Answers That Matter.

HESI Annual Meeting

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Cardiac Biomarker Working Group – Past, Present, and Future

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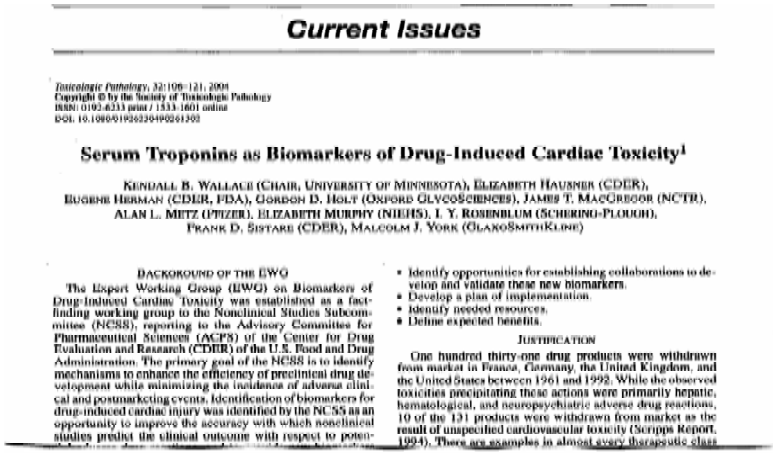
May 11-13, 2010

History

~1998 -- FDA formed Expert Working Group to investigate potential use of cardiac troponins in animals used in preclinical toxicity testing.

~2002 -- Expert Working Groups on Measurement of Cardiac Troponins HESI Biomarker Committee



Current Issues

Toxicologic Pathology, 32:105–121, 2004
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Serum Troponins as Biomarkers of Drug-Induced Cardiac Toxicity[1]

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BACKGROUND OF THE EWG

The Expert Working Group (EWG) on Biomarkers of Drug-Induced Cardiac Toxicity was established as a fact-finding working group to the Nonclinical Studies Subcommittee (NCSS), reporting to the Advisory Committee for Pharmaceutical Sciences (ACPS) of the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration. The primary goal of the NCSS is to identify mechanisms to enhance the efficiency of preclinical drug development while minimizing the incidence of adverse clinical and postmarketing events. Identification of biomarkers for drug-induced cardiac injury was identified by the NCSS as an opportunity to improve the accuracy with which nonclinical studies predict the clinical outcome with respect to poten-

- Identify opportunities for establishing collaborations to develop and validate these new biomarkers.
- Develop a plan of implementation.
- Identify needed resources.
- Define expected benefits.

JUSTIFICATION

One hundred thirty-one drug products were withdrawn from market in France, Germany, the United Kingdom, and the United States between 1961 and 1992. While the observed toxicities precipitating these actions were primarily hepatic, hematological, and neuropsychiatric adverse drug reactions, 10 of the 131 products were withdrawn from market as the result of unspecified cardiovascular toxicity (Scripps Report, 1994). There are examples in almost every therapeutic class

~2008 -- Cardiac Biomarkers Working Group joins new HESI Cardiac Safety Technical Committee

Expert Working Group's Mission

- Advance the scientific basis for the development and application of biomarkers of target organ toxicity.

- Develop a systematic approach based on newly available technologies for the identification and evaluation of biomarkers that *bridge* from the pre-clinical to clinical stages of drug development.

- Provide a scientific forum for building consensus regarding how to apply and reach regulatory acceptance for biomarkers of toxicity in risk assessment.

Initial Focus: Cardiac Troponin

- Analytical and Biological Validation Conducted
- Outcomes
  - **Inherent differences of response of cTn assays in different laboratory animals were identified.**
  - All assays gave variable cTn responses in dog and monkey.
  - All Assays except Tosoh, Ortho and DPC gave adequate but variable responses in the rat. Tosoh assay not acceptable for the rat.
  - DPC and Ortho gave minimal cTnI responses in 2 strains of rat.

Clinical Chemistry 54:12
1982–1989 (2008)

Analytical Characteristics of Commercial Cardiac Troponin I and T Immunoassays in Serum from Rats, Dogs, and Monkeys with Induced Acute Myocardial Injury

Fred S. Apple,[1*] MaryAnn M. Murakami,[1] Ranka Ler,[1] Dana Walker,[2] and Malcolm York,[3] for the HESI Technical Committee of Biomarkers Working Group on Cardiac Troponins[4†]

BACKGROUND: Information is needed regarding analytical characteristics of cardiac troponin (cTn) assays used in preclinical studies.

