Integrated Systems Approaches to Understand and Predict Cancer Treatment Related Adverse Drug Events

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Pharmacological Mechanism-Based Drug Safety Assessment and Prediction

DR Abernethy[1,2], J Woodcock[1,2] and LJ Lesko[1,2]

Advances in cheminformatics, bioinformatics, and pharmacology in the context of biological systems are now at a point that these tools can be applied to mechanism-based drug safety assessment and prediction. The development of such predictive tools at the US Food and Drug Administration (FDA) will complement ongoing efforts in drug safety that are focused on spontaneous adverse event reporting and active surveillance to monitor drug safety. This effort will require the active collaboration of scientists in the pharmaceutical industry, academe, and the National Institutes of Health, as well as those at the FDA to reach its full potential. Here, we describe the approaches and goals for the mechanism-based drug safety assessment and prediction program.

Systems Pharmacology to Predict Drug Toxicity: Integration Across Levels of Biological Organization*

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- Is it possible to identify off-target pharmacological effects of medicines *and* sensitive (or susceptible) patients to predict the probability of serious adverse events in advance?

- Can we construct computational models to generate mechanistic *and* testable biological hypotheses about adverse events – systems pharmacology?

- What types of nonclinical *and* clinical data, information, and analytical tools, are needed to build these models and would such data be shared among stakeholders?

Predicting Adverse Events -1

Goal: Identify potential mechanisms that can used to help decide clinical trial composition and post-marketing surveillance

Needed

Database integrating human interactome and drug target interactions

Identification of neighborhoods in the human interactome associated with adverse events (phenotypes)

Relationships between key nodes in the neighborhoods and cell physiology

Determination of quantitative relationship between drug-target interactions and cellular and tissue phenotypic events (enhanced pharmacodynamic models)

Association of genomic characteristics of susceptible population with enhanced pharmacodynamic models

Outcome: Risk/Benefit ratio for populations stratified on a genomic basis

Predicting Adverse Events -2

Goal Identify individual susceptibility to adverse events for a drug or a combination of drugs

Needed

General

• **Database integrating human interactome and drug target interactions**

• **Neighborhoods in the human interactome associated with adverse events**

•**Quantitative relationship between drug-target interaction and clinical phenotype**

Specific

• **Clinical observations of the individual**

• **Genomic makeup of the individual**

 Outcome: Risk/Benefit ratio for the individual patient

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Integrating information: challenges

External Information

Content

- Competitor compounds
- Mechanistic information

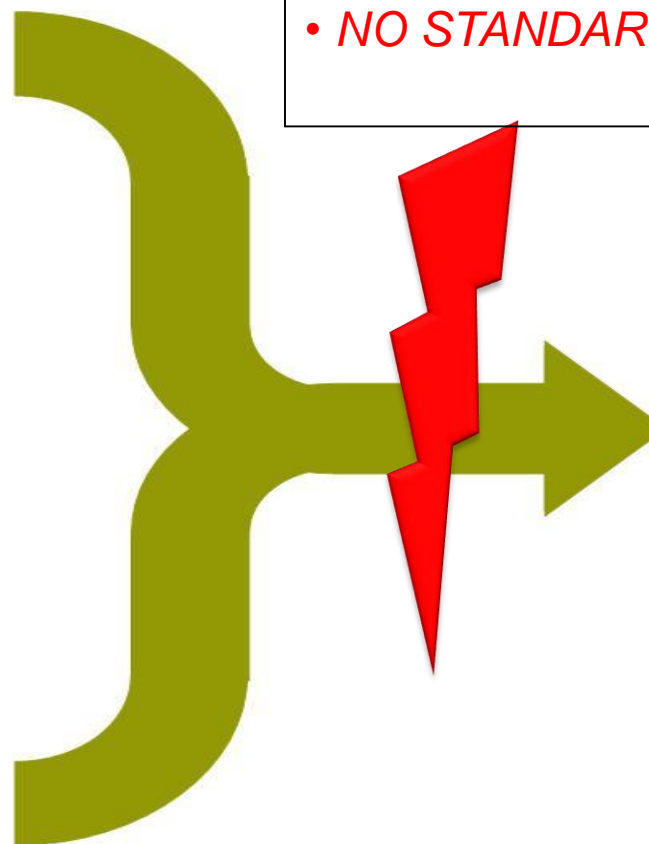Amount of information: Huge

"Dilution factor": High

- *Different sources*
- *Different vocabularies*
- *NO STANDARDS*

Integrated views of data

Internal Information

Content

- Proprietary compounds
- Screening information
- Clinical outcomes etc.

Amount of information: Large

"Dilution factor": Low

Mechanism-Based Search for Adverse Event Signals

to Compliment

Data-Mining Search for Adverse Event Signals

Goal—To Limit "False-Positive" Signals and Improve Detection of Real Signals

The Challenge

1. How do you make hypotheses about potential toxic events, when these have not yet been observed in the clinic or in models?

2. How can you distinguish between a drug effect, versus an underlying co-morbidity?

3. How can you link classes of drugs or mechanisms to classes of toxicities or to idiosyncratic AEs?

4. How do you go beyond the obvious and explicitly already known?

5. How can this become a standardized workflow?

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What are the pieces to be developed?

Systematic database for molecular toxic targets

Linkage of molecular toxic targets to organ-level toxicity

Linkage of molecular toxic targets to MedRA terms

Linkage of chemical systems biology and biological pathways databases

Examples of the utility of this approach

Moving forward – future direction

- Building an application suite that combines the heterogeneous data to help constructing the computational mechanistic system.

- The application suite to perform the generalizable tasks, not specific only to the TKI-induced cardiotoxicity question

- ***Using integrative translation framework and suite of tools***
  - ***Need communication protocol between layers of information***
  - ***Need multiple modeling tools that analyze data from different aspects (e.g. compound structure, interaction network)***
  - ***Need a framework that accommodates all of above***

Mechanism-based TKI Toxicity Prediction

Non QT Tyrosine Kinase Inhibitor Cardiotoxicity

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How Specific are Kinase Inhibitors?

