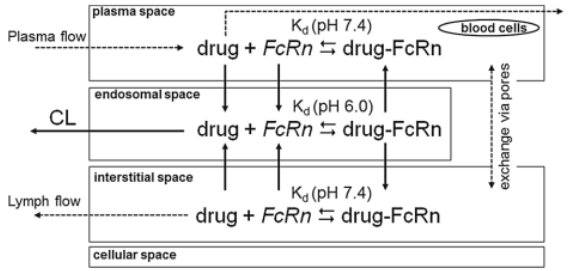
3. Flow from interstitial fluid to systemic circulation via lymph node
4. Flow from interstitial fluid to systemic circulation via local capillaries
5. Distribution of drug to blood cells
6. Generic function for local metabolism
7. Local endosome distribution
8. Endosomal clearance

Subcutaneous absorption model

- Implementation in MoBi - 2

- Reactions - FcRn binding model extended to InjectionSite
- Movement of drug from Plasma and Interstitial to Endosome
- Binding of drug with FcRn in Endosome
- Clearance of unbound drug from Endosome into EndosomalClearance
- Movement of drug-FcRn complex out of Endosome space into Plasma and Interstitial space
- Disassociation of drug in Plasma and Interstitial space

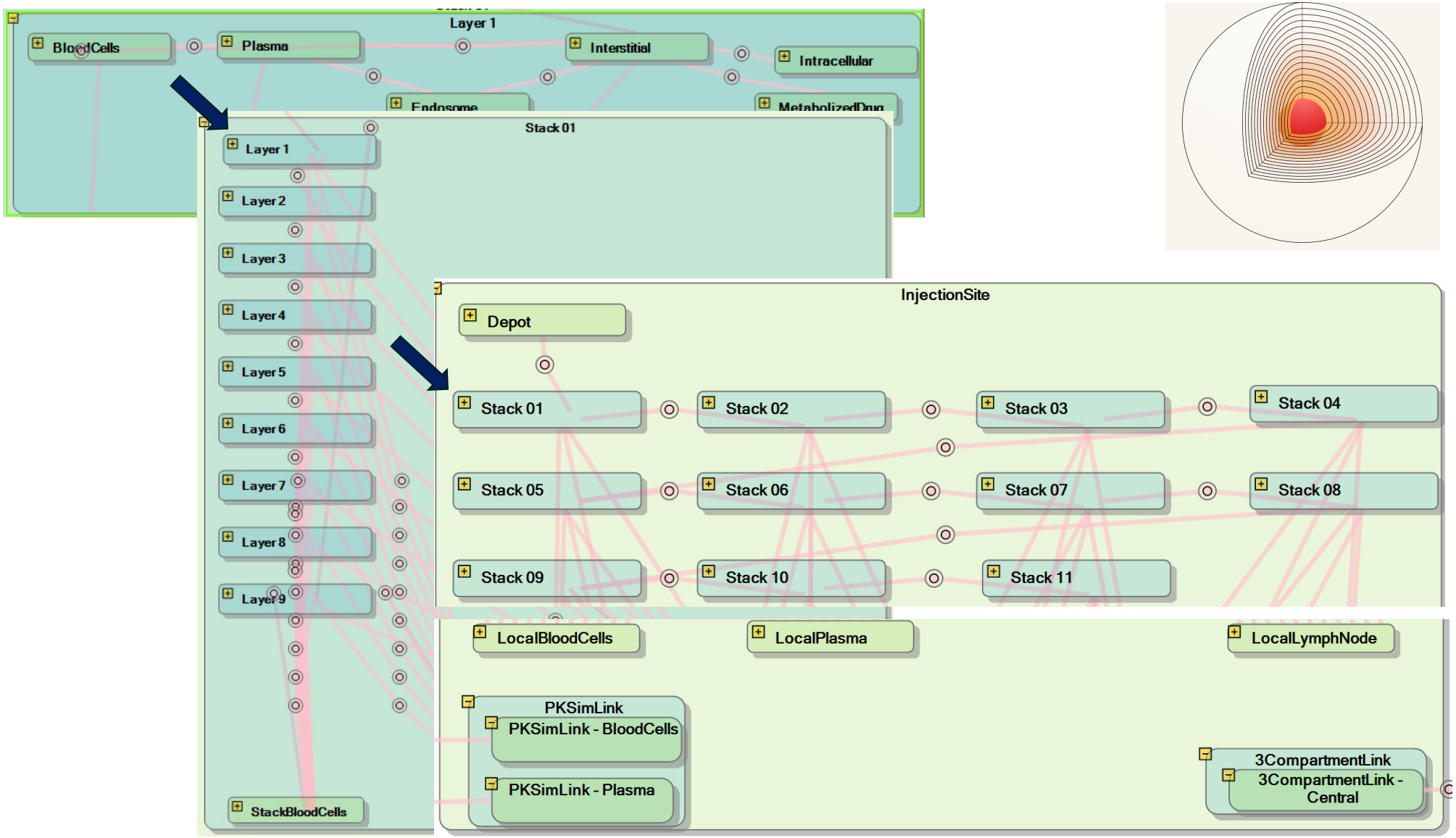




Niederalt, C., Kuepfer, L., Solodenko, J., Eissing, T., Siegmund, H. U., Block, M., ... & Lippert, J. (2018). A generic whole body physiologically based pharmacokinetic model for therapeutic proteins in PK-Sim. Journal of pharmacokinetics and pharmacodynamics, 45, 235-257.

Subcutaneous absorption model

- Implementation in MoBi - 3



Immunogenicity model

Immunogenicity model

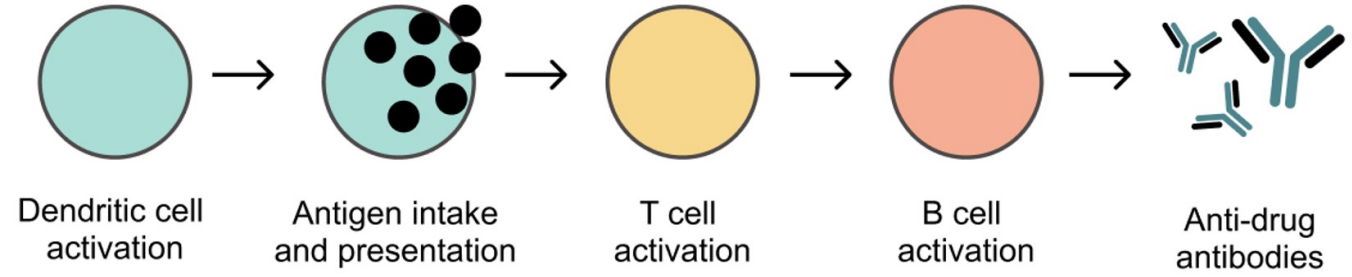
- Systemic immunogenicity according to Chen et al. 2014

A Mechanistic, Multiscale Mathematical Model of Immunogenicity for Therapeutic Proteins

CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e133; doi:10.1038/psp.2014.30 [part 1]
CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e134; doi:10.1038/psp.2014.31 [part 2]

*".. the **starting framework** to integrate various in silico, in vitro, in vivo, and clinical immunogenicity assessment results to help meet the challenge of immunogenicity prediction".*

Organization of immunogenicity model



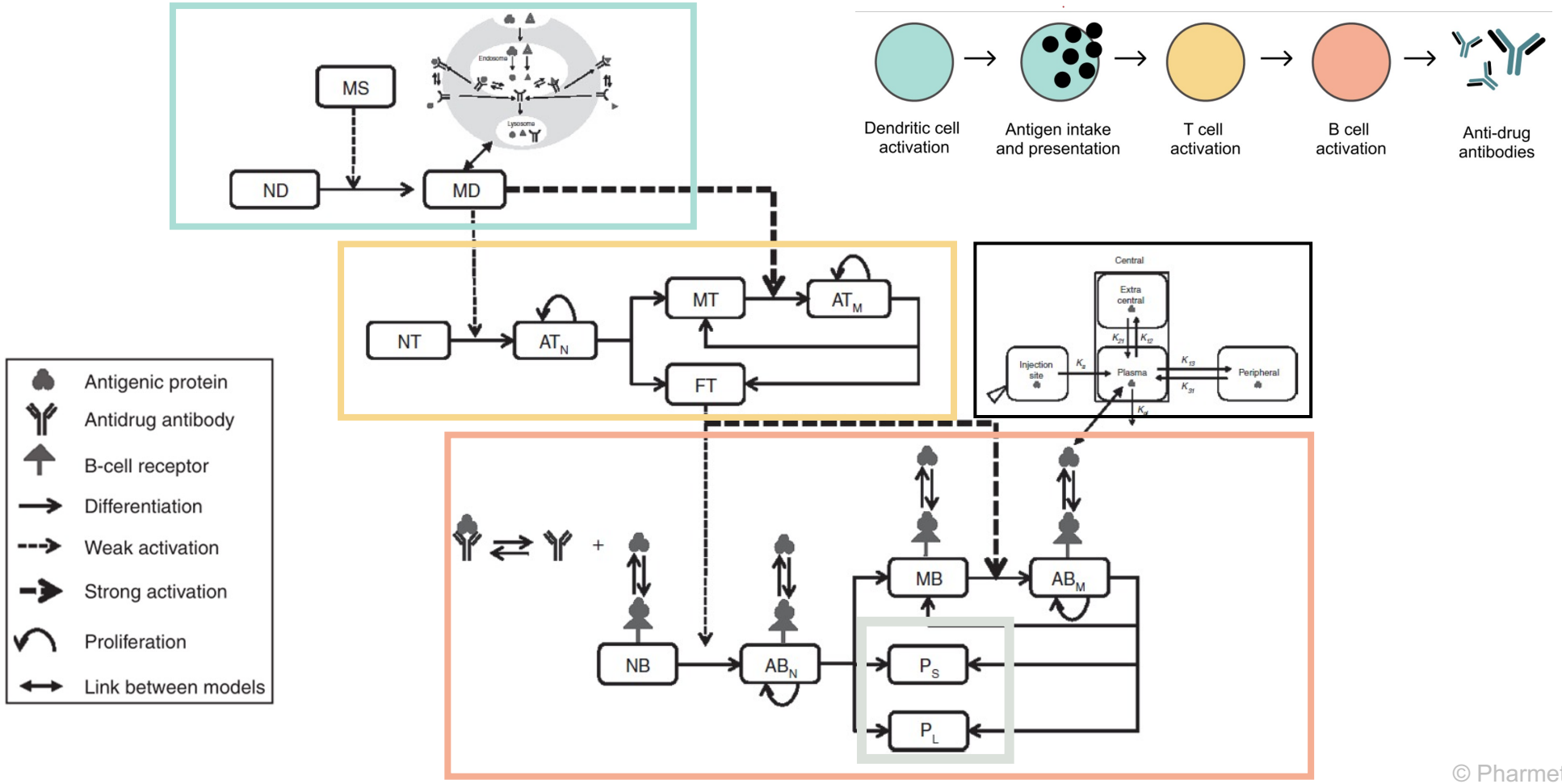
Model input

- Number of peptides (T-epitopes)
- Epitope-MHC-II binding affinity
- Number of naïve T cells

