Technical Committee on Cardiac Safety (TCCS)

HESI Board of Trustees Program Strategy and Stewardship (PSSC) Review – July 2009
I. Introduction to Committee Composition, History, and Objectives: 
   Brian Berridge, GlaxoSmithKline (5 minutes)

II. ProArrhythmia Project – Jean-Pierre Valentin, AstraZeneca (10 minutes)

III. Cardiac biomarkers project – Malcolm York, GlaxoSmithKline (10 minutes)

IV. Structure-Function project – Dusty Sarazan, Covance (10 minutes)

V. Summary and Petition – Brian Berridge, GSK (5 minutes)
Mission

• To develop and disseminate improved data, approaches, and resources for the evaluation of preclinical and clinical cardiovascular toxicity.

• Bring preclinical scientists, clinicians, and regulators together to address issues of contemporary concern relating to clinical cardiovascular safety.
Some background...

- Cardiac Safety Technical Committee was born of strategic reorganization of existing programs - not de novo committee formation!

- HESI BOT authorized this reorganization in concept at July 08 board mtg.

- Cardiac Safety TC initiated as an official assessing committee on Jan 1 ‘09.
Why this consolidation?

- Avoids duplication of effort and facilitates communication across HESI’s cardiovascular efforts;

- Creates opportunities for synergy and shared resources/expertise;

- Creates expanded membership base for existing cardiac projects;

- Responsive to FDA’s Critical Path directive to undertake programs to evaluate cardiac markers and cardiac safety.
Committee Composition

Currently the coordinating body for:

- Biomarkers of Cardiac Toxicity Project
- ProArrhythmia Models Project
- Structural and Functional Evaluation of CV Safety Project
- Outreach with other related cardiac programs (e.g., Duke CSRC)
Committee Participation

- 17 International Pharmaceutical Companies
- Government (FDA, EMEA, Japan)
  - Regulatory
  - Research
- Academia
  - Nonclinical and clinical research
- Medical
  - Clinical cardiologists
- Other Consortia
  - Duke Cardiac Safety Research Consortium
Advisory Team

Advisory Team of Senior Scientists Established to Provide Input on Overall Program Direction and Impacts

- Dr. Norman Stockbridge, US FDA (Dir. FDA CardioRenal)
- Dr. Eugene Herman, US FDA
- Dr. Malcolm York, GlaxoSmithKline
- Dr. Jean-Pierre Valentin, AstraZeneca
- Dr. Kendall Wallace, U. of Minnesota
- Dr. Brian Berridge, GlaxoSmithKline
- Dr. Dana Walker, Bristol-Myers Squibb
- Dr. Dusty Sarazan, Covance
- Dr. John Koerner, FDA

- Liaisons to Duke CSRC:
  - Dr. Mitch Krucoff, MD, Duke U. (liaison to CSRC)
  - Dr. Jon Finkle, MD, GlaxoSmithKline (liaison to SCRC)

Staff: Syril D. Pettit, MEM, HESI Associate Director
Value of Merged Oversight of HESI Cardiac Programs

Establishes HESI as a leading resource for collaborative Cardiac Safety programs. This is a uniquely integrated effort unparalleled within the industry.

➢ *Hope to show you evidence of this today!*
A HESI Consortium Approach to Assess the Human Predictive Value of Non-clinical Repolarization Assays

Project Co-Chairs
Dr. Jean-Pierre Valentin, AstraZeneca
Dr. John Koerner, FDA
To develop a better fundamental understanding of the emerging science, trends, and techniques associated with developing better predictors of drug-induced Torsades de Pointes (TdP).
Project Objectives

**Stage I** - To assess the concordance between non-clinical repolarization assays and clinical measures of QT interval prolongation;

**Stage II** - To investigate the mechanisms for any discrepancy identified between non-clinical and clinical results and to determine successful alternative approaches to identify these compounds; and

**Stage III** - To assess the proarrhythmic potential of such compounds.
Stage 1 Goals

- Quantitative integrated risk assessment (i.e., concentration-response relationship) based on both non-clinical and clinical repolarization assays.

