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

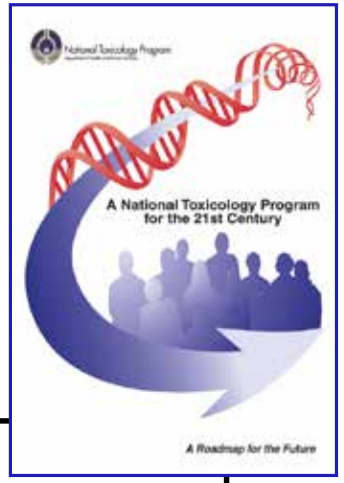
Need ⟷ Opportunity

Strategy ↓ Confidence

Application

Need

NTP National Toxicology Program
U.S. Department of Health and Human Services



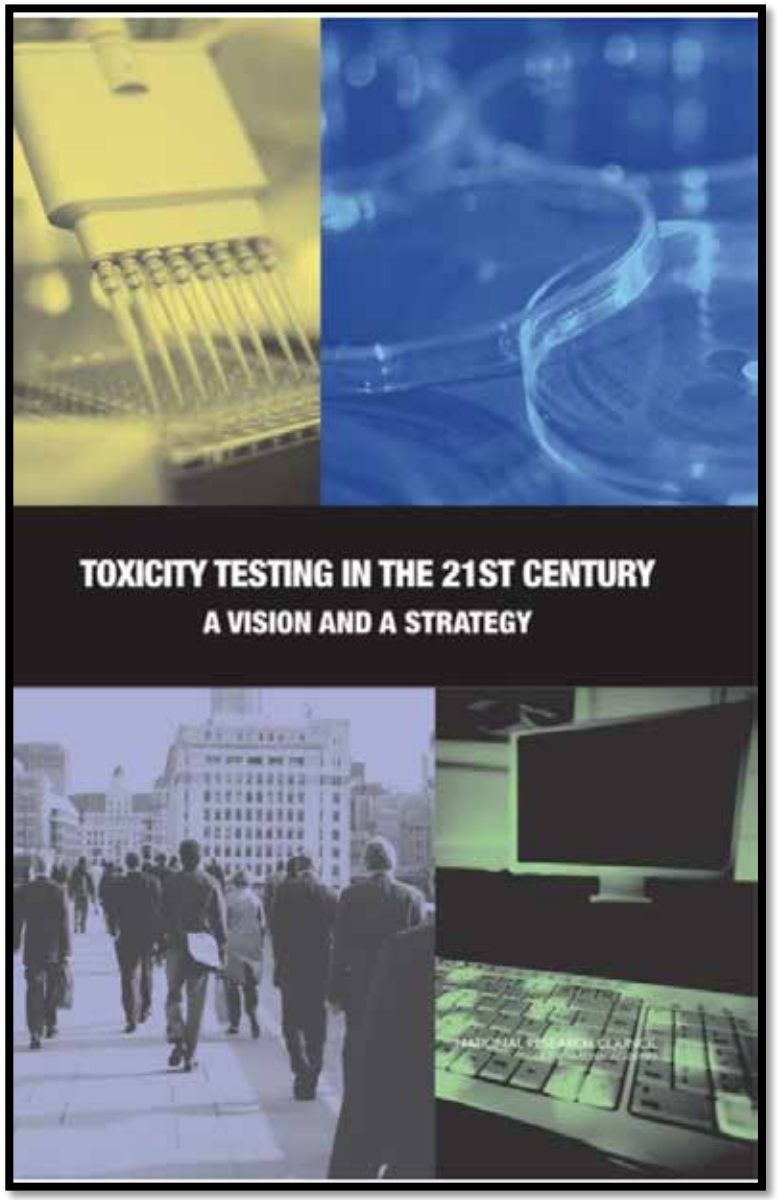
Mission
To evaluate agents of public health concern, by developing and applying tools of modern toxicology and molecular biology.

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:

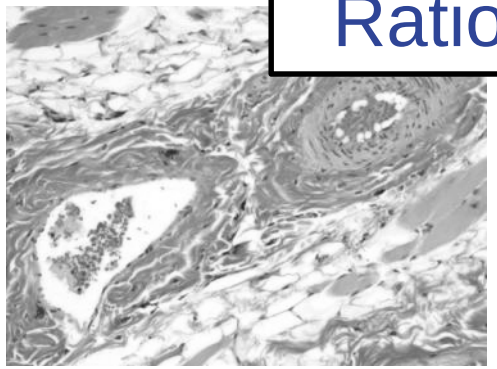
- Test large numbers of existing chemicals, many of which lack basic toxicity data.
- Test the large number of new chemicals and novel materials, such as nanomaterials, introduced into commerce each year.
- Evaluate potential adverse effects with respect to all critical end points and life stages.
-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

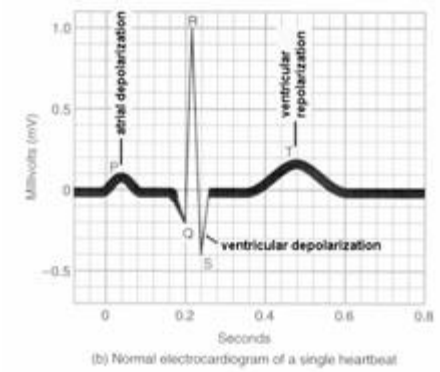
National Academies Press, 2007

Rationalizing the current paradigm

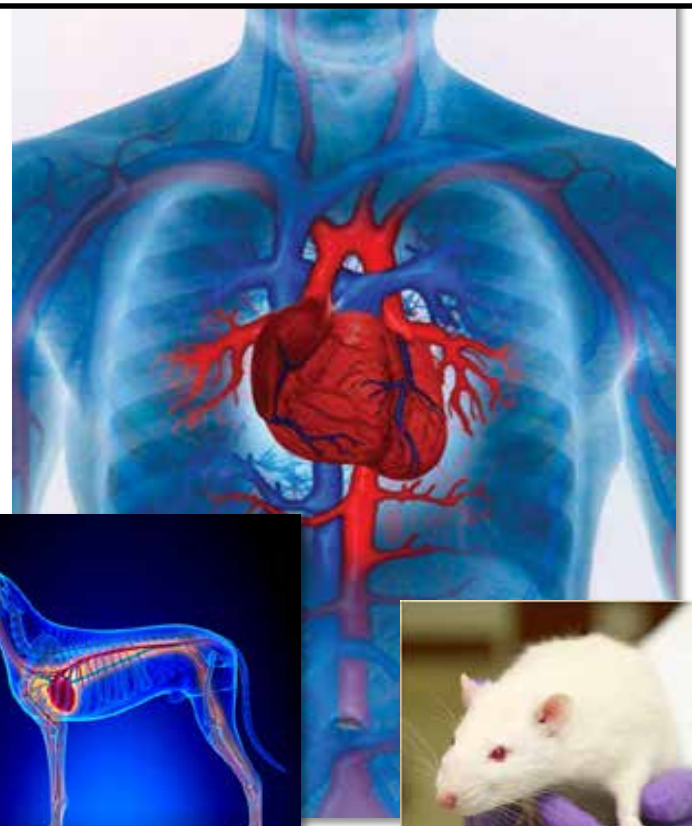
Biological conservation



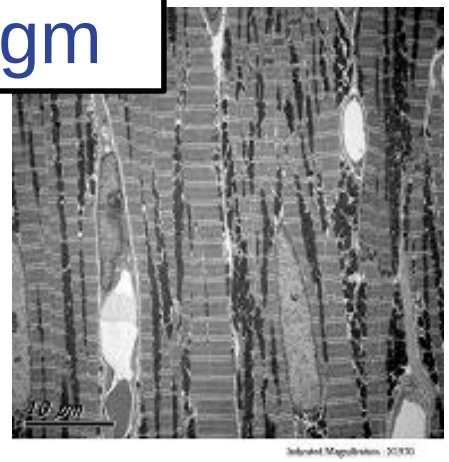
Blood vessels conduct blood to the heart itself as well as the rest of the body.



