A framework for immunogenicity data integration and prediction: Applying mathematical modeling to immunogenicity of biopharmaceuticals

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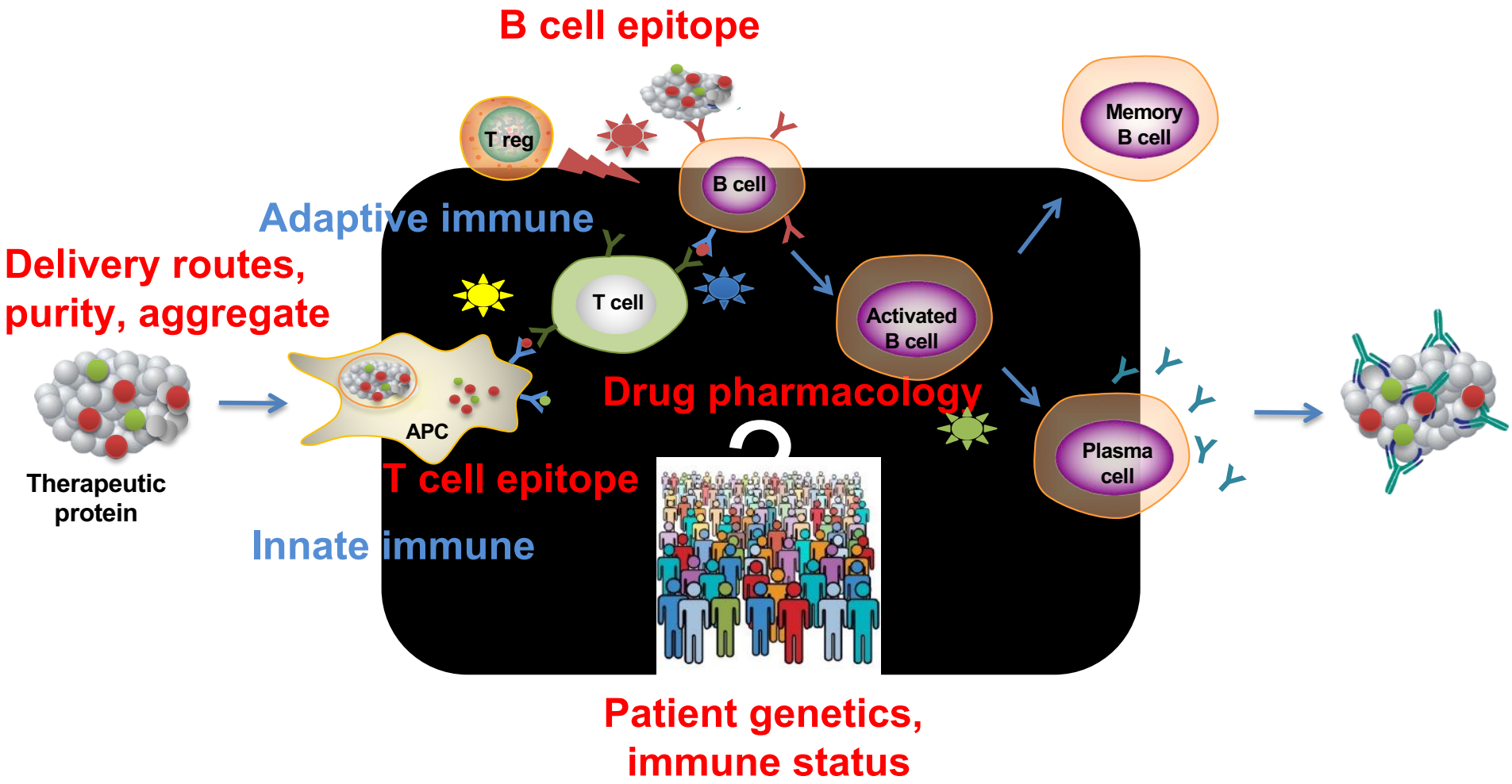
New technologies for immunogenicity assays/prediction

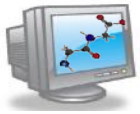
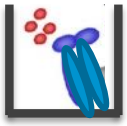
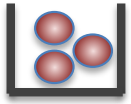
European Immunogenicity Platform February 23-25, 2015

