NTP
National Toxicology Program

Health Effects Innovation at the National Toxicology Program

Brian R. Berridge, DVM, PhD, DACVP
Associate Director, NTP
Scientific Director, DNTP
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 18, 2019

Aims of Health Effects Innovation

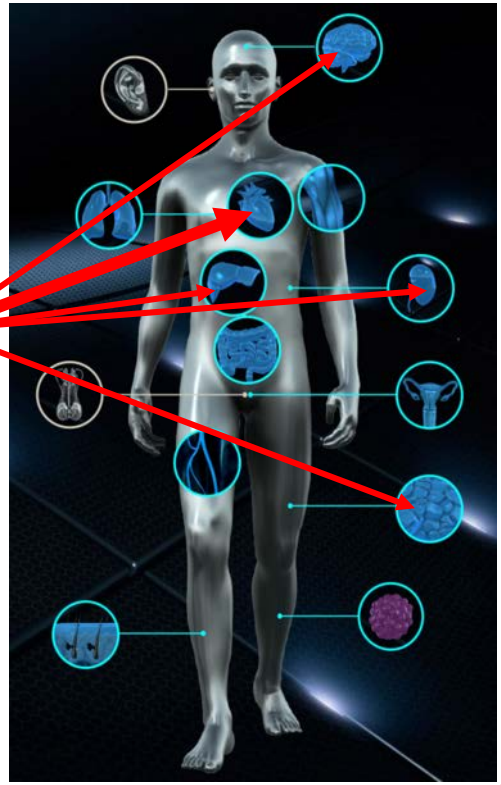
- Define and build a strategic assessment pipeline for key health effects
- Understand the mechanism of action, mode of action (MOA), health effect continuum for these areas
- Increase confidence in the predictivity of MOA assessments
- Align our capability development to problems we're trying to solve
- Maximize the collective strength of the NTP organization
- Build novel partnerships in and outside NIH

Opportunity for Flipping the Paradigm

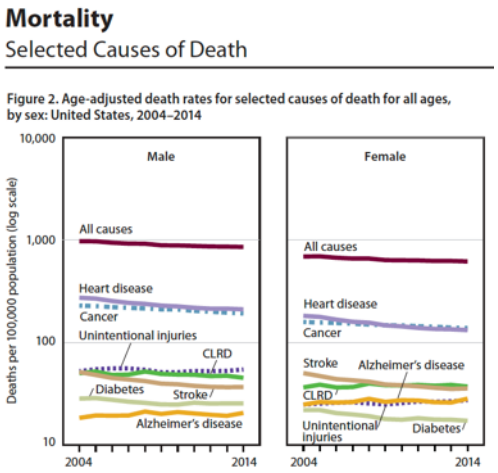
X lbs./yr. commercial production

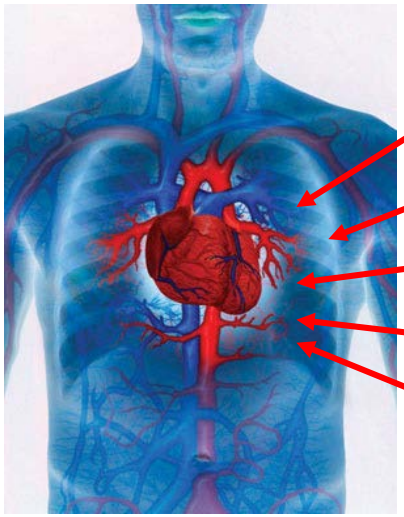
Initial Focus

Agent Y



https://ncats.nih.gov/tissuechip/chip





Agent A

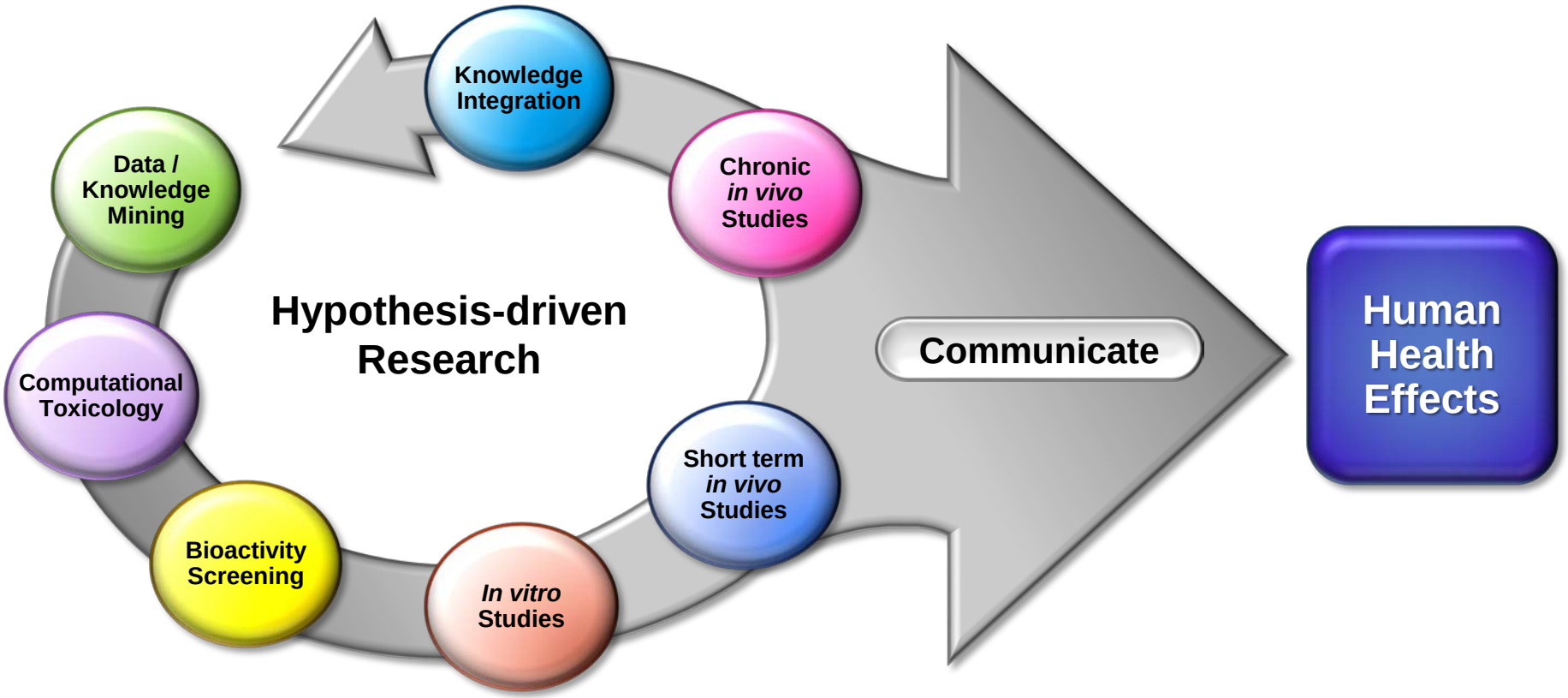
Agent B

Agent C

Agent Y

Agent Z

Our Framework: Translational Toxicology Pipeline



Expected Outcomes (Benefactors)

- Novel capabilities (DNTP, Environmental toxicology community)
- Advancement of our current knowledge of how environmental exposures contribute to diseases of concern (Public health community)
- A paradigm shift (Environmental toxicology community)
- Peer-reviewed manuscripts (DNTP, individual contributing scientist)
- Presentations (DNTP, individual contributing scientist)
- Expertise (DNTP, individual contributing scientist)

NTP
National Toxicology Program

Health Effects Innovation: Cardiovascular Hazard Assessment in Environmental Toxicology

Brian R. Berridge, DVM, PhD, DACVP
Associate Director, NTP
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National Institute of Environmental Health Sciences

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CV HEI Team

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Screening Branch

Michelle Cora
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Pathology Branch

Mark Cesta
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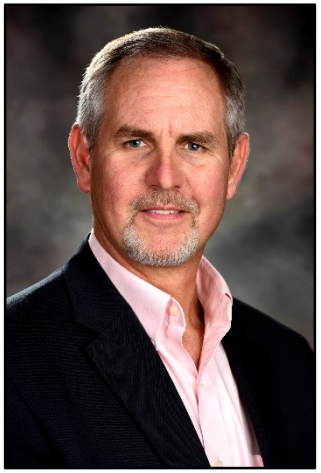
Pathology Branch

Nicole Kleinstreuer
NICEATM

Janine Santos
NTP Laboratory

Kick-off Meeting
on 29 May 2019



Brian Berridge
DNTP Scientific Director

CV HEI Rationale

AIM

VALUE

Cardiovascular disease is a major cause of death and disability worldwide. In the United States, heart disease and stroke are leading causes of death in both men and women and contribute significantly to direct health expenditures. The goal of the Cardiovascular Hazard Assessment in Environmental Toxicology HEI is to create a program that fully leverages and applies NTP's capabilities in deliberate, integrated, and complementary ways along the toxicology translational pipeline–from data/knowledge mining to in silico/in vitro approaches to in vivo testing–and use that knowledge to improve our understanding about how environmental agents affect the cardiovascular system in humans.

