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

B. R. Berridge
Cardiac Safety Technical Committee

Outline

- Rationale for a novel approach
- Aims and value proposition
- Enablers
- Strategic approach
- Opportunities

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Rationale

- 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

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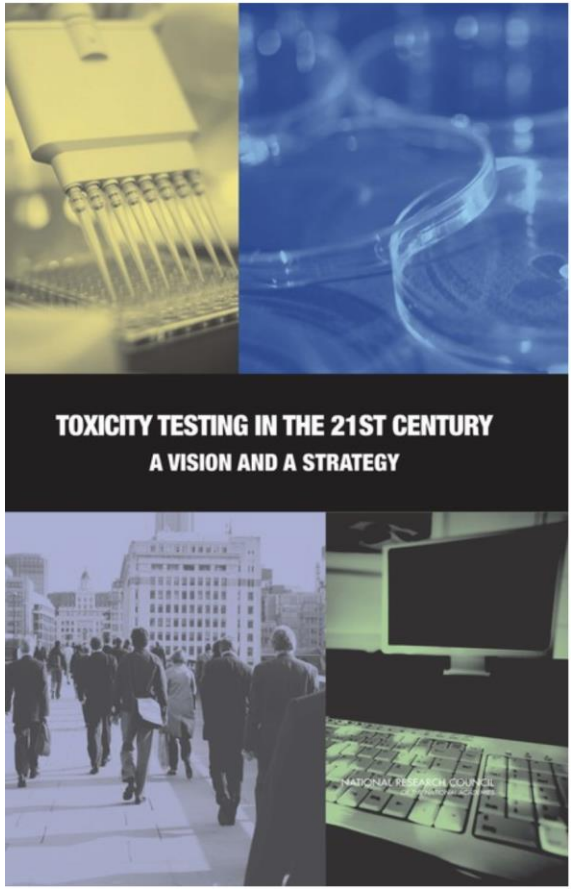
Larger Context



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.

National Academies Press, 2007

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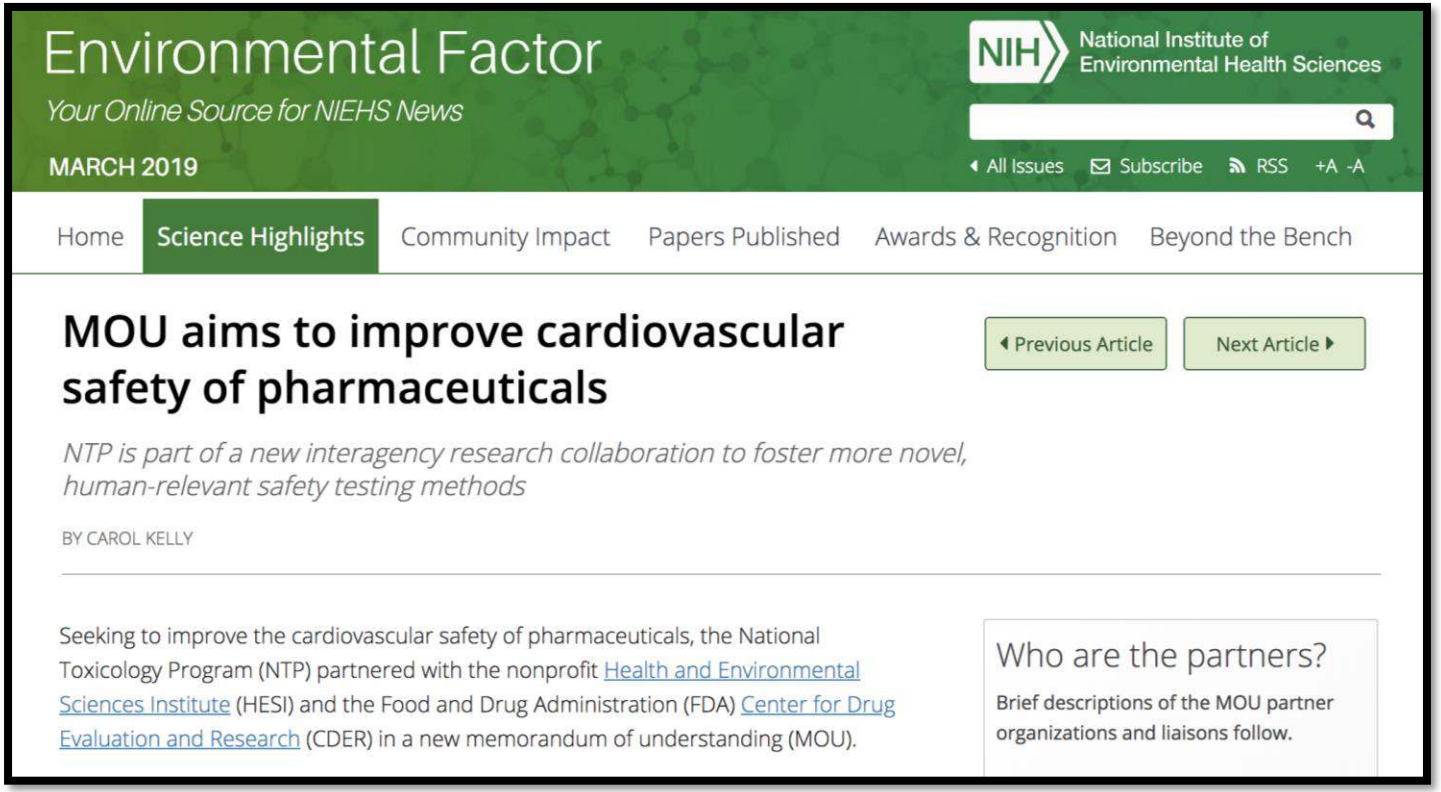
Mechanistic, Human-relevant Cardiovascular Safety Assessment: A HESI Cardiac Safety Technical Committee Initiative

