NTP
National Toxicology Program

Cardiovascular Health Effects Innovation Program

Brandy Beverly, PhD
Division of the NTP
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
December 3-4, 2020

Cardiovascular Health Effects Innovation Program

The Team

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Biomolecular Screening Branch

Michelle Cora
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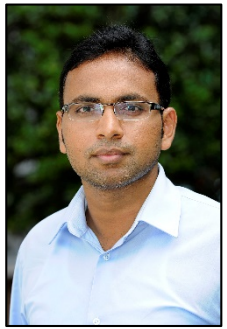
Nicole Kleinstreuer
NICEATM



Sreenivasa Ramaiahgari
Biomolecular Screening Branch

Arif Rahman
Post-Doctoral Fellow
(Mentor: Scott Auerbach)

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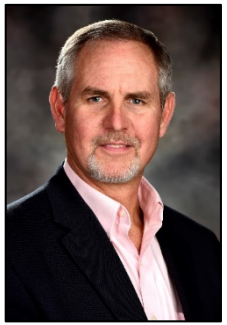
Post-Doctoral Fellow
(Mentor: Nicole Kleinstreuer)



Brian Berridge
DNTP Scientific Director

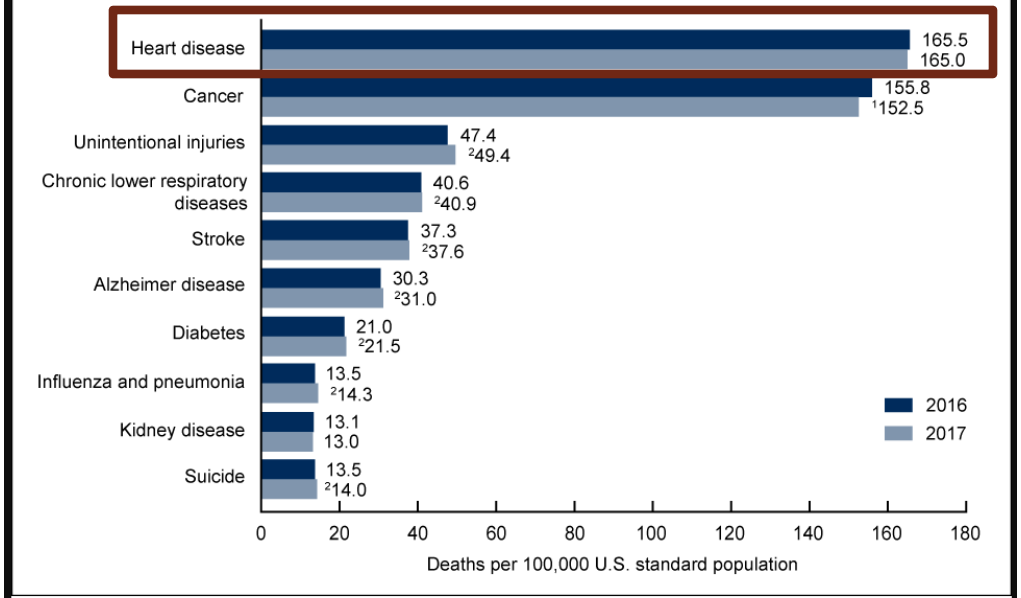
Problem Statement

- Chronic progressive cardiovascular (CV) disease is a primary cause of morbidity and mortality in the United States and globally.
- Current approaches to environmental hazard assessment do not include specific assessments of CV bioactivity and hazards
- There is no defined approach to identify agents that might be contributing to contemporary and common CV diseases.

Why this?

To improve our understanding about how environmental exposures could affect the CV system in humans

Top 10 US causes of deaths, 2016 and 2017



[1]Statistically significant decrease in age-adjusted death rate from 2016 to 2017 ($p < 0.05$).
[2]Statistically significant increase in age-adjusted death rate from 2016 to 2017 ($p < 0.05$).
NOTES: A total of 2,813,503 resident deaths were registered in the United States in 2017. The 10 leading causes accounted for 74.0% of all deaths in the United States in 2017. Causes of death are ranked according to number of deaths. Rankings for 2016 data are not shown. Data table for Figure 4 includes the number of deaths for leading causes. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db328_tables-508.pdf#4.
SOURCE: NCHS, National Vital Statistics System, Mortality.

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To improve our understanding about how environmental exposures could affect the CV system in humans

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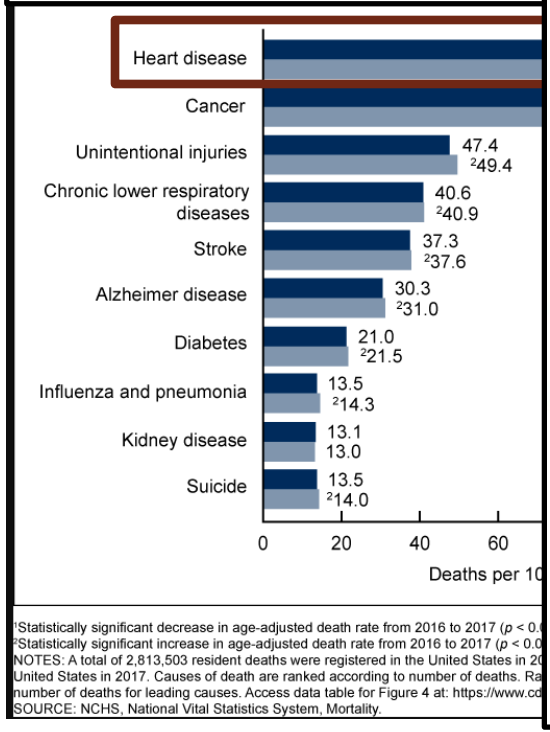

