



Interagency Coordinating Committee on the Validation of Alternative Methods

New Approach Methodologies: Translational Impact and Human Relevance of Microphysiological Systems

Brian R. Berridge, DVM, PhD, DACVP

National Institute of Environmental Health Sciences

National Toxicology Program

SACATM Meeting

September 19-20, 2019

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Institute of Standards and Technology • National Library of Medicine • Occupational Safety and Health Administration

Microphysiological Systems

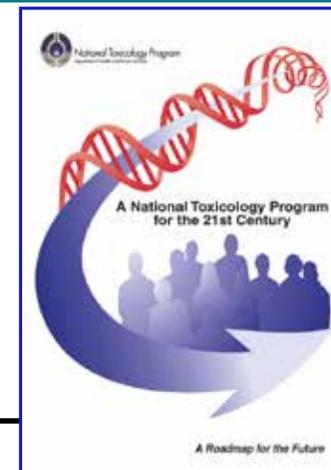
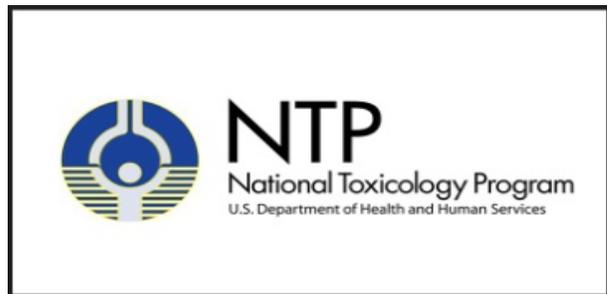
Need  Opportunity

Strategy

Confidence

Application

Need



Mission

To evaluate agents of public health concern, by developing and applying tools of modern toxicology and molecular biology.

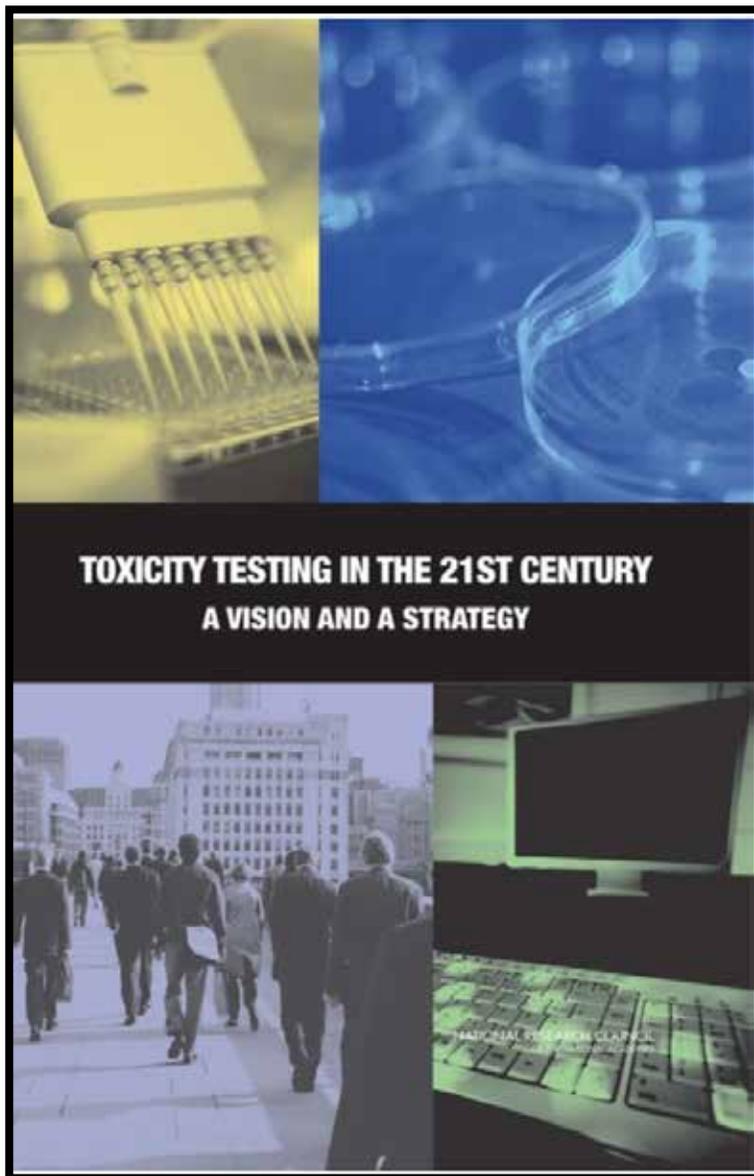
<http://ntp.niehs.nih.gov>; April 2015

21st Century Vision

To support the evolution of toxicology from a predominately observational science at the level of disease-specific models to a predominately predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.

A National Toxicology Program for the 21st Century, November 2004

Need



NRC Committee on Toxicity Testing and Assessment of Environmental Agents

“Toxicity testing is under increasing pressure to meet several competing demands:

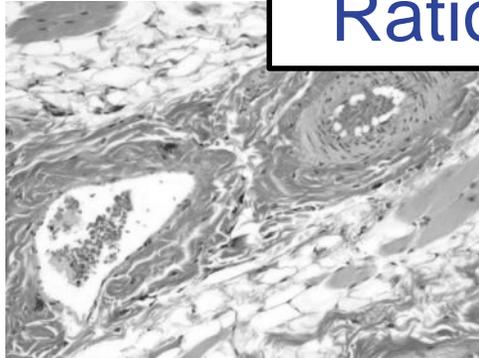
- Test **large numbers** of existing chemicals, many of which lack basic toxicity data.
- Test the large number of new chemicals and novel materials, such as nanomaterials, introduced into commerce each year.
- Evaluate potential adverse effects with respect to all critical end points and life stages.
- **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.

i.e. “Translational Impact and Human Relevance...”

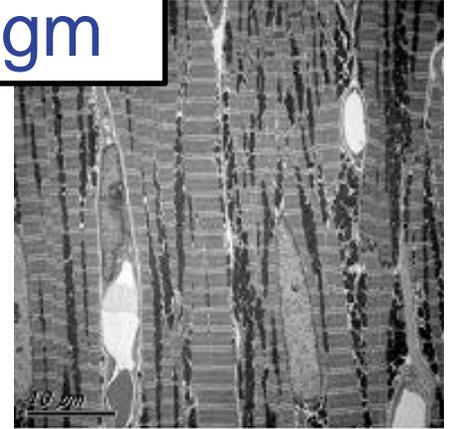


Rationalizing the current paradigm

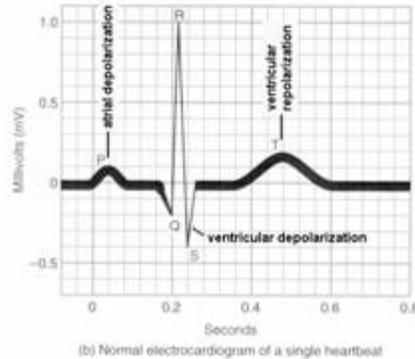
Biological
 conservation



Blood vessels conduct blood to the heart itself as well as the rest of the body.



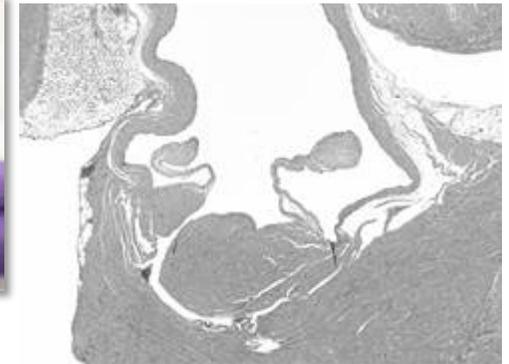
Cardiomyocytes are contractile cells with immense energy needs



Rhythmic waves of electrical activity ensure coordinated contraction of different regions of the heart.