A quantitative analysis of kinase inhibitor selectivity
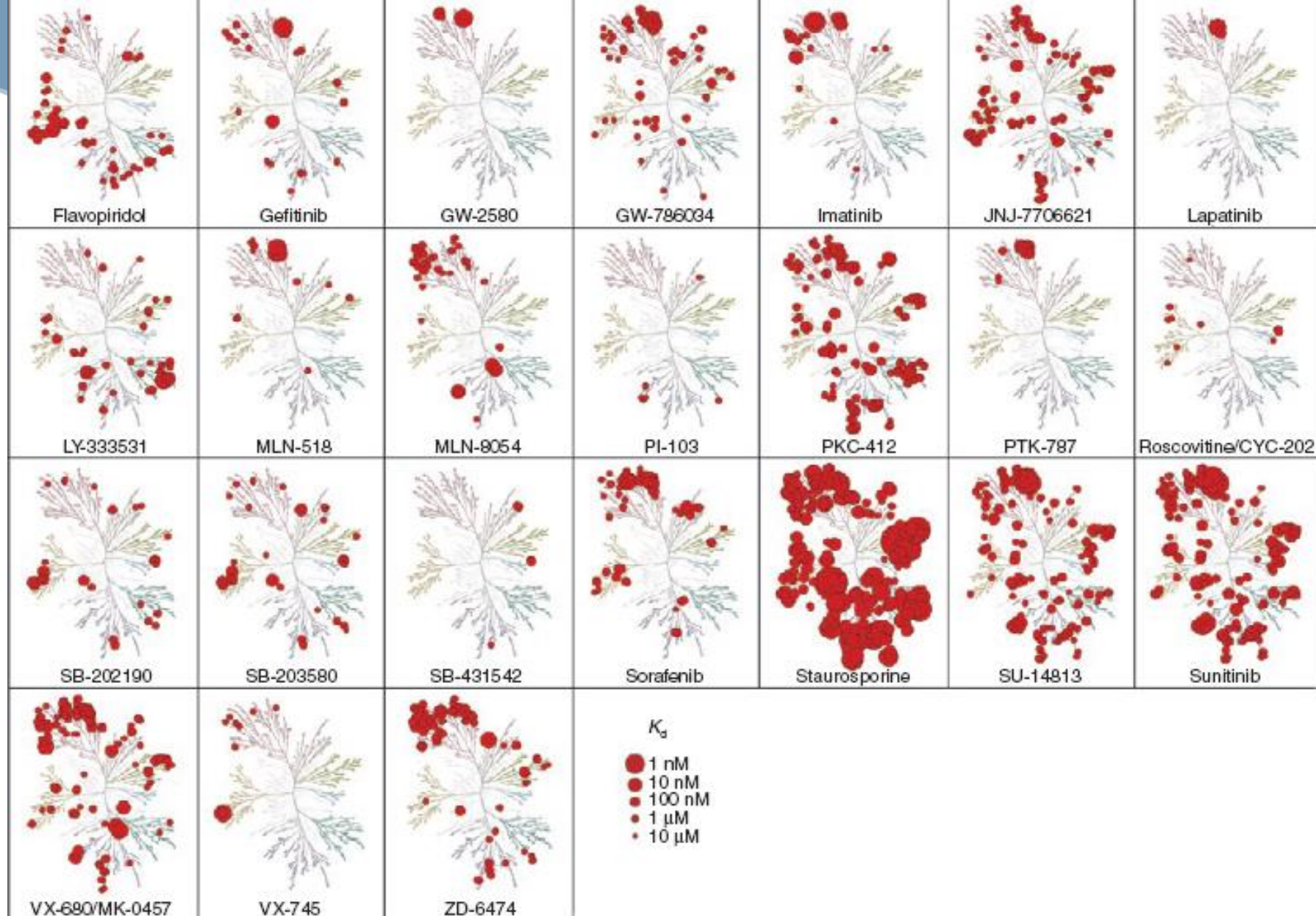Karaman et al, Nature Biotechnology 2008;26:127-132

Figure 1 Small molecule–kinase interaction maps for 38 kinase inhibitors. Kinases found to bind are marked with red circles, where larger circles indicate higher-affinity binding. Interactions with $K_d < 3\ \mu M$ are shown. Complete results can be found in **Supplementary Table 2** online. The data set is also available through an interactive website (http://www.ambitbio.com/technology/publications). The kinase dendrogram was adapted and is reproduced with permission from *Science* (http://www.sciencemag.org/) and Cell Signaling Technology, Inc. (http://www.cellsignal.com/).

Needs for an Expanded Ontology-Based Classification of Adverse Drug Reactions and Related Mechanisms

PE Zhichkin[1], BD Athey[2], MI Avigan[3] and DR Abernethy[1]

The growing significance of bioinformatics and systems biology in drug safety research requires a system of adverse-event classification that goes beyond a simple vocabulary. This opinion piece outlines the need for development of an ontology-based framework of describing adverse drug reactions (ADRs) and describes the potential applications for such a framework.

Building an ontology that creates the structure for linkage of data across different levels of biological complexity

Protein targets, biochemical pathways and biological processes are dependent on organ and cell types.
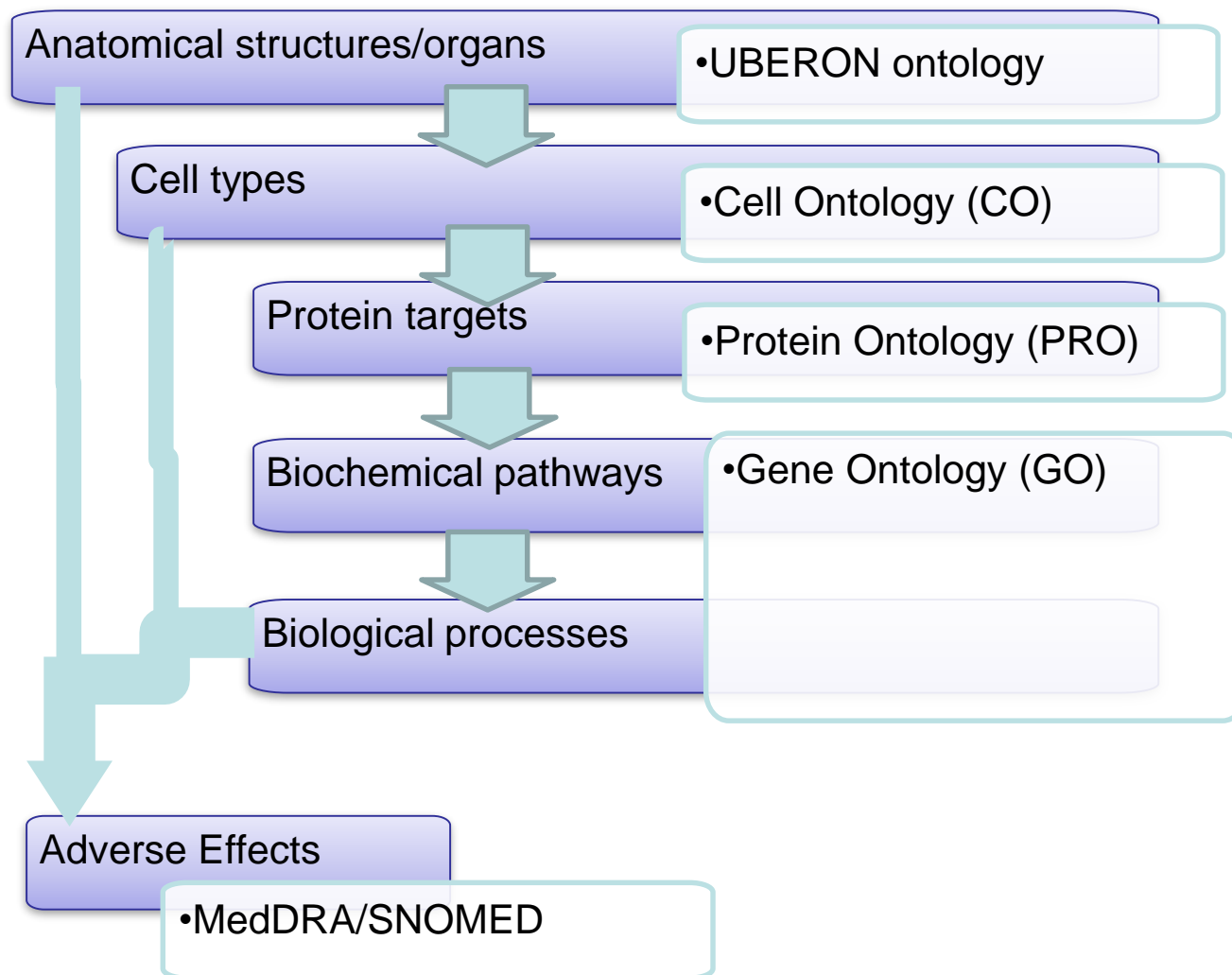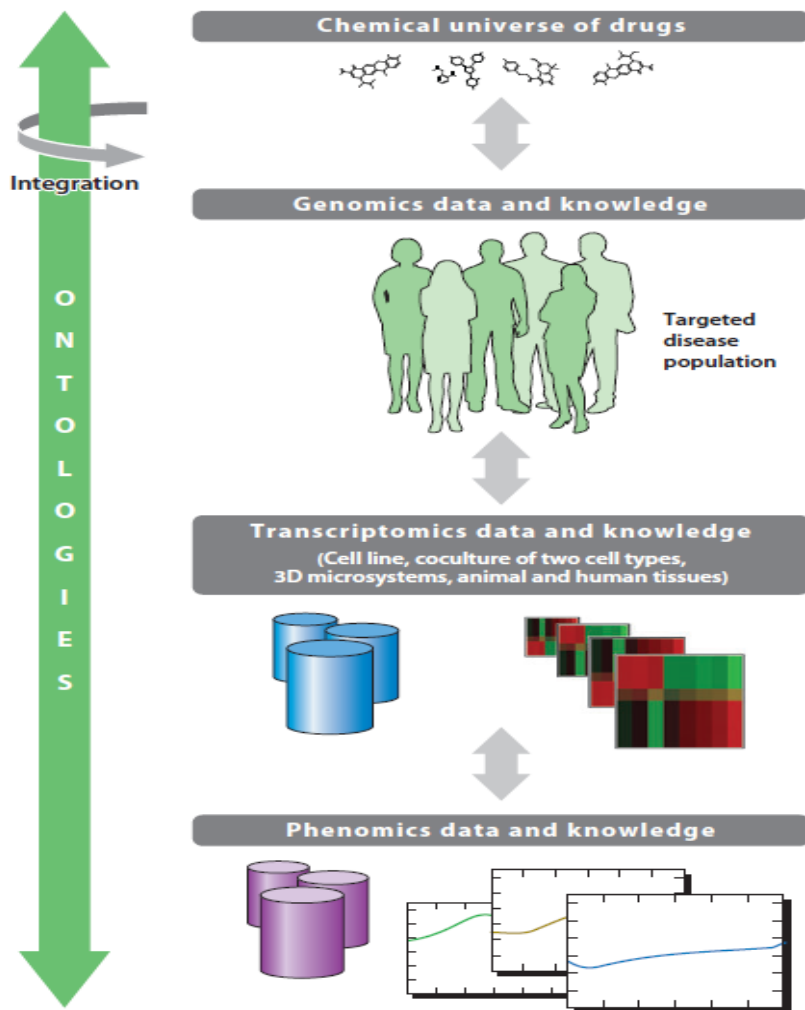
Jane P.F. Bai and Darrell R. Abernethy Annu. Rev. Pharmacol. Toxicol. 2013. 53:22.1–22.23