METHODS: We measured cTnI and cTnT in serum from normal animals and animals with induced myocardial injury [Sprague–Dawley (SD) and Wistar rats, beagle dogs, and rhesus (Rh) and cynomolgus (Cy) monkeys]. We evaluated the following assays: for cTnI, Abbott Architect, Bayer Centaur (first and second generation), Beckman Access, DPC Immulite, Dade Dimension, Ortho Vitros ES, Tosoh AIA, and species-specific enzyme immunoassays; for cTnT, Roche Elecsys.

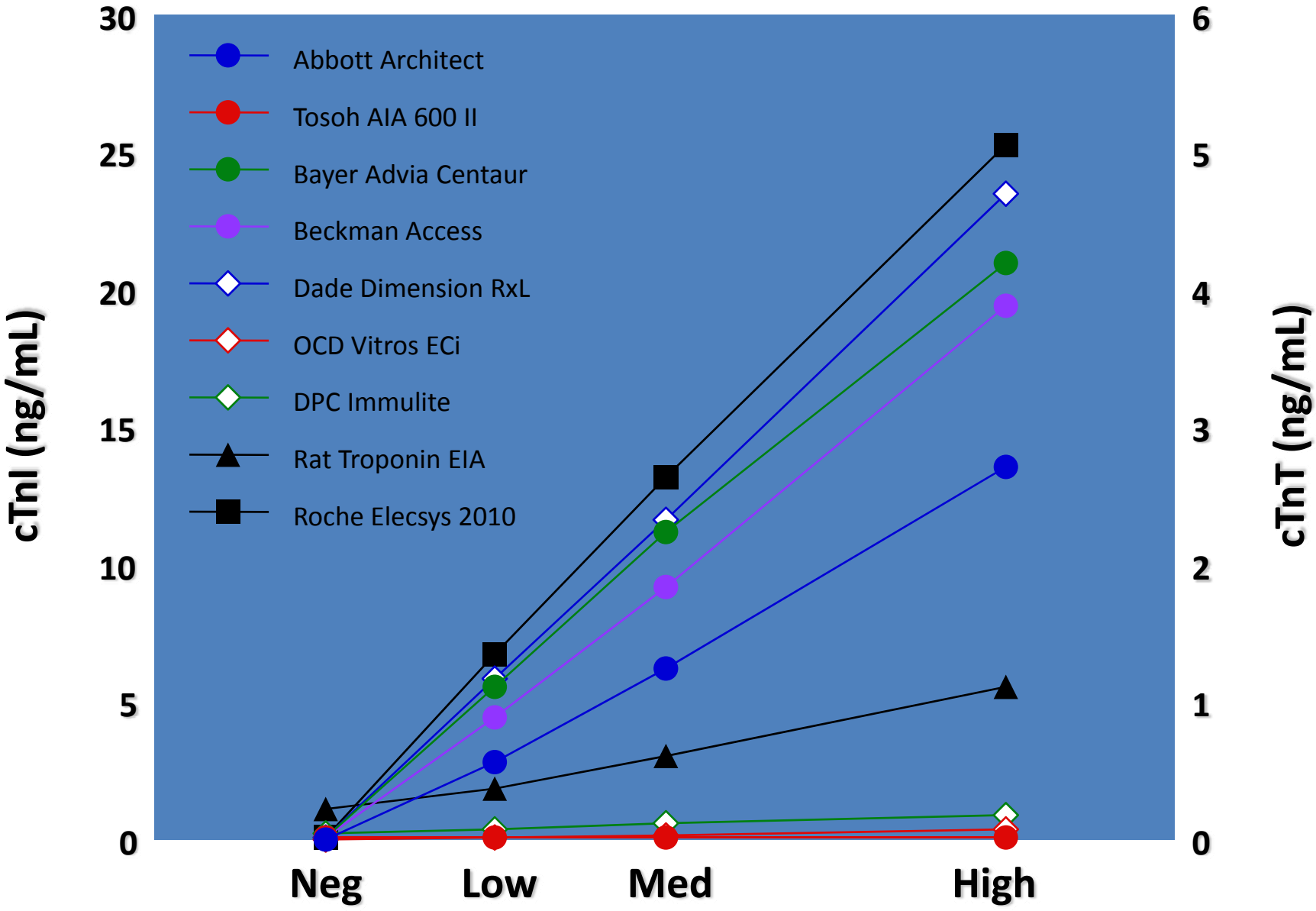
RESULTS: We found different species-specific responses for the troponin assays evaluated. Abbott, Bayer Ultra, Beckman, and Dade assays gave good responses across

