A public–private consortium advances cardiac safety evaluation: Achievements of the HESI Cardiac Safety Technical Committee

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2.5 million deaths per year (Prüss-Ustün & Corvalan, 2006; Weinhold, 2011). In the context of both drug and environmental safety concerns, the Cardiac Safety Technical Committee is working to develop improved predictors of adverse cardiac events.

Drug cardiovascular safety has been a priority at HESI for over a decade. In the year 2000, the need to better understand the scientific basis for drug-induced delayed ventricular repolarization (QTc prolongation) and Torsades de Pointes (TdP) was proposed as a timely and important area of focus for HESI and the drug safety community. An exploratory meeting was held in August of 2001 at ILSI headquarters in Washington D.C. and later that year, HESI initiated an experimental program to better characterize nonclinical models as predictors of QTc prolongation. While this work matured and evolved from 2000 to 2008, a cardiac biomarker (i.e. troponin) research program was initiated within the context of a broadly based HESI Biomarker development committee. In 2008, the present-day Cardiac Safety Technical Committee was endorsed by the HESI Board of Trustees to centralize cardiac-focused efforts at HESI and synergize resources, expertise, and outcomes. Since its inception, the Cardiac Safety Technical Committee has expanded its program of work to support an improved understanding of cardiovascular structure and function and its assessment for safety and risk. This work can serve as an important resource in reducing unanticipated adverse drug effects and evaluating the potential impact of environmental or chemical exposures.

The diverse base of the Cardiac Safety Technical Committee allows HESI to combine resources (intellectual, experimental, and financial) to pursue innovative strategies in a collaborative, non-biased approach. This diversity comes from more than 21 industry organizations and 23 academic and government institutions from North America, Europe, and Asia. The members are a cross-disciplinary group of scientific experts from the fields of clinical medicine, pathology, imaging, safety pharmacology, physiology, toxicology, bioinformatics and many more.

The working groups of the Cardiac Safety Technical Committee evolved from the expertise of the members, the need to address cardiac safety issues as a major cause of attrition in drug development, and concern around cardiac effects potentially resulting from environmental exposures. The current working groups include: proarrhythmia, cardiac biomarkers, integrated strategies, and stem cell-derived cardiomyocytes subteam. The evolution and current projects of the working groups are described in more detail below.

Since its inception in 2008, the HESI Cardiac Safety Technical Committee has informed the practice and philosophy of cardiac safety evaluation through a significant body of novel research and expert consultation. For example, the program has already:

- Increased the translational relevance of nonclinical studies by developing data on the utility of cardiac troponin as a marker of cardiac injury in nonclinical models (i.e. animal toxicity testing);
- Supported accurate and efficient safety decision-making by generating and analyzing datasets that inform the selection and interpretation of nonclinical models to predict TdP risk;
- Enriched the field of cardiac safety by creating multi-disciplinary forums for interaction and program formulation between structurally focused cardiac safety scientists (e.g., pathology) and those primarily focused on cardiac functional endpoints (e.g., safety pharmacology);
- Created a successful, multi-sector and international network of experts that are coordinated through a committee infrastructure capable of identifying and pursuing new challenges to address continued cardiovascular safety issues.

In the last 4 years, this program of work has yielded 13 articles in the peer-reviewed literature, presentations at 32 scientific meetings, and 5 independently convened workshops or meetings. As the Committee maintains several active work streams and is continually adopting new areas of focus, additional impacts and outcomes are anticipated in the months and years to follow (Fig. 1).

2. Committee evolution

At the time of finalization of the ICH-S7A guideline (EMA, 2000), a note was incorporated to the document stating that “there is no scientific consensus on the preferred approach to, or internationally recognized guidance on, addressing risks for repolarization-associated ventricular tachyarrhythmia (e.g., TdP). A guideline (S7B) will be prepared to present some currently available methods and discuss their advantages and disadvantages. Submission of data to regulatory authorities to support the use of these methods is encouraged.”