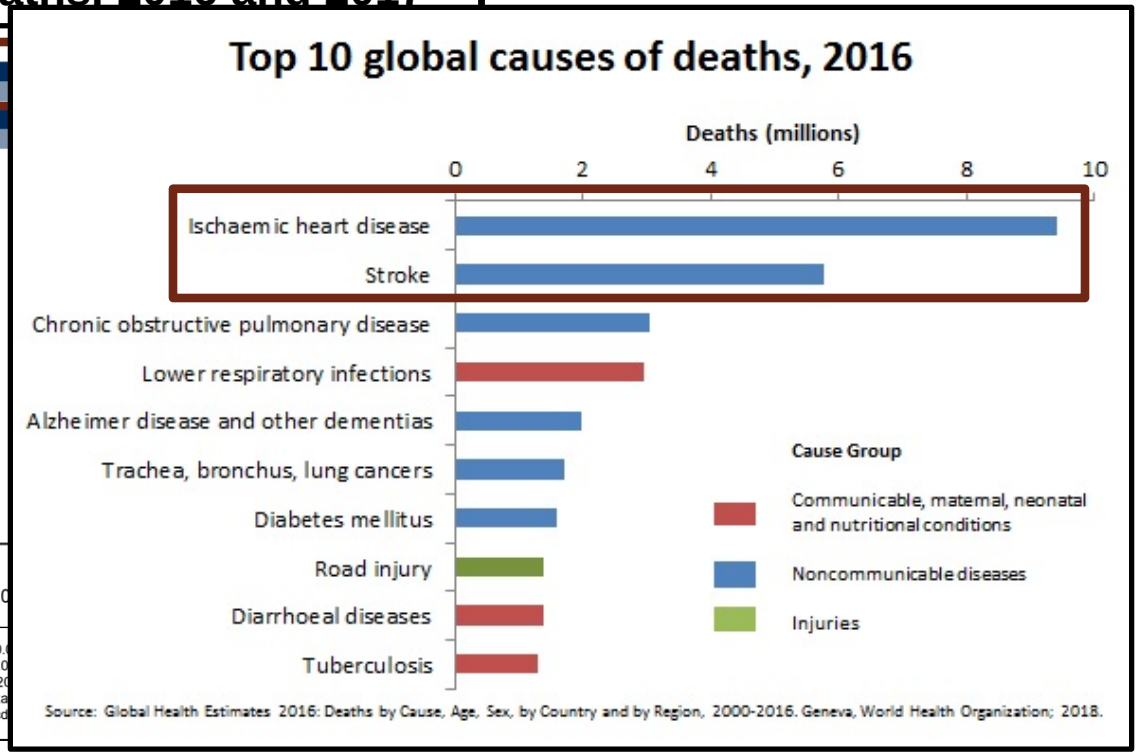

Why this?

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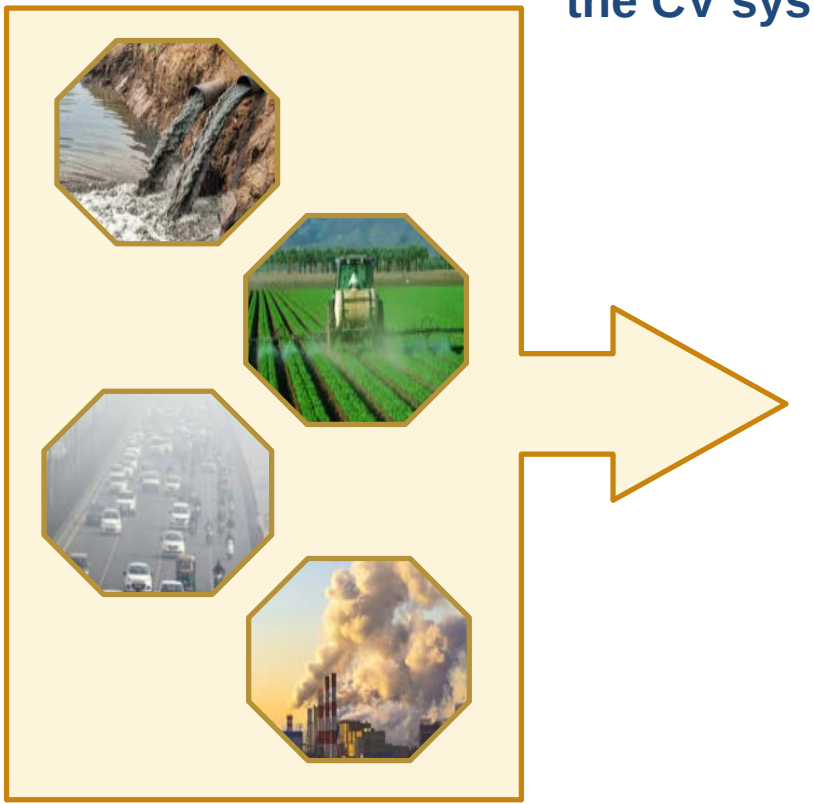
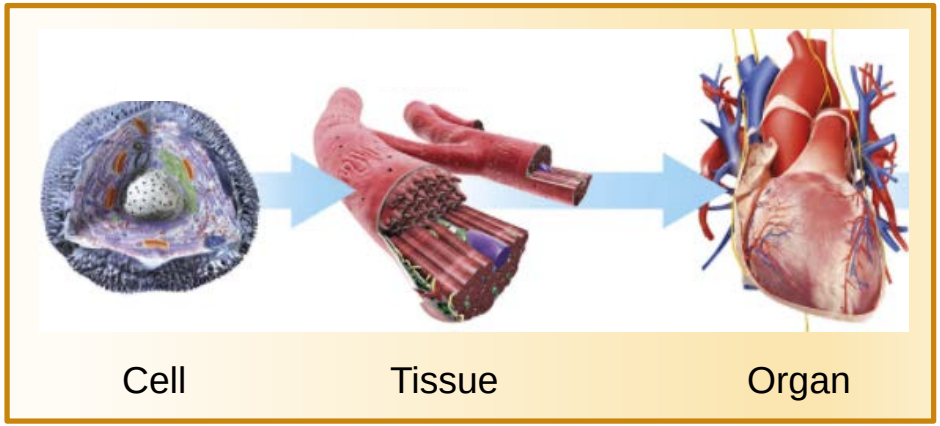