the Bayer first generation (rat, monkey), Roche cTnT (rat, dog), and DPC (rat) assays.

CONCLUSIONS: Not all cTn assays are suitable for monitoring cTn in each animal species or strain. Individual assay characterization by animal species is needed to prevent misinterpretation of myocardial injury–based cardiac troponin findings.

Cardiac troponin I (cTnI)[5] and T (cTnT) are definitive biomarkers for detection of myocardial injury in humans (*1–4*) and have proven utility in preclinical studies for drug-induced cardiac injury in animals (*5–7*). Increases in serum cTn also correlate with morphological changes in the heart (*7*). The concordance between

Comparison of cTn Measurement in the SD Rat



Apple *et al.,* Clinical Chemistry. 2008; 54, 1982-1989.

HESI Validation Plan

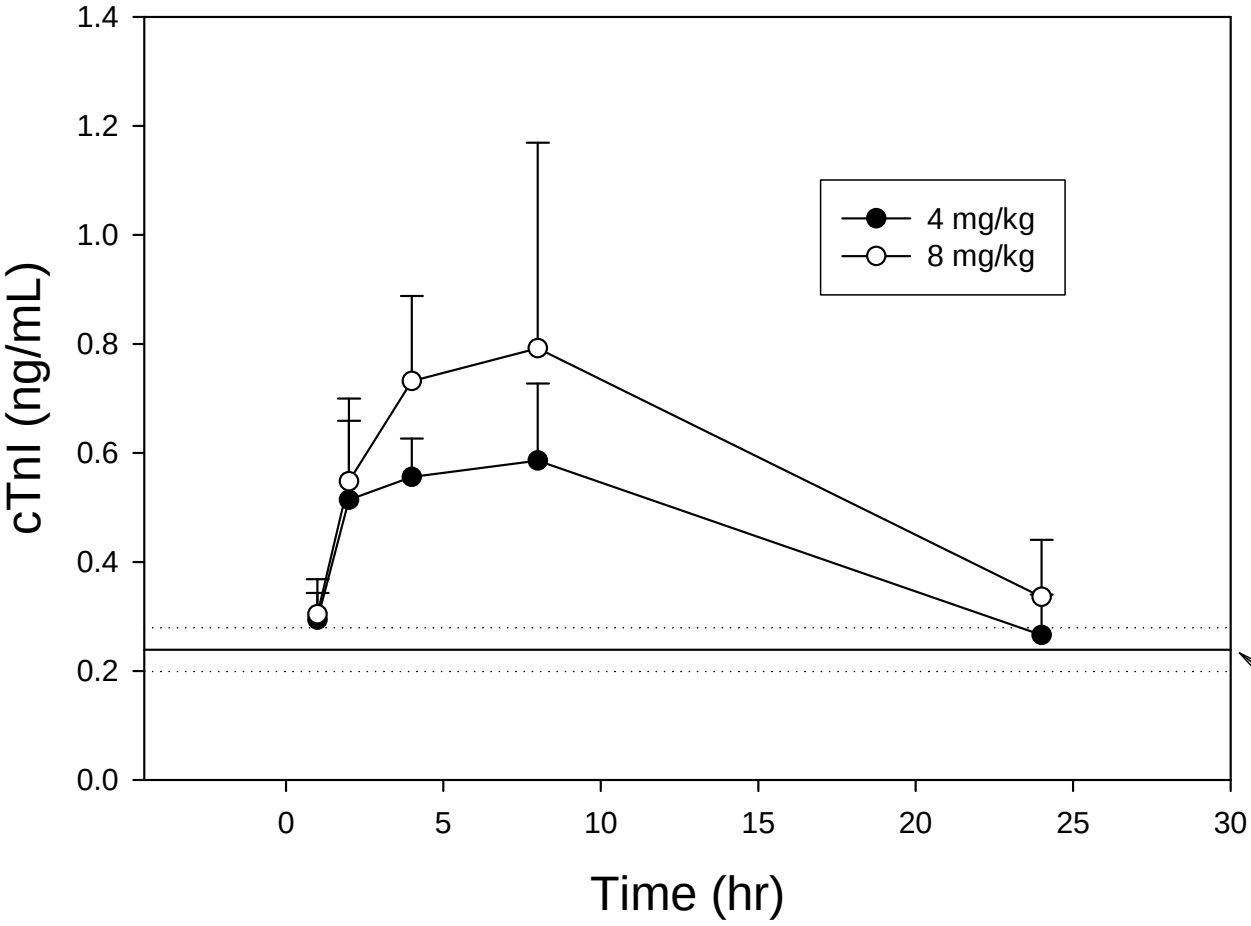
Phase II – Biologic Validation (*work in progress*)