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

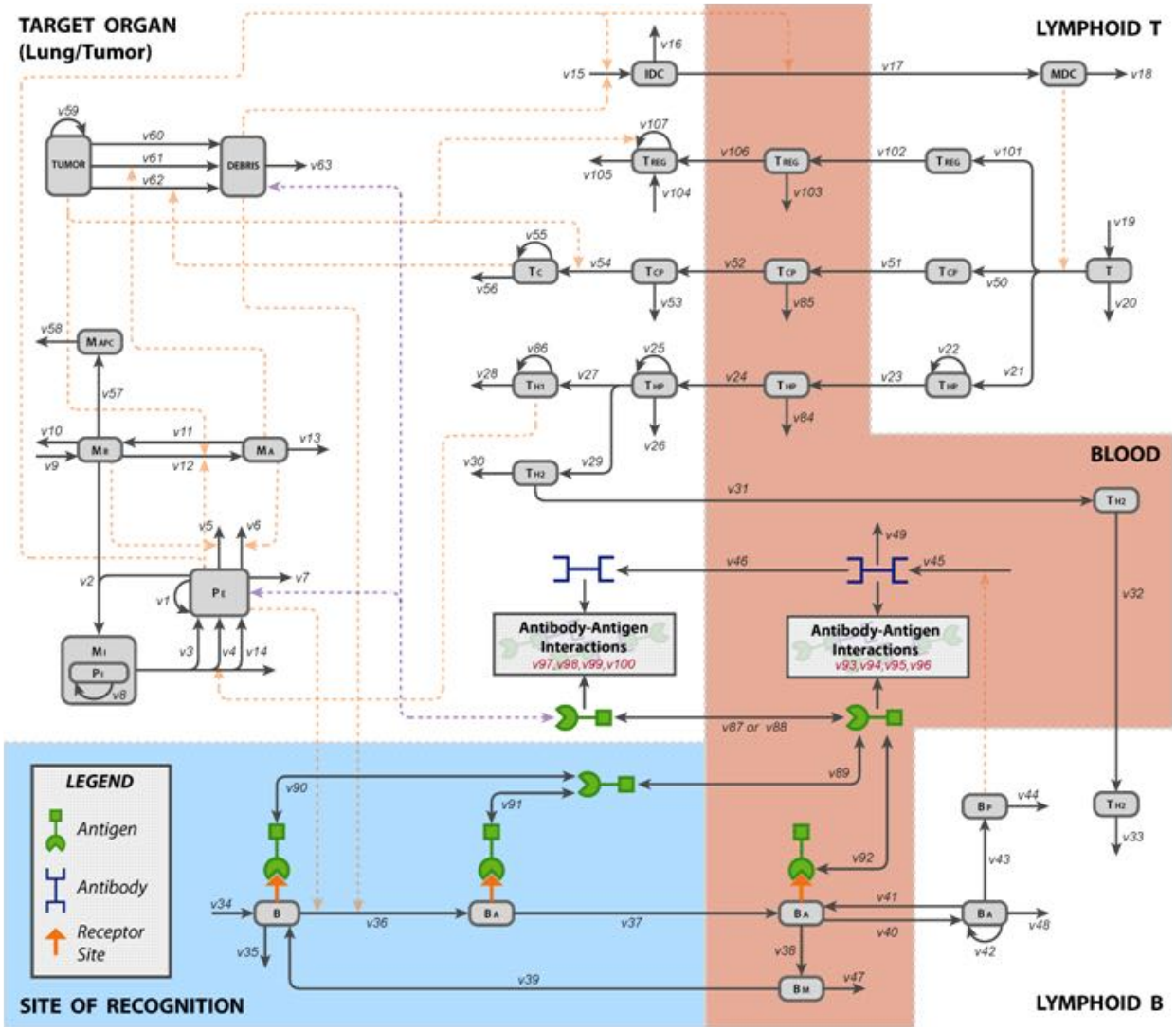
Complexity of Immunogenicity



Current progress

- **Many technology platforms are developed for early immunogenicity risk assessment**
  - *In silico* prediction tools 
  - T-epitope-MHC binding assays 
  - In vitro cell assays 
  - Animal models 
- **However, these platforms usually look at only one or two risk factors at a time**
  - Lack of information integration
  - Difficult to intuitively interpret
  - Hard to directly correlate with end point (immunogenicity rate, ADA response, etc)

Reconnecting with Systems Biology: Immune Response Dynamics



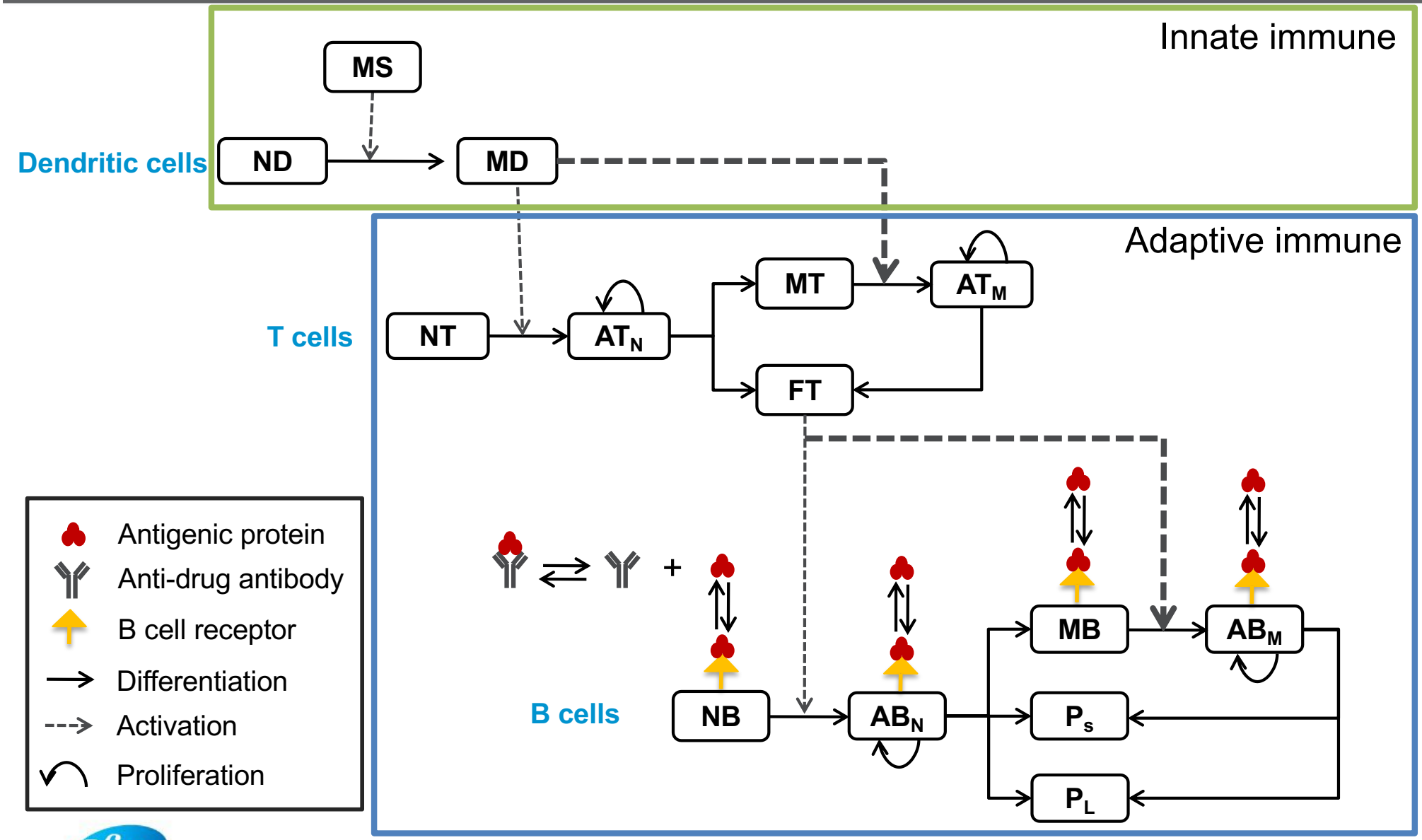
The development of a fully-integrated immune response model (FIRM) simulator of the immune response through integration of multiple subset models. Palsson S, Hickling TP, Bradshaw-Pierce EL, Zager M, Jooss K, O'Brien PJ, Spilker ME, Palsson BO, Vicini P. BMC Syst Biol. 2013 Sep 28;7:95.

