Conference on Clinical Cancer Research

October 20, 2010 ~ Washington, DC

Panel 2 - Identification and Elucidation of the Biology of Adverse Events: The Challenges of Safety Assessment and Translational Medicine

Kenneth W. Turteltaub, PhD

Exec. Director, Center for Fundamental & Applied Systems Toxicology

Battelle Memorial Institute

Goals

- Define whether systems biology offers major improvements in the safety evaluation of new chemical entities with indications in oncology
- Discuss where it adds value, how it could be implemented, what its limitations are
- Determine whether guidance documentation is needed to help accelerate the adoption of systems biology for regulatory science

Systems Biology

- Elucidation of the complex interactions of a biological system and how it gives rise to the function or loss of function of a system
  - Holistic rather than reductionist
  - Combines biological, pharmacological, molecular and biochemical properties of a system
  - Moves away from one target, one outcome
  - Defines the interactions of the system components

Technologies making systems biology a reality

- High density arrays
  - Genomics, transcriptomics…
- Mass spectrometry and NMR
  - Metab(an)olomics, glycomics, lipidomics..
- Computational and bioinformatics
  - Pattern recognition and differential analysis defines interactions within a system
- Imaging technologies (MRI, PET)
- 3D tissue culture & other models

Premises

- New drugs are approved upon establishment of appropriate benefit risk determination for a specific indication
- Current animal testing methods are useful, necessary, but not sufficient to address the future safety needs of new therapeutics
  - REMS- vs. REMS+
- Preclinical safety assessments of new chemical entities have been dramatically affected by emergence of new techniques which enable quantification of molecular changes related to organ system damage

Premises (cont)

- Systems level understanding of the biology of adverse events can significantly improve the detection, measurement & monitoring of potential liabilities and characterize the risk to humans
  - Most relevant toxicology outcomes involve differential molecular expression signaling changes and/or metabolism

- Guidance on the application of systems biology will help in its adoption and consequent demonstration in drug development

Systems Biology can measure molecular effects relevant to adverse events

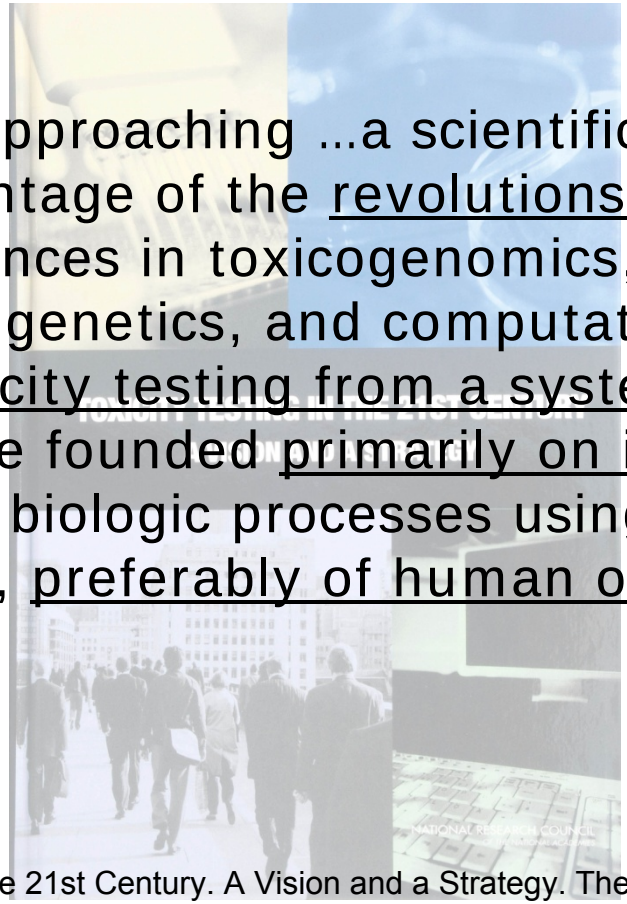
Genomics
Transcriptomics
Proteomics
Metabolomics
Lipidomics
Glycomics
PTM's

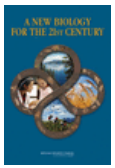
Informatics/ computational methods

Mechanisms of action
Secondary pathways of effect
Targets for drug interaction
Relevant polymorphisms
Biomarkers of adverse events
Human relevance
Specific hypothesis testing

Toxicity Testing in the Twenty-first Century: A Vision and a Strategy *

"Toxicity testing is approaching …a scientific pivot point. It is poised to take advantage of the revolutions in biology and biotechnology. Advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology could transform toxicity testing from a system based on whole animal testing to one founded primarily on in vitro methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin."





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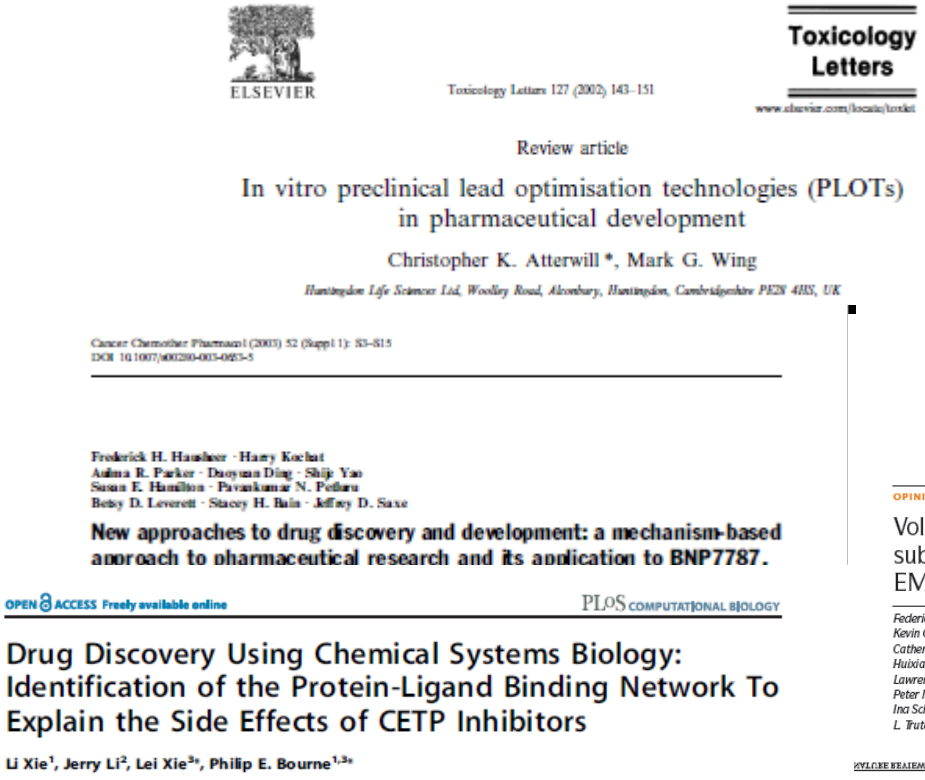
- NRC. (2007). Toxicity Testing in the 21st Century. A Vision and a Strategy. The National Academies Press, Washington, D.C.
- NRC (2009). A New Biology for the 21st Century. The National Academies Press, Washington, D.C.

