Systems immunology applied to the integration of non-clinical immunogenicity data

Integration of non-clinical immunogenicity data and its clinical relevance

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling workshop, 26th January 2021

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Roche pRED

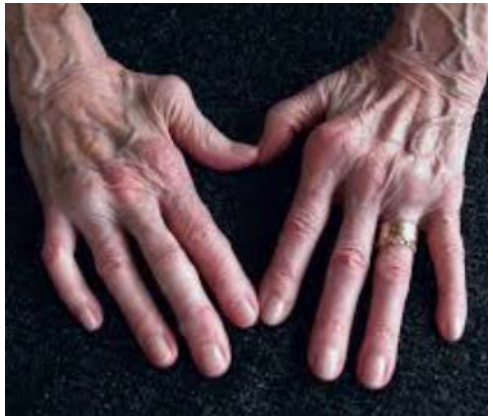
A case for systems vs. linear thinking

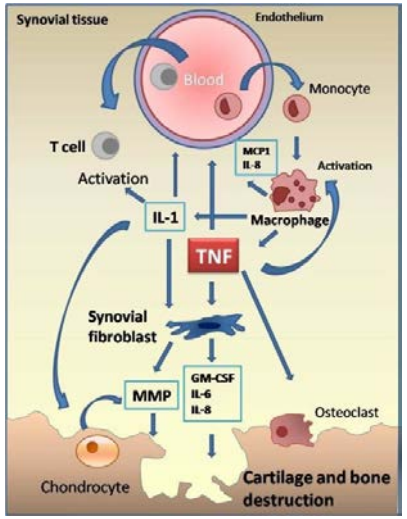
Observed effect

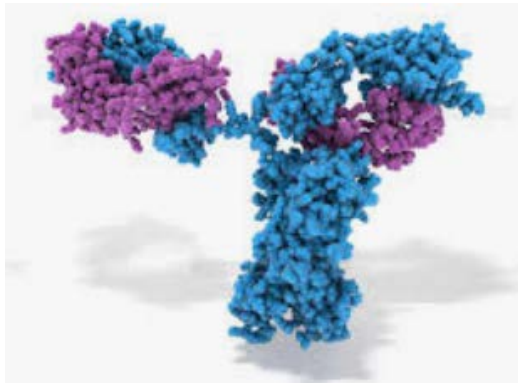
Cause

Solution

A more complex problem…



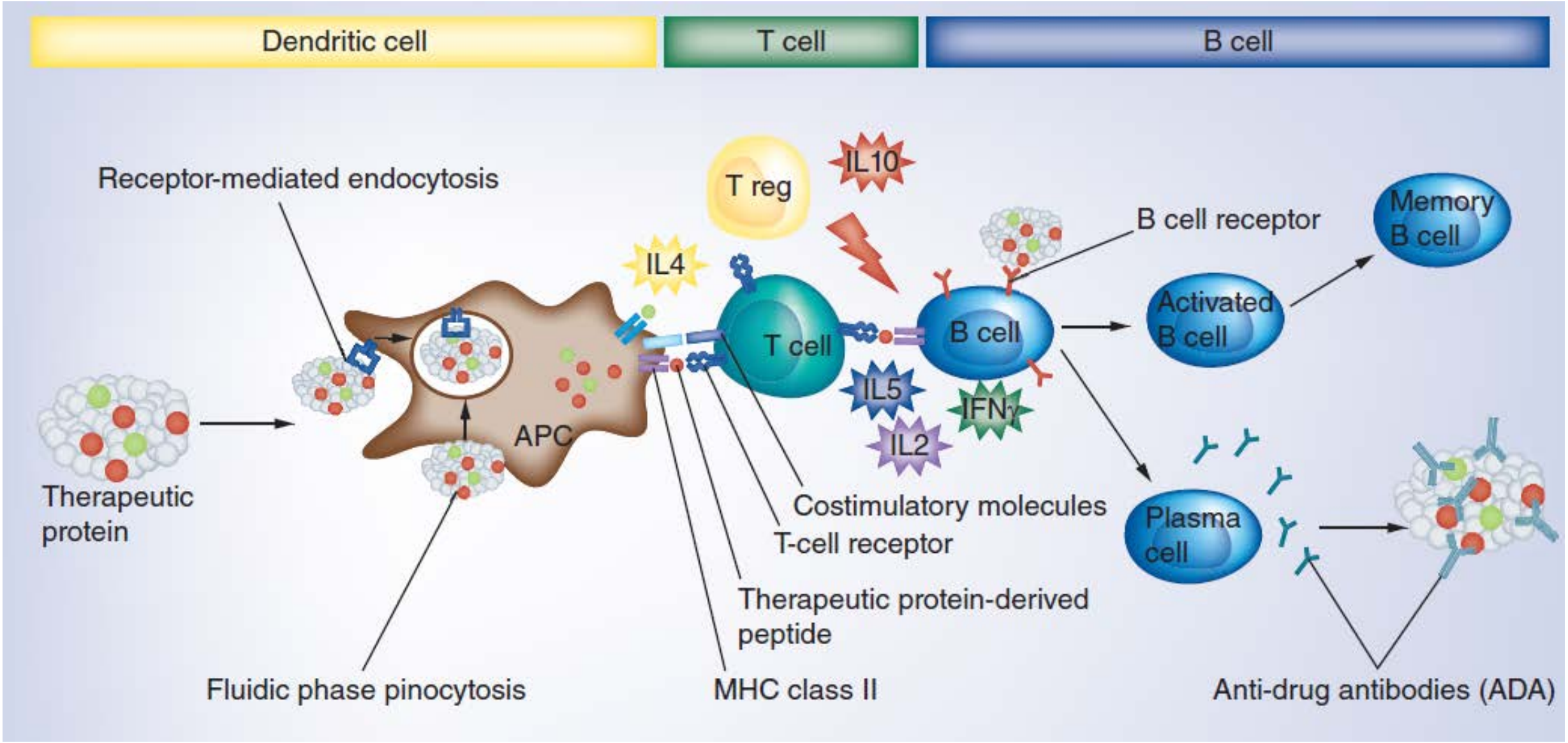




e.g. TNFi

Complex problems need us to go beyond linear thinking to find solutions

Immune system components

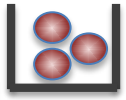


Tourdot & Hickling, 2019 Bioanalysis