A muscular pump and its delivery system.

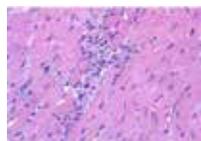


Heart valves ensure unidirectional flow of blood.

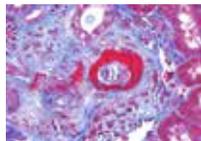
Rationalizing the current paradigm

Pathobiological conservation

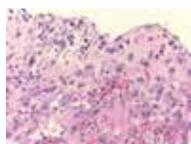
Structural injuries



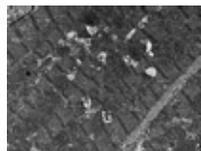
cardiomyocyte injury



vascular injury



valvulopathy



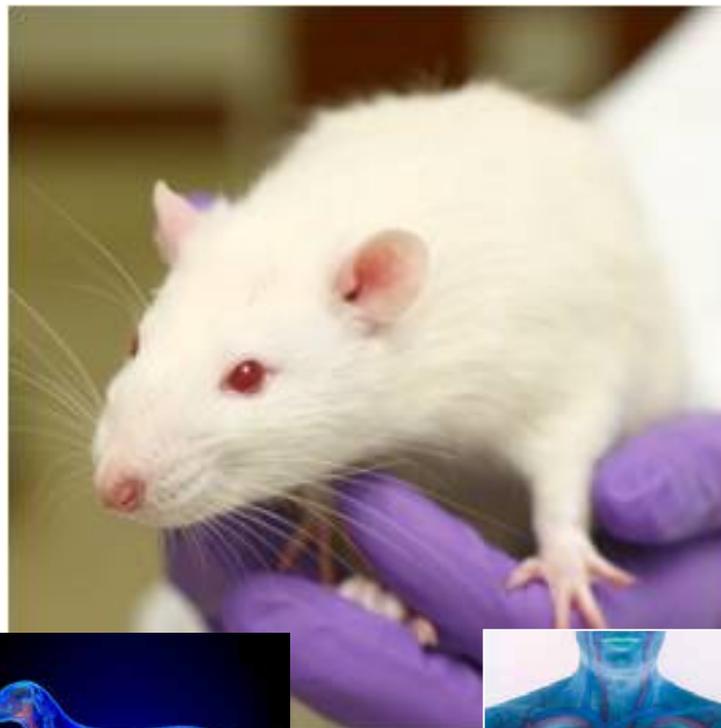
ultrastructural injury



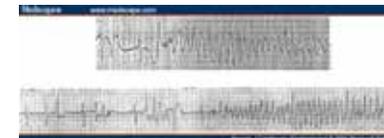
Δ cardiac mass



Neoplasia



Functional changes



Arrhythmia

Δ BP Δ HR

Δ contractility

Changes in disease

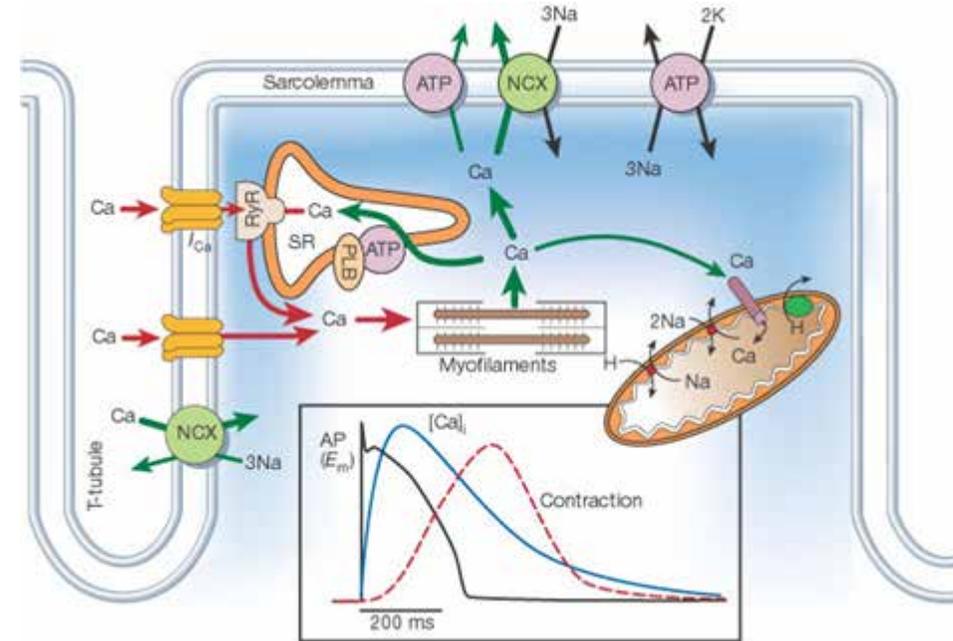
- Ischemic events
- Coronary artery dz
- Heart failure
- Cerebrovascular events
- Hypertension
- Metabolic disease



Rationalizing the current paradigm

Mechanistic conservation

- Calcium is primary mediator
- Excitation-contraction coupling is “energy-requiring”
- Mitochondria critical as stores of calcium and producers of ATP
- Myocardial relaxation is more sensitive to ATP depletion than is the process of myocardial contraction (cf. diastolic dysfunction)



Bers, DM. Nature 415:198-205, 2002

Excitation-Contraction Coupling



“For all that, current approaches to safety or hazard assessment are imprecise.”

National Toxicology Program

Headquartered at the National Institute of Environmental Health Sciences NIH-HHS

Tox21: Chemical testing in the 21st century

Comprehensive Analyses and Prioritization of Tox21 10K Chemicals Affecting Mitochondrial Function by in-Depth Mechanistic Studies

Menghang Xia,¹ Ruili Huang,¹ Qiang Shi,² Windy A. Boyd,³ Jinghua Zhao,¹ Nuo Sun,⁴ Julie R. Rice,³ Paul E. Dunlap,³ Amber J. Hackstadt,⁵ Matt F. Bridge,⁵ Marjolein V. Smith,⁵ Sheng Dai,¹ Wei Zheng,¹ Pei-Hsuan Chu,¹ David Gerhold,¹ Kristine L. Witt,³ Michael DeVito,³ Jonathan H. Freedman,⁶ Christopher P. Austin,¹ Keith A. Houck,⁷ Russell S. Thomas,⁷ Richard S. Paules,³ Raymond R. Tice,³ and Anton Simeonov¹

Modes of action Environmental Health Perspectives 126(7) July 2018

Article

Identification of Compounds That Inhibit Estrogen-Related Receptor Alpha Signaling Using High-Throughput Screening Assays

Caitlin Lynch¹, Jinghua Zhao¹, Sriatha Sakamuru¹, Li Zhang¹, Ruili Huang¹, Kristine L. Witt², B. Alex Merrick², Christina T. Teng^{2,*} and Menghang Xia^{1,*}

Molecular events Molecules 2019, 24, 841; doi:10.3390,



RESEARCH ARTICLE

A hybrid gene selection approach to create the S1500+ targeted gene sets for use in high-throughput transcriptomics

Deepak Mav^{1,†}, Ruchir R. Shah^{1,†}, Brian E. Howard¹, Scott S. Auerbach², Pierre R. Bushel³, Jennifer B. Collins⁴, David L. Gerhold⁵, Richard S. Judson⁶, Agnes L. Karmaus^{6,†}, Elizabeth A. Maul², Donna L. Mendrick², B. Alex Merrick², Nisha S. Sipes², Daniel Svoboda¹, Richard S. Paules^{2,*}

Pathways PLOS ONE | <https://doi.org/10.1371/journal.pone.0191105> February 20, 2018

