Toward Quantitative Modeling of Toxicity Pathways

Richard Brennan
Sanofi
Waltham, MA

richard.brennan@sanofi.com
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- Richard Brennan is a former employee and shareholder of Thomson Reuters – a provider of systems biology software and services.
Outline

● Systems Toxicology & Applications in Pharmaceutical R&D

● AOPs and Pathways of Toxicity (PoT) as Mechanistic Descriptors of Toxicological Responses to Pharmacologic Agents

● Development of Quantitative Toxicity Pathway Models
  ● Correlative → Causal → Qualitative → Quantitative understanding and prediction of AE
  ● Constructing hypothetical PoT
  ● Systems Pharmacology Modeling adapted to PoT
  ● Challenges and Perspectives
What is (Quantitative) Systems Toxicology?

Sturla et al.  

Systems Toxicology is aimed at decoding the toxicological blueprint of active substances that interact with living systems. It resides at the intersection of Systems Biology with Toxicology and Chemistry. It integrates classic toxicology approaches with network models and quantitative measurements of molecular and functional changes occurring across multiple levels of biological organization.
The Potential

Provide framework to integrate knowledge from literature, competitors, preclinical data

Provide target safety profile with qualitative assessment of desired and undesired effects

Predict safety issues by systems modeling based on in silico and in vitro activity profiles

Predict clinical safety based on animal in vitro/in vivo and human in-vitro to support candidate selection & trial design

Provide mechanistic insights and risk assessment of clinical safety signals

Extrapolate clinical risk assessment to broader populations, disease states (e.g. healthy volunteers vs. compromised liver function)
Pathway and Network Analysis Supports Target Safety Assessment

GO Biological Processes

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1-Step Transcriptional Regulatory Network from Target Indicates Cell Cycle Effects Likely

Potential for toxicity to hematopoietic and high turnover epithelial tissues

(Expanding to 2-step network gives similar pathology result with higher representation of transcriptional processes)
Off-Target inhibition has the potential to increase genome instability, therefore target selectivity is desirable. Off-Target activity may show as positive responses in genetox assays (micronucleus, chromosomal aberration, SCE, Comet)

Off-Target Autoexpand Network. Proteins associated with GO Biological Process “Response to DNA Damage Stimulus” highlighted (p<1.1x10e-4)

Off-Target physically interacts with RAD9 and increases its activity
Prediction of Off-Target Activities & Liabilities

Integrated safety profiling (Slink)

- For 6 out of 16 categories, predictions reach precision levels of 60% under 10-fold cross-validation.

Tiered application strategy: Computational models for numerous off-target interactions allow for systematic prediction of drug-target interactions. Target engagement in adverse pathways can be analyzed with pathway databases, supporting the toxicity risk assessment and mode-of-toxicity evaluation of drugs.

Biological network analysis

Predicted target inhibition

Network relationships:
- Enhances an effect
- Inhibits an effect
- Inconsistent literature findings
- Any effect

AchE: Airway obstruction, behavioural effects
CHRM1: ventricular tachycardia, constriction of bronchia

Findings: Cardiotoxicity observed at mid and high dose, @10 mg/kg mice showing severe dyspnea, tachycardia and trembling, mortality at high dose

Consistent with predicted effects
Multi-Scale Computational Models
DILIsym

Mitochondrial dysfunction

Cellular life-cycle

Drug distribution & metabolism

Patient variability (SimPops™)

Kuepfer 2010, Molecular Systems Biology

Institute for Drug Safety Sciences
DILIsym Modeling Applied to Understand Clinical AE

- Potential for DDI with clinical compound and concomitant APAP use
  - Clinical ↑ALT observed association with APAP usage
  - DILIsym team was contracted to model the potential interaction
    - Inputs were mitochondrial functional data, other biochemical parameters, drug and metabolite PK, clinical trial data
- Results indicate low risk of hepatotoxicity with drug alone
- Low potential for Drug-APAP interaction in healthy subjects, but increased potential for ↑ALT with low body weight and nutritional deficits
- Likelihood of severe liver damage is extremely small
- DILIsym team trained two Sanofi scientists as part of the project
AOPs and Toxicity Pathways

Sturla et al.