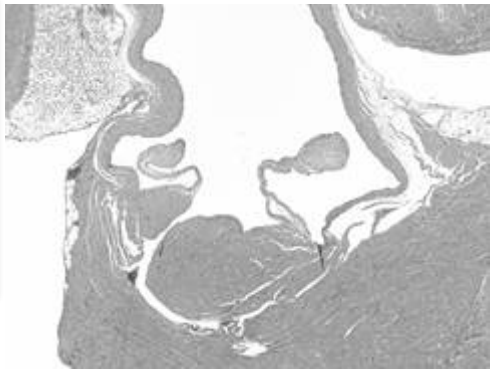
Rhythmic waves of electrical activity ensure coordinated contraction of different regions of the heart.



A muscular pump and its delivery system.



Cardiomyocytes are contractile cells with immense energy needs

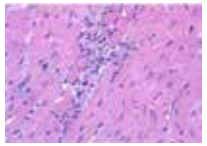


Heart valves ensure unidirectional flow of blood.

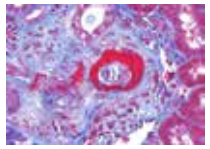
Pathobiological conservation

Rationalizing the current paradigm

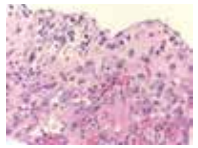
Structural injuries



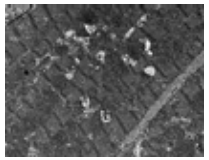
cardiomyocyte injury



vascular injury

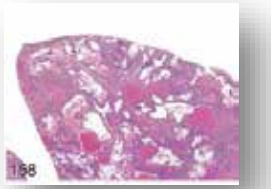


valvulopathy

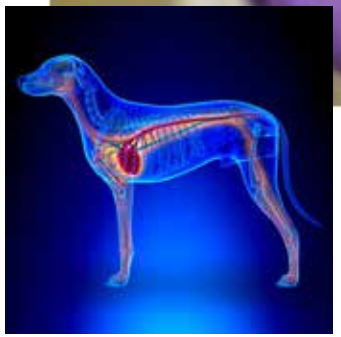


ultrastructural injury

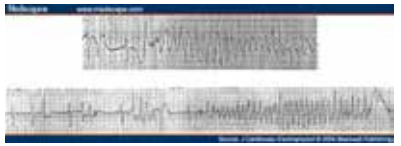
Δ cardiac mass



Neoplasia



Functional changes



Arrhythmia

Δ BP Δ HR

Δ contractility

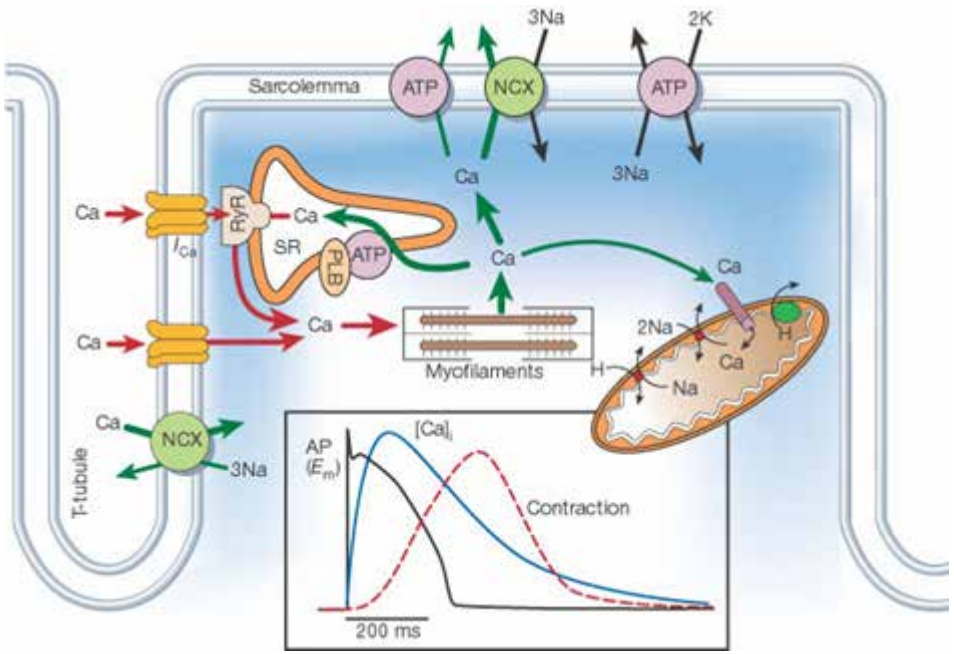
Changes in disease

- 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

molecules MDPI

Article

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

Caitlin Lynch [1], Jinghua Zhao [1], Srilatha Sakamuru [1], Li Zhang [1], Ruili Huang [1], Kristine L. Witt [2], B. Alex Merrick [2], Christina T. Teng [2,*] and Menghang Xia [1,*]

Molecular events

Molecules 2019, *24*, 841; doi:10.3390,

PLOS ONE

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. Howard[1], Scott S. Auerbach[2], Pierre R. Bushel[3], Jennifer B. Collins[4], David L. Gerhold[5], Richard S. Judson[6], Agnes L. Karmaus[6¤], Elizabeth A. Mauli[2], Donna L. Mendrick[7], B. Alex Merrick[2], Nisha S. Sipes[2], Daniel Svoboda[1], Richard S. Paules[2]*

Pathways

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

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 Simeonov[1]

Modes of action

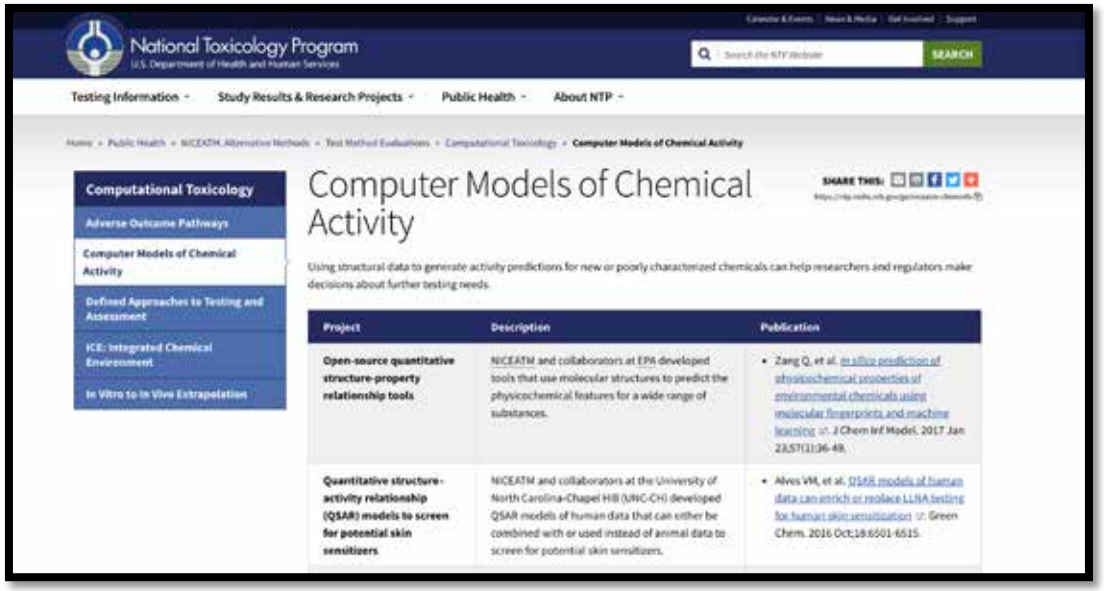
Environmental Health Perspectives 126(7) July 2018

