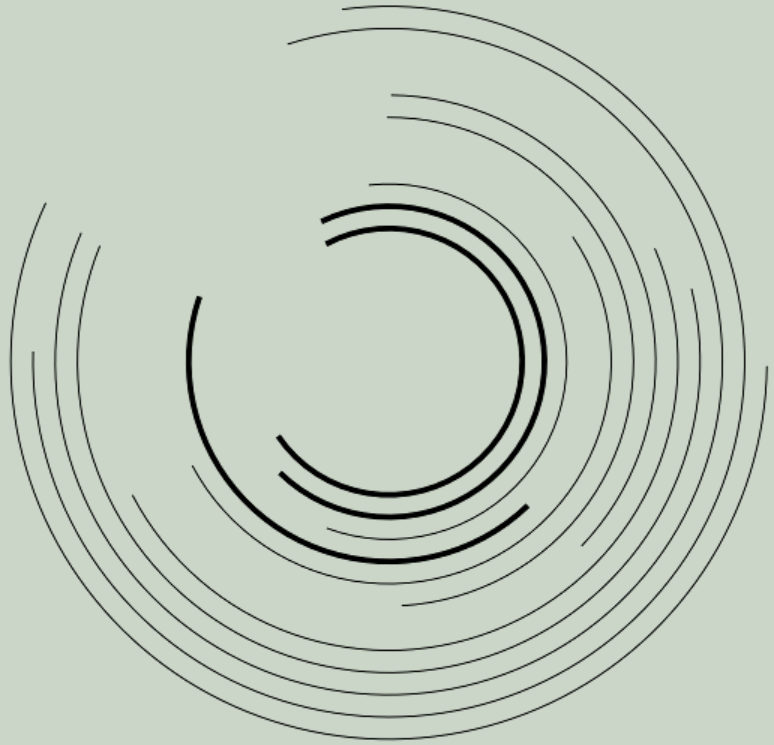
OSP Community Conference 2026

Benchmarking a Mechanistic Anti-Drug Antibody Predictor: Bridging Sequence based Prediction with Clinical Data.



Gianluca Selvaggio,

Pharmetheus

September 25th, 2026

Agenda

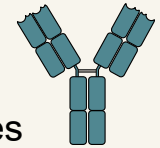
Topic
Introduction
Objective
Immunogenicity Model
Workflow
Benchmarking
Conclusion

Introduction

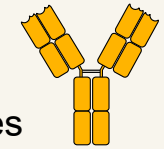


Immunogenicity and Anti-Drug Antibodies

Therapeutic protein (i.e. mAbs) may elicit an immune-mediated response if part of them (epitopes) are recognized as non-self eventually leading to the production of antidrug antibodies (ADAs)

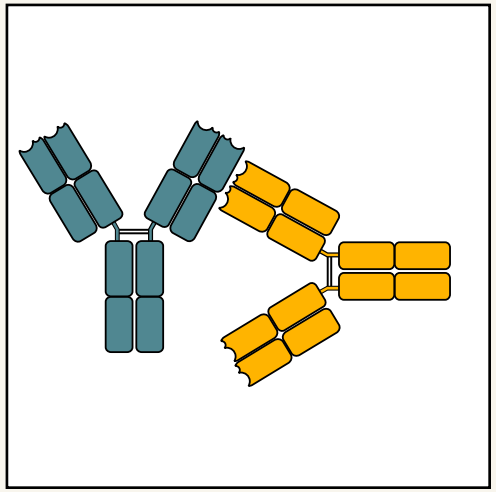


Therapeutic Antibodies

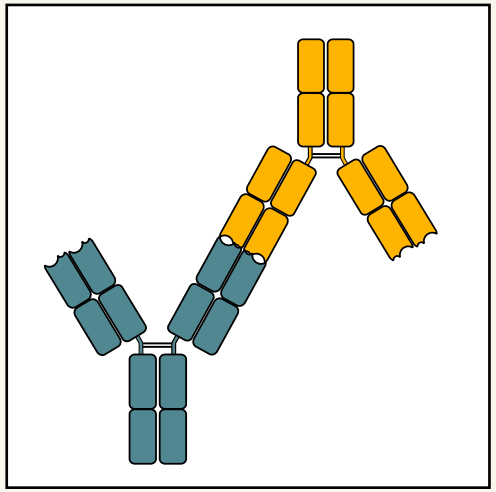


Anti-Drug Antibodies

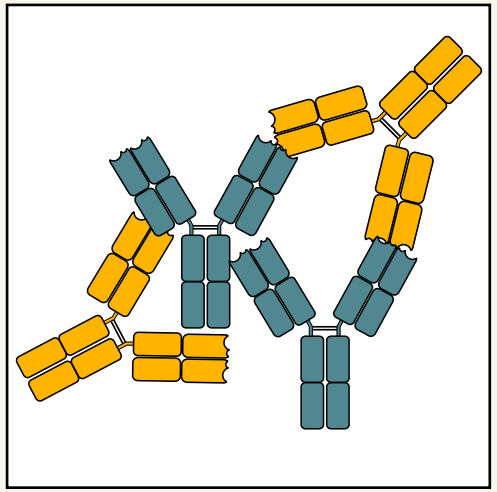
A) Altered clearance (FcγR-mediated)



B) Neutralization (blocking binding site)



C) Adverse reaction (immune complex formation)



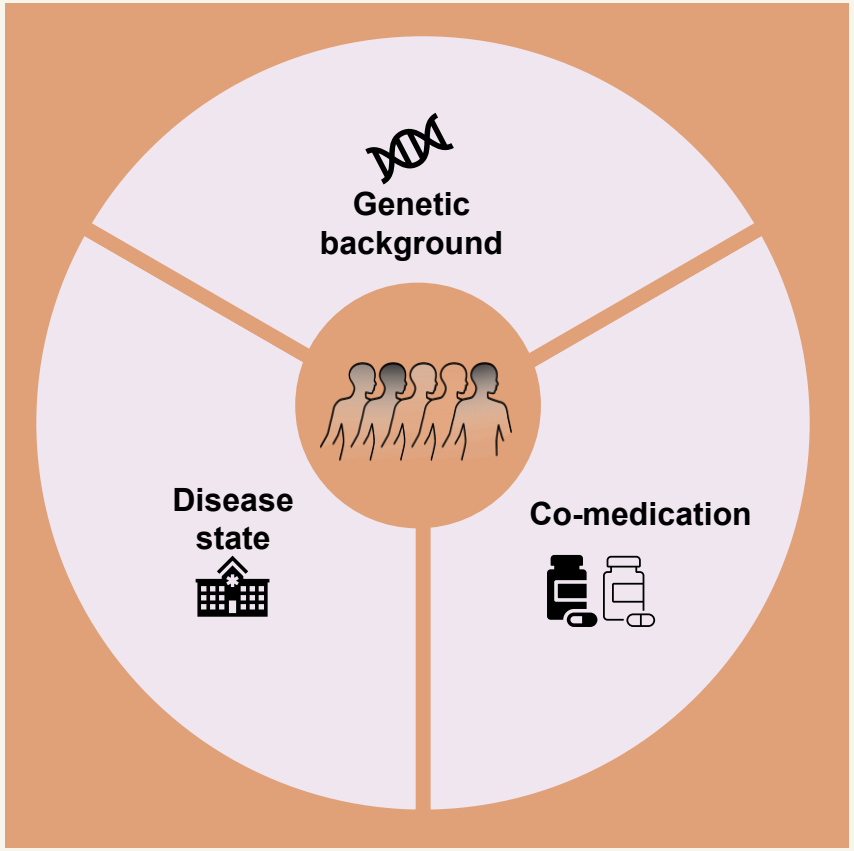
ADAs may affect the product: **A)** Pharmacokinetics **B)** Pharmacodynamics **C)** Safety

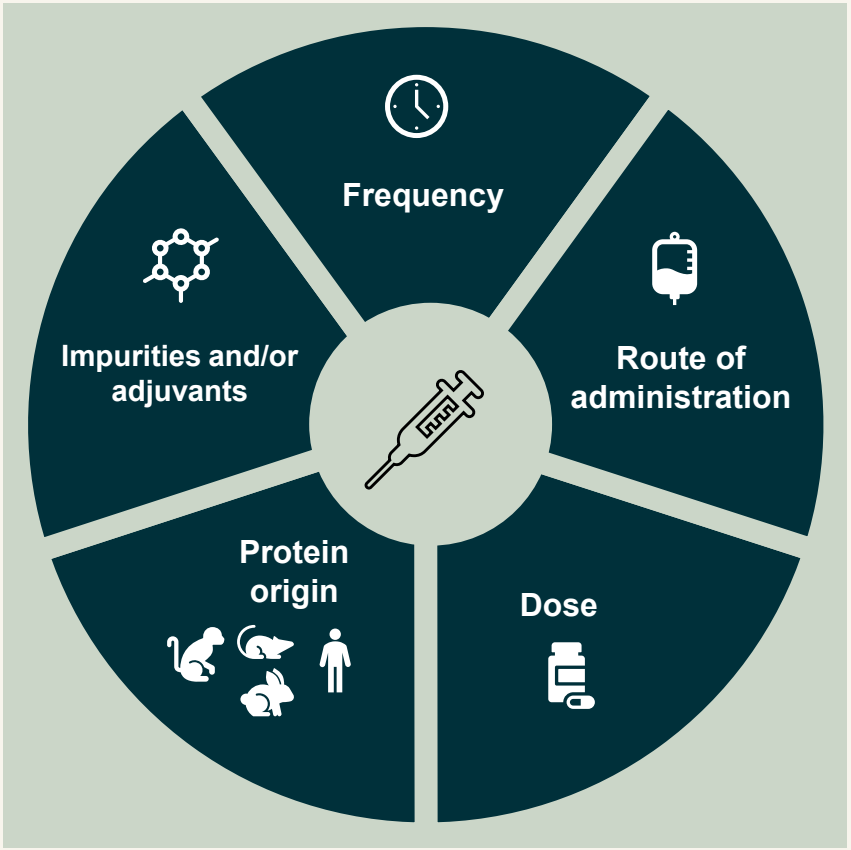
Adapted from Strand et al 2021

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Drug and Patient related factors influencing ADA Formation

Immunogenicity is a multi-faceted phenomenon driven by drug or patient specific elements