At the same time, HESI scientists identified cardiovascular safety as a high priority topic and formed the Cardiovascular Safety Subcommittee. This Subcommittee convened the first working group in 2001 that explored drug-induced cardiac QT interval prolongation and TdP. As a result, the Cardiovascular Safety Subcommittee formed two subteams to further explore nonclinical in vitro and in vivo assays as well as clinical studies to refine formatting for ECGs, heart rate and QT values.

The Nonclinical Cardiovascular Studies Subteam engaged in comprehensive evaluation to compare the utility of selected nonclinical approaches in assessing ventricular repolarization liability using a panel of 12 drugs with either no association or a strong association to TdP as supported by extensive clinical data on their propensity to elicit QTc prolongation and proarrhythmia in man. These studies demonstrated a high degree of association between hERG blockade potency and clinical QTc prolongation and proarrhythmia. In vivo canine electrocardiograms (ECGs) were also shown to be a good predictor of QTc prolongation and arrhythmogenic risk. However, the canine Purkinje fiber assay was found to show a low predictive value towards the clinical outcomes. An additional goal of the studies was to provide information on the interlaboratory variability in hERG assay results. Results of these studies were influential in the subsequent development of theTopic S7B guideline by the ICH Expert Working Group, which requires the hERG assay and in vivo non-rodents ECGs but does not require an action potential assay (e.g., the Purkinje fiber assay) (J Koerner, personal communication, February 22, 2013), (Hanson et al., 2006). The Methods and Methodology Subteam developed background information on the strengths and weaknesses of current cardiovascular toxicity assays and determined the extent to which the existing assays worked independently or in tandem to predict clinical outcomes. This document also provided input to the ICH-S7B Cardiovascular Safety Expert Working Group (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002841.pdf).

The Hanson et al. (2006) article was the first of its kind to show that nonclinical safety pharmacology data can be used to understand cardiac safety. Detecting these cardiac risks earlier in the drug development process and distinguishing a drug that prolongs QT interval and is not proarrhythmic from one that leads to TdP has benefits for both the industry and patient safety. The results from that study (Hanson et al., 2006), together with the Japanese Pharmaceutical Manufacturer Association Project for Database Construction (JPMA QT PRODACT) study (Nakaya & Hashimoto, 2005) were instrumental in defining the nonclinical cardiac repolarization assays required before first administration of a drug to humans as outlined in the ICH-S7B (EMA, 2005).

The Cardiovascular Pro-Arrhythmia Models Project Committee replaced the Cardiovascular Pro-Arrhythmia Models Project Committee in 2005 to further focus on drug-induced TdP. This project committee convened a workshop that resulted in several publications on improving predictivity based on the workshop recommendations (Bass, Darpo, Breidenbach, et al., 2008; Bass, Darpo, Valentin, Sager, & Thomas, 2008). The main
recommendations produced from the workshop were to standardize the hERG assay, which evaluates the rapid component of the delayed rectifier potassium current (IKr); conduct a series of studies to collect beat-to-beat QT and RR interval data in key species and models, further standardize the process of model and protocol development, select test parameters for verification studies and; develop a multi-institution validation program. Several programs of work emerged as a consequence of this workshop, although not necessarily managed under the HESI umbrella, e.g., i) the need to look at cardiac contractility, and evaluate assay sensitivity in the nonclinical arena (Sarazan et al., 2011); see below)); ii) the evaluation of the predictive value of non-clinical repolarisation assays to QTc in Phase I clinical trials (Valentin et al., 2009); and iii) the development of nonclinical cardiovascular best practices (Leishman et al., 2012).

3. Current working groups

The Cardiac Safety Technical Committee formed in 2008 and absorbed the activities of the Cardiovascular Pro-Arrhythmia Project Models Committee as well as cardiac-related activities from the Development and Application of Biomarkers of Toxicity Technical Committee. This reorganization allowed HESI to create opportunities for synergy, share resources and expertise between the working groups and avoid duplication of efforts across HESI.