Data integration has been limited by reductionism and variable biological models

- **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)

Features of systems

- **Systems are composed of lots of interconnected parts**
- Changing one part of the system affects other parts, sometimes with non-obvious connections.
- Connections are as important as the parts themselves
- **System relationships are dynamic**
- Change of components over time obscures system behaviors
- Delays and loops are common
- Feedback and feedforward loops (+ve and –ve) complicate predictions
- **Lots of data is needed to describe and model these systems**

A systems model of immunogenicity

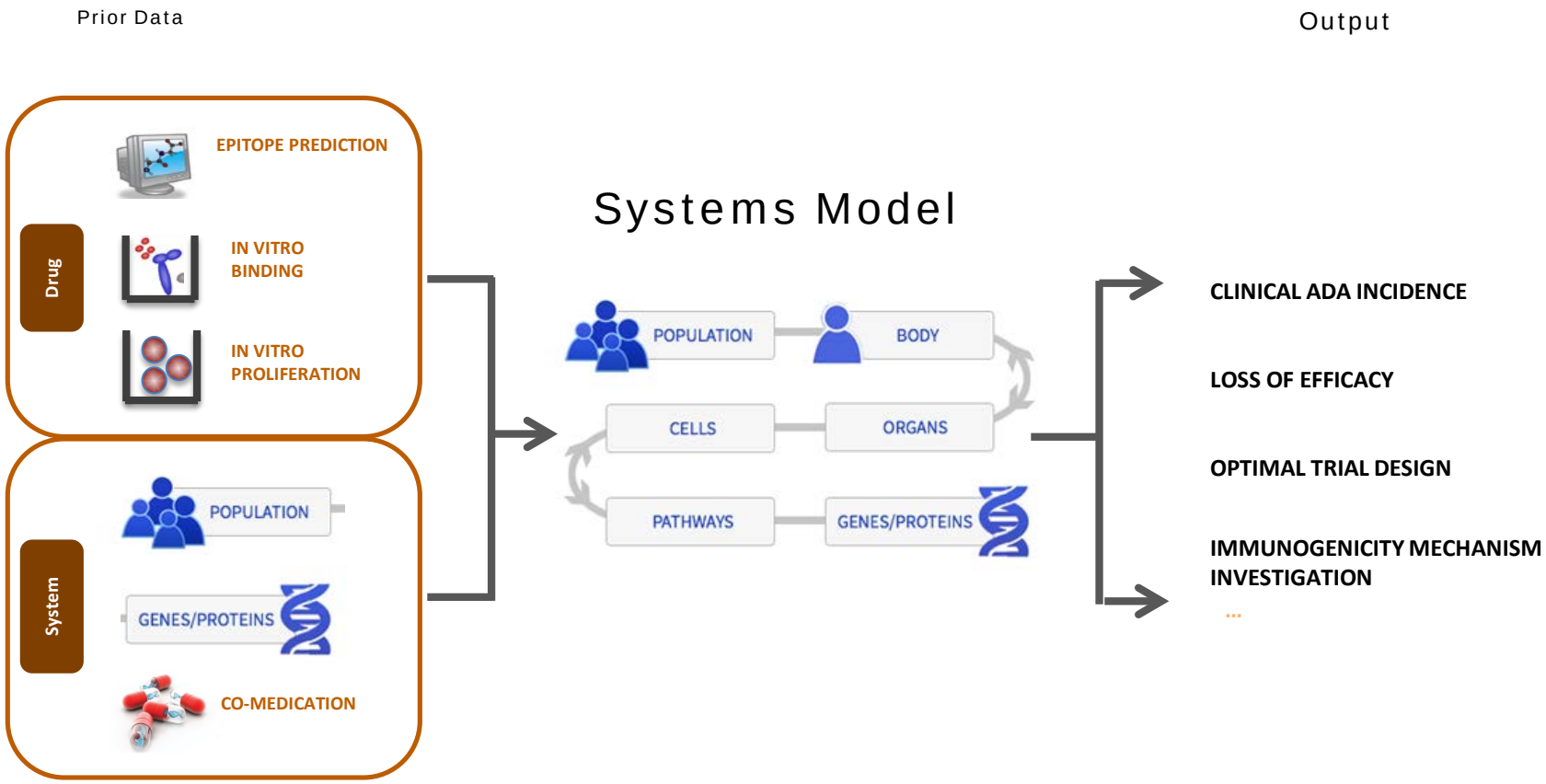
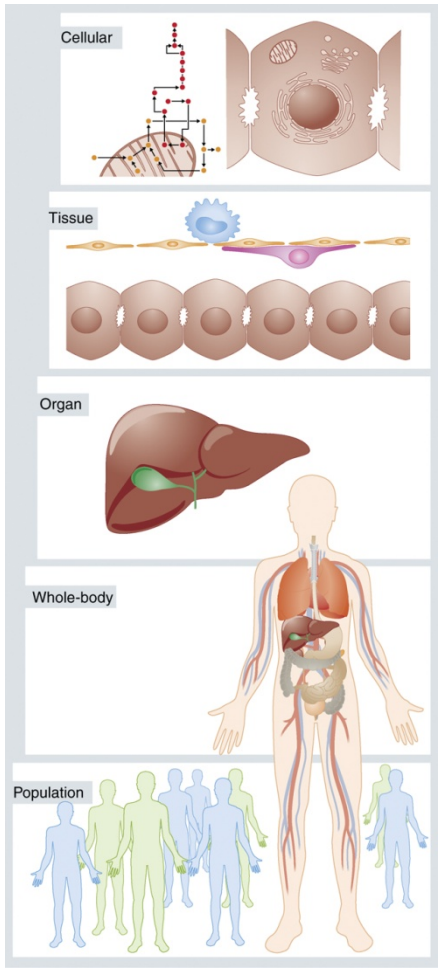