Adapted from Vaisman-Mentesh et al 2020

Immunogenicity assessment

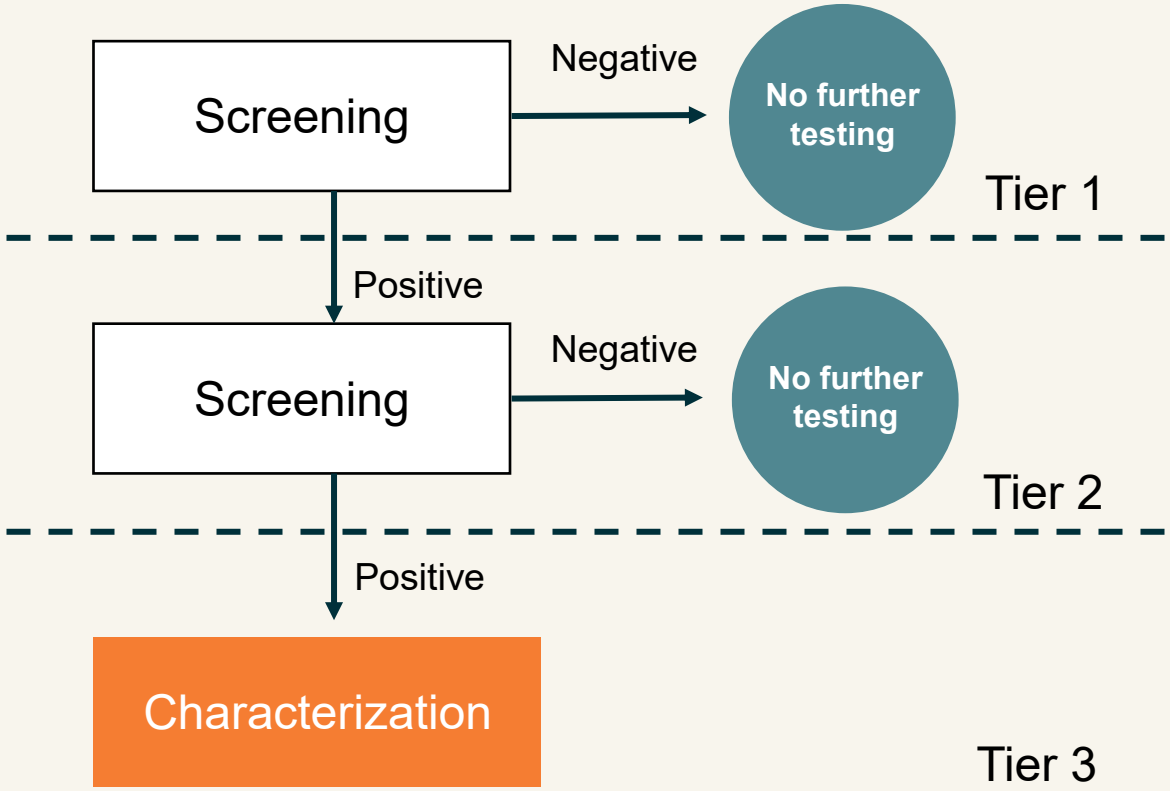
FDA Guidance for Industry

- Immunogenicity Testing of Therapeutic Protein Products—Developing and Validating Assays for Anti-Drug Antibody Detection (2019).

Tiered Testing Strategy typically includes:

- **Screening assays** to detect the presence of ADAs.
- **Confirmatory assays** to verify the positive results.
- **Titration and neutralization assays** to determine if the ADAs inhibit the biological activity of the therapeutic protein.

FDA and EMA recommend multi-tiered testing strategy for ADA detection



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Assays for ADA detection and variability in results

FDA and EMA provide core principle for immunogenicity testing but lack detailed harmonized guidance

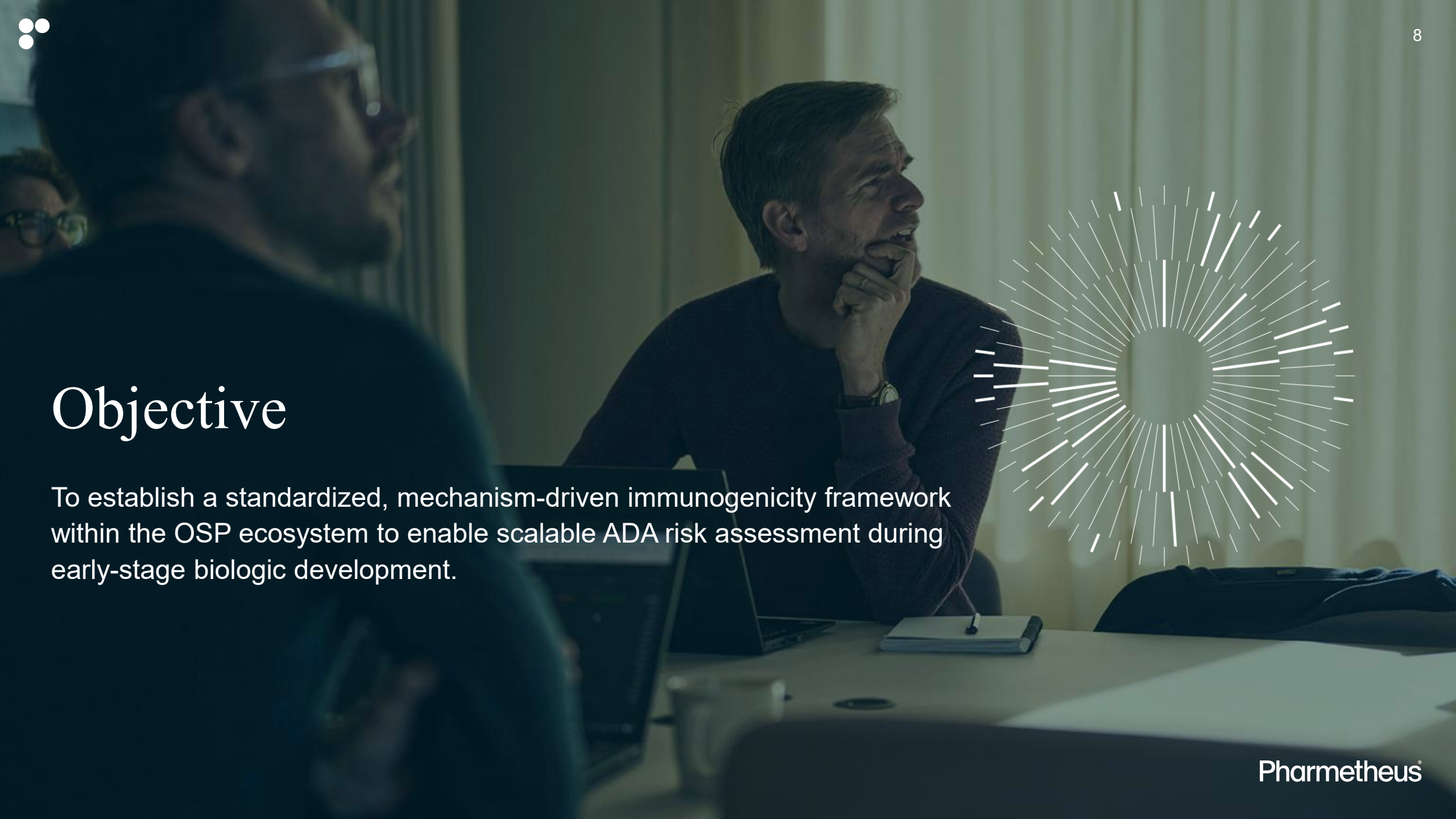
- **Inter-laboratory discrepancies**: Different laboratories can report significantly varied results when testing the same samples.
- **Assay-dependent results:** The ADA incidence rates reported for the same drug is directly influenced by the specific analytical method and platform used (e.g. ECL vs ELISA)
- **Variable cut-points:** The threshold for determining a positive ADA response or cut-point can be calculated using different statistical methods, leading to inconsistent results.
- **Inconsistent data reporting:** The lack of a standardized reporting format for immunogenicity and of a harmonized lexicon leads to confusion in both regulators and clinicians and can results in a complicated review of the submission

! Caution

Due to very significant assay developments in recent years, there can be significant caveats in pooling/comparing data from different studies*

- Bioanalytical expertise should be consulted to help understand potential limitations with the source data

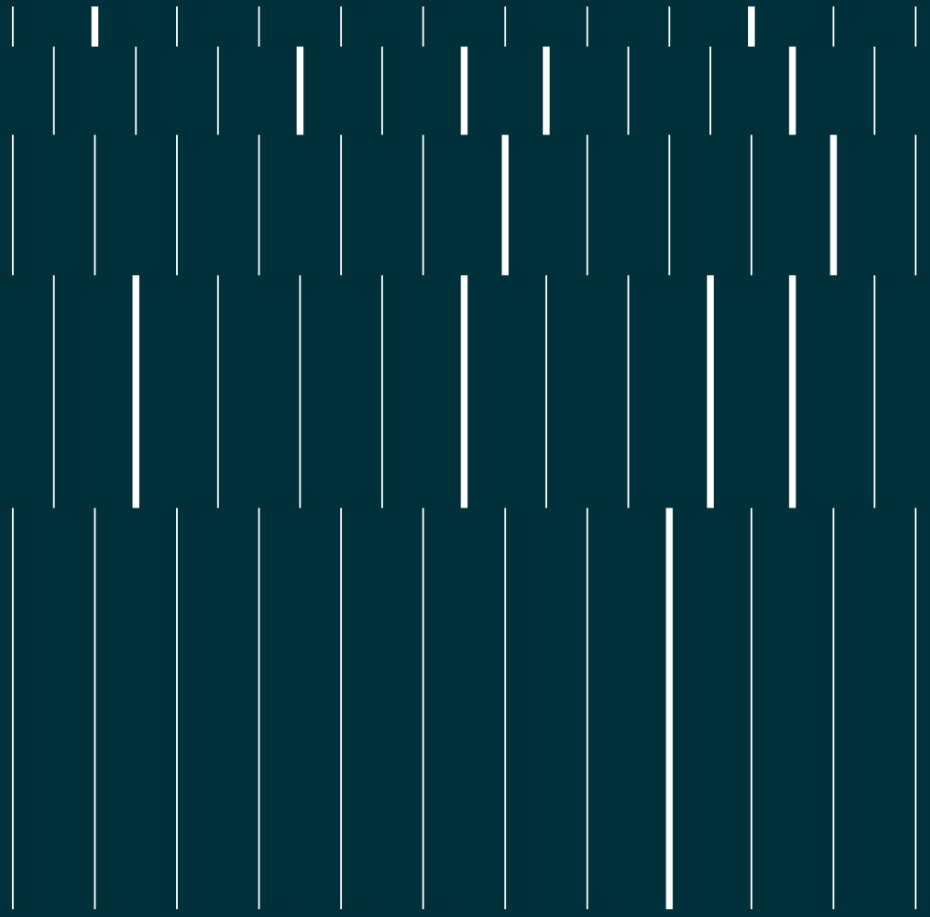
** This is explicitly pointed out in: FDA. (2022). Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format (Draft Guidance). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research.*



Objective

To establish a standardized, mechanism-driven immunogenicity framework within the OSP ecosystem to enable scalable ADA risk assessment during early-stage biologic development.