The Committee began by facilitating a variety of research collaborations that brought together nonclincial scientists and clinicians to address issues of contemporary concern relative to clinical safety. The Committee’s research activities collectively and independently responded to the FDA’s Critical Path Opportunities List which called for innovative and collaborative approaches to identifying markers and mechanisms of cardiac toxicity (Piccini et al., 2009).

The committee developed a mission1 and three working groups were collated to meet the mission: Cardiovascular Pro-Arrhythmia Models, Biomarkers of Cardiac Toxicity and an Integrative Strategies Working Group. While these groups have evolved over time, they continue to develop and disseminate improved data, approaches, and resources for the evaluation of nonclinical and clinical cardiac safety.

4. Pro-arrhythmia Working Group

The objectives of the Cardiovascular Pro-Arrhythmia Working Group, are three-fold i) to assess the concordance between nonclinical repolarization assays and clinical measures of QT interval prolongation; ii) to investigate the mechanisms for any discrepancy identified between nonclinical and clinical results and to determine viable and successful alternative approaches to identify these compounds;

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1 The HESI Cardiac Safety Technical Committee mission is: to reduce unanticipated adverse cardiovascular events by developing and disseminating improved data/data analysis, approaches, testing methods/guidelines/best practices, and resources for the evaluation of cardiac toxicity in vitro, in vivo, and in clinical settings, and to unify an interdisciplinary team of scientists (toxicology, physiology, pathology, pharmacology, chemistry, clinical medicine, modeling, etc.) to address issues of contemporary concern relative to human cardiac safety.
and iii) assess the proarrhythmic potential of such compounds (Trepakova, Koerner, Pettit, & Valentin, 2009). To that end in 2009, the working group began a retrospective analysis of nonclinical and clinical data submitted in support of Investigational and New Drug Applications (INDs and NDAs) as well as a supplemental literature review of public domain data to establish a quantitative integrated risk assessment for each compound and assess concordance. These activities represent the first phase of a long-term project to assess concordance between nonclinical and clinical QT prolongation. Ultimately, the outcome of such a project might alleviate the need for a mandatory requirement for a thorough clinical assessment of QT/QTC for all drugs. As was noted by Dr. N. Stockbridge, Director of the Division of Cardiovascular and Renal Products, US FDA CDER, in 2008, “The HESI Cardiovascular Pro-Arrhythmia Models Project is an important component of our community approach to advance the science behind the regulatory response to the proarrhythmic potential of drugs. This particular effort may result in a shift from heavy reliance upon clinical evaluation of QT to a battery of nonclinical tests. And, even if the time is not upon us for such a transition, the meta-analysis of existing data is a landmark in the process of validating the nonclinical testing strategy” (ILSI-HESI, 2008).

The database effort was completed in the third quarter of 2012 and is the culmination of over three years of collaborative efforts among industry members and FDA. This ground-breaking program is the only example at this time of a joint public–private effort to analyze IND & NDA data submitted to a regulatory body. The successful execution of this program required a significant effort and commitment by all parties and demonstrates their shared goal of utilizing existing data sets as a resource for improving safety decisions and optimizing resources. A total of 257 compounds were reviewed and 150 included in the HESI/FDA database; another set of 185 compounds were included in the literature review. Publication of the results of these analyses is pending, but the process has already generated valuable discussion and insights that are likely to improve the way in which these data are generated, submitted, and analyzed.

Not only has the HESI/FDA database impacted our understanding of nonclinical to clinical concordance, the partnership on this project has spurred internal FDA discussions on significance of finding acceptable ways to securely share submitted data in a way that allows analysis of the pooled data to benefit the broader scientific community. This collaborative effort was recently commended in Science Translational Medicine as an exemplary model for leveraging nonclinical and clinical data (Dambach & Uppal, 2012).

Once the Pro-Arrhythmia Working Group members submit the HESI/FDA database and literature review manuscripts, they plan to initiate phase 2 of the project, which is to investigate the mechanisms of non-concordance. This effort may include evaluation of integrated sensitivity values for QTc effects, pooling available in-house data to assess positive controls, or use existing and new data to develop a position paper about the importance of high quality nonclinical arrhythmia and TQT study conduct and reporting practices.