Our Working Hypothesis To Understand Immunogenicity

- A mathematical model that describes the **key underlying mechanisms** for immunogenicity could:
  - **Integrate information** from various sources;
  - **Generate simulations or predictions** that can be subjected to experimental validation;
  - May **help meet the challenge** to predict human immunogenicity
    - Clinical ADA incidence and loss of efficacy
    - Early differentiation between leads

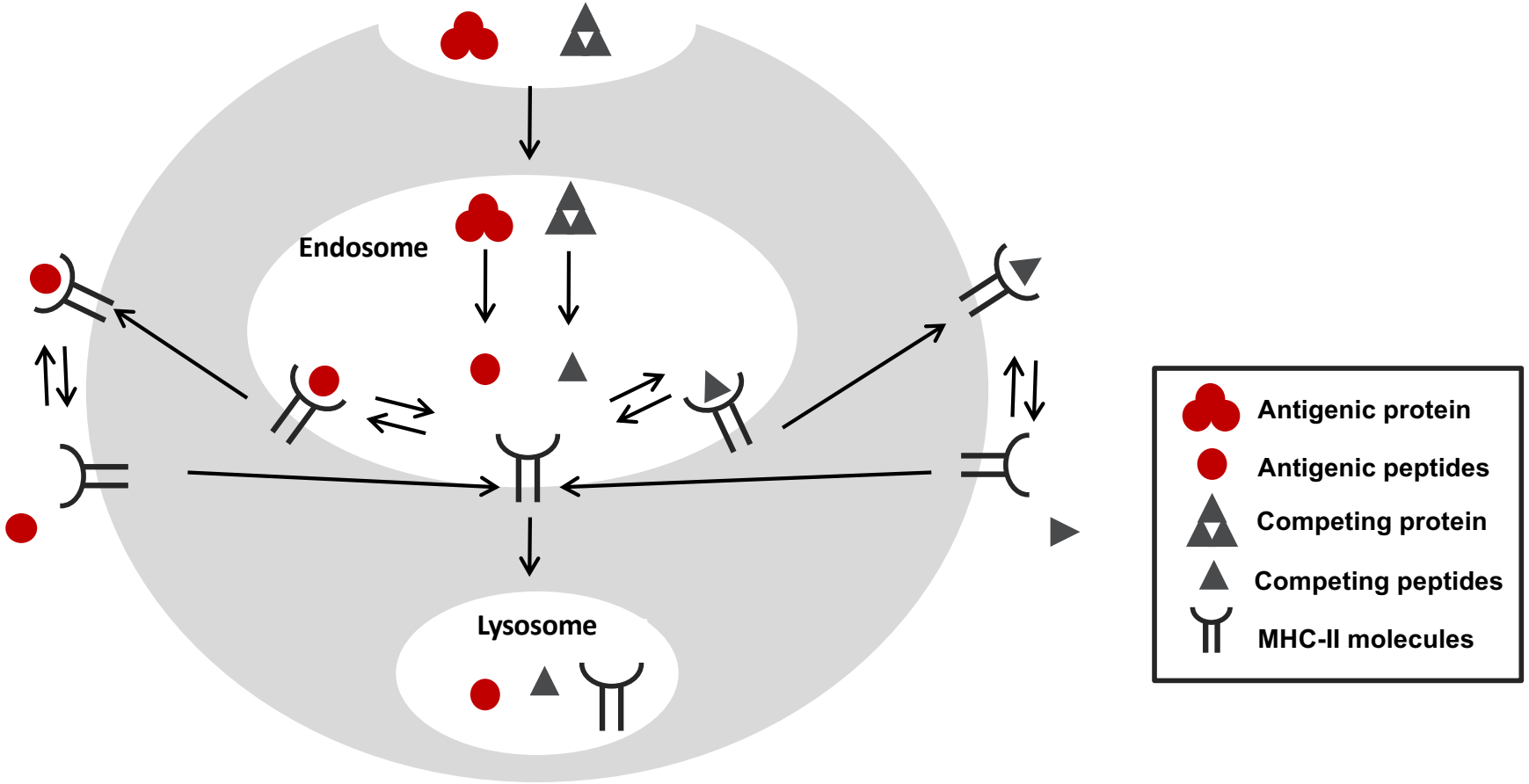
Chen X, Hickling T, Vicini P. A Mechanistic, Multi-Scale Mathematical Model of Immunogenicity for Therapeutic Proteins [Part 1 and 2]. Clinical Pharmacology and Therapeutics: Pharmacometrics and Systems Pharmacology