Identifying Attributes That Influence In Vitro-to-In Vivo Concordance by Comparing In Vitro Tox21 Bioactivity Versus In Vivo DrugMatrix Transcriptomic Responses Across 130 Chemicals

William D. Klaren,^{*,1} Caroline Ring,^{†,1} Mark A. Harris,[‡] Chad M. Thompson,[‡] Susan Borghoff,[§] Nisha S. Sipes,[¶] Jui-Hua Hsieh,^{||} Scott S. Auerbach,^{||} and Julia E. Rager^{†,2}

Predictive extrapolation TOXICOLOGICAL SCIENCES, 167(1), 2019, 157–171



Interagency Coordinating Committee on the Validation of Alternative Methods

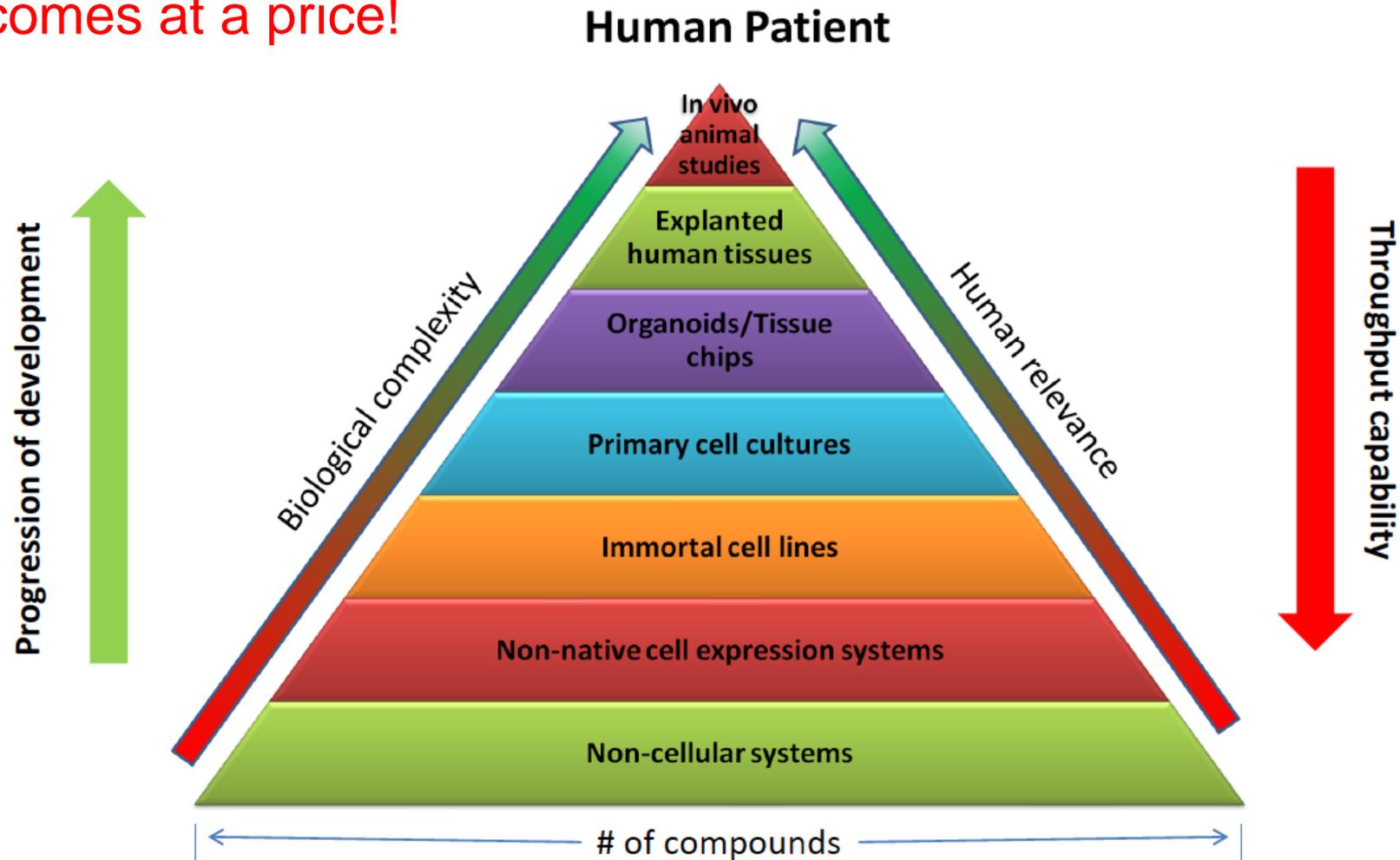
The screenshot shows the NTP website page for "Computer Models of Chemical Activity". The page features a navigation menu with "Testing Information", "Study Results & Research Projects", "Public Health", and "About NTP". A sidebar on the left lists categories: "Computational Toxicology", "Adverse Outcome Pathways", "Computer Models of Chemical Activity", "Defined Approaches to Testing and Assessment", "ICE: Integrated Chemical Environment", and "In Vitro to In Vivo Extrapolation". The main content area includes a sub-header "Computer Models of Chemical Activity" and a brief description: "Using structural data to generate activity predictions for new or poorly characterized chemicals can help researchers and regulators make decisions about further testing needs." Below this is a table with two rows of project information.

Project	Description	Publication
Open-source quantitative structure-property relationship tools	NICEATM and collaborators at EPA developed tools that use molecular structures to predict the physicochemical features for a wide range of substances.	Zang Q, et al. In silico prediction of physicochemical properties of environmental chemicals using molecular fingerprints and machine learning . <i>J Chem Inf Model</i> . 2017 Jan 23;57(1):36-49.
Quantitative structure-activity relationship (QSAR) models to screen for potential skin sensitizers	NICEATM and collaborators at the University of North Carolina-Chapel Hill (UNC-CH) developed QSAR models of human data that can either be combined with or used instead of animal data to screen for potential skin sensitizers.	Alves VA, et al. QSAR models of human data can enrich or replace LLNA testing for human skin sensitization . <i>J Green Chem</i> . 2016 Oct;18:6501-6515.

Supporting in silico tools

The screenshot shows the NTP website page for "In Vitro to In Vivo Extrapolation". The page features a navigation menu with "Testing Information", "Study Results & Research Projects", "Public Health", and "About NTP". A sidebar on the left lists categories: "Computational Toxicology", "Adverse Outcome Pathways", "Computer Models of Chemical Activity", "Defined Approaches to Testing and Assessment", "ICE: Integrated Chemical Environment", and "In Vitro to In Vivo Extrapolation". The main content area includes a sub-header "In Vitro to In Vivo Extrapolation" and a brief description: "A workflow for conducting in vitro to in vivo extrapolation (NIVE) analyses is now available in the Integrated Chemical Environment." Below this is a paragraph explaining the importance of NIVE and a reference to a 2016 workshop. Further down, there is a paragraph about NICEATM's computational toxicologists developing methods for conducting NIVE analyses, with references to publications in Applied In Vitro Toxicology and Environmental Health Perspectives.

Throughput comes at a price!