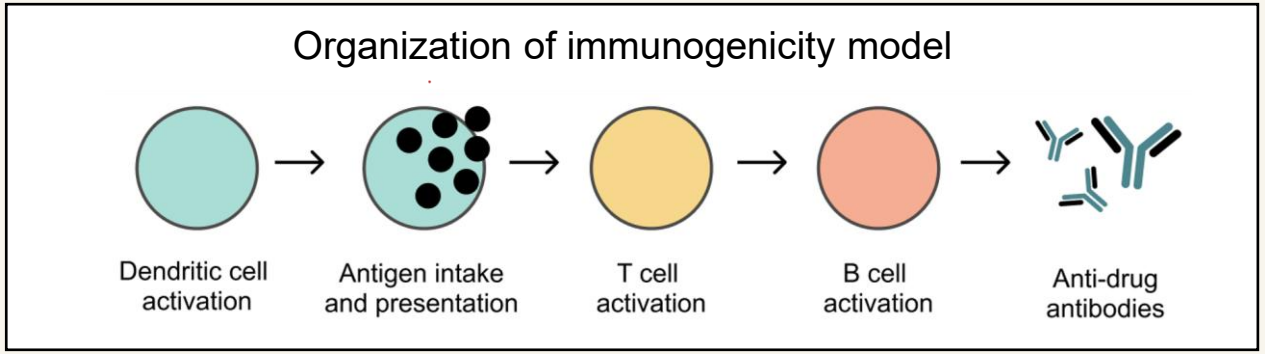
Immunogenicity platform

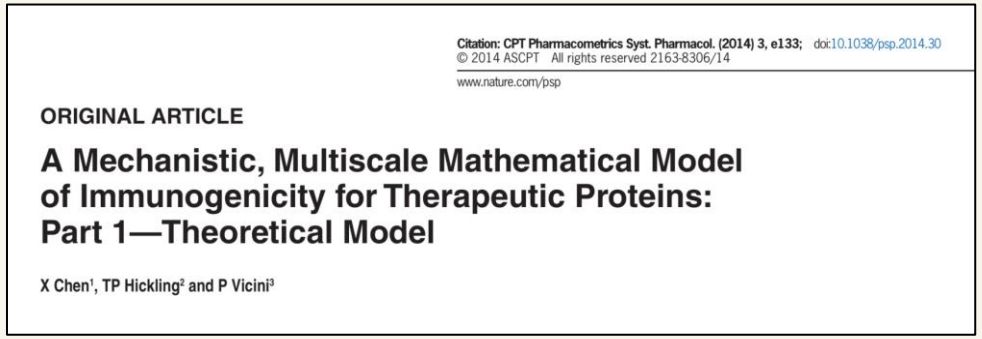


Systemic immunogenicity – core mechanisms

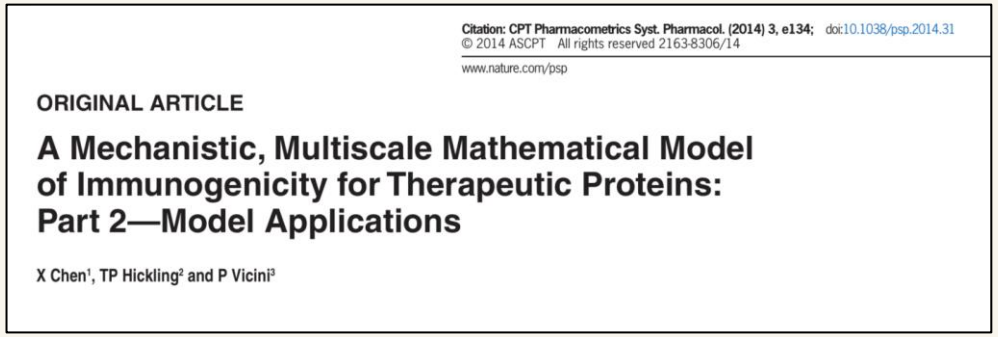
A Mechanistic, Multiscale Mathematical Model of Immunogenicity for Therapeutic Proteins – Chen et al 2014

*".. 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".*





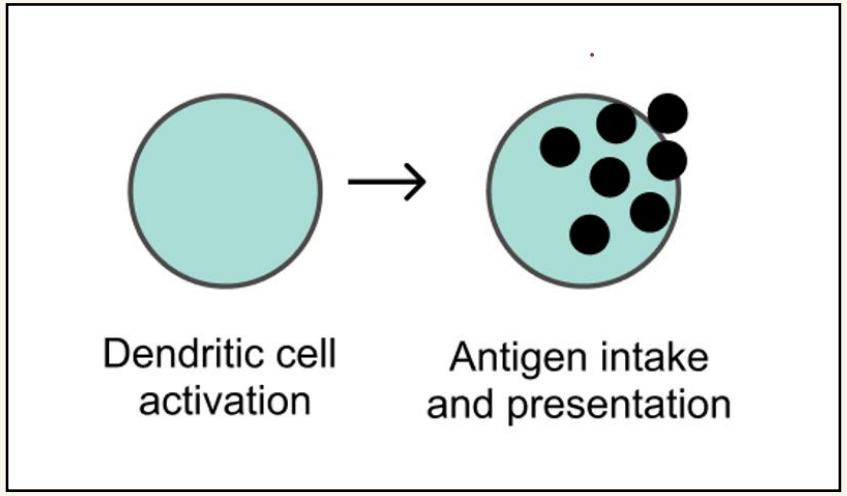
CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e133; doi:10.1038/psp.2014.30 [part 1]

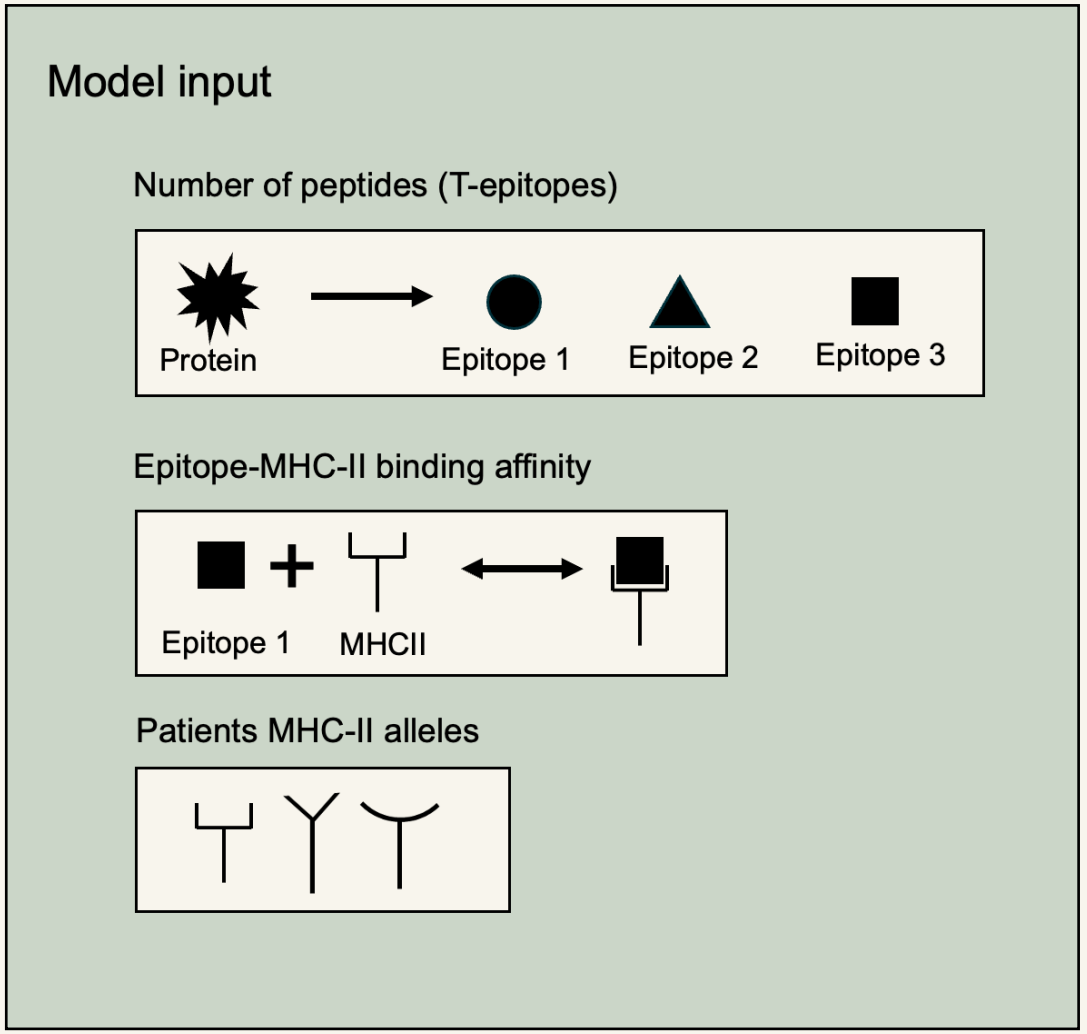


CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e134; doi:10.1038/psp.2014.31 [part 2]

Antigen processing and presentation parameters are the required input to the model

Dendritic cells processing of the protein is pivotal. In silico tools as NetMHCIIpan provide a way to predict necessary parameters