2015?

April, 2018

Innovation Partners



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MOU aims to improve cardiovascular safety of pharmaceuticals

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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.

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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.

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Mission Statement

Aim

Value proposition

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.

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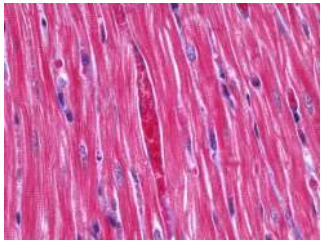
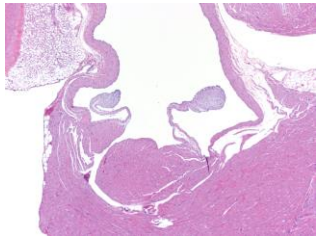
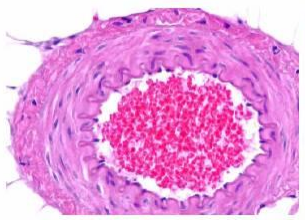
Key Assumptions

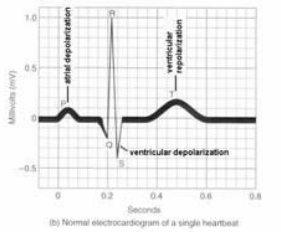
- There are a finite number of primary responses to CV toxicity- i.e. failure modes (principles of pathology)
- Behind those failure modes, there are a finite number of key cellular and or molecular 'mechanistic' events (modes of action) that initiate and drive their pathogenesis which are 'screenable' (principles of molecular biology)
- The likelihood of a xenobiotic inducing a failure mode is a product of it's 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!

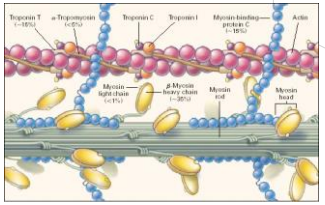


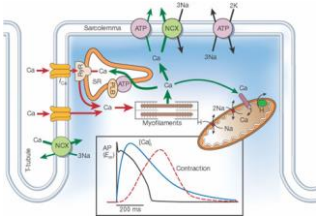


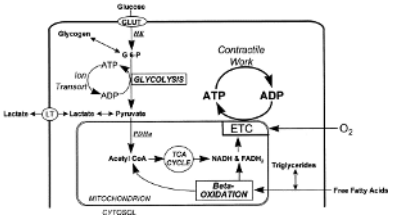


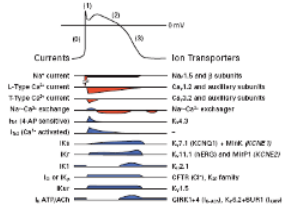


It's plumbing, electromechanics and energetics!









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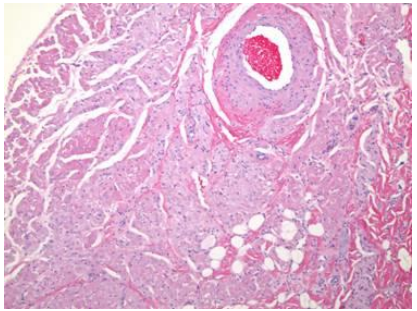
Enabler: We understand many control systems!



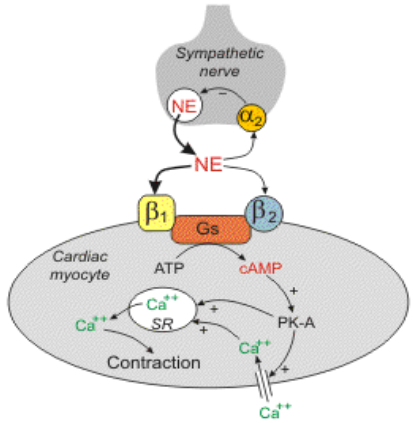
Frank-Starling Law

Natriuretic peptides

Renin-angiotensin system

NO, Endothelin

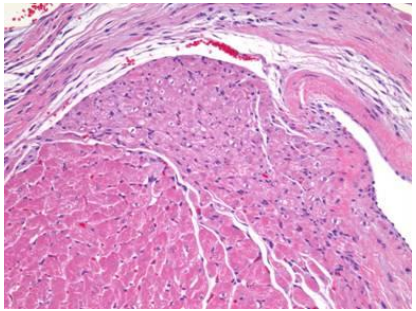
- β-adrenergic agonist
  - non-selective for β_1, β_2
  - β_1 = ↑ cardiac inotropy, chronotropy
  - β_2 = vasodilation



Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum

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

Sympathetic-	norepinephrine	↑ discharge
Parasympathetic-	acetylcholine	↓ discharge



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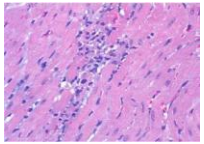
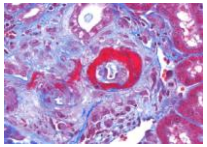
Enabler: We know what cardiovascular toxicity looks like!

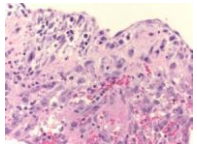
Structural injuries



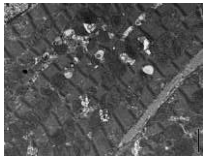
cardiomyocyte injury



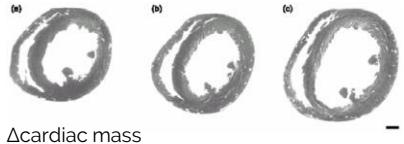
vascular injury



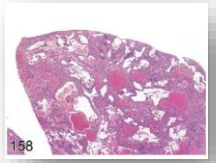
valvulopathy



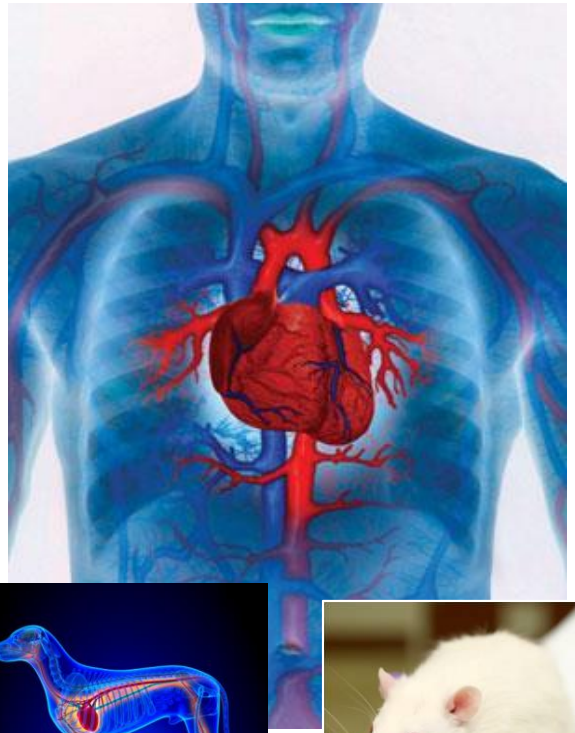
organellar injury

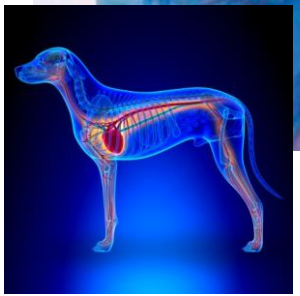


Δcardiac mass

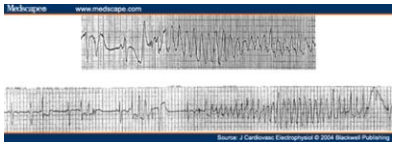


Neoplasia





Functional changes



Arrhythmia

Δ BP Δ HR

Δ contractility

Changes in disease

Ischemic events
Coronary artery dz
Heart failure
Cerebrovascular events
Hypertension
Metabolic disease

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Enabler: Modeling technology

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Toxicology and Applied Pharmacology

