Our Mission

Improve public health by reducing unanticipated cardiovascular-related adverse effects from drugs or chemicals.

Develop innovative approaches to support early detection and prediction as well as improved understanding of cardiovascular toxicology and pathobiology.
What does cardiovascular toxicity look like?

**Nonclinical CV Toxicity**
- cardiomyocyte injury
- valvulopathy
- ultrastructural injury

**Clinical CV Toxicity**
- "Adverse CV events" (Vioxx, Darvocet)
- Congestive Heart Failure (TZDs, TKIs)
- Decreased EF (TKIs)
- Valvulopathy (Fen-Phen)
- QT prolongation
- Non-QT arrhythmias
- Increased blood pressure (Torcetrapib)
- Vasculitis
- Altered Clotting

Changes:
- ∆BP
- ∆HR
- ∆contractility
Getting on the same page!

**Preclinical**
- Functional changes
  - Hypo-, hypertension
  - Tachy-, bradycardia
  - Arrhythmia
  - QT prolongation
- Structural changes
  - Increased, decreased cardiac mass
  - Myocellular degeneration/necrosis
  - Cardiomyopathy

**Clinical**
- Functional changes
  - Hypo-, hypertension
  - Tachy-, bradycardia
  - Arrhythmia
  - QT prolongation
  - Heart failure
  - Ischemic events
  - Adverse CV events
- Structural changes
  - Myocardial infarctions
  - Changes in serum cTn
A growing list of marketed compounds with CV safety concerns

Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib


Cardiotoxicity of the cancer therapeutic agent imatinib mesylate

Risto Kerckē1,2, Luanda Graziutzi2, Cinat Yoobil, Cesar Illescu, Richard Patten, Caro Bearmh, Brian Walters, Sergei Shertsov1,2, Stéphanie Peasant2, Fred J Cliby2, Anthony Rosenzweig2, Robert N Salomon2, Richard A Van Etten2, Joseph Alroy2, Jean-Bernard Durand1 & Thomas Force1,2
Cardiovascular toxicity is also an environmental concern!

**Particulate air pollution and coronary heart disease**
Boris Z. Simkhovich\textsuperscript{a,b}, Michael T. Kleinman\textsuperscript{c} and Robert A. Kloner\textsuperscript{a,b}

**Adverse cardiovascular effects of air pollution**
Nicholas L Mills\textsuperscript{*}, Ken Donaldson, Paddy W Hadoke, Nicholas A Boon, William MacNee, Flemming R Cassee, Thomas Sandström, Anders Blomberg and David E Newby

**Review Article**
Toxic Effects of Mercury on the Cardiovascular and Central Nervous Systems
Contemporary Challenges

• Predicting cardiovascular risk in target patient populations
  – target patient populations have lots of pre-existing disease
    • diabetes mellitus
    • ischemic heart disease
    • hypertension
  – ‘special populations’ are special challenges- e.g. pediatrics
  – varying therapeutic indications have very different risk:benefit tolerances
  – patients are living longer
    • long term implications of toxicity become more important

• Nonclinical models don’t look like target patients

• Mitigating risk in the clinics with sensitive and relevant biomarker strategies
  – Difficult to mitigate risk you don’t recognize (i.e. see challenges above)
  – “Mitigating” means early detection before clinically meaningful injury and avoiding patients at higher risk for adverse outcomes

• Early detection of “chronic” toxicities to mitigate investment in bad drugs
  – It’s bad for the patient and bad for business to detect risks late in development or post-marketing
Engaging the Challenges

• Refine current approaches
  – Assay predictivity
  – Assay sensitivity
  – Biomarker correlations

• Development of novel approaches
  – Biomarker strategies
  – Mechanistic approaches
  – Alternative modeling

• Better understanding of cardiovascular toxicobiology- both clinical and nonclinical

• Build a robust, multi-disciplinary community of translational cardiovascular pathobiologists
Pro-Arrhythmia Working Group

Leadership:

• Jean-Pierre Valentin, AstraZeneca
• John Koerner, US FDA

A Singular Project

• **ONLY** example of a joint public-private effort to analyze submitted IND-NDA data from behind a regulatory agency firewall

• Represents significant effort and commitment by all parties to enhance the common scientific understanding and interpretation of existing data for public health
Long QT Syndrome (LQTS) as a drug liability

- Characterized by prolonged QT interval in the surface ECG
  - propensity for syncope and sudden cardiac death [torsades de pointes (TdP)]

- Congenital and acquired forms
  - drug-induced most common cause of acquired form
Objectives

• To assess the concordance between signals in non-clinical repolarization assays and clinical QT interval prolongation

• To investigate mechanisms for any discrepancy identified between non-clinical and clinical results and to determine viable and successful alternative approaches to identify these compounds

• To assess the proarrhythmic potential of such compounds
CSRC-HESI-FDA Meeting DRAFT Agenda

Rechanneling the Current Cardiac Risk Paradigm: Arrhythmia Risk Assessment During Drug Development Without the Thorough QT Study

10903 New Hampshire Avenue, Silver Spring, Maryland 20993

White Oak Facility, FDA Headquarters • Silver Spring, MD • July 23, 2013

• Next generation approaches to pro-arrhythmia risk assessment
  • mechanistic approaches