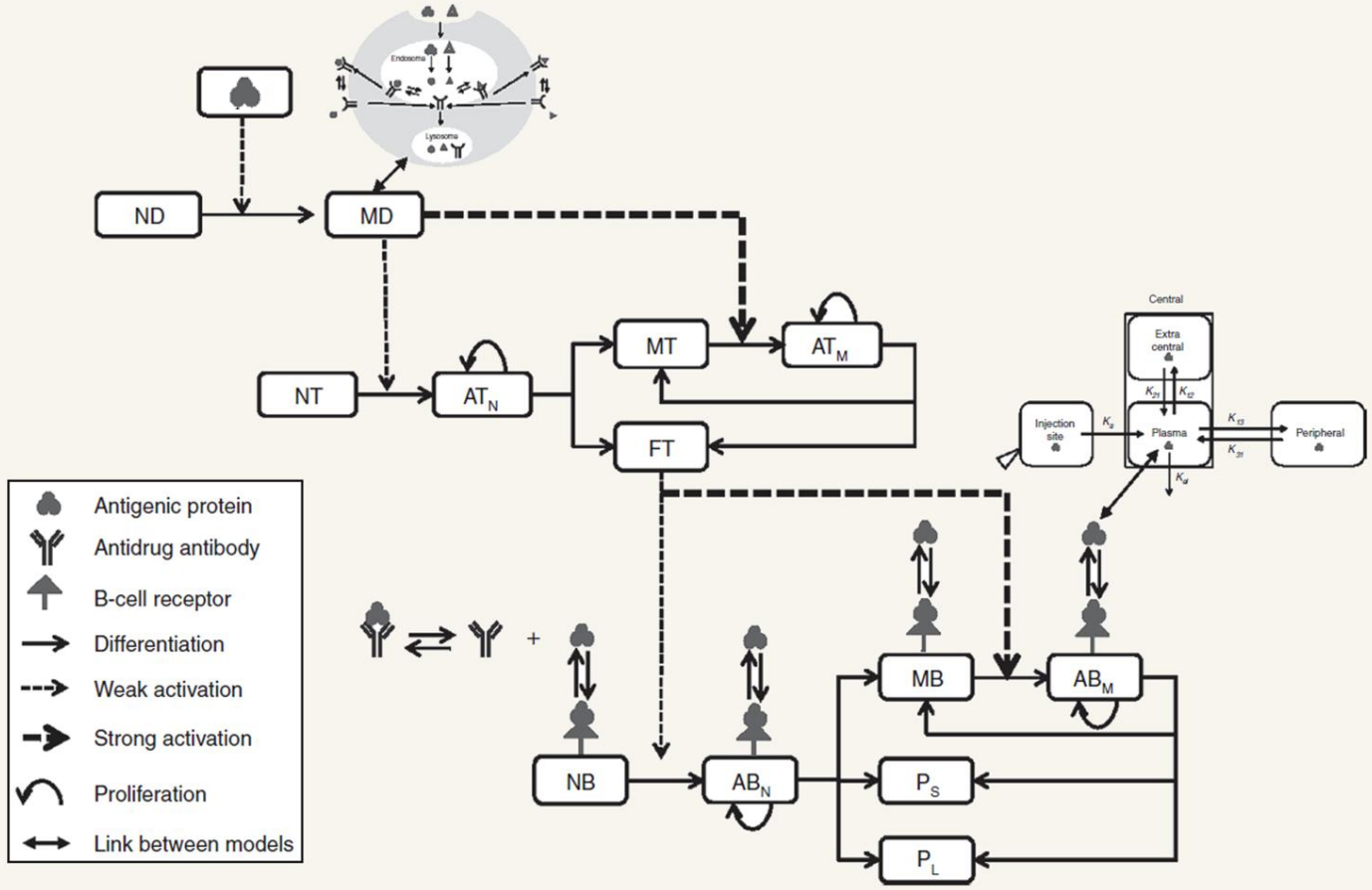
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Systemic immunogenicity – model structure

Multiscale model:

- **Subcellular**, antigen presentation and processing by dendritic cells
- **Cellular**, T and B cell kinetics during the humoral response
- **Whole body**, protein disposition



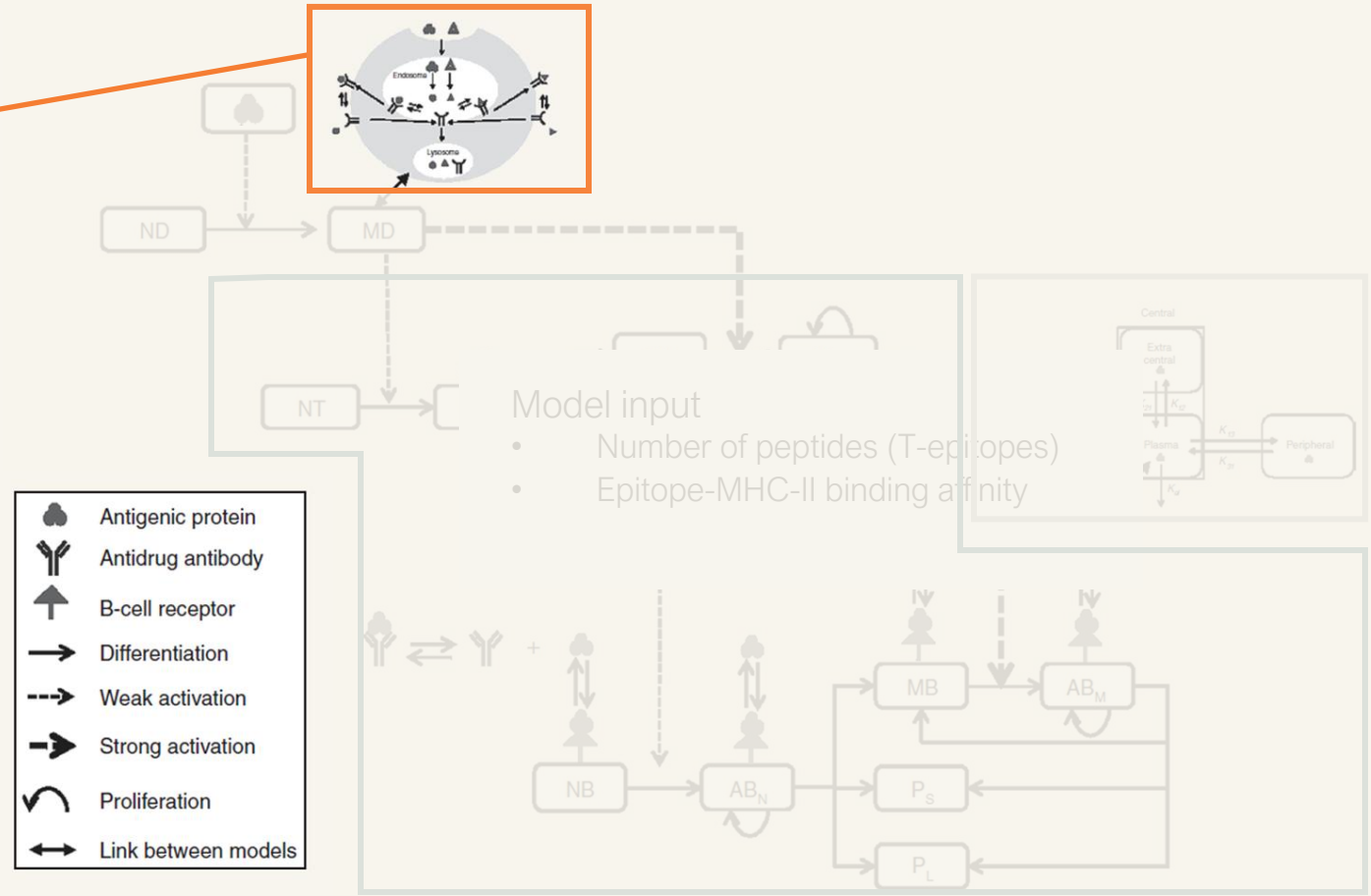
CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e133; doi:10.1038/psp.2014.30 [part 1]

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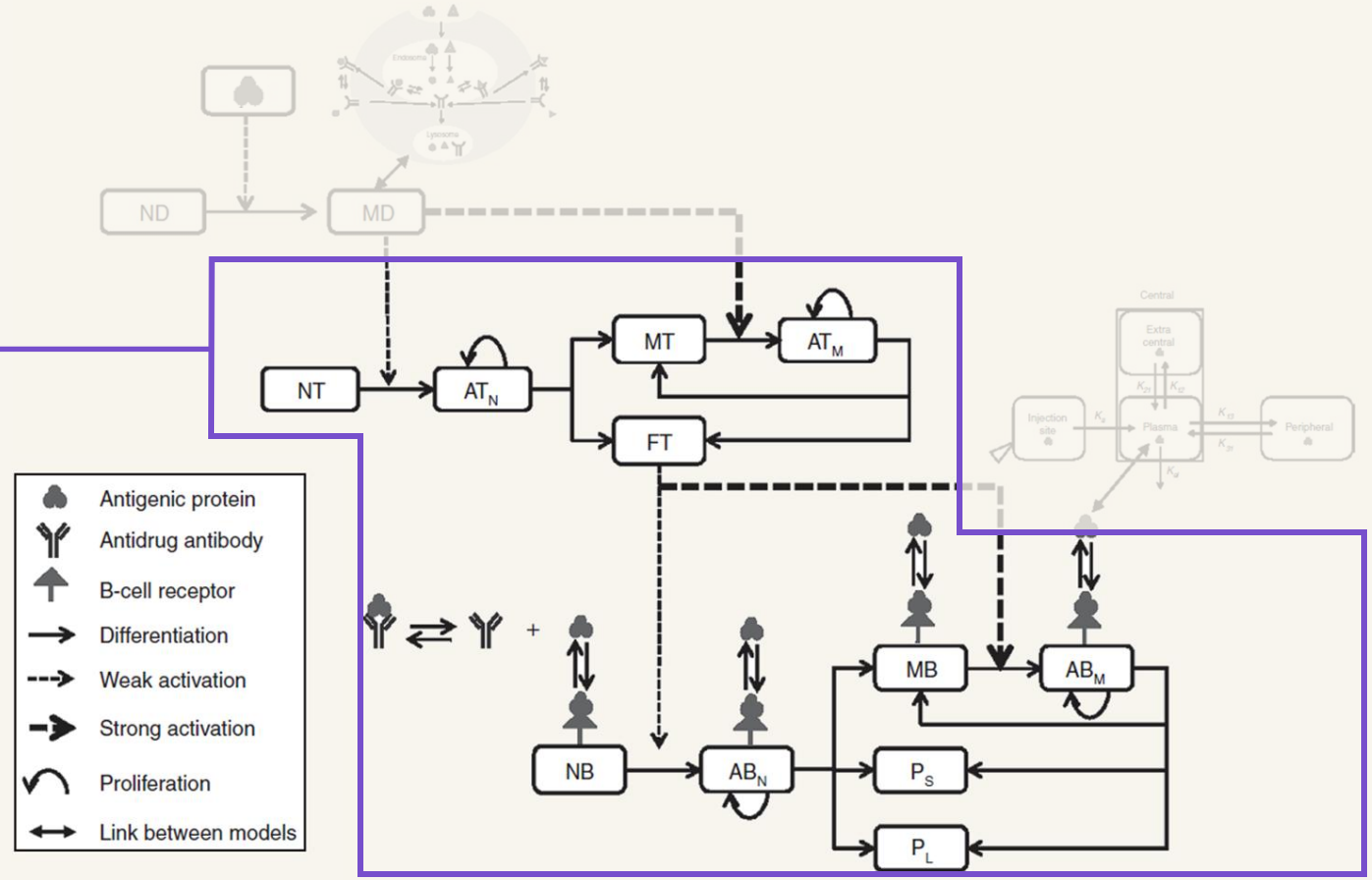
CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e133; doi:10.1038/psp.2014.30 [part 1]