Application of these principles are already happening, we need to increase adoption

FDA Initiative on advancing Regulatory Science (ARS)



ELSEVIER

Toxicology Letters 127 (2002) 143–151

Toxicology Letters

www.elsevier.com/locate/toxlet

Review article

In vitro preclinical lead optimisation technologies (PLOTs) in pharmaceutical development

Christopher K. Atterwill *, Mark G. Wing

Huntingdon Life Sciences Ltd, Woolley Road, Alconbury, Huntingdon, Cambridgeshire PE28 4HS, UK

Cancer Chemother Pharmacol (2003) 52 (Suppl 1): S3–S15

DOI 10.1007/s00280-003-0655-5

Frederick H. Hausheer · Harry Kochat
Aalina R. Parker · Duoyuan Ding · Shiji Yao
Susan E. Hamilton · Pavankumar N. Pothuru
Betsy D. Leverett · Stacey H. Bain · Jeffrey D. Saxe

New approaches to drug discovery and development: a mechanism-based approach to pharmaceutical research and its application to BNP7787.

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Drug Discovery Using Chemical Systems Biology: Identification of the Protein-Ligand Binding Network To Explain the Side Effects of CETP Inhibitors

Li Xie[1], Jerry Li[2], Lei Xie[3]*, Philip E. Bourne[1,3]*

NIH/FDA collaboration on Translational and Regulatory Science

REVIEWS

A GUIDE TO DRUG DISCOVERY

The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates

Jeffrey A. Kramer*, John E. Sagartz[1] and Dale L. Morris[§]

PERSPECTIVES

OPINION

Voluntary exploratory data submissions to the US FDA and the EMA: experience and impact

Federico M. Goodsaid, Shashi Amur, Jiri Aubrecht, Michael E. Burczynski, Kevin Carl, Jennifer Catalano, Rosane Charlab, Sandra Close, Catherine Cornu-Artis, Laurent Essioux, Albert J. Fornace Jr, Lois Hinman, Huixiao Hong, Ian Hunt, David Jacobson-Kram, Ansar Jawaid, David Laurie, Lawrence Lesko, Heng-Hong Li, Klaus Lindpaintner, James Mayne, Peter Morrow, Marisa Papaluca-Amati, Timothy W. Robison, John Roth, Ina Schuppe-Koistinen, Leming Shi, Olivia Spleiss, Weida Tong, Sharada L. Truter, Jacky Vonderscher, Agnes Westelinck, Li Zhang and Issam Zineh

in an investigational new drug application (IND), new drug application (NDA) or biologics license application (BLA). VGDS meetings have also expanded in scope to include non-genomic biomarkers, and so the submissions have been renamed voluntary exploratory data submissions (VXDSs) to reflect the broad diversity of biomarker data received.

The goals of VXDSs are to offer sponsors insights into the FDA's scientific perspective on a biomarker (or biomarkers) in a given research context and to provide the FDA reviewers opportunities to learn how biomarker data are generated and analysed by sponsors. In contrast to special protocol assessments, the outcome of VXDS meetings is only a scientific, clinical, statistical and/or technical discussion, and is not intended

Questions for the Panel

- Are current animal testing methods insufficient?
- Are the issues correctly defined and phased?
- What changes to the current testing paradigm will have the biggest impact?
- Is systems biology sufficiently developed to add value?
- Has understanding the MOA helped? Does it influence regulatory decision making?
- What needs to be done to implement incorporation?
- How can industry, academia and govt work together to define principles of application and foster implementation?

Agenda

- Adam Clark, Ph.D.
  - Director, Scientific and Federal Affairs, *FasterCures*
  - Definition of the Problem

- Leigh Ann Burns-Nass, Ph.D.
  - DSRD Therapeutic Area Leader-Oncology Pfizer Inc
  - Case Study 1. Drug-Induced vascular injury & how systems biology helped elucidate phosodiesterase inhibitor pathophysiology in animals and define potential biomarkers for humans

Agenda

- Myrtle Davis, DVM, Ph.D.
  - Chief, Toxicology and Pharmacology Branch, Division of Cancer Treatment and Diagnosis, NCI/NIH
  - Case Study 2. Anticancer kinase Inhibitors & importance of defining MOA and establishing selectivity and off-target effects

- John K. Leighton, Ph.D.
  - Assoc. Director, Pharmacology/Toxicology, FDA/OODP
  - Status and Perspective on Current & Emerging Approaches to Safety Assessment

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Innovative and Efficient Pre-Clinical Testing

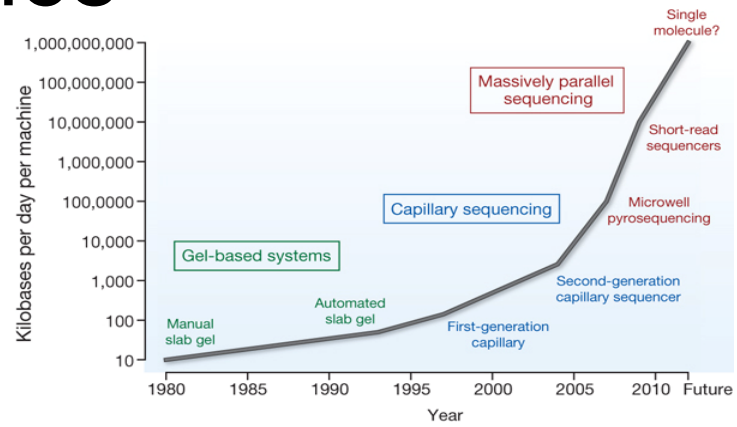
Adam M. Clark, Ph.D.