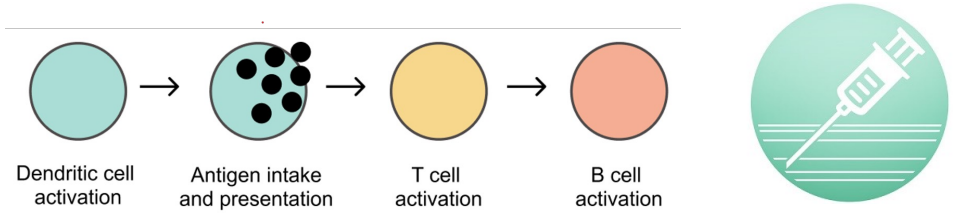
Immunogenicity model

- Systemic immunogenicity according to Chen et al. 2014

Model structure on the cellular level, including cells, antigen, antidrug antibody, and B-cell receptor

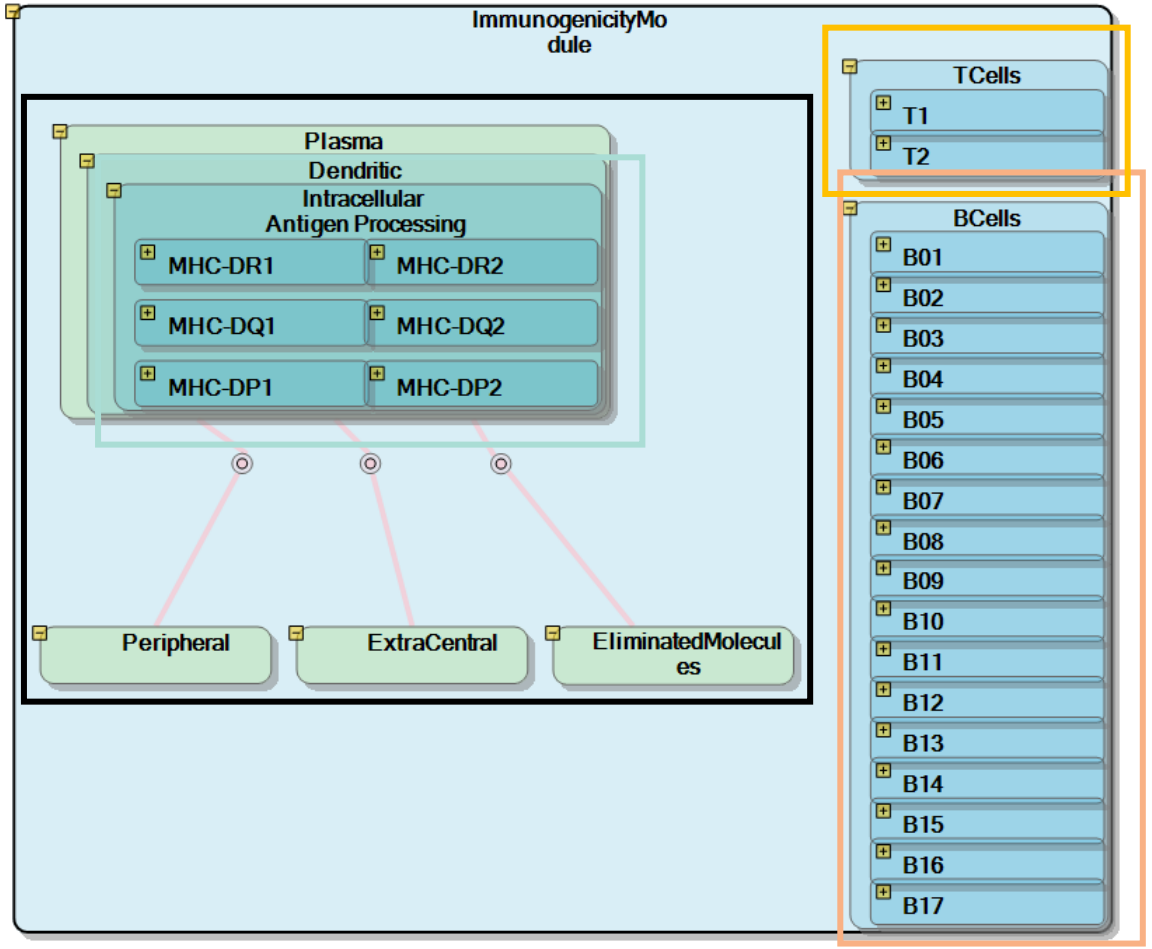


Systemic immunogenicity
- Implementation in MoBi



- Dendritic cells
  - Immature, Mature, Maturation signal cascade
- T cells
  - One for each peptide (example n=2)
- B cells
  - Polyclonal B-cell lineages as a population (n=17) with different antigen-binding affinities.
  - Binding affinities are 2-fold different in adjacent groups to cover a physiologically plausible range
- Systemic disposition
  - Compartmental PK
  - WB-PBPK structure (PK-Sim)

Spatial structure



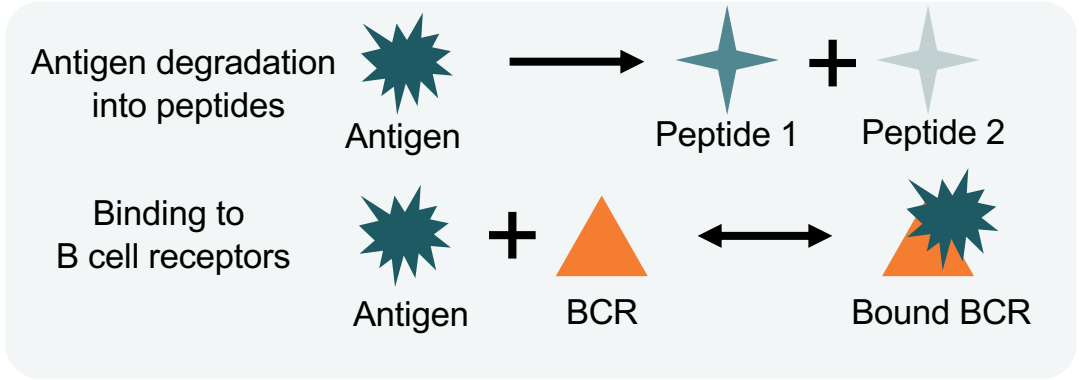
Systemic immunogenicity
- Implementation in MoBi

Molecules

- Antigen
  - Free
  - Internalized by B cells
  - Degrades into n peptides
- MHC-II molecules
  - 6 types: DP1, DP2, DQ1, DQ2, DR1, DR2
  - 6 x n complexes = 6 MHC-II molecules x n peptides
  - 6 complexes = 6 MHC-II molecules x 1 competing peptide
- Anti-drug antibodies (ADAs)
  - 17 groups
  - 3 states: free, one site bound, and two sites bound
- B cell receptors (BCRs)
  - 17 groups
  - 2 states: free and bound

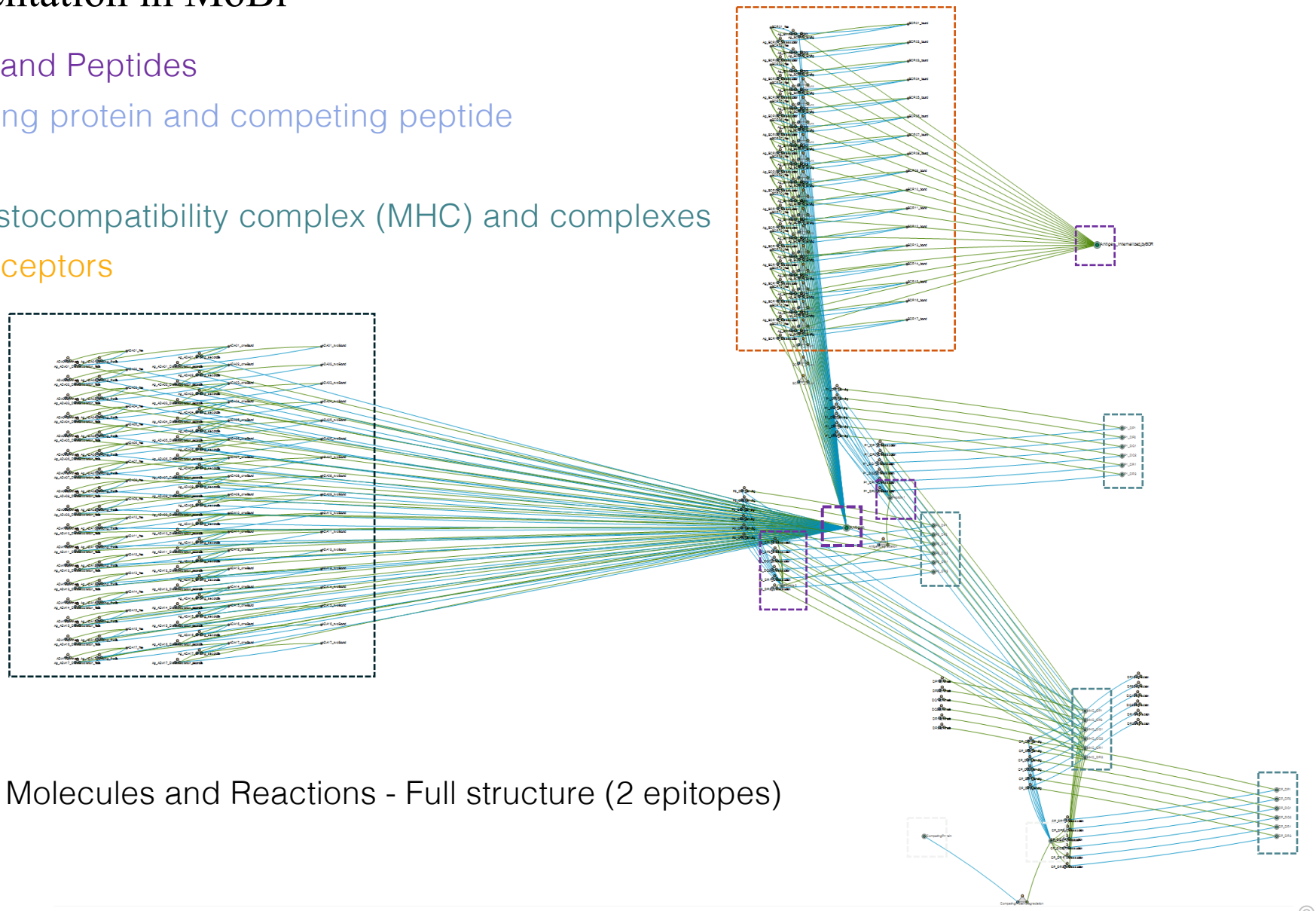
Reactions

- Degradation of proteins into peptides
- Peptide binding to MHC-II molecules
- Antigen binding to ADAs (two sites) and BCRs
- Antigen internalization into B cells by BCRs



Systemic immunogenicity model
- Implementation in MoBi

- Antigen and Peptides
- Competing protein and competing peptide
- ADA
- Major histocompatibility complex (MHC) and complexes
- B-cell receptors



Molecules and Reactions - Full structure (2 epitopes)

Systemic immunogenicity model
- Evaluation of implementation – pt.2: Clinical translation

- Virtual population simulations for clinical predictions

Virtual population generation

(1)

MHC-II allele	Allele frequency in North America	Epitope 1 binding affinity (nmol/l)	Epitope 2 binding affinity (nmol/l)
DRB1*04:01	0.089	123	85
DRB1*04:03	0.053	78.52	147.85
DRB1*04:04	0.036	180	38
DRB1*04:07	0.085	124.73	104.16
DRB1*04:11	0.15	57.44	101.5
DRB1*07:01	0.0083	75	77
DRB1*08:02	0.069	306	292
DRB1*08:11	0.0015	112.43	4,000
DRB1*11:01	0.0436	317	293
DRB1*14:04	0.00075	53.7	4,000
DRB1*15:01	0.0083	148	4,000
Rest of DRB1 alleles	0.46	4,000	4,000

(2)