Gutsel and Russell
"A molecular definition of cellular processes shown to mediate adverse outcomes of toxicants"

Kleensang et al, ALTEX. 2014;31(1):53-61

Hamon et al. BMC Systems Biology 2014, 8:76
Causal Biological Network Modeling

1. A Knowledge Assembly Model (KAM), a large network of causal relationships, is assembled from scientific findings.

2. HYP networks are derived from the KAM.

3. Differential measurements are mapped to the HYPs.

4. Significance statistics are calculated to evaluate and prioritize HYPs as explanations for the data.

Scientific findings (literature, experiments, etc.)

Data set of differential measurements

Catlett et al. BMC Bioinformatics 2013, 14:340
Summary Findings

- Target was shown to contribute to the generation of a pro-inflammatory macrophage cytokine profile
- Target expression was shown to increase upon T cell activation and B cell activation
- Target expressing were shown to be prominent in inflamed tissues from various human inflammatory autoimmune diseases
- Taken together, these results provide evidence for a previously unknown role for Target in inflammation.

Existing Patent Indicated Potential of Target for Inflammatory Disease Indications

Trace Pathways algorithm used to link Target to cytokines.

Expression data from autoimmune inflammatory disorder overlaid
Big Data Initiative Opportunity Area: Predictive Toxicology
Mechanisms of Adverse Pharmacological Response (MAPR)

Description

- On-and off-target pharmacology of drugs may result in unintended adverse effects, often poorly understood. Understanding these adverse effects is critical to successful prediction and monitoring of AE's for de-risking Sanofi R&D programs.
- Mapping “Pathways of toxicity” will enable prediction of adverse effects from compound activity profiles and reveal biomarkers of AE or of impact on causal mechanistic pathways.
- A pilot PoC project, DART-MAPR, will expand on our existing computational toxicology modeling capabilities with systems approaches to better understand developmental and reproductive toxicity.
- We will build a library of mechanistic “Pathways of Toxicity” for DART outcomes. This will improve risk evaluation in discovery projects where DART is a particular area of concern.
- We will build-out additional endpoints following high-priority existing needs.
- We will develop tools & process for new Pathways of Toxicity generation to support arising target or project issues.

Estimated duration
4-6 months (PoC)

Application of finding

1. Support projects facing putative mechanism-based DART concerns (Improve risk/benefit analyses) through:
   - Better understanding of mechanisms of pharmacology-driven DART in discovery programs
   - Identification of DART biomarkers
   - Enabling modeling and simulation of DART mechanisms

2. Support identification and validation of targets by:
   - Improving AE prediction based on target profiles (in silico and/or in vitro)
   - Enabling modeling and simulation of AE mechanisms

Target product/project
DART alerts in Discovery programs
Teratogenic mechanisms of medical drugs

Marleen M.H.J. van Gelder¹,4, Iris A.L.M. van Rooij¹, Richard K. Miller², Gerhard A. Zielhuis¹, Lolkje T.W. de Jong-van den Berg³, and Nel Roeleveld¹


- Folate Antagonism
- Neural Crest Cell Disruption
- Endocrine Disruption: Sex Hormones
- Oxidative Stress
- Vascular Disruption
- Specific Receptor- or Enzyme-mediated Teratogenesis
Dynamic Biological Network Modeling

Support Development Transition

Support Project initiation

**Systems Pharmacology Modeling**

**Target Credentialing & Drug Candidate Validation**

**Modeling**

**Simulation**

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**drug candidate**  
- Simulate and predict clinical effect of drug candidate based on human in-vitro data

**virtual drug**  
- Simulate and predict clinical effect of target modulation using virtual drug

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**System Knowledge** + **“Drug Profile”**

**Systems Pharmacology Model**

**Predicted Drug Effect**

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**(predicted) human PK**

human in-vitro*

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**SANOFI**
Leveraging Systems Pharmacology Experience

**PK model**

- **Subcutaneous Depot**
  - Fast release (formulation)
  - Slow release (precipitate)