Mechanistic model – cellular level

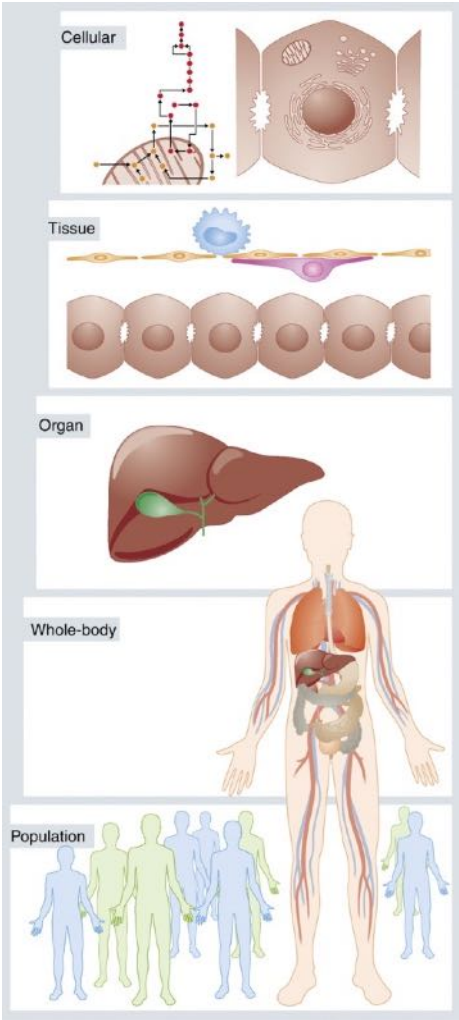


Mechanistic model – subcellular level

Antigen presentation in mature dendritic cells

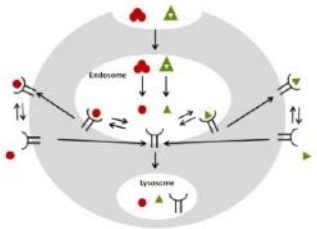


Multi-scale mechanistic model

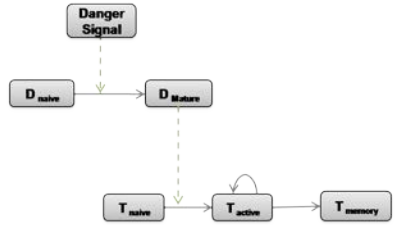


kuepfer 2010 molecular system biology

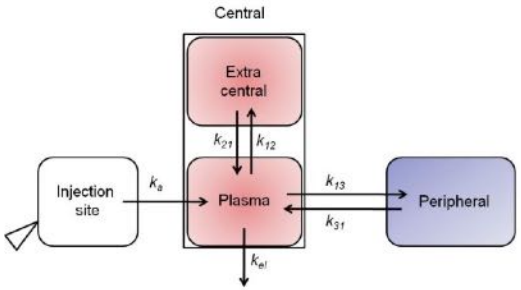
Antigen presentation



Cell life cycle



Drug distribution and elimination

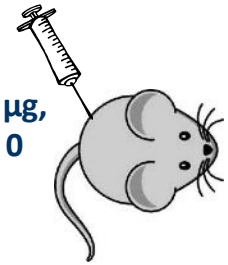


Patient MHC II genotype

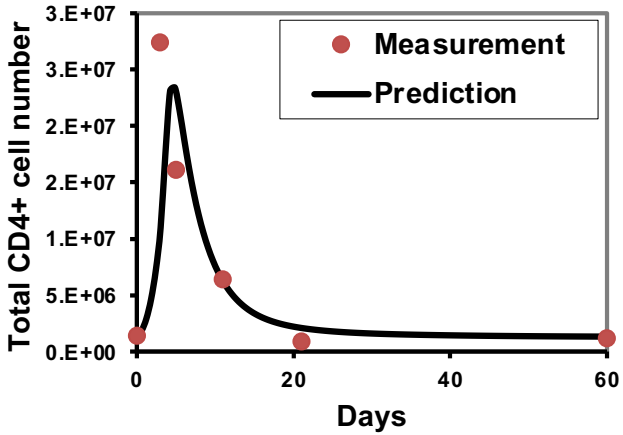
	Patient MHC allele		
Patient ID	DRB1 *01:01	DRB1 *03:01	DRB1 *04:01
1204	Y		Y
1205		Y	
1206	Y		
1207			Y

Case study 1: Model validation/fitting using mouse studies with ovalbumin challenge