Abstract- NTP BSC, June 2019

CV Health Effects Opportunities

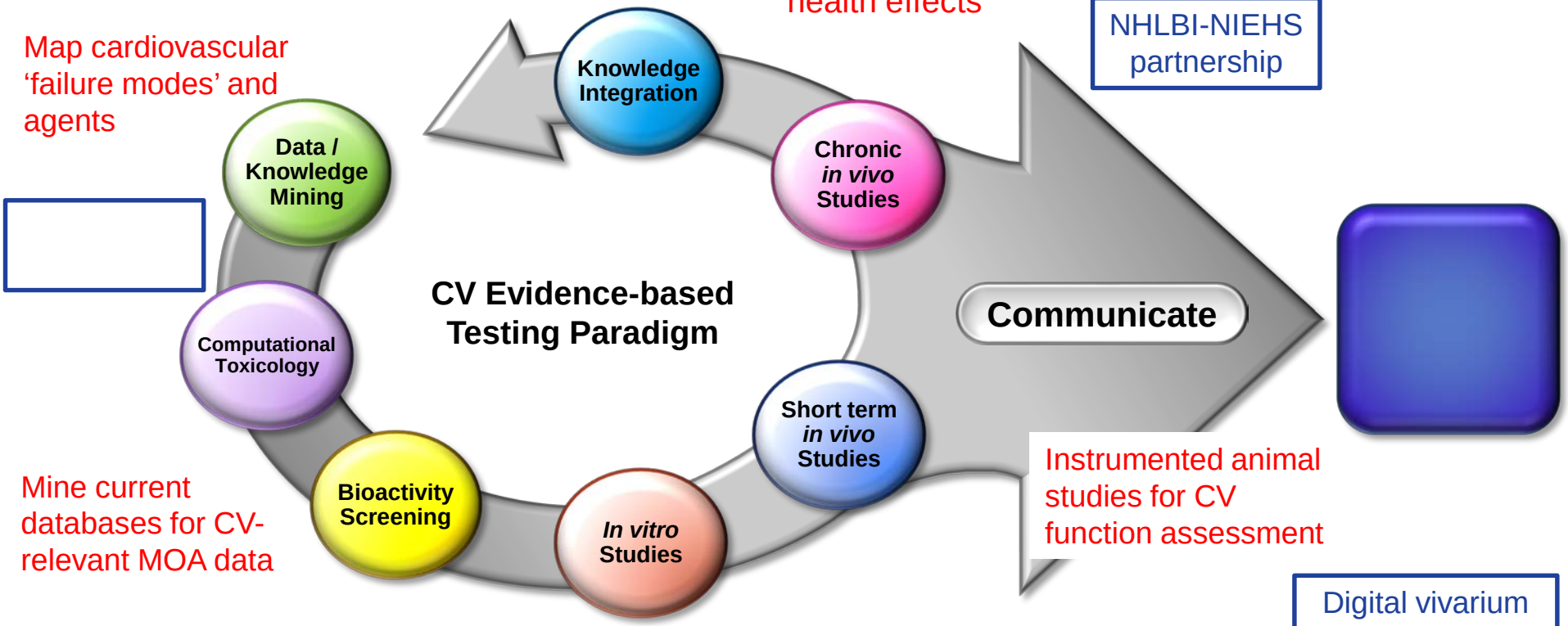
Contributing projects
Partners and opportunities

Regulatory and public health stakeholders

Identify translational biomarkers of chronic CV health effects

NHLBI-NIEHS partnership

Map cardiovascular 'failure modes' and agents



Mine current databases for CV-relevant MOA data

Instrumented animal studies for CV function assessment

Digital vivarium technology

HESI Cardiac Safety Technical Committee

Define primary mechanistic screening strategy

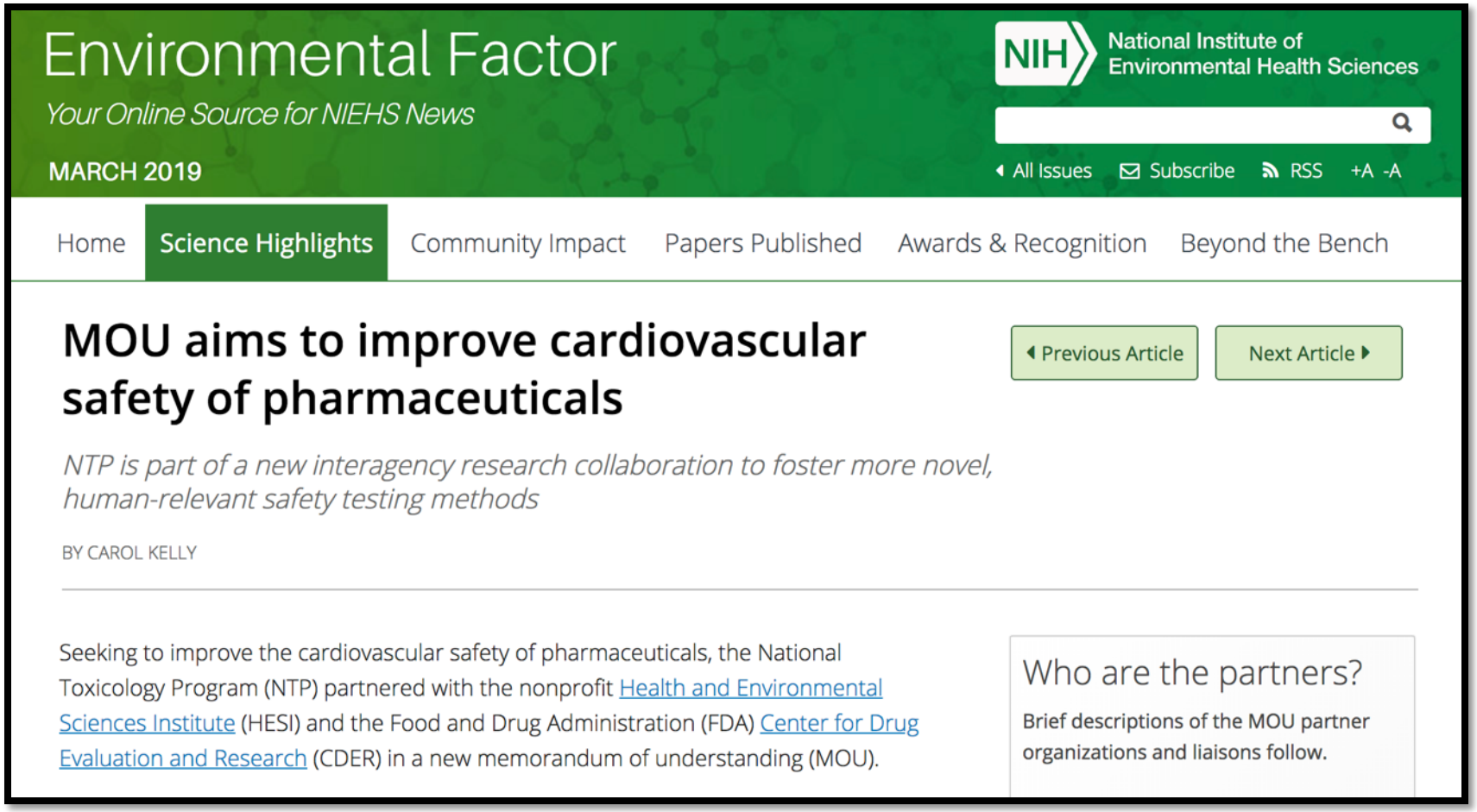
Define and test Tier II 3D cardiomyocyte and vascular modeling systems

NCATS, IQ, NCTR partnerships

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

B. R. Berridge, DVM, PhD, DACVP
Co-Chair, HESI Cardiac Safety Technical Committee
Associate Director, NTP
Scientific Director, NIEHS DNTP
29 Mar 2019

Innovation Partners



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MOU aims to improve cardiovascular safety of pharmaceuticals

Previous Article | Next Article

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.

FDA-NTP-HESI CV Mission Statement

Aim

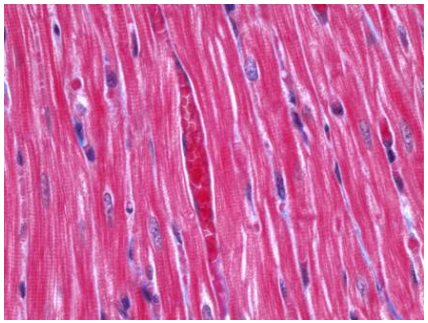
Value proposition

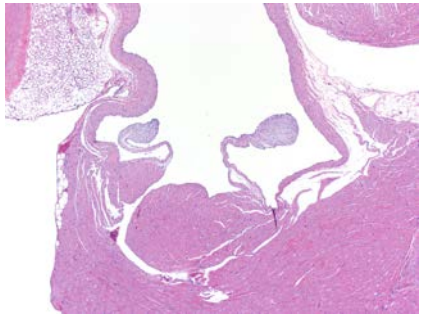
Contemporary pharmaceutical cardiovascular safety assessment would benefit from an approach that is more efficient in cost and time, mechanistically informative and human relevant. Such an approach would enable earlier recognition of development-limiting liabilities, fewer false positives leading to 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.