Objectives

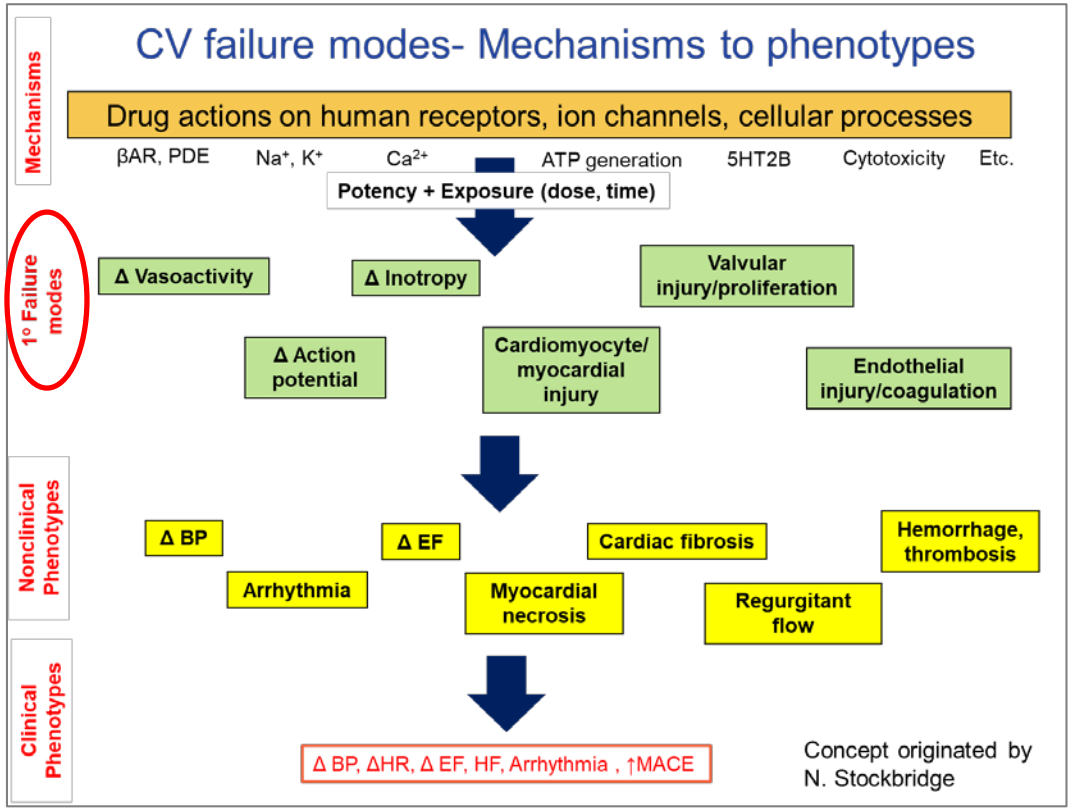
- Leverage existing knowledge to define key ’failures modes’ as a biological framework for modeling, link those modes to mediators of mechanistic bioactivity and screen existing databases to identify putative CV hazards.

- Develop a suite of assay/testing/modeling/knowledge management capabilities that aligns to the current Division of the National Toxicology Program (DNTP) Translational Toxicology Pipeline and apply it, in an integrated fashion, to provide an evidence-based approach to assessing CV bioactivity of environmental substances.

- Develop and implement an innovative capability for identifying potential environmental contributors to specific and contemporary clinical CV diseases.