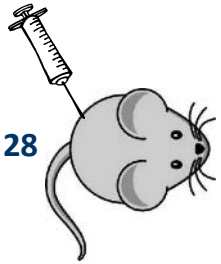
Ovalbumin, 100 µg, i.v. dosed at day 0



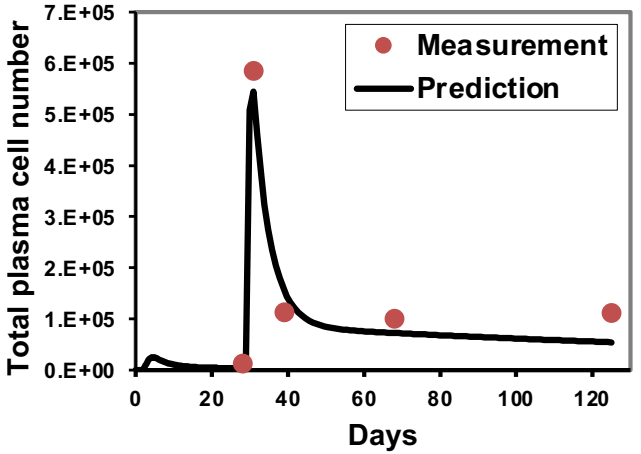
Immuno-staining for CD4+ cell



Ovalbumin, 100 µg, i.p. dosed at day 0 and day 28



Measure plasma cell specific for ovalbumin

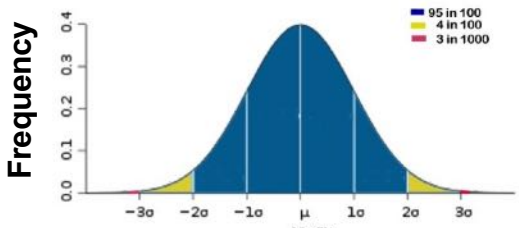


Simulation process: from one subject to a population

MHC and T-epitope

MHC-II allele	Allele frequency in North America	Epitope 1 binding affinity (nM)	Epitope 2 binding affinity (nM)
DRB1*04:01	0.089	123	85
DRB1*04:03	0.053	78.52	147.85
DRB1*04:04	0.036	180	38
DRB1*14:04	0.00075	53.7	4000
…	…	…	…
Rest of DRB1	0.46	4000	4000

Population PK



Drug clearance rate

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

Obtain MHC-II binding affinity for the T-epitopes

Randomly generate Drug clearance rate

MHC-II allele	Epitope binding affinity to MHC (nM)		k_{el} (day^{-1})
	Epitope 1	Epitope 2	
DRB1 *04:01	123	85	0.1137
DRB1 *04:07	124.73	104.16	
DPA1 *02:01	4000	4000	
DPA1 *03:01	4000	4000	
DQA1 *04:01	4000	4000	
DQA1 *05:01	4000	4000	

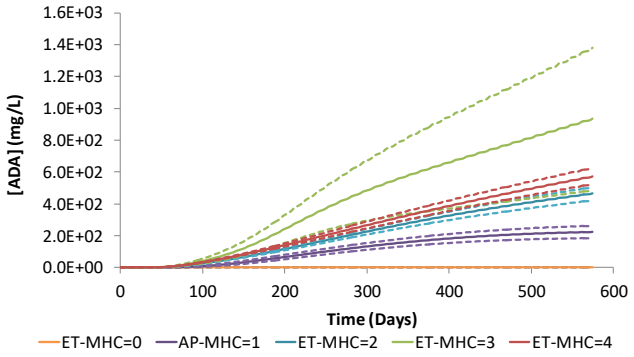
Repeat for 1000 patients

Simulate immune response for a population

Case Study Adalimumab: Simulating 1000 patients

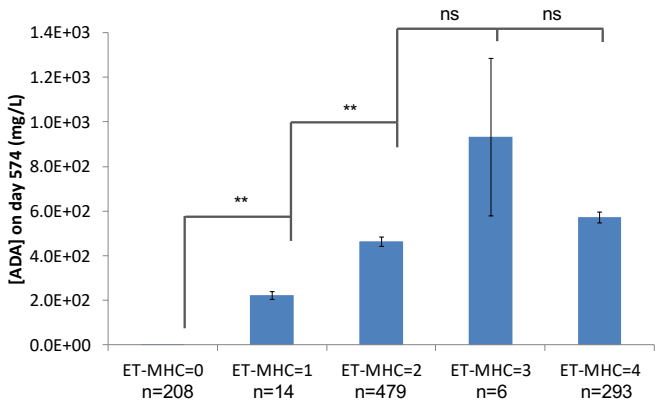
Stratify the patients according to their epitope-MHC (ET-MHC) binding pairs