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]

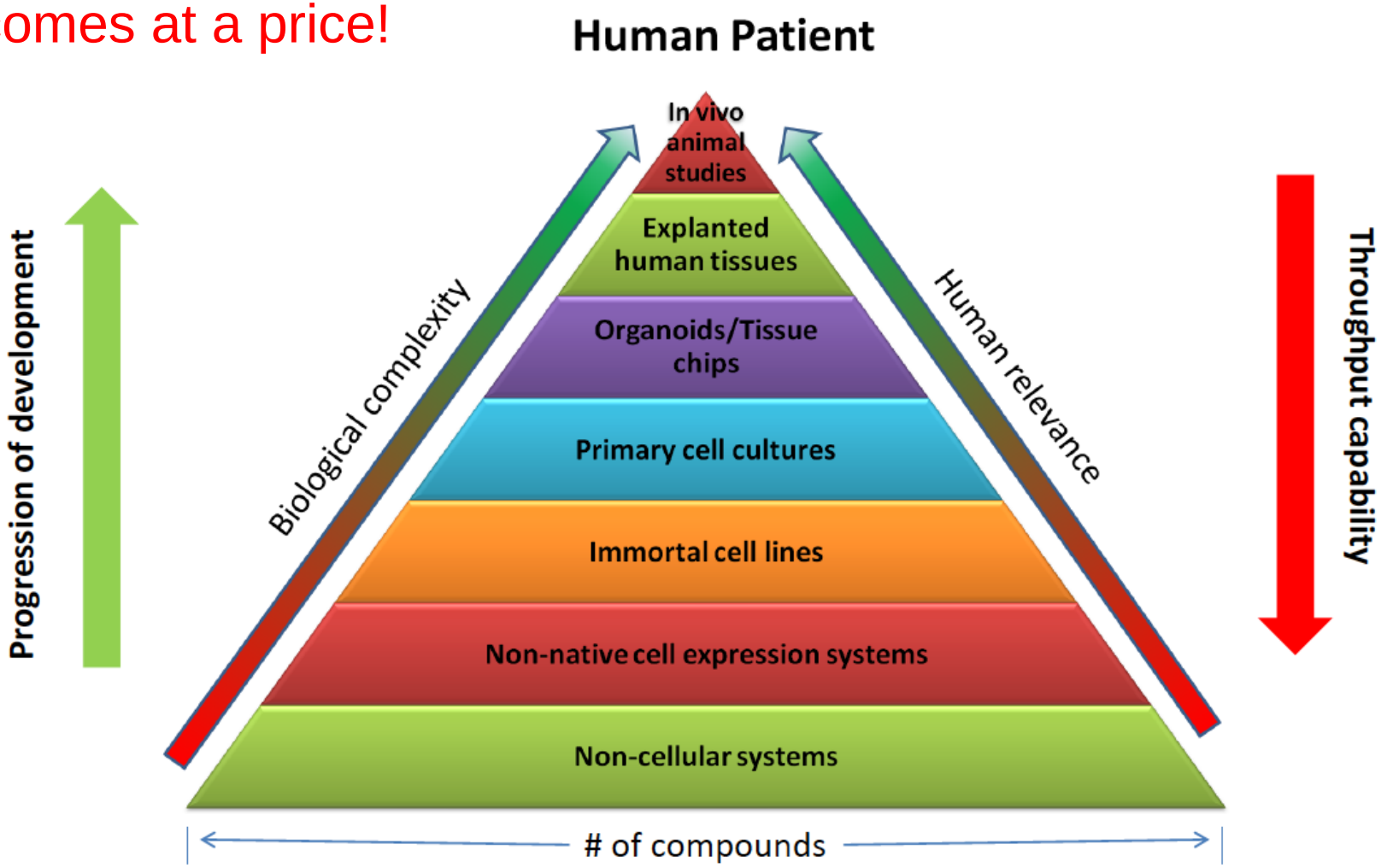
Predictive extrapolation

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



Supporting in silico tools

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

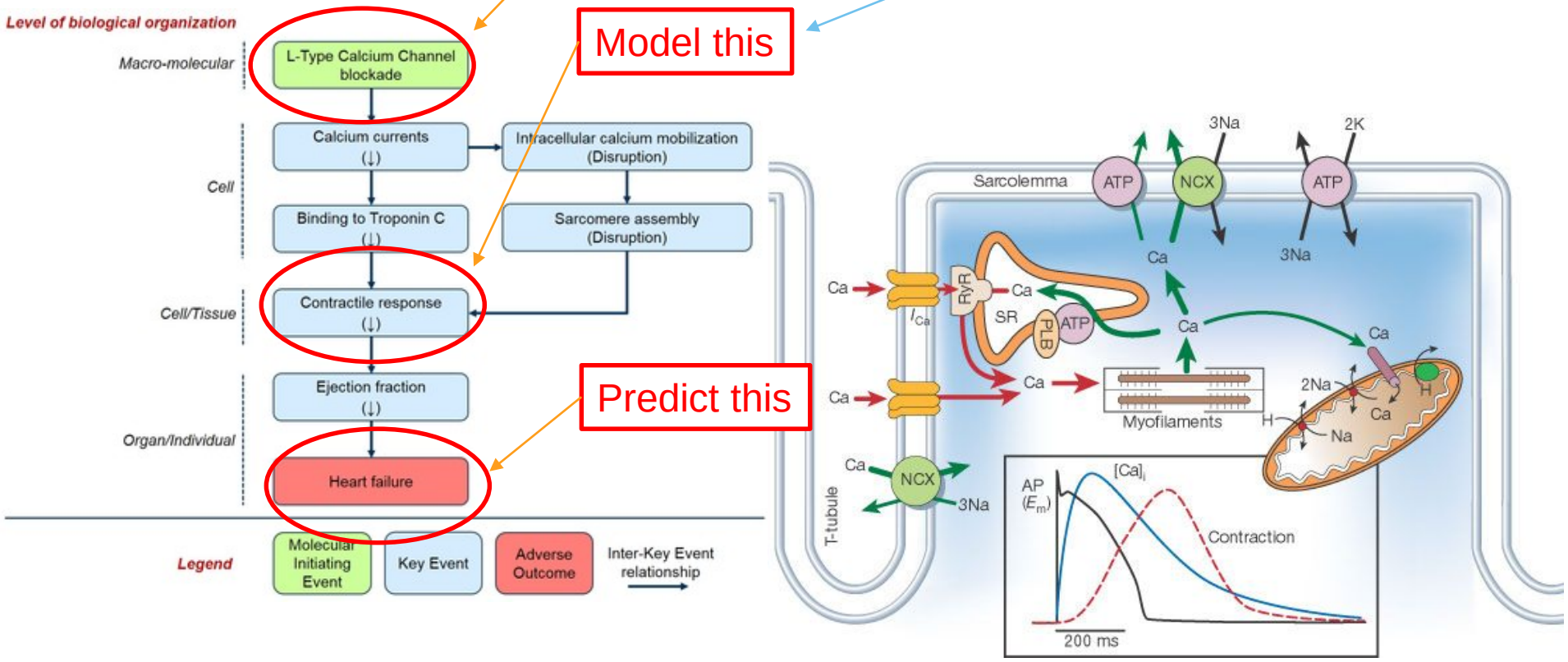
Secondary pharmacology

Screen this

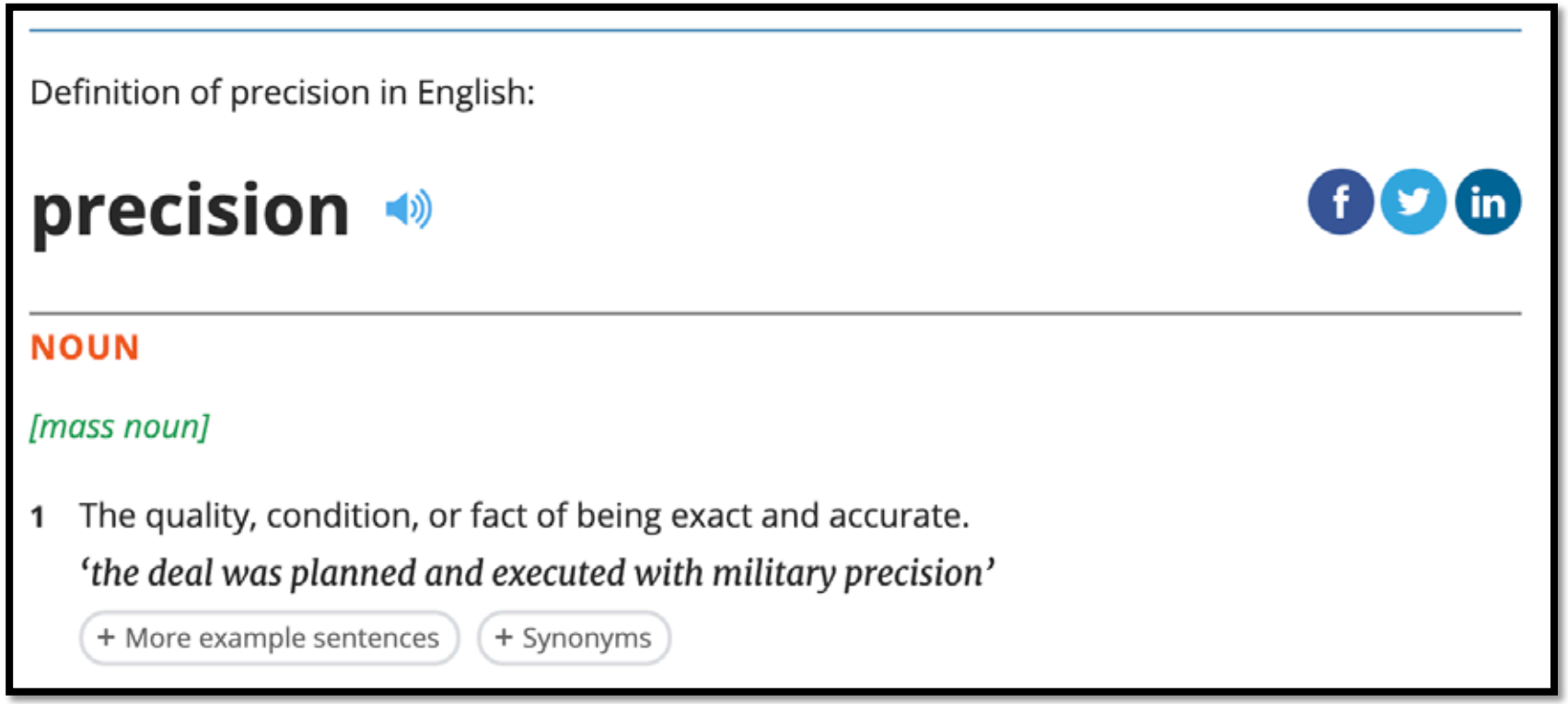
iPSC cardiomyocytes?

Model this

