NTP
National Toxicology Program

Evolving the Paradigm: In Vivo to In Vitro Extrapolation

Microphysiological Systems-Enabled 'Virtual Human' Hazard Assessment: A Concept

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National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
February 21, 2020

Aims

- Reflect on the primary stakeholder in our hazard assessment efforts
- Acknowledge current approaches
- Challenge whether a novel approach could be developed
- Identify key existing enablers
- Get your perspective

Primary stakeholder

Environmental public health interests

Personal interests

Pharma interests

Animal studies as human surrogates

The New England Journal of Medicine

Special Article

FIFTY YEARS LATER: THE SIGNIFICANCE OF THE NUREMBERG CODE

EVELYNE SHUSTER, PH.D.

THE NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential.

   This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Animal research has an important role in protecting public health

Regulatory expectations

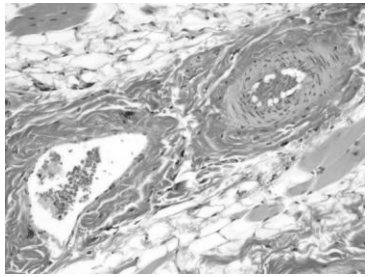
Guidance for EPA Staff

EPA provided pesticide program staff with "Guiding Principles for Data Requirements" to assist them in focusing on the information most relevant to the assessment. EPA's goal is to ensure there is sufficient information to reliably support registration decisions that are protective of human health and the environment, while avoiding the generation and evaluation of data that do not materially influence the scientific certainty of a regulatory decision. It is important to only require data that adequately inform regulatory decision making and thereby avoid unnecessary use of time and resources, data generation costs, and animal testing. As a companion to this guidance, EPA provided OPP staff with "Guidance on Data Compensation Considerations in Connection with Decisions to Waive Typical Data Requirements."

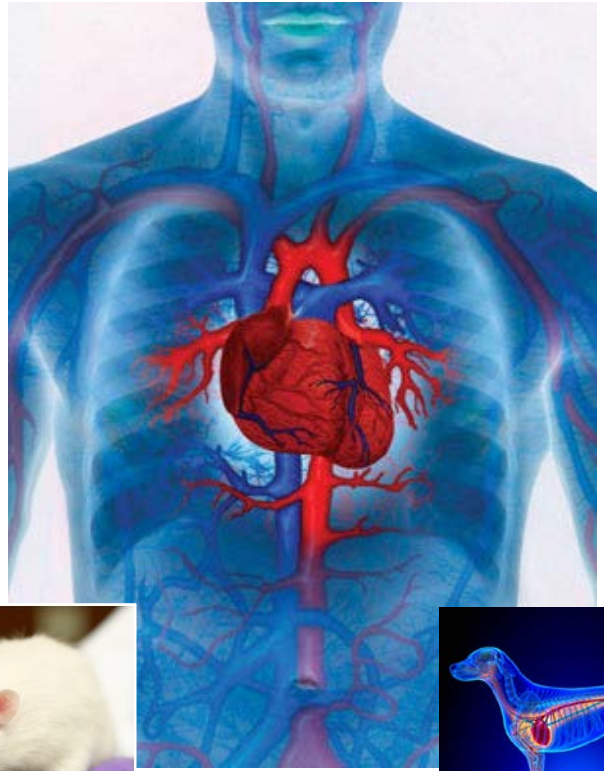
1.4. General principles

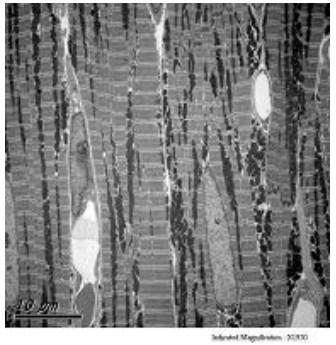
The development of a pharmaceutical is a stepwise process involving an evaluation of both animal and human efficacy and safety information. The goals of the nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility. This information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects. The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported.