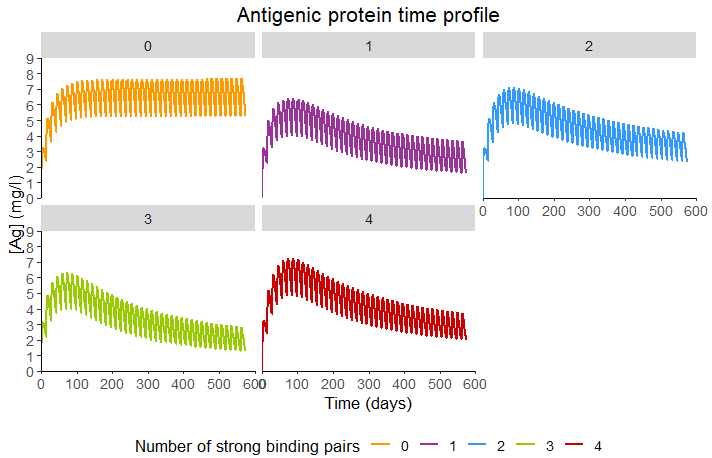
Randomly select MHC-II alleles for a virtual subject based on allele frequency

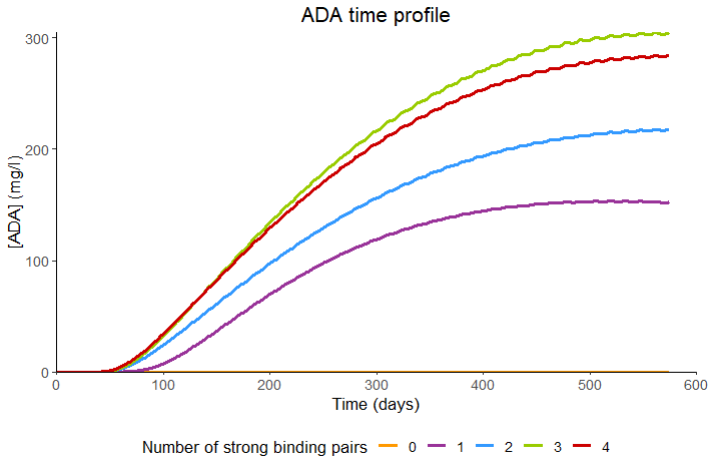
Obtain MHC-II binding affinity for the T-epitopes

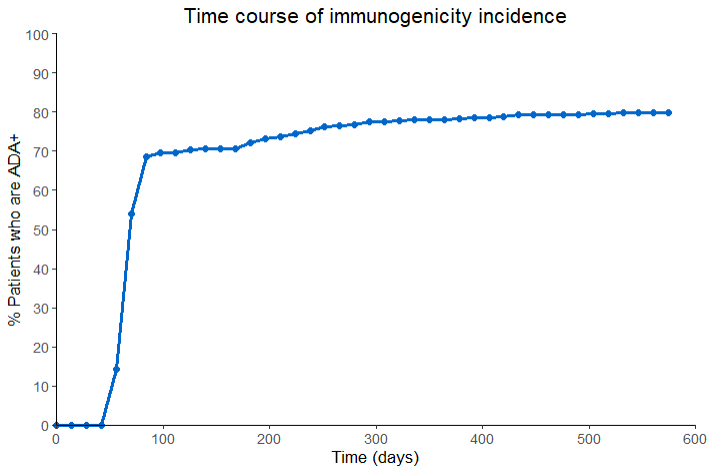
MHC-II allele	Epitope binding affinity to MHC (nmol/l) Epitope 1	Epitope 2
DRB1 *04:01	123	85
DRB1 *04:07	124.73	104.16
DPA1 *02:01	4,000	4,000
DPA1 *03:01	4,000	4,000
DQA1 *04:01	4,000	4,000
DQA1 *05:01	4,000	4,000

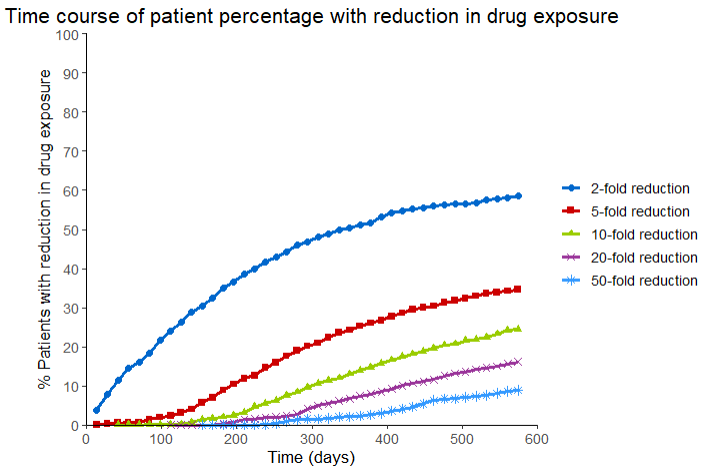
Simulate immune reponse for this virtual subject *

(3) Repeat step (2) for 1,000 subjects



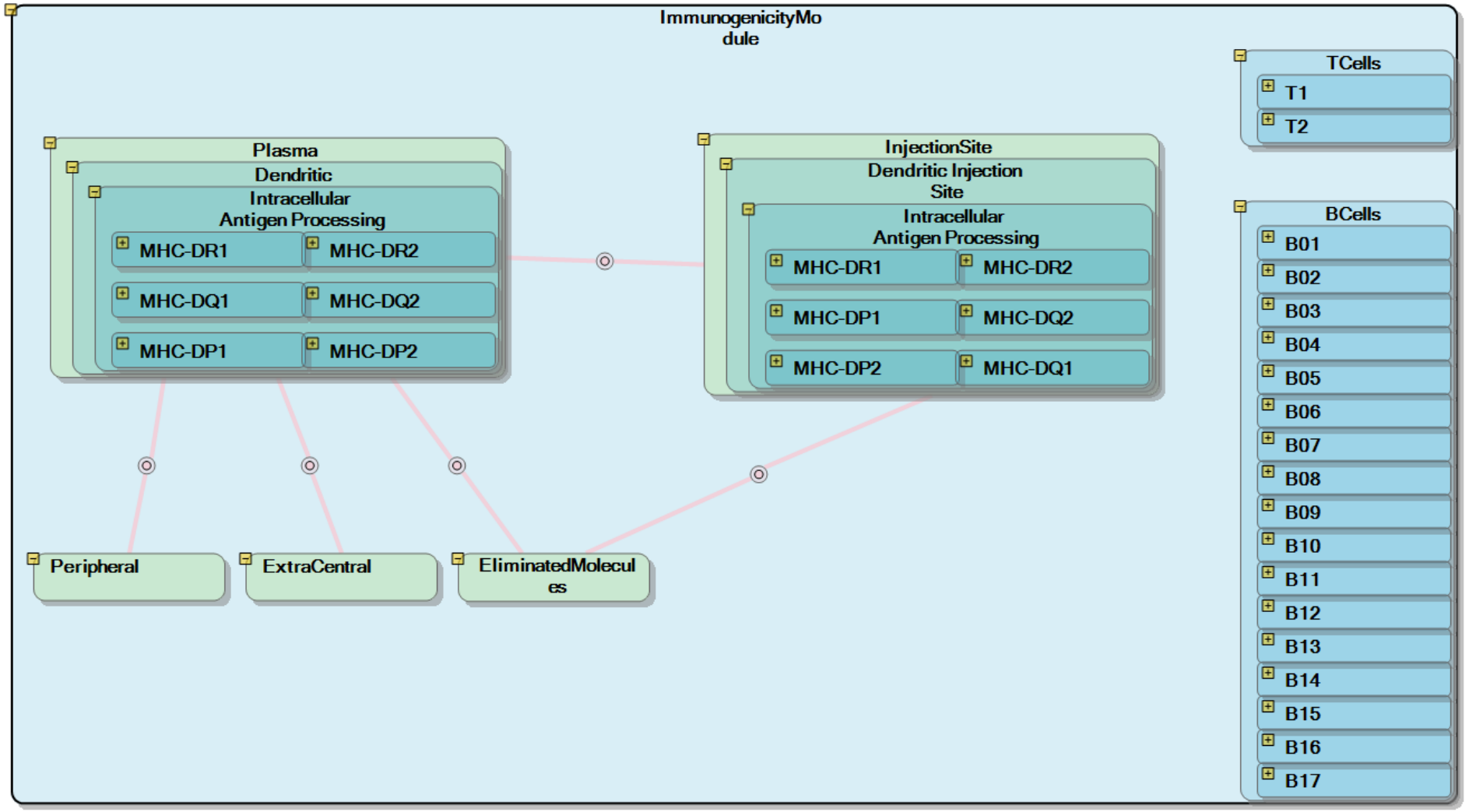






Systemic and local subcutaneous immunogenicity model
- Implementation in MoBi

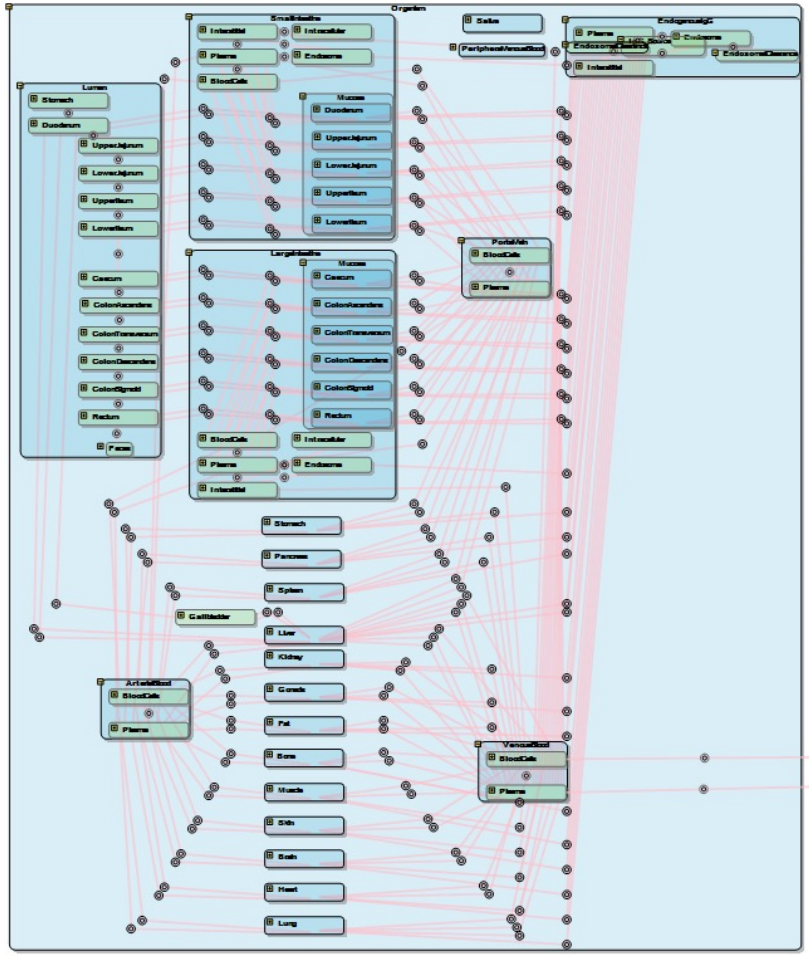
Spatial structure



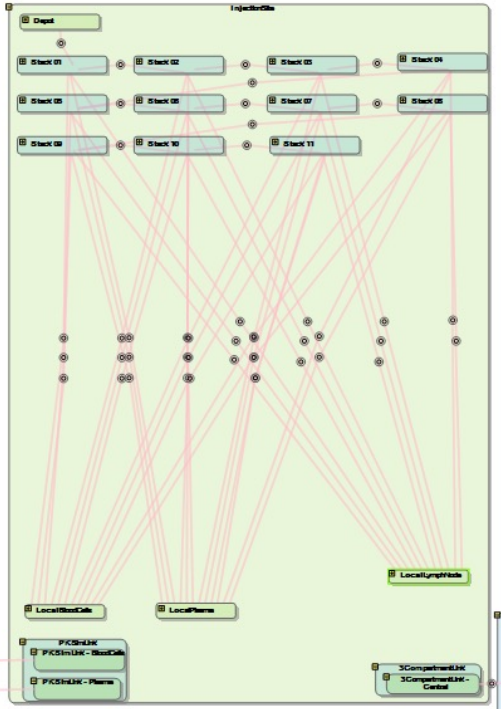
Subcutaneous drug absorption and immunogenicity