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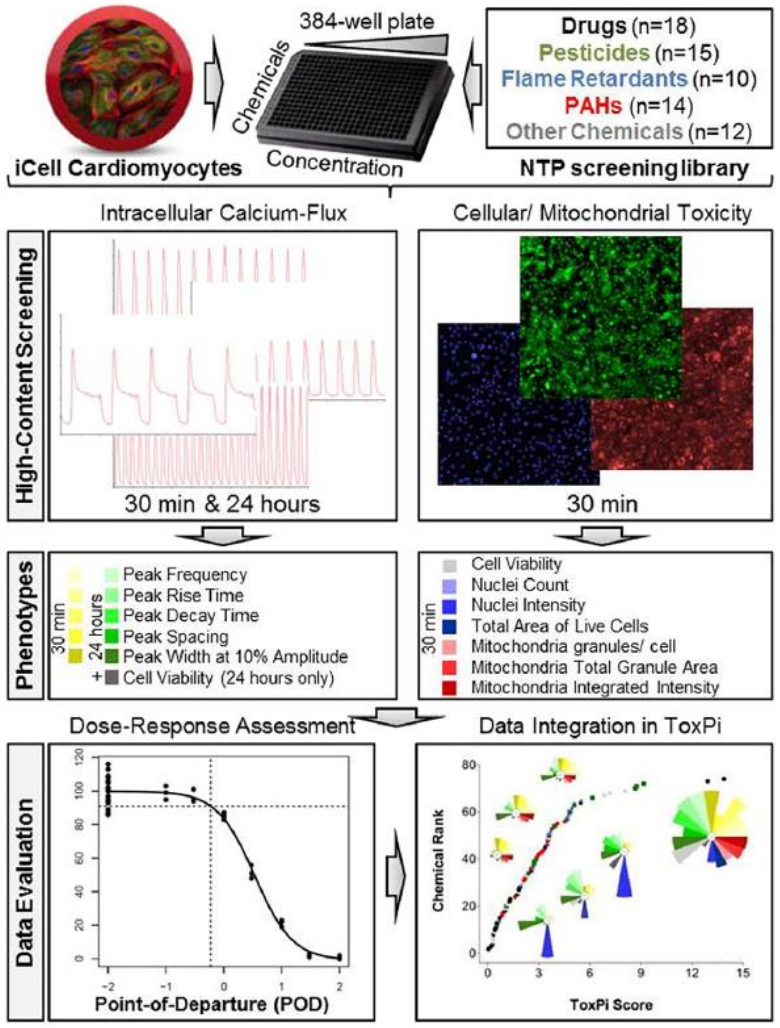
In vitro cardiotoxicity assessment of environmental chemicals using an organotypic human induced pluripotent stem cell-derived model

Oksana Sirenko [a,*,1], Fabian A. Grimm [b,1], Kristen R. Ryan [c], Yasuhiro Iwata [b], Weihsueh A. Chiu [b], Frederick Parham [c], Jessica A. Wignall [d], Blake Anson [e], Evan F. Cromwell [f], Mamta Behl [c], Ivan Rusyn [b], Raymond R. Tice [c]



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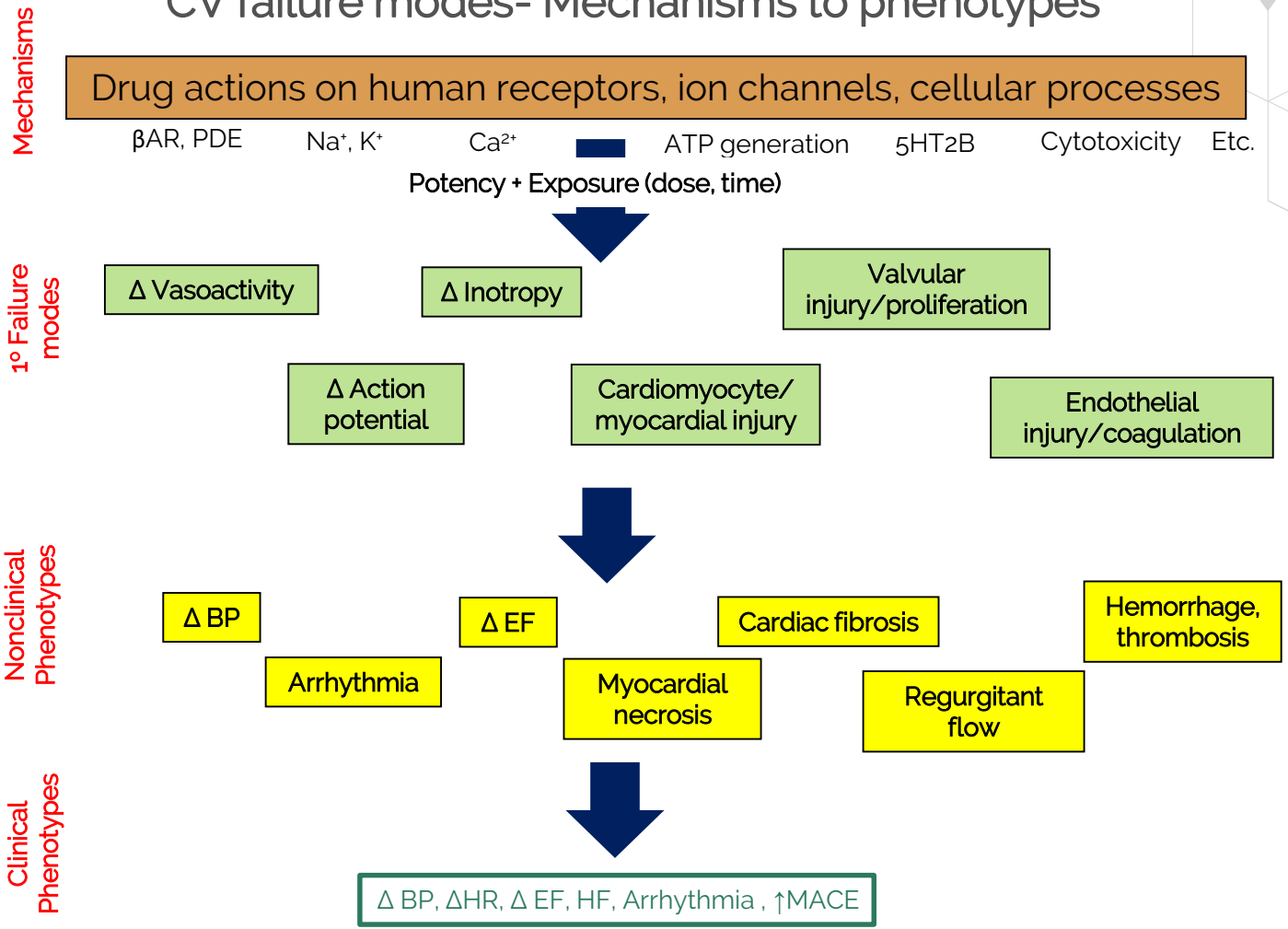
CV failure modes- Mechanisms to phenotypes