Evolution and Experience = Confidence

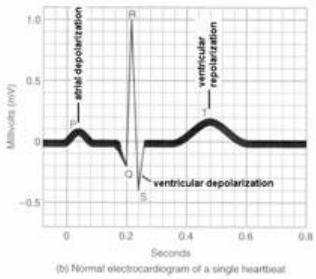


Blood vessels conduct blood to the heart itself as well as the rest of the body.

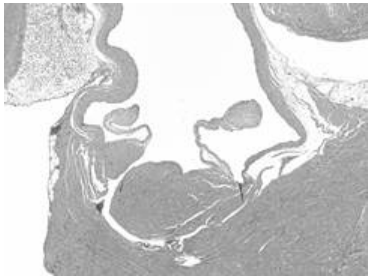




Cardiomyocytes are contractile cells with immense energy needs



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



Heart valves ensure unidirectional flow of blood.

Data is supportive

Toxicology and Applied Pharmacology 334 (2017) 100–109

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

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

Current nonclinical testing paradigm enables safe entry to First-In-Human clinical trials: The IQ consortium nonclinical to clinical translational database

toxicity in animal studies strongly predicts a similar outcome in the clinic. These results support the current regulatory paradigm of animal testing in supporting safe entry to clinical trials and provide context for emerging alternate models.

Regulatory Toxicology and Pharmacology 96 (2018) 94–105

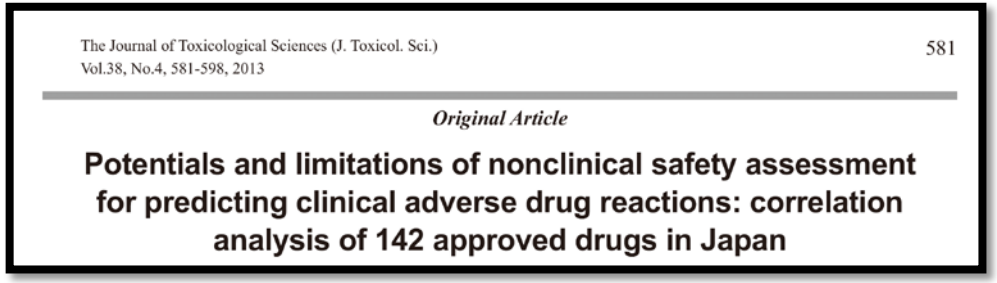
Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

A big data approach to the concordance of the toxicity of pharmaceuticals in animals and humans

The majority of animal-human concordance studies is based on assessment of true positives or true positive rate (TP/(TP + FN)), with limited analysis of the false positives. The fact that many animal positives cannot be distinguished between true or false because they are avoided by not progressing drugs to clinical trials is an inevitable reality of concordance analysis. *



The Journal of Toxicological Sciences (J. Toxicol. Sci.)
Vol.38, No.4, 581-598, 2013

Original Article

Potentials and limitations of nonclinical safety assessment for predicting clinical adverse drug reactions: correlation analysis of 142 approved drugs in Japan

detect concordant animal toxicity. This study collectively demonstrated a significant value of nonclinical safety assessment in predicting ADRs in humans. It also identified the subset of ADRs with poor predictability, highlighting the need for advanced testing that enables successful translation of animal toxicity to clinical settings with better accuracy and sensitivity.

Current questions

- Under the conditions of this study, does this agent have a biological effect?
  - “Conditions” = Non-human species, point in time, route of administration
- Where does that effects occur (e.g., target organ characterized at the organ/tissue level)?
- What is the morphologic character of that effect?
- Is the effect adverse?
- At what dose/exposure does the effect occur?

Challenges to the current questions

- Human questions in a non-human system
- Restricted to “conditions”
  - those conditions don’t generally mimic the ‘human’ condition
- Not personalized
- Pathogenesis is speculative
- Mechanism of action unknown

Future questions

Could we leverage advances in modeling technology to ask different questions and still protect human health?