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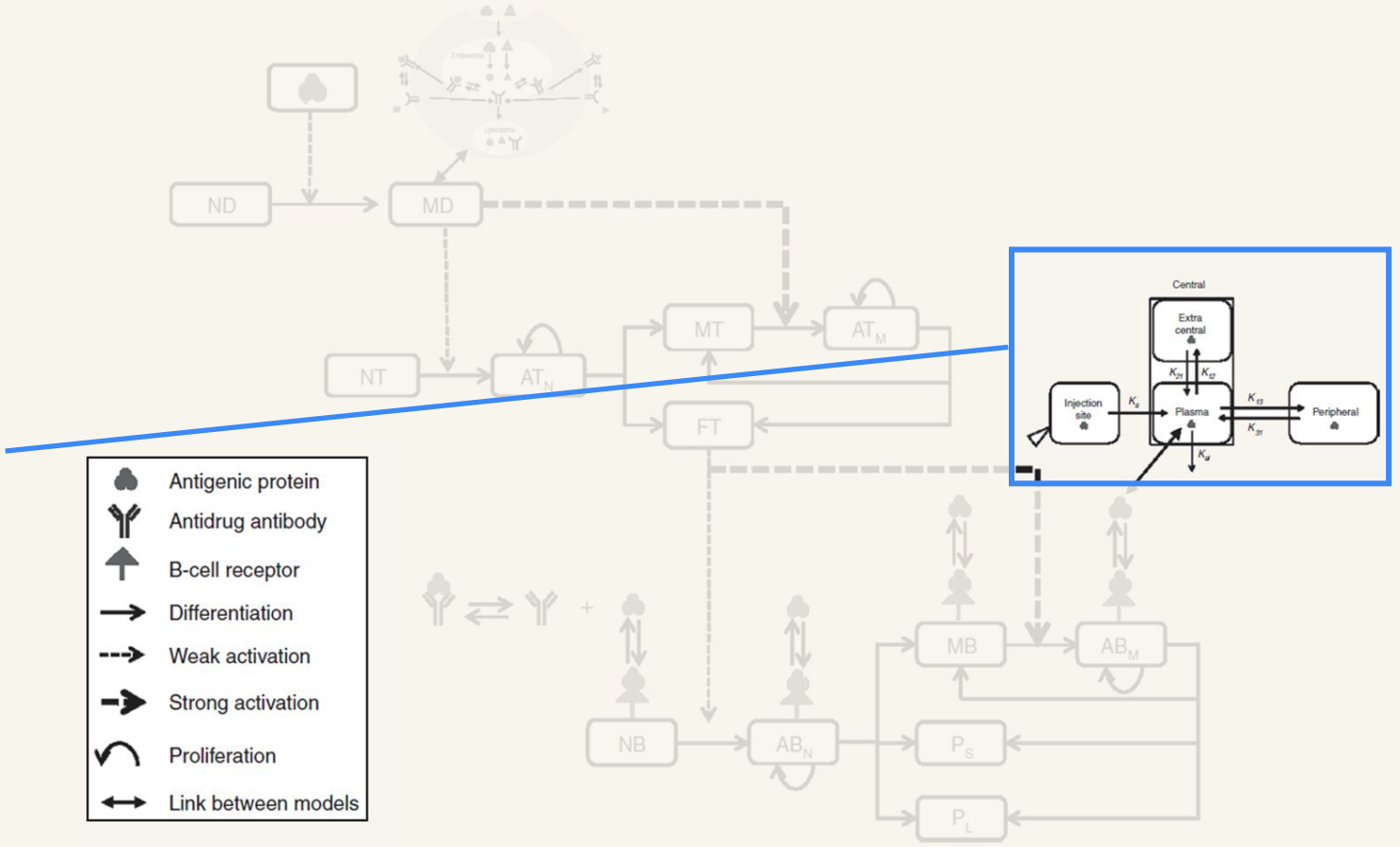
CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e133; doi:10.1038/psp.2014.30 [part 1]

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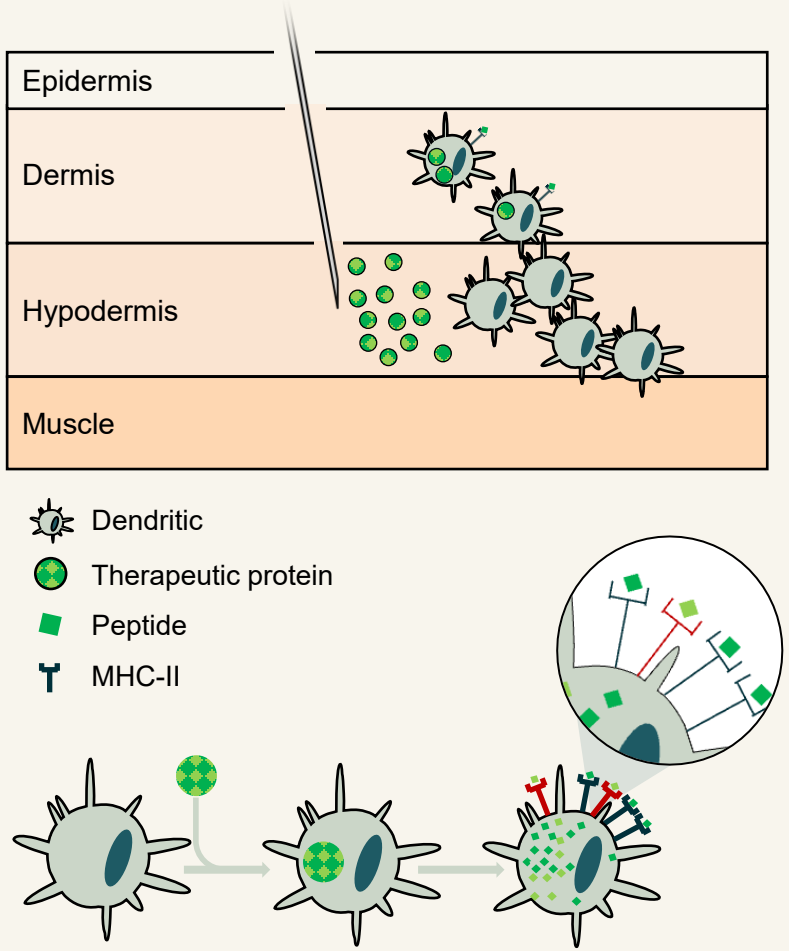


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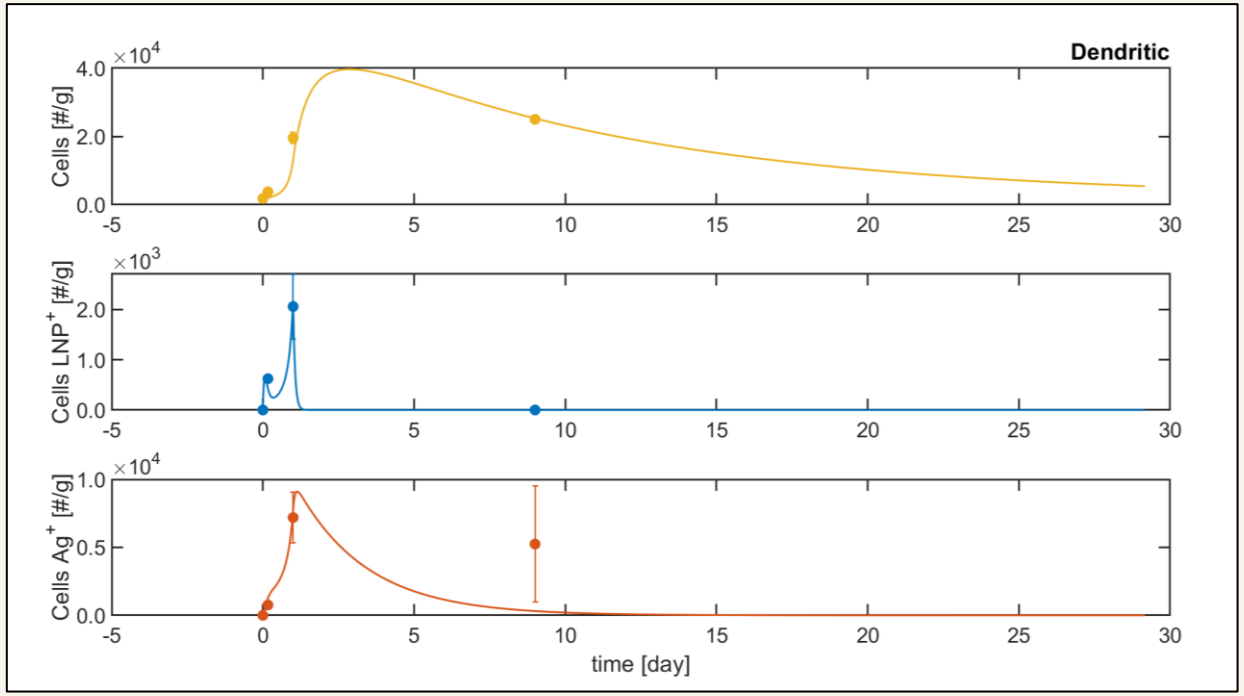
CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e134; doi:10.1038/psp.2014.31 [part 2]