Director, Scientific and Federal Affairs

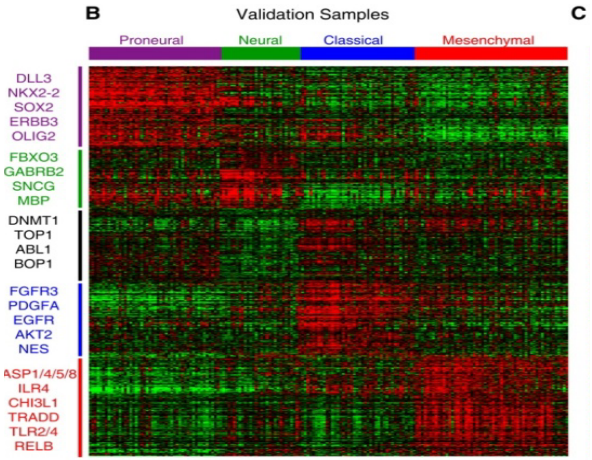
FasterCures

Safety Testing: From Science Fiction to Science

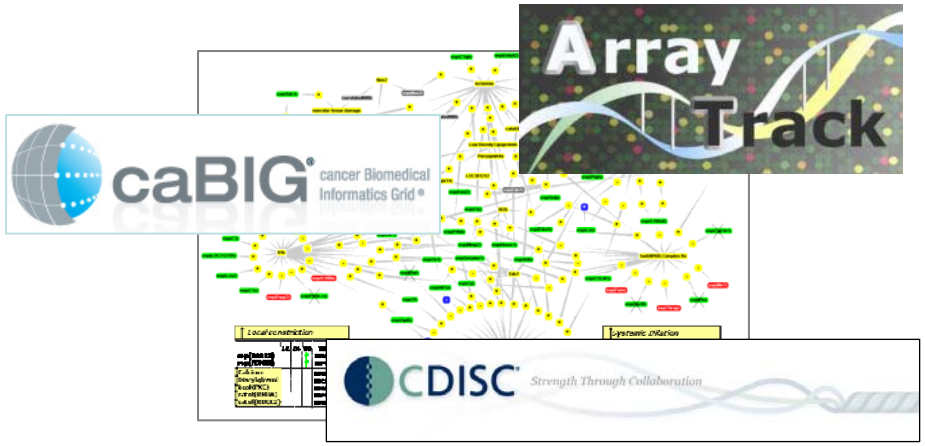
- Genomics
- Proteomics
- Metabolomics
- Bioinformatics
- Stem cells



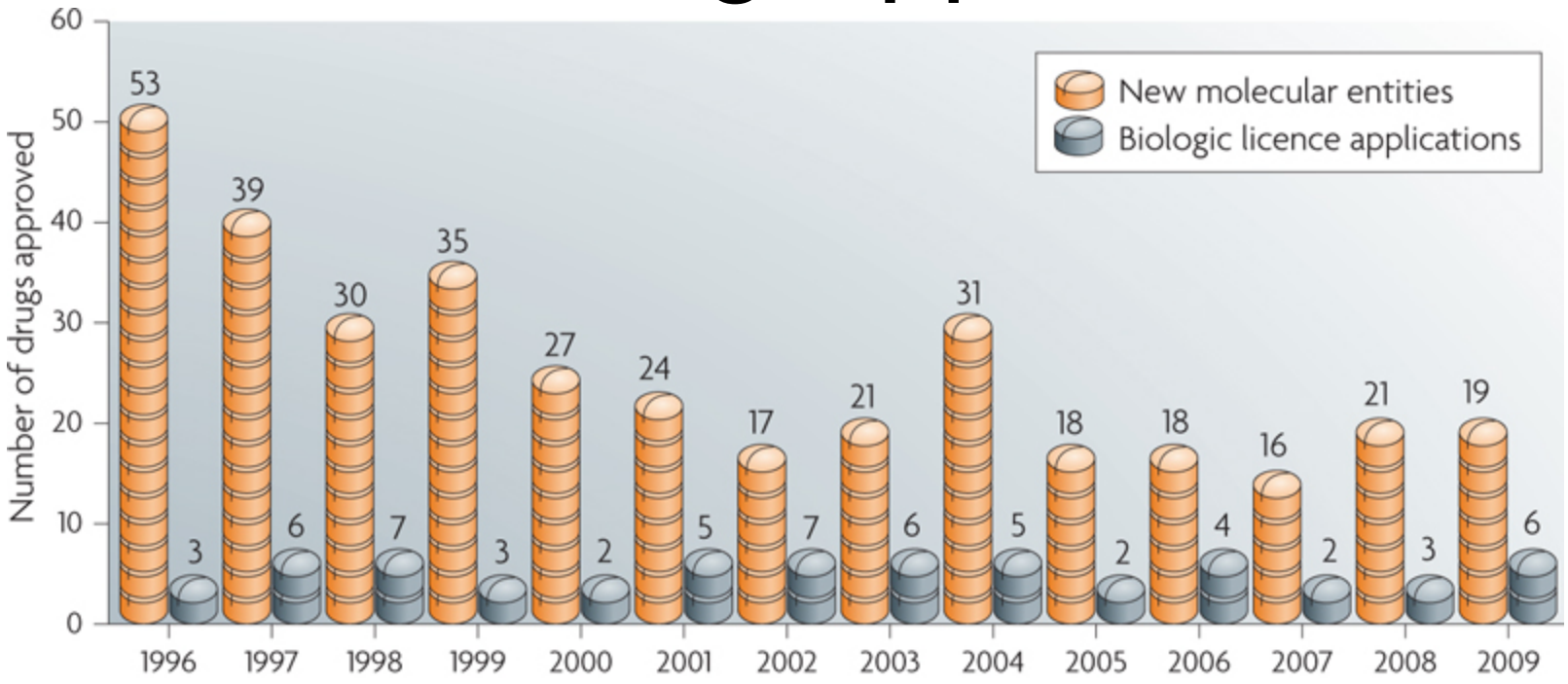
Stratton *et al. Nature* **458**, 719-724 (2009)



Cancer Cell **17**, 98-110 (Jan 19, 2010)



FDA Drug Approvals



Nature Reviews | Drug Discovery

Hughes, B. 2010. Nature Reviews Drug Discovery **9**, 89-92

Need for Improved Models of Toxicity and Patient Benefit

- Animal Models of Carcinogenicity
  - 19/28 compounds tested in coffee are rodent carcinogens
  - Half of natural plant pesticides are rodent carcinogens

(Ames and Gold. Biotherapy. 1998;11(2-3):205-20)

- Thalidomide and Clinical Applications
  - Well known teratogen
  - “On May 26, 2006, the U.S. Food and Drug Administration granted accelerated approval for thalidomide (Thalomid, Celgene Corporation) in combination with dexamethasone for the treatment of newly diagnosed multiple myeloma (MM) patients”

(www.cancer.gov)

Imperfections with Animal Models of Toxicity

November 23, 1977:

Congress passes the Saccharin Study and Labeling Act to stop the FDA from banning the chemical sweetener. The legislation instead requires a warning on the label of products containing saccharin stating, "Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals."