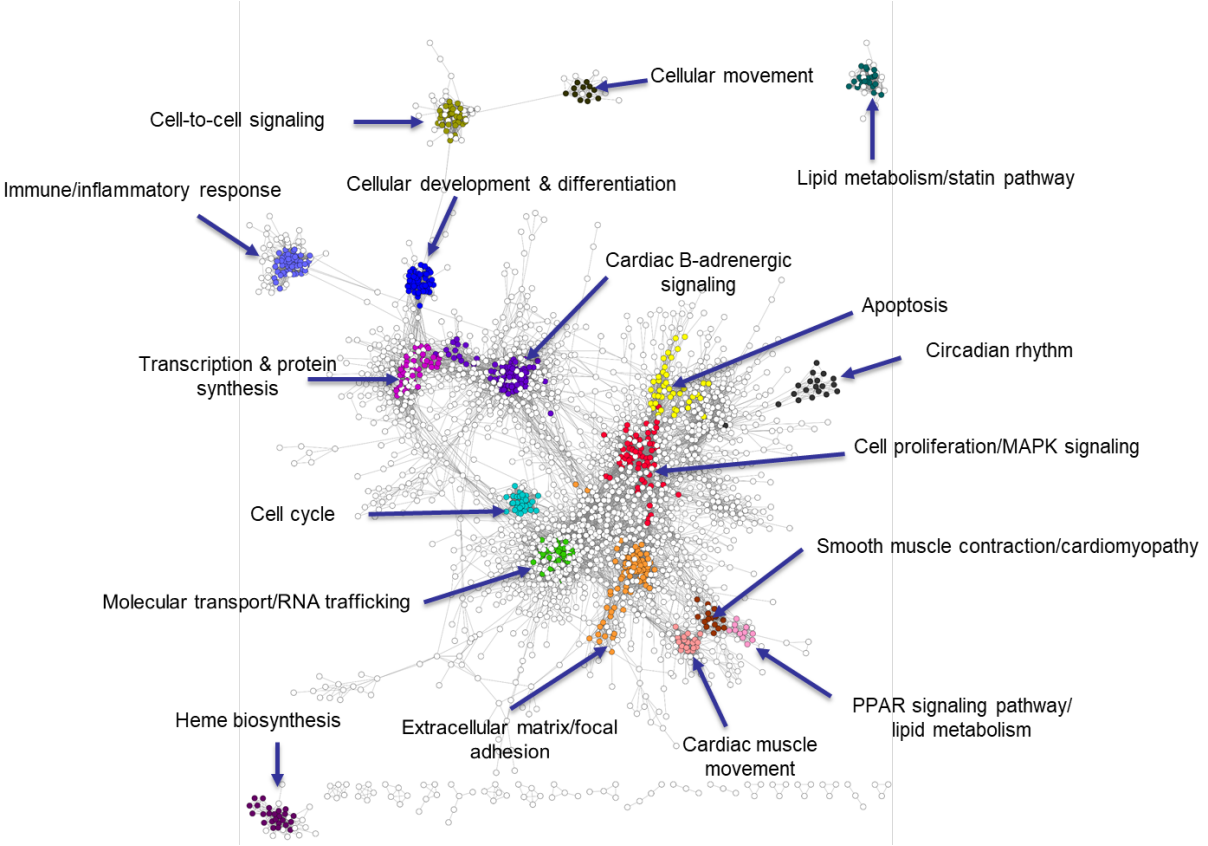
Using CV Failure Modes as a framework

CV 'failure modes': discrete ways in which the CV system responds to injury



Linking Failure Modes to mediators of mechanistic bioactivity

Pearson correlation-based gene expression network



Arif Rahman, Scott Auerbach

Objective 1: Leveraging existing knowledge

Using CV Failure Modes as a framework to screen existing databases

CV-relevant bioactivities

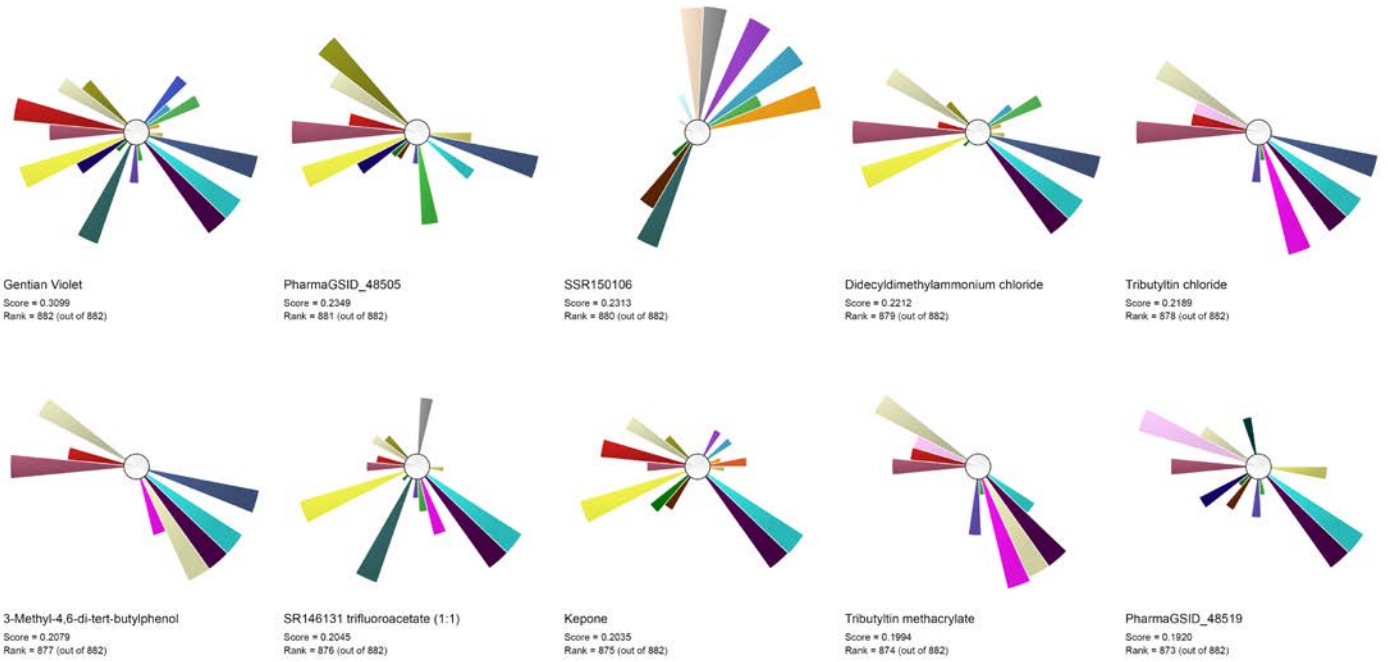
Slice	Traget name	Effect	Slice Color
ADORA	Adenosine Receptor	Vasodialation, alterations in BP	
ADRB	Adrenergic Receptor	Arrhythmia, Alterations in BP	
CHRM	Muscarinic Acetylcholine Receptor	Alterations in BP and HR, tachycardia	
DRD	Dopamine Receptor	Alterations in BP and HR, Vascular relaxation	
EDNR	Endothelin Receptor	Alterations in BP, Can exert adverse effects during	
HTR	Serotonine Receptor	Alterations in BP, Potential cardiac valvulopathy	
AVPR	Vasopressin Receptor	Alterations in BP and HR, Cardiac hypertrophy	
CHRNA	Cholinergic receptor	Alterations in BP and HR	
CACNA	Voltage-Gated Calcium Channel	Alterations in BP, QT prolongation, Arrhythmia	
KCNH2	Potassium Voltage Gated Channel	Prolongation of QT interval of ECG	
VEGF	Vascular Endothelial Growth Factor	Alterations in BP , Cardiac Ischemia	
VascularTissue	Vascular Tissue	Myocardial ischemia, cardiac Arrhythmias	
OxidativeStress	Oxidative Stress	Cellular Hypertrophy; Cardiac Cell Death	
MtDysfunction	Mitochondrial Dysfunction	Cardiac dysfunction; Cardiomyopathy	
TissueFactor	Tissue Factor	Alterations in BP and ventricular hypertrophy	
PDE	Phosphodiesterase	Alterations in cardiac contractility, HR and BP	
MAO	Monoamine Oxidase	Alterations in BP	
JNK	c-Jun N-terminal kinase	Vascular injury, cardiac hypertrophy	
TyrKinase	Tyrosine Kinase	Alterations in BP, LV dysfunction, conduction	
AroPro	Aromatase Protein	Ischemic heart disease	
ERAlpha	Estrogen receptor Alpha	Abnormal cardiac contractility, cardiac hypertrophy	
NR3C1	Glucocorticoid receptor	Alterations in BP; Arrhythmia	
PPARG	Peroxisome Proliferator Activated Receptor γ	Cardiac hypertrophy , Atherosclerosis	
AP	Activating Protein	Atherosclerosis	
HIF	Hypoxia Inducible Factor 1	Ischaemia disease	
NFKB	NF Kappa B	Atherosclerosis	
TP53	Tumor Protein p53	Alteration in cardiac function	
ICAM1	Intercellular adhesion molecule 1	Markers of endothelial dysfunction	
IL6	Interleukin 6	Markers of inflammation and oxidative stress	
t-PA	Tissue Type plasminogen activator	Markers of endothelial dysfunction	
PAI -1	Plasminogen activator inhibitor type	Markers of endothelial dysfunction	
NPA	Natriuretic peptide A	Release in response to elevation in LV filling pressure	
SAA1	Serum amyloid A1	Direct promotion of vascular dysfunction through SAA within vascular tissues	