Model extension - local immunogenicity

Subcutaneous injected proteins induces local recruitment of antigen presenting cells and their activation



NHP were injected intradermally with LNP carrying mCherry mRNA.
Dendritic cell total count (yellow), LNP⁺ (blue) and mCherry⁺ (orange).
Lines are the model fit while points are experimental data



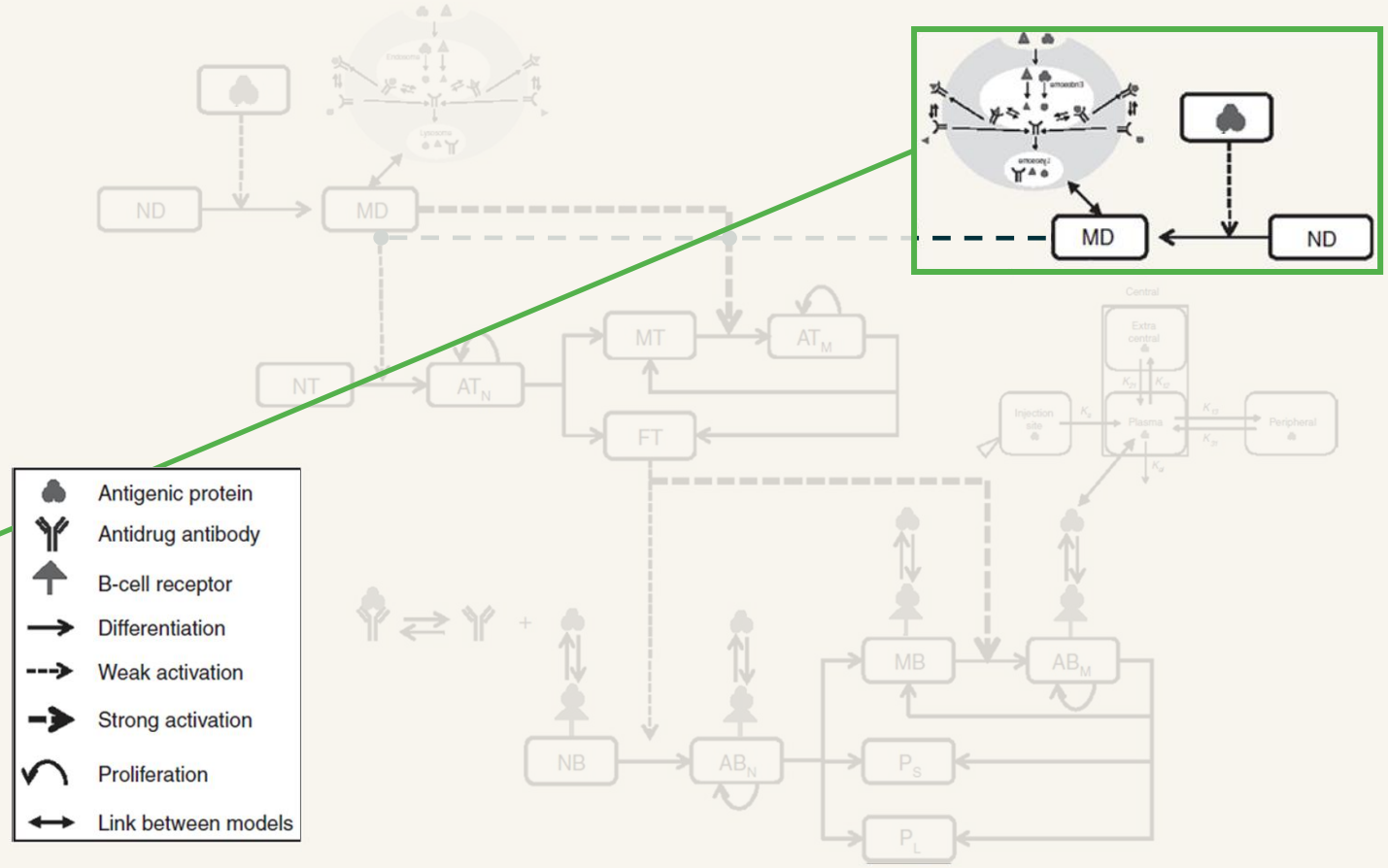
Liang et a 2017

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Local immunogenicity – model structure

Multiscale model:

- **Subcellular**, antigen presentation and processing by dendritic cells
- **Cellular**, T and B cell kinetics during the humoral response
- **Whole body**, protein disposition
- **SubQ**, antigen uptake and processing by dendritic resident cells



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

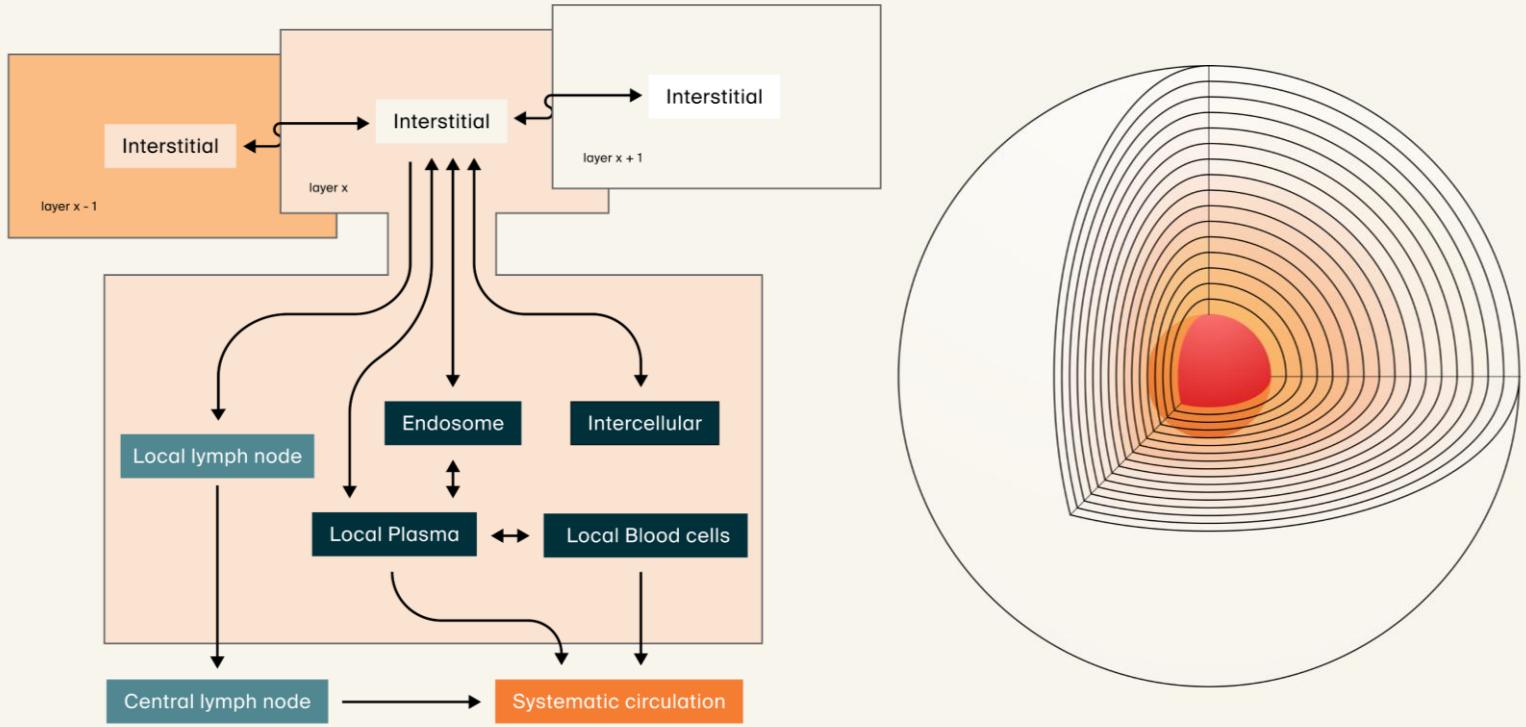
CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e134; doi:10.1038/psp.2014.31 [part 2]

Subcutaneous drug absorption

Physiologically based model structure and biopharmaceutics

- Describes the spatial-temporal drug disposition in SC tissue
- Alignment to OSP structure
  - Parameterization and structure
  - 2-pore theory for extravasation
  - Endosomal clearance/FcRn-binding

Schematic representation of the subcutaneous absorption and disposition model.



