A Novel Framework for Human-relevant and Failure Mode-based Assessment of Cardiovascular Safety in Nonclinical Drug Development

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Outline

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

Safety-related attrition 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
NRC Committee on Toxicity Testing and Assessment of Environmental Agents

“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.
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.
There are a finite number of primary responses to CV toxicity - i.e. failure modes

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’

The likelihood of a xenobiotic inducing a failure mode is a product of it’s potency for functionally perturbing a cellular event and the likely \textit{in vivo} exposure in dose and time

- 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)
- 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
Feasibility: We know what the CV system looks like and how it works!

It’s plumbing, electromechanics and energetics!
Feasibility: We understand many control systems!

- $\beta$-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

Natriuretic peptides

Frank-Starling Law

Renin-angiotensin system

NO, Endothelin

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

Structural injuries
- Cardiomyocyte injury
- Vascular injury
- Valvulopathy
- Organellar injury
- Cardiac mass
- Neoplasia

Functional changes
- BP
- HR
- Contractility

Arrhythmia

Changes in disease
- Ischemic events
- Coronary artery dz
- Heart failure
- Cerebrovascular events
- Hypertension
- Metabolic disease
CV failure modes - Mechanisms to phenotypes

Drug actions on human receptors, ion channels, cellular processes

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

Potency + Exposure (dose, time)

Δ Vasoactivity
Δ Inotropy
Valvular injury/proliferation

Cardiomyocyte/myocardial injury

Δ Action potential

Endothelial injury/coagulation

Hemorrhage, thrombosis

Δ BP, Δ EF, Cardiac fibrosis, Regurgitant flow

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

Mechanisms

1st Failure modes

Nonclinical Phenotypes

Clinical Phenotypes
CV failure modes - Mechanisms to phenotypes

Drug actions on human receptors, ion channels, cellular processes

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

Nonclinical Phenotypes

Δ Vasoactivity  Δ Inotropy  Valvular injury/proliferation

Δ Action potential  Cardiomyocyte/myocardial injury  Endothelial injury/coagulation

Δ BP  Δ EF  Myocardial necrosis  Hemorrhage, thrombosis

Arrhythmia  Cardiac fibrosis  Regurgitant flow

Clinical Phenotypes

This is what we’re worried about

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

**Mechanisms**

- Cardiomyocyte/myocardial injury
- Valvular injury/proliferation
- Δ Vasoactivity
- Δ Inotropy
- Δ Action potential
- Cardiomyocyte/myocardial injury
- Δ BP, Δ HR, Δ EF, HF, Arrhythmia, ↑MACE

**Drug actions on human receptors, ion channels, cellular processes**

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

**Potency + Exposure (dose, time)**

**1° Failure modes**

- Δ Vasoactivity
- Δ Inotropy
- Valvular injury/proliferation
- Δ BP
- Δ EF
- Cardiac fibrosis
- Regurgitant flow
- Endothelial injury/coagulation

**Clinical Phenotypes**

- Hemorrhage, thrombosis

**Nonclinical Phenotypes**

- Δ BP
- Δ EF
- Myocardial necrosis

**This is what we model**

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

Drug actions on human receptors, ion channels, cellular processes

Mechanisms

1st Failure modes

Nonclinical Phenotypes

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

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Δ Vasoactivity

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

This is where we want to be!
Do AOPs have a role in this?

Excitation-contraction coupling

Calcium channel blockade and heart failure
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

• Ability to be applied earlier in development than traditional animal studies (e.g. at molecular design rather than candidate profiling)
How many of these events are likely to be identified in a cardiomyocyte model?
Doxorubicin cardiotoxicity - two (of many?) mechanisms:

• Oxidative stress
• Top2B inhibition

But, that’s okay because we know a lot about ‘modes’!
Transition from normal to abnormal is generally not binomial.

Thresholds of biological perturbation that represent ‘toxicity’ are difficult to define and not generally well understood mechanistically.

Contextualizing those perturbations in a myriad of possible individual susceptibilities is even more difficult.
Key Challenges - Validation-Qualification Continuum

Building confidence

Analytical validation

Key Enablers

- replicate biology
- demonstrate pharmacology and toxicology
- test for analytical reproducibility
- comparative studies
- evolution of use
- learn to make decisions
- clinical outcomes
- tincture of time/experience

Translational qualification
Questions?