- Implementation in MoBi

PK-Sim WB-PBPK

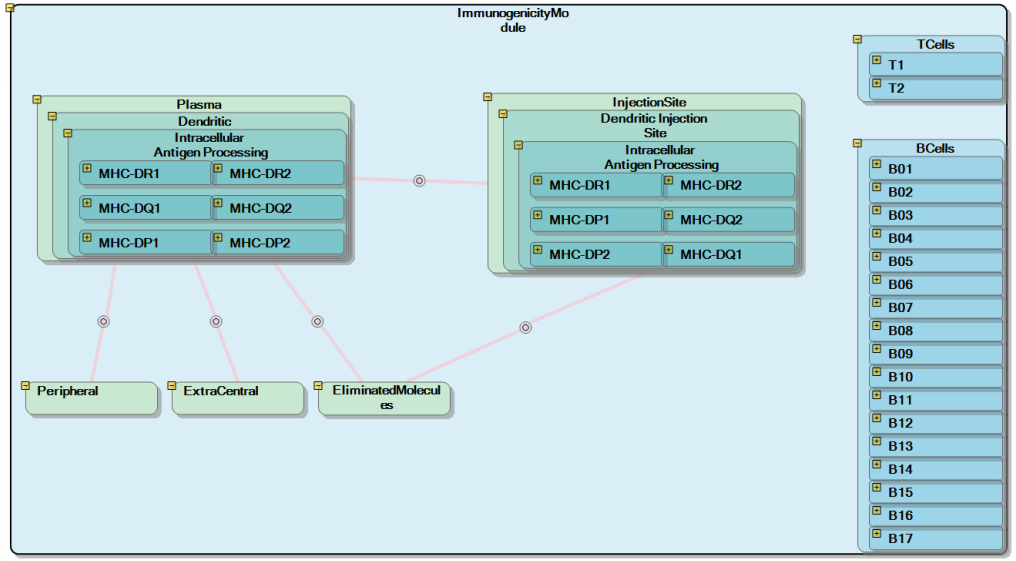


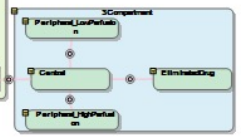
Injection Site



Systemic immunogenicity

Local SC immunogenicity





3-compartment PK

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- Uppsala University, Sweden: Ilse Dubbelboer
- AstraZeneca RD, Sweden: Xavier Pepin, Iain Grant
- SweDeliver, Swedish Drug Delivery Centre
- Vinnova, Sweden’s Innovation Agency.

Thank you for your attention

Predicting monoclonal antibody pharmacokinetics and bioavailability following subcutaneous administration

Salih Benamara

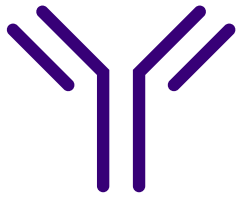
sanofi Pharmetheus amU Aix Marseille Université OSP OPEN SYSTEMS PHARMACOLOGY

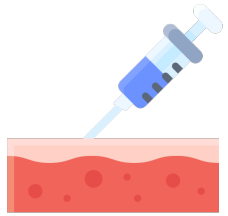
Monoclonal antibodies and subcutaneous administration

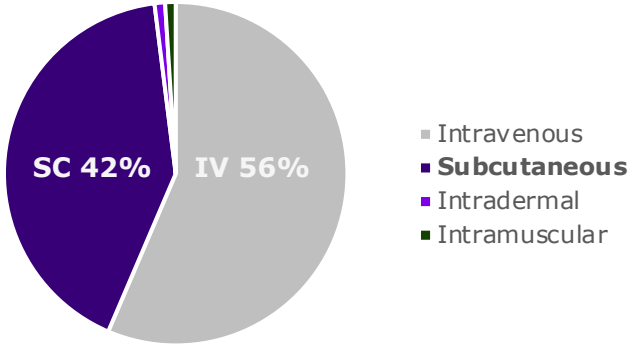
Therapeutic monoclonal antibodies

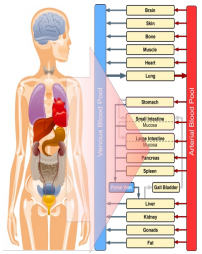
Almost half of the marketed antibodies are administered subcutaneously[1]

Physiologically based pharmacokinetic modeling and SubQ







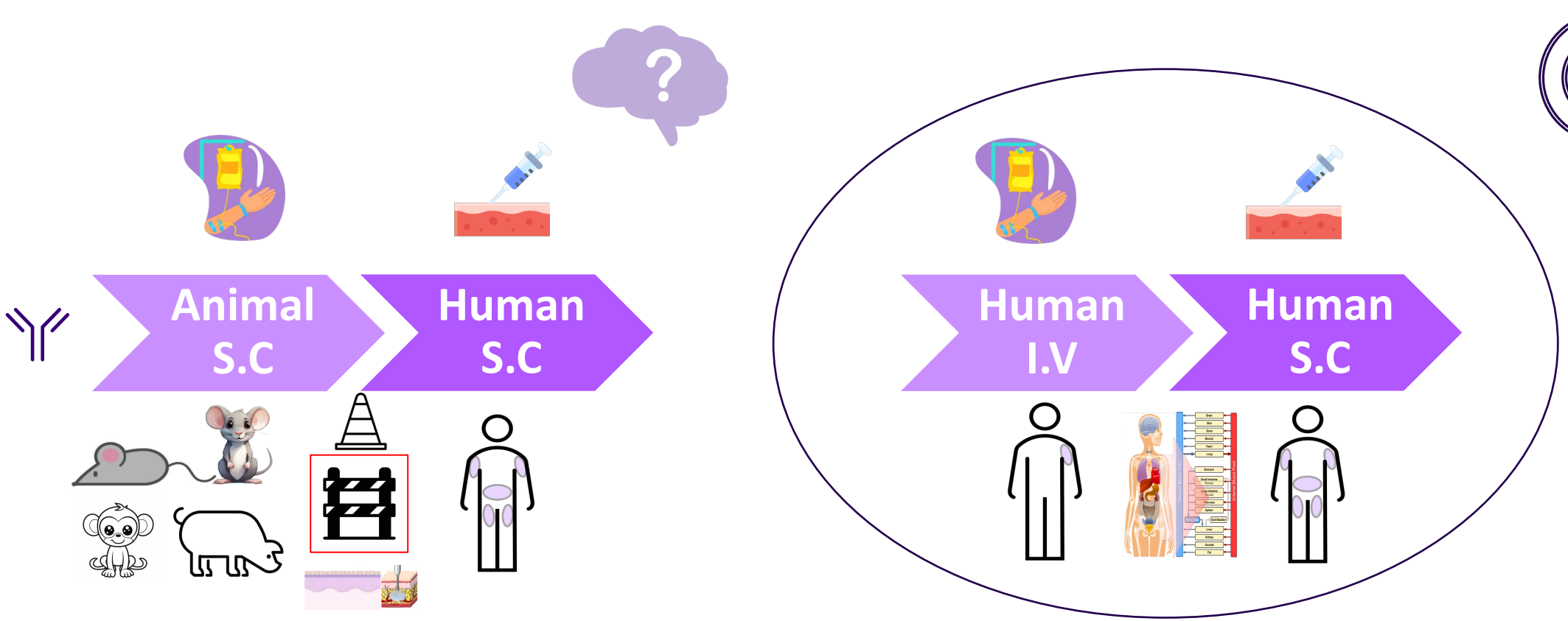


Despite longstanding use, many aspects of the bioavailability of monoclonal antibodies remain poorly understood

sanofi

1. K. P. Martin et al Trends in industrialization of biotherapeutics: a survey of product characteristics of 89 antibody-based biotherapeutics.*Mabs. vol. 15. no. 1. 2023*

Prediction of monoclonal antibodies pharmacokinetics after subcutaneous administration



The main objective is to predict human PK after subcutaneous administration from PK data following intravenous administration using PBPK modeling

Predict human PK after S.C administration from PK data following I.V administration using PBPK modeling

1. Database

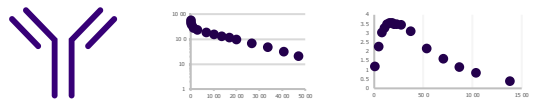
- In vitro drug properties
- In vivo I.V PK data
- In vivo S.C PK data

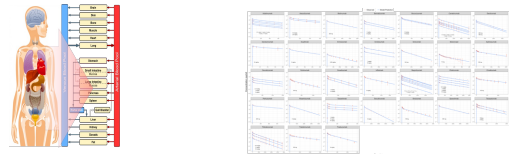
2. I.V PBPK Modeling

- Reference I.V plasma concentrations
- FcRn Kd estimation
- I.V PBPK simulation

3. S.C PBPK Modeling

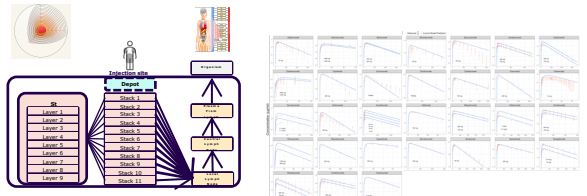
- Reference S.C plasma concentrations
- S.C PBPK modeling
- S.C PBPK prediction





I.V PBPK modeling

I.V PBPK simulation



S.C Injection site

S.C PBPK prediction

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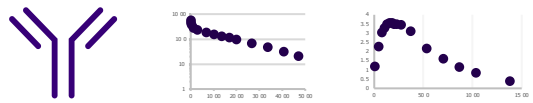
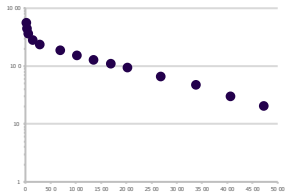


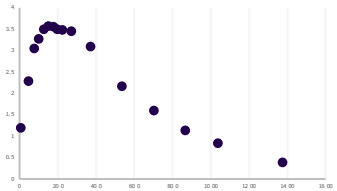
1. Database

In vitro drug properties

In vivo I.V PK data



In vivo S.C PK data



- Criteria for bibliographic search
  - Monoclonal antibody
  - Drug properties
  - Population characteristics
  - IV linear pharmacokinetics
  - I.V and S.C Data
  - Full time-course available

53 Molecules

20 mAbs with only I.V or S.C data

- Project II : *Predictability of human PK after IV administration of mAbs by using an average FcRn Kd*

31 molecules with both IV and SC data

- 30 mAbs
- 1 fusion protein-mAb like *(Etanercept)*

2 mAbs with FcRn Binding mutations

- Suvratoxumab
- Elezanumab *(Kd FcRn = 0.25 / 0.1 µmol)*

Predict human PK after S.C administration from PK data following I.V administration using PBPK modeling

