Challenging the Status Quo: Mechanistic and Human-Relevant Screening for Cardiovascular Liabilities

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Outline

- Rationale for a novel approach
- Aims and value proposition
- Enablers
- Strategic approach
- Opportunities
Drug development attrition is a significant challenge

Safety-related attrition is a significant contributor

Cardiovascular liabilities identified in animal studies late in development are prominent source of attrition prior to clinical testing

Cardiovascular liabilities identified in patients are worse
  - most problematic liabilities are those associated with imbalances in MACE

Animal liabilities may or may not be human liabilities

Cardiovascular-specific assessments not generally a component of environmental hazard evaluation
Toxicity testing is under increasing pressure to meet several competing demands:

- Test large numbers of existing chemicals, many of which lack basic toxicity data.
- Test the large number of new chemicals and novel materials, such as nanomaterials, introduced into commerce each year.
- Evaluate potential adverse effects with respect to all critical end points and life stages.
- Minimize animal use.
- Reduce the cost and time required for chemical safety evaluation.
- Acquire detailed mechanistic and tissue-dosimetry data needed to assess human risk quantitatively and to aid in regulatory decision-making.
Mechanistic, Human-relevant Cardiovascular Safety Assessment: A HESI Cardiac Safety Technical Committee Initiative

2015?
April, 2018
MOU aims to improve cardiovascular safety of pharmaceuticals

NTP is part of a new interagency research collaboration to foster more novel, human-relevant safety testing methods

BY CAROL KELLY

Seeking to improve the cardiovascular safety of pharmaceuticals, the National Toxicology Program (NTP) partnered with the nonprofit Health and Environmental Sciences Institute (HESI) and the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) in a new memorandum of understanding (MOU).

Who are the partners?

Brief descriptions of the MOU partner organizations and liaisons follow.
Mission Statement

Contemporary pharmaceutical cardiovascular safety assessment would benefit from an approach that is more efficient in cost and time, mechanistically informative and human relevant. Such an approach would enable earlier recognition of development-limiting liabilities, fewer false positives leading to premature development termination, more relevant biomarkers and decreased late-stage attrition. The HESI Cardiac Safety Technical Committee will work across its working groups and with other stakeholders to design, test and implement such an approach.
Contemporary pharmaceutical cardiovascular safety assessment would benefit from an approach that is more efficient in cost and time, mechanistically informative and human relevant. Such an approach would enable earlier recognition of development-limiting liabilities, fewer false positives leading to premature development termination, more relevant biomarkers and decreased late-stage attrition. The HESI Cardiac Safety Technical Committee will work across its working groups and with other stakeholders to design, test and implement such an approach.
Key Assumptions

- There are a finite number of primary responses to CV toxicity—i.e. failure modes (principles of pathology).
- Behind those failure modes, there are a finite number of key cellular and/or molecular ‘mechanistic’ events (modes of action) that initiate and drive their pathogenesis which are ‘screenable’ (principles of molecular biology).
- The likelihood of a xenobiotic inducing a failure mode is a product of its potency for functionally perturbing a cellular event and the likely *in vivo* exposure in dose and time (principles of toxicology and probability).
  - Our confidence in a phenotypic outcome for a mechanistic activity relates to our experience with it—i.e. some activity at a mechanistic level can be directly related to a phenotypic outcome (e.g. 5HT2b agonism) (principles of human behavior).
  - Other activities will require phenotypic confirmatory testing (i.e. Tier 2) in more complex biological systems to build confidence in the phenotypic outcome.
- A relevant mechanistic testing strategy should enable clinical risk assessment, progression decisions and the development of clinical monitoring strategies.
Enabler: We know what the CV system looks like and how it works!

It's plumbing, electromechanics and energetics!
Enabler: We understand many control systems!

- Natriuretic peptides
- Renin-angiotensin system
- NO, Endothelin

Frank-Starling Law

- β-adrenergic agonist
- non-selective for $\beta_1$, $\beta_2$
- $\beta_1 = \uparrow$ cardiac inotropy, chronotropy
- $\beta_2 = \text{vasodilation}$

Heart rate (chronotropy) determined by rate of spontaneous SA nodal discharge
Spontaneous SA nodal discharge determined by balance of autonomic control

Sympathetic: norepinephrine $\uparrow$ discharge
Parasympathetic: acetylcholine $\downarrow$ discharge

Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum
Enabler: We know what cardiovascular toxicity looks like!

**Structural injuries**
- Cardiomyocyte injury
- Vascular injury
- Valvulopathy
- Organellar injury
- Δ cardiac mass

**Functional changes**
- Δ BP
- Δ HR
- Δ contractility

**Changes in disease**
- Ischemic events
- Coronary artery dz
- Heart failure
- Cerebrovascular events
- Hypertension
- Metabolic disease
Enabler: Modeling technology

In vitro cardiotoxicity assessment of environmental chemicals using an organotypic human induced pluripotent stem cell-derived model

Oksana Sirenko, Fabian A. Grimm, Kristen R. Ryan, Yasuhiro Iwata, Weihsuch A. Chiu, Frederick Parham, Jessica A. Wignall, Blake Anson, Evan F. Cromwell, Manta Behl, Ivan Rusyn, Raymond R. Tice
CV failure modes - Mechanisms to phenotypes

Drug actions on human receptors, ion channels, cellular processes

Mechanisms
- βAR, PDE
- Na⁺, K⁺
- Ca²⁺
- ATP generation
- 5HT2B
- Cytotoxicity
- Etc.