The Ontology of Adverse Events

- OAE 'adverse event':
    - = def. a OGMS: 'pathological bodily process' that occurs after a medical intervention.
    - Does not assume causality
    - 'causal adverse event' assumes causality

- >1,000 specific AE terms in OAE now, mapped to MedDRA terms

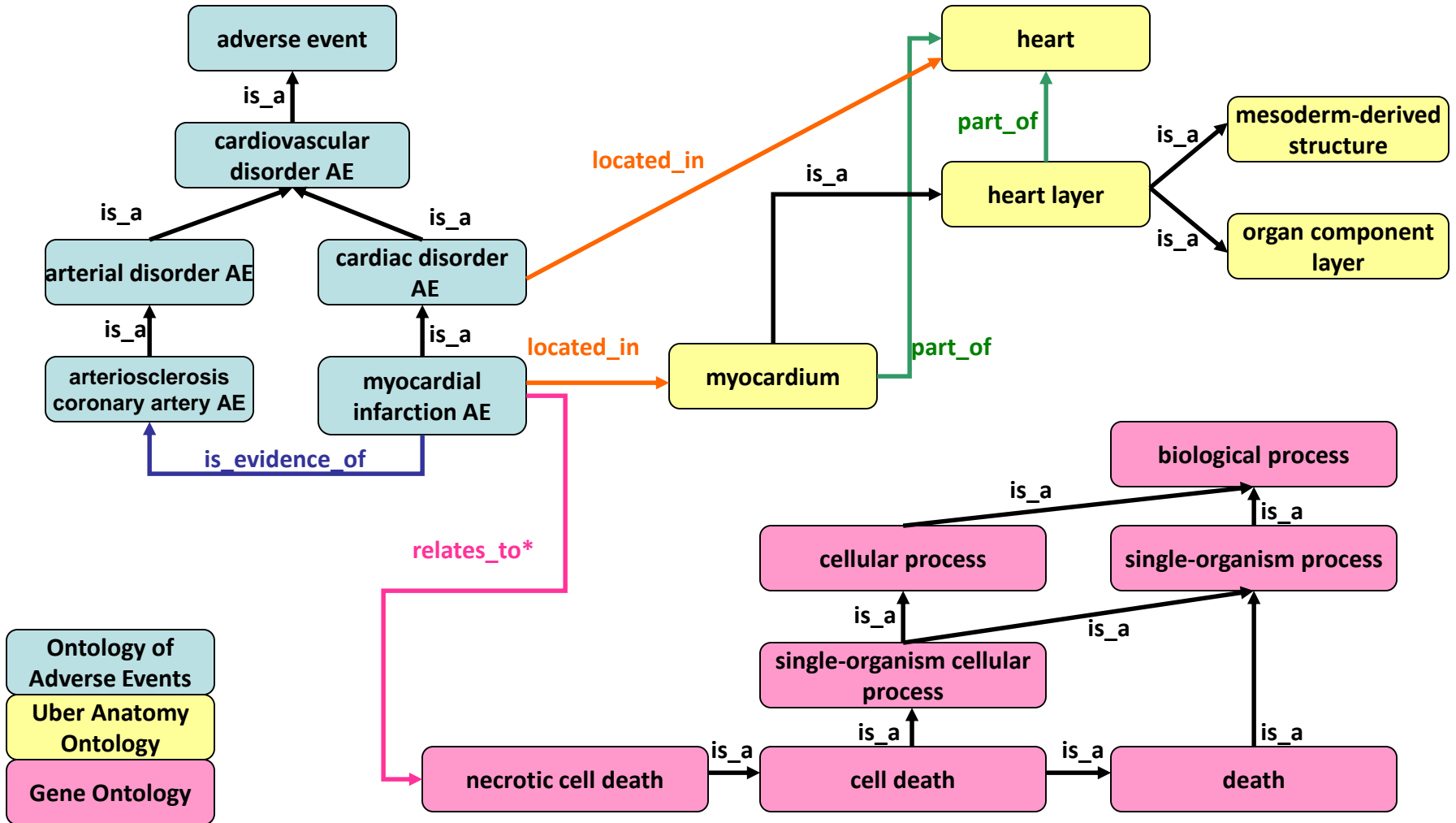- http://www.oae-ontology.org/

Why ONTOLOGY…

- Terminology standard

- Computational capability

- Knowledge transfer

- Reusability of concepts

- Knowledge discovery

Integration of knowledge
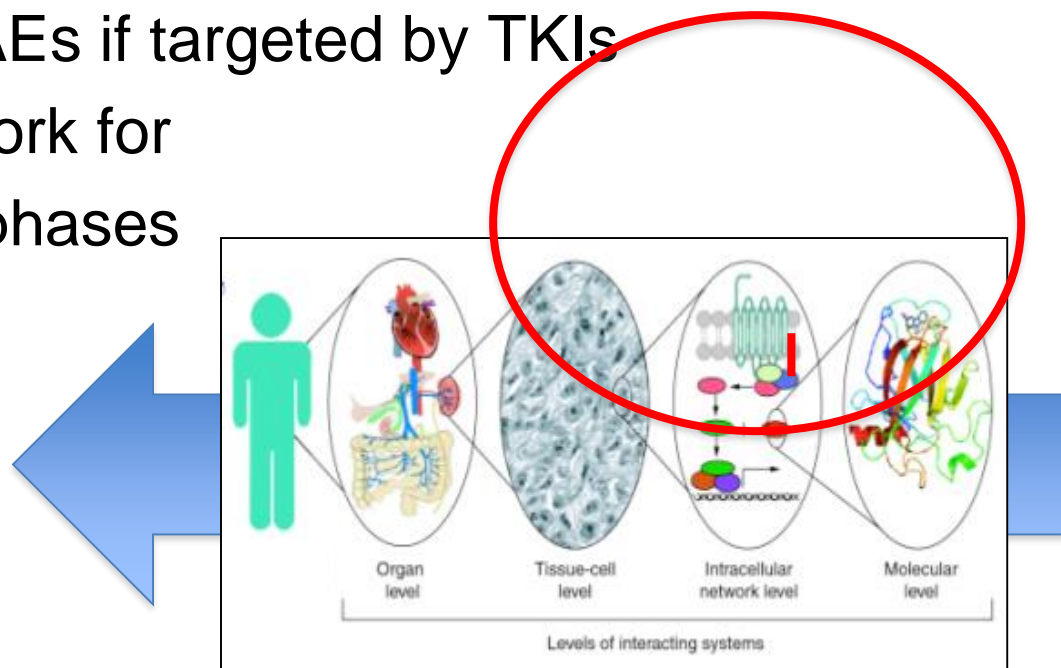
Connecting ontologies – the two levels of mapping
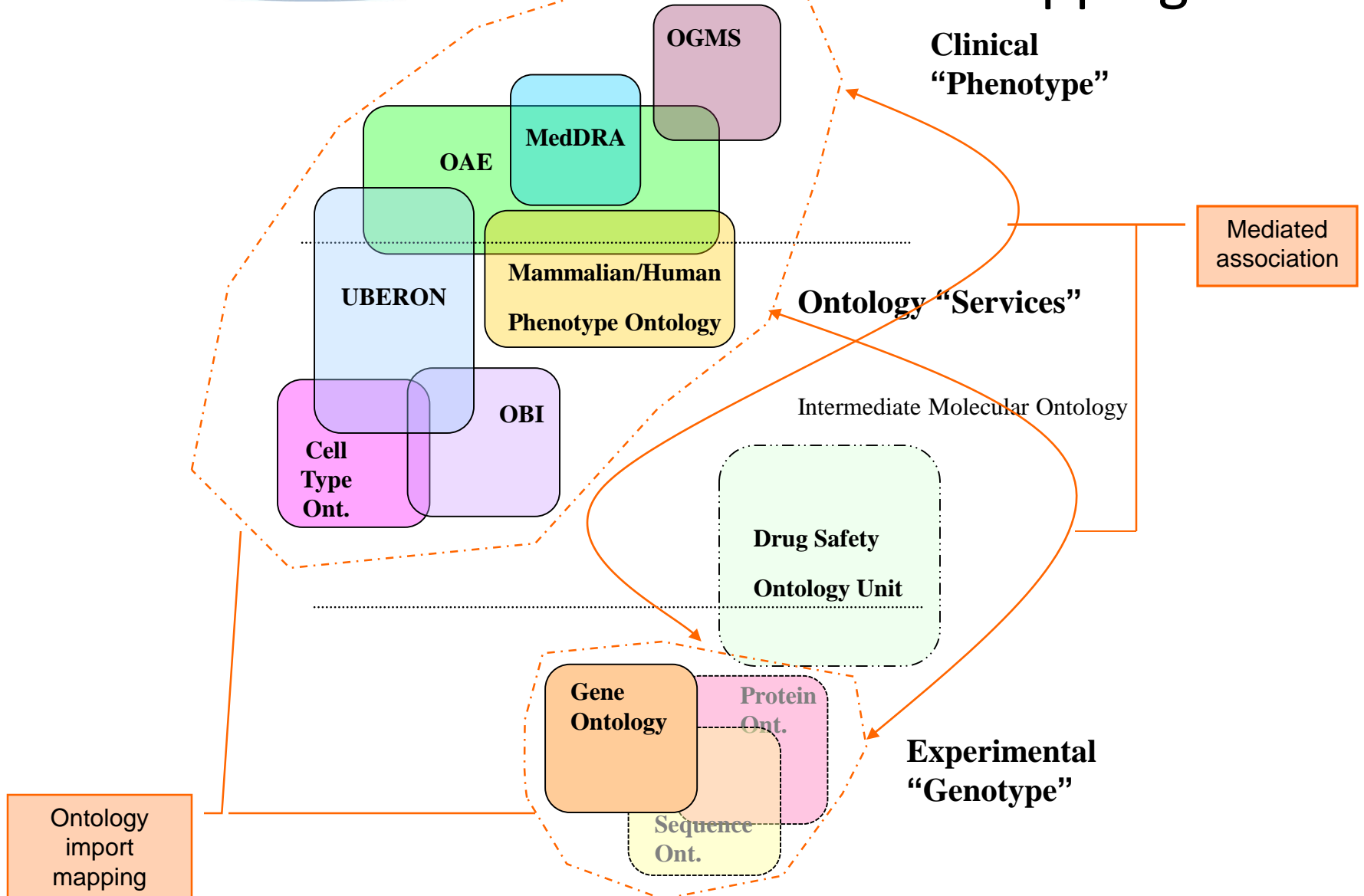
Sarntivijai et al., unpublished

Data Mining Activities

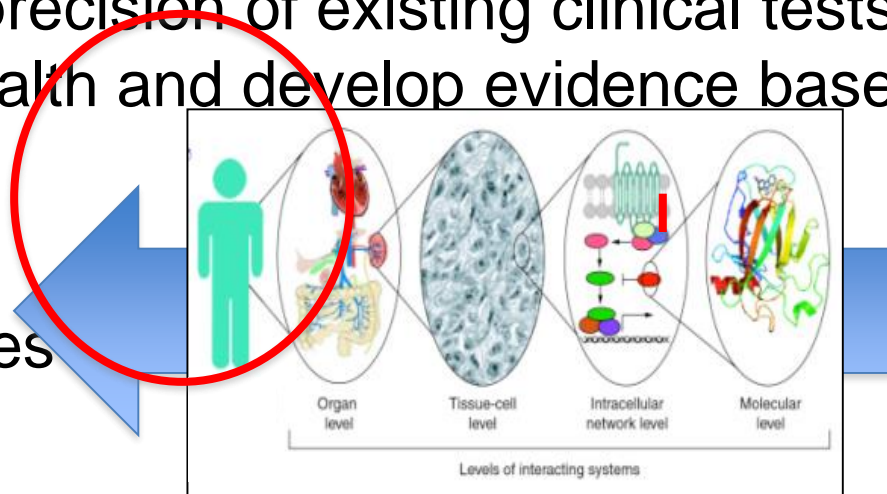## Work Stream 1. Assessing Preclinical Data

