20th International Symposium on
Microsomes and Drug Oxidations

SYSTEMS PHARMACOLOGY: An Industry Perspective

LYO-X GmbH

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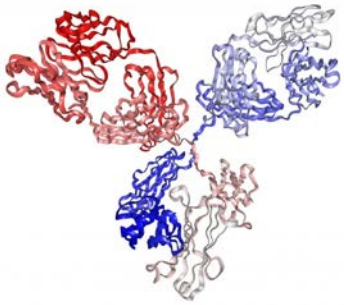
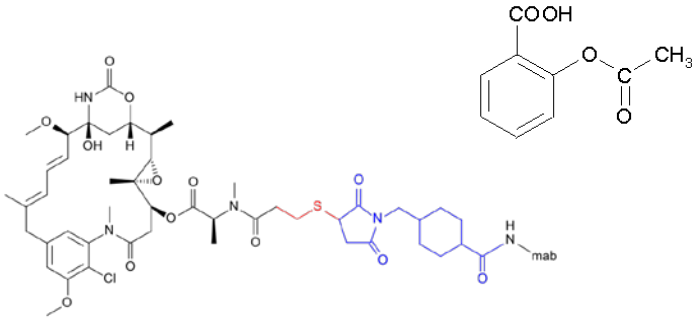
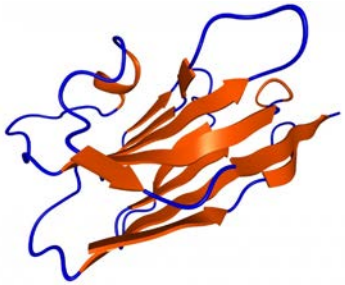
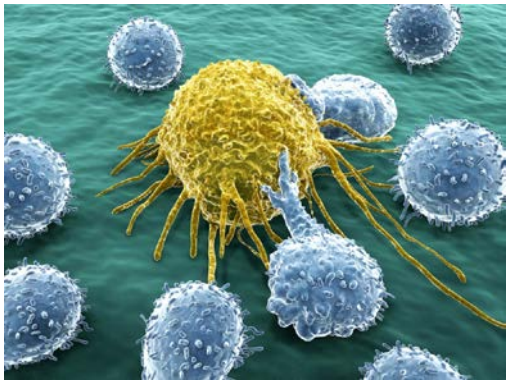
Dr. Matthias Machacek