Predict this



“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

https://www.lexico.com/en/definition/precision

https://www.lexico.com/en/definition/precision

Definition of imprecision in English:

imprecision

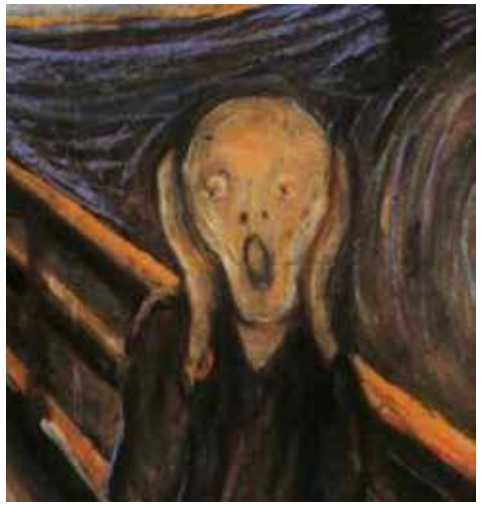
NOUN

[mass noun]

Lack of exactness or accuracy.

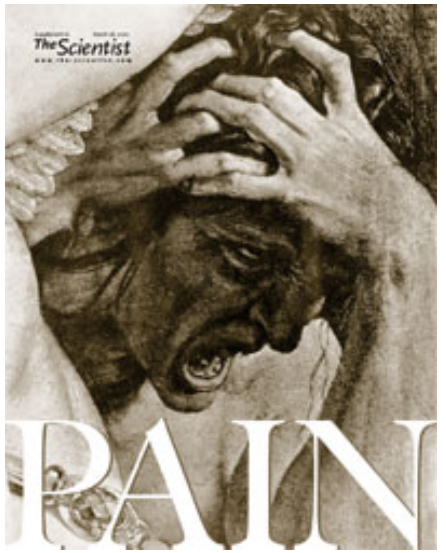
'all scientific measurements come with some degree of imprecision'