[ADA] time course in groups

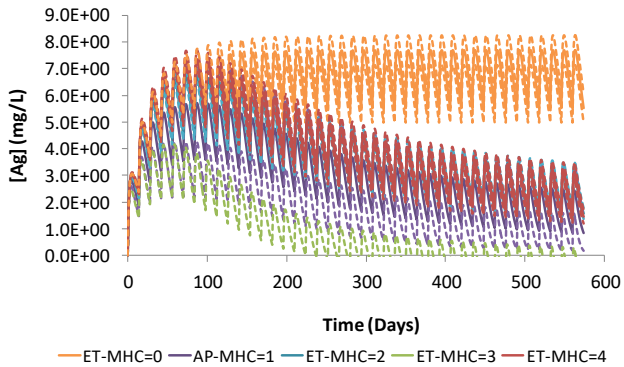


ADA conc defined for given time points

[ADA] in groups

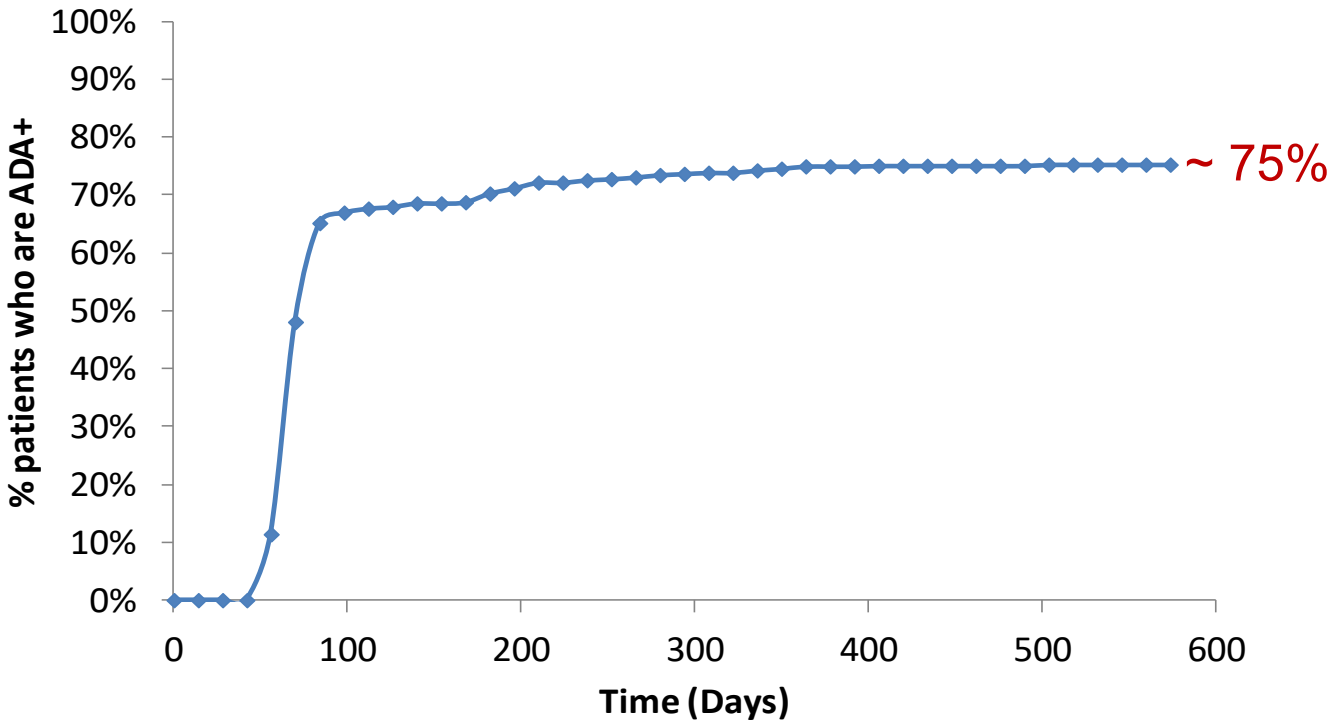


[Ag] time course in groups



ADA development impacts concentration of drug

Simulated immunogenicity incidence



Above: Time course of the development of ADA in 1000 virtual patients.

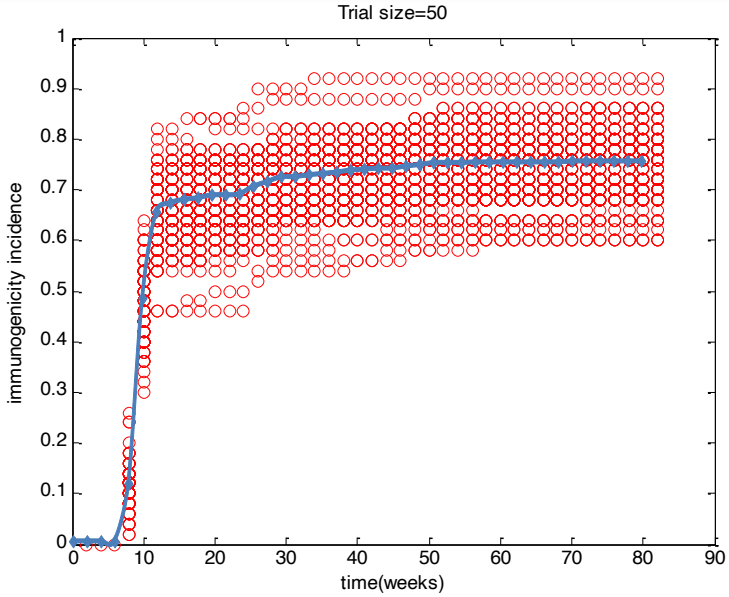
Assumed thresholds for ADA+:

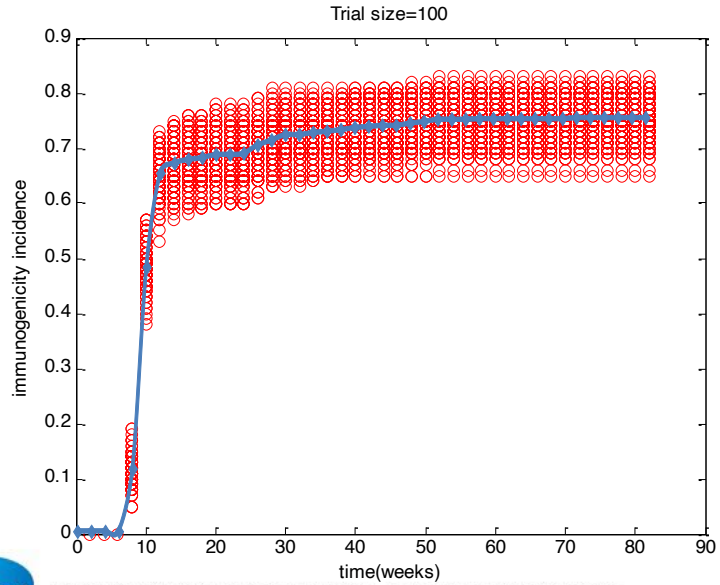
- Absolute ADA concentration > 250 ng/mL
- Molar ratio of ADA over Ag > 1 for drug tolerance