In 2000, the National Toxicology Program determined that saccharin should no longer be listed as a potential cancer-causing agent.

www.fda.gov

Creating Opportunity in the "Valley of Death"

- VoD is the gulf between discovering a promising new drug and demonstrating its effectiveness in humans
- Preclinical drug discovery accounts for 32% of the costs of developing a drug
- 8% of NMEs will make it from preclinical selection to launch. Therefore,12 products are needed in the preclinical development phase for one successful NME launch
- Preclinical development prior to Phase I trials costs about $5 million per product

Paul et al. Nat Rev Drug Discov. 2010 Mar;9(3):203-14

Pharmaceutical Value Equation

$$P\alpha \frac{WIP \times p(TS) \times V}{CT \times C}$$

- P= R&D Productivity
- WIP = Work in Progress (NMEs in the pipeline)
- *p*(TS) = Probability of a Technical Success
- V= Value
- CT = Cycle Time
- C= Cost

Paul et al. Nat Rev Drug Discov. 2010 Mar;9(3):203-14

Systems Toxicology in Preclinical Testing and the Value Equation

- WIP - Effective safety screening could increase a company's product line portfolio
- *p*(TS) – Effective screening of targeted drugs could increase the probability of success in sub-populations
- V – Effective screening of "true" toxicities could elucidate health outcomes and the benefit:risk ratio
- CT – Efficient screening could reduce cycle time for products to move to clinical testing

$$P\alpha \frac{WIP \times p(TS) \times V}{CT \times C}$$

State of New Drug Delivery to Patients

- Developments of new therapies is in decline
- Cost of bringing drugs to market is rising
- Era of personalized medicine is pressuring a changing dynamic in the desire for more tailored treatments and identifying responder sub-populations
- Effective and efficient safety screening serves to benefit drug developers and patients by increasing the potential for promising new therapeutics to make it to the clinic

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Innovative and Efficient Pre-Clinical Testing

Leigh Ann Burns Naas, PhD, DABT, Fellow ATS

Senior Director, Drug Safety Research & Development

Pfizer

Drug-Induced Vascular Injury (DIVI)

Challenges for Risk Management and Regulatory Policy

- Vasculitis is not a single disease entity in humans or animals
- Drug-induced vascular injury in non-clinical models differs from human clinical syndromes
  - Drug-induced in animals not immune mediated
- Inadequate methods to differentiate spontaneous vasculitis from drug-induced in animals
- Lack of specific and sensitive clinical biomarkers

Nonclinical DIVI

- Lesions develop acutely, within hours to days and is characterized histologically by one or more of the following: inflammation, necrosis, hemorrhage, medial thickening
- Caused by several types of drugs (PDEi, dopamine agonists, endothelin receptor antagonists, etc.) with differences between species (rat mesenteric arteries vs. canine coronary arteries)
- Lesions can only be detected by histopathology; there are no diagnostic or predictive circulating biomarkers
- Corresponding findings not reported in humans
- Significant challenge for pharmaceutical companies; many compounds terminated from development because of DIVI and the inability to monitor in the clinic

There is a clear need for translatable biomarkers to detect and monitor DIVI.

Using Systems Biology…

- the pathophysiology of a well-known, but enigmatic phenomenon of chemically induced vascular injury has been elucidated
- approach essential to the characterization of the signals and pathways of these events, but long-sought-after candidate biomarkers were also identified

PDE4i Toxicity

Mesenteric Vascular Injury & Inflammation in Rats

Lesion Development
Begins <24 hours

Primary site: Mesentery*

Time

Focal Inflammatory Infiltrates

↓

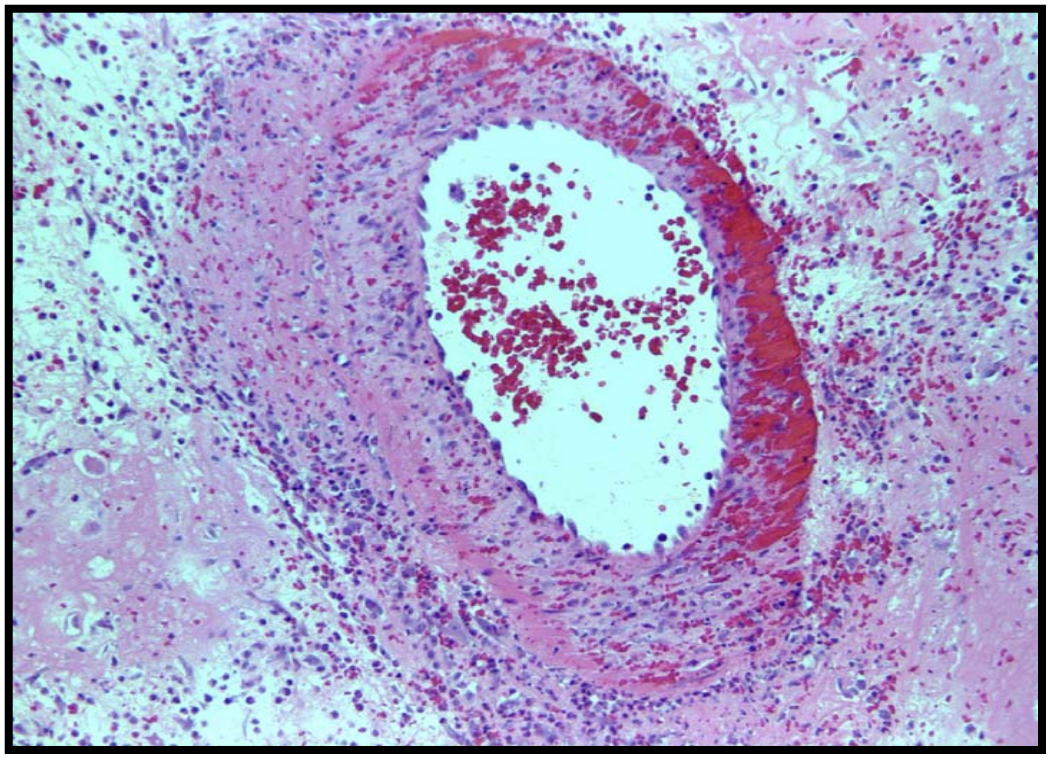
Arterial wall hemorrhage

↓

Arterial wall necrosis

↓

Arterial/Periarterial
Inflammation



Molecular Pathways? Molecular Mechanisms?