- Establish the sensitivity, specificity and overall predictivity of each assays alone or in combination with respect to the clinical outcome.

- Identify compounds for which there is a lack of concordance between non-clinical and clinical assays.

Projected completion date – December 2010
Stage I Strategy

- Develop database structure to house and allow for analysis of available data.
- Generate information on ~100 drugs
  - a wide range of chemical, pharmacological and therapeutic classes
- Establish **quantitative** criteria regarding the predictive value to man of non-clinical repolarisation assays
  - Evaluate each pre-clinical signal against multiples of the free (or total) therapeutic concentration of the compounds tested in the First Time in Man (FTIM) and TQT study
  - Compare the concentration response curves in all assays
- Establish correlation between assays
- Establish concordance between each pre-clinical assays and the clinical outcome in relation to the therapeutic free (or total) concentration
Concentration-Response Curve Examples

**Concordance**

- hERG
- Predicted therapeutic free Cmax
- QTc Dog
- QTc Human

**Non-Concordance**

- hERG
- Predicted therapeutic free Cmax
- QTc Dog
- QTc Human
Stage I Status

- Database structure constructed by FDA staff with significant input from HESI team;
- Nonclinical data (submitted to FDA by sponsors) on ~50 compounds entered by FDA staff, clinical data to be entered over summer for these compounds.
- HESI project team proposed formats for data export/presentation to facilitate analysis while maintaining anonymity/CBI of the data;
- Project has stimulated high level internal discussions at FDA about value/options for sharing data so that the pooled resources of FDA datasets can be a benefit to broader drug safety community;
- Initial assessments of concordance on limited dataset to be performed in August 2009.
- Preliminary data assessment to be presented at SPS in Sep ‘09, France.
Stage 1 - Publication

Proposed Stage II Goal

Attempt to understand the mechanistic basis for the lack of concordance between non-clinical and clinical repolarization assays for compounds identified in Stage I and determine whether non-clinical assays and/or clinical approaches can be put in place to detect them

Projected completion date – December 2012
Stage II Strategy

• Exploratory non-clinical studies will be conducted to elucidate the “apparent” discrepancies between non-clinical and clinical repolarization assay outcomes

• The selected compounds could be evaluated in the most relevant and promising assays based on the suspected scientific issues and our scientific understanding of the issues at the time

• Models may include but are not limited to assessment of:
  – Trafficking of the hERG channel protein to the plasma membrane;
  – Drug accumulation in the cardiac tissue; trapping within the hERG channel;
  – Drug effects on autonomic tone;
  – Activity at other cardiac ion channels e.g., IKs, ICa, INa;
  – Hypoglycaemia / hypothermia
Anticipated Impact

- **Short term**: To increase our understanding and confidence of the predictive value to humans of pre-clinical electrophysiological studies

- **Long term**: Potentially to alleviate the need for a mandatory requirement of the “thorough QT/QTc study”
Br. Journal Pharmacology
Volume 154 Issue 7, Pages 1379 – 1553
(August 2008)


Cellular basis of drug-induced torsades de pointes (p 1502-1507). D M Roden

The impact of varying autonomic states on the dynamic beat-to-beat QT–RR and QT–TQ interval relationships (p 1508-1515). A A Fossa

In vitro models of proarrhythmia (p 1516-1522). C L Lawrence, C E Pollard, T G Hammond, J-P Valentin

Literature-based evaluation of four 'hard endpoint' models for assessing drug-induced torsades de pointes liability (p 1523-1527). M A Vos

Sensitive and reliable proarrhythmia in vivo animal models for predicting drug-induced torsades de pointes in patients with remodelled hearts (p 1528-1537). A Sugiyama

Strategies to reduce the risk of drug-induced QT interval prolongation: a pharmaceutical company perspective (p 1538-1543). C E Pollard, J-P Valentin, T G Hammond

Key clinical considerations for demonstrating the utility of preclinical models to predict clinical drug-induced torsades de pointes (p 1544-1549). P T Sager

Cardiac Biomarkers Project

Chair: Dr. Malcolm York, GlaxoSmithKline
Vice-Chair: Dr. Dana Walker, Bristol-Myers Squibb
ILSI HESI Cardiac Troponins Initiative – Major Goals:

- **Analytical Validation** - of selected cTn assays, establish degree of assay cross-reactivity, linearity, detection limit and imprecision for rat, dog and monkey

- **Biological Qualification** - establish diagnostic window for detectable signal with drug-induced active cardiomyocyte injury and:
  - Establish the diagnostic window of cTn in different forms of cardiomyocyte injury
  - Correlation with cardiac histopathology
  - Whether diagnostic advantage to measuring cTnI +/- or cTnT

- **Identifying Gaps and Best Practices** – providing forum for discussion on use of cTn for cardiac safety in nonclinical and clinical settings.
Analytical Characteristics of cTn I and T Immunoassays with Sera from Rats, Dog and Monkeys Subjected to Acute Myocardial Injury - “Cross-reactivity”

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G-good response; A-adequate response; W-weak response; N-no response.

Time Course Characterization of Serum cTn and Morphologic findings with Isoproterenol-Induced Acute Myocardial injury in the Rat

SUMMARY

• Increased serum cTn and myocardial morphologic changes were both seen at the earliest time point (0.5h)
• Increased serum cTn and lesion scores were dose-dependent
• Serum cTn values peaked in the early phases of myofiber degeneration (2-3h). Time course and magnitude (fold change) of cTnI and cTnT were comparable
• Highest morphologic lesion scores occurred during intervals of declining cTn values
• Temporal disconnect between maximal serum cTn and histopathology findings in this experimental model

Clements et al 2007, preliminary communication
Full manuscript for journal submission by YE ‘09
Communicating Results

• FDA Grand Rounds on Cardiac Troponin. Committee Chair presented overview of HESI research and future activities to Agency staff at White Oak, MD.

  – December 2008
Clinical Pathology, cTnT and Heart Histology Findings

6-Week Intravenous Injection Toxicity Study with Doxorubicin and Etoposide in Rats

A collaborative effort with HESI Genomics Committee
‘doxorubicin study’
Progressive low level increase in Cardiac Troponin T levels over 6 weeks in Rats dosed with Doxorubicin at 2 and 3 mg/kg/week
Macro- and microvesicular vacuolation of individual cardiac myocytes was present in the atria and ventricles of doxorubicin-treated animals and was associated with low level increases in cTnT.

- Vacuolation occurred with increasing frequency and severity over time with or without continued weekly exposure to drug.
- Minimal to mild vacuolation could be seen in individual animals not given doxorubicin and was often difficult to distinguish from doxo-associated vacuolar change.
- Morphologic changes at the light microscopic level may under-represent the severity of cellular injury and dysfunction.
- Other forms of cardiac injury (e.g. myocardial necrosis, rodent progressive cardiomyopathy) were occasional and coincidental changes.
- The cTnT signal fold change was greater than the cTnI signal (Access) in animals with macro and microvesicular vacuolation.
6-Week Intravenous Injection Toxicity Study with Doxorubicin and Etoposide in Rats

**Further Investigations-Assay of cTnI using a research ultrasensitive method (in progress)**

- Collaboration with Nanosphere inc- A nanotechnology based molecular diagnostics company
- Assess cTnI release in samples collected from Doxorubicin study using a research ultrasensitive method developed by Nanosphere
  - Assay has been designed, immunoreactivity established using purified cTnI standards (Hytest)
  - Confirmed immunoreactivity in samples obtained from the rat with isoproterenol- induced myocardial injury
  - Data generated during May 2009 (2 years post sampling)
cTnI Measurement Using the Nanosphere Research Ultrasensitive Assay

Samples collected during Week 4 of the study (following 4 weekly doses of Doxorubicin).
Number of animals per group = 6

![Graph showing Group mean cTnI (pgs/mL) + 1SD for different Doxorubicin dosing schedules](image)

- control
- 2mg/kg/wk + 2R
- 3mg/kg/wk + 2R
- 2mg/kg/week
- 3mg/kg/wk
- CONTROL
- 1mg/kg/wk
- 2mg/kg/wk
- 3mg/kg/wk