- Examining which kinases/combination of kinases may be involved in cellular signaling networks that could potentially lead to AEs if targeted by TKIs

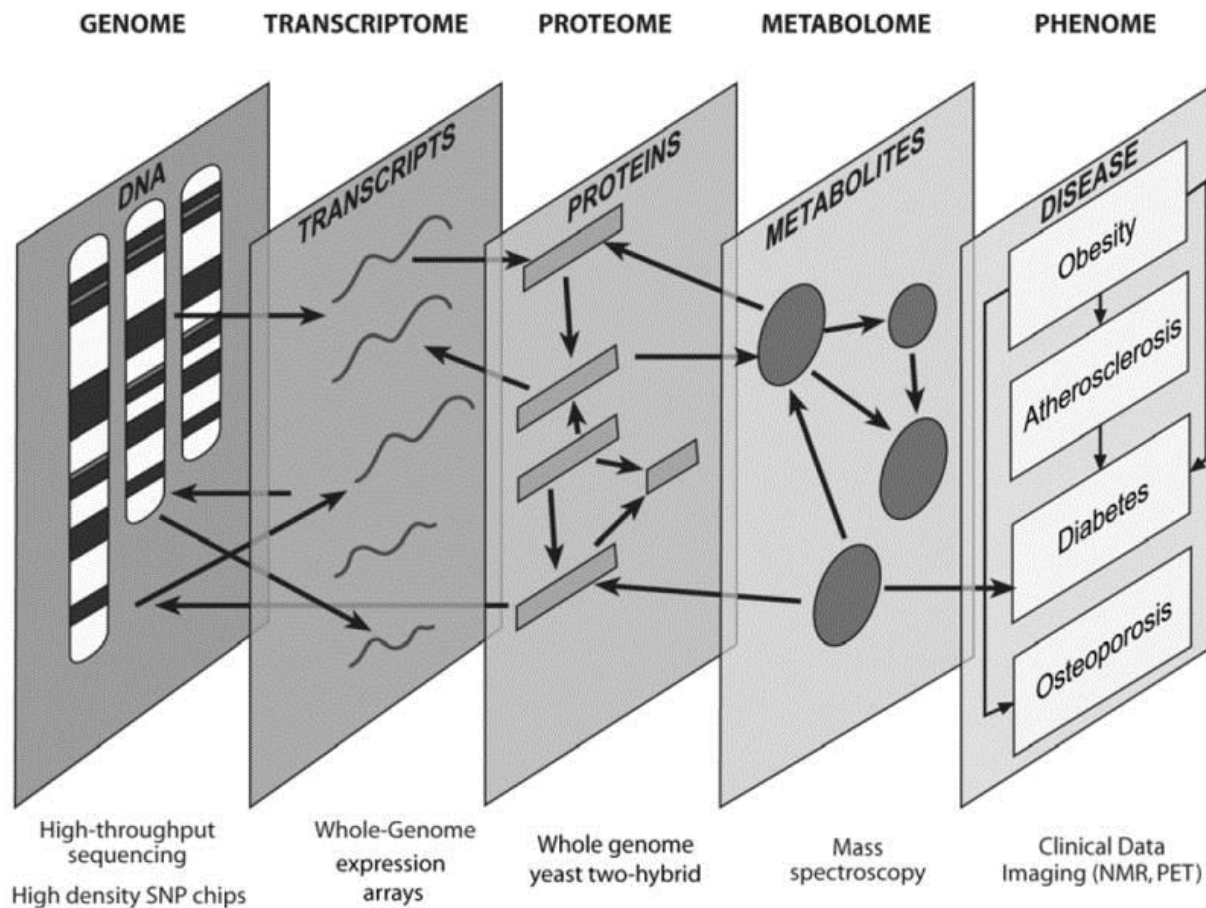- Molecular groundwork for modeling in future phases

Organ level | Tissue-cell level | Intracellular network level | Molecular level

Levels of interacting systems

Data Mining Activities

Work Stream 2. Assessing Clinical Data

- Determine what cardiac effects patients are experiencing

- Determine the incidence and define the severity of those cardiac AEs

- Examine patient variability and generate greater understanding of the propensity and risk factors for cardiotoxicity

- Examine accuracy and precision of existing clinical tests for assessing cardiac health and develop evidence base for best practices

- Clinical groundwork for modeling in future phases

Organ level   Tissue-cell level   Intracellular network level   Molecular level

Levels of interacting systems

Concept of tranSMART on data level

The Challenge…

- Lack of standardized definition of clinical phenotype
- Lack of robust definition of clinical phenotype of cardiotoxicity
- What terminology?
  - International Classification of Disease 9/10
  - Health Level 7
  - Common Terminology Criteria for Adverse Event
  - Systematized Nomenclature of Medicine Clinical Terms
  - MedDRA