- **Blood Plasma**
  - Insulin (Monomer)
  - Insulin (Precipitate)

- **KHSIf**
  - HSA-Insulin
  - HSA-Anti-Insulin

**Insulin Absorption Profile**

- $I_0$ [IU/mL]
- time [h]

**Insulin Receptor in Hepatocytes**
Koschorreck & Gilles 2008 [1]

**Insulin Receptor in Adipocytes**
Brännmark et al 2013 [2]

**Endogenous Glucose Production**

**Glucose Infusion Rate**

**Peripheral Glucose Uptake**

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SANOFI
Anaxomics Therapeutic Performance Mapping System (TPMS)

Step 1: Published Expert Knowledge
- Client Private Knowledge

Step 2: Ax Health DB
- Protein network

Step 3: Training and validation
- Mathematical model
  - Mathematical transformation to simulate behaviour

Step 4: Conclusions
- Mechanism of action
- New biomarkers
- Therapeutic targets
- Safety and Efficacy
- Drug repositioning
- Drug combinations
Quantitative Toxicity Pathway Models

Hamon et al. BMC Systems Biology 2014, 8:76

Systems biology modeling of omics data: effect of cyclosporine a on the Nrf2 pathway in human renal cells
Challenges

- With certain, mostly well-known exceptions, it is difficult to link target-based activity data to adverse outcomes
- Knowledge of “Pathways of Toxicity” is limited
- Biological networks are complex, robust, and often redundant, several “hits” may be needed within or across pathways
- Quantification of risk is difficult
  - Hazard identification is a start
  - Cross-functional skill sets needed (biology, toxicology, mathematics)
- Large amounts of diverse molecular data needed to support modeling efforts
  - Need for public-private consortia
- Core components of PoT will be redundant
  - Need for public repository of PoT to avoid “reinventing the wheel”
- Regulatory acceptance required for use in risk assessment
Innovative Medicines Initiative
QST Proposal

IMI2 6th Call For Proposals, August 6th 2015
Topic 1: Development of Quantitative System Toxicology (QST) approaches to improve the understanding of the safety of new medicines

- Collaborative proposal development (Abbvie, Eli Lilly, Sanofi, Servier, AstraZeneca, GSK, J&J, Orion)
- Scope: Develop QST models for drug-induced toxicity with the focus on four different organ systems: heart, liver, kidney and the gastrointestinal (GI)-immune system. Use this QST approach for the prediction of clinical toxicity using preclinical data
- Objective 1: Develop an open (for the consortium members), focused and sustainable knowledge database to build system toxicology models.
- Objective 2: Provide a clearer understanding of the translational confidence from non-clinical species to human
- Objective 3: Support key risk assessment decisions, such as safety margin, clinical monitoring and reversibility, using mechanistic and quantitative modelling.
- Objective 4: Provide improved methods for visualizing and analyzing complex high content data to support drug safety assessment
- Objective 5: Help inform regulatory decisions by providing evidence supporting the usefulness of QST modelling to support safety risk assessments
Developing QST at Sanofi
A Roadmap

**External**
- Engage with external efforts
  - Public & private consortia
  - Regulatory agency efforts
  - Academic labs

**Internal**
- Build resource knowledgebase
  - Key practitioners & KOLs
  - Existing and emerging models
- Educate & engage toxicologists & project teams
  - Contract and collaborative pilot projects

**Routine application to (appropriate) problems**
- Characterize strengths and weaknesses
- Adopt useful technologies (and people?)

**Build internal expertise**
- Cross-disciplinary training
- Integrate with existing M&S community
- Leverage external collaborations
Roadmap is More of a Network…

- Build resource knowledgebase
- Engage with external efforts

**BIG DATA Initiative**

**Build internal expertise**

**Assessment of therapeutic vs. AE potential, DART-MAPR**

**Discovery Projects**

- Contract pilot projects
- Educate & engage project teams
- Collaborative pilot projects

**Build internal expertise**

**Assessment of DILI and DDI risk**

**Clinical Development**

**Cross-training on DILIsym application**
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Anaxomics

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James Stevens (Eli Lilly)
IMI2 QST Team

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