1. Database

In vitro drug properties

In vivo I.V PK data

In vivo S.C PK data

2. I.V PBPK Modeling

Reference I.V plasma concentrations

FcRn Kd estimation

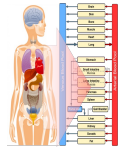
I.V PBPK simulation

3. S.C PBPK Modeling

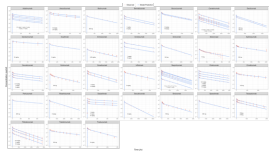
Reference S.C plasma concentrations

S.C PBPK modeling

S.C PBPK prediction



I.V PBPK modeling



I.V PBPK simulation

S.C Injection site

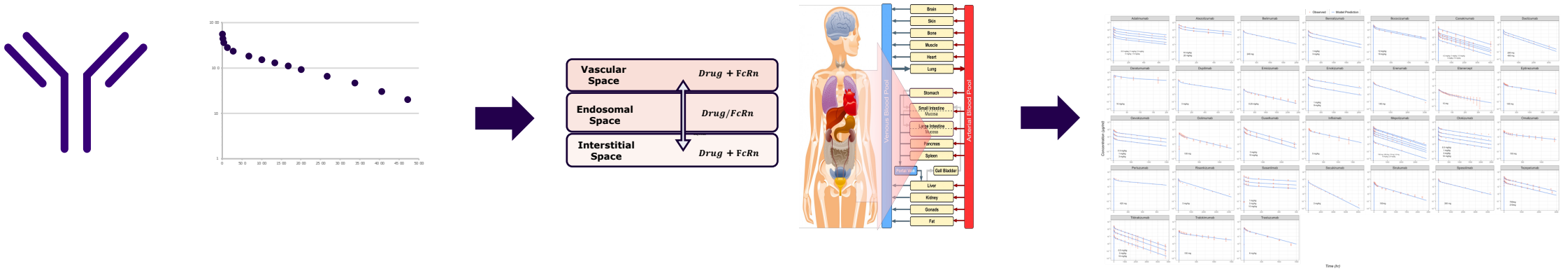
S.C PBPK prediction

2. I.V PBPK Modeling

Reference I.V plasma concentrations

FcRn Kd estimation

I.V PBPK simulation

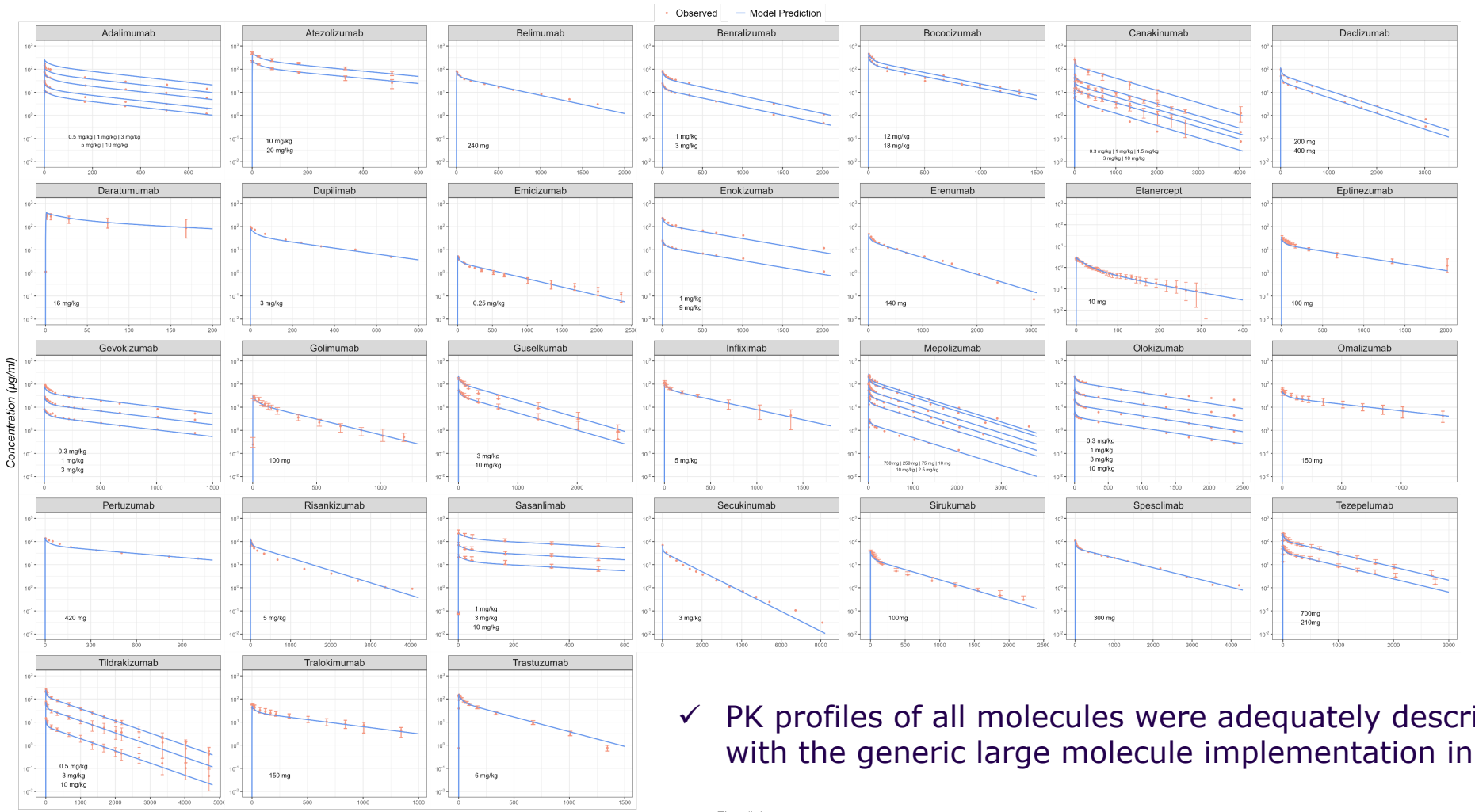


I.V PBPK modeling **Kd FcRn estimation**

For each drug utilize reference I.V plasma concentrations data to establish systemic PBPK models via estimation of affinity to the FcRn receptor (FcRn Kd)

2. I.V PBPK Modeling

I.V PBPK simulation

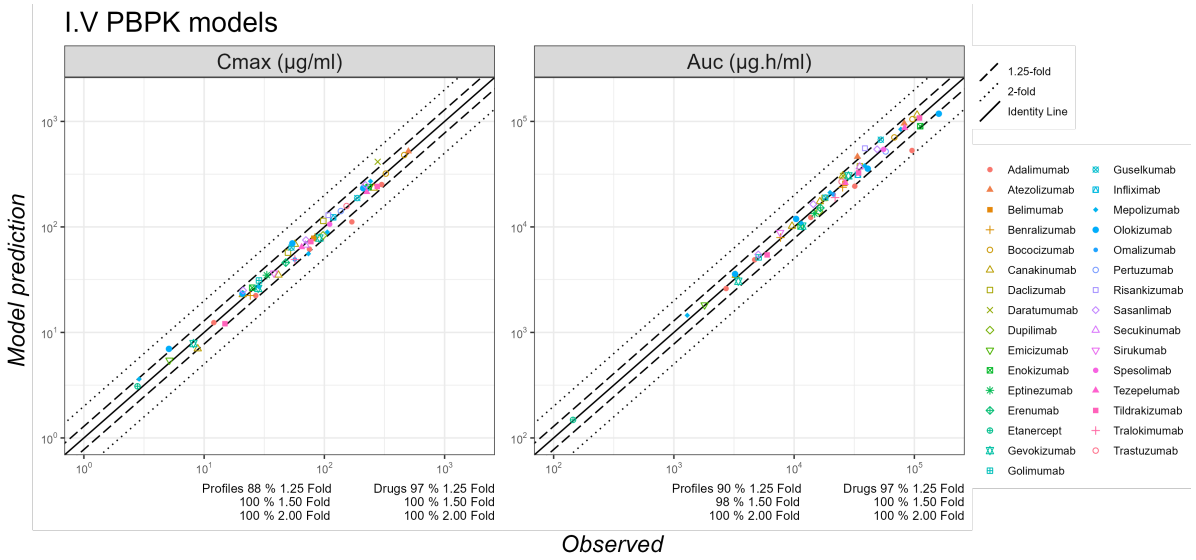


✓ PK profiles of all molecules were adequately described with the generic large molecule implementation in PK-Sim

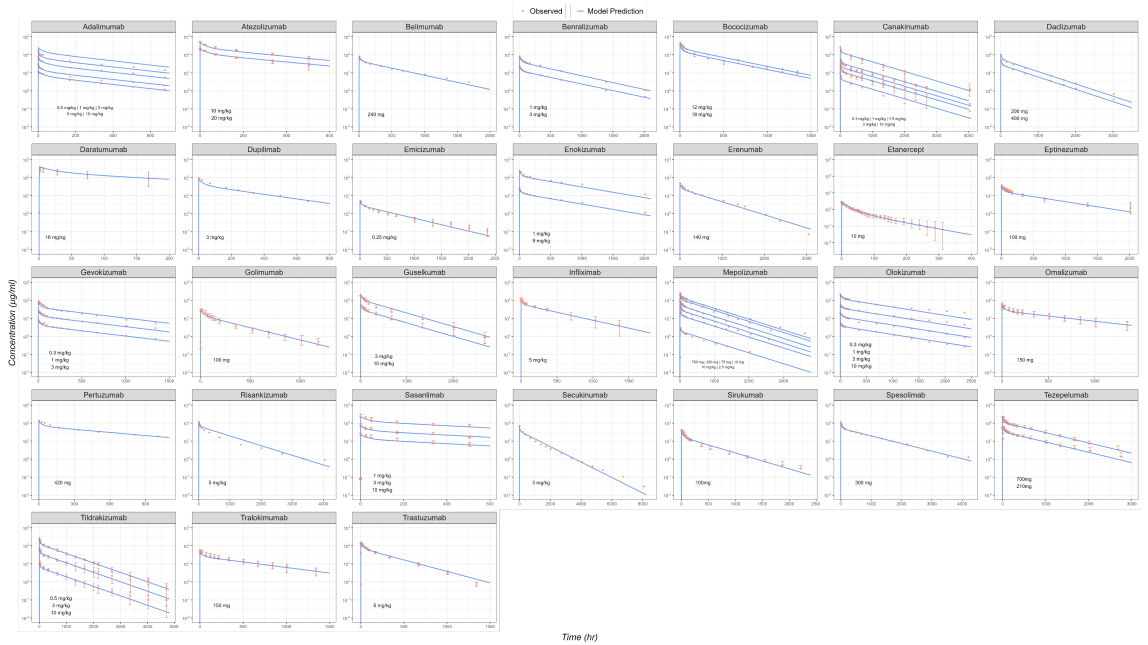
2. I.V PBPK Modeling

I.V PBPK simulation

Observed versus I.V PBPK model simulated PK parameters Cmax and AUC



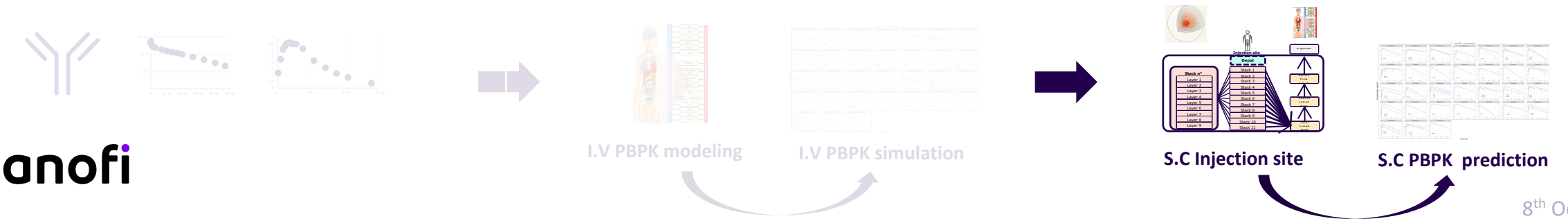
Observed versus I.V PBPK model simulated PK