5. Cardiac Safety Biomarkers Working Group

Initiated as the Expert Working Group (EWG) on Biomarkers of Drug-Induced Cardiac Toxicity, the group reviewed biomarkers of cardiac injury, which are defined in this paper as measurable biological molecules found in blood, other body fluids, or tissues that are signs of a cardiac condition, biologic process or disease, and advocated the use of cardiac troponin – a marker in use at the time by cardiologists and some other physicians – as a nonclinical biomarker to predict and monitor cardiac injury in drug toxicity studies (Wallace et al., 2004). In 2008, the EWG was expanded by the addition of scientists from related disciplines and moved from HESI’s Development and Application of Biomarkers of Toxicity Technical Committee to the newly formed HESI Cardiac Safety Technical Committee as the Cardiac Troponin Working Group. The working group focused on the analytical validation of available human cardiac troponin assay kits in a variety of laboratory animals including rats, dogs, and monkeys. Collaborating with Fred Apple, clinical chemist at the University of Minnesota, the group evaluated 10 commercially available assays developed for measurement of cTn in human serum or plasma samples to compare measures of the assay’s performance in laboratory animals. This program provided critical foundational data to support the technical feasibility of ‘reverse translation’ of cardiac troponin in nonclinical models. Specifically, the research identified important differences in assay reactivity and precision among species and identified those assays most suited to particular species as well as recommending against the use of some of the commercial assays for accurate measurement of cTn concentration in specific nonclinical (laboratory animal) phase testing (Apple, Murakami, Ler, Walker, & York, 2008). Having successfully defined the analytical properties of cTn assays in laboratory animals, the group began the biologic validation of cTn as a marker of cardiac injury in nonclinical studies. Using the isoproterenol-treated rat as an animal model of acute cardiac myofiber injury, the group compared and contrasted the ability of several biomarkers to predict and monitor myocardial injury, plotted the kinetics of cardiac troponin release, and correlated results of cTn concentration with detailed histopathologic examination of cardiac tissue (Clements et al., 2010). This study provided novel insights into the kinetics of cTn release and thus its potential value as a prodromal marker in nonclinical studies. The data demonstrated that increases in cTn concentration precede histologic evidence of cardiac injury, and that cTn is therefore well-suited for further study as a nonclinical, predictive biomarker of drug-induced acute cardiomyocyte injury. The significance and quality of this publication were recognized by the Society of Toxicologic Pathology who awarded it their “Best Paper” commendation for the year 2010.

Next, the Cardiac Troponin Working Group bridged existing efforts within HESI to analyze cardiac troponin concentrations in a model of chronic, low level cardiac injury in rats. The working group provided data for a joint HESI Biomarkers-HESI Committee on Genomics doxorubicin study that compared assays for cTnI and cTnT with an ultra-sensitive cTnI assay (Reagan et al., 2013). The group also provided a detailed histopathologic analysis of the vascular changes within the myocytes of the cardiac atria and ventricles of rats given doxorubicin. The assays for cTnI and cTnT concentrations and the high-sensitivity cTnI assay effectively identified cardiac injury in doxorubicin-treated rats. Further these studies showed that the pattern of release of cTn after cardiac injury is affected by the histologic nature of the lesion within the heart. Vascular changes within cardiac myocytes, such as those induced by doxorubicin administration in rats, result in smaller, more subtle increases in cTn release compared to the acute necrosis typical of isoproterenol and other better-characterized cardiac toxicants. The studies described above provided previously unavailable data demonstrating the potential to link nonclinical toxicity study outcomes to a measurable clinical endpoint via cardiac troponin (Berridge et al., 2009). These data and the efforts of the HESI Development and Application of Biomarkers of Toxicity Technical Committee were cited in materials submitted to FDA as part of a 2012 FDA decision to qualify the conditional use of cTnI and cTnT as biomarkers in safety assessment studies. Nonclinical characterizations of troponin biomarker pathobiology have also effectively informed clinical applications of troponin outside of traditional applications like acute coronary syndrome patients (Berridge et al., 2009).