The vision of Drug Safety Data Warehouse (DSDW)
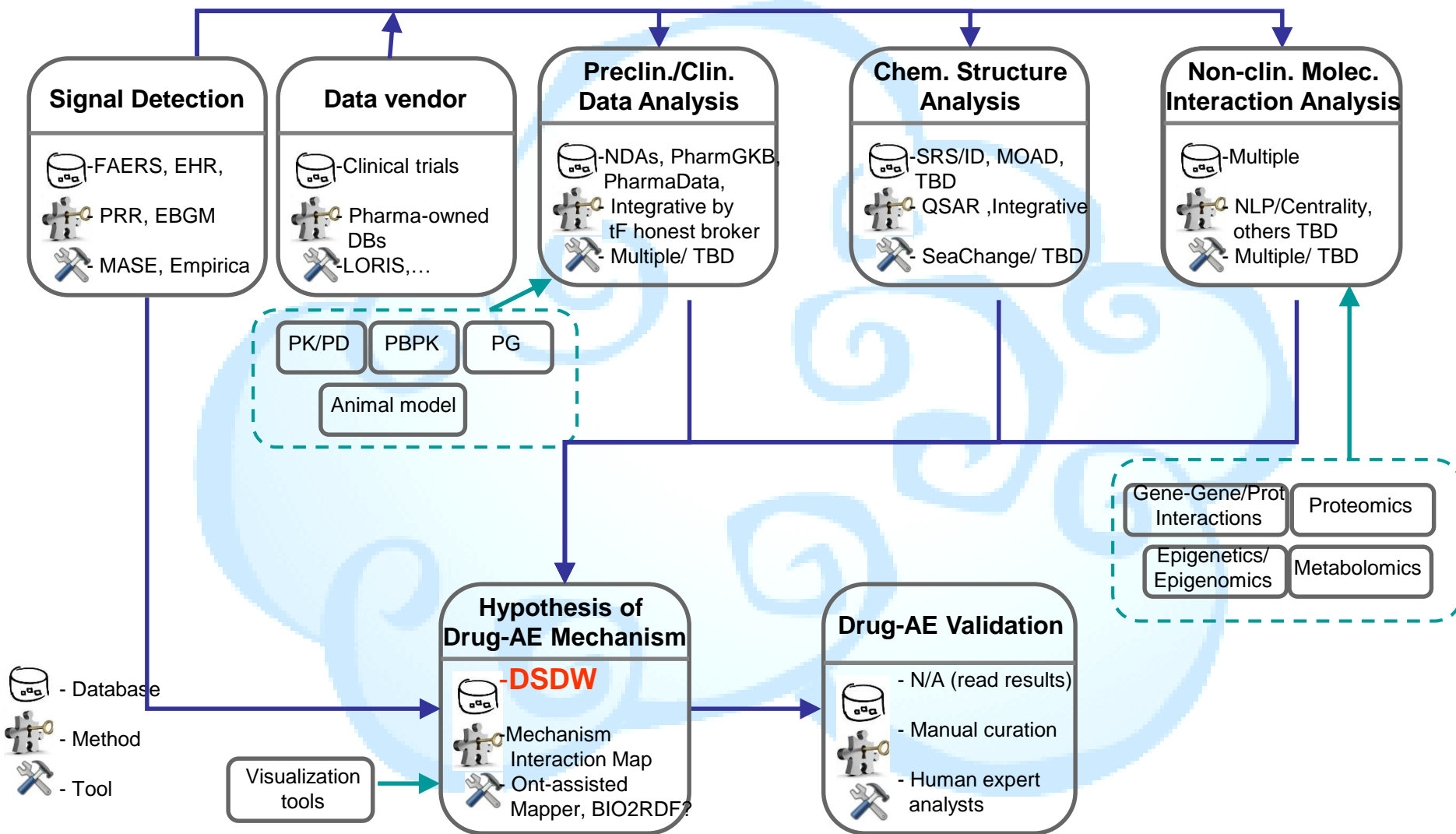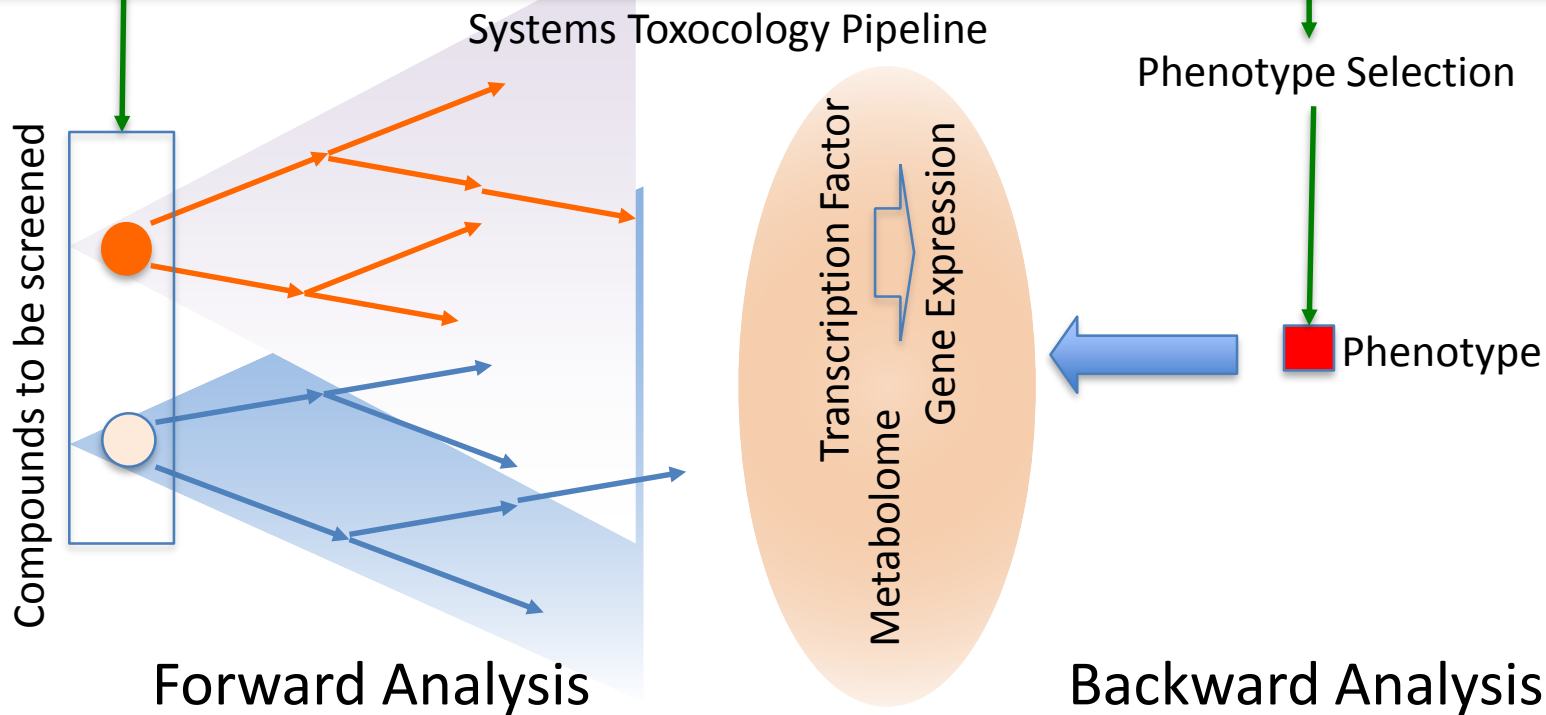
Stages of Adverse Event Progression