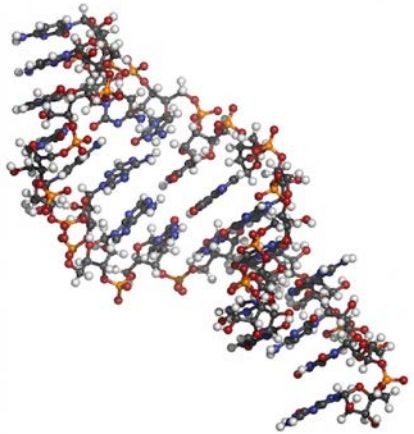
Current landscape

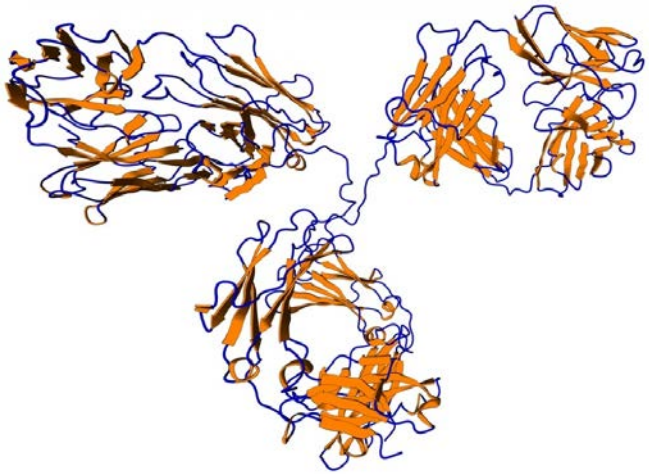




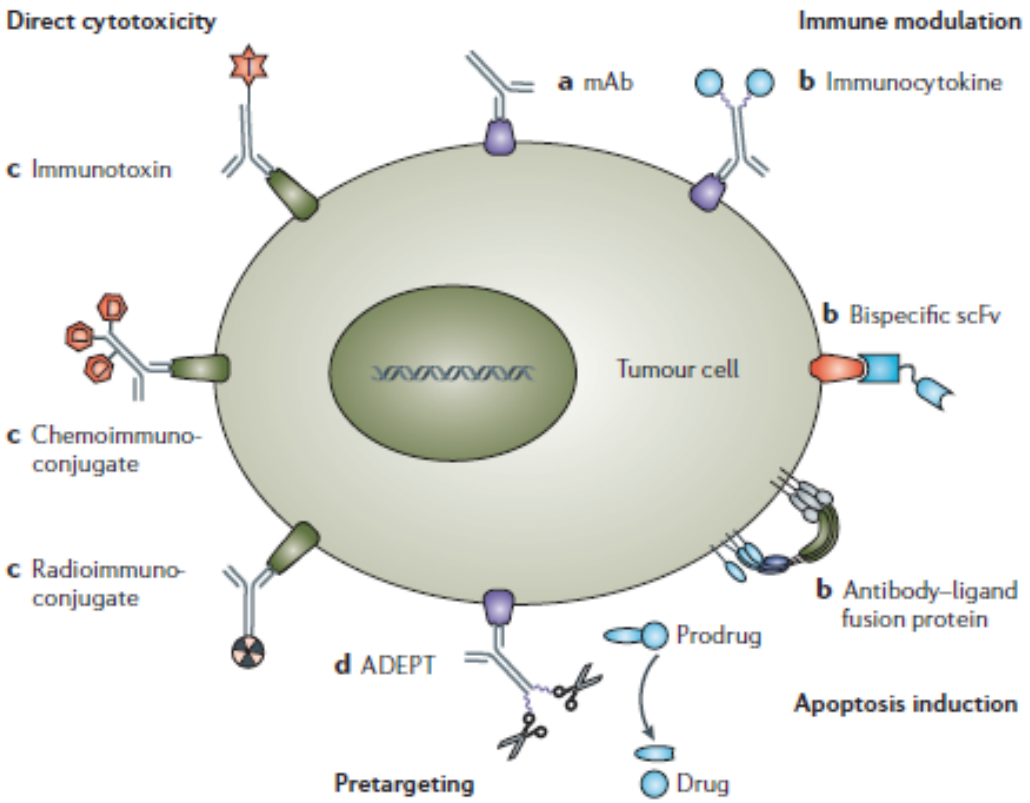








Novel therapeutic strategies: What will bring us from conceptual ideas to solutions to land our compounds on target?



Antibody targeted drugs as cancer therapeutics. *D. Schrama et al.* Nature Reviews Drug Discovery. Vol 5 2006