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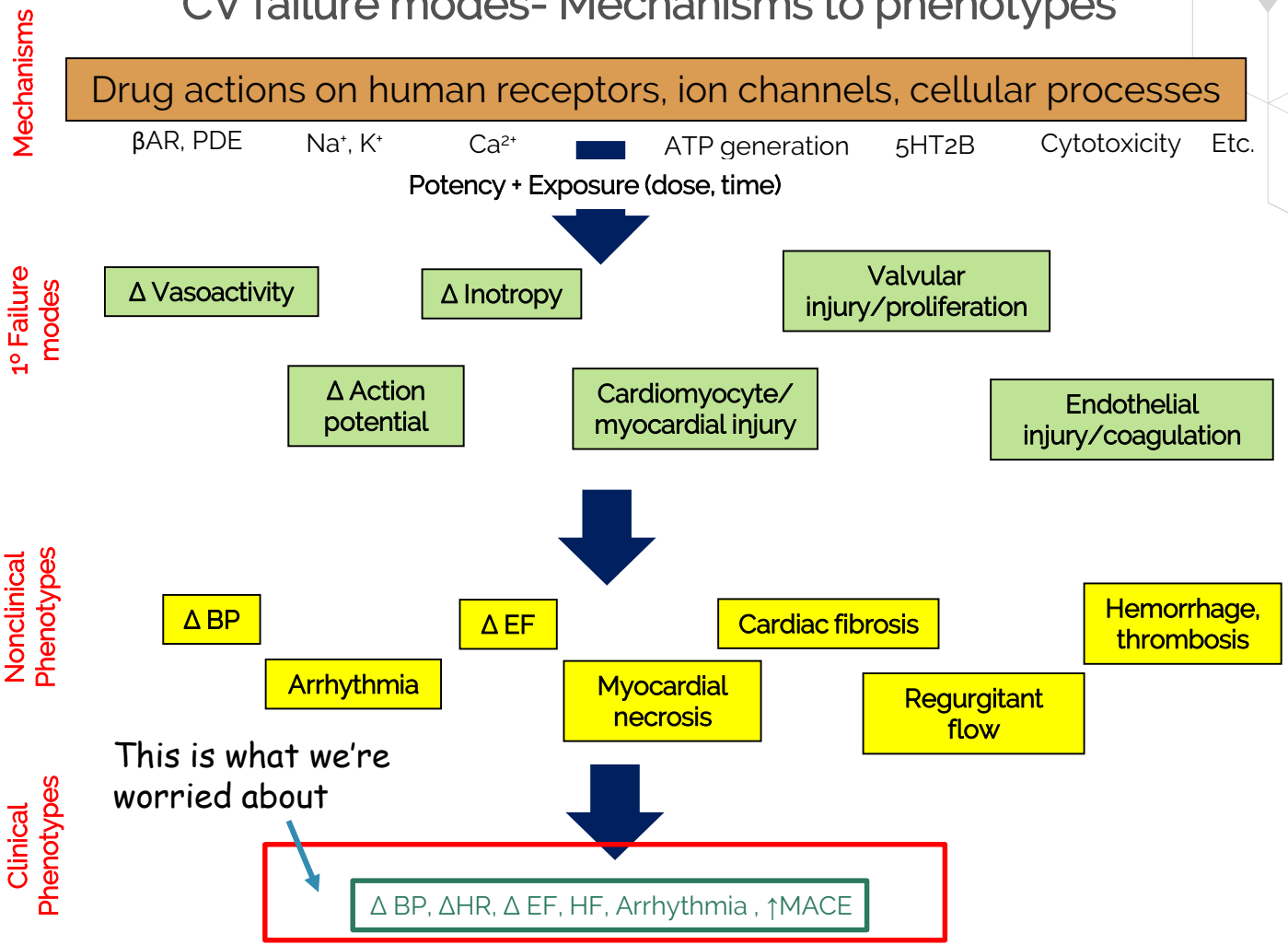
CV failure modes- Mechanisms to phenotypes