UNCERTAINTY



Uncertainty factors

Margin of safety

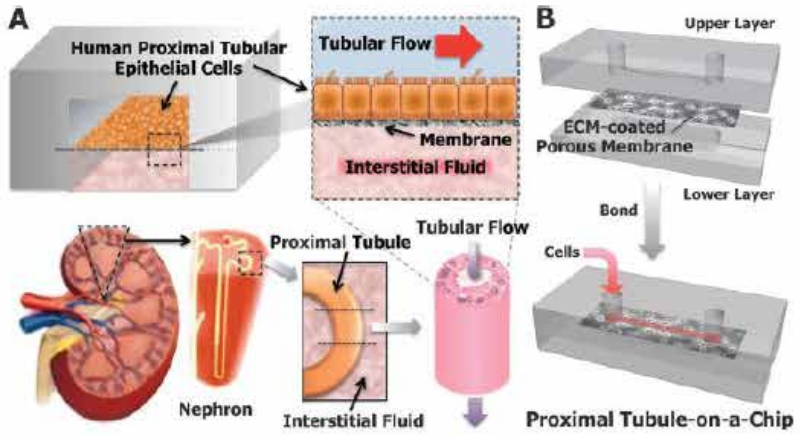


https://www.edvardmunch.org/the-scream.jsp

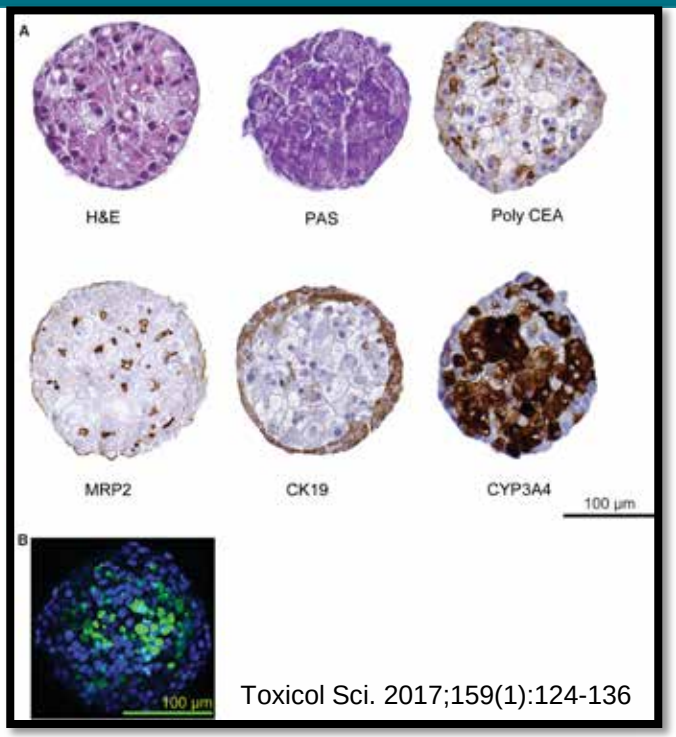
Opportunity

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.

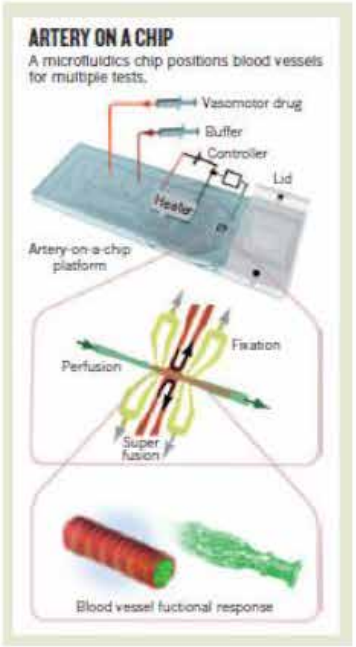
Microphysiological Systems



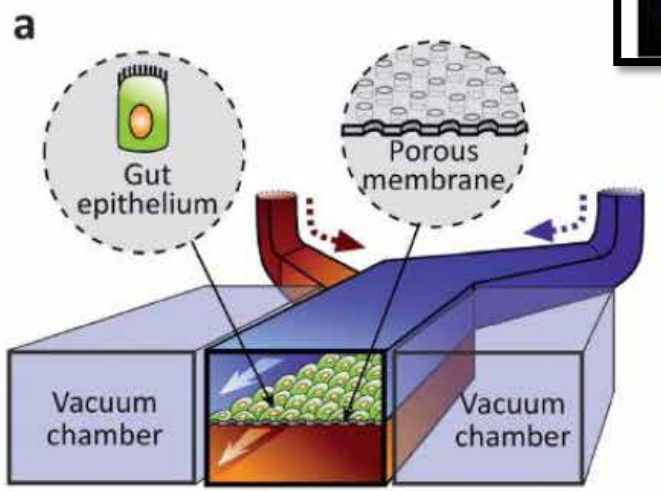
Integr. Biol., 2013, **5**, 1119–1129



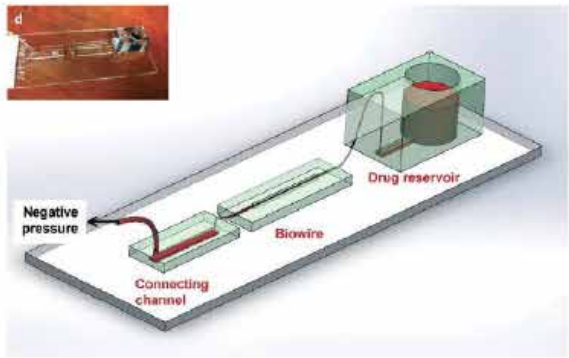
Toxicol Sci. 2017;159(1):124-136



NATURE | VOL 471 | 31 MARCH 2011



Lab Chip 2012



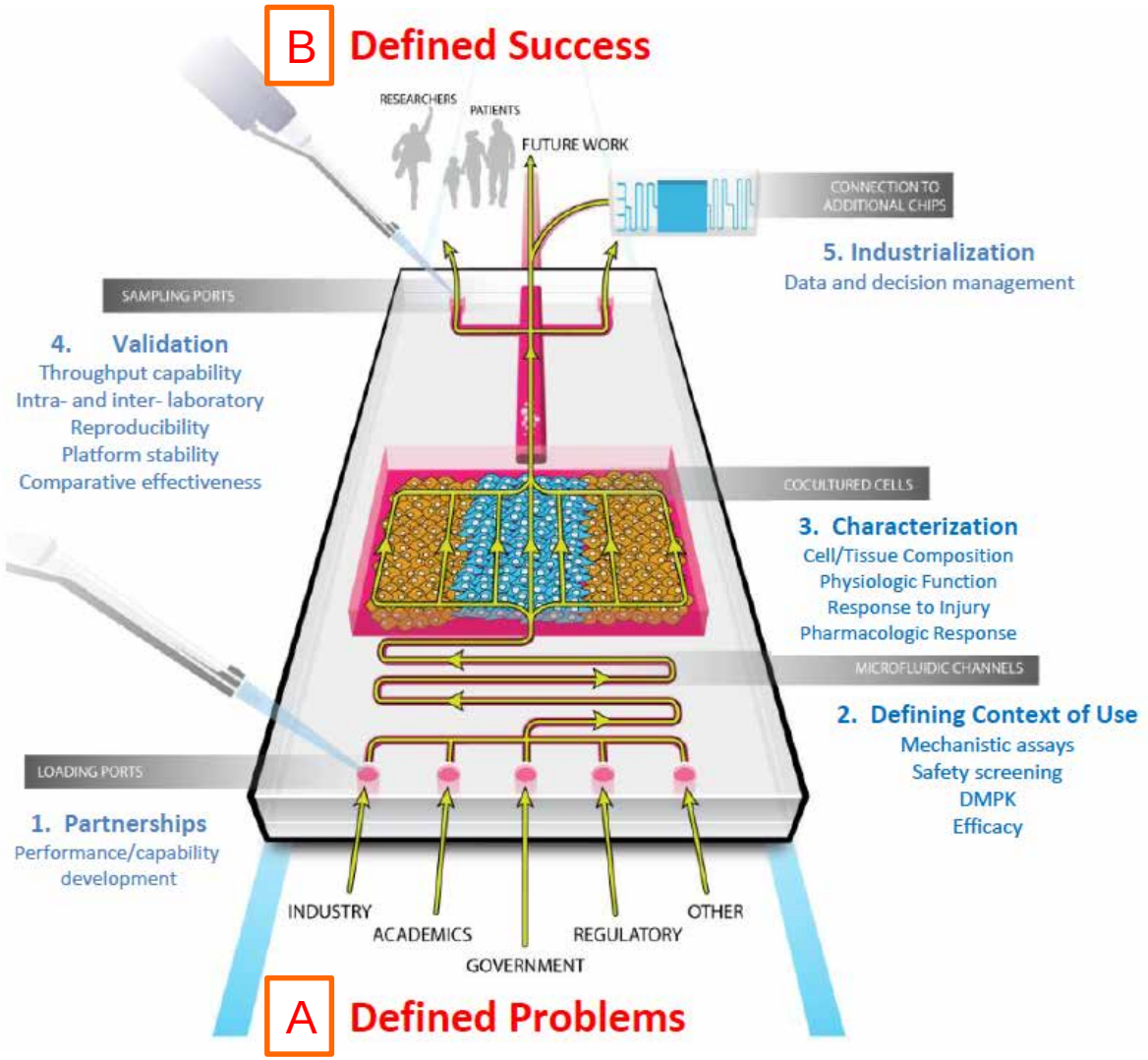
Lab Chip, 2014, **14**, 869–882

Strategy

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

Lorna Ewart[1], Kristin Fabre[2], Ananthsrinivas Chakilam[3], Yvonne Dragan[4], David B Duignan[5], Jeetu Eswaraka[6], Jinping Gan[7], Peggy Guzzie-Peck[8], Monicah Otieno[8], Claire G Jeong[9], Douglas A Keller[10], Sonia M de Morais[11], Jonathan A Phillips[12], William Proctor[13], Radhakrishna Sura[11], Terry Van Vleet[11], David Watson[14], Yvonne Will[15], Danilo Tagle[16] and Brian Berridge[9]