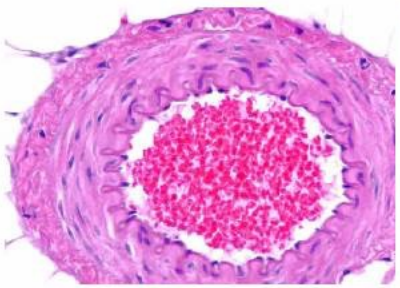
Key Assumptions

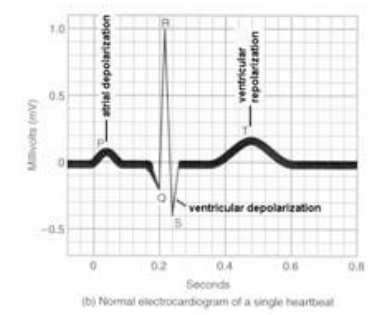
- There are a finite number of primary responses to CV toxicity- i.e. failure modes (Principles of Pathology)
- Behind those failure modes, there are a finite number of key cellular and or molecular 'mechanistic' events (modes of action) that initiate and drive their pathogenesis which are 'screenable' (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)
  - 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 (Principles of Translational Toxicology Pipeline)
- A relevant mechanistic testing strategy should enable clinical risk assessment, progression decisions and the development of clinical monitoring strategies (Mission of NTP)

Reason to believe: We know a lot about the CV system

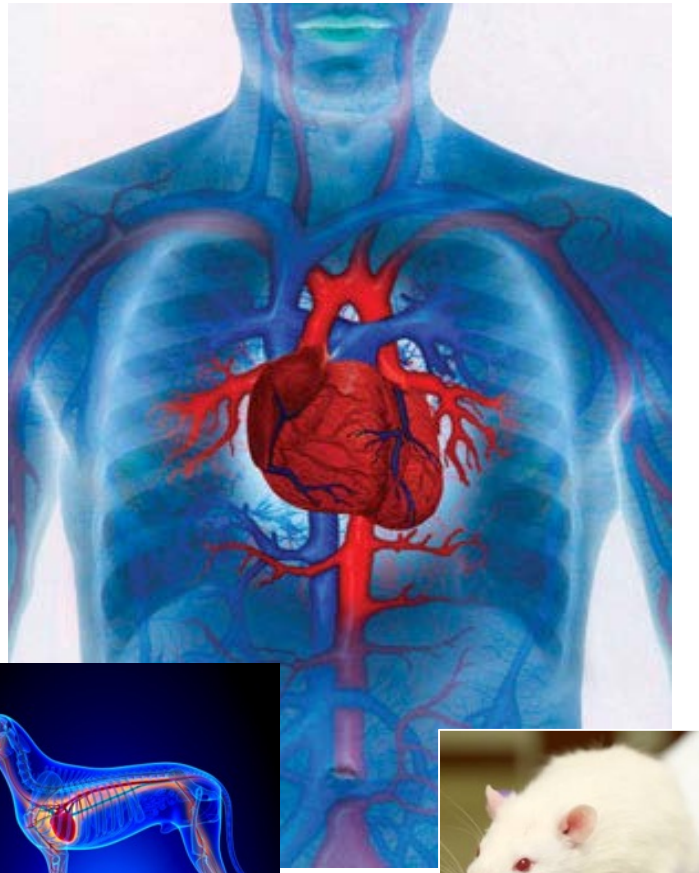


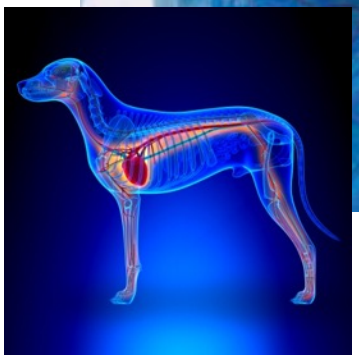


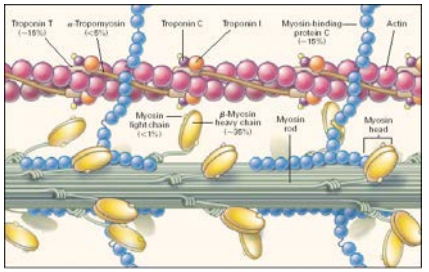


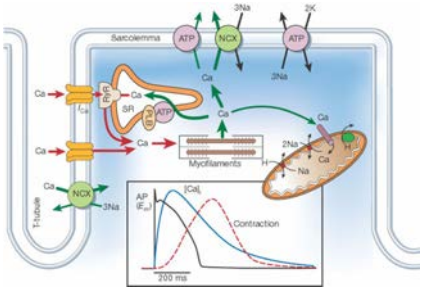


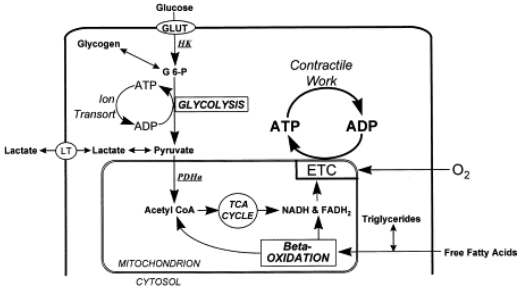
- Plumbing, electro-mechanics and power!
- Adaptive but not regenerative
- Relatively conserved

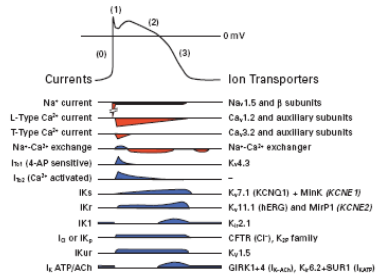




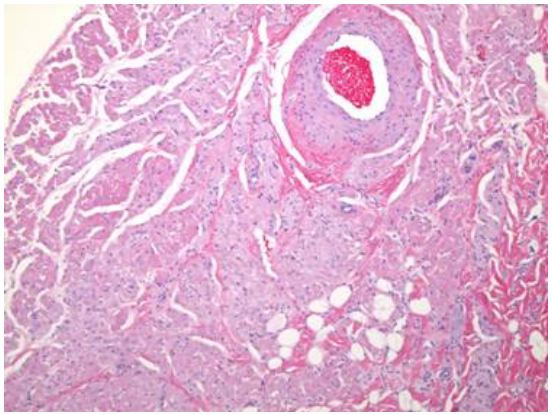








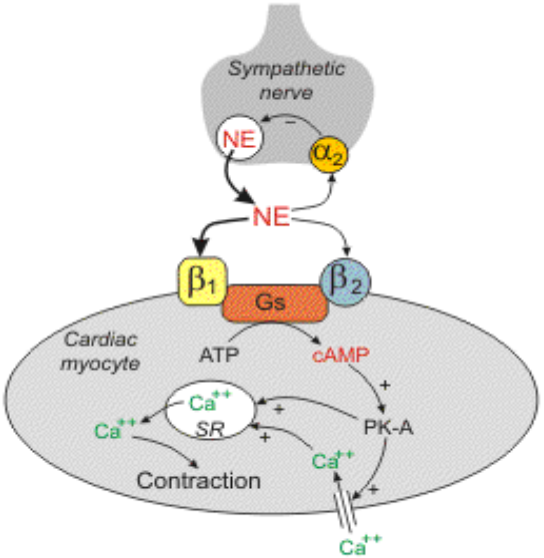
Reason to believe: We know a lot about what controls it



Frank-Starling Law

Natriuretic peptides

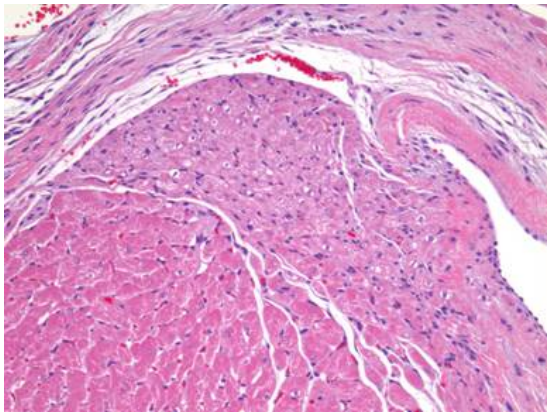
- β-adrenergic agonist
  - non-selective for β_1, β_2
  - β_1 = ↑ cardiac inotropy, chronotropy
  - β_2 = vasodilation