- Acute models of cardiac toxicity (isoproterenol, allymine HCl) (*work completed; manuscript submitted*)

- Chronic models of cardiac toxicity (doxorubicin, PPARs, others) (*work completed, manuscript in preparation*)

cTnI in Rats

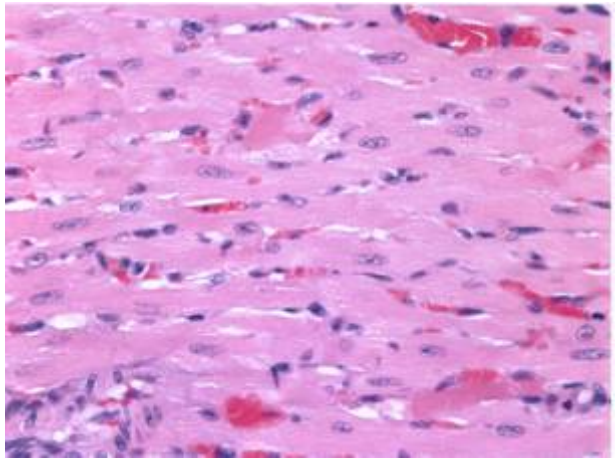
Timecourse of cTnI in serum following sc injection of isoproterenol-HCl
(n=5 male F344 rats per dose per timepoint with Std Deviation error bars)



Histologic injury is not evident until 24-48 hours.

Temporal development of isoproterenol-induced cardiac injury

- 4 mg/kg sc. in F344 rats



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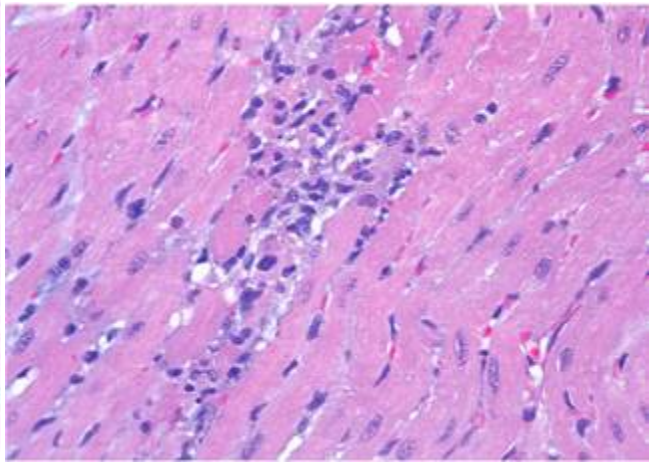

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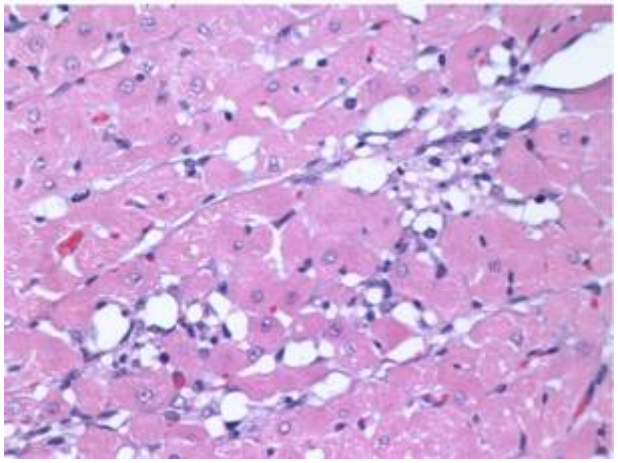