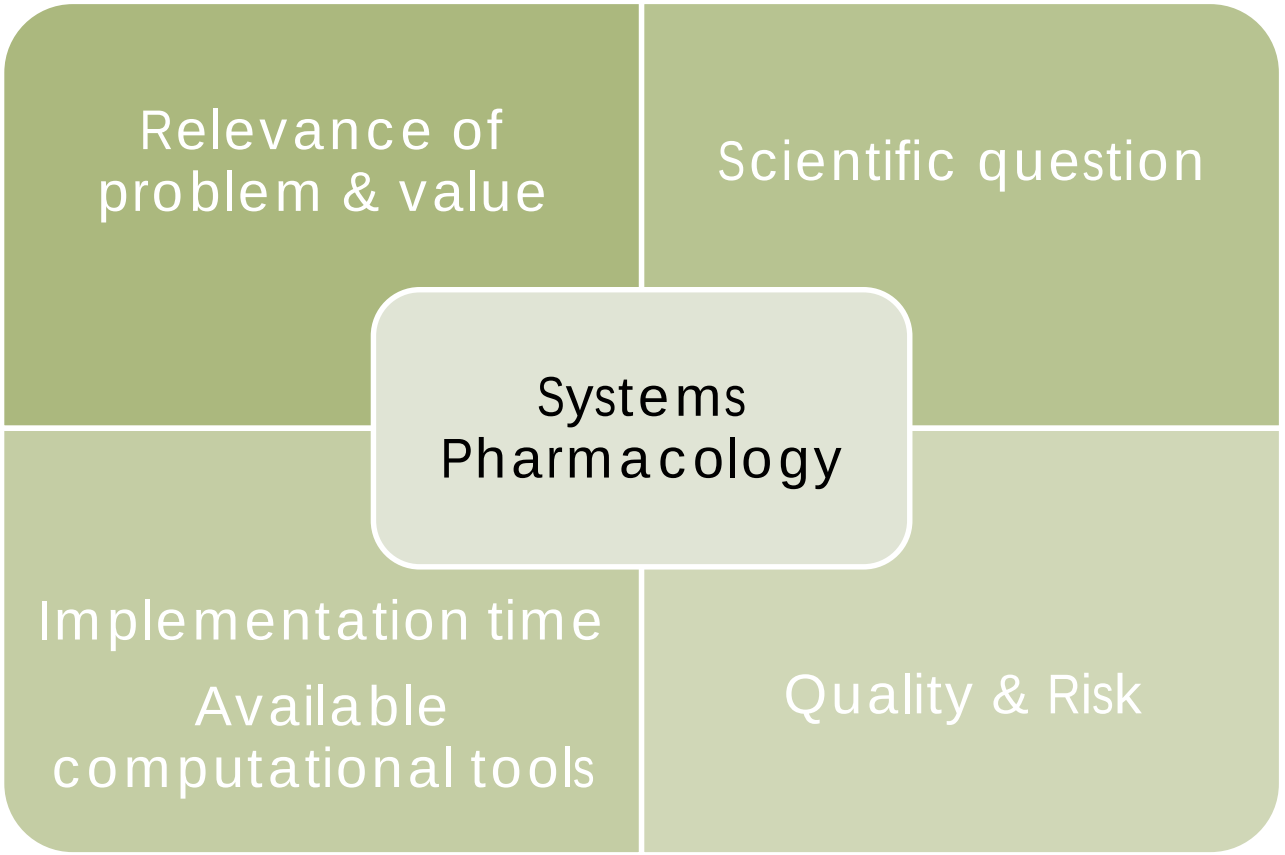
Current challenges in Drug Discovery and Drug Development

- Novel biotherapeutic modalities and technologies may address unmet needs.
- Projects have fundamental challenges:
  1. Science: Pharmacology of new modalities often unknown
  2. Competition: Fierce for targets; Intellectual Property issues
  3. Corporate organization: Relevant data from different departments
- How can we support informed decision-making for:
  - Target assessment
  - Modality selection
  - Compound design
  - Candidate selection
  - Dose and regimen selection

  ... and bring the most competitive drugs to patients?

➡ ***Systems Pharmacology: quantitatively integrate information in support of success of novel approaches***

Convergence towards a sustainable use of modeling in Research and Drug Development



Systems Pharmacology for Drug Development

Merging advantages of Systems Biology and Pharmacometrics

	Systems Biology	Systems Pharmacology	Pharmacometrics
Model focus	• Biological pathways • Cell	• PK-PD • Tissues • Target • Patient and population	• PK-PD • Plasma • Patient and population • Covariates
Modeling intention	Understanding of molecular and cell biology	Drug concentration in relevant tissues, interaction with target, clinical response	Blood drug concentration, clinical response
Model characteristics	Mechanistic	Semi-mechanistic	Statistical
Main advantages	Predictive	Accurate and predictive	Very accurate for interpolation
Main disadvantage	Complexity	Not established	Extrapolation at risk
Value for drug discovery and drug development	Little documented value	Large potential value	Sucessfully established
Model building effort	Large	Controllable	Controllable
Availability of commercial computational tools	Few	Pharmacometrics tools can be used	Available

Systems Pharmacology addresses key scientific, competitive, organizational challenges

Science

- Address complexity in PKPD of novel biotherapeutic modalities
- Integrate kinetics of compounds & biology, linking PK with target binding, target biology and patho-physiological effectors
- Quantitative integration & comparison efficacy & safety across experiments
- Support design of informative animal experiments; reduce studies
- Assist early translation of animal to human PKPD
- Justify dose and dosing interval

Competition

- Integrates and positions competitor *vs*. in-house data
  → Assess differentiation potential; Intellectual Property
  → Support scenario assessment, solutions for differentiation.