**Doxorubicin Dosing Schedule**
Serial Measurements of Serum cTnI Correlated with Cardiac Histopathology

- Male rats administered weekly combination of Dexrazoxane (50 mg/kg) and Doxorubicin (2mg/kg)
- Measured with Nanosphere Research ‘ultrasensitive assay’
Preliminary (Draft) conclusions from Investigation into Nanosphere assay using samples from IV toxicity study with Doxorubicin and Etoposide in Rats

• cTnI levels in control males ranged from 0 to 4.5 pg/mL, with the majority of values <3.0 pg/mL

• Assay precision in duplicates variable (mean CV = 46%)

• Progressive response in serum cTnI concentration observed, proportionate to dose administered and to duration of dosing.

• Correlation of increased cTnI values with cardiac histopathology in individual animals at study intervals of 4 and 6 weeks (see spreadsheet), reflecting doxorubicin associated vacuolation in the atrium or ventricles or incidental findings of myocardial injury.

• Responses obtained in samples approximately 2 years old

• The assay can potentially add value in the investigation of low level cardiomyocyte injury in the rat.
INVITATIONAL WORKSHOP ON BRIDGING PRECLINICAL AND CLINICAL UNDERSTANDING OF CARDIAC TROPONINS AS A TOOL TO EVALUATE DRUG-INDUCED CARDIOTOXICITY

February 2008
Washington, D. C.

Attendees from Pharma, clinical medicine and regulatory bodies
Nonclinical Recommendations

A sampling...

- Monitoring of circulating cTn in preclinical studies should be considered appropriate for application as a relevant and sensitive biomarker for drug-induced active cardiomyocyte injury.

- Selection of an appropriate assay should include consideration of the relative sensitivity and specificity of the available assays in relation to the species being evaluated. New assays should be subject to appropriate analytical validation and biological qualification in laboratory animal species prior to use.

- Interpret cTn data with respect to individual animal variability, group means, dose response, histological correlates, thresholds of concern.
Clinical Recommendations

A sampling...

- Appropriate clinical monitoring strategies should consider the preclinical *in vivo* findings (including the character of the cardiac lesion, dose-response curve and the potential reversibility of damage) as well as include appropriate correlative endpoints (e.g., echocardiography, serum markers like BNP, etc.).

- Clinical cTn data should be interpreted in light of several factors, such as the risk identified in the preclinical studies, the relevant reference ranges for each tested population, individual baseline values for each patient, correlative clinical signs, and the relevant clinical history.

- Responses to changes in cTn concentrations should consider the risk identified for the drug, patient risk factors (e.g. pre-existing or concurrent disease), and the potential risk to benefit ratio for the drug being administered.
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.

Brian R. Berridge, DVM, PhD; Syril Pettit, MS; Dana B. Walker, DVM, PhD; Alan S. Jaffe, MD; Albert E. Schultze, DVM, PhD; Eugene Herman, PhD; William J. Reagan, DVM, PhD; Steven E. Lipshultz, MD; Fred S. Apple, PhD; Malcolm J. York, Mphil

Accepted on April 23, 2009, to the Am. Heart Journal
Exploring Next Steps for Cardiac Biomarkers

- Completion of planned/ongoing manuscripts

- Exploring possibility of a ‘normal animal’ cTn database with NIEHS.

- Working group discussing ideas stimulated during June workshop. Proposals under consideration by team members and to be developed in coming weeks.

  - Other markers of cardiac injury?
  
  - Other models?
Newly Initiated Cardiac Efforts at HESI

- January 14, 2009: First joint meeting of newly formed Cardiac Safety Technical Committee
  - Workshop on Structural and Functional Cardiac Toxicity proposed at this meeting

Just over 4 months later....

Workshop held June 2, 3, 4, 2009
CURRENT PRACTICE IN STRUCTURAL AND FUNCTIONAL ASSESSMENT OF CARDIOVASCULAR TOXICITY: ISSUES AND OPPORTUNITIES

JUNE 2-4, 2009
THE MADISON HOTEL
WASHINGTON, DC 20005
Overview

• Discussion of morphologic and functional evaluation of potential cardiovascular toxicity of pharmaceuticals.