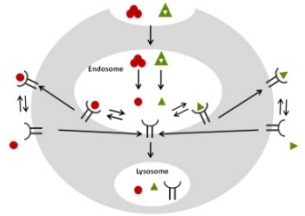
Image credit: http://blog.wolfram.com/2014/12/23/wolfram-technologies-in-systems-pharmacologya-case-study-on-type-2-diabetes/

Multi-scale mechanistic model

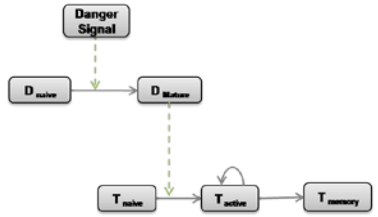


kuepfer 2010 molecular system biology

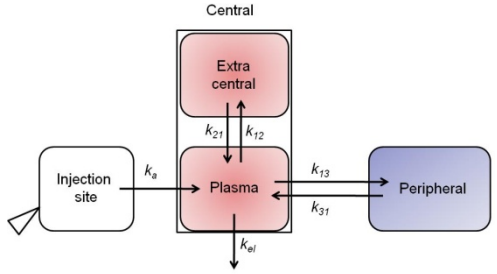
Antigen presentation



Cell life cycle



Drug distribution and elimination

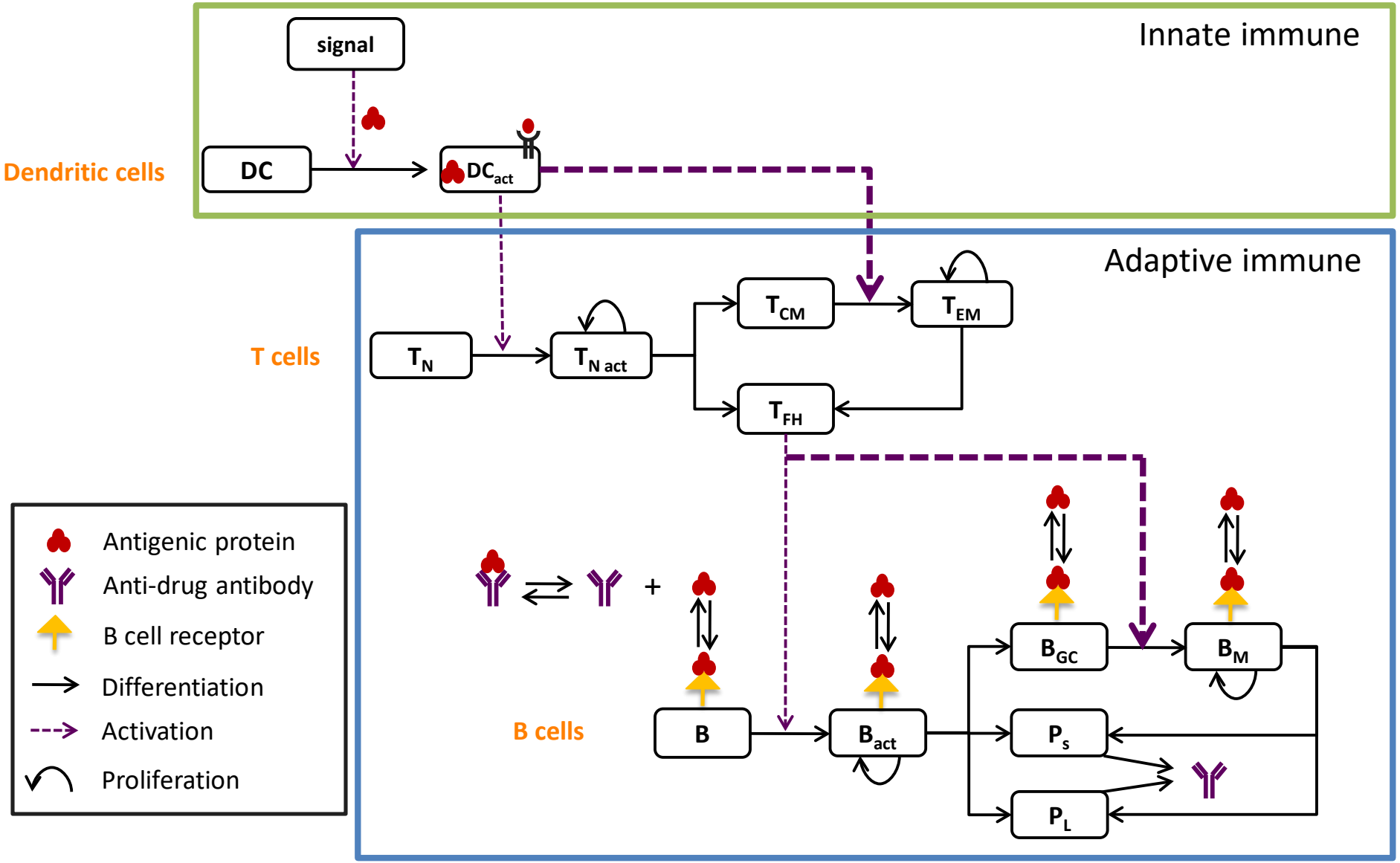


Patient MHC II genotype

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

Chen X et al 2014 CPT:PSP.