Objective 1: Leveraging existing knowledge

Using CV Failure Modes as a framework to screen existing databases

ToxPi = visualization tool that represents relative potency of bioactivities

CardioToxPi images for 10 most active chemicals



Objective 2: Developing capabilities

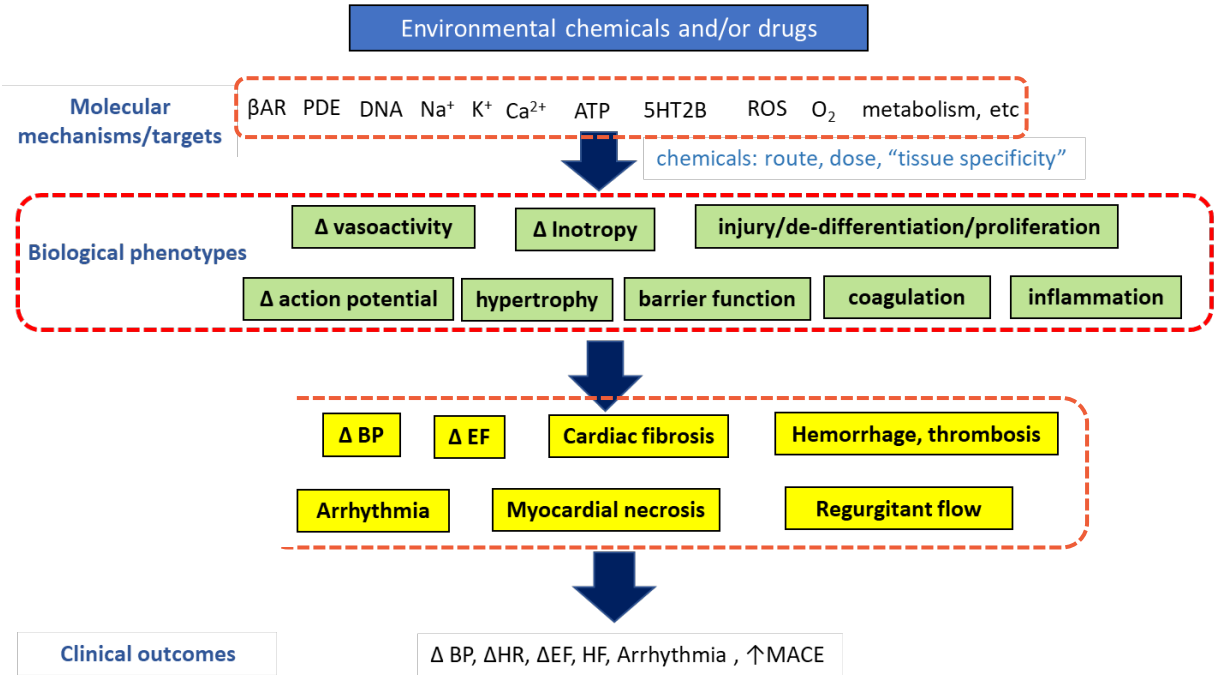
Assay, testing, modeling, knowledge management

CV failure modes- Mechanisms to phenotypes

Focus of bioactivity screening

Focus of in vitro modeling

In vivo endpoints



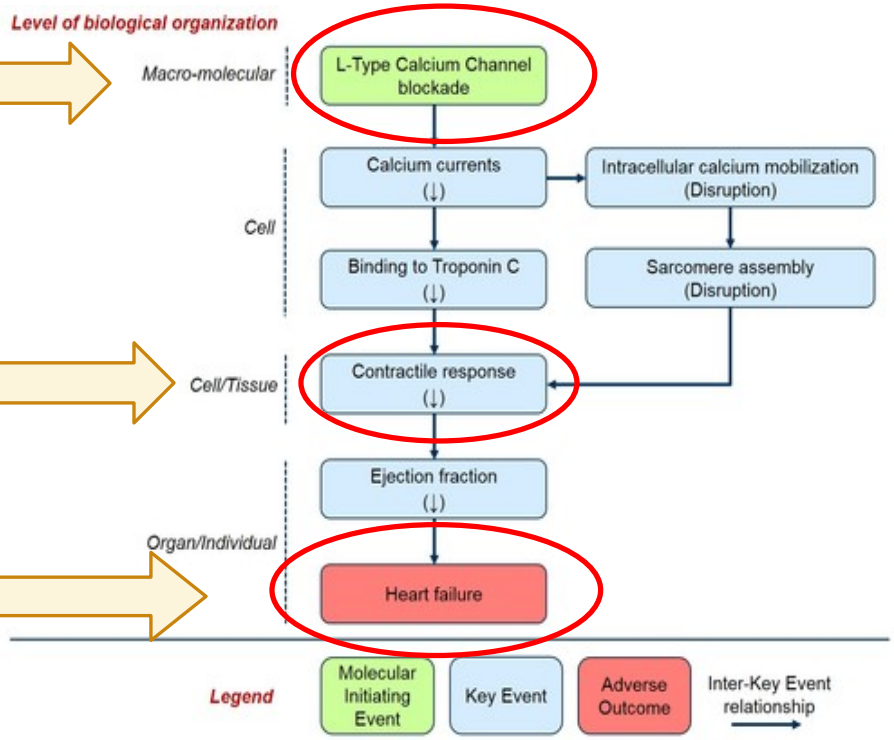
Objective 2: Developing capabilities

Assay, testing, modeling, knowledge management

Screen this
(QSAR, HTC)