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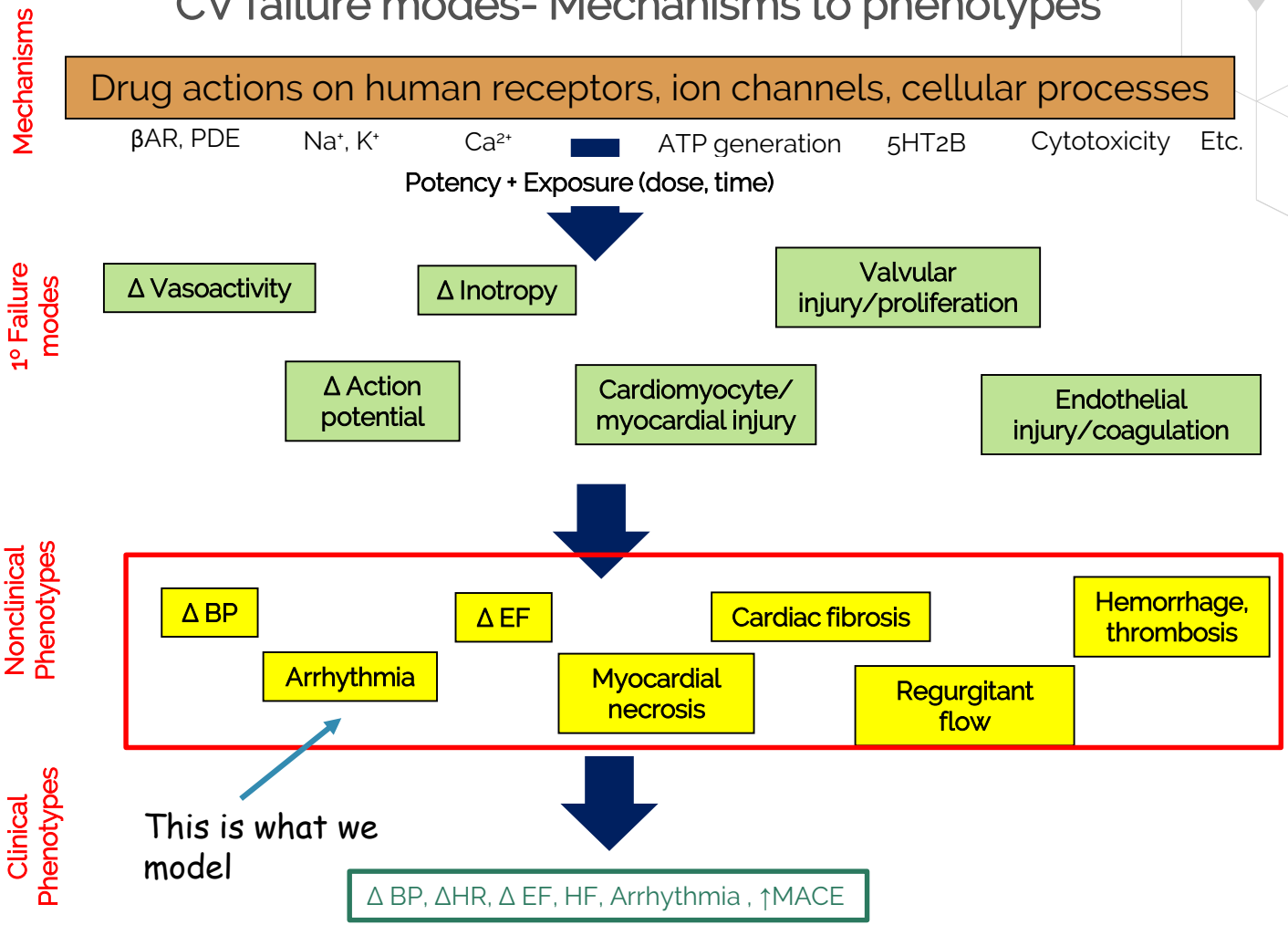
CV failure modes- Mechanisms to phenotypes