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

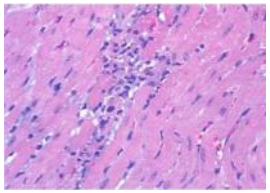


Renin-angiotensin system

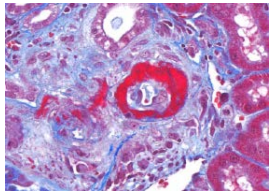
NO, Endothelin

Reason to believe: We know how it responds to injury

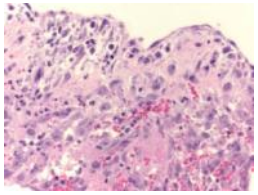
Structural injuries



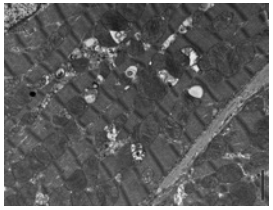
cardiomyocyte injury



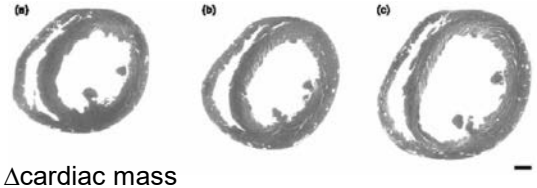
vascular injury



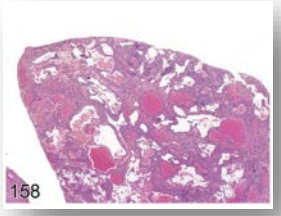
valvulopathy



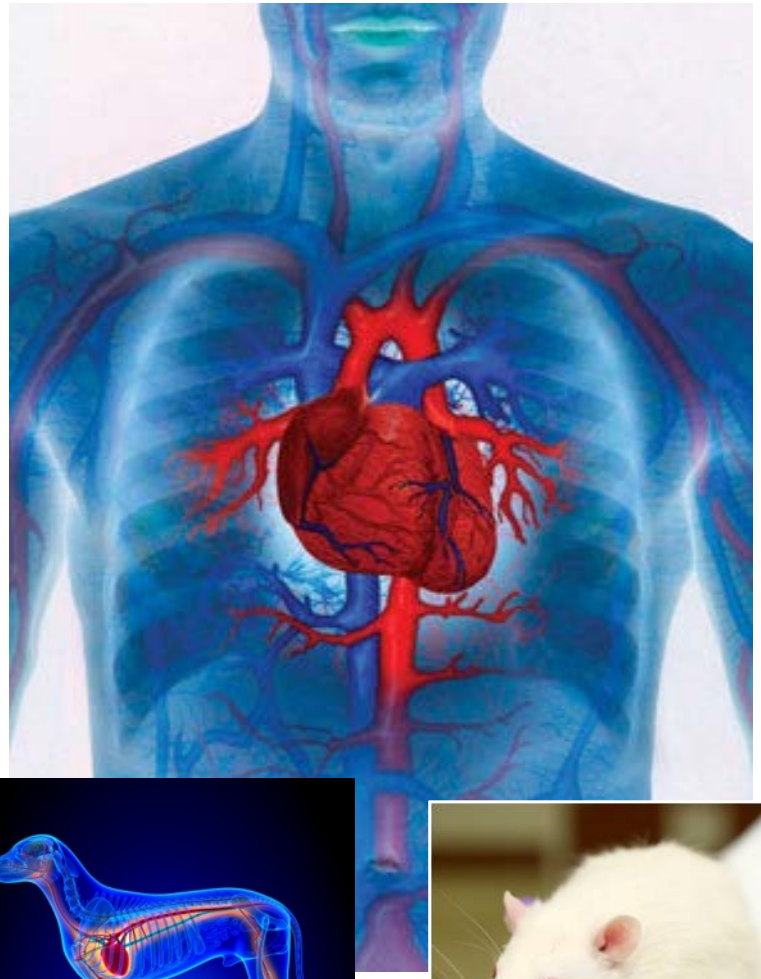
organellar injury

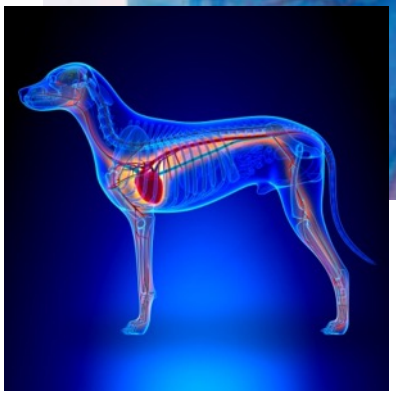


Δcardiac mass

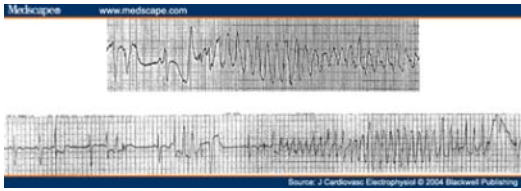


Neoplasia





Functional changes



Arrhythmia

Δ BP Δ HR

Δ contractility

Changes in disease

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

Learning from Existing Practices

Current Paradigms in Preclinical Drug Safety Assessment

Acute/Single Dose Safety Pharmacology Studies

Functional assessments

In vitro/Ex vivo

Purkinje fiber assay

Patch clamp ion channel assays

Rabbit wedge assay

In vivo

Individual animal; continuous recordings for 24+ hrs; Latin square design; dose-response; low 'n'

Rodents

CV Fxn Screen

- Instrumented rat
- Heart rate
- ECG (quantitative)
  - No QT
- Blood pressure
- Contractility- LVP, QA

Non-Rodents

FTIH-enabling GLP CV Study

- Instrumented dog, mini-pig or monkey
- Heart rate
- ECG (quantitative)
- Blood pressure
- Contractility- LVP, QA

Current Paradigms in Preclinical Drug Safety Assessment

In Vivo Repeat-Dose General Toxicity Studies

Rodents

Non-Rodents

4 days

Repeat-dose studies of increasing length at super-pharmacologic doses

2 years

Morphologic endpoints

Organ weight
Gross
Microscopic
- light microscopy
- ultrastructure

Blood/urine biomarkers

Serum chemistry
Hematology
Hemostasis
Urinanalysis

Functional endpoints

Heart rate
ECG
(qualitative)

* Repeat dose studies biased toward morphologic endpoints

Leveraging Experiences- Mechanistic Screening Isn't New!

A GUIDE TO DRUG DISCOVERY — OPINION

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

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

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

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

Reason to Believe: Technology

Toxicology and Applied Pharmacology 322 (2017) 60–74

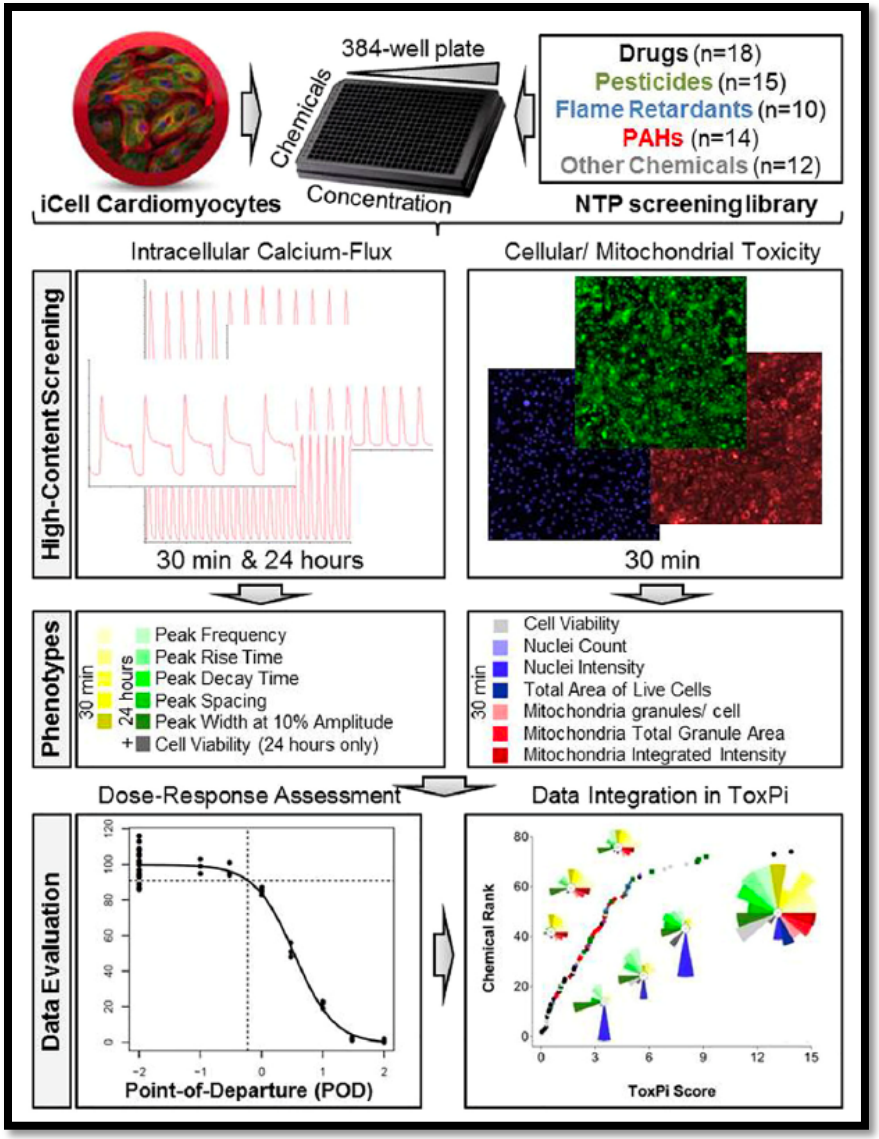
Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap

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]