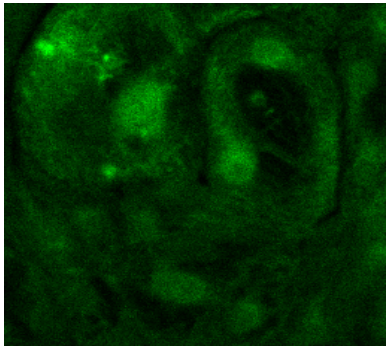
Model this
(iPSC cardiomyocytes)

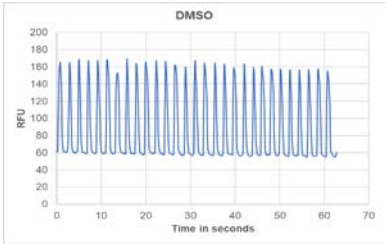
Predict this
(In vitro, in vivo studies)



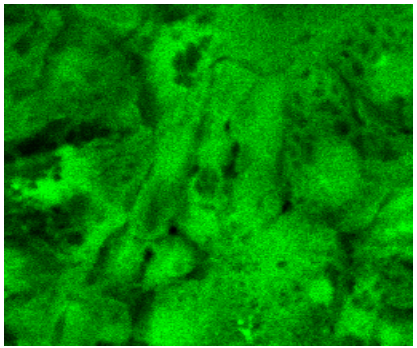
Human iPSC-derived cardiomyocytes

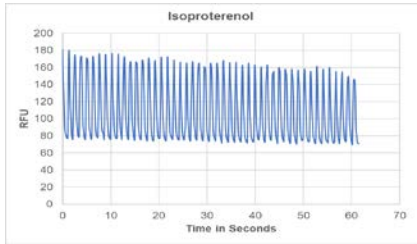
DMSO





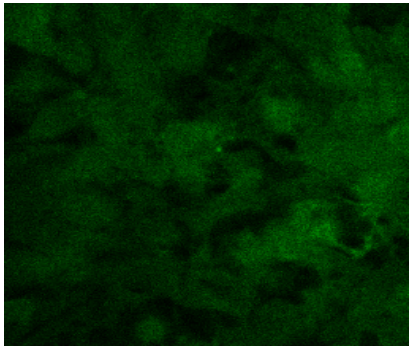
Isoproterenol

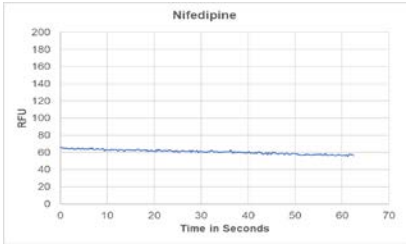




- Non-selective β adrenoreceptor agonist
- Used for the treatment of bradycardia
- Enhances Ca2+ release

Nifedipine

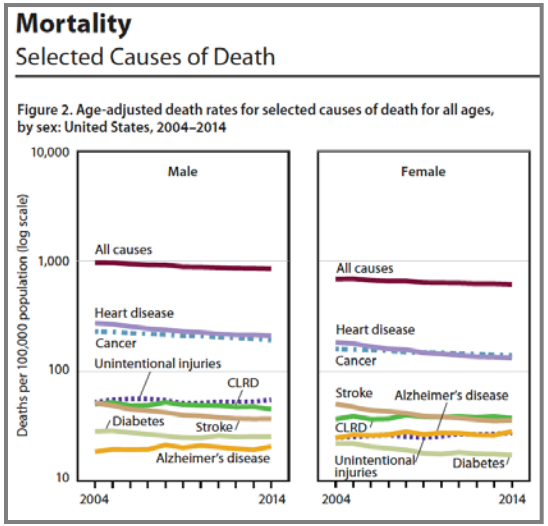




- Calcium channel blocker-specific to the L-type calcium channels
- Used to treat high blood pressure

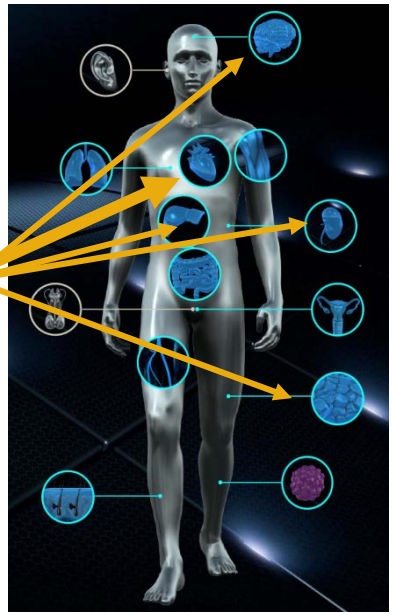
Objective 3: Developing approaches to understand CV diseases