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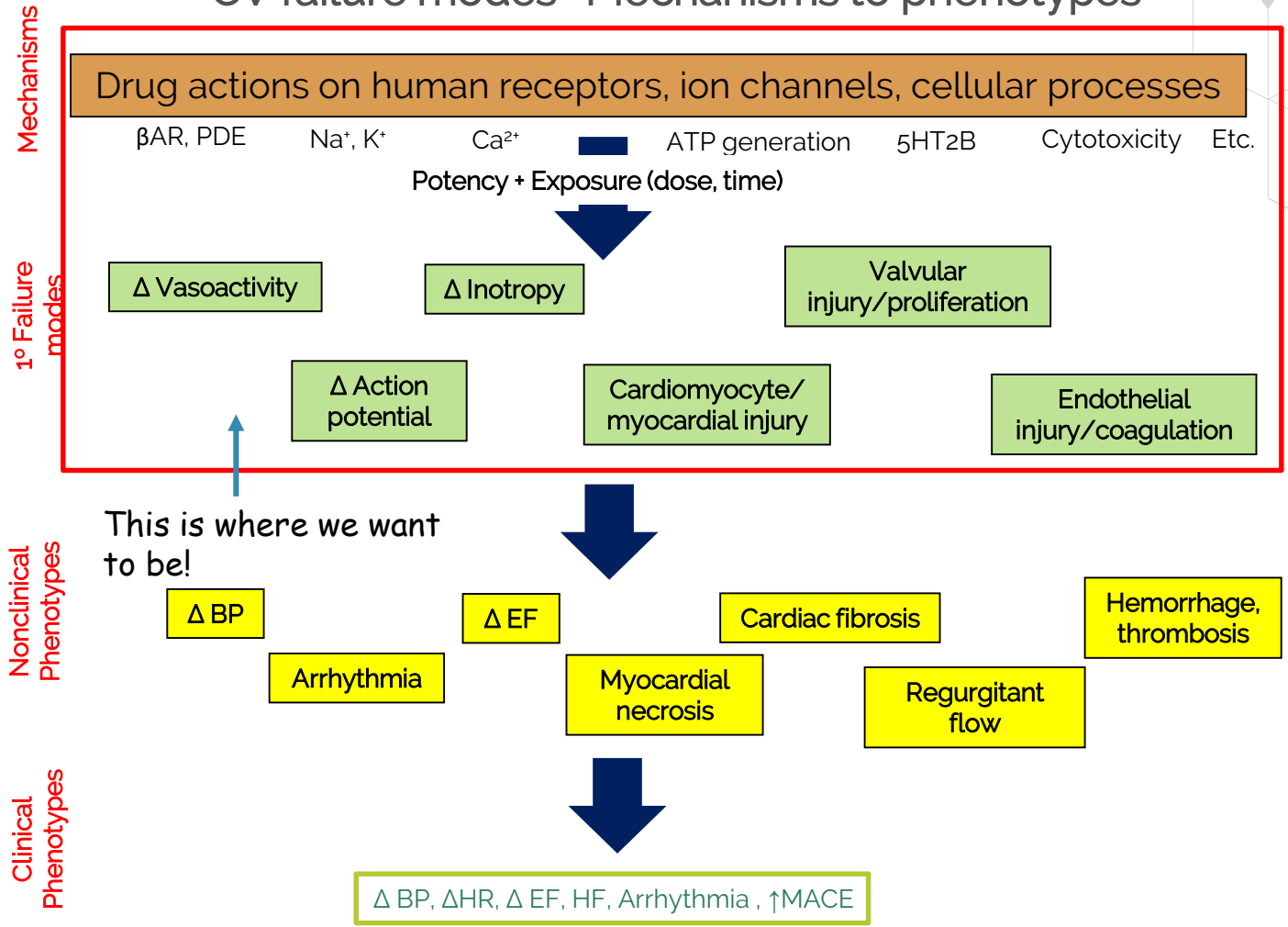
CV failure modes- Mechanisms to phenotypes



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Mechanistic screening isn't new!

A GUIDE TO DRUG DISCOVERY — OPINION

Reducing safety-related drug attrition: the use of *in vitro* pharmacological profiling

Table 1 | **Recommended targets to provide an early assessment of the potential hazard of a compound or chemical series**

Targets (gene)	Hit rate*		Main organ class or system	Effects		Refs[§]
	Binding	Functional or enzymatic		Agonism or activation	Antagonism or inhibition	
G protein-coupled receptors						
Adenosine receptor A_{2A} (*ADORA2A*)	High	Low (agonist)	CVS, CNS	Coronary vasodilation; ↓ in BP and reflex; ↑ in HR; ↓ in platelet aggregation and leukocyte activation; ↓ in locomotor activity; sleep induction	Potential for stimulation of platelet aggregation; ↑ in BP; nervousness (tremors, agitation); arousal; insomnia	57
α_{1A}-adrenergic receptor (*ADRA1A*)	High	Low (agonist); high (antagonist)	CVS, GI, CNS	Smooth muscle contraction; ↑ in BP; cardiac positive ionotropy; potential for arrhythmia; mydriasis; ↓ in insulin release	↓ in smooth muscle tone; orthostatic hypotension and ↑ in HR; dizziness; impact on various aspects of sexual function	58
α_{2A}-adrenergic receptor (*ADRA2A*)	High	Low (agonist); medium (antagonist)	CVS, CNS	↓ in noradrenaline release and sympathetic neurotransmission; ↓ in BP; ↓ in HR; mydriasis; sedation	↑ in GI motility; ↑ in insulin secretion	59
β_1-adrenergic receptor (*ADRB1*)	Medium	NA	CVS, GI	↑ in HR; ↑ in cardiac contractility; electrolyte disturbances; ↑ in renin release; relaxation of colon and oesophagus; lipolysis	↓ in BP; ↓ in HR; ↓ in CO	60
β_2-adrenergic receptor (*ADRB2*)[‖]	High	Medium (agonist); medium (antagonist)	Pulmonary, CVS	↑ in HR; bronchodilation; peripheral vasodilation and skeletal muscle tremor; ↑ in glycogenolysis and glucagon release	↓ in BP	61
Cannabinoid receptor CB_1 (*CNR1*)	Medium/ high	Medium (antagonist)	CNS	Euphoria and dysphoria; anxiety; memory impairment and poor concentration; analgesia; hypothermia	↑ in weight loss; emesis; depression	62
Cannabinoid receptor CB_2 (*CNR2*)	Medium	Medium (agonist)	Immune	Insufficient information	↑ in inflammation; ↓ in bone mass	63
Cholecystokinin A receptor (*CCKAR*)	Low/ medium	NA	GI	↓ in food intake; gallbladder contraction; pancreatic enzyme secretion; ↑ in GI motility; activation of dopamine-mediated behaviour	↑ in development of gallstones	64
Dopamine receptor D_1 (*DRD1*)[‖]	Medium/ high	Medium (antagonist)	CVS, CNS	Vascular relaxation; ↓ in BP; headaches; dizziness; nausea; natriuresis; abuse potential	Dyskinesia; parkinsonian symptoms (tremors); anti-emetic effects; depression; anxiety; suicidal intent	65
Dopamine receptor D_2 (*DRD2*)[‖]	Medium/ high	Medium/high (agonist); medium (antagonist)	CVS, CNS, endocrine	↓ in HR; syncope; hallucinations; confusion; drowsiness; ↑ in sodium excretion; emesis; ↓ in pituitary hormone secretions	Orthostatic hypotension; drowsiness; ↑ in GI motility	66
Endothelin receptor A (*EDNRA*)	Low	NA	CVS, development	↑ in BP; aldosterone secretion; osteoblast proliferation	Teratogenicity	67