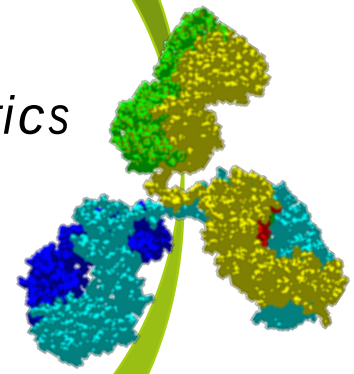
Corporate organization

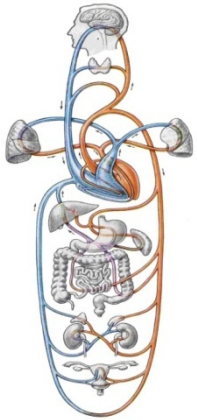
- Integrate data from clinical development and market into quantitative PKPD framework to support research.
- Integrate relevant data from multiple departments.
- Provide scientists with knowledge of biology, pharmacology and computational science

Typical structure of a Systems Pharmacology model

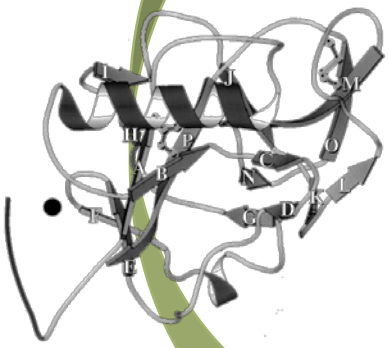
Delivery

Pharmacokinetics
Distribution
Tissue access





Binding modality



Production
Release

Target kinetics:
Soluble molecules
Receptors
Molecular meshwork
Cells

Clearance
Receptor mediated
Catabolic

Clearance
Secretion
Storage
Ligand interaction

- **Time**
- **Space, tissues**
- **Variability**

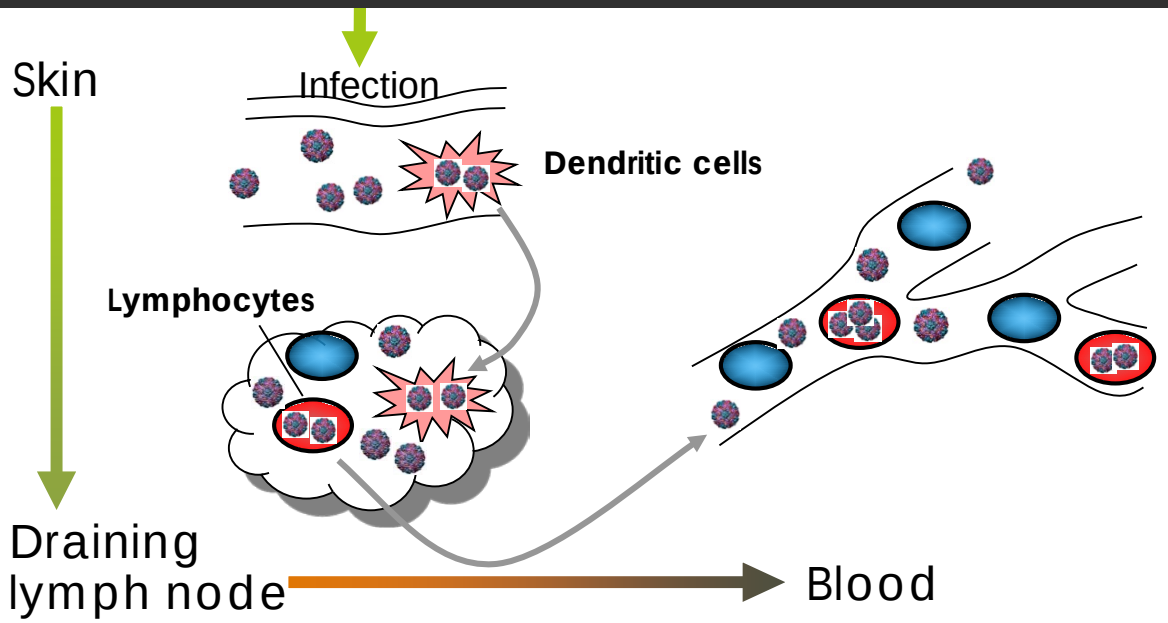
Effect

Enabling Systems Pharmacology: Integrated computational tools

Domain	Computational Tool	Functionality
Statistical PKPD modeling & Pharmacometrics	Monolix *	Non-linear mixed effects modeling, Population PKPD, Parameter estimation
Systems Pharmacology & Systems Biology	MLXplore *	Links with Monolix Complex systems exploration, within/between patient variability, dosing