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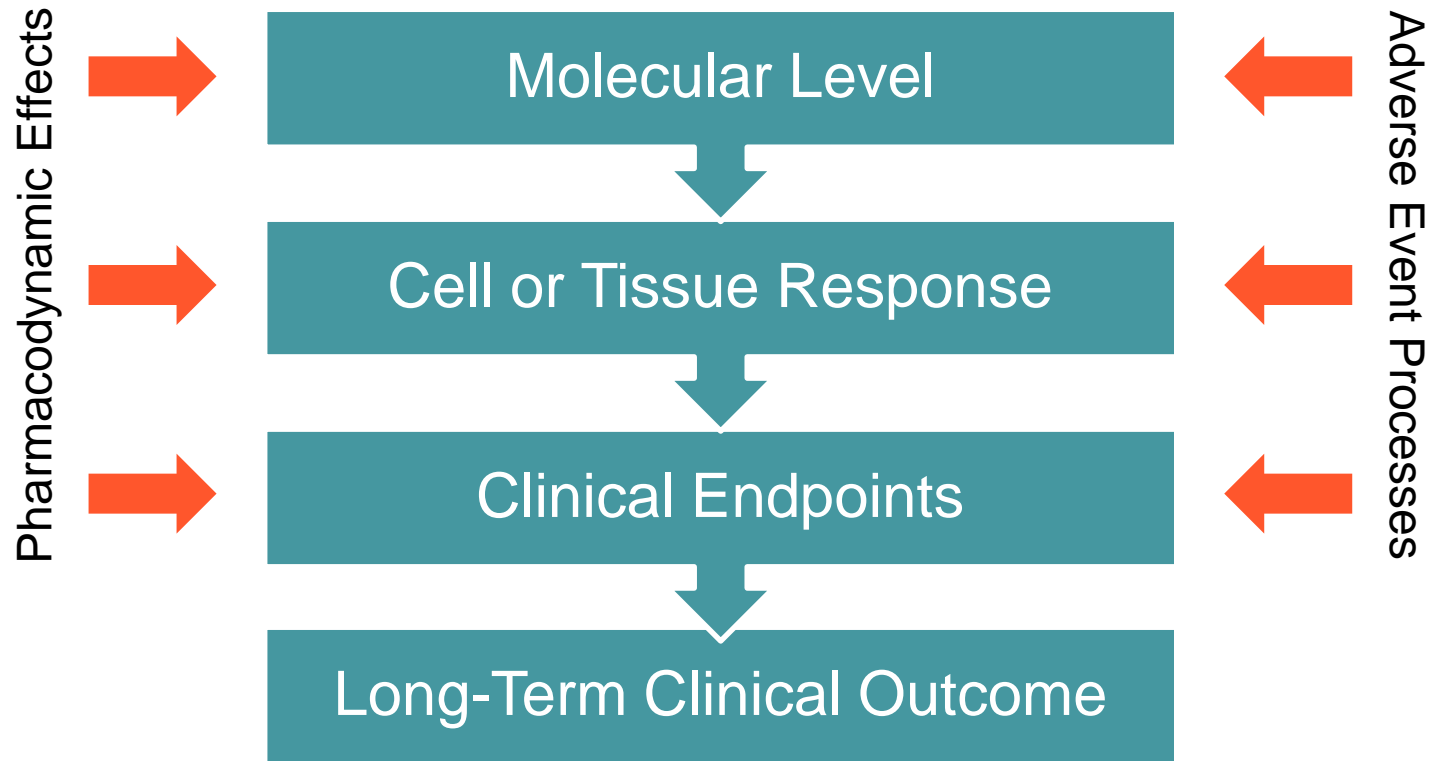
OECD-AOP

| Chemicals | Macro molecular interactions | Cellular Responses | Organ Responses | Individual Responses | Population Responses |