In 2010, the working group broadened its mission to include evaluation of novel markers of cardiac physiology and safety while continuing its evaluation of cardiac troponin (and changed its name

2 Note: Dataset was housed at the FDA and data were anonymized prior to being shared with the Committee for analysis and discussion.
to the HESI Cardiac Safety Committee Cardiac Biomarkers Working Group.) The working group is evaluating several potential predictive biomarkers of cardiovascular toxicity. A systematic approach is being used to select analytes that can be integrated into nonclinical testing and subsequently incorporated into early clinical trials to bridge multiple stages of drug development. In preparation for this work, a recent survey paper from the Cardiac Biomarkers Working Group identified important gaps in current nonclinical drug development practices of the biopharmaceutical industry (Schultze et al., 2012). Thromboembolism is a common cause of morbidity and mortality for patients with pre-existing cardiovascular disease. Non-invasive, antemortem nonclinical testing lacks adequate sensitivity to identify prothrombotic conditions in animals. The survey results demonstrated a critical need for validated, predictive biomarkers of hypercoagulability and subclinical thrombosis for use in laboratory animal safety studies. The working group is therefore reviewing animal models of altered hemostasis that mimic human prothrombotic conditions and investigating novel analytes relevant to the pathologic pathways leading to overt cardiovascular complications of drug therapy. Future translational studies are planned for 2013 and beyond to qualify and validate new biomarkers that improve the efficiency and reliability of drug safety assessment practices.

6. Integrated Strategies Working Group

The Integrated Strategies Working Group formed as a result of a June 2009 HESI Think Tank entitled, “Current Practice In Structural and Functional Toxicity: Issues And Opportunities.” That meeting focused on the potential to more effectively synergize approaches to cardiovascular structure and function and to create new networks for engaging both clinicians and nonclinical scientists in the design, conduct, and interpretation of drug safety studies. During the meeting, participants identified the need for a more integrated approach to conducting nonclinical assays to create more readily translatable and informative data of value to the clinic (Pettitt, Berridge, & Sarazan, 2010). In late 2009, two working groups (Functional CV strategies, and Integrative CV strategies) were established to address some of the challenges identified at this workshop. The Functional Cardiovascular Strategies Working Group published the outcome of their deliberations in the International Journal of Toxicology in 2011 (Sarazan et al., 2011).

The HESI Functional Cardiovascular Working Group concluded that the public health threat due to drug related QT interval prolongation and associated proarrhythmia has been largely resolved. The group acknowledged that further work is indicated to improve the selectivity of nonclinical assays to avoid eliminating promising drugs that may not be proarrhythmic in clinical use. The working group also found that drug effects on blood pressure and cardiac function (contractility) are very important, although controversy exists regarding optimal animal models, parameters and their interpretation. For many compounds, cardiovascular safety pharmacology data are now being collected in repeat dose toxicity studies in addition to, or in the case of biologics instead of, purpose-designed safety pharmacology telemetry studies. The sensitivity of nonclinical cardiovascular function studies has historically been poorly characterized (if at all). Therefore, these studies have had little impact on regulatory and clinical decision making.

In 2012, the Integrative Strategies Working Group decided to focus on the importance of drug effects on cardiac function (contractility) and the characterization of the sensitivity of nonclinical cardiovascular function studies. The working group further pursued these through a collaboration to conduct prospective conscious dog studies using implantable telemetry and using positive control drugs with known clinical effects. When these global multi-site studies are completed and the data analyzed by the HESI working group during 2013, objective information on the actual sensitivity and specificity of \textit{in vivo} contractility assays will be shared internationally in posters, lectures and peer-reviewed manuscripts. The team is also evaluating proposals for use of diseased animal models to assess structural and functional effects in a nonclinical setting that more closely resembles potential patient health status.