* Lixoft

Design of Monoclonal Antibodies for the Treatment of Dengue

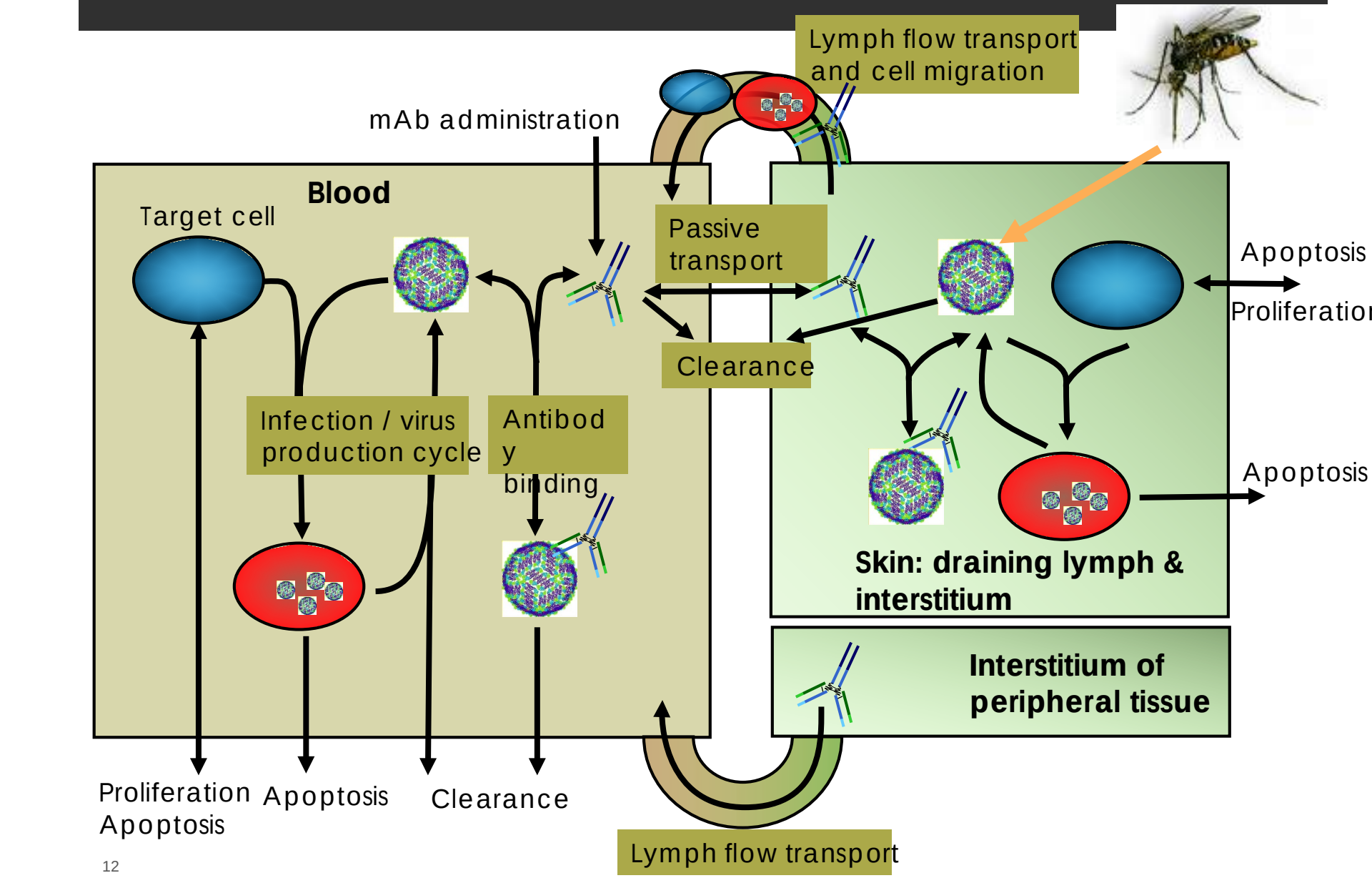


Infection through skin | Incubation **2-10 days** | Active Period **4-5 days** | Convalescence **slow recovery**