• Prototype for approaches to other risks?
Leadership:
- Eric Schultze, Eli Lilly
- Marjory Brooks, Cornell University

Objectives:
- Support the development and application of biomarkers of cardiac toxicity
- Develop systematic approach to evaluate biomarkers that bridge pre-clinical to clinical stages of drug development
- Expand previous cardiac troponin work to encompass markers of pro-thrombotic risk
Cardiac Troponins

- Protein components of the cardiomyocyte contractile apparatus
- Cardiac and skeletal muscle isoforms (allows specificity for cardiac muscle injury; cf. CK)
- 3 isoforms present in cardiac muscle
  - cTnT- binds tropomyosin
  - cTnC- binds calcium and allows contraction
  - cTnl- inhibits contraction in the absence of calcium

- Low circulating levels of cTn and rapid release with cardiomyocyte injury allow for early detection of injury

- Small cytoplasmic pool (5-10%) but largely linked to structural elements
Historically, best characterized application of serum cTn as a biomarker of cardiac injury is in the setting of acute coronary syndrome (ACS).

Increased concentrations of serum cTn included in the diagnostic “definition” for clinical myocardial infarctions (MI).

This history has been both a gift and a challenge for broadening the use of serum/plasma concentrations of cTn as a biomarker of cardiac injury.
Troponin as a preclinical biomarker

A survey of potential cardiotoxicity biomarker candidates concluded that cTn was most viable

Analytical validation of commercial assays

A translational approach to detecting drug-induced cardiac injury with cardiac troponins: Consensus and recommendations from the Cardiac Troponins Biomarker Working Group of the Health and Environmental Sciences Institute

Am Heart J 158:21-9, 2009
Serum troponin time course in rats given a single dose of isoproterenol (4 mg/kg)

Extracted from Clements PJ, et al. Tox Path 2010
cTn as a “qualified” nonclinical biomarker

February 23, 2012

ATTN: PJ O’Brien (University College, Dublin, Ire)
      WJ Reagan (Pizer Inc, Groton, CT, USA)
      MJ York (GlaxoSmithKline, Ware, Herts, UK)
      MC Jacobsen (AstraZeneca, Macclesfield, UK)

RE: Biomarker Qualification Decision

I. Qualification Decision and Context of Use

The Biomarker Qualification Review Team (BQRT) has completed its review of your submission and concludes, as does your proposal, that in safety assessment studies in rats and dogs, serum/plasma cTnT and cTnl are qualified biomarkers for the following contexts of use:

1. When there is previous indication of cardiac structural damage with a particular drug, cardiac troponin testing can help estimate a lowest toxic dose or a highest non-toxic dose to help choose doses for human testing. In this case, cardiac troponins may serve as a clinical chemistry correlate to the histology. For example, in a safety assessment study, lower doses without increases in cardiac troponins may be used to support a no observed effect level (NOEL) identified by histology.

2. When there is known cardiac structural damage with a particular pharmacologic class of a drug and histopathologic analyses do not reveal structural damage, circulating cardiac troponins may be used to support or refute the inference of low cardiotoxic potential.

3. When unexpected cardiac structural toxicity is found in a nonclinical study, the retroactive (“reflex”) examination of serum or plasma from that study for cardiac troponins can be used to help determine a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL). The results of this testing may support inclusion of cardiac troponin testing in subsequent safety assessment studies.

HESI Data played important role in supporting this validation

Prospective use

Context of use = in the presence of structural damage

Discharge risk

Retrospective use
Continual development of analytical capabilities offers new opportunity for applications but also requires continual refinement of our understanding of the marker!


improving cardiovascular risk assessment. Based on results of this survey, the authors believe there is a gap in the preclinical laboratory testing for the detection of prothrombotic and hypercoagulable states that warrants investigation of new or different tests by the HESI Cardiac Biomarkers Working group. The goal of new tests will be particularly focused on improving risk assessment of prothrombotic conditions that might predispose to myocardial infarctions, thrombosis/thromboembolism, and/or stroke. The gaps and opportunities listed above will be the focus of the HESI Cardiac Biomarkers Working Group in the near future.
Integrative Strategies Working Group

Leadership:

• Brian Berridge, GlaxoSmithKline
• Dusty Sarazan, DSI

Objectives

• To span the structure-function interface assessing the sensitivity of current assessments, identifying new opportunities and filling gaps
• Structural and functional assessments often assessed separately in contemporary drug development

• We’ve done such a great job handling acute risks that chronic risks are now more of an issue

• Multi-disciplinary workshop held
  • recommend more integrated and holistic approaches
Cardiovascular Function in Nonclinical Drug Safety Assessment: Current Issues and Opportunities

R. Dustan Sarazan, Scott Mittelstadt, Brian Guth, John Koerner, Joanne Zhang, and Syril Pettit

Regulatory Toxicology and Pharmacology 65 (2013) 38–46

Integrated and translational nonclinical in vivo cardiovascular risk assessment: Gaps and opportunities

Decreased Contractility (- inotrope)

Reduced ability to do work

Heart Failure

beta blockers

Increased Contractility (+ inotrope)

Increases work performed by the heart

Catecholamines, PDE4 inhibitors, calcium sensitizers, etc

Increases myocardial oxygen consumption, which can be detrimental in the face of limited coronary perfusion, precipitating regional myocardial ischemia.