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A Forum for Discussion Between Nonclinical and Clinical Communities

HESI

ILSI Health and Environmental Sciences Institute

INVITATIONAL WORKSHOP ON BRIDGING PRECLINICAL AND CLINICAL APPLICATION OF CARDIAC TROPONINS AS A SAFETY BIOMARKER
February 14-15, 2008

9:00 am – 9:15 am	**Introduction: Statement of goals for the workshop, key issues to be discussed (e.g., gaps in translating preclinical to clinical, etc.)** -
9:15 – 10:15	**Cardiac Troponins in Preclinical Safety Assessment** o **Technical assay validation issues: HESI Troponins Committee Experience.** M. York-GSK. 20 min. (confirmed) o **Isoproterenol and Doxorubicin** (G. Herman, FDA)
10:15 – 11:05	**Interpreting Cardiac Troponins in the Context of Clinical Trials – A Case Study from the Pharmaceutical Sector** - R. Lewis, GSK
11:20 – 11:50	**Issues in Interpretation and Application of cTn data – Perspective from a Regulatory Scientist.** Robert Kane, MD, FACP, Division of Drug Oncology Products, CDER, FDA. Confirmed.
12:00– 12:20	**Databases and Data storage of Cardiac data at FDA** – J.Levine/T. Papoian (FDA).
1:30 – 2:15	**Use of Troponins in the Clinic – Current Practice and Issues.** – Alan Jaffe, M.D., Mayo Clinic. (confirmed)
2:30 – 3:15	**Cardiac Troponin Evaluation in Oncology** – Dr. Stephen Lipshutz, U. Miami *(confirmed)*
3:45 – 4:30	**Evaluation of Cardiac Troponin in Clinical Trials** - Dr. David Morrow, Brigham and Women's Hospital, Harvard University. *(confirmed)*
4:30 – 4:45	**Q&A**
4:45	**Wrap-up and Adjourn Day One**
5:00 – 6:30	**RECEPTION**

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Volume 158, Issue 1, Pages 21-29 (July 2009)

previous 7 of 34 next

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[a], Syril Pettit, MS[b], Dana B. Walker, DVM, PhD[c], Alan S. Jaffe, MD[d], Albert E. Schultze, DVM, PhD[e], Eugene Herman, PhD[f], William J. Reagan, DVM, PhD[g], Steven E. Lipshultz, MD[h], Fred S. Apple, PhD[i], Malcolm J. York, MPhil[j]

Received 23 April 2009; accepted 23 April 2009.

Cardiac troponins (cTns) are established biomarkers of ischemic heart disease in humans. However, their value as biomarkers of cardiac injury from causes other than ischemic heart disease is now being explored, particularly in drug development. In a workshop sponsored by the Cardiac Troponin Biomarker Working Group of the Health and Environmental Sciences Institute, preclinical, clinical, and regulatory scientists discussed the application of cTns in their respective environments, issues in translating the preclinical application of cTn to clinical studies, and gaps in our understanding of cTn biology and pathobiology. Evidence indicates that cTns are sensitive and specific biomarkers of cardiac injury from varying causes in both animals and humans. Accordingly, monitoring cTns can help ensure patient safety during the clinical evaluation of new drugs. In addition, preclinical characterization of cardiac risk and cTns as biomarkers of that risk can guide relevant clinical application and interpretation. We summarize here the outcomes of the workshop which included consensus statements, recommendations for further research, and a proposal for a cross-disciplinary group of clinical, regulatory, and drug development scientists to collaborate in such research.