• Unique opportunity to learn from:
  ✓ Industry, academia, medical practitioners, and government (regulatory and research) scientists
  ✓ Nonclinical and Clinical Scientists
  ✓ Structural and Functional Approaches

~60 scientists from US, Europe, and Japan

- ‘Think tank’ format = limited slides, lots of discussion
Proposed Project Areas for Exploration

**Subteam 1:** Functional Assessment. Focus on evaluation of current practice, the strengths and limitations of current interrogation approaches for risk assessment.
- Acute focus
- Repeat dose focus (including biologics)
- Assay sensitivity
- Structural link
- Clinical link

**Action:** HESI to identify interested parties on Committee to consider organizing an expert panel/white paper → work group/research?

**Subteam 2:** Predictive Strategies. Focus on short to long term preclinical predictions, preclinical to clinical predictions. Will consider integration of structural and functional aspects.

**Actions:** HESI to identify interested parties on Committee to consider formation of working group to ID best practices and new strategies. May lead to white paper and/or research recommendations.
Proposed Project Areas for Exploration

**Subteam 3:** Case Studies. Team will identify one or more compounds for which clinical and nonclinical data are accessible and can be subject of a retrospective analysis (what did we see, do, could have done better).

- **Action:** HESI to identify interested parties on Committee to identify process and focus for case study evaluation. If project moves forward, it is anticipated to result in publication and/or workshop with results, lessons learned.

**Subteam 4:** Rapid Communication of key outcomes from this workshop

- **Action:** Workshop Chairs and HESI manager to take the lead in drafting a ‘communique’ that can be rapidly prepared with focus on high level consensus and next steps from the meeting.

- **NOTE:** Document prepared and to be submitted to journal by July 15
Engaging Other Consortia

- Established informal partnership with Duke Cardiac Safety Research Consortium
- Co-sponsored Cardiac Safety Think Tank Meeting (Bethesda, MD) October 2008, clinical and preclinical attendees, senior regulatory FDA, pharmaceutical, academia
  - Workshop Publication – Accepted American Heart Journal, June 09.
- May consider joint workshop in 2010
In Sum...

- **Between 2008 and 2009**
  - 13 publications accepted or published
  - Organized 3 separate public workshops/symposia (publications completed for all 3)
  - First CRO member to HESI via this committee

- Strong and enthusiastic membership base established;

- Scientific portfolio having significant impact via publications and outreach/meetings;

- Collection of projects within a single header has created the ‘cross-talk’ and synergies that were anticipated (*e.g.*, following June workshop on strux-funx new ideas were stimulated for work by cardiac biomarkers team)
2009 YE

- ProArrhythmia Project continues data entry – initial data analysis
- New Structure Function Project Teams Initiate = expansion of project activities
- Biomarkers – Analysis of ultrasensitive data, publication drafting, new program area designation (e.g., database, ?)

2010

- ProA Project – complete upload, data analysis complete
- Strux Funx Teams – Project areas fully implemented (white papers, case studies, etc.) Will Update PSSC in July ’10 on Timelines and Objectives!
- Biomarkers – Finalize dox and iso publications, proceed with dbase project and ?
- Co-sponsor HESI-Duke CSRC workshop

2011

- ProA Project to phase 2
- Strux Function projects ongoing
- Cardiac Biomarkers – (may or may not be active in this year)
Portfolio of projects (and per company assessment) anticipated to expand in 2010 – member commitment is high.

Budget projections and project membership interest and commitments suggest strong future program.

Budget to be formally reviewed by Cmte in July ’09 – interim review by leadership done.

REQUEST TO PSSC

Committee seeks 3 year charter* to allow for impact of current and planned activities to be maximized.

*Note: Cmte to check in with PSSC with written update on status/timelines of emerging programs (e.g., structure function and future for biomarkers) in July 2010
# Drug attrition, ADRs, drug withdrawal

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<th>CD-FTIM Information</th>
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<th>Ph I to III Attrition</th>
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Legend: Yellow: 0-10%  Orange: 10-20%  Red: >20%