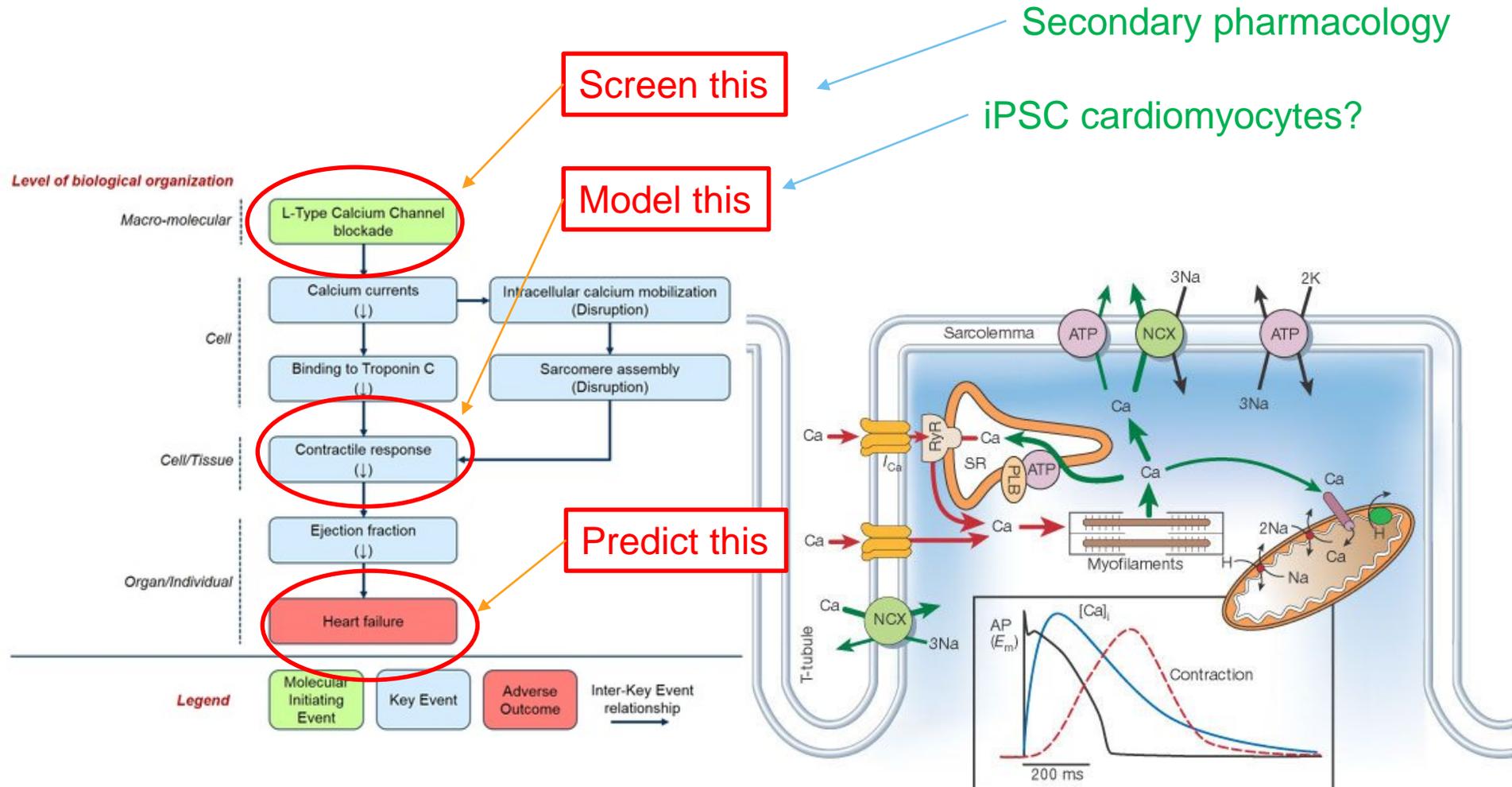


Current approaches trade human in vivo relevance for throughput and analytical clarity.

Gap = Linking Mechanisms to Phenotypes

Need

E.g. Calcium handling, contractility and heart failure





“Current approaches to ‘predictive’ safety or hazard assessment are even more imprecise.”

Definition of precision in English:

precision



NOUN

[mass noun]

1 The quality, condition, or fact of being exact and accurate.

'the deal was planned and executed with military precision'

+ More example sentences

+ Synonyms

Definition of imprecision in English:

imprecision 

NOUN

[mass noun]

Lack of exactness or accuracy.
'all scientific measurements come with some degree of imprecision'



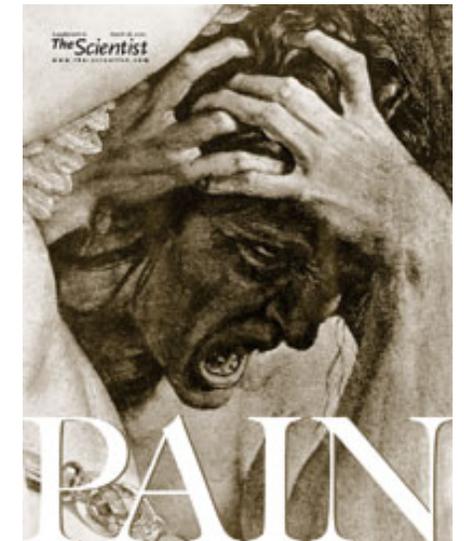
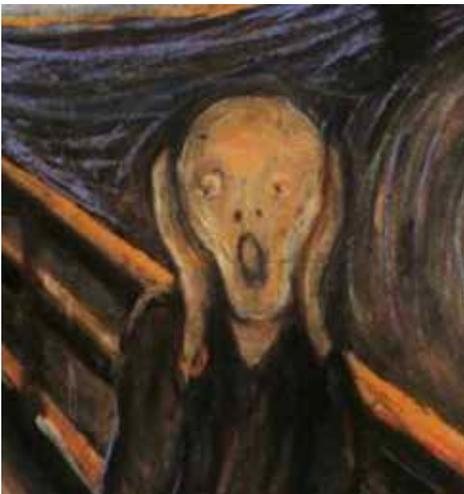
UNCERTAINTY



Uncertainty factors



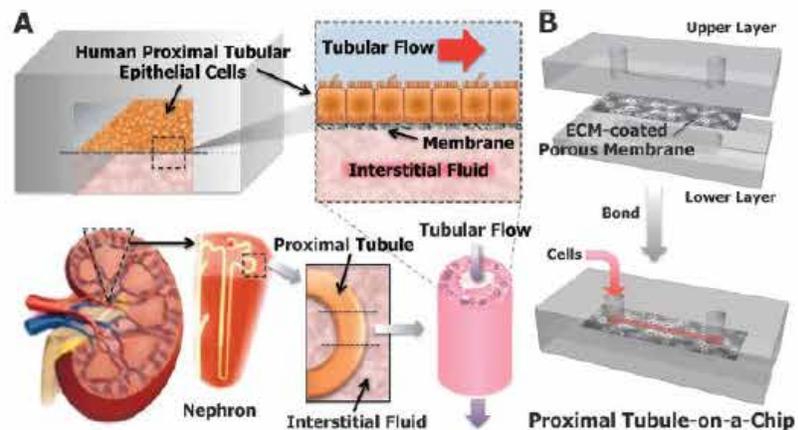
Margin of safety



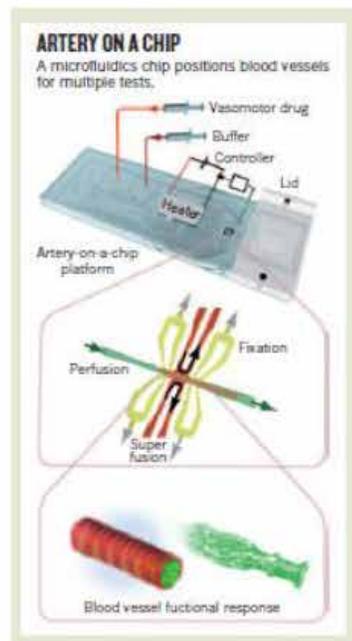
Microphysiological Systems

Opportunity

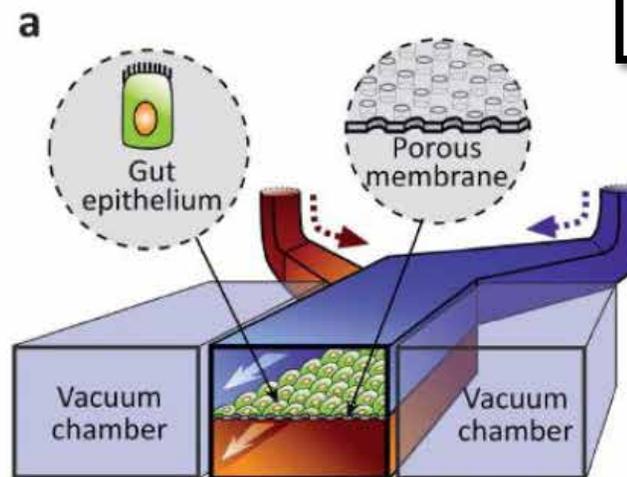
For the purposes of this presentation, MPS are defined as small scale *in vitro* devices that recreate the dynamic *in vivo* cellular environment by incorporating components of 3-dimensional tissue architecture, extracellular matrix, cellular interactions and *in vivo* physiologic function.