Potency + Exposure (dose, time)

1° Failure modes
- Δ Vasoactivity
- Δ Inotropy
- Δ Action potential
- Cardiomyocyte/myocardial injury
- Endothelial injury/coagulation

Nonclinical Phenotypes
- Δ BP
- Δ EF
- Arrhythmia
- Cardiac fibrosis
- Hemorrhage, thrombosis

Clinical Phenotypes
- Δ BP, ΔHR, Δ EF, HF, Arrhythmia, ↑MACE

βAR, PDE, Na⁺, K⁺, Ca²⁺, ATP generation, 5HT2B, Cytotoxicity, etc.

Δ Vasoactivity, Δ Inotropy, Valvular injury/proliferation

Δ Action potential, Cardiomyocyte/myocardial injury, Endothelial injury/coagulation

Δ BP, Δ EF

Arrhythmia, Myocardial necrosis, Regurgitant flow

Δ BP, ΔHR, Δ EF, HF, Arrhythmia, ↑MACE
CV failure modes - Mechanisms to phenotypes

Drug actions on human receptors, ion channels, cellular processes

- $\beta$AR, PDE, Na$^+$, K$^+$, Ca$^{2+}$, ATP generation, 5HT2B, Cytotoxicity, Etc.

Potency + Exposure (dose, time)

1º failure modes

- $\Delta$ Vasoactivity
- $\Delta$ Inotropy
- Valvular injury/proliferation
- $\Delta$ Action potential
- Cardiomyocyte/myocardial injury
- Endothelial injury/coagulation

Nonclinical phenotypes

- $\Delta$ BP
- $\Delta$ EF
- Cardiac fibrosis
- Hemorrhage, thrombosis
- Arrhythmia
- Myocardial necrosis
- Regurgitant flow

Clinical phenotypes

This is what we're worried about

$\Delta$ BP, $\Delta$HR, $\Delta$ EF, HF, Arrhythmia, ↑MACE
CV failure modes - Mechanisms to phenotypes

Drug actions on human receptors, ion channels, cellular processes

Mechanisms

- βAR, PDE
- Na⁺, K⁺
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Nonclinical Phenotypes

- Δ BP
- Δ EF
- Cardiac fibrosis
- Myocardial necrosis
- Regurgitant flow
- Hemorrhage, thrombosis

Clinical Phenotypes

This is what we model

Δ BP, ΔHR, Δ EF, HF, Arrhythmia, ↑MACE
CV failure modes - Mechanisms to phenotypes

Drug actions on human receptors, ion channels, cellular processes

Mechanisms

βAR, PDE, Na⁺, K⁺, Ca²⁺, ATP generation, 5HT2B, Cytotoxicity, Etc.

Potency + Exposure (dose, time)

1° Failure modes

Δ Vasoactivity
Δ Inotropy
Δ Action potential
Cardiomyocyte/myocardial injury
Valvular injury/proliferation
Endothelial injury/coagulation

Nonclinical phenotypes

This is where we want to be!

Δ BP
Δ EF
Arrhythmia
Cardiac fibrosis
Myocardial necrosis
Reguritant flow

Clinical phenotypes

Δ BP, ΔHR, Δ EF, HF, Arrhythmia, ↑MACE

HESI
Mechanistic screening isn’t new!

Are there other targets we should be adding to this primary screen?
Designing and executing the framework

Mobilize experts in CV toxicology and safety assessment

Map phenotypic outcomes of CV toxicity (i.e. failure modes) linked to cellular targets and known mechanistic pathogeneses

Define a portfolio of potential testing platforms - e.g. binding assays vs. cellular function assays vs. 3D tissues

Crowd source the development of the needed assays

Validate the assays and qualify the paradigm

Socialize and launch
Salient features of the framework

- Knowledge-based
  - aligned to what we know about the mechanisms, pathogeneses and phenotypes of CV toxicity

- Human-relevant
  - systems that reflect human biology at the subcellular, cellular or tissue level
  - testing at in vivo concentrations/exposures

- Mechanisms
  - goes beyond phenotypic outcomes and probes underlying cellular mechanisms/modes of action

- Ability to be applied earlier in development than traditional animal studies (e.g. at molecular design rather than candidate profiling)
Why HESI?

- It’s an existing collaboration of the relevant experts.
- The HESI platform for collaboration facilitates inter-disciplinary and cross-sector partnerships in areas of innovation that uniquely serves all contributors.
- HESI’s scientific expertise complements the expertise of the Committee participants.
- HESI’s role in supporting the advancement of scientific and collaborative innovation is becoming more and more important in an increasingly noisy and frenetic world.
Opportunities for engagement

- Current HESI Cardiac Safety Technical Committee is composed of cardiovascular pathobiology and safety experts, CV clinicians, government scientists and modeling platform developers
  - always recruiting new members

- Crowd sourcing solutions will be an important component of this effort
  - aim = fitting solutions to problems vs. problems to solutions

- Ultimate success of this initiative predicated on success of partnerships rather than technology

- Important to involve participants in the full life cycle of CV data to knowledge to decision
Acknowledgements

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- HESI Cardiac Safety Steering Committee
- HESI Cardiac Safety Committee Members
Questions?