- ✓ All molecules PK were simulated with AUC and Cmax values within the 2-fold range compared to the observed data
- ✓ PK profiles of all molecules were adequately described with the generic large molecule implementation in PK-Sim

Predict human PK after S.C administration from PK data following I.V administration using PBPK modeling

1. Database	2. I.V PBPK Modeling	**3. S.C PBPK Modeling**
In vitro drug properties	Reference I.V plasma concentrations	Reference S.C plasma concentrations
In vivo I.V PK data	FcRn Kd estimation	S.C PBPK modeling
In vivo S.C PK data	I.V PBPK simulation	S.C PBPK prediction

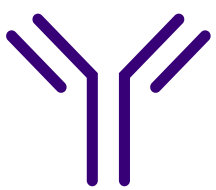


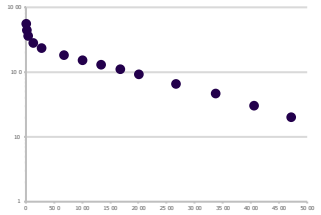
3. S.C PBPK Modeling

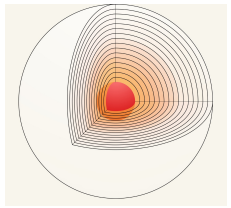
Reference S.C plasma concentrations

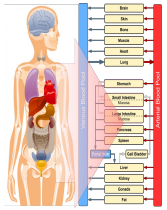
S.C PBPK modeling

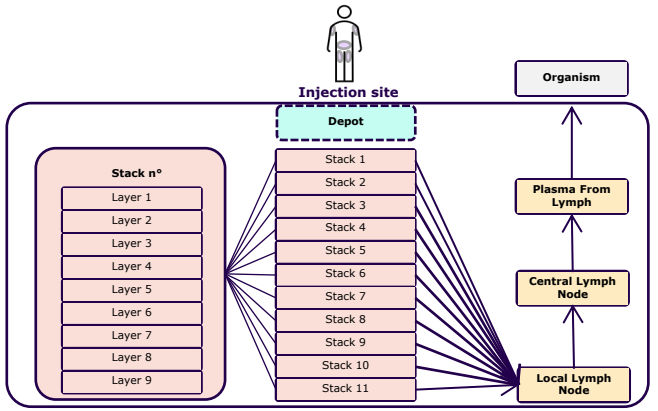
S.C PBPK prediction

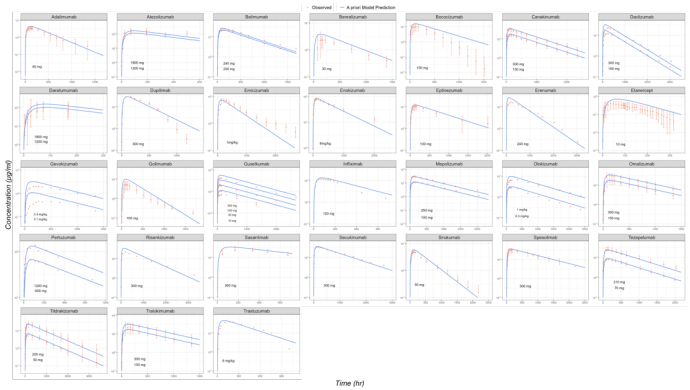












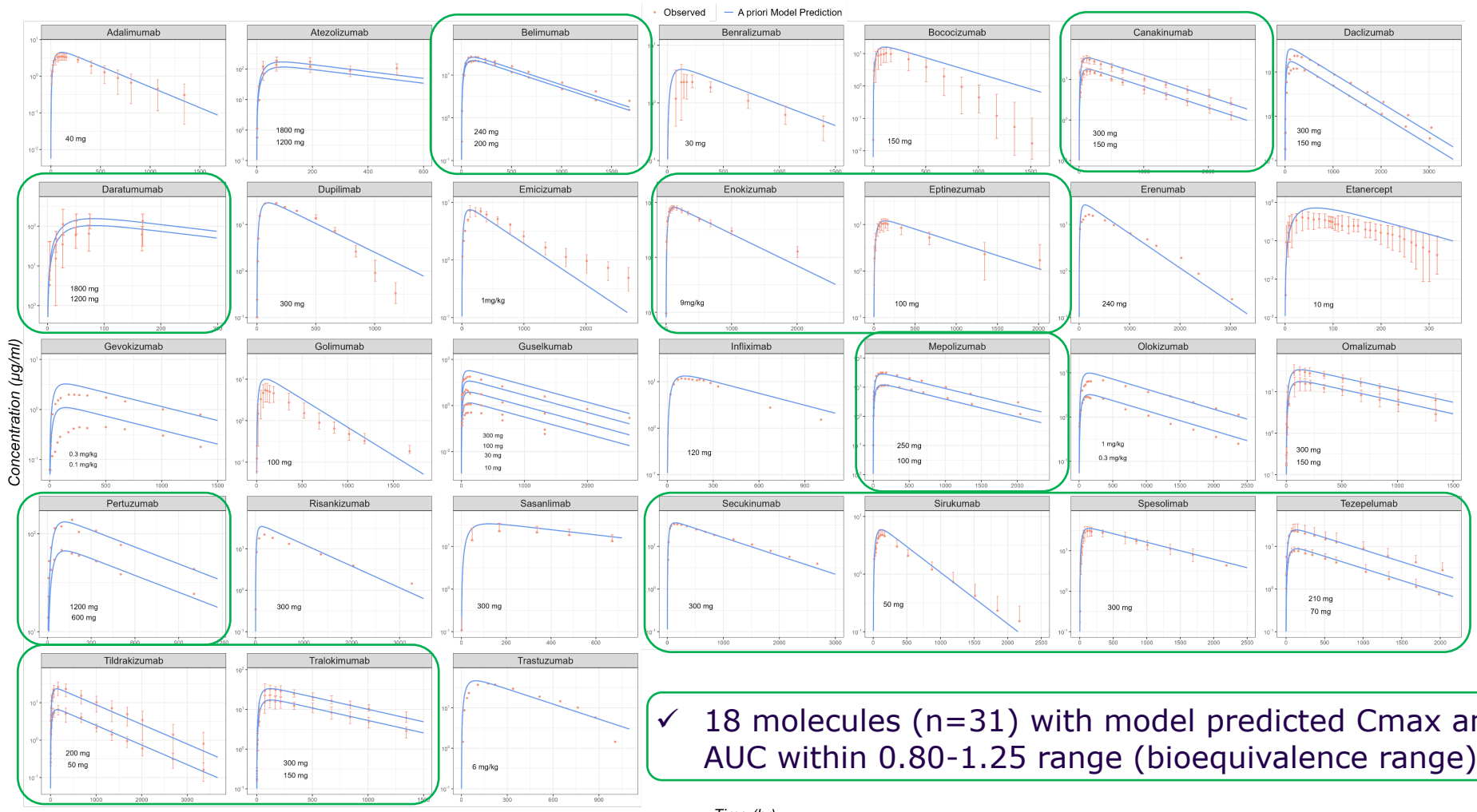
S.C Injection site

S.C PBPK prediction

Expand the developed PBPK I.V models for each drug by a mechanistic S.C model describing the injection site

3. S.C PBPK Modeling

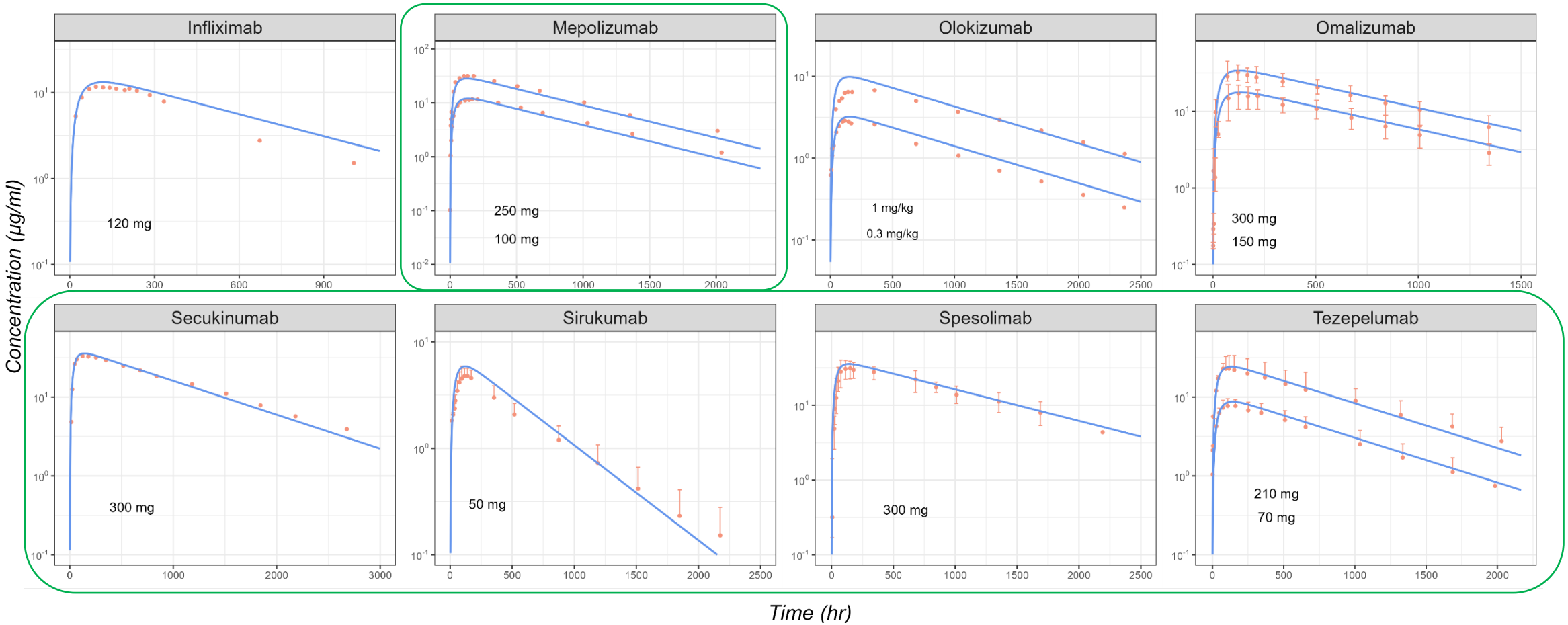
S.C PBPK prediction



✓ 18 molecules (n=31) with model predicted Cmax and AUC within 0.80-1.25 range (bioequivalence range)