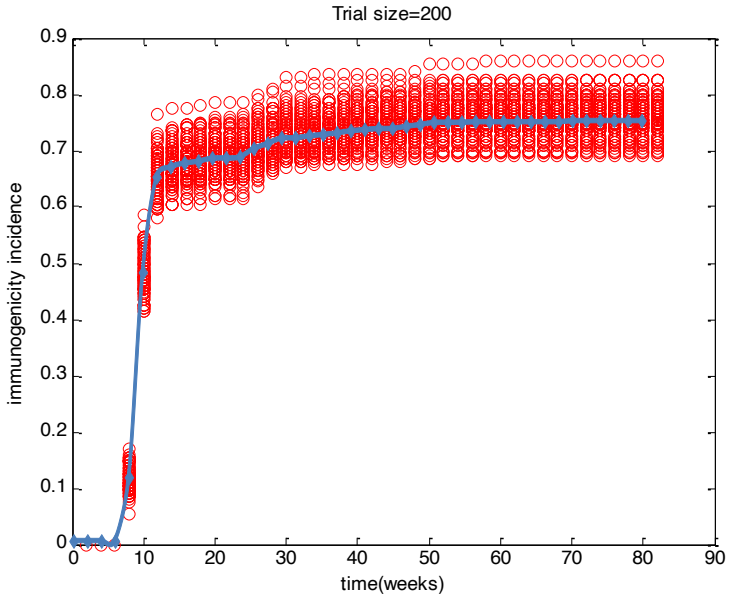
Impact of trial size on immunogenicity incidence estimation

Trial size	Low (95% CI)	High (95% CI)	Range
50	62.4 %	88.2 %	25.9 %
100	67.6 %	83.2 %	15.5 %
200	69.1 %	81.5 %	12.4 %

100 random trials with the specified trial size were simulated; each circle represents the simulated immunogenicity incidence for one trial.



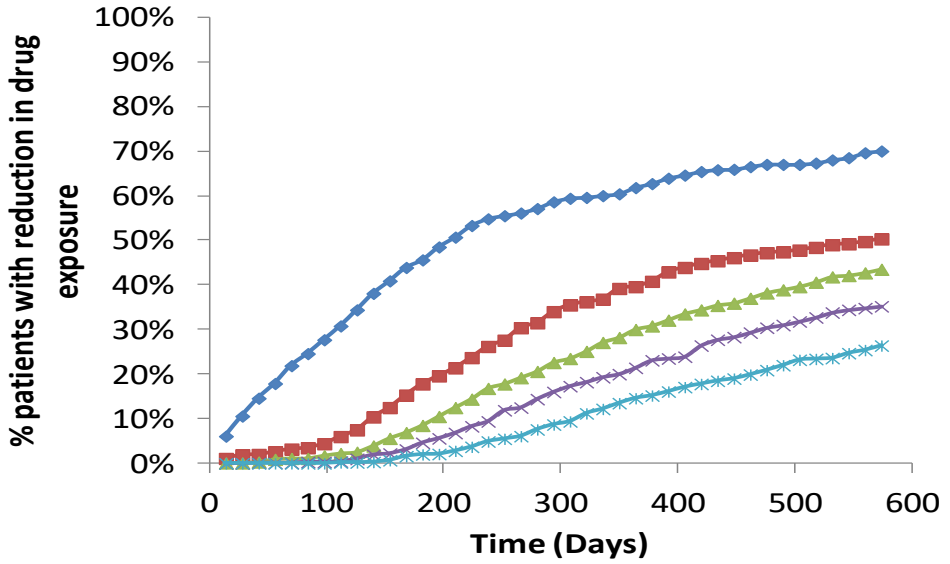


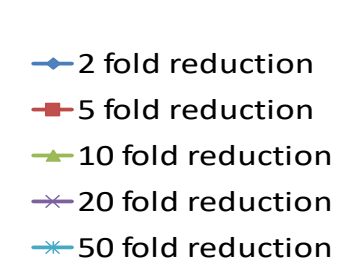


Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

Simulated reduction in drug exposure due to ADA generation

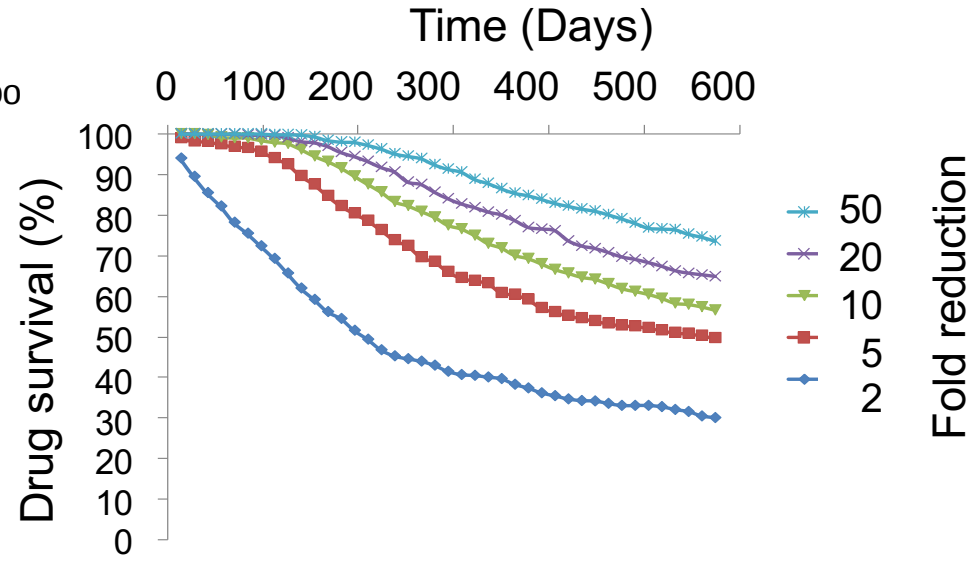
Time course of the reduction in drug exposure in the 1000 virtual patients. The percentage of patients with 2, 5, 10, 20, and 50 fold reduction in mAb trough concentration was plotted.