Are there other targets we should be adding to this primary screen?

Table 1 (cont.) | **Recommended targets to provide an early assessment of the potential hazard of a compound or chemical series**

Targets (gene)	Hit rate*		Main organ class or system	Effects		Refs[§]
	Binding	Functional or enzymatic		Agonism or activation	Antagonism or inhibition	
G protein-coupled receptors (cont.)						
Muscarinic acetylcholine receptor M_1 (*CHRM1*)	High	Low (agonist); high (antagonist)	CNS, GI, CVS	Proconvulsant; ↑ in gastric acid secretion; hypertension; tachycardia; hyperthermia	↓ in cognitive function; ↓ in gastric acid secretion; blurred vision	73
Muscarinic acetylcholine receptor M_2 (*CHRM2*)[‖]	High	Low (agonist); medium (antagonist)	CVS	↓ in HR; reflex; ↑ in BP; negative chronotropy and inotropy; ↓ in cardiac conduction (PR interval); ↓ in cardiac action potential duration	Tachycardia; bronchoconstriction; tremors	74
Muscarinic acetylcholine receptor M_3 (*CHRM3*)	High	NA	GI, pulmonary	Bronchoconstriction; ↑ in salivation; GI and urinary smooth muscle constriction	Constipation; blurred vision; pupil dilation; dry mouth	75
5-HT_{1A} (*HTR1A*)	Medium/ high	Low (agonist); medium (antagonist)	CNS, endocrine	↓ in body temperature; reduced REM sleep; ↑ in ACTH; cortisol and growth hormone secretion	Potentially anxiogenic	76
5-HT_{1B} (*HTR1B*)	High	High (agonist); medium (antagonist)	CVS, CNS	Cerebral and coronary artery vasoconstriction; ↑ in BP	↑ in aggression	77
5-HT_{2A} (*HTR2A*)[‖]	Very high	Low/medium (agonist); medium/high (antagonist)	CVS, CNS	Smooth muscle contraction; platelet aggregation; potential memory impairments; hallucinations; schizophrenia; serotonin syndrome	Insufficient information	78
5-HT_{2B} (*HTR2B*)	High/ very high	Low (agonist); high (antagonist)	CVS, pulmonary, development	Potential cardiac valvulopathy; pulmonary hypertension	Possible cardiac effects, especially during embryonic development	79
Vasopressin V_{1A} receptor (*AVPR1A*)	Medium	High	Renal, CVS	Water retention in body; ↑ in BP; ↓ in HR; myocardial fibrosis; cardiac hypertrophy; hyponatraemia	Insufficient information	80
Ion channels						
Acetylcholine receptor subunit α1 or α4 (*CHRNA1* or *CHRNA4*)[‖]	Medium/ high	Low (opener); very high (blocker)	CNS, CVS, GI, pulmonary	Paralysis; analgesia; ↑ in HR; palpitations; nausea; abuse potential	Muscle relaxation; constipation; apnoea; ↓ in BP; ↓ in HR	81
Voltage-gated calcium channel subunit α Cav1.2 (*CACNA1C*)[‖]	NA	Medium/high (blocker)	CVS	Insufficient information	Vascular relaxation; ↓ in BP; ↓ in PR interval; possible shortening of QT interval of ECG	82

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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**

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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

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Acknowledgements

- Norman Stockbridge, Co-Chair HESI Cardiac Safety Technical Committee
- HESI Staff- Jennifer Pierson, Stan Parish, Syril Pettit
- HESI Cardiac Safety Steering Committee
- HESI Cardiac Safety Committee Members

Questions?

HESI