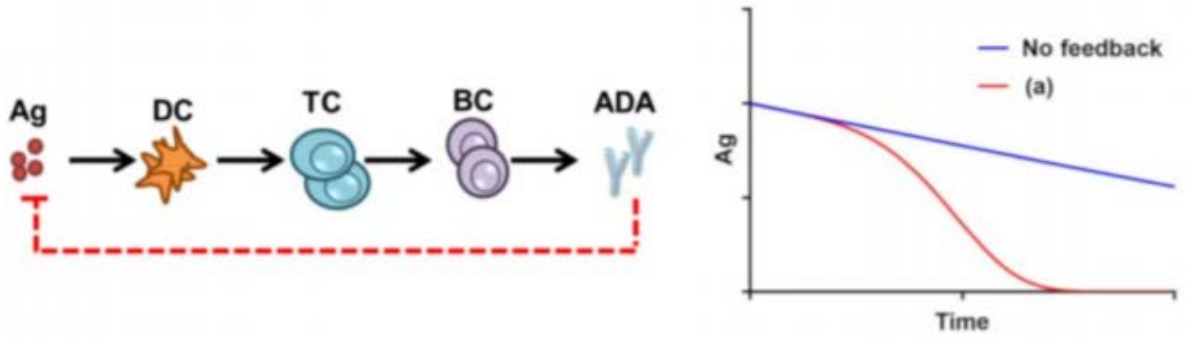
Schematic of Systems Model at the Cellular Level



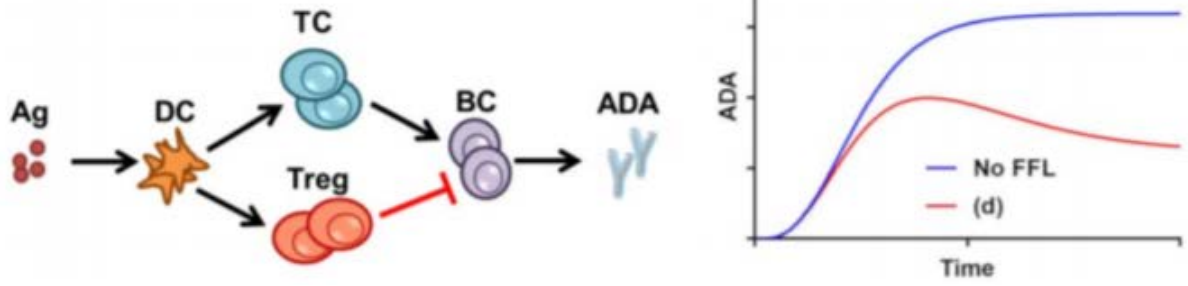
Behavior in complex systems

Rational and logical for each individual component can become obscure as complexity increases