A roadmap from Point A to Point B

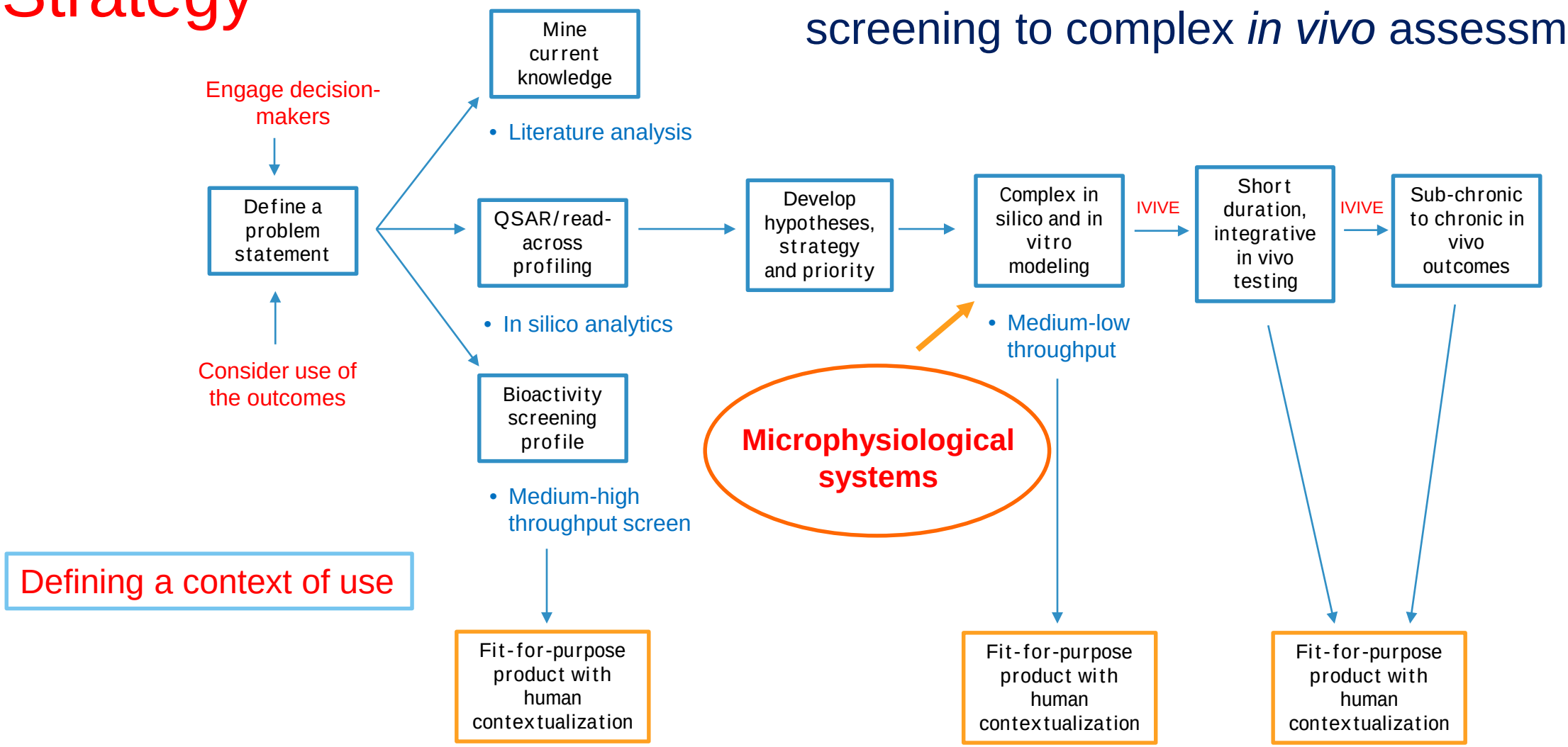


Experimental Biology and Medicine 2017; 242: 1579–1585.