Shifting from agent-based to disease-focused health effect assessments

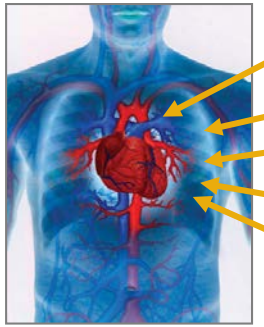


X lbs./yr. commercial production

Agent Y



Incidence of common diseases



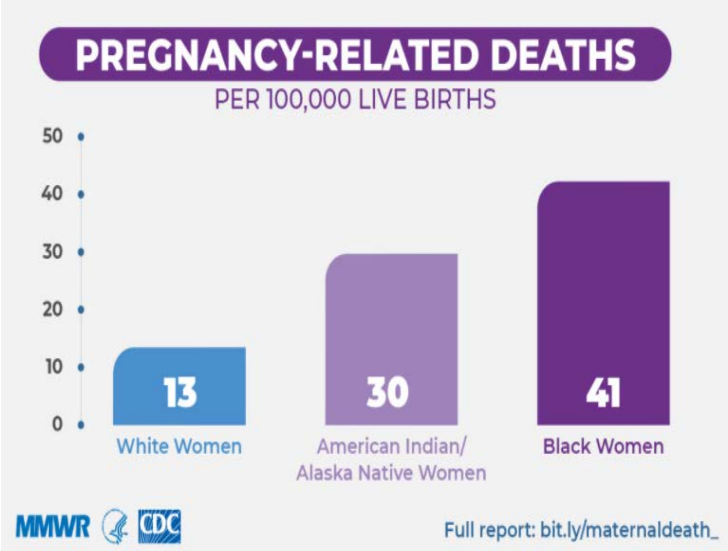
Agent A
Agent B
Agent C
Agent Y
Agent Z

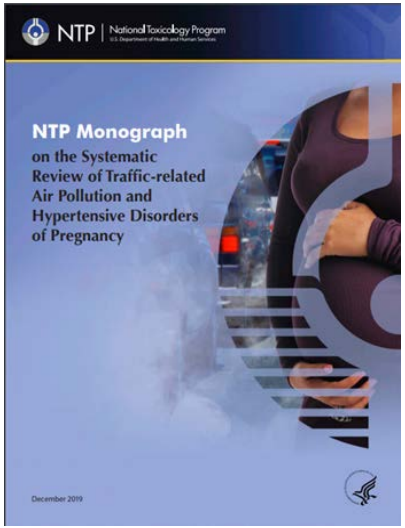
https://ncats.nih.gov/tissuechip/chip

Objective 3: Developing approaches to understand CV diseases

Environmental contributors to hypertensive disorders of pregnancy

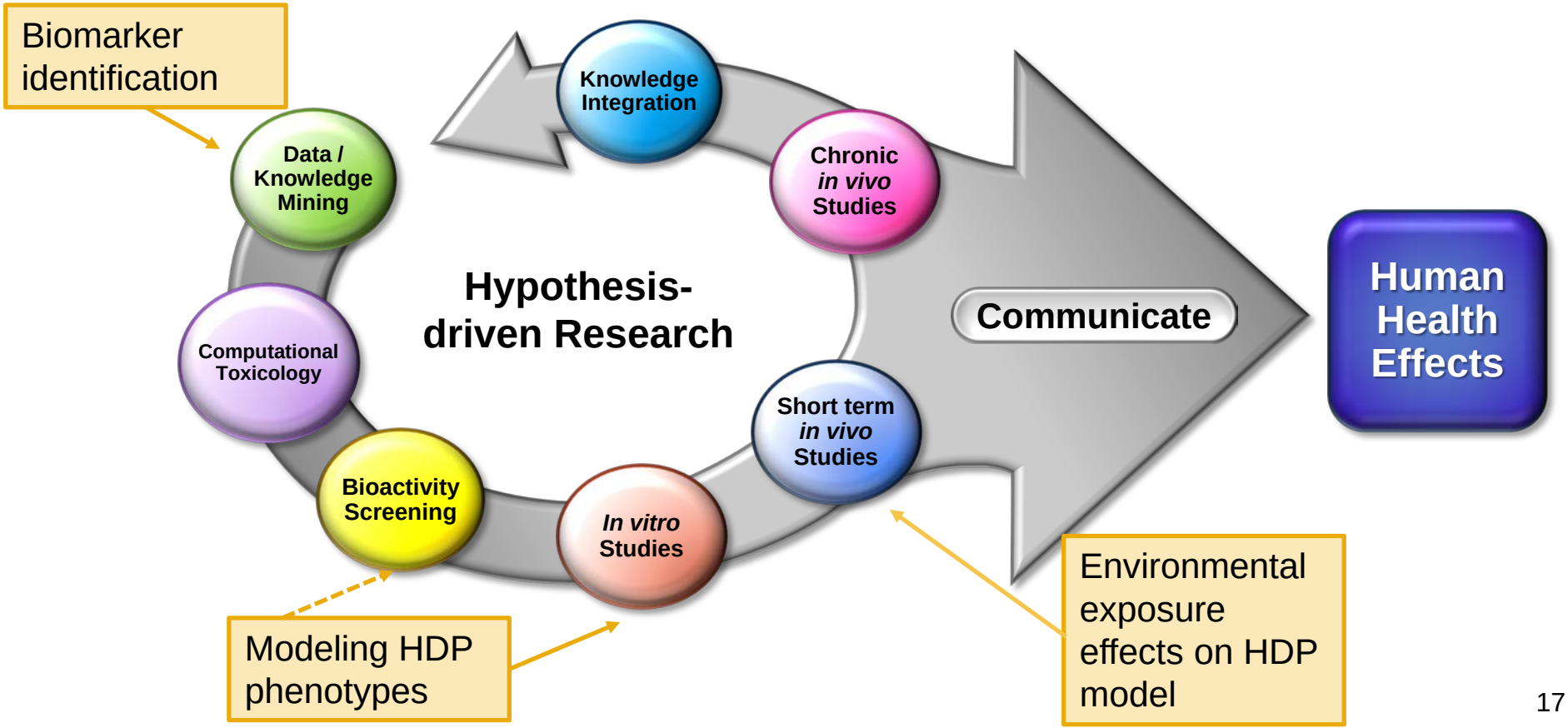
Causes of maternal deaths each year





Objective 3: Developing approaches to understand CV diseases

Environmental contributors to hypertensive disorders of pregnancy (HDP)



Working together to understand environmental exposures and CV toxicity

HESI.