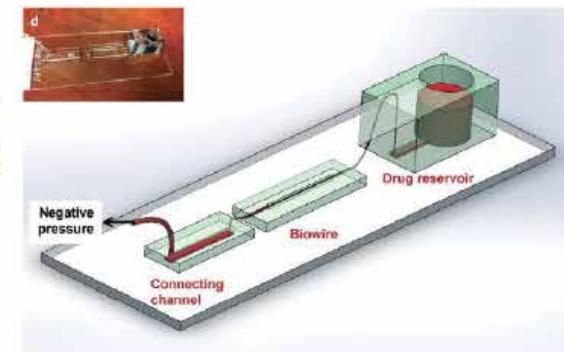
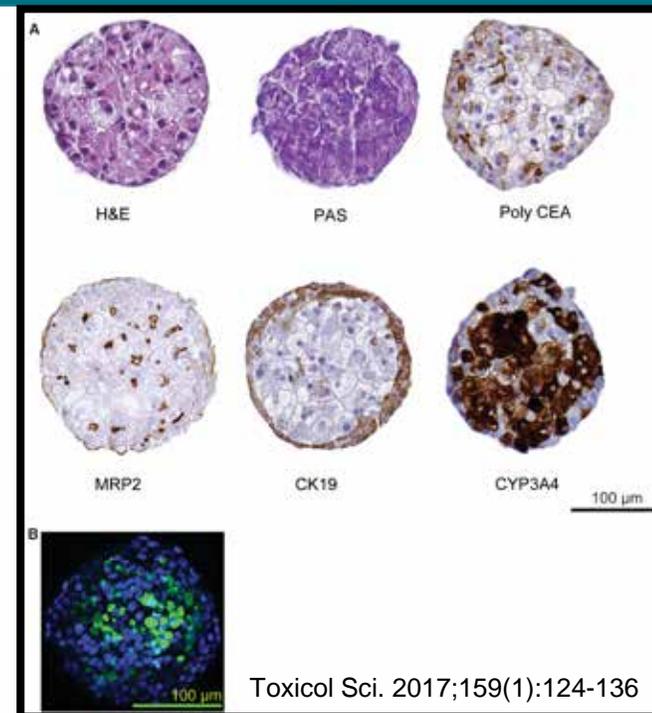
Integr. Biol., 2013, 5, 1119–1129



NATURE | VOL 471 | 31 MARCH 2011



Lab Chip 2012

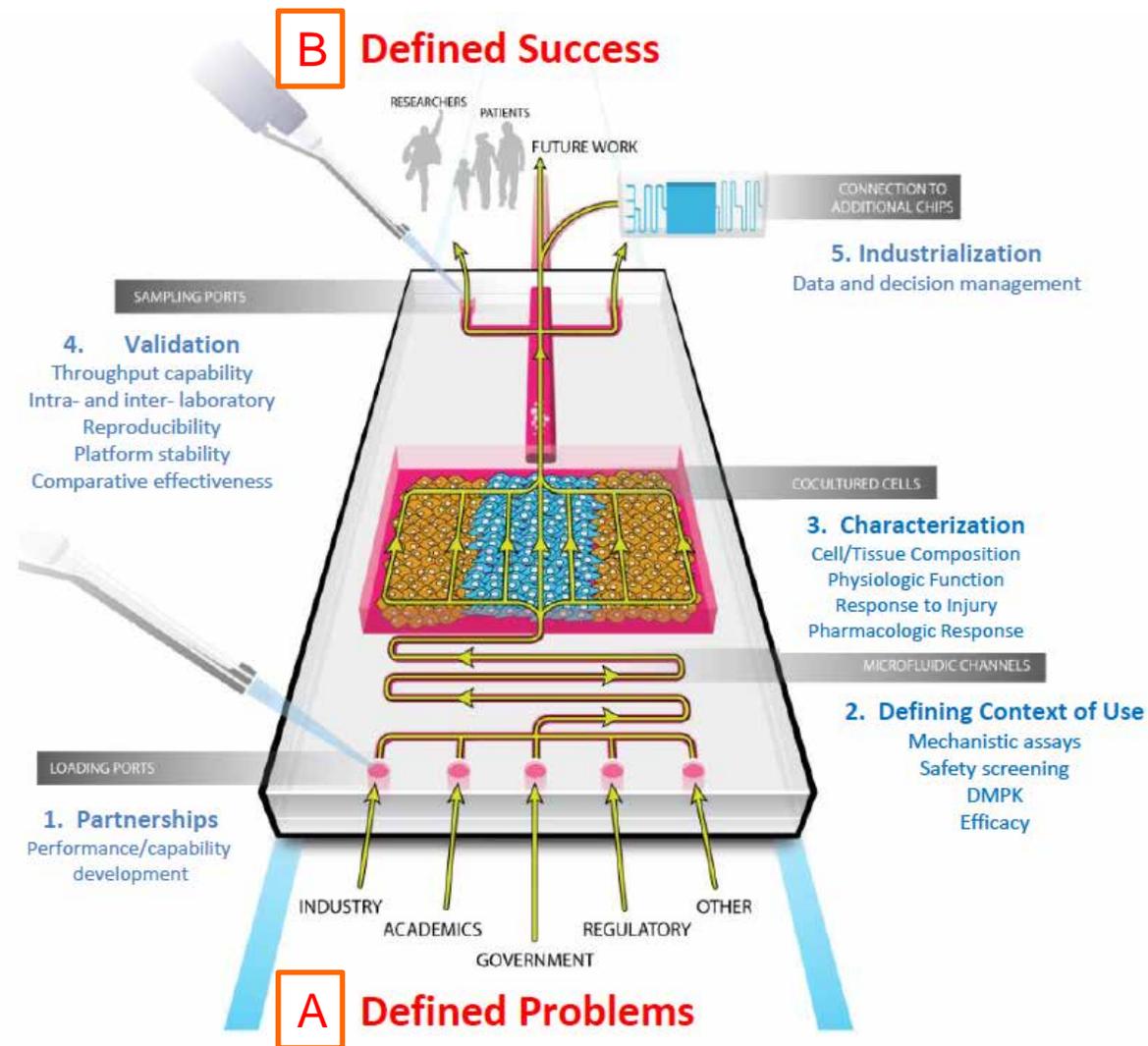


Lab Chip, 2014, 14, 869–882

Strategy

Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective

Lorna Ewart¹, Kristin Fabre², Ananthsrinivas Chakilam³, Yvonne Dragan⁴, David B Duignan⁵, Jeetu Eswaraka⁶, Jinping Gan⁷, Peggy Guzzie-Peck⁸, Monicah Otieno⁸, Claire G Jeong⁹, Douglas A Keller¹⁰, Sonia M de Morais¹¹, Jonathan A Phillips¹², William Proctor¹³, Radhakrishna Sura¹¹, Terry Van Vleet¹¹, David Watson¹⁴, Yvonne Will¹⁵, Danilo Tagle¹⁶ and Brian Berridge⁹