*Other sites: liver, epididymis, intestine

Experimental Approach

Perform in-life studies

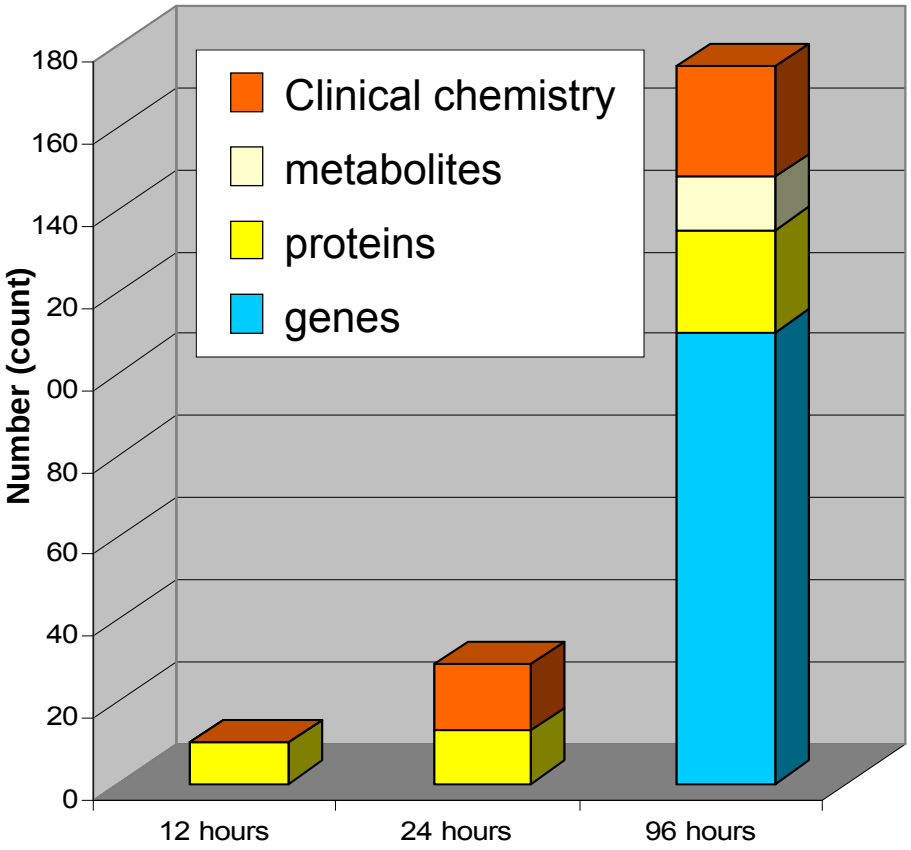
Generate pathology and ‘omic data

Collaborate with Genstruct to build vasculitis model and generate hypotheses/biomarkers

Review, prioritize, test hypotheses/biomarkers

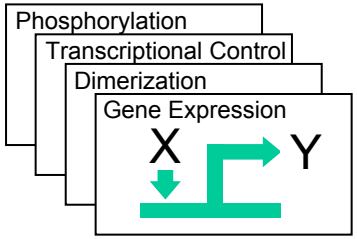
In Vivo Panomic Profiling

- Used to identify candidate mechanisms and biomarkers of vascular injury with multiple compounds
  - RNA profiling of mesenteric artery tissue
  - Serum proteomics
  - Urine metabolite analysis
  - Serum ELISA assays for specific proteins
  - Serum & urine metabolite analysis