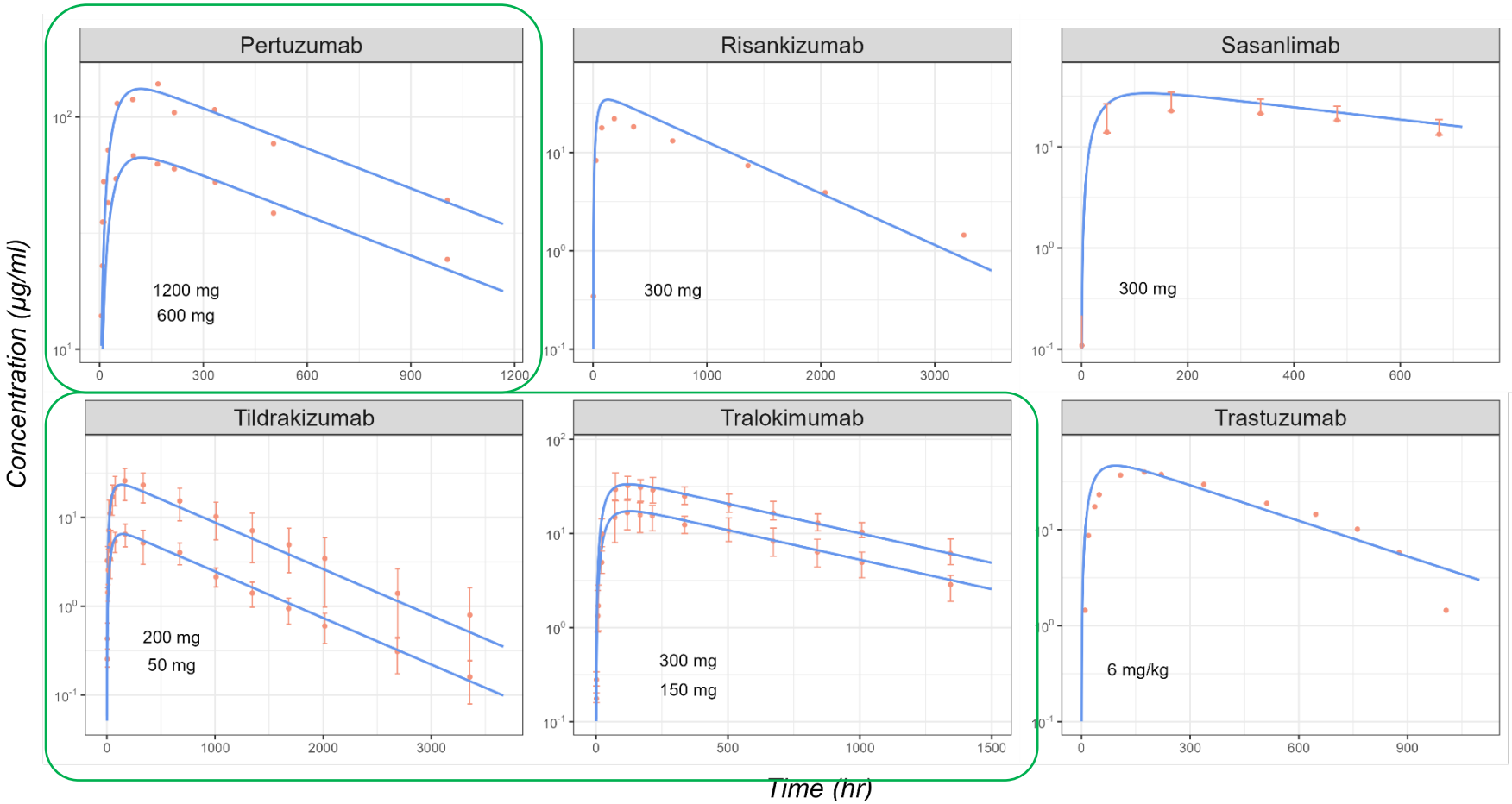
3. S.C PBPK Modeling

S.C PBPK prediction



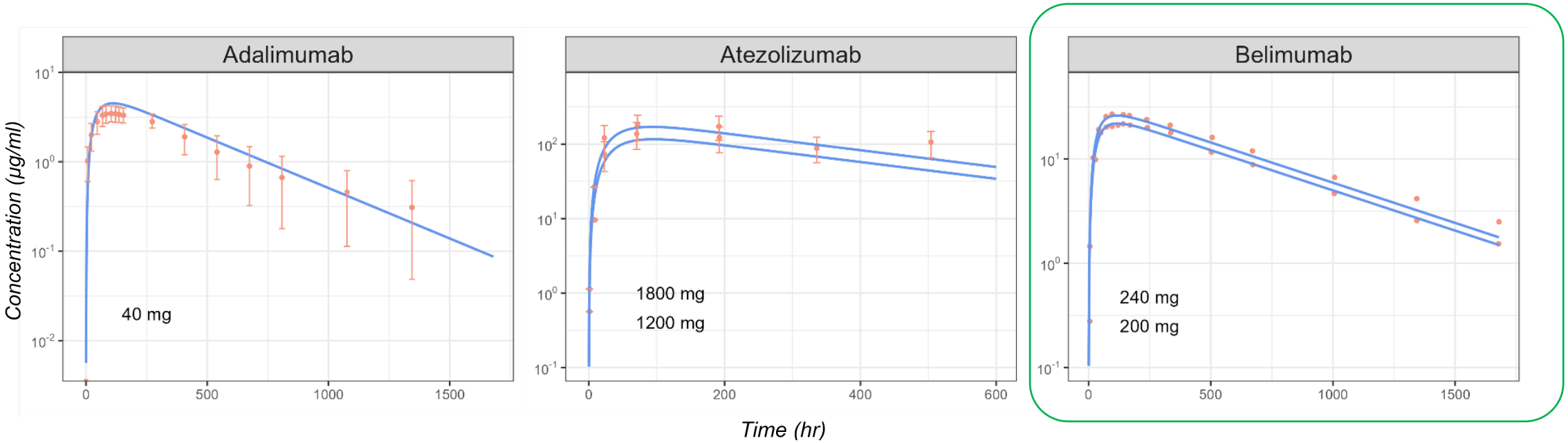
3. S.C PBPK Modeling

S.C PBPK prediction



3. S.C PBPK Modeling

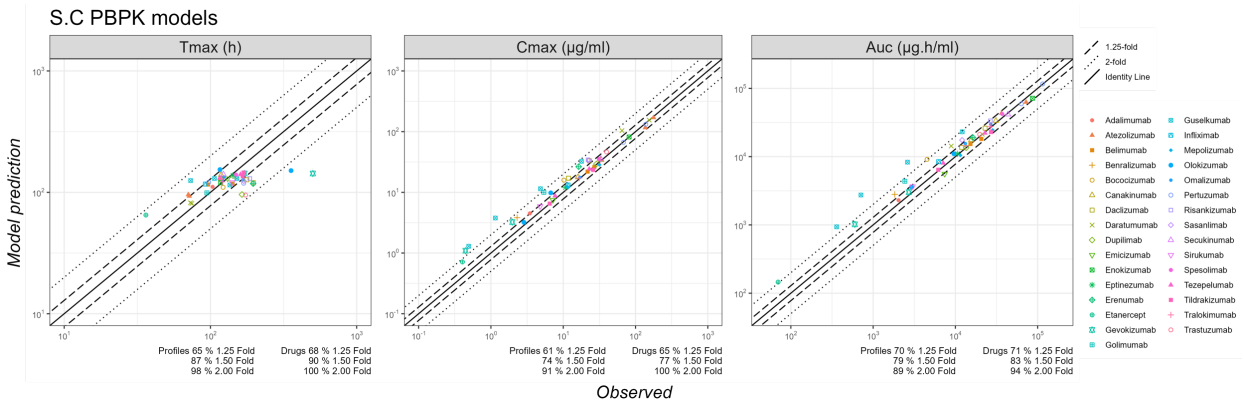
S.C PBPK prediction



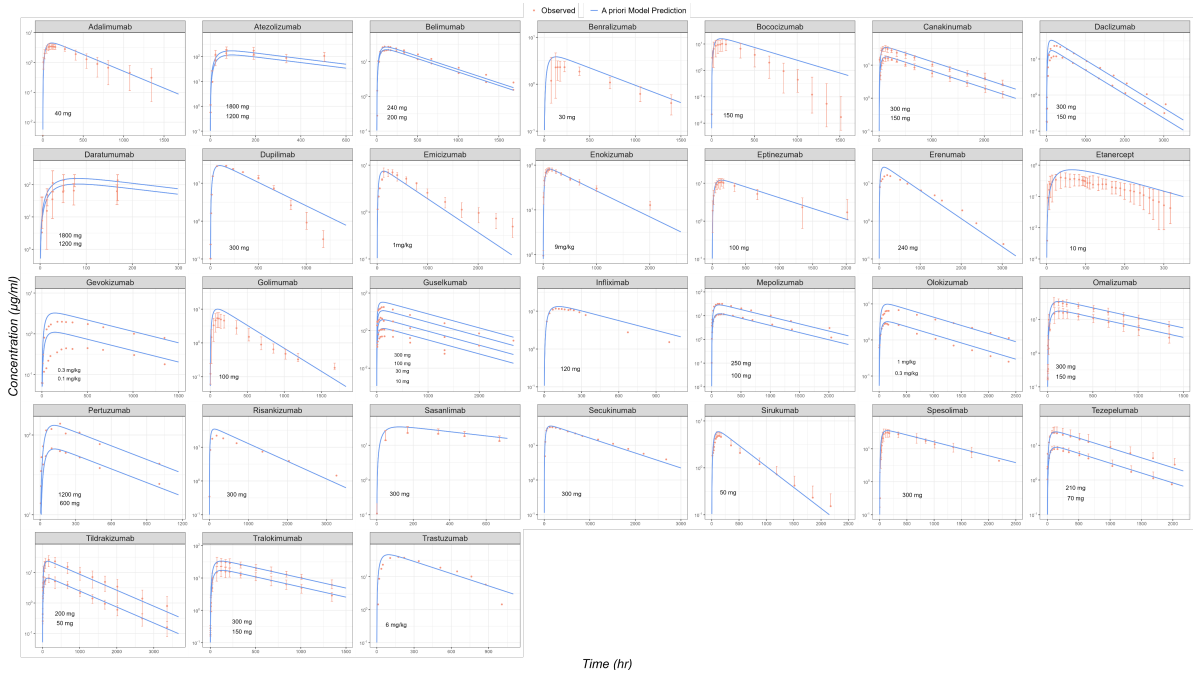
3. S.C PBPK Modeling

S.C PBPK prediction

Observed versus S.C PBPK model predicted PK parameters Tmax, Cmax and AUC



Observed versus S.C PBPK model predicted PK



✓ 29 molecules (from 31) were predicted with Tmax, Cmax and AUC values within the 2-fold range compared to the observed data

✓ 18 molecules with model predicted Cmax and AUC within 0.80-1.25 range (bioequivalence range)

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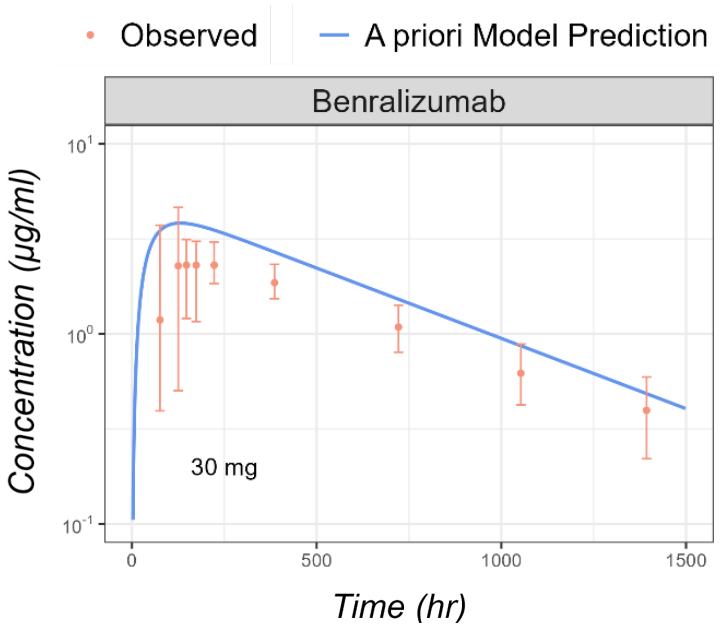
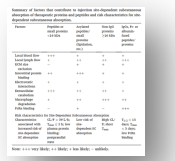
3. S.C PBPK Modeling