Reason to Believe: Technology

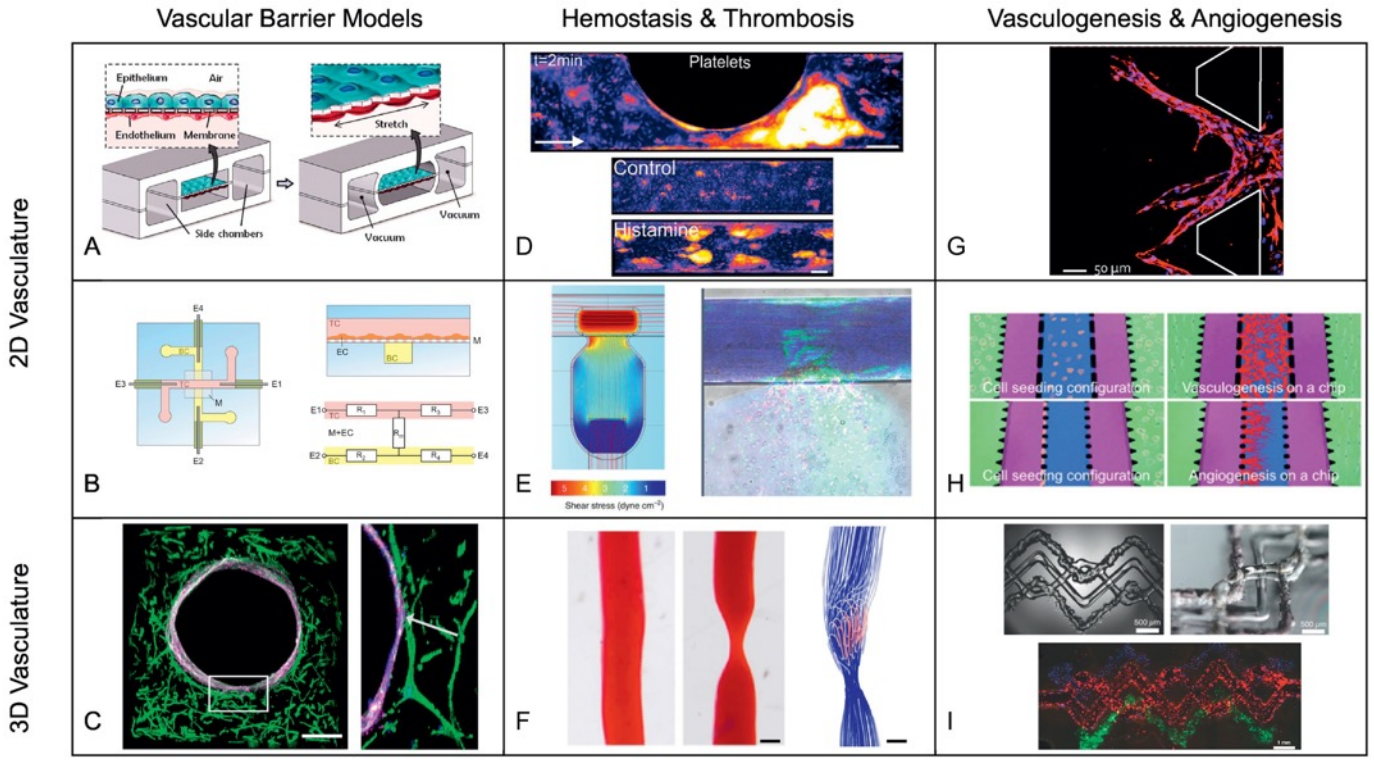
Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Advanced *in vitro* models of vascular biology: Human induced pluripotent stem cells and organ-on-chip technology

Amy Cochrane [a,1], Hugo J. Albers [b,c,1], Robert Passier [a,c], Christine L. Mummery [a,c], Albert van den Berg [b], Valeria V. Orlova [a,2], Andries D. van der Meer [c,*,2]



Reason to Believe: Technology

High Performance Computing Applications

Presented to: Secretary of Energy Advisory Board (SEAB)

Fred Streitz, Director
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Lawrence Livermore National Laboratory

Lawrence Livermore National Laboratory

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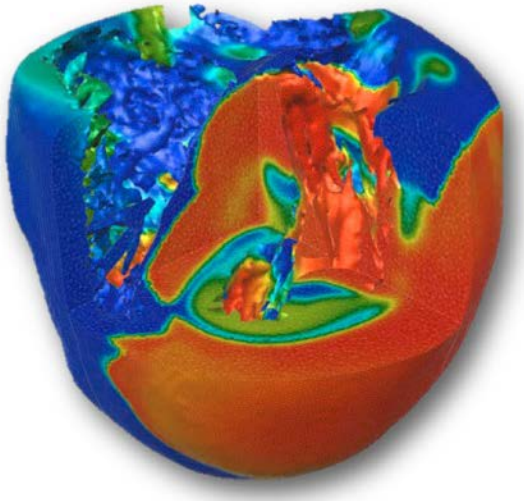
Whole heart modeling at cellular resolution in real time

Example of joint capability development



- Bring together multi-disciplinary, multi-institutional team (IBM-LLNL)
- Develop high resolution, realistic model of human heart
- Create *Cardioid* code to model electrophysiology of heart
- Leverage 20 PF Sequoia (Blue Gene/Q) resource
- Investigate development of arrhythmia

- "Bake out" period on new architecture enables discovery-class open science
- Publishable, newsworthy work returns favorable press for DOE and NNSA
- Scaling, load balance and resilience issues are worked out prior to program use

Reason to Believe: Smart Scientists

- Arif Rahman, PhD

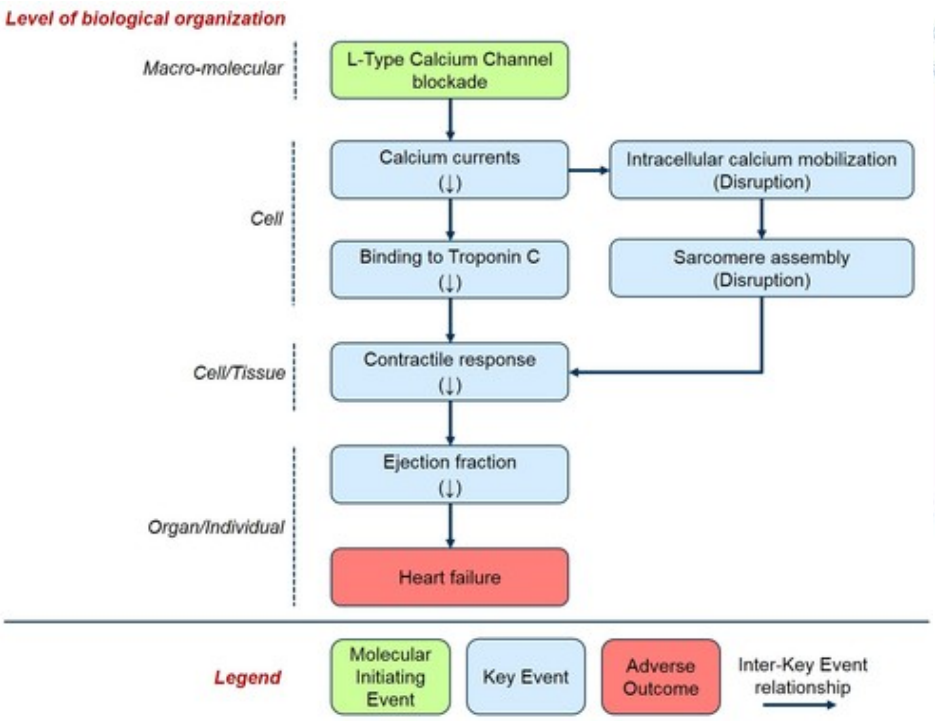
  - FDA ORISE Fellow
  - Mentor = Scott Auerbach
  - Project- Develop a WGCNA (Whole Genome Co-Expressed Network Analysis) tool for CV hazard assessment

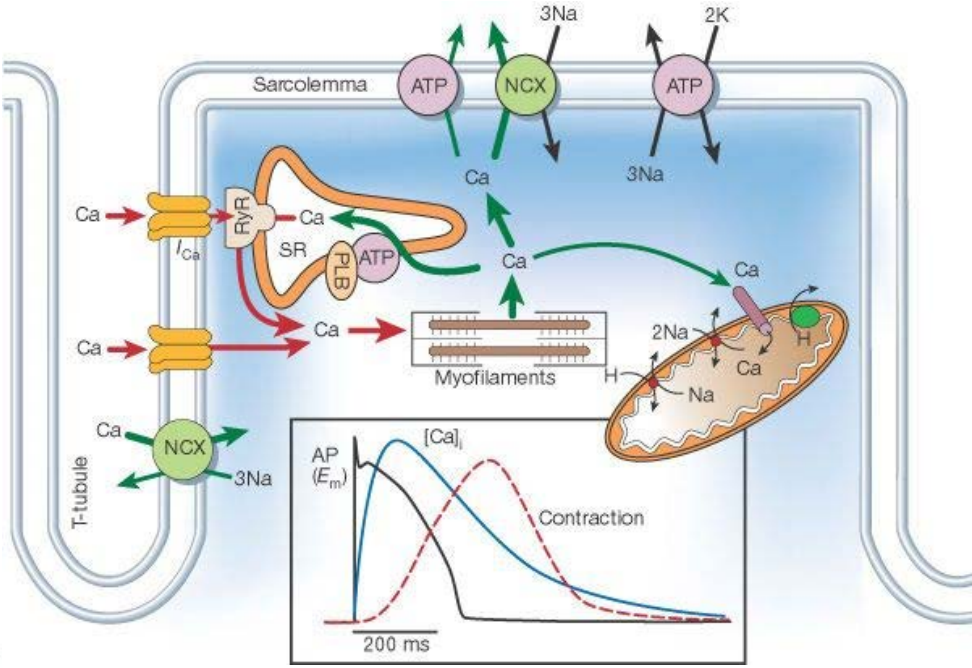
- Shagun Krishna, PhD

  - DNTP Post-Doc Fellow
  - Mentor = Nicole Kleinstreuer
  - Project- Develop computational CV QSAR tools and integrated testing strategies using publicly-available data (e.g. Tox21)

