Challenges and Needs for Systems Pharmacology in the Pharma Industry

Dr. Lourdes Cucurull-Sanchez
Computational Biology, R&D
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The main problem in the pharmaceutical industry

Large attrition rates...

... for 3 main reasons

Back to basics - what does Pharma produce?
The key and recurrent question along the pipeline
Systems evolution in Pharma pipeline

- **Target - Drug**
  - Pathway - Tissues
  - PKPD - Organism
  - Disease - Population

- **Exploratory**
  - In-vitro Binding Assays
  - In-vitro Functional Assays
  - Cell lines
  - Ex-vivo tissues
  - High/Low Throughput

- **Development**
  - In-vivo models
  - Healthy volunteers
  - Patients

- **Clinical**
Birth and evolution of a Systems Pharmacology Model

Qualitative pathway map (Static Network)

Kinetics

Quantitative pathway map (Dynamic Network)

Response biomarkers

Efficacy mathematical model

Physiology / PK

Genetic variants

Variant response models ('Personalised' Response)

Mechanistic PK/PD model(s)
How much target inhibition is needed to suppress inflammatory signal?

How variable are target receptor levels?

How does Teff proliferation affect tissue damage?

\[ \alpha_E > 0 - 2 \]

\[ \alpha_E = 0 \]

What goes on behind the scenes?

\[
\frac{d([CD3_{endosome} \cdot V_{\text{unnamed}}])}{dt} = + V_{\text{unnamed}} \left( [CD3_{surface}] \cdot (k_{CD3_{endocytosis}} + k_{CD3_{PKC_{endocytosis}}} \cdot [PKC]) \right) - V_{\text{unnamed}} \left( k_{CD3_{recycling}} \cdot [CD3_{endosome}] \right) - V_{\text{unnamed}} \left( k_{CD3_{deg}} \cdot [CD3_{endosome}] \right) + V_{\text{unnamed}} \left( k_{CD3_{syn}} \cdot [source] \right)
\]

\[
\frac{d([CD3_{surface} \cdot V_{\text{unnamed}}])}{dt} = - V_{\text{unnamed}} \left( [CD3_{surface}] \cdot (k_{CD3_{endocytosis}} + k_{CD3_{PKC_{endocytosis}}} \cdot [PKC]) \right) + V_{\text{unnamed}} \left( k_{CD3_{recycling}} \cdot [CD3_{endosome}] \right)
\]

CD3_Surface_Concentration_Percentage = \frac{100 \cdot [CD3_{surface}]}{[CD3_{surface}_0]}

Systems Pharmacology requirements

Model building (information)

- Network topology
- Compartment volumes
- Species (Nodes) steady state levels
- Processes (Edges) kinetic equations and parameters
- Biomarkers relevant to the disease
- Physiological parameters
- Drug pharmacokinetics
- Responses in clinical studies

Model analysis (tools)

- Time-course simulations
- Scan simulations
- Parameter fitting
- Sensitivity analysis
- Steady-state analysis
- Metabolic control analysis
What’s available at the moment?

- **Standard languages**
  - SBML, CellML
  - BioPAX (SBPAX), SBGN...

- **Software**
  - **Analysis**: COPASI, SimBiology (MATLAB), DBSolve, Berkeley Madonna...
  - **Visualisation**: CellDesigner, Cytoscape...

- **Databases**
  - **BioModels**: [http://www.ebi.ac.uk/biomodels-main/](http://www.ebi.ac.uk/biomodels-main/)
  - Ingenuity IPA, GeneGo...

- **Publications**
  - **Systems Biology**: BMC systems biology, Molecular systems biology...
  - **Biology**: Journal of theoretical biology, Biophysical journal, PloS one...
  - **Pharmaceutical**: Journal of pharmacokinetics and pharmacodynamics, Journal of clinical pharmacology...

- **Organisations**
  - SBML.org, BBSRC (UK), EBI-EMBL (Europe)
Which are the key challenges?

- Sparse case studies applied to pharmaceutical endpoints
- Incomplete databases of kinetic models
- Integration of systems from within cell up to full human population
- Building trust on methodology
- Unique experts background: mathematics, biology, pharmacology, statistics, medicine...
Systems Pharmacology is gaining momentum.

**Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms**

*An NIH White Paper by the QSP Workshop Group – October, 2011*

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**CPT: Pharmacometrics & Systems Pharmacology**

Moving towards quantitative and systems pharmacology

The NIH has released a white paper on the value of ‘Quantitative and Systems Pharmacology’, even as universities start stepping up to the challenge.

**The lowdown:** A 48-page report for the US National Institutes of Health (NIH) has called for the development of Quantitative and Systems Pharmacology (QSP), a merger of systems biology and pharmacology that aims to develop and combine mathematical, computational and experimental methods towards understanding how drugs modulate physiological-based models.

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CPT: Pharmacometrics and Systems Pharmacology

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Open Access: A New Model in Pharmacological Science

**TUTORIAL**

Basic Concepts in Pop and Model-Based Drug Development

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**About The Systems Pharmacology Group**

The Systems Pharmacology Group has been set up to bridge the activities between the Centre for Applied Pharmacokinetic Research (CAPKR) and Manchester Centre for Integrative Systems Biology (MCSB). CAPKR is part of the School of Pharmacy and Pharmaceutical Sciences which is a premier academic centre for pharmacokinetic research in Europe. Work at this centre extends from basic studies of transport and metabolism to clinical application in drug development.
The take home message...

If you see some value in Systems Pharmacology, and can help this discipline to grow... go for it!
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Questions