How effectively do we capture these effects in animal studies?
HESI Survey of pharmaceutical companies: What contractility Studies Are Conducted?

- Data from 5 responding companies
  - 15 different models
  - 65 different compounds
- Little consistency in models used
- Large number of compounds used to validate models with little overlap of models and compounds
- No obvious basis upon which to base a cross-lab comparison with existing data
- Available data doesn’t allow for assessment of sensitivity to pick up subtle effects!
New HESI Experimental Study: How predictive are preclinical models for clinically relevant changes in contractility?

- Designed and initiated multi-site experimental study to assess the predictivity of non-clinical contractility studies for known clinical outcomes (positive and negative inotropes);
- Harmonized study protocol (with 6 participating labs) for in vivo telemetry (dog and rat) and echocardiography (dog only). Studies will assess two positive and two negative inotropes;
- Engaged US FDA statistics expert; outreach to academia for further statistics assistance.
Cardiotoxicity of kinase inhibitors: the prediction and translation of preclinical models to clinical outcomes

Thomas Force* and Kyle L. Kolaja†
<table>
<thead>
<tr>
<th>Patient susceptibility conditions</th>
<th>Measurable endpoints (in vitro or in vivo)</th>
<th>Comment</th>
<th>What's the 'alternative' model of this susceptibility?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ischemia/reduced cardiac perfusion</td>
<td>measures of cell injury (e.g. cTn release) or decreased contractility in low O2 conditions</td>
<td>primarily that ischemia that occurs secondary to coronary artery disease</td>
<td>acute coronary ligation; cell culture under hypoxic conditions</td>
</tr>
<tr>
<td>mitochondrial dysfunction</td>
<td>contractility; measures of cell injury/death; measures of oxidative stress</td>
<td>would include both heritable and acquired forms of mitochondrial dysfunction; e.g. as a sequela to metabolic syndrome</td>
<td>transgenic model of mito dysfxn; pre-treatment with anthracycline</td>
</tr>
<tr>
<td>decreased cardiac reserve</td>
<td>measures of contractility under stress (echo)</td>
<td>that might occur as a sequela to any progressive cardiac dz</td>
<td>dobutamine challenge</td>
</tr>
<tr>
<td>basal decrease in contractility</td>
<td>echocardiography assessment of contractility</td>
<td>manifestation of a remodeled heart or significant mitochondrial dysfxn</td>
<td>chronic heart failure model?</td>
</tr>
<tr>
<td>heart block/arrhythmia</td>
<td>ECG</td>
<td>representing pre-existing electrical dysfunction (are there common forms like atrial fib that should be considered</td>
<td>?arrhythmia model</td>
</tr>
</tbody>
</table>
HESI-SPS WORKSHOP:

STEM CELL-DERIVED CARDIOMYOCYTES AS MODELS OF CARDIAC PATHOBIOLOGY AND TOXICITY

MARCH 18-19, 2013
CAMBRIDGE, MA, AMGEN, INC.

Workshop Co-Chairs: Hugo Vargas (Amgen), Dr. Kevin Dreher (US EPA)

Objective: To bring together an international and multi-disciplinary group of scientists to evaluate the use of stem cell platforms and associated technologies in the nonclinical cardiovascular risk assessment of pharmaceuticals and environmental chemicals.

Next generation of opportunities!
In Summary

- HESI cardiovascular safety efforts are world-leading
- Strong engagement of a multi-disciplinary group of academic, government, and industry scientists worldwide
- Effective scientific communication and outreach activities and plans (SOT, SPS, ACT, China SOT, FDA, EMA, PMDA)
- Set apart from other initiatives…
  - FDA-HESI partnership on IND/NDA data
  - Global approaches to Integrated CV Evaluation
  - Impacting best practices to improve safety, health, and appropriate resource use
Acknowledgements

Cardiac Safety Committee Advisory Panel
Advisory Team of Senior Scientists Established to Provide Input on Overall Program Direction and Impacts

Dr. Norman Stockbridge, US FDA
Dr. Eugene Herman, US FDA
Dr. Eric Schultze, Lilly
Dr. Jean-Pierre Valentin, AstraZeneca
Dr. Kendall Wallace, University of Minnesota
Dr. Dusty Sarazan, Data Sciences International
Dr. John Koerner, FDA
Dr. Marjory Brooks, Cornell University
Dr. Frank Sellke, Lifespan Heart Center
Dr. Brian Berridge, GlaxoSmithKline, Co-Chair
Dr. Kevin Dreher, US EPA, Co-Chair
Dr. Hugo Vargas, Amgen, Inc.

Staff: Syril D. Pettit, MEM, HESI Executive Director
Jennifer B. Pierson, MPH, HESI Scientific Program Manager

+ member organizations + great scientific collaborators

ILSI Health and Environmental Sciences Institute