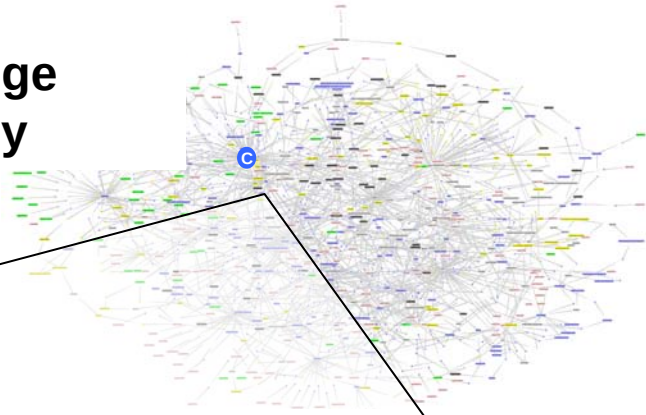
Modeling Approach

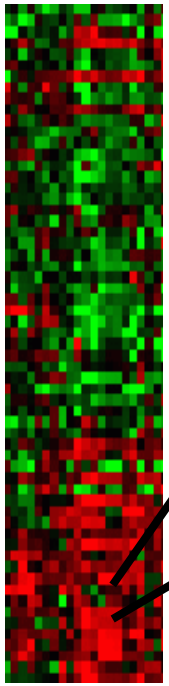
Literature and Databases

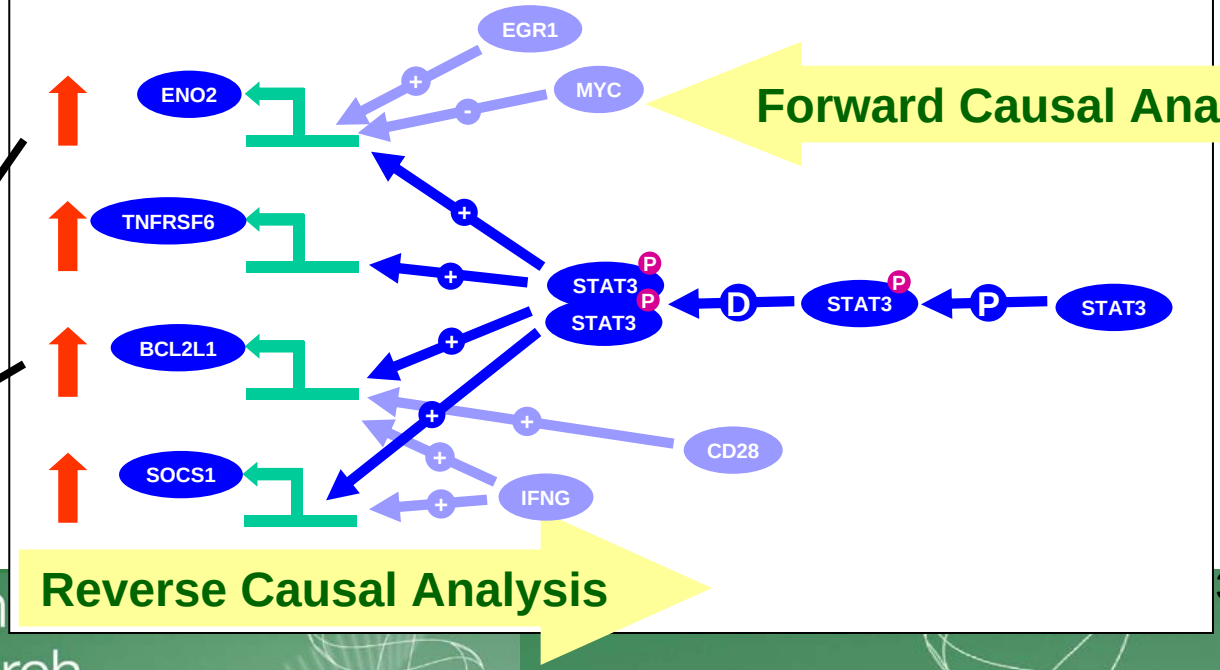


Computable Representation

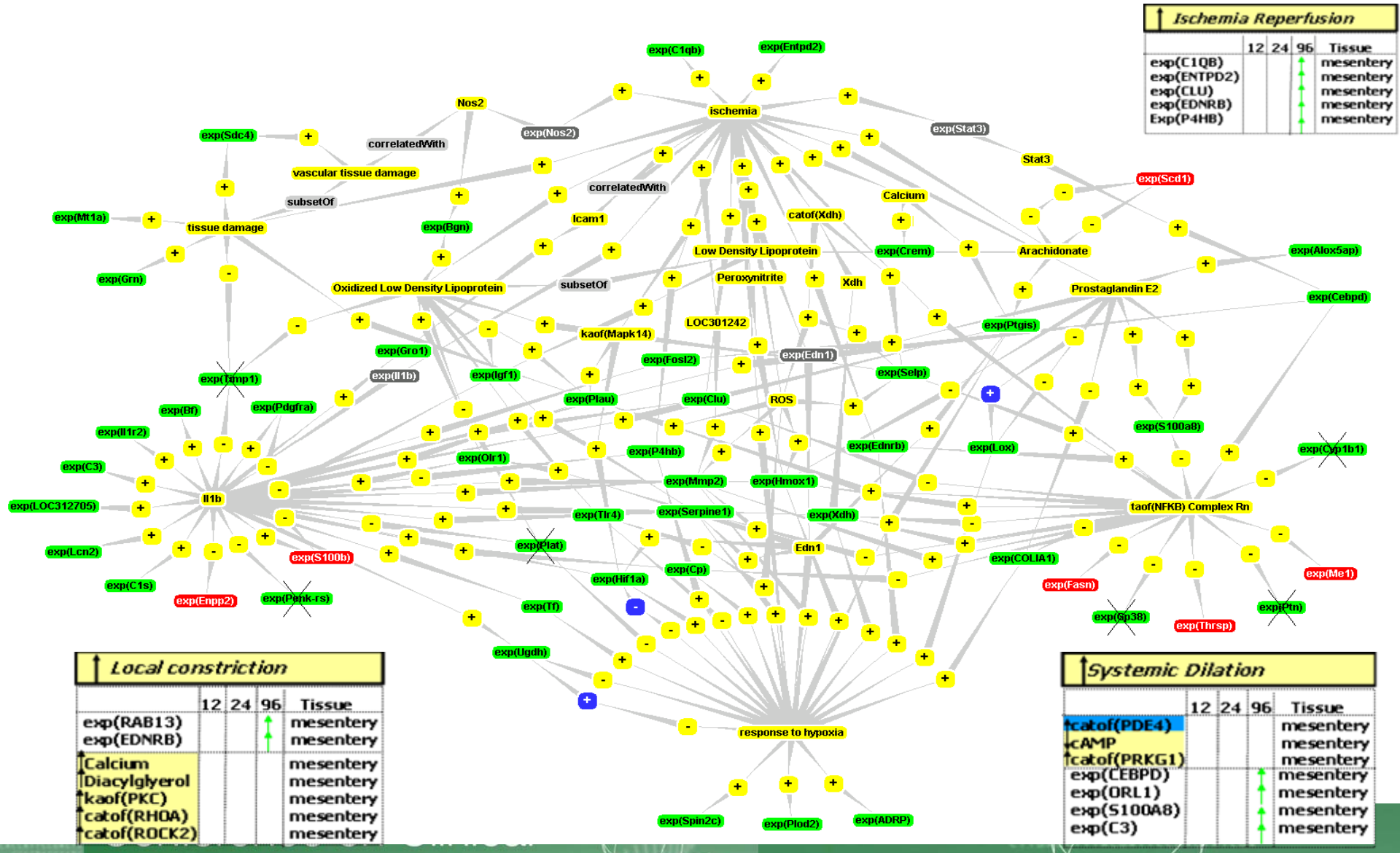
Knowledge Assembly



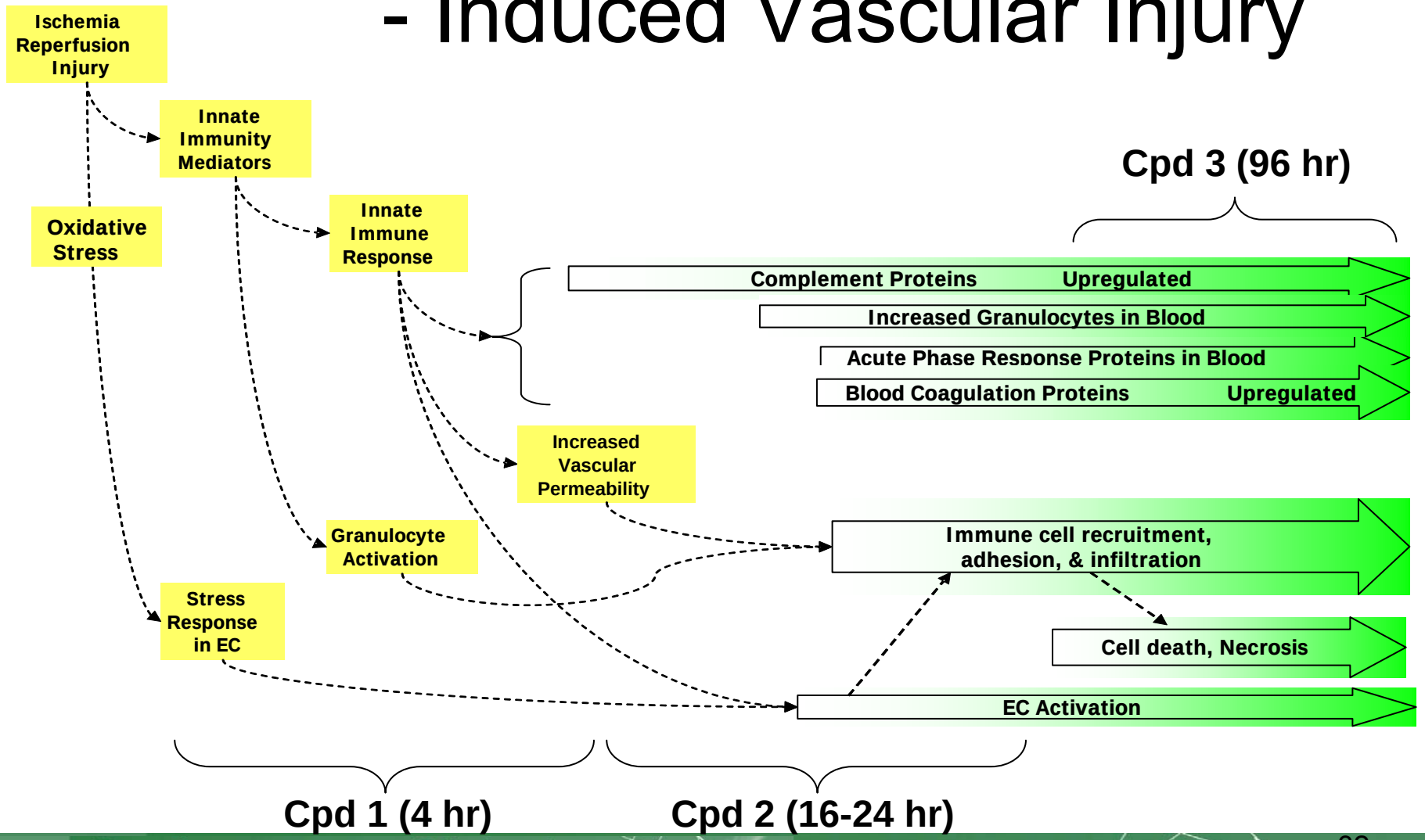




Evidence for Ischemia Reperfusion



Proposed Pathogenesis of PDE4i - Induced Vascular Injury



Ischemia Reperfusion Injury Hypothesis

- PDE4i can induce ischemia-reperfusion like injury
  - Continued systemic vasodilation in the face of local mesenteric vasoconstriction can induce vasospasms and non-occlusive mesenteric ischemia
- Hypothesis supported by markers of ischemia
  - C1QB, ENTPD2, CLU, EDNRB, P4HB
- Many downstream events of ischemia reperfusion injury observed
  - Increased XDH activity
  - Increased leukotriene and eicosanoid synthesis via arachidonate
  - Innate immunity mediator releases IL6, IL1β, TNF
  - Complement activation

When You Wish Upon A Star…

- Understanding the translation (or not) of nonclinical safety signals to the patient