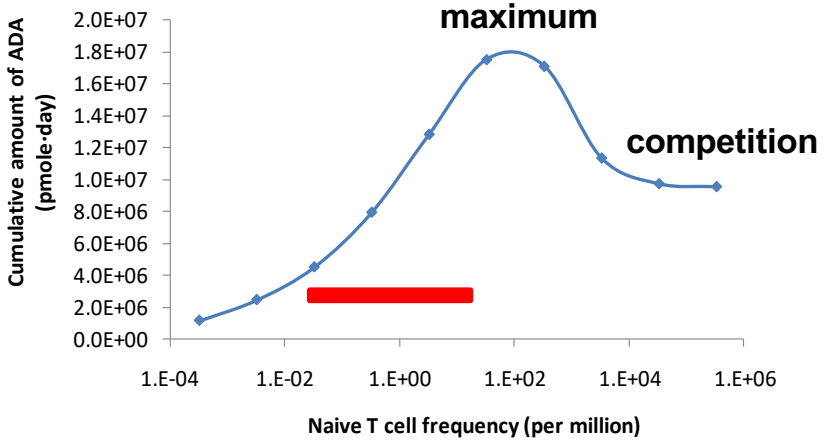
Assumption: Elimination rate of immune complex is 10 fold higher.

Potential loss of efficacy in patients due to reduced exposure based on different trough concentrations required for efficacy

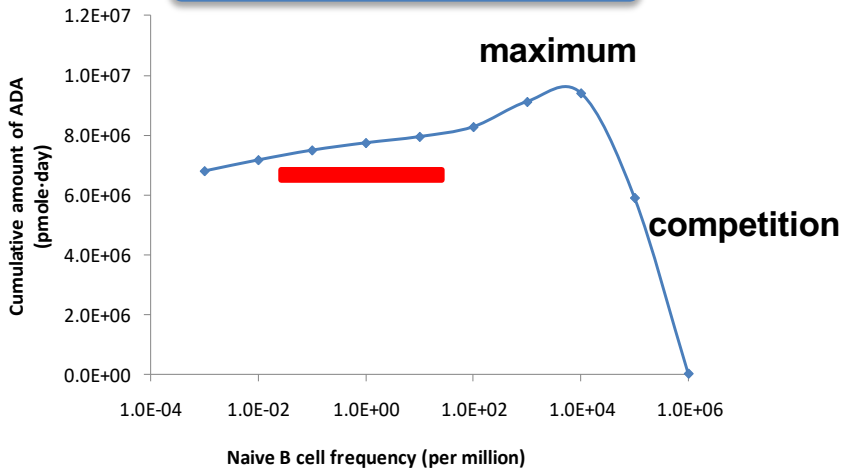


ADA response correlations (sensitivity analysis): Crucial measurements from ex vivo and in vitro assays

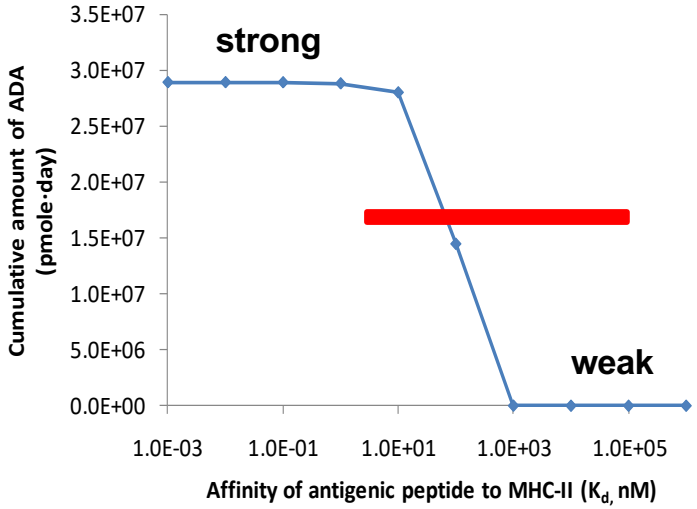
Naïve T cell number



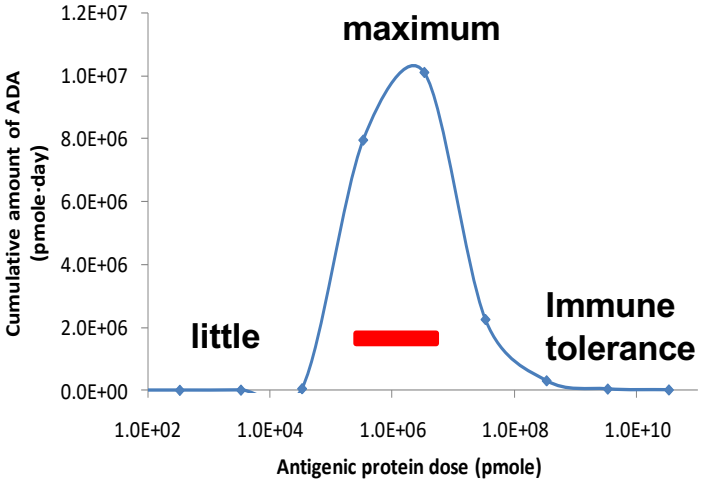
Naïve B cell number



T-epitope MHC binding affinity



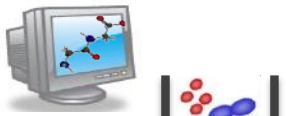
Ag dose

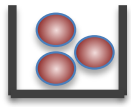


Summary

- Model output for ADA incidence and magnitude is reliant on T cell epitopes
  - Consistent with requirement of T help for class switch/high expression

- Several assay formats enable risk assessment for T epitopes
  - *In silico*
  - *In vitro* binding assays
  - *Ex vivo* activation assays





- Current forecasts for immunogenicity incidence and impact can be made, though a truly predictive model will likely require more extensive data for integration and a broad range of therapeutics for validation

Acknowledgements

- Xiaoying Chen
  - Model design and implementation, simulation running, refinement
- Liusong Yin
  - Model extension and simulation
- Paolo Vicini
  - Model design, refinement

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  - Mary Spilker
  - Michael Zager
  - Bonnie Rup