S.C PBPK prediction

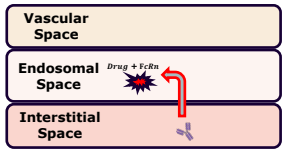
1. A priori model prediction



2. Hypothesis

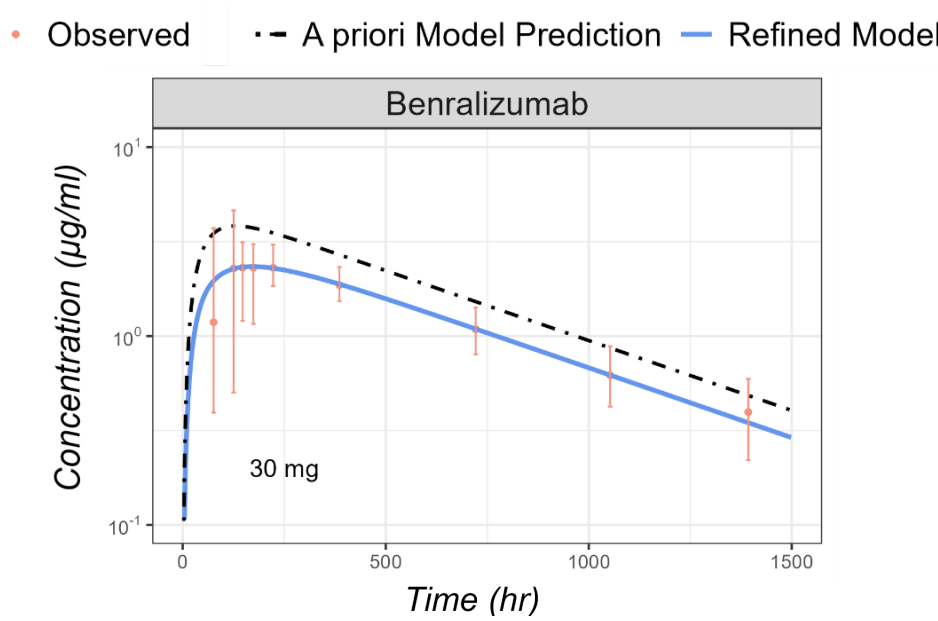


Endosomal clearance



Lymph flow transport

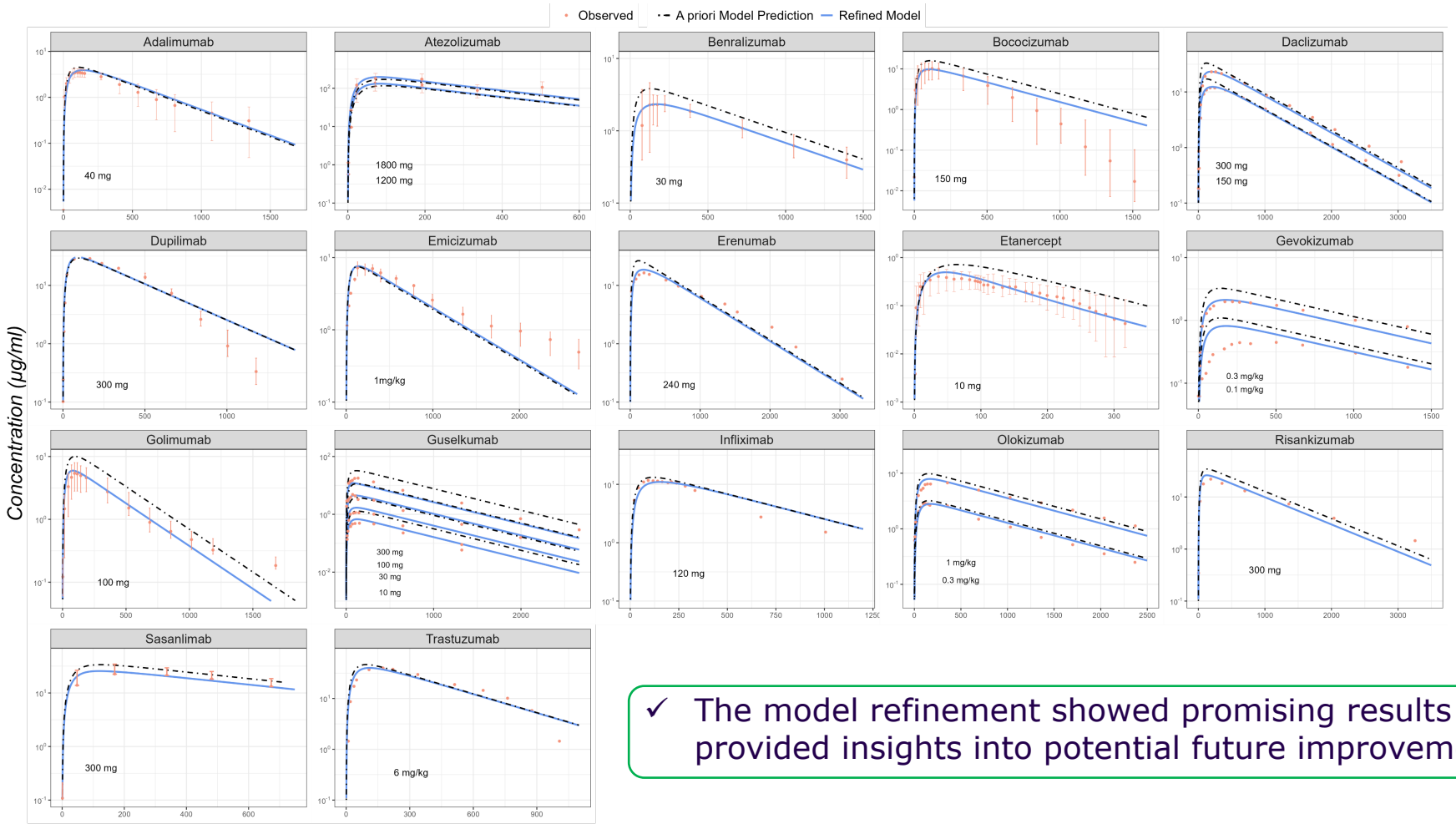
3. Model optimization



- **Rate endosomal uptake *3 : Higher clearance**
- **Lymph flow proportionality factor *0.50 : Slower transport**

3. S.C PBPK Modeling

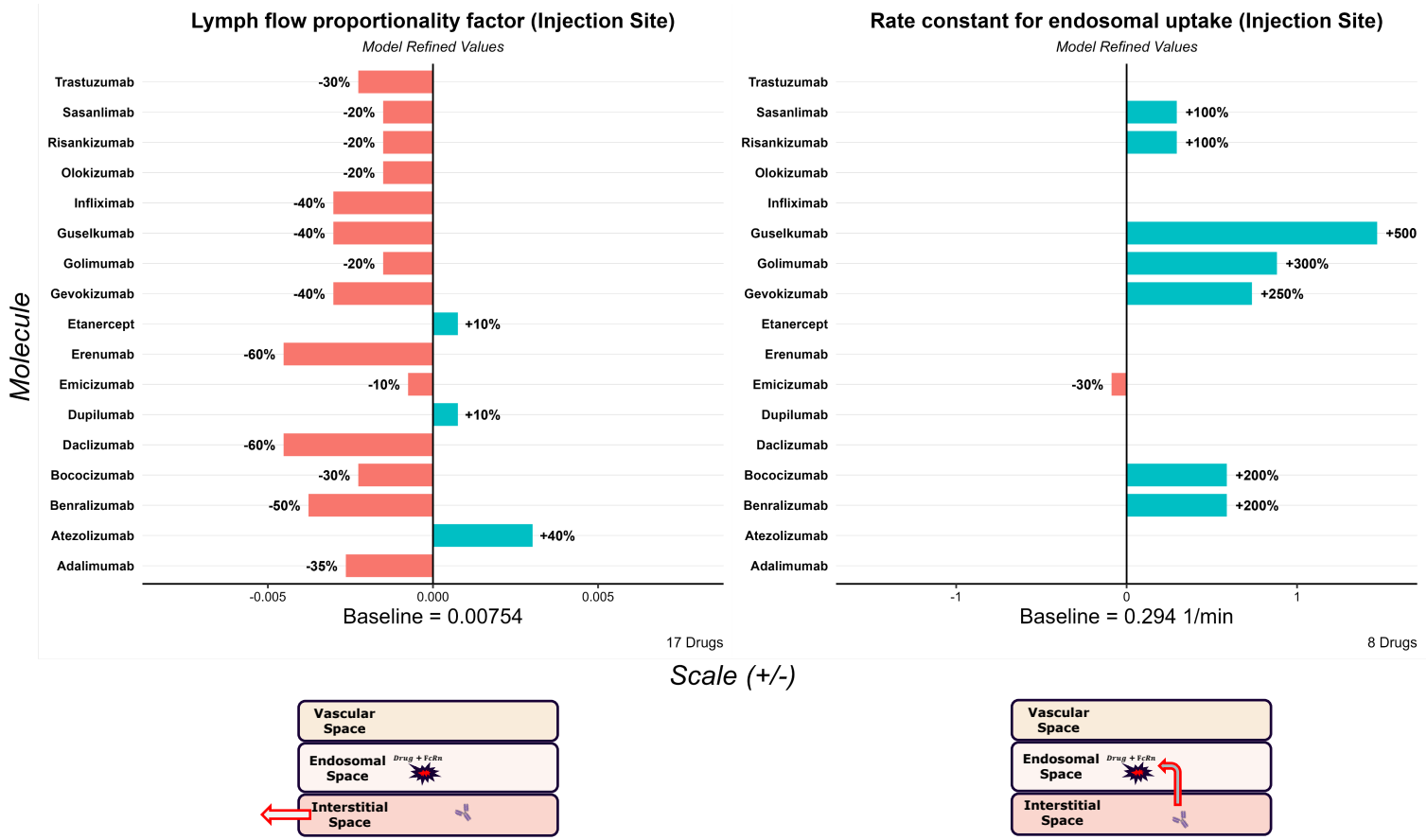
S.C PBPK prediction



✓ The model refinement showed promising results and provided insights into potential future improvements

3. S.C PBPK Modeling

S.C PBPK prediction



- **82% of drugs require a slow lymph flow, which could represent a longer residence time (interstitial retention) of the molecule at the injection site**
- **41% need a higher clearance, with a maximum scale of 5 for the value of the rate constant for endosomal uptake**

Conclusion

The model's predictive performance for switching the clinical administration route from I.V to S.C for mAbs was successfully evaluated

PK exposure parameters were predicted within a 0.80-1.25 range for ~ 65 % of included reference cases

Processes related to interstitial retention and endosomal uptake were identified as focus for further model developments

The IV data of mAbs have been used to calculate an average FcRn Kd which can be used to predict PK after S.C administration when I.V data are not available

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Acknowledgements

- Sanofi R&D Translational Medicine and Early Development, Vitry-Sur-Seine, France: Donato Teutonico, Antoine Deslandes, Laurent Nguyen

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Thank you for your attention

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