- Onco-PLUS! Building a better drug
- Understanding the potential safety impact on individuals by understanding relationship to key personal omic signatures

Challenges

- Timelines
  - VWG established 2001
    - academia, industry, regulatory participation
  - First VGDS 2006
  - FDA/EMA consultation on clinical translational testing plan in October, 2010
  - Earliest proposed regulatory adoption of biomarker(s) – late 2014

Challenges

- Preclinical Modeling and Clinical Translation in the face of Confounding Factors
  - Contributions of disease state or secondary disease
  - Prior therapies
  - Evolving con-meds, some with related adverse effects with possible different mechanisms

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Innovative and Efficient Preclinical Testing

Myrtle Davis, DVM, Ph.D.

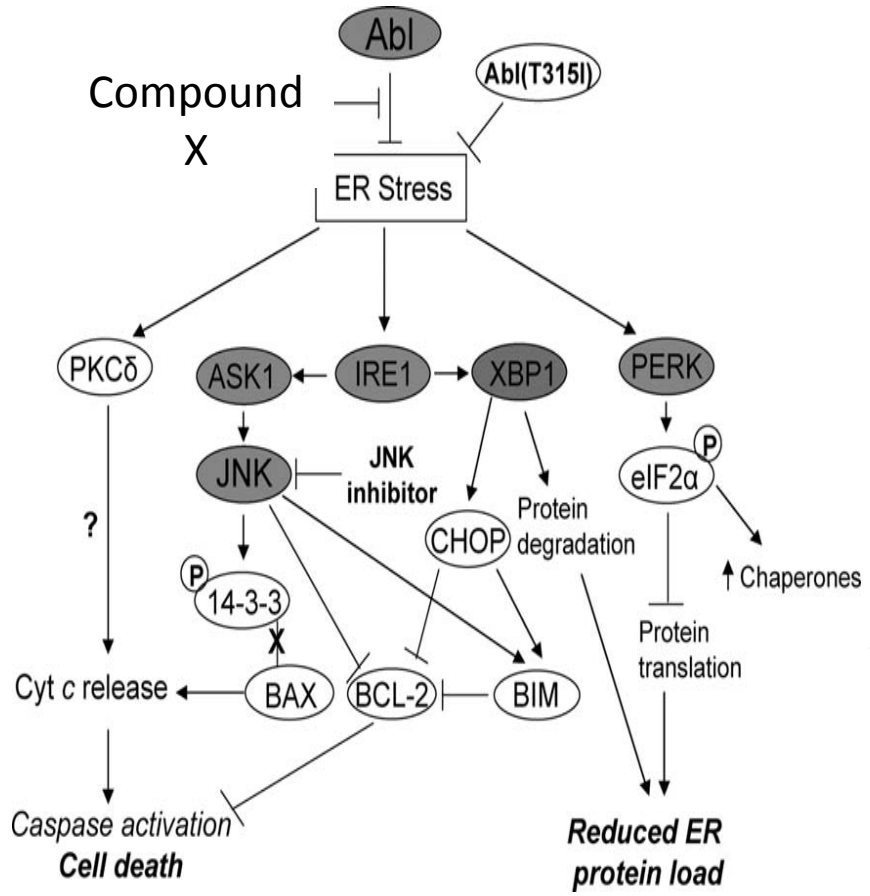
Chief, Toxicology and Pharmacology Branch
Division of Cancer Treatment and Diagnosis,
The National Cancer Institute, NIH

“The views presented do not reflect an official position or policy of the National Cancer Institute or the U.S. Government.”