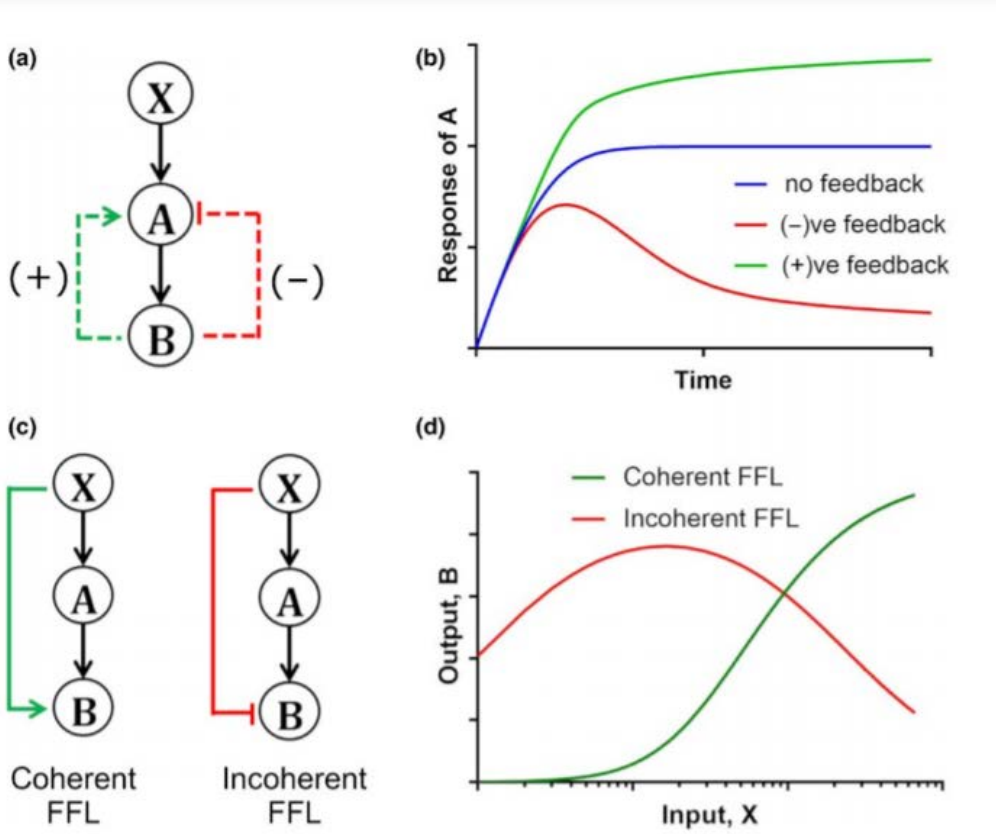
- ADA impact on exposure



- Treg impact on ADA levels



- Feedback and feedforward loops



Rahman A *et al* 2018 CPT:PSP

What can we measure in non-clinical assays?

Identify T cell epitope(s)

Identify T cell response

In silico

Protein sequence

Adaptive immunity

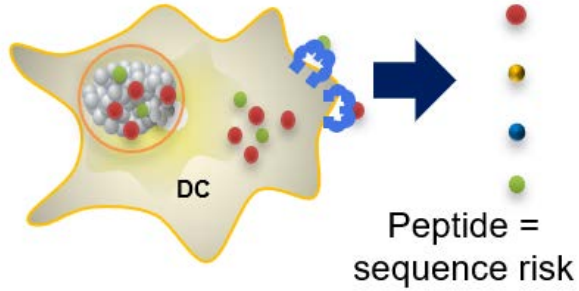
Frame Start	AA Sequence	Frame Stop	DRB1*0101 Z-Score	DRB1*0301 Z-Score	DRB1*0401 Z-Score	DRB1*0701 Z-Score	DRB1*0801 Z-Score	DRB1*1101 Z-Score	DRB1*1301 Z-Score	DRB1*1501 Z-Score	Hits
282	SSLYISQFI	290								1.44	0
283	SLYISQFII	291									0
284	LYISQFIIM	292		1.75		1.33			1.36		1
285	YISQFIIMY	293		1.73	1.41			1.47	2.39		2
286	ISQFIIMYS	294						1.34		1.6	0
287	SQFIIMYSL	295									0
288	QFIIMYSLD	296									0
289	FIIMYSLDG	297	2.95	1.84	3	1.9	2.45	3.01	1.81	2.71	8
290	IIMYSLDGK	298									0
291	IMYSLDGKK	299								1.32	0
292	MYSLDGKKW	300				1.53					0