Linking Mechanisms to Phenotypes

E.g. Calcium handling, contractility and heart failure





Linking Mechanisms to Phenotypes

E.g. Calcium handling, contractility and QSAR, HTS Ire

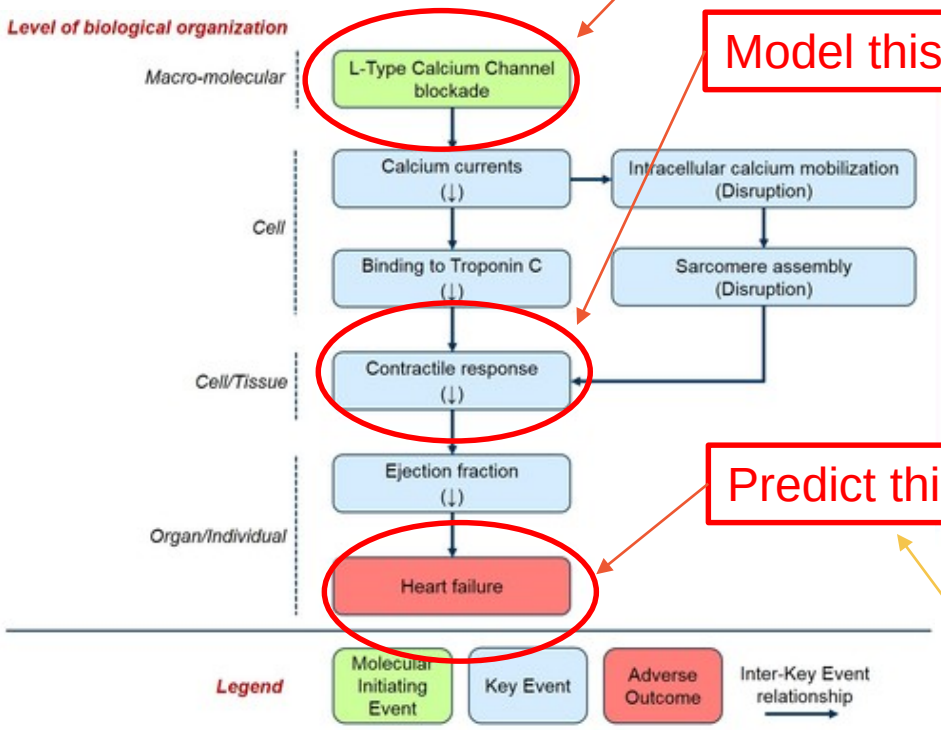
Screen this

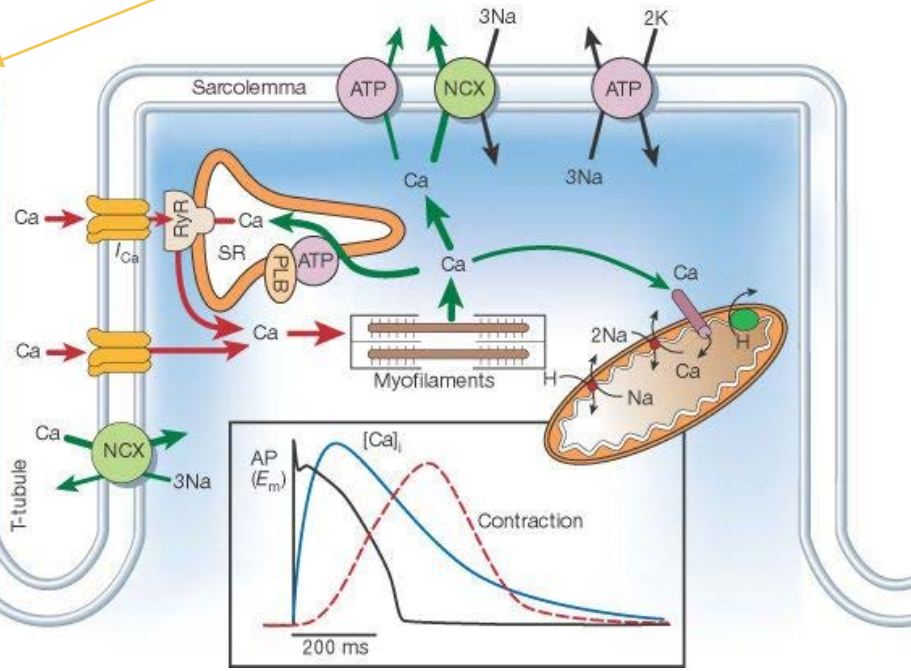
Model this

Predict this

iPSC cardiomyocytes?

WGCNA, In vitro, In vivo studies





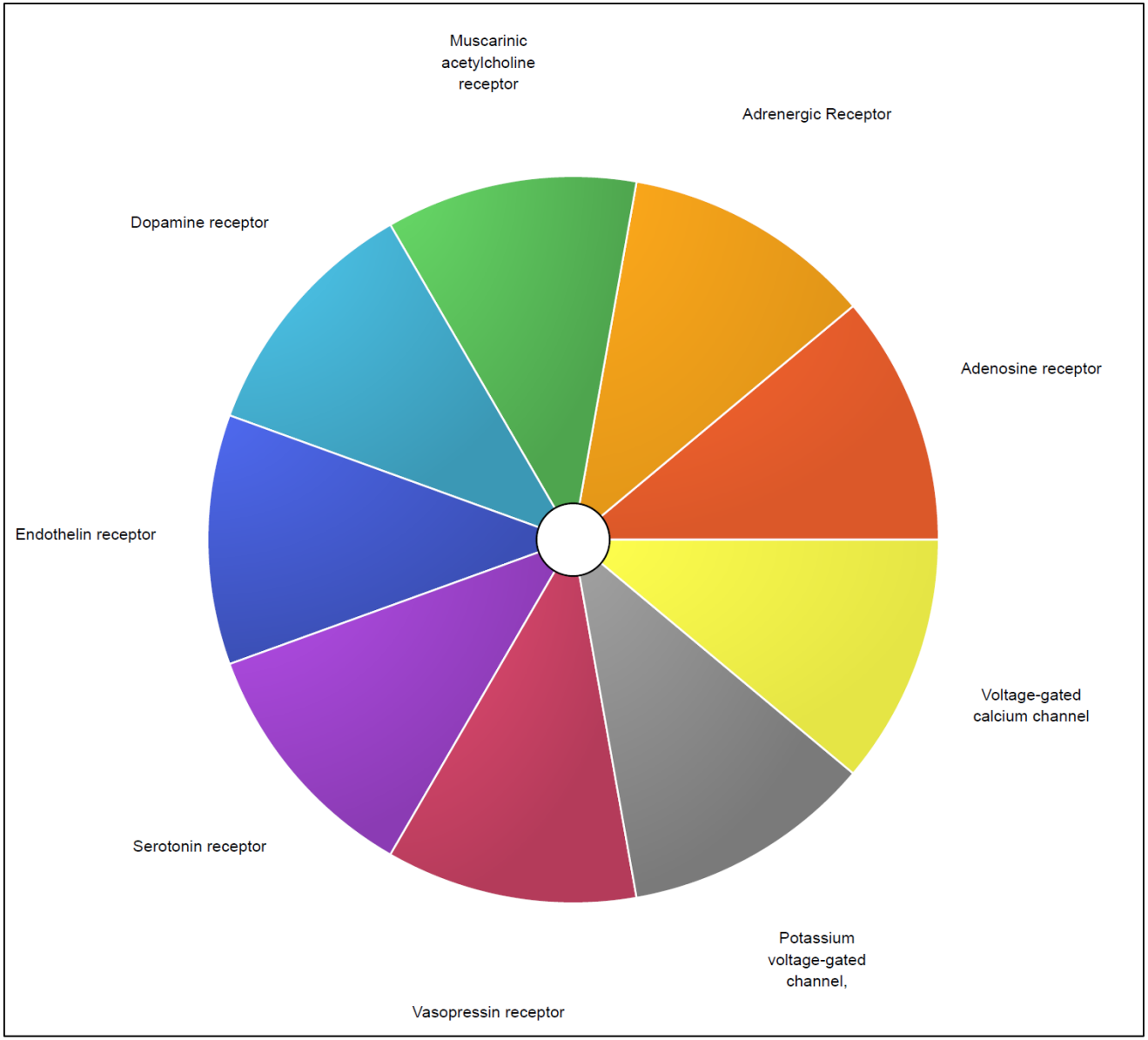
CardioToxPi v1

- A visualization tool to understand chemical activity against the available *in vitro* assays in ToxCast HTS database with CV related targets.
- Rank chemicals based on bioactivity against these targets
- Available data in Toxcast (invitroDB_v3)