ABSTRACT
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PII: S0002-8703(09)00297-X

doi:10.1016/j.ahj.2009.04.020

previous 7 of 34 next

Cardiac Biomarkers Working Group

- **Chair:** Dr. Eric Schultze, Lilly

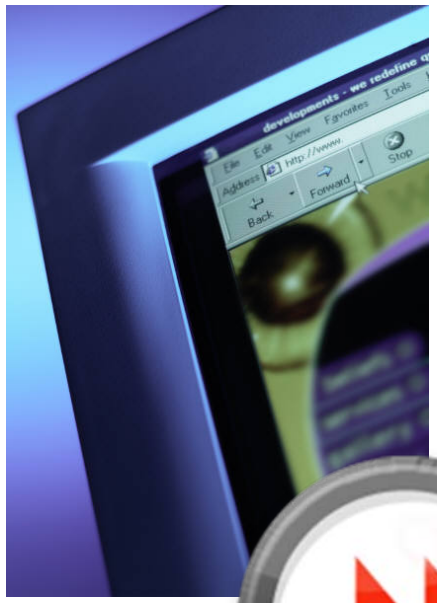
- **Objectives:**
  - Develop and disseminate improved data, methods, approaches, and resources for the evaluation and interpretation of preclinical and clinical biomarkers of cardiac toxicity
  - Expand previous cardiac troponin work to encompass other markers of cardiac physiology and safety

- **Current Focus:** Evaluate current experimental practice in assessment of hemostasis.

Biomarker Development Strategies

Forward development:

- Preclinical ➡ Clinical
- HESI Biomarkers of Nephrotoxicity Committee, C-Path Institute Predictive Safety Testing Consortium (PSTC)
- Evaluation of nephrotoxicity
  - Alpha-GST, u-GST, RPA-1, KIM-1, Albumin, Clusterin, Trefoil Factor-3,Total protein, B2 Microglobulin, Cystatin C
- Some attrition expected
- Slower development



Biomarker Development Strategies

Reverse development:

- Clinical ➡ Preclinical
- “Pick the low-hanging fruit”
- Higher probability of success
- Cardiac troponins I and T
- ILSI/HESI Troponin Expert Working Group
- Management enthusiasm

New Directions

ISSUE

- **Thromboembolic risk** is a significant clinical concern for compounds with putative cardiovascular effects - particularly in Western patient populations.

- Currently used screening assays, particularly in those used in rodents, often **lack adequate sensitivity and specificity** to detect chronic but important changes in hemostasis (both tendencies for hypercoagulable and hypocoagulable conditions) which may affect cardiac health and function.

Working Group Action

- Review and expand the investigation of biomarkers of thrombosis and hemostasis as they apply to determining risk of cardiovascular disease and translational medicine.

Hemostasis Survey Objectives

- **Define current state of practice** re: endothelial injury markers for most pharmaceutical companies in screening mice, rats, dogs, and monkeys.

- **Establish how, when, and where** the pharmaceutical development community is evaluating alterations in the hemostatic system in drug development? What assays/techniques are used?

- **Collect input on the availability of "novel" markers** of endothelial injury, platelets, coagulation, and fibrinolytic factors that would provide more value for cardiac safety as translational biomarkers?

Development of Web-Based Survey

- Online survey
- Distributed to nonclinical and clinical scientists (industry, government, and academia)
- Anonymous responses allowed

Hemostasis Survey Content

- Contact Information – ID or anonymous
- Organization/Affiliation
- Endothelial thrombotic properties
- Endothelial antithrombotic properties
- Blood vessels
- Platelets – quantitative
- Platelets -- function

[SURVEY PREVIEW MODE] Hemostasis Survey - Windows Internet Explorer

http://www.surveymonkey.com/s.aspx?PREVIEW_MODE=DO_NOT_USE_THIS_LINK_FOR_COLLECTION&sm=J810qNas%2b8KMfSFQWkQXyY231WZnvYFwJs%2bWKs9Ml6U%3d

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Exit this survey

Hemostasis Survey

2. Contact Information - OPTIONAL!

25%

Note: even if you choose to include this information it will NOT be cited in the collective analysis and distribution of the results. It will be used only as a means of contacting you to clarify responses and provide summary results of the survey.

