20th International Symposium on Microsomes and Drug Oxidations

SYSTEMS PHARMACOLOGY:
An Industry Perspective

LYO-X GmbH

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

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

- Relevance of problem & value
- Scientific question
- Implementation time
- Quality & Risk
- Available computational tools
- Systems Pharmacology
# Systems Pharmacology for Drug Development

Merging advantages of Systems Biology and Pharmacometrics

<table>
<thead>
<tr>
<th></th>
<th>Systems Biology</th>
<th>Systems Pharmacology</th>
<th>Pharmacometrics</th>
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</thead>
</table>
| **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 | Successfully 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

Clearance
- Receptor mediated
  - Catabolic

Production
- Release

Target kinetics:
- Soluble molecules
- Receptors
- Molecular meshwork
- Cells

Clearance
- Secretion
- Storage
- Ligand interaction

Binding modality

• Time
• Space, tissues
• Variability

Effect
Enabling Systems Pharmacology: Integrated computational tools

<table>
<thead>
<tr>
<th>Domain</th>
<th>Computational Tool</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical PKPD modeling &amp; Pharmacometrics</td>
<td>Monolix *</td>
<td>Non-linear mixed effects modeling, Population PKPD, Parameter estimation</td>
</tr>
<tr>
<td>Systems Pharmacology &amp; Systems Biology</td>
<td>MLXplore *</td>
<td>Links with Monolix, Complex systems exploration, within/between patient variability, dosing</td>
</tr>
</tbody>
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* 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

**Diagram:**
- Skin → Infection → Dendritic cells → Lymphocytes → Draining lymph node → Blood
Dengue Virus - antibody model

- mAb administration
- Blood
- Target cell
- Infection / virus production cycle
- Antibody binding
- Clearance
- Lymph flow transport
- Skin: draining lymph & interstitium
- Interstitium of peripheral tissue
- Proliferation
- Apoptosis
- Lymph flow transport and cell migration
$k_{on}$ Has Profound Impact on Viremia Suppression

Treatment scenario

Infection → Treatment → Assessment

Viremia

Time

$k_{on} = 10$

$k_{on} = 100$

Dose (mg)

Viremia

$K_d = A$

$K_d = A$

$B$

$B$

$C$

$C$

$D$

$D$

$E$

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

<table>
<thead>
<tr>
<th></th>
<th>$k_{on}$ (M$^{-1}$s$^{-1}$)</th>
<th>$k_{off}$ (s$^{-1}$)</th>
<th>$K_d$ (nM)</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palivizumab</td>
<td>1.3</td>
<td>35</td>
<td>3.4</td>
<td>3</td>
</tr>
<tr>
<td>Variant 1</td>
<td>5.5</td>
<td>0.2</td>
<td>0.03</td>
<td>0.07</td>
</tr>
<tr>
<td>Variant 2</td>
<td>4.7</td>
<td>2.9</td>
<td>0.6</td>
<td>0.02</td>
</tr>
</tbody>
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4 fold improvement in $k_{on}$ leads to a ~20 improvement in potency regardless of $k_{off} *$

Explanation:
Once the virus infects a cell it's 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

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
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
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