- 9215 Chemicals (Tox21/ToxCast library, tested to varying degrees in the target assays)
- 66 *in vitro* assays that map to pharmacological screening targets for 9 families of selected proteins
- Generate CardioToxPi and provide chemical bioactivity ranking against selected targets

S. Krishna

ToxCast CV Targets



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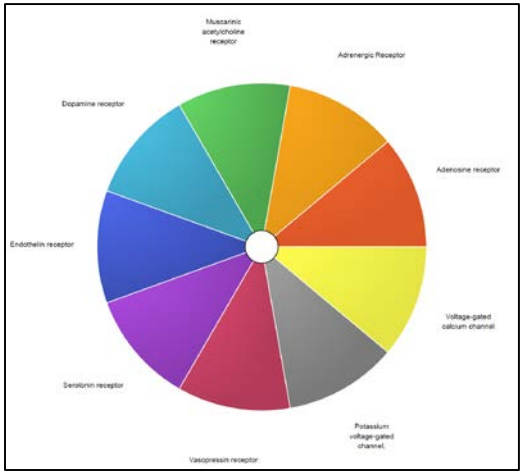
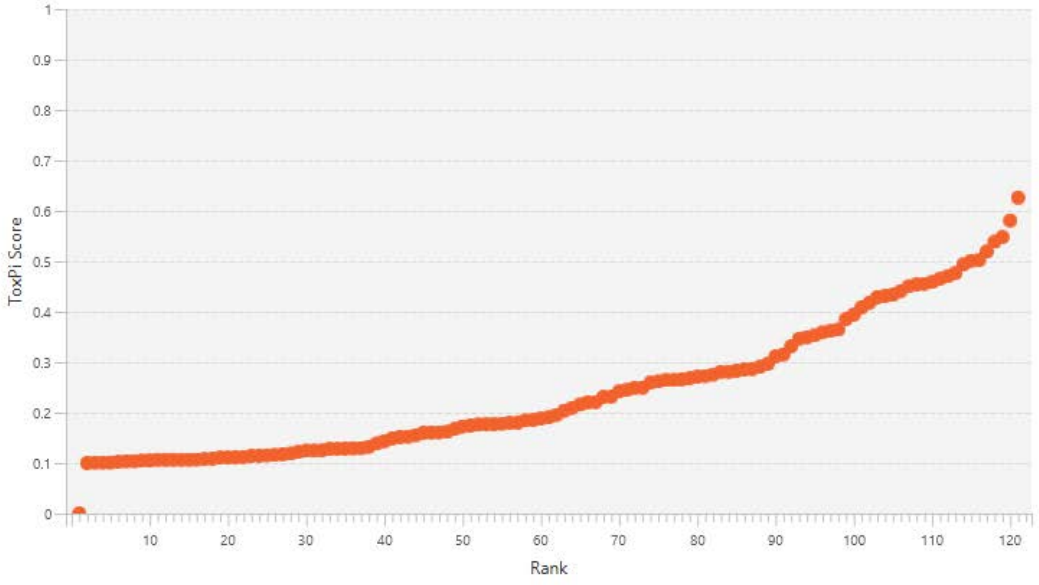
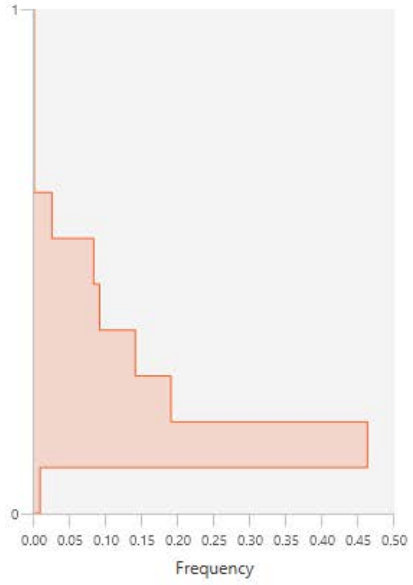
CardioToxPi v1 Ranking

- CardioToxPi ranked 9215 chemicals based on ToxCast Score (negative log scaling):
- ToxPiScore Range: 0.6260 - 0
  - 0.620 - 0.10 (120 Chemicals)
  - 0.10 - 0.00 (9095 Chemicals)







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Top 10 Chemicals with CardioToxPi v1 Score

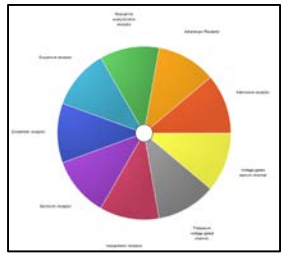
Tributyltin chloride
Score = 0.6261
Rank = 121 (out of 121)
Adenosine receptor 0.6097
Adrenergic Receptor 0.7390
Muscarinic acetylcholine receptor 0.4284
Dopamine receptor 0.7074
Endothelin receptor 0.6289
Serotonin receptor 0.6816
Vasopressin receptor 0.5716
Potassium voltage-gated channel, 0.6120
Voltage-gated calcium channel 0.6560

Gentian Violet
Score = 0.5808
Rank = 120 (out of 121)
Adenosine receptor 0.6372
Adrenergic Receptor 0.8866
Muscarinic acetylcholine receptor 0.6933
Dopamine receptor 0.6628
Endothelin receptor 0.3301
Serotonin receptor 0.7277
Vasopressin receptor 0.0000
Potassium voltage-gated channel, 0.6624
Voltage-gated calcium channel 0.7137

Tributyltin methacrylate
Score = 0.5480
Rank = 119 (out of 121)
Adenosine receptor 0.6056
Adrenergic Receptor 0.9262
Muscarinic acetylcholine receptor 0.6447
Dopamine receptor 0.7120
Endothelin receptor 0.6290
Serotonin receptor 0.7634
Vasopressin receptor 0.0000
Potassium voltage-gated channel, 0.0000
Voltage-gated calcium channel 0.6508

Clomiphene citrate (1:1)
Score = 0.5386
Rank = 118 (out of 121)
Adenosine receptor 0.6448
Adrenergic Receptor 0.7184
Muscarinic acetylcholine receptor 0.6530
Dopamine receptor 0.6393
Endothelin receptor 0.5395
Serotonin receptor 0.5869
Vasopressin receptor 0.0000
Potassium voltage-gated channel, 0.6584
Voltage-gated calcium channel 0.4069

SSR150106
Score = 0.5193
Rank = 117 (out of 121)
Adenosine receptor 0.0000
Adrenergic Receptor 1.0000
Muscarinic acetylcholine receptor 0.6160
Dopamine receptor 0.7997
Endothelin receptor 0.0000
Serotonin receptor 0.8722
Vasopressin receptor 0.0000
Potassium voltage-gated channel, 0.6732
Voltage-gated calcium channel 0.7124



Chlorpromazine hydrochloride
Score = 0.5020
Rank = 116 (out of 121)
Adenosine receptor 0.0000
Adrenergic Receptor 0.8798
Muscarinic acetylcholine receptor 0.7758
Dopamine receptor 0.9257
Endothelin receptor 0.0000
Serotonin receptor 0.9060
Vasopressin receptor 0.0000
Potassium voltage-gated channel, 0.5587
Voltage-gated calcium channel 0.3821

AVE6324
Score = 0.5012
Rank = 115 (out of 121)
Adenosine receptor 0.5903
Adrenergic Receptor 0.6223
Muscarinic acetylcholine receptor 0.5467
Dopamine receptor 0.4770
Endothelin receptor 0.2730
Serotonin receptor 0.6377
Vasopressin receptor 0.0000
Potassium voltage-gated channel, 0.6832
Voltage-gated calcium channel 0.6862

Phenylmercuric acetate
Score = 0.4937
Rank = 114 (out of 121)
Adenosine receptor 0.6954
Adrenergic Receptor 0.8370
Muscarinic acetylcholine receptor 0.7241
Dopamine receptor 0.5897
Endothelin receptor 0.3417
Serotonin receptor 0.7506
Vasopressin receptor 0.0000
Potassium voltage-gated channel, 0.0000
Voltage-gated calcium channel 0.3049