Cardiotoxicity associated with Anticancer Kinase Inhibitors

- Compound x (targets Bcr-Abl) induces LV dysfunction and CHF; Compound B a TKI that like Comp. x (targets Bcr-Abl) reports a 4% incidence of heart failure after only 6 to 12 months of therapy
- Binding to unintended targets = "off-target" effects intended target = on target effects
  - If one of these targets plays a critical role in the heart, off-target toxicity may include cardiotoxicity.
  - These targets may play a role in disease progression and inhibition may <u>also</u> lead to better anticancer efficacy.
  - *Note: Cardiotoxicity is **<u>not</u>** a class effect of kinase inhibitors*

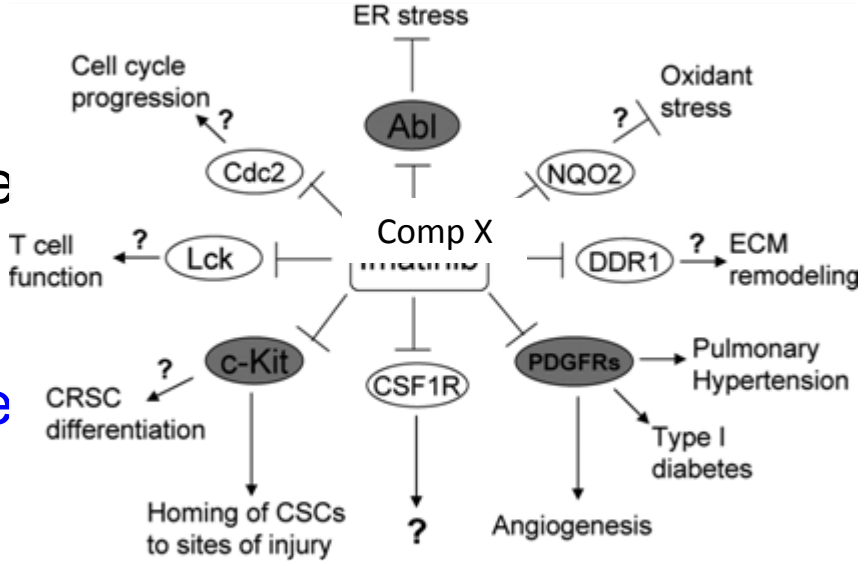
Mechanisms of Cardiotoxicity



- To identify mechanisms of compound x-induced cardiotoxicity, Investigators used rat cardiomyocytes in culture to demonstrate that incubation of cells with compound x, led to activation of the endoplasmic reticulum (ER) stress response.
- This included sustained activation of the IRE1 kinase arm of the response, culminating in activation of the ASK1/JNK pathway and cell death

Target profiling

- There were several protein targets indentified for compound x that could mediate cardiomyocyte death
- Investigators used the Abl (T315I) point mutant that renders the kinase resistant to compound x to demonstrate rescue of cardiomyocyte death following gene transfer of T315I, but not wild-type Abl
- The T315I mutant was used as a molecular tool to implicate compound x-mediated inhibition of c-Abl in mediating ER stress and driving cell death.



Note: c-Kit and Lck are not expressed in adult cardiomyocytes

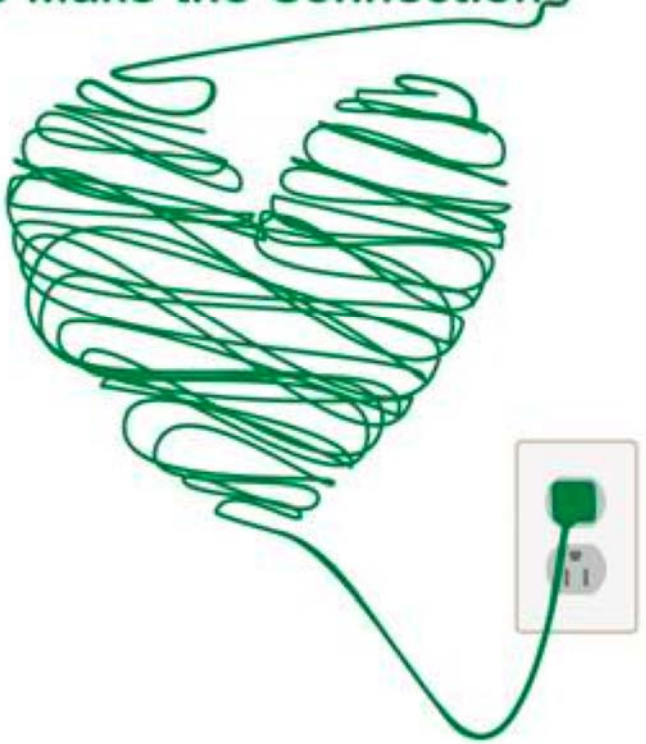
Impact of Redesigning a Molecule Based on Mechanism of Toxicity and Profiling Data

- Redesigned compound X to no longer inhibit Abl; cardiotoxicity was not seen with this agent in mouse models.
- The redesigned drug was also ineffective in treating CML (driven by Bcr-Abl), it was equally effective to Compound X in treating GIST models driven by c-Kit mutations.
- By knowing the mechanism of toxicity and redesigning the drug accordingly, one could theoretically reduce cardiotoxicity in GIST patients.
- If this is true, the on-target toxicity of compound x-mediated inhibition of Abl could be unavoidable in CML patient

Path Forward?

- What would the path forward look like for a redesigned compound x ?
- What information can be harvested from mechanism of toxicity to inform clinical monitoring and enable biomarker exploration?
- Are time frames for mechanistic studies and drug development compatible?
  - Are groups publishing mechanistic data rapidly enough?

You Have the Power
To Make the Connections



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Innovative and Efficient Preclinical Testing

John K Leighton

Associate Director for Pharmacology/Toxicology, FDA/OODP

Disclaimer

This presentation is not an official FDA guidance or policy statement. No official support or endorsement by the FDA is intended or should be inferred.

Where we are: ICH S9

- ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals
  - Published Federal Register March 2010
  - Describes nonclinical studies to support clinical trials in patients with advanced cancer
  - Applies to small molecules and biotechnology-derived products

Goals of Nonclinical Studies in Oncology

- Identify starting dose
- Identify organ toxicities
- Identify reversibility of toxicities, if needed
- Guide dosing regimens and escalation schemes

Nonclinical Studies Conducted to Support an Initial Clinical Trial

- Pharmacology/Pharmacodynamics
- Pharmacokinetics
- Safety Pharmacology
  - Includes cardiovascular safety assessment
- General Toxicology (GLP)

Perspective on Emerging Approaches to Safety Assessment

- Exploratory approaches
  - Genomics, metabolomics, proteomics, etc
  - Pathway analysis
  - Differentiated stem cells
  - Cardiac safety assessment
- Biomarkers
  - Cardiac troponins
  - Renal biomarkers