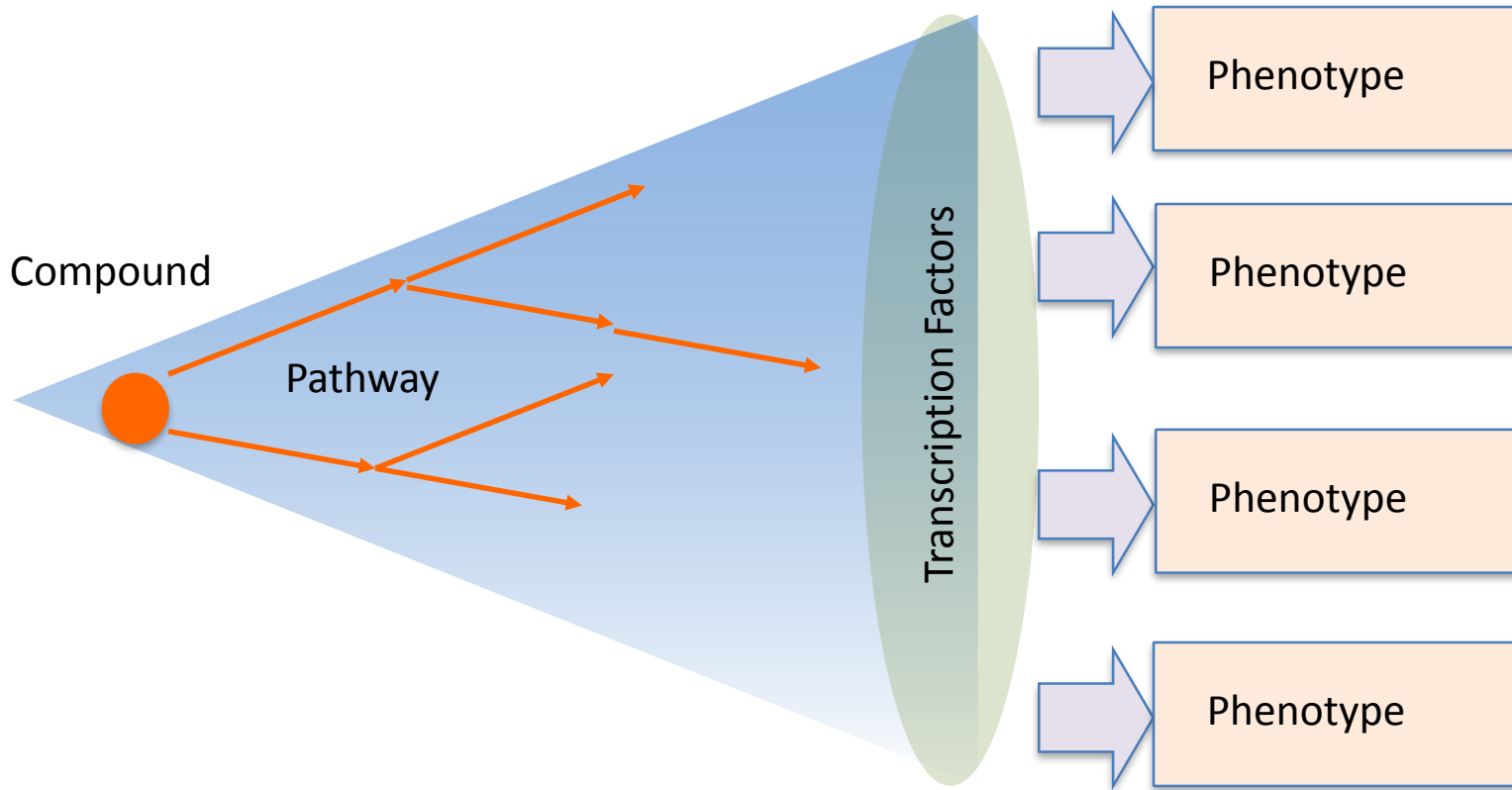Systems Toxocology Pipeline

Compounds to be screened

Forward Analysis

Transcription Factor

Gene Expression

Metabolome

Phenotype Selection

Phenotype
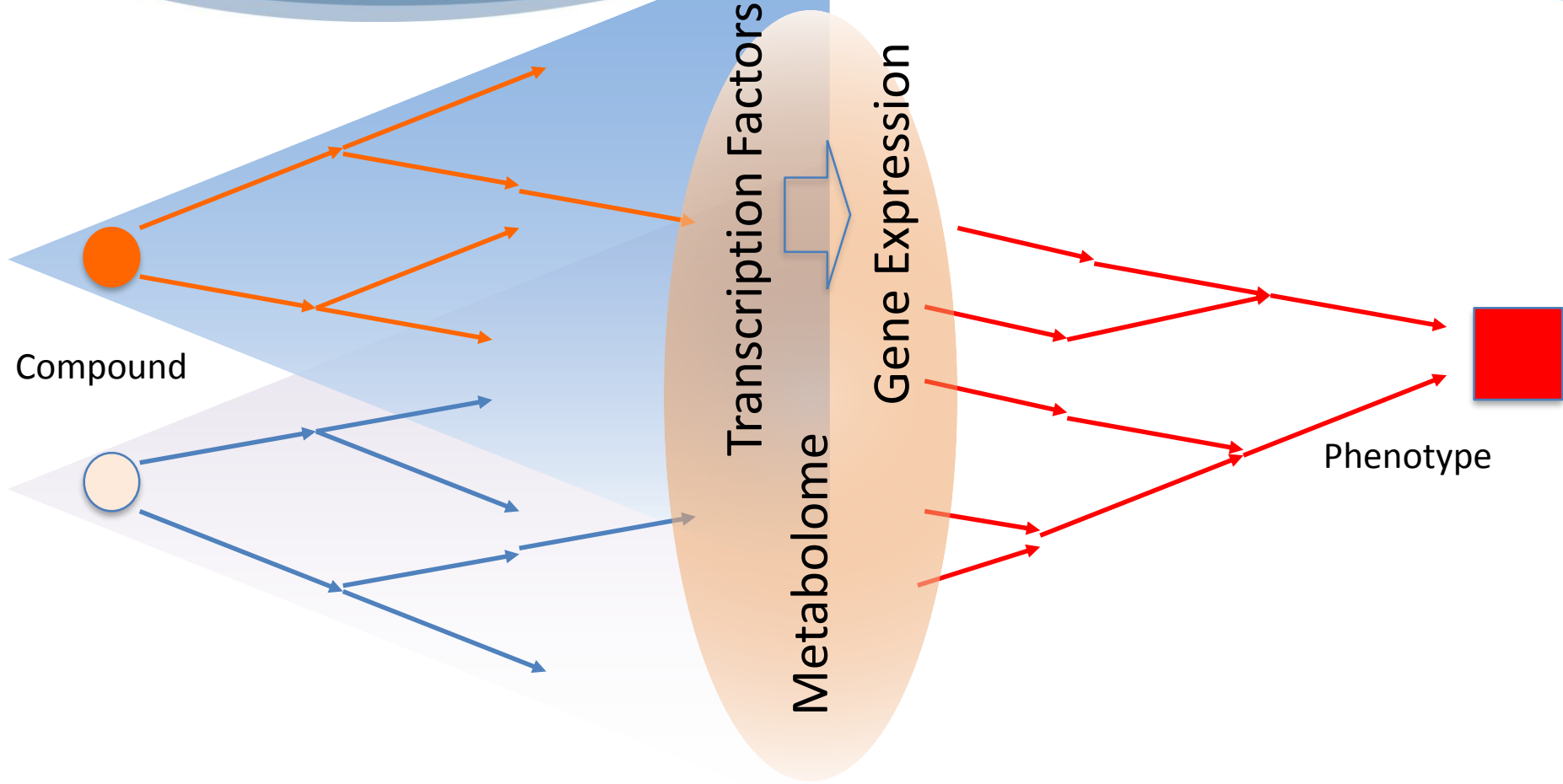
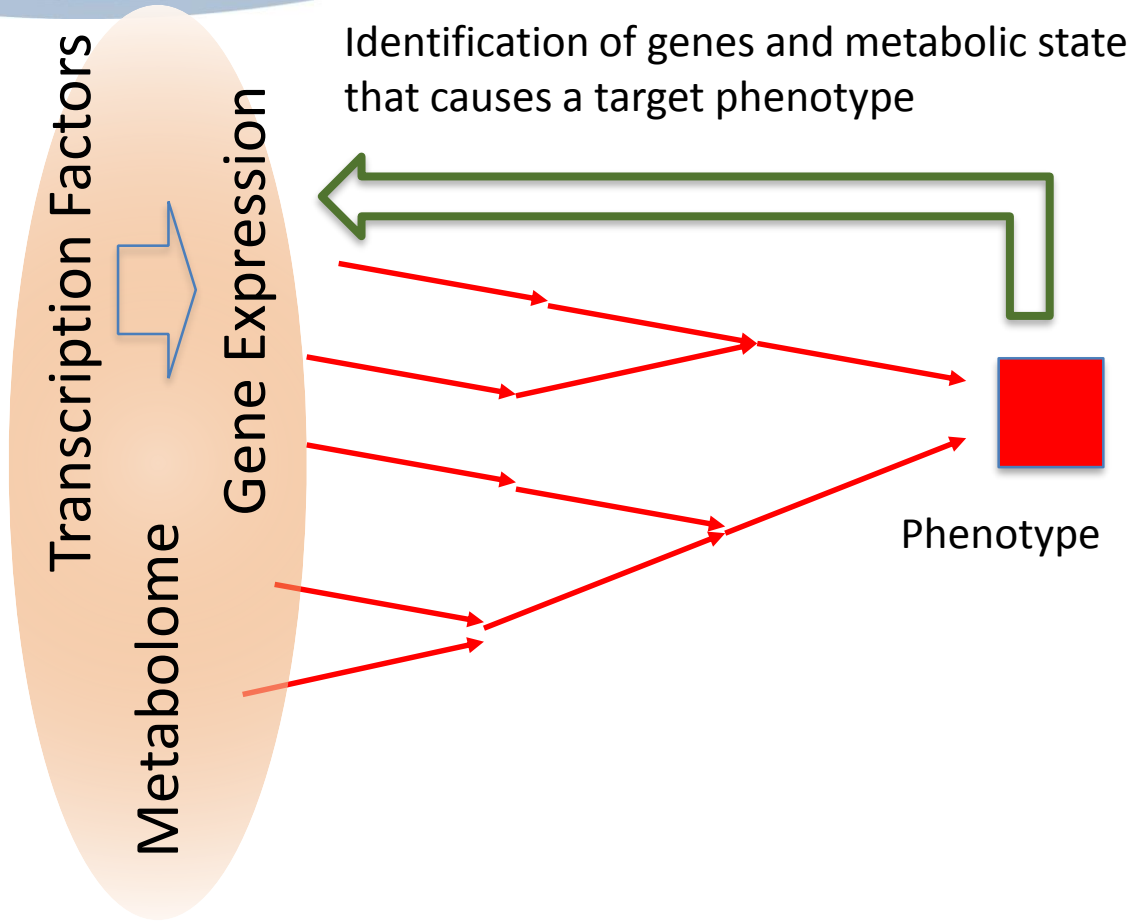Backward Analysis

Forward Analysis

Moving forward…

- *Building ontological infrastructure to lay down this integrative framework is essential.*

- *Need consensus of definition and measurement thresholds (e.g. grading of symptom, unifying subjective value reading)*

- *May require standardized protocol in practice, not just standardization of vocabulary*

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FDA Efforts/Commitment

- **Support of Predictive Safety Team and other activities**
- **BAA, Critical Path, Regulatory Safety Research Funding**
- **Development of collaborations to advance this program with**
  - **NCI**
  - **NCATS**
  - **NIGMS**
  - **DARPA**
  - **Academic Groups**
  - **PhRMA Companies**

Next Steps
•**Formation of a Collaborative Group Interested in Sharing Precompetitive Data**
•**Formation of a Workgroup to Develop Computational Solutions to Solve Problems in these Complex Integrated Biological Systems**

Pharmacological Mechanism-Based Drug Safety Assessment and Prediction

- **Bridge Disciplines to Foster Collaborative Safety Science**

- **Bridge Organizations (FDA, NIH, Academe, PhRMA) to Foster Collaborative Safety Science**

- **Define Areas and Approaches to Integrate Science (Cheminformatics, Bioinformatics, Systems Pharmacology. . .)**

- **Define Opportunities for New Science to Fill in the Gaps**

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Questions?

Thank you