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

FDA

NIH National Center for Advancing Translational Sciences

COLLABORATE. INNOVATE. ACCELERATE.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

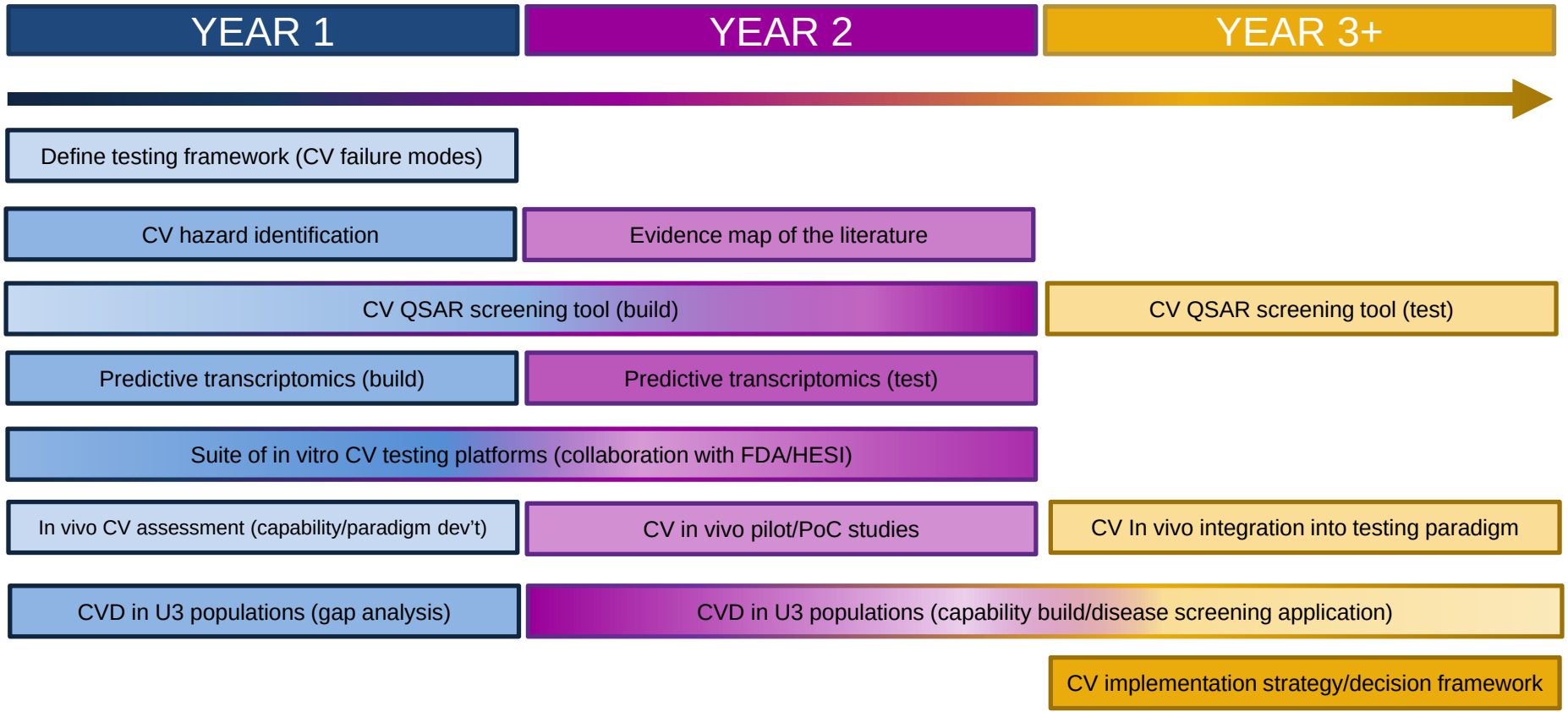
Need meets evidence + capabilities + expertise

- Leverage existing knowledge
- Develop capabilities
- Investigate complex CV diseases

Progress to date

Complete	Ongoing	Pending
Manuscript: CardioToxPi analysis (in review)	Evaluation of in vitro CV capabilities	Manuscript: CV testing framework
Manuscript: CV-relevant drug matrix data and WCGNA modules (in preparation)	Evidence mapping of CV outcomes and environmental exposures	
CV HEI concept presentation	Literature-based analysis of HDP biomarkers	
	Literature-based analysis of CVD in U3 populations	

Milestones


YEAR 1
YEAR 2
YEAR 3+
Define testing framework (CV failure modes)
CV hazard identification
Evidence map of the literature
CV QSAR screening tool (build)
CV QSAR screening tool (test)
Predictive transcriptomics (build)
Predictive transcriptomics (test)
Suite of in vitro CV testing platforms (collaboration with FDA/HESI)
In vivo CV assessment (capability/paradigm dev't)
CV in vivo pilot/PoC studies
CV In vivo integration into testing paradigm
CVD in U3 populations (gap analysis)
CVD in U3 populations (capability build/disease screening application)
CV implementation strategy/decision framework

NTP
National Toxicology Program

Thank You!

Question 1

What are you most excited about?

Question 2

Please share your insights about the Program regarding:

a. how the objectives address the problem/opportunity
b. the boldness of the approach to achieve the objectives
c. the alignment of the metrics to the desired impact

Question 3

Considering DNTP's capabilities and expertise, what mechanisms do you suggest that we consider to be able to effectively execute against the objectives? With whom might we partner to ensure success?

Question 4

The disease-focused approach of the Health Effects Innovation Programs is novel in toxicology and hazard assessment. What unique challenges are we likely to encounter in taking that approach for CV disease? What near and mid-term deliverables might reinforce our decision to take that approach?

Question 5

A key theme of the NIEHS Strategic Plan is ‘Data to Knowledge to Action’. At what level of detail do we need to characterize CV hazards to enable public health-protective decisions by individuals, regulatory scientists and policy makers? For example, at the level of bioactivity in the CV system, induction of adverse changes in morphology or function or at the mechanistic level?