Potential epitopes

MAPPs

Whole protein

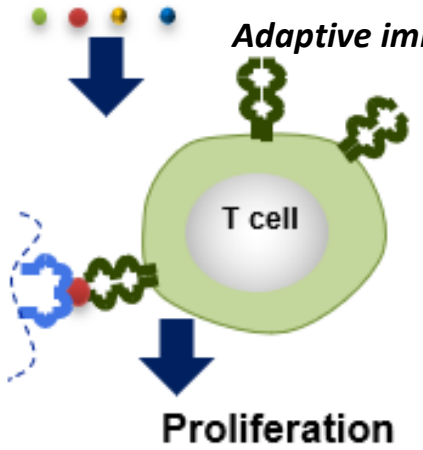
Adaptive immunity



PBMC assay

Peptide sequence

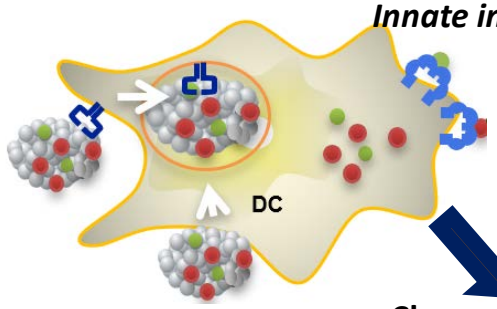
Adaptive immunity



DC activation

Whole protein

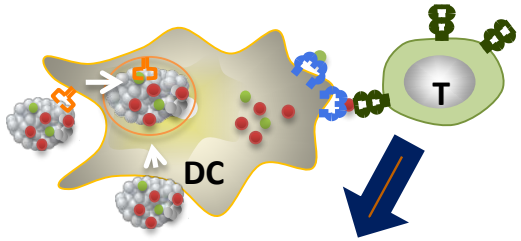
Innate immunity



DC:CD4 proliferation

Whole protein

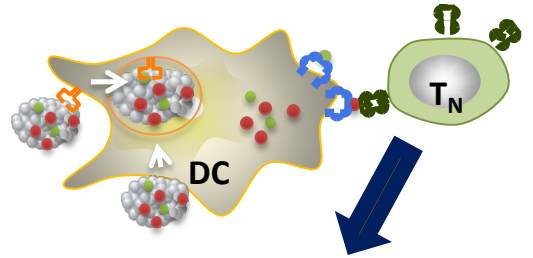