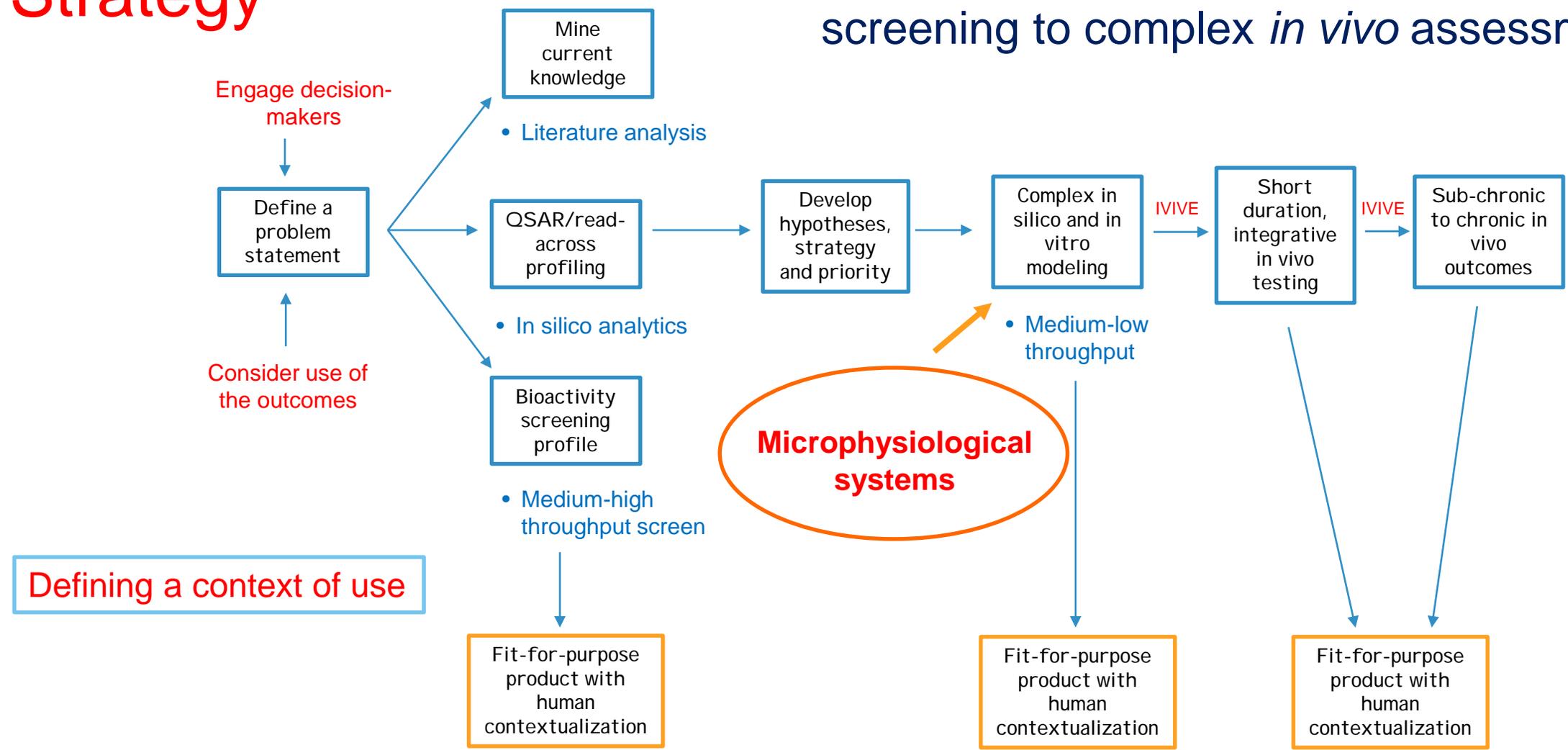


A roadmap from Point A to Point B

NTP Translational Toxicology Pipeline

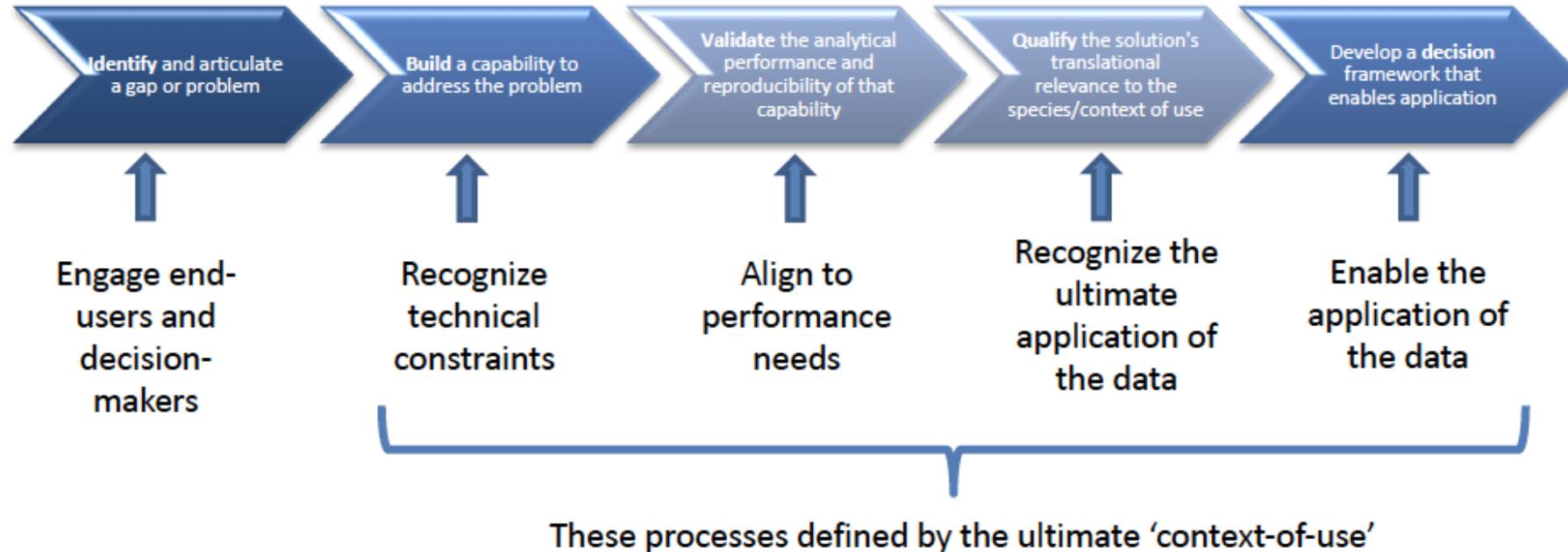
Strategy

Building bridges from simple *in vitro* screening to complex *in vivo* assessments