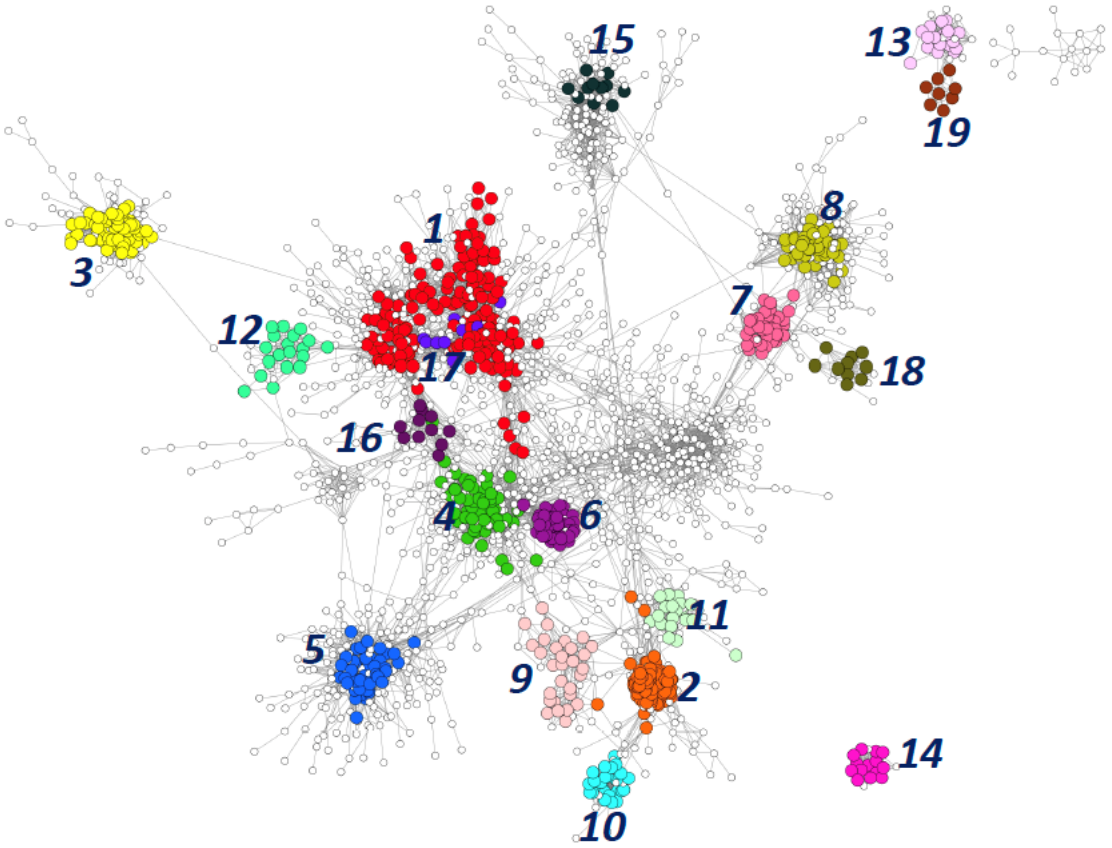
SAR 150640
Score = 0.4766
Rank = 113 (out of 121)
Adenosine receptor 0.6019
Adrenergic Receptor 0.7213
Muscarinic acetylcholine receptor 0.6017
Dopamine receptor 0.6043
Endothelin receptor 0.0000
Serotonin receptor 0.4496
Vasopressin receptor 0.0000
Potassium voltage-gated channel, 0.5629
Voltage-gated calcium channel 0.6585

Mercuric chloride
Score = 0.4701
Rank = 112 (out of 121)
Adenosine receptor 0.6103
Adrenergic Receptor 0.8733
Muscarinic acetylcholine receptor 0.7836
Dopamine receptor 0.7192
Endothelin receptor 0.5836
Serotonin receptor 0.4184
Vasopressin receptor 0.0000
Potassium voltage-gated channel, 0.0000
Voltage-gated calcium channel 0.3225

Work is ongoing to expand the ToxPi to include phenotypic endpoints such as Mitochondrial Function, Oxidative Stress, VEGF Pathway, and Vascular Cell Cytotoxicity

S. Krishna

DrugMatrix- Cardiac Gene Modules

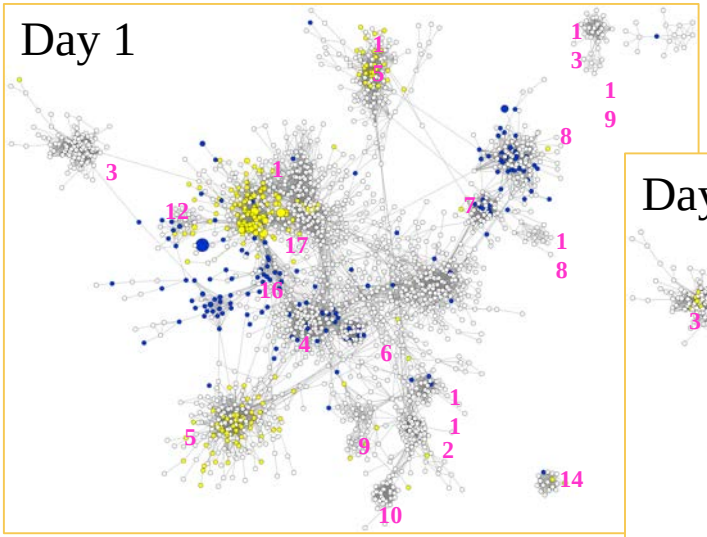


Heart Gene Modules

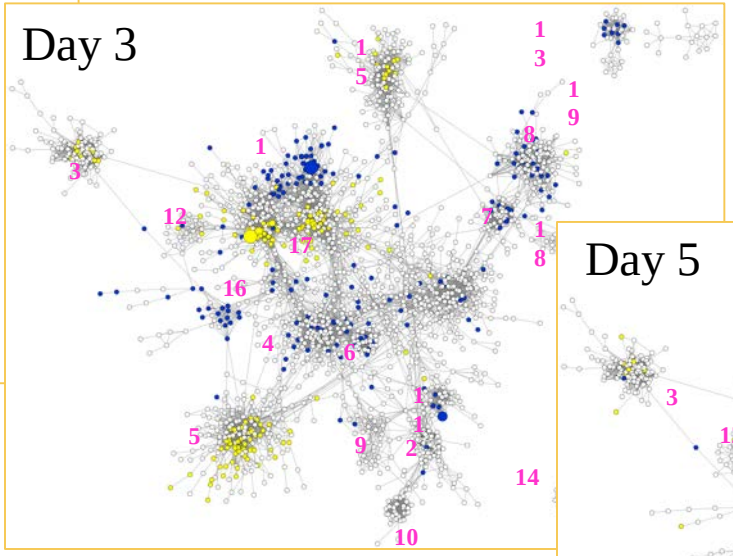
Modules	Biological pathways
Node Group 1	Cellular stress/Inflammation
Node Group 2	Metabolic/stress response/EV
Node group 3	Immune response
Node Group 4	Extracellular matrix
Node group 5	Metabolism/Myocyte repair/hypertrophy
Node Group 6	Cell cycle/division
Node group 7	Tissue morphogenesis
Node Group 8	Protein/lipid synthesis
Node group 9	Energy/heat production/metabolism
Node group 10	Lipid metabolism
Node group 11	Iron homeostasis/ muscle contraction
Node Group 12	Circadian/cardiac rhythm
Node group 13	Carbohydrate metabolism
Node Group 14	Lipid/protein metabolism
Node group 15	Cardiac remodeling; carcinogenesis
Node Group 16	Inflammation
Node group 17	Immune regulation
Node group 18	Protein maturation
Node group 19	Heme biosynthesis

A. Rahman

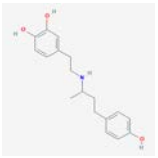
E.g., Dobutamine WGCNA



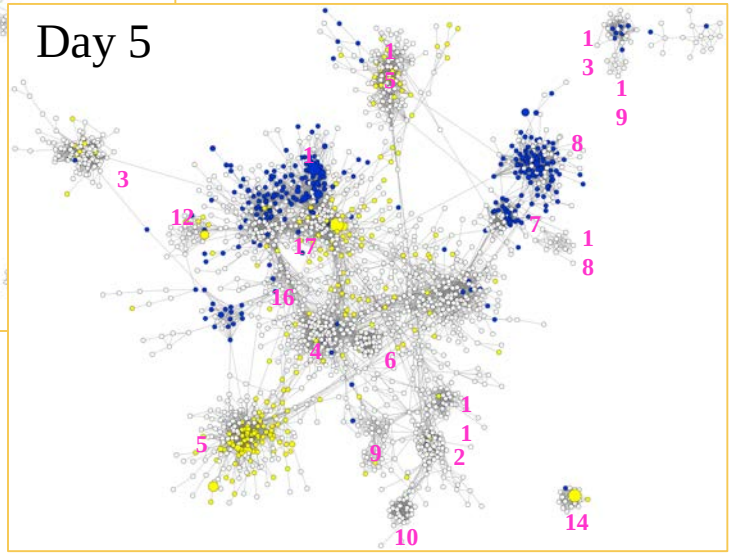
Up-(1,5,15)- Stress response/inflammation, myocyte repair, cardiac remodeling
Down-(4,7,8,16)- Extracellular matrix, protein/lipid synthesis, inflammation



Up-(1,3,5,15)- Stress/immune/metabolic response
Down-(1,8,11,16)- Inflammation, lipid/protein synthesis, muscle contraction



15mg-kg-d in corn oil by oral gavage



Up-(1,5,14,15)- Stress response, myocyte repair, lipid metabolism, cardiac remodeling
Down-(1,7,8,13)-Inflammation, tissue morphogenesis, lipid/protein synthesis, carb metabolism

Associating changes in gene modules of relevance to the CV system with phenotypic evidence of adaptation, injury and progression.

A. Rahman

DNTP CV HEI Task List

- Define discrete problem statements
- Scope the biology/pathobiology of interest
- Capability and knowledge gap analysis
  - Map stakeholders
  - Map current capabilities (internal and external) and data sources
  - Identify what parts of a functional pipeline are missing
- Identify contemporary environmental toxicology problems to which to align capability development
  - E.g. PFAS, BPA, PAHs
- Develop a CV HEI Program/Project Strategic Plan
  - Presentation to DNTP LT Governance Committee
- Build a project and data management framework

Questions?