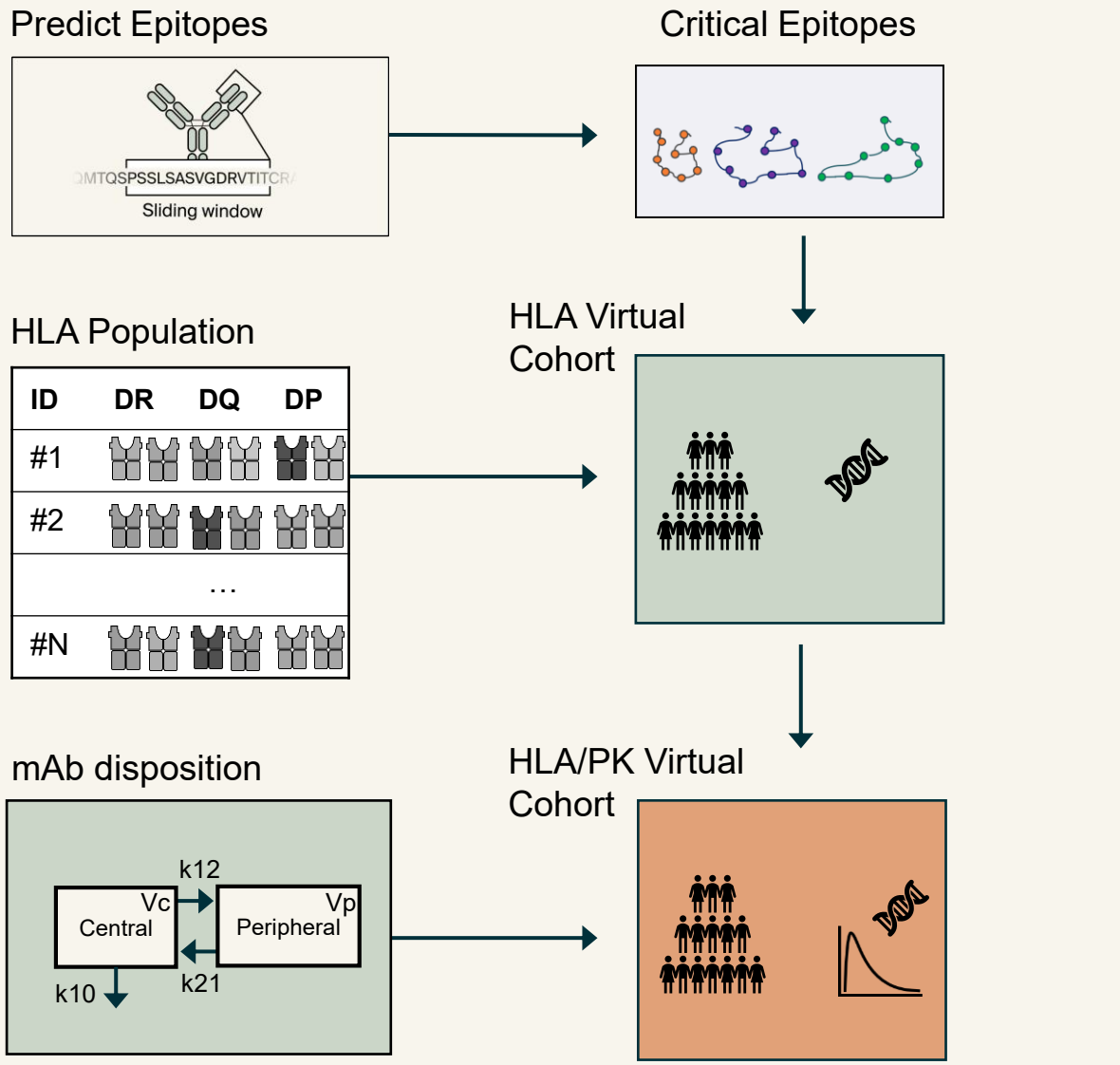
PAGE 32 (2024) Abstr 11022 [www.page-meeting.org/?abstract=11022]

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Immunogenicity Platform Workflow

Workflow

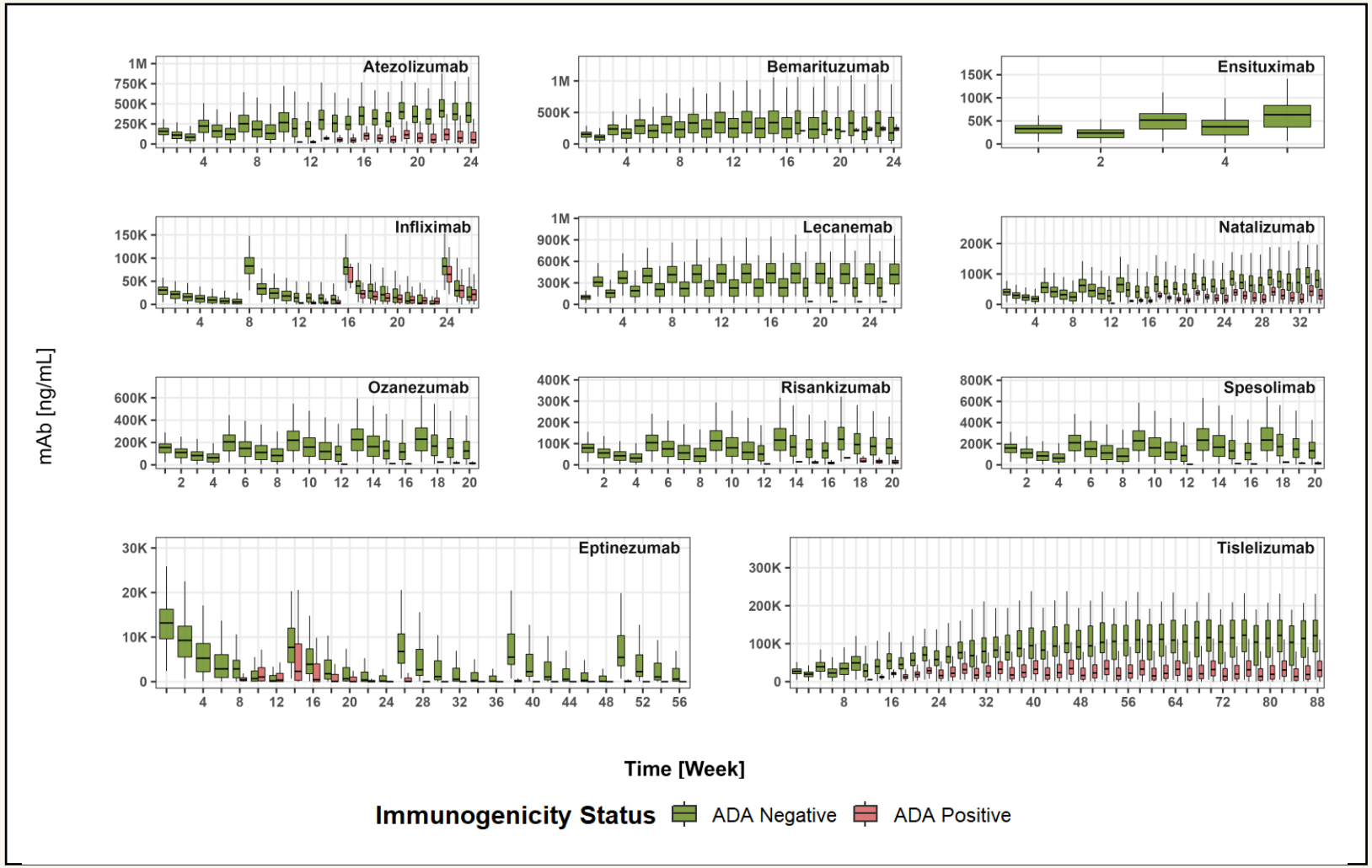
- **Epitope processing and Prioritization:** mAb sequences are analyzed with NetMHCIIpan to identify and rank potential T-cell epitopes
- **Virtual Cohort generation and epitope matching:** generate a virtual population, matching specific HLA-DR, HLA-DQ, and HLA-DP alleles combinations to the most critical epitope per class
- **Integration of Subject-Specific Pharmacokinetics**: assign to each individual a PK parameter set from the distribution model.



Benchmarking

Multi-mAb Platform Application: Translating Sequence to Immune Dynamics

- **Broad Workflow Application**
  - Processed 11 distinct mAb through the end-to-end pipeline.
- **Sequence-Driven Differentiation**
  - The platform successfully differentiates immune response profiles.



Platform Behavior Under Repeated Administration

Systematic Response Inflation in repeated administration regimens

- Mechanistic immune models risk overestimating active B-cell expansion and memory accumulation when subjected to repeated drug exposure without compensatory dampening mechanisms (Hamuro et al. 2019).

Defining Platform Capabilities

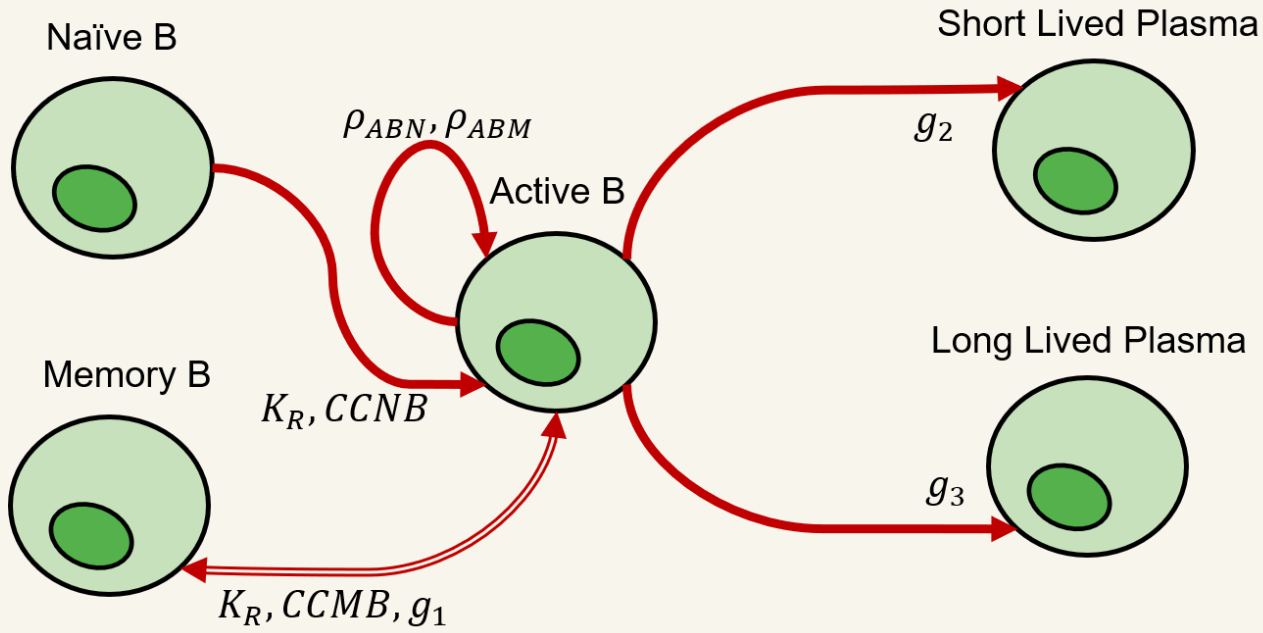
- Understanding these repeat-dosing boundaries is essential to determine what the raw, uncalibrated model can predict versus where targeted parameter dampening is required.