Confidence

Progression in confidence



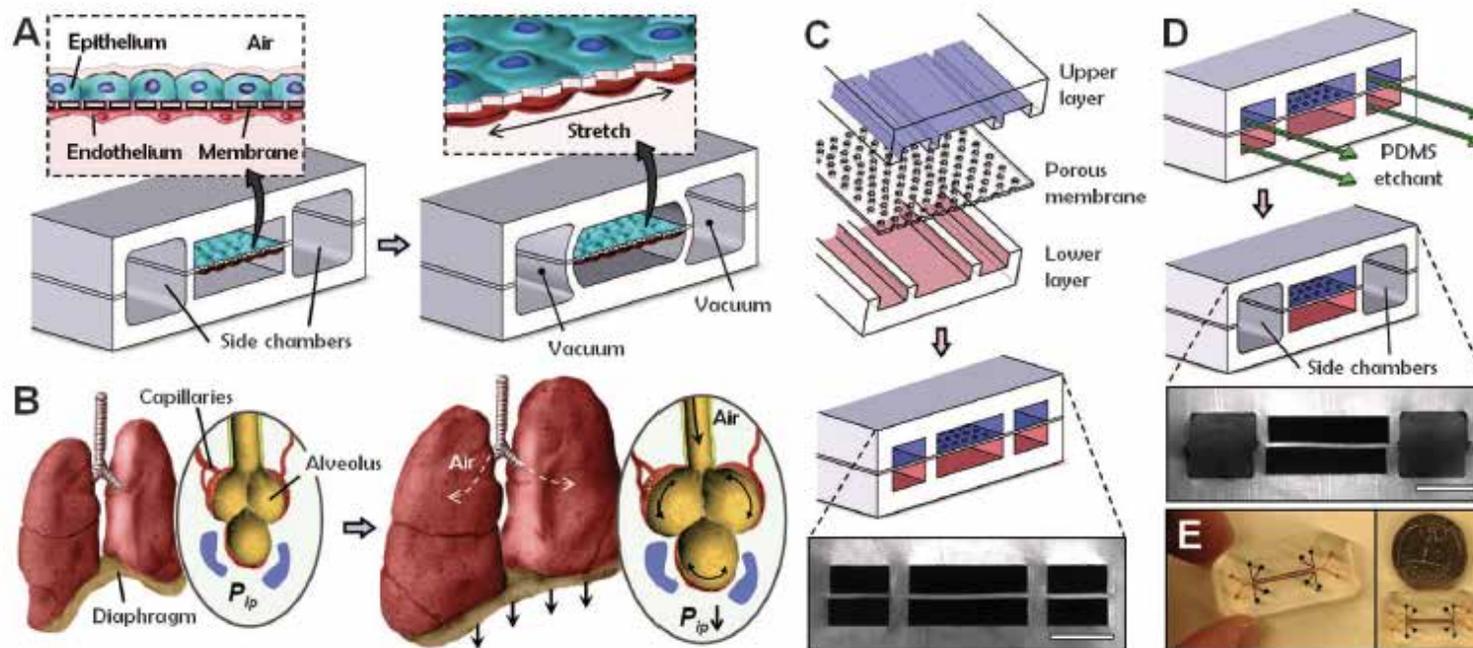
Confidence evolves and is enabled by key elements of the process!

Reconstituting Organ-Level Lung Functions on a Chip

Dongeun Huh,^{1,2} Benjamin D. Matthews,^{2,3} Akiko Mammoto,² Martín Montoya-Zavala,^{1,2}
 Hong Yuan Hsin,² Donald E. Ingber^{1,2,4*}

25 JUNE 2010 VOL 328 SCIENCE www.sciencemag.org

Application



RESEARCH ARTICLE

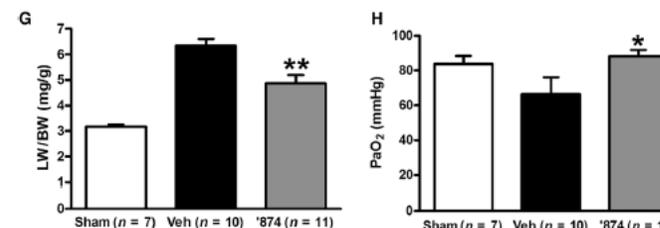
PULMONARY EDEMA

An Orally Active TRPV4 Channel Blocker Prevents and Resolves Pulmonary Edema Induced by Heart Failure

Kevin S. Thorneloe,^{1*} Mui Cheung,¹ Wei-ke Bao,¹ Hasan Alsaïd,¹ Stephen Lenhard,¹ Ming-Yuan Jian,² Melissa Costell,¹ Kristeen Maniscalco-Hauk,¹ John A. Krawiec,¹ Alan Olzinski,¹ Earl Gordon,¹ Irina Lozinskaya,¹ Lou Elefante,³ Pu Qin,¹ Daniel S. Matasic,¹ Chris James,¹ James Tunstead,⁴ Brian Donovan,⁵ Lorena Kallal,⁶ Anna Waszkiewicz,⁶ Kalindi Vaidya,⁶ Elizabeth A. Davenport,⁶ Jonathan Larkin,³ Mark Burgert,⁷ Linda N. Casillas,⁸ Robert W. Marquis,⁸ Guosen Ye,¹ Hilary S. Eidam,¹ Krista B. Goodman,¹ John R. Toomey,¹ Theresa J. Roethke,¹ Beat M. Jucker,¹ Christine G. Schnackenberg,¹ Mary I. Townsley,² John J. Lepore,¹ Robert N. Willette¹

www.ScienceTranslationalMedicine.org 7 November 2012 Vol 4 Issue 159 159ra148

Application



Aortic-banded mouse HF

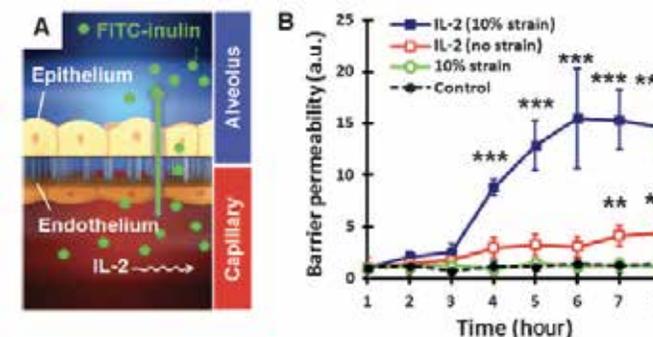
RESEARCH ARTICLE

BIOENGINEERING

A Human Disease Model of Drug Toxicity-Induced Pulmonary Edema in a Lung-on-a-Chip Microdevice

Dongeun Huh,^{1,2,3} Daniel C. Leslie,^{1,2} Benjamin D. Matthews,^{2,4} Jacob P. Fraser,¹ Samuel Jurek,² Geraldine A. Hamilton,¹ Kevin S. Thorneloe,⁵ Michael Allen McAlexander,⁶ Donald E. Ingber^{1,2,7*}

www.ScienceTranslationalMedicine.org 7 November 2012 Vol 4 Issue 159 159ra147





The screenshot shows the DARPA website for the Microphysiological Systems (MPS) program. At the top left is the DARPA logo with the text "DEFENSE ADVANCED RESEARCH PROJECTS AGENCY". To the right are navigation links: "ABOUT US / OUR RESEARCH / NEWS / EVENTS / WORK WITH US". Below the navigation is the program title "Microphysiological Systems (MPS)" and the name "Dr. Brad Ringelsen". The main content area features a composite image: on the left, a scientist in a lab coat works with a multi-well plate; in the center, a diagram shows various biological systems (e.g., Liver, Heart, Lung, Kidney, Intestine, Bone Marrow, Adipose Tissue, Blood Vessel, Endothelial Cell, Epithelial Cell, Fibroblast, Neuron, Immune Cell) connected to a central hub; on the right, a 3D anatomical model of a human torso is shown.

The Microphysiological Systems (MPS) program supports military readiness by enabling timely evaluation of the safety and efficacy of novel medical countermeasures against a wide range of natural and man-made health threats, including emerging infectious disease and chemical or biological attack.

The banner features the NIH logo on the left and the text "National Center for Advancing Translational Sciences" on the right. Above the NIH logo, it says "U.S. Department of Health & Human Services" and "National Institutes of Health".