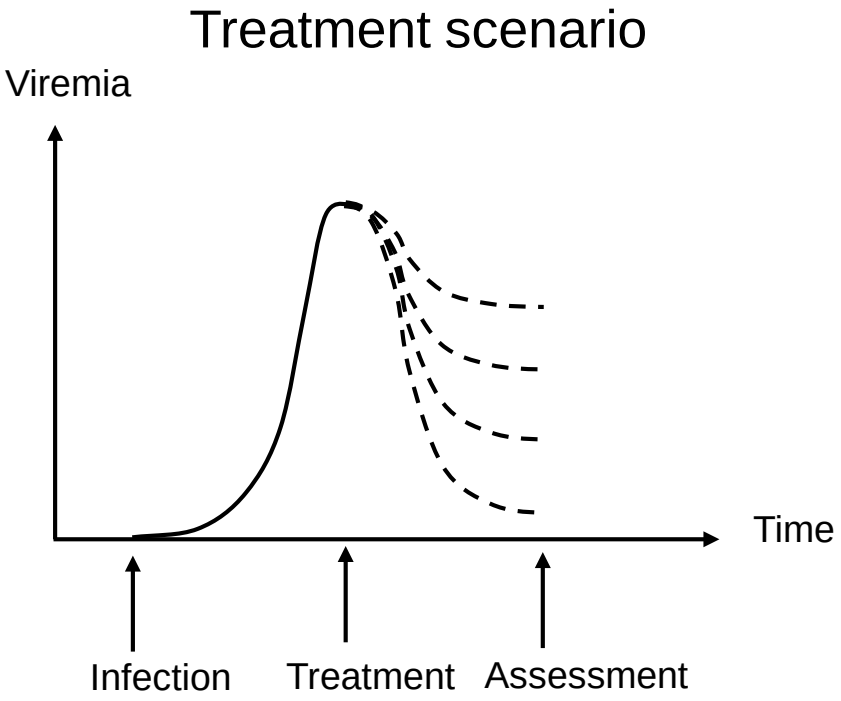
Therapy goal:
10 fold inhibition of virus levels

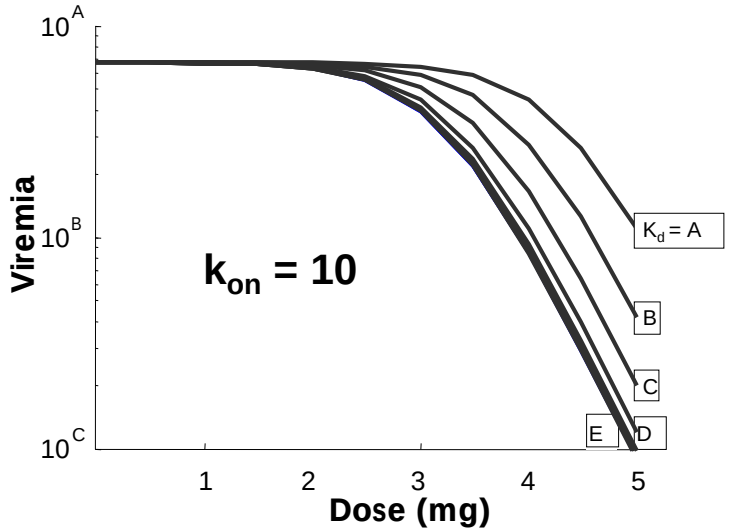
Hemorrhagic fever
Increase capillary permeability
Severe bleeding
Lethal complications