Dampening B-cell responsiveness

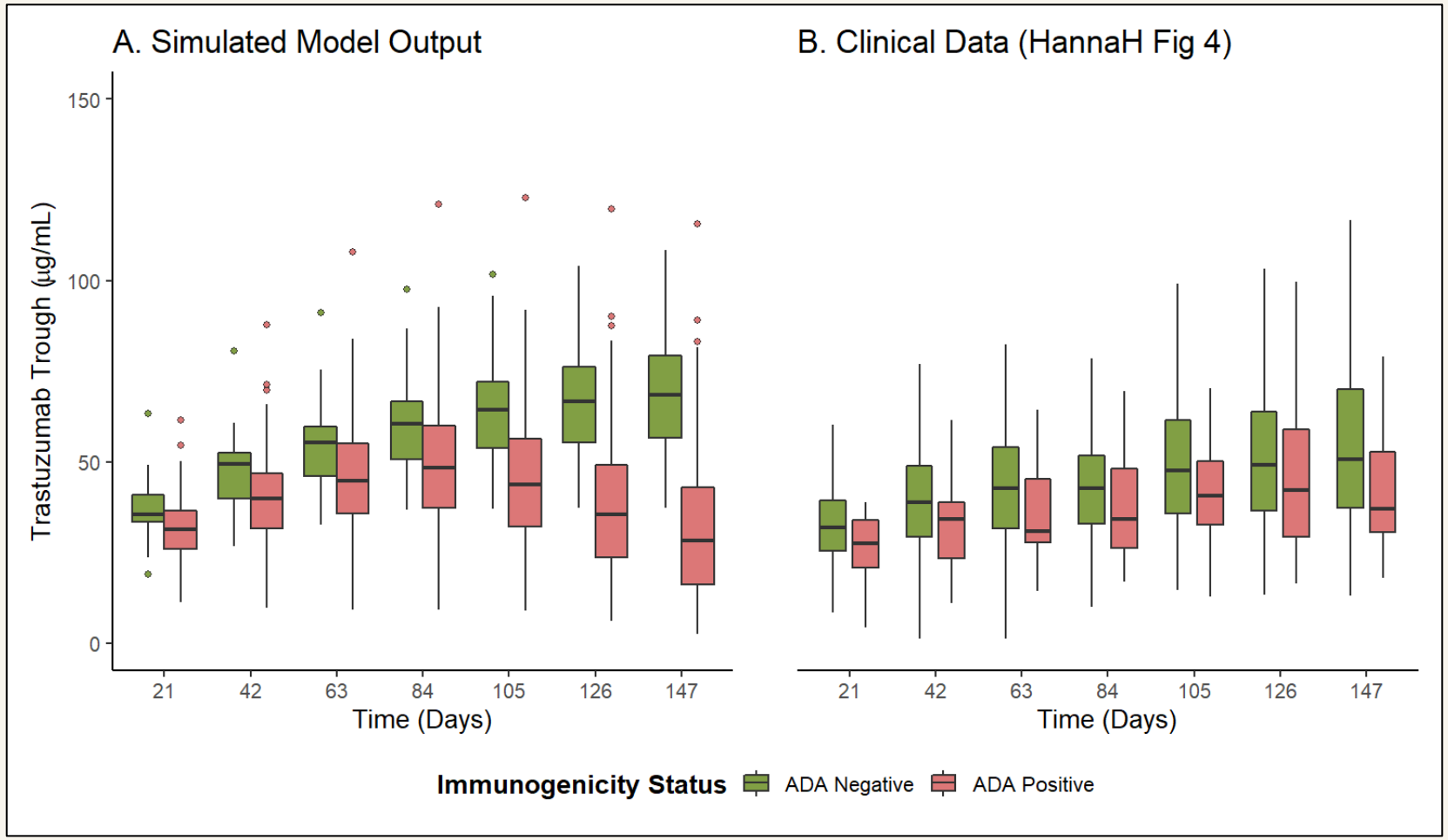
From a relative and qualitative analysis of the immunogenic response to a quantitative simulation

Moving from a relative and qualitative analysis of the immunogenic response to a quantitative simulation requires a modulation of the B-cell response.

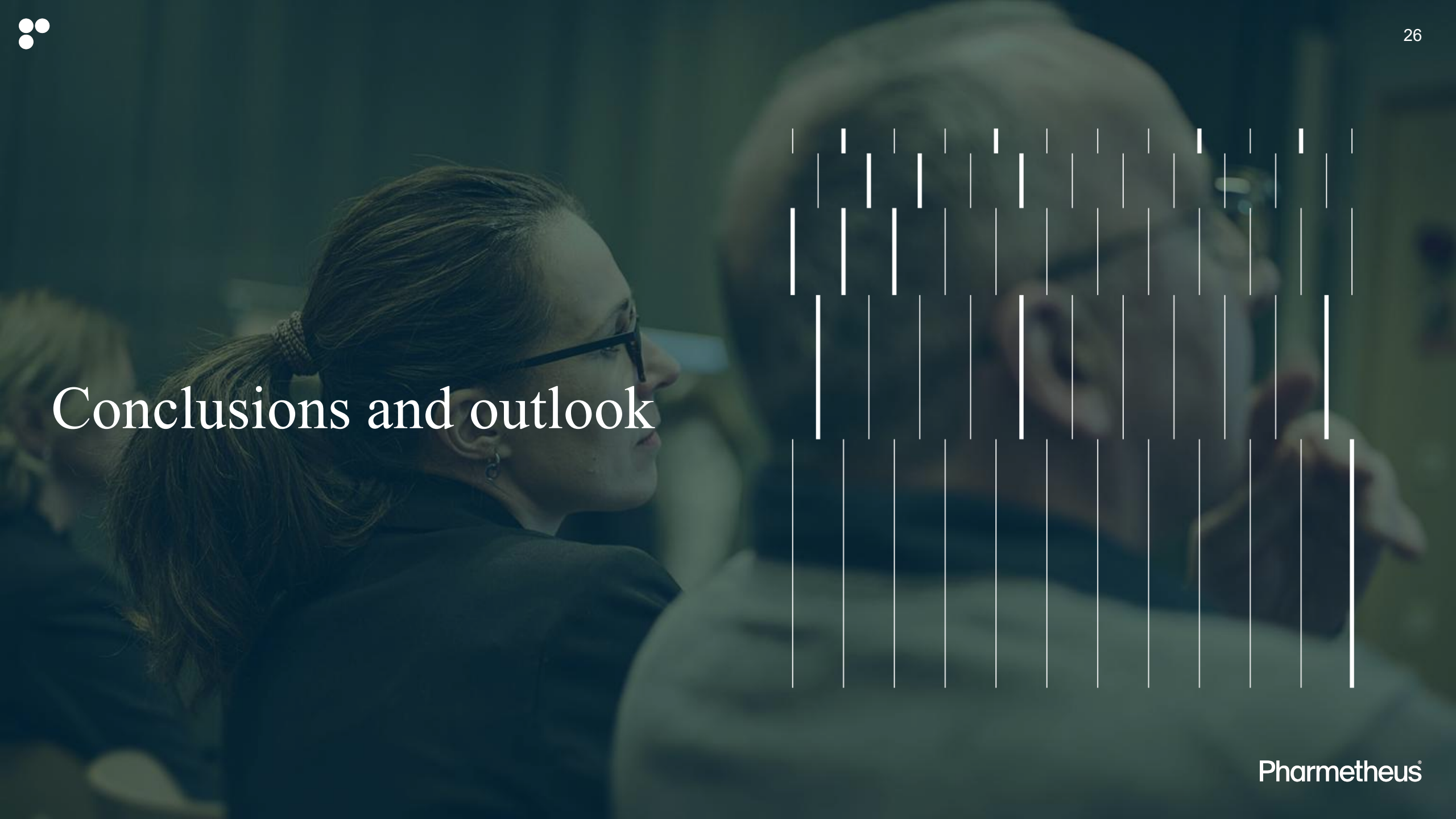
Parameter Name	Symbol	Tuning
Maximum proliferation rate of Activated B cells from Naïve	ρ_{ABN}	↓
Maximum proliferation rate of Activated B cells from Memory	ρ_{ABM}	↓
Carrying capacity for Naïve B cells	$CCNB$	↓↓
Carrying capacity for Memory B cells	$CCMB$	↓↓
Differentiation of Active B in Memory B	g_1	↓↓
Differentiation of Active B in Short Lived Plasma cells	g_2	↓↓
Differentiation of Active B in Short Long Plasma cells	g_3	↓↓
Half-maximal activation threshold for B cells	K_R	↑↑↑



Comparison of simulated and observed TSZ C_{trough}



Conclusions and outlook



Benchmarking and Parameterizing the Immunogenicity Platform

Sequence-to-Clinical Risk Pathway

- Coupled sequence-based epitope prediction with virtual HLA populations and PopPK to establish an end-to-end immunogenicity assessment framework enabling relative immunogenicity ranking across candidates.

Targeted B-Cell Responsiveness Calibration

- Addressed systematic ADA overestimation by dialing down B-cell pool hypersensitivity (eg modulating proliferation, carrying capacities, differentiation, and activation thresholds) without increasing complexities.

Anchor for a Multi-mAb Calibration Strategy

- Re-parameterizing against the HannaH trial served as the initial anchor dataset, establishing a standardized workflow to integrate additional clinical mAb into a robust calibration framework

De-risking Biologics: Immunogenicity Platform Outlook

Platform Characteristics

- **Integrating Biology and Model extension**
  - The model includes a mechanistic description of SubQ events and can be integrated with PMX absorption model.
  - Furthermore, it avoids steady state assumptions.
- **Open-Source & Transparency**
  - The model runs on OSP-Suite (PKSim®/MoBi®), ensuring a white box approach with easily verifiable results
- **Amenable to modification**
  - While ready-to-use, the mode can be adapted to specific characteristics (e.g. leveraging PKSim® PBPK representation)

Use cases

- **Early Discovery and Lead Optimization**
  - *In silico* comparison of lead candidates, ranking by predicted immunogenicity
- **Preclinical Development**
  - Inform study design and provide basis the initial immunogenicity risk assessment
- **Clinical Development (Phase I-III)**
  - Explore dosing regimens, predict immunogenicity in untested special populations (e.g. pediatric)
- **Regulatory submission**
  - Complement the required Integrated Summary of Immunogenicity with mechanistically grounded simulations.

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