Adaptive immunity



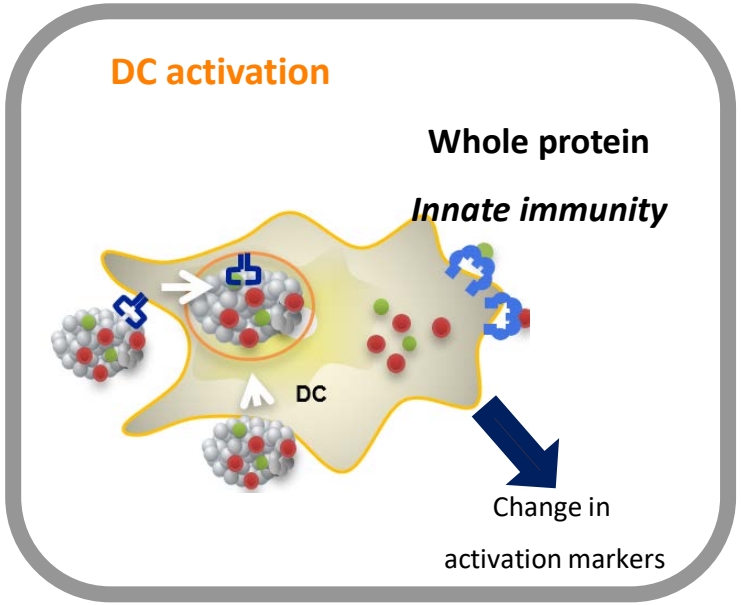
Naïve T cell number

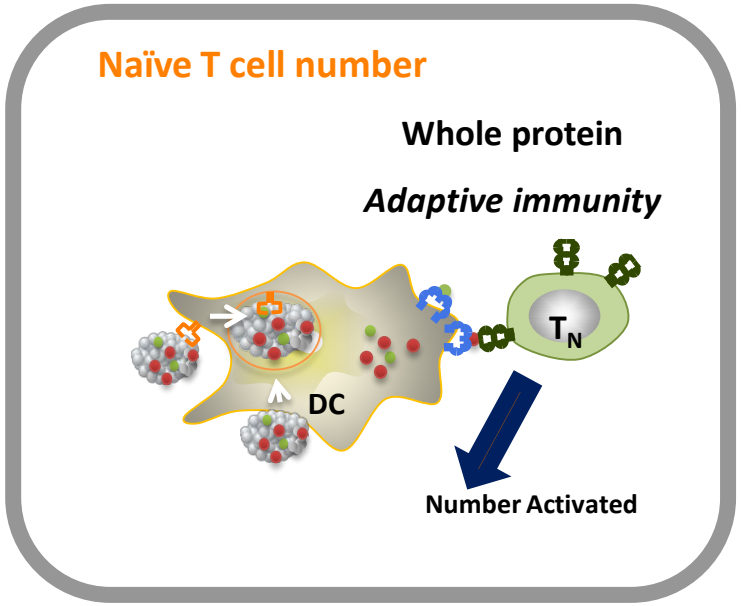
Whole protein

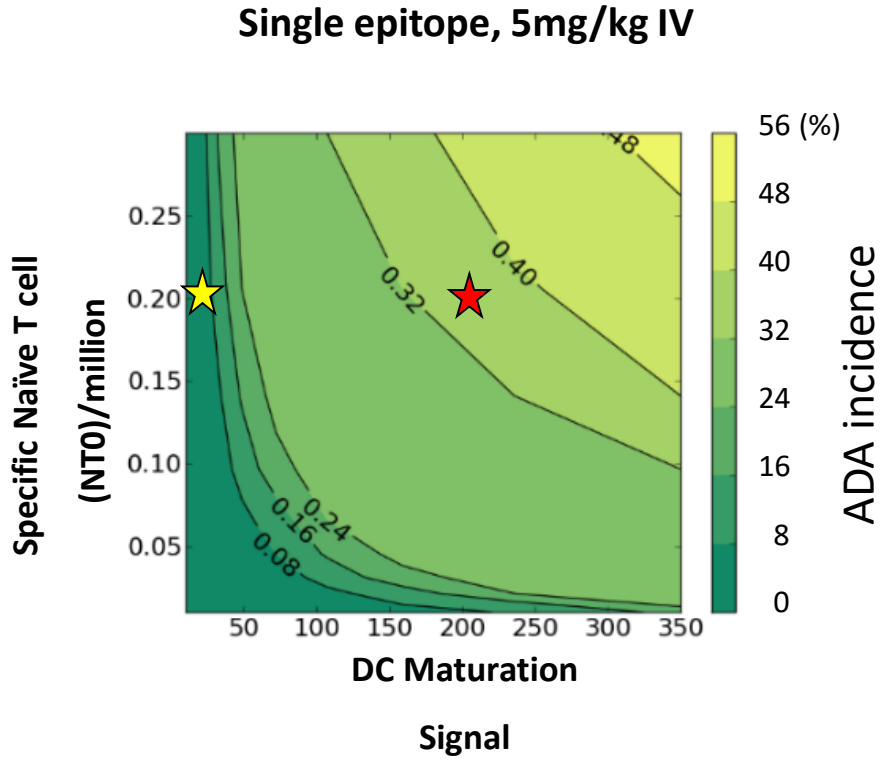
Adaptive immunity



Example of how variables measured *in vitro* could impact immunogenicity





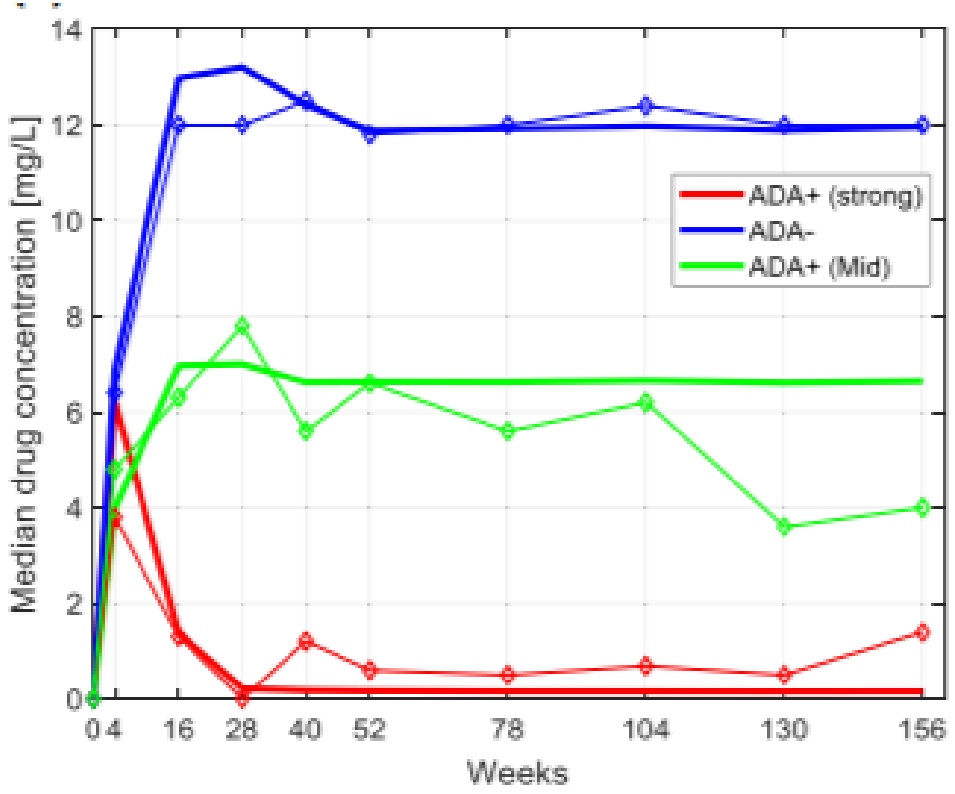


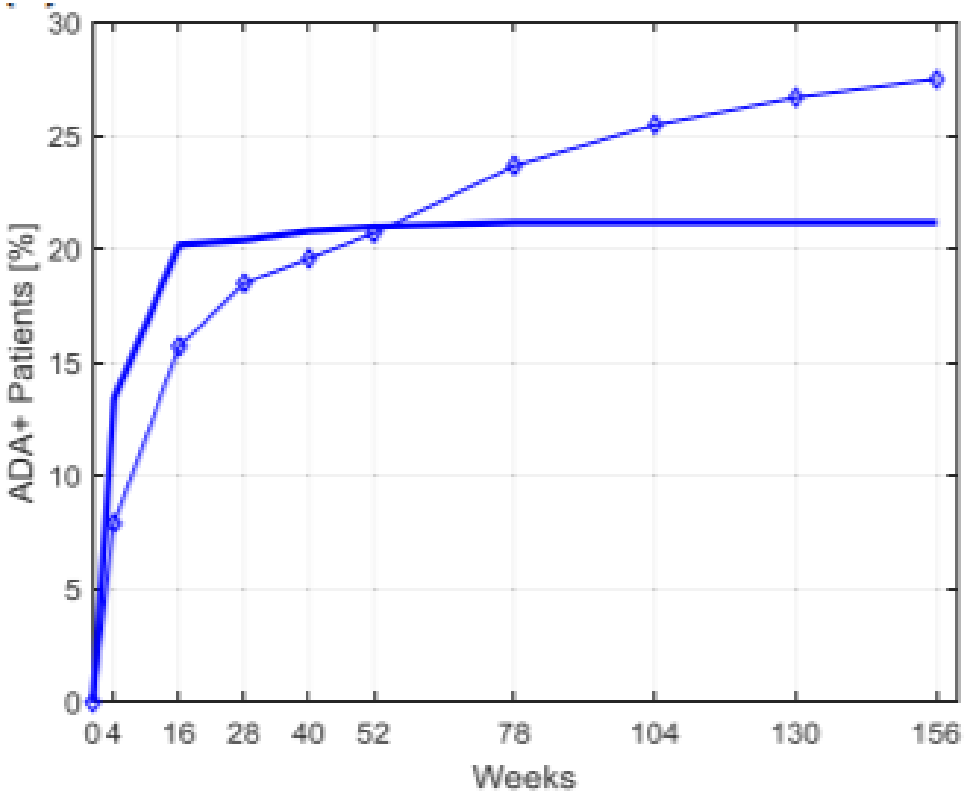
mAb example:

- NT0 = 0.2/million
- DC MS scenarios
  - 50 = 5% ADA
  - 200 = 35% ADA

Simulation vs clinical trial data: Example 1

Adalimumab



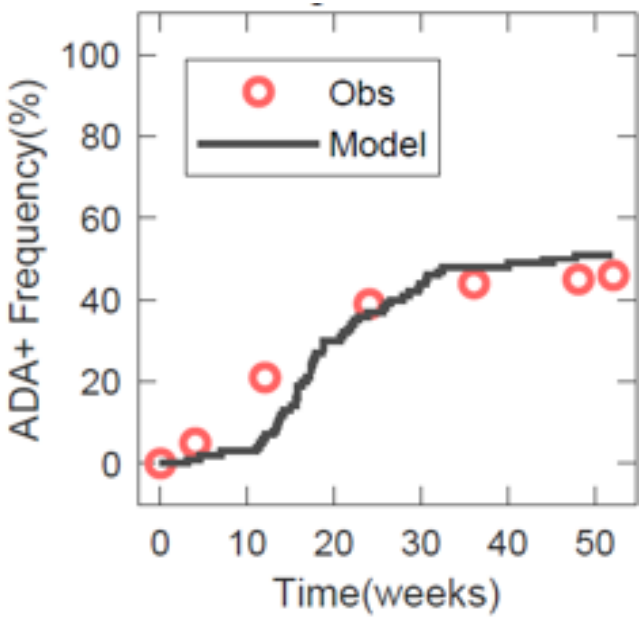


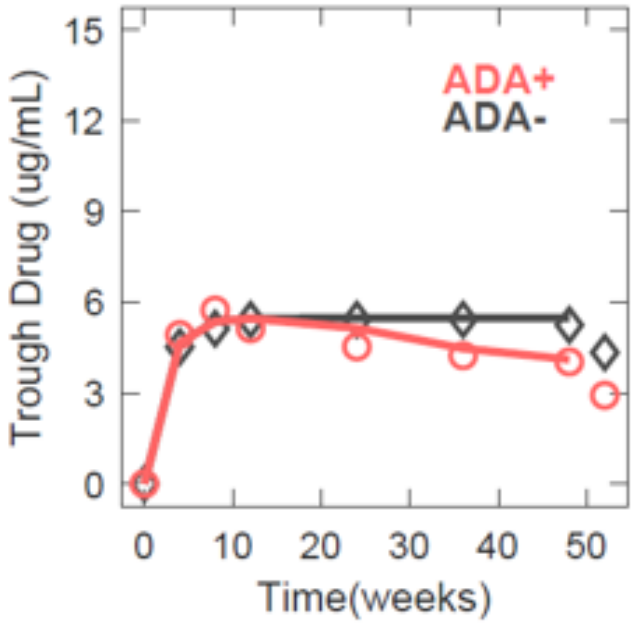
Clinical Data (Bartelds *et al* 2011), simulations Kierzek A et al 2019

Simulation vs clinical trial data: Example 2

Bococizumab (Ridker PM *et al* 2017)

Incidence and clinical impact of immunogenicity at the population level





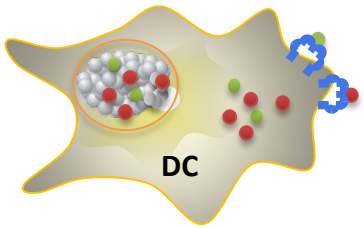
Simulations presented at CHI Immunogenicity and Bioassay Summit October 2019

A learning cycle to facilitate quantitative prediction of immunogenicity

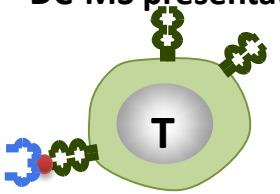
Roche

Assays

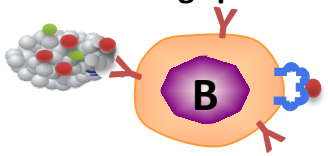
- **DC activation**
- DC uptake/trafficking



- DC:T proliferation
- **DC-MS presentation**

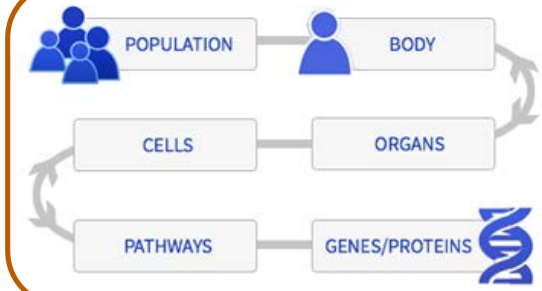


- **T cell epitopes (*in silico*)**
- **T cell: drug specific naïve**



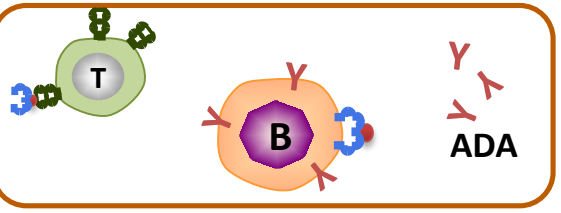
- B cell activation
- B cell epitopes (*in silico*)

Data Integration



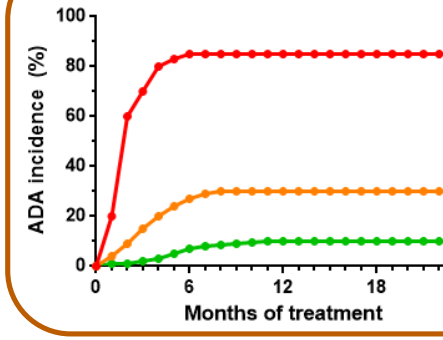
Learn and Confirm

Clinical Samples

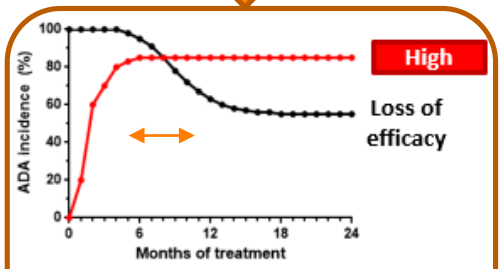


Simulations & Observations

Kinetics of ADA formation



Prediction of ADA/PK/PD



ADA occurrence to impact

Conclusions

- Systems modeling helps us understand connections and relationships in complex systems

- Integrating data for immunogenicity risk assessment through systems modeling enables simulations of clinical outcomes

- Iterative cycles of tests, simulations and sampling are needed to refine models to enhance predictive capability

Acknowledgements

- Xiaoying Chen
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- Anisur Rahman
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- Sophie Tourdot
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- IG simulator consortium
- Epivax

Doing now what patients need next