NTP Translational Toxicology Pipeline

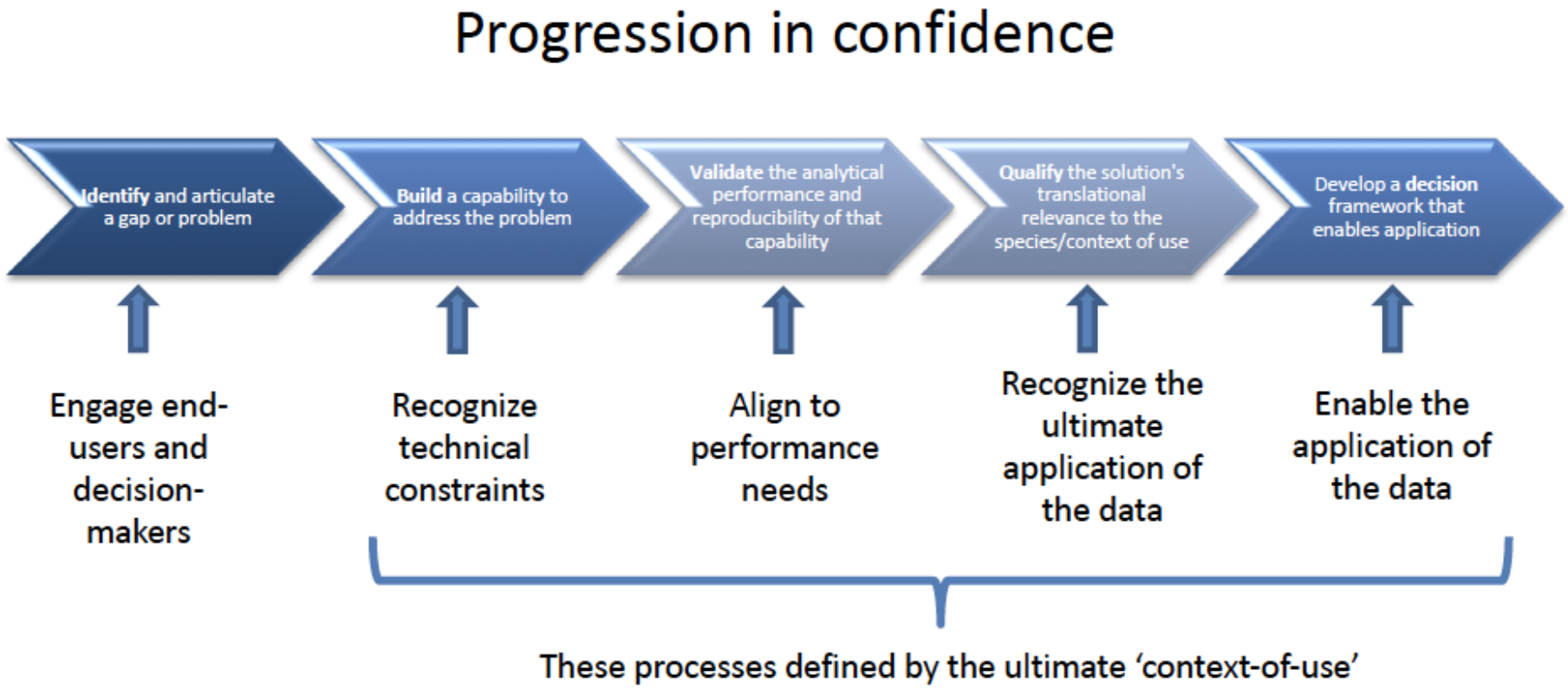
Strategy

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



Defining a context of use

Confidence



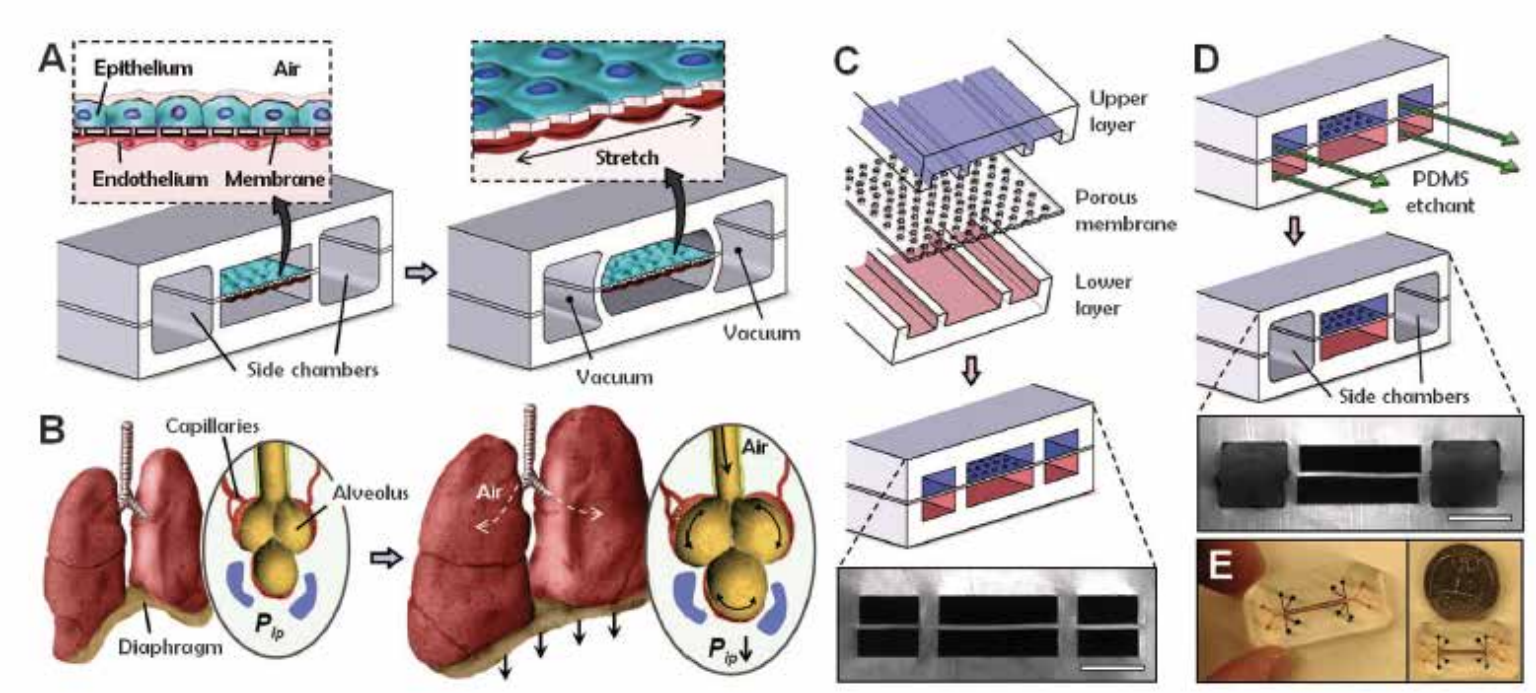
Confidence evolves and is enabled by key elements of the process!

Application

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

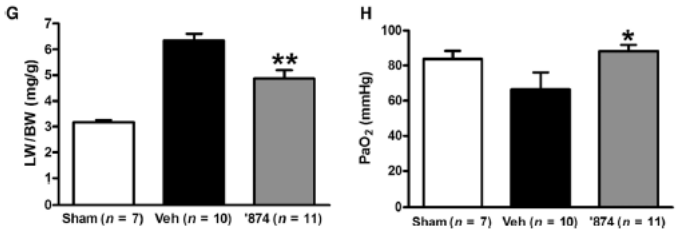
RESEARCH ARTICLE

PULMONARY EDEMA

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

Kevin S. Thorneloe,[1]* Mui Cheung,[1] Weike Bao,[1] Hasan Alsaid,[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. Willette[1]

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



Aortic-banded mouse HF

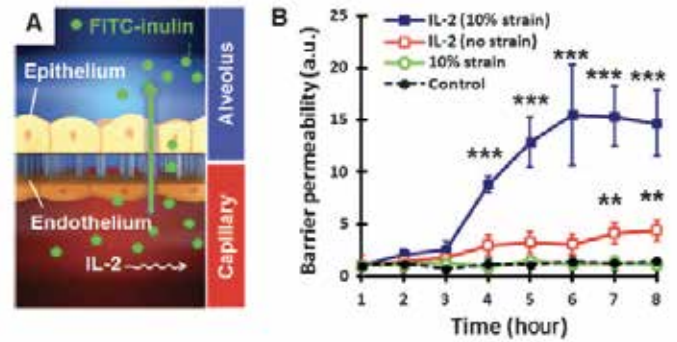
RESEARCH ARTICLE

BIOENGINEERING

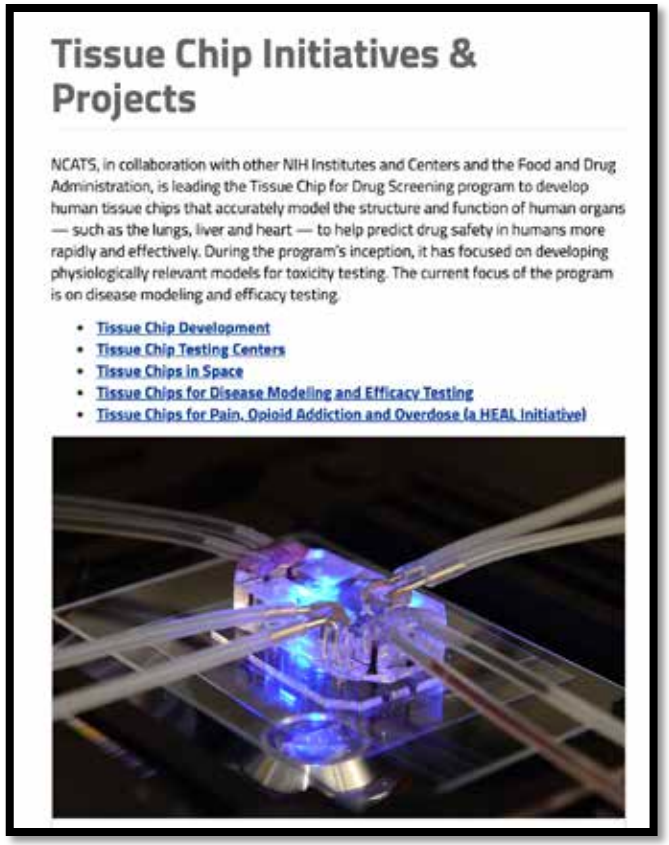
A Human Disease Model of Drug Toxicity–Induced Pulmonary Edema in a Lung-on-a-Chip Microdevice

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 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.