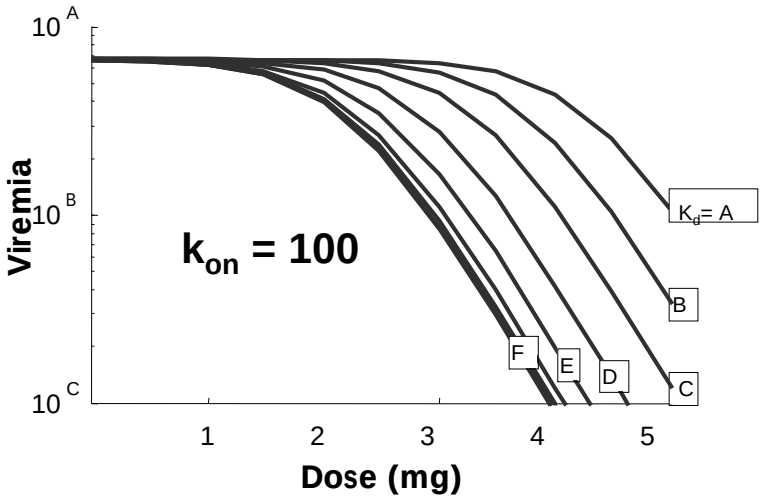
Dengue Virus - antibody model



k_{on} Has Profound Impact on Viremia Suppression



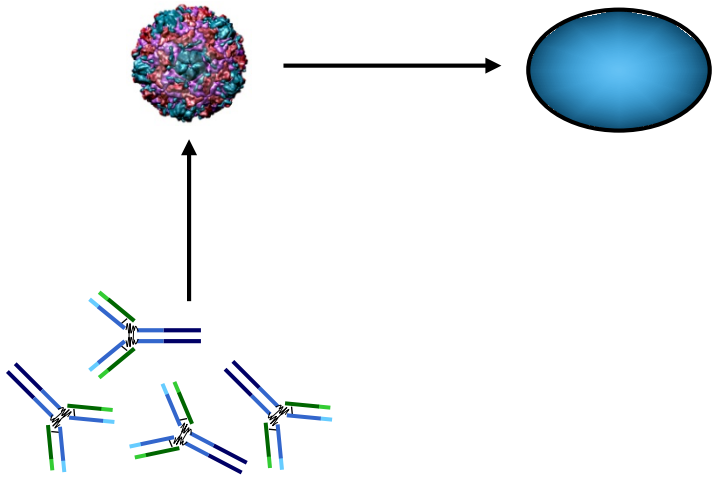




Data from Palivizumab, an anti-Respiratory Syncytial Virus antibody, support key role of k_{on}

	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	K_d (nM)	IC50 (nM)
Palivizumab	1.3	35	3.4	3
Variant 1	5.5	0.2	0.03	0.07
Variant 2	4.7	2.9	0.6	0.02

4 fold improvement in k_{on} leads to a ~20 improvement in potency regardless of k_{off} *



Explanation:
Once the virus infects a cell its gone
→ > 150 mAbs must bind before cell entry
→ k_{on} determines the ability to bind fast

Short virus life time ($T_{1/2}$= 2 h)
→ virus needs not be bound > 6 hours
→ k_{off} determines how long mAb stays bound

* **H. Wu, et.al. *Journal of Molecular Biology* 350 (1):126-144, 2005.**

Vision for Systems Pharmacology

- Engineering of biomolecules to obtain
  better drugs for patients and
  better differentiation from competitors:
  - **Design** for superior PKPD properties
  - **Select and validate** best candidates
  - **Advise on experimental and animal-to-human translation strategy**
- What needs to be in place to get there
  - Recognize that we are bad at discovery but better at Engineering
  - Need quality and execution speed in the modeling efforts by using
    - Commercial computation tools
    - Curated models with commercial quality
    - Data across corporate organization and from literature

Challenges executing systems pharmacology vision

- **Science**:
  - How quickly can we scale up systems pharmacology modeling science?
  - Collect the right data to understand the system, especially in human?
  - How can we capture and show value in decision making?

- **Corporate organization**:
  - How can we get senior leadership support and organizational position?
  - Increase cross-project team strategic thinking on data and analysis

- **People**:
  - Academic programs are not training Systems Pharmacology scientists
  - Most educational programs do not integrate the Engineering with the Pharmacology-molecular, genetic, whole organ
  - Drug Development science not taught systematically in academia
  - Much industry training “on the job” using past education as starting point

Two Examples: Diabetes and Cardiac Toxicity

- Highly relevant medical problems, critical for drug development
- Well researched and science is established
- Amenable for modeling: physics, feedback loops
- Large number of available mathematical models:
  - Electrophysiology:
    CELLML.org: 264 models
  - Diabetes:
    EMBL BioModels Database: 1030 models

Contact

machacek@lyo-x.com