1. Name

2. Affiliation/Company

3. Email Address

4. Mailing Address

*** 5. Please choose the option that best describes your current area of work in drug development (select all that apply)**

- Drug discovery/Lead optimization (nonGLP studies)
- Preclinical (animal) GLP/Regulatory studies
- Human Clinical Trials

*** 6. Job Description of Respondant (check all that apply)**

- Veterinary clinical pathology
- Veterinary anatomic pathology
- Toxicology
- Discovery science
- Laboratory technician

Done Internet 100%

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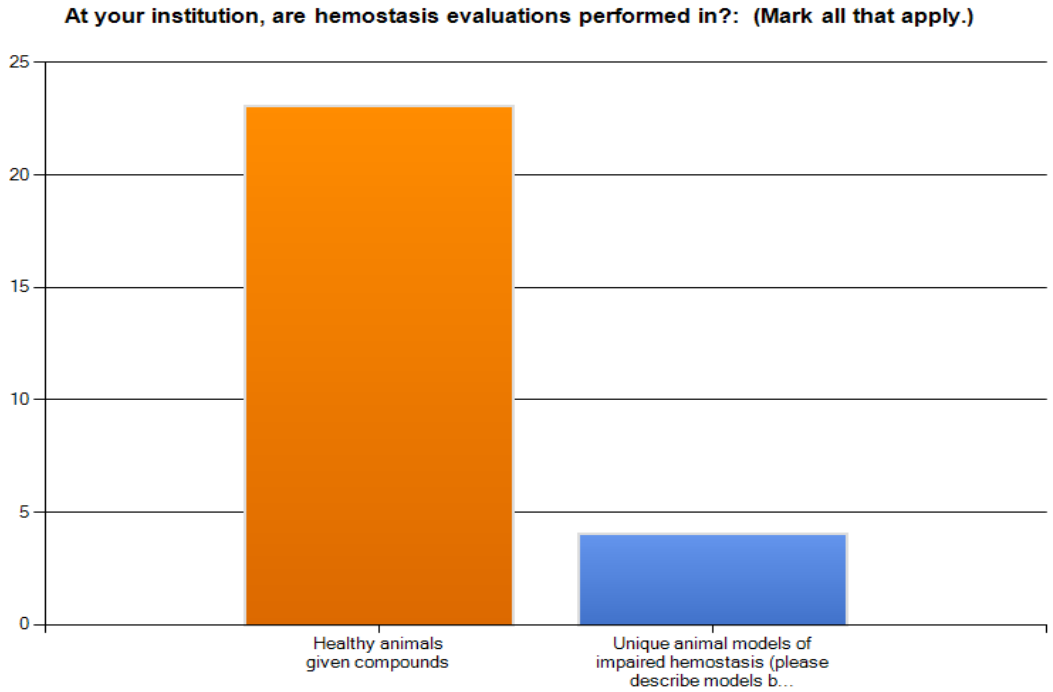
Hemostasis Survey (continued)

- Coagulation
- Fibrinolysis
- Current practices – animal models
- Hemostasis gaps in preclinical and clinical studies
- Successful translational biomarkers
- Comfort level of tests results for hemostasis testing in various animal species

Just a sampling…



2. At your institution, what is the most prominent gap in hemostasis testing in preclinical studies?

- *No coagulation studies done on exploratory rat and mouse*
- *Studies are too minimal – no systemic exposures assessed, studies not done routinely.*
- *Lack of readily available D-dimer assay with good cross reactivity in rat/mouse*
- *Lack of translational capabilities for many non-standard biomarkers (like TAT)*
- *Interaction between platelets and endothelium not well characterized.*
- *No evaluation of hypercoagulability*
- *Lack of appropriate animal models.*

Interim Data Analysis Suggests

- Significant variability in the types and frequency of approaches;
- Many respondents felt there was a need for more routine and ‘informed’ testing approaches;
- Translation of nonclinical results – and sharing of these data – with clinical teams needs improvement.

Applying the Data

Utilize data from survey and expert network to build cross-sector consensus on:

- Appropriate and sensitive hemostatic system testing approaches (assays, protocols, and timing) in animals during drug development;

- Work with experts in the area of test development for the hemostatic system to evaluate these and other tests of endothelial injury and optimize the tests for use in animals, particularly rodents.

Future

Status

- Online survey on hemostasis practices developed by multi-sector team and distributed in April 2010.

Next Steps

- Survey responses to be collated in late May/early June 2010.
- Survey results may be integrated into a publication on current practice, and will be used to inform next steps for work group.