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]*

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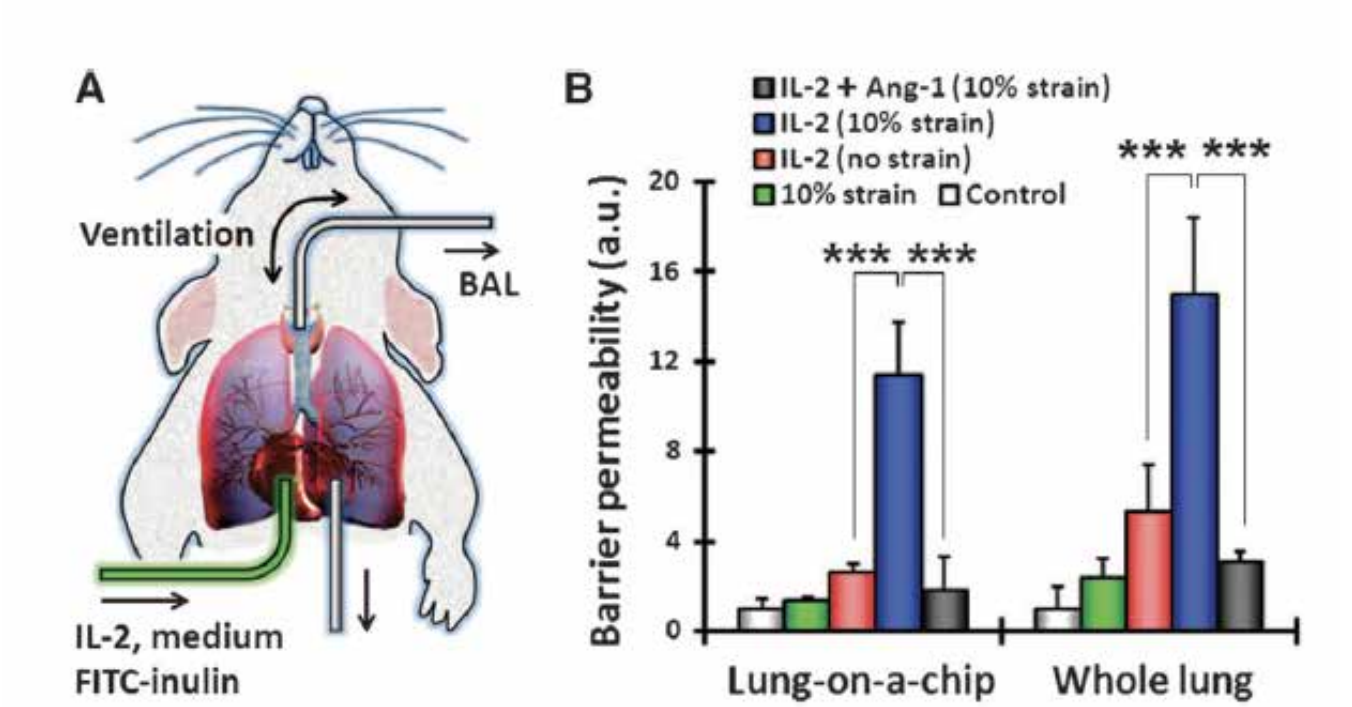
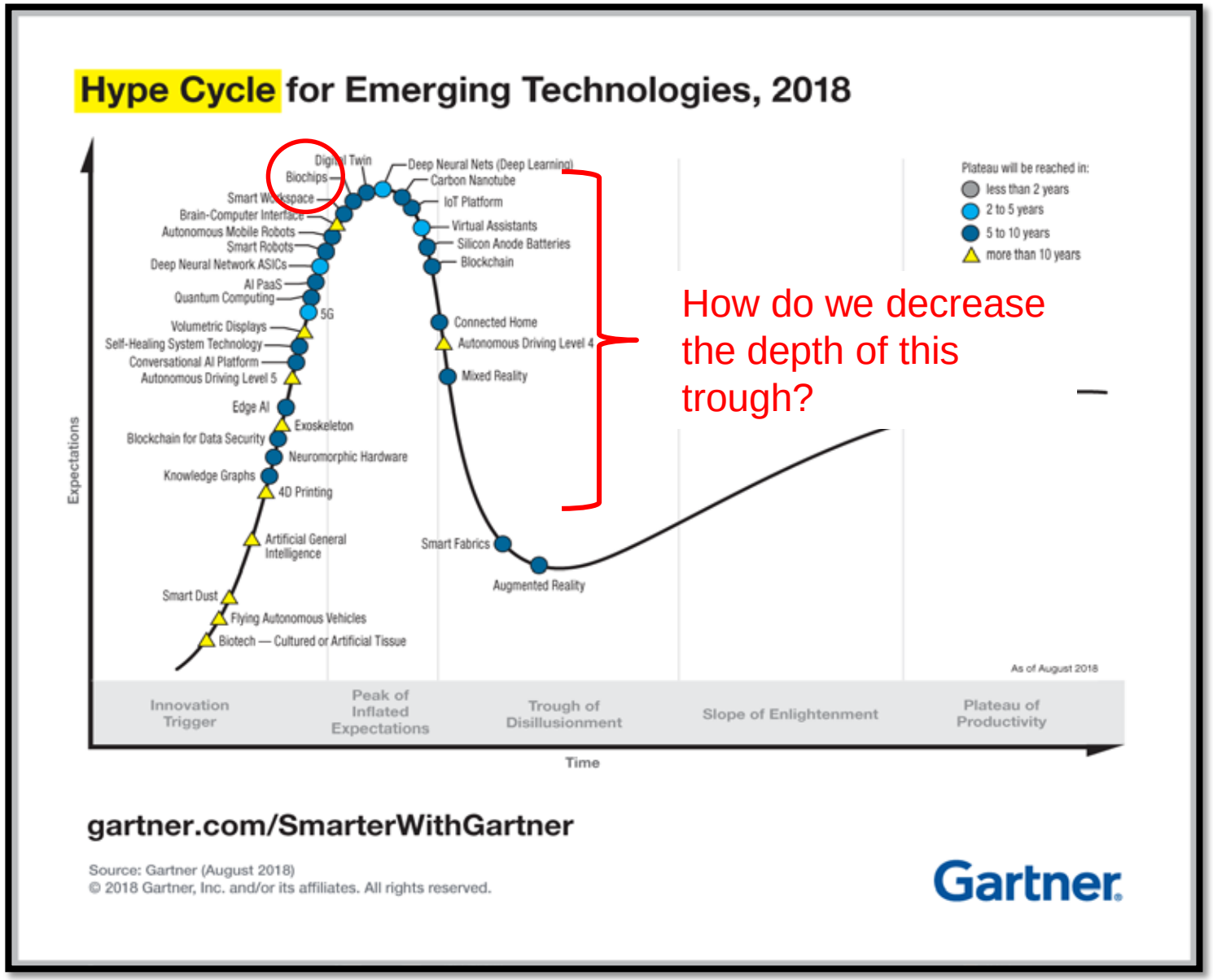


Altering the usual trajectory



Thank you!

Questions?