Tissue Chip Initiatives & Projects

NCATS, in collaboration with other NIH Institutes and Centers and the Food and Drug Administration, is leading the Tissue Chip for Drug Screening program to develop human tissue chips that accurately model the structure and function of human organs — such as the lungs, liver and heart — to help predict drug safety in humans more rapidly and effectively. During the program's inception, it has focused on developing physiologically relevant models for toxicity testing. The current focus of the program is on disease modeling and efficacy testing.

- [Tissue Chip Development](#)
- [Tissue Chip Testing Centers](#)
- [Tissue Chips in Space](#)
- [Tissue Chips for Disease Modeling and Efficacy Testing](#)
- [Tissue Chips for Pain, Opioid Addiction and Overdose \(a HEAL Initiative\)](#)



Confidence

Irony = Animal studies as a source of confidence in translational non-animal studies

- We're building humanized systems to model human outcomes
- But, the current approach and experience in environmental hazard assessment and drug development make the human outcome a challenging qualifying measure
 - Low 'n'
 - Mixed and variable exposures
 - Co-morbidities
 - Acute vs. chronic progressive effects
- Animal studies are likely a necessary surrogate measure for informing approaches and building confidence in phenotypic outcomes

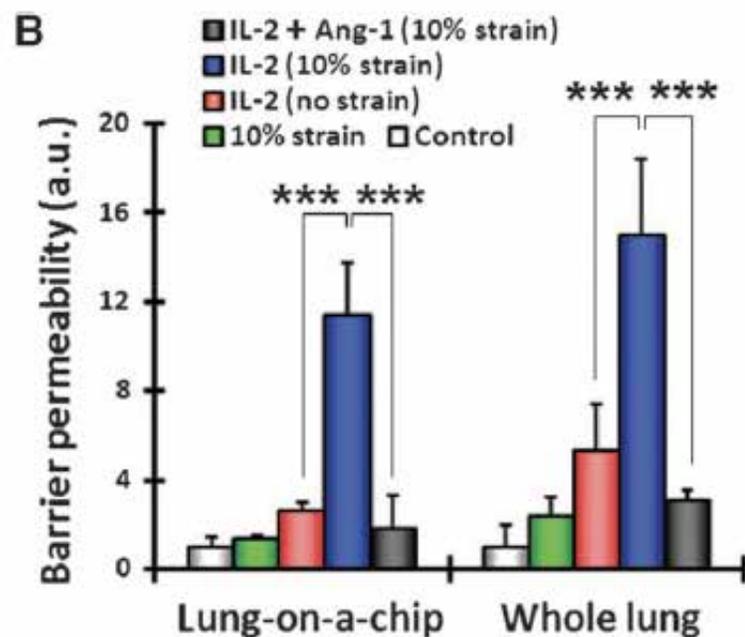
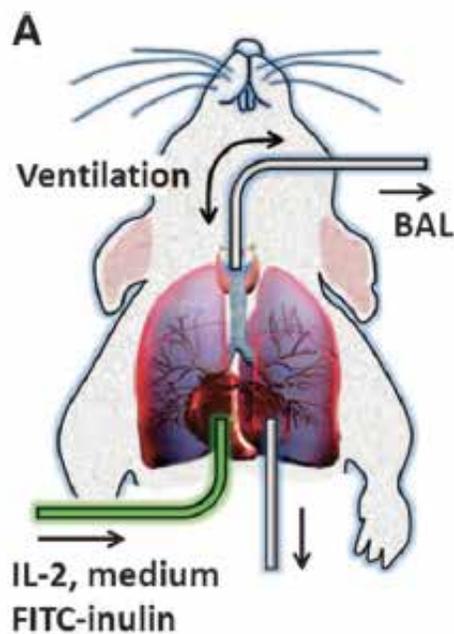
RESEARCH ARTICLE

BIOENGINEERING

A Human Disease Model of Drug Toxicity-Induced Pulmonary Edema in a Lung-on-a-Chip Microdevice

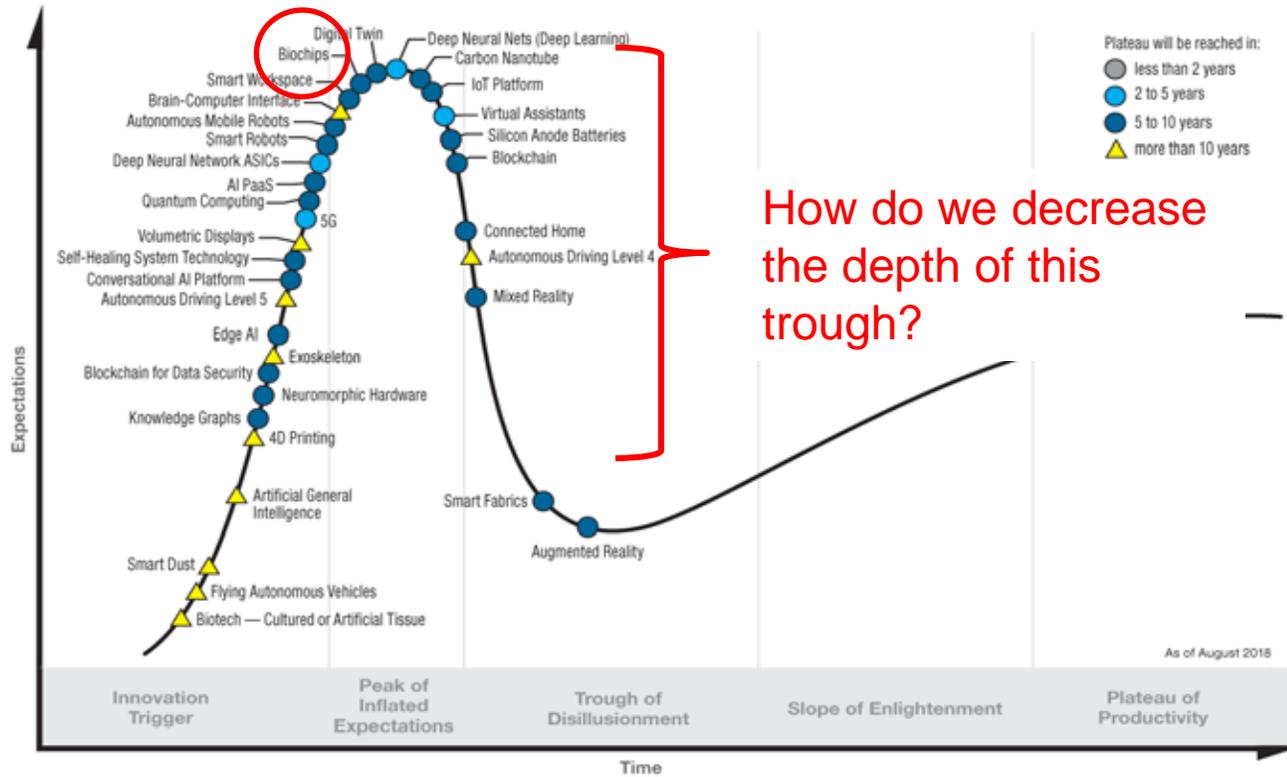
Dongeun Huh,^{1,2,3} Daniel C. Leslie,^{1,2} Benjamin D. Matthews,^{2,4} Jacob P. Fraser,¹ Samuel Jurek,² Geraldine A. Hamilton,¹ Kevin S. Thorneloe,⁵ Michael Allen McAlexander,⁶ Donald E. Ingber^{1,2,7*}

www.ScienceTranslationalMedicine.org 7 November 2012 Vol 4 Issue 159 159ra147



Altering the
 usual trajectory

Hype Cycle for Emerging Technologies, 2018



How do we decrease
 the depth of this
 trough?

gartner.com/SmarterWithGartner

Source: Gartner (August 2018)
 © 2018 Gartner, Inc. and/or its affiliates. All rights reserved.





Thank you!

Questions?