The predictive cardiovascular strategies subgroup took a broad look across contemporary nonclinical cardiovascular risk assessment paradigms and put them in the context of persisting clinical challenges to identify opportunities for bridging that gap (Berridge et al., 2013). A particular interest was put on nonclinical strategies that might better inform clinical outcomes (i.e. that would be more predictive). A number of primary gaps were recognized: i) Short duration nonclinical safety studies do not model chronic outcomes in either clinical or nonclinical studies; ii) Robust assessment of CV function is not a routine component of repeat-dose general toxicity studies; and iii) Nonclinical safety studies do not model diseased patient populations.

Likewise, opportunities for enhancing current practices were also recognized and represented possible ‘actionables’ for our consortium working group. A few of the opportunities identified are being interrogated by existing groups — e.g. circulating biomarkers and hemostasis assessments (HESI Cardiac Biomarkers WG, PSTC Cardiac Hypertrophy WG), microRNAs (HESI Application of Genomics to Mechanism-Based Risk Assessment Technical Committee), preclinical imaging (HESI Preclinical Imaging WG), and functional endpoints in repeat-dose toxicity studies (Safety Pharmacology Society). An opportunity not being explored by any other working group to our knowledge but a subject of increasing conversation in multiple venues is that of alternative animal modeling for cardiovascular risk identification. Accordingly, this group is exploring this further and will establish clinical partnerships to better understand patient susceptibilities that might be the focus of alternative modeling approaches. This group is very aware of the sensitivities and complexity of ‘diseased’ models for risk assessment and is therefore also exploring ‘stressed heart’ models (e.g., dobutamine stress) as potentially informative tools.

7. Stem cell workshop

In 2011, the Integrated Strategies Working Group adopted a proposal to convene a workshop focused on stem-cell derived cardiac myocytes (SC-CM) and their potential role in cardiac safety assessments. Stem cell technology is an emerging area of science that has the potential for broad biomedical applications in nonclinical and clinical research, including the evaluation of drug or chemical induced cardiac toxicity (Kraushaar et al., 2012; Sison-Young et al., 2012). However, the harmonized utilization and application of human SC-CM in the cardiac safety evaluation of drug candidates and chemicals will require a coordinated effort to validate and qualify the use of SC-CM for risk assessment (Michele & Ball, 2010). To meet this need a HESI workshop, co-sponsored by the Safety Pharmacology Society (www.safetypharmacology.org), brought together experts to address this issue (“Pluripotent Stem Cells: Applications for Cardiovascular Risk Assessment”; March 18–19, 2013; Amgen Inc., Cambridge, Massachusetts.) The objective of this workshop was to assemble an international and multi-disciplinary group of scientists to discuss the use of induced pluripotent SC-CM, and the associated analytical technologies used to assess changes in SC-CM function, for the nonclinical cardiovascular risk assessment of pharmaceuticals and chemicals. The workshop focused on key topics, such as: i) What are current approaches to applying and developing stem cell-derived cardiomyocyte assay platforms? ii) How can this stem cell technology be used to inform CV risk assessment or pathway evaluation now, and what are the opportunities in the future? and iii) What additional standards or data are needed to facilitate the use of these data for translational science decision-making? A publication of the key discussion points and recommendations from the workshop is planned.
8. Summary

Since the program's initiation in 2000, the HESI Cardiac Safety Technical Committee has matured and developed into several working groups that function in tandem to create a robust, multi-disciplinary portfolio. By identifying predictive and translational biomarkers of cardiovascular toxicity, developing best practice guidelines, optimizing testing strategies, and promoting innovative technologies and approaches, the HESI Cardiac Safety Technical Committee has had and will continue to have significant impact on the efficiency and translational relevance of cardiac safety evaluation. This work supports public health via safe medicines and environments. The committee's efforts have been shared widely through numerous scientific publications, presentations, meetings and workshops. In addition, new venues for collaboration, data compilation and analysis, and dissemination of results and guidelines are now in development. Numerous manuscripts reflecting the work of the committee are in development and communication and outreach efforts to further share the work are planned.

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