- Does this agent have human bioactivity?
- What human cell or tissue types are most susceptible to that bioactivity?
- Under what human conditions does that susceptibility occur (genetically variable vs. perturbed biology)?
- Is that human bioactivity adaptive, maladaptive, reversible?
- At what human exposures does that activity occur?
- What is the temporal and cellular pathogenesis of the activity?
- Can this information be more broadly extrapolated to the complex *in vivo* human condition?

Future questions

Could we leverage advances in modeling technology to ask different questions and still protect human health?

- Doe
- Wha
- Und perturbed biol
- Is th
- At w
- Wha
- Can this information be more broadly extrapolated to the complex human condition?

Fundamental shifts

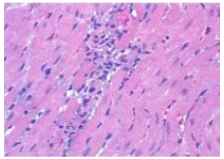
- Animal to Human
- ”Effect” to “Activity”
- Population to Precision

- Could an approach asking these fundamental questions be more human-relevant?
- Could it be higher throughput?
- Could it enable more ‘precision toxicology’?
- Do we have the technology and knowledge to make this shift?

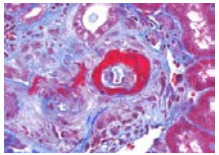
What current knowledge and capabilities might enable such a fundamental shift in how we model hazards?

We know what failure looks like

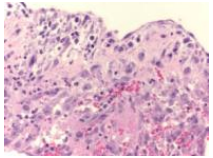
Structural injuries



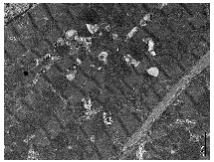
cardiomyocyte injury



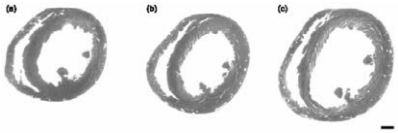
vascular injury



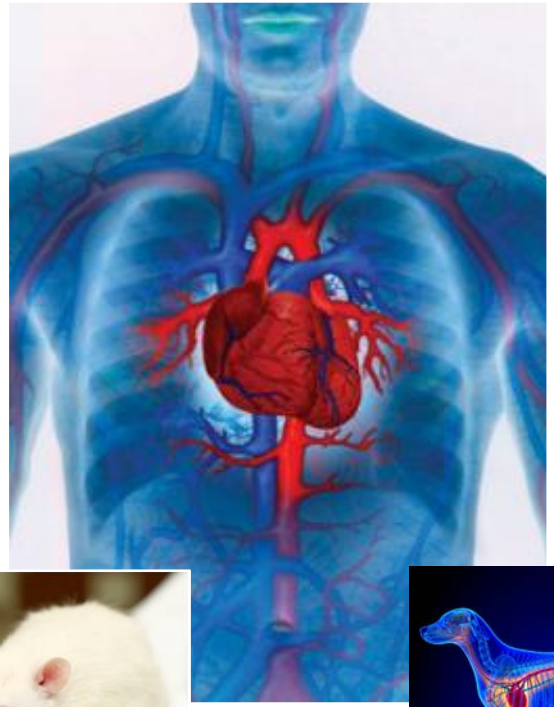
valvulopathy

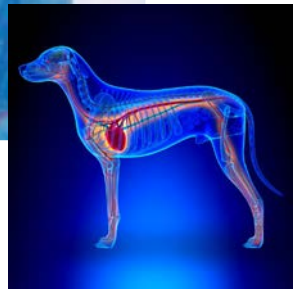


organellar injury

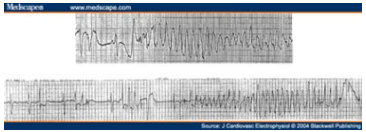


Δcardiac mass





Functional changes



Arrhythmia

Δ BP Δ HR

Δcontractility

Changes in disease

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

We know some mechanisms of failure

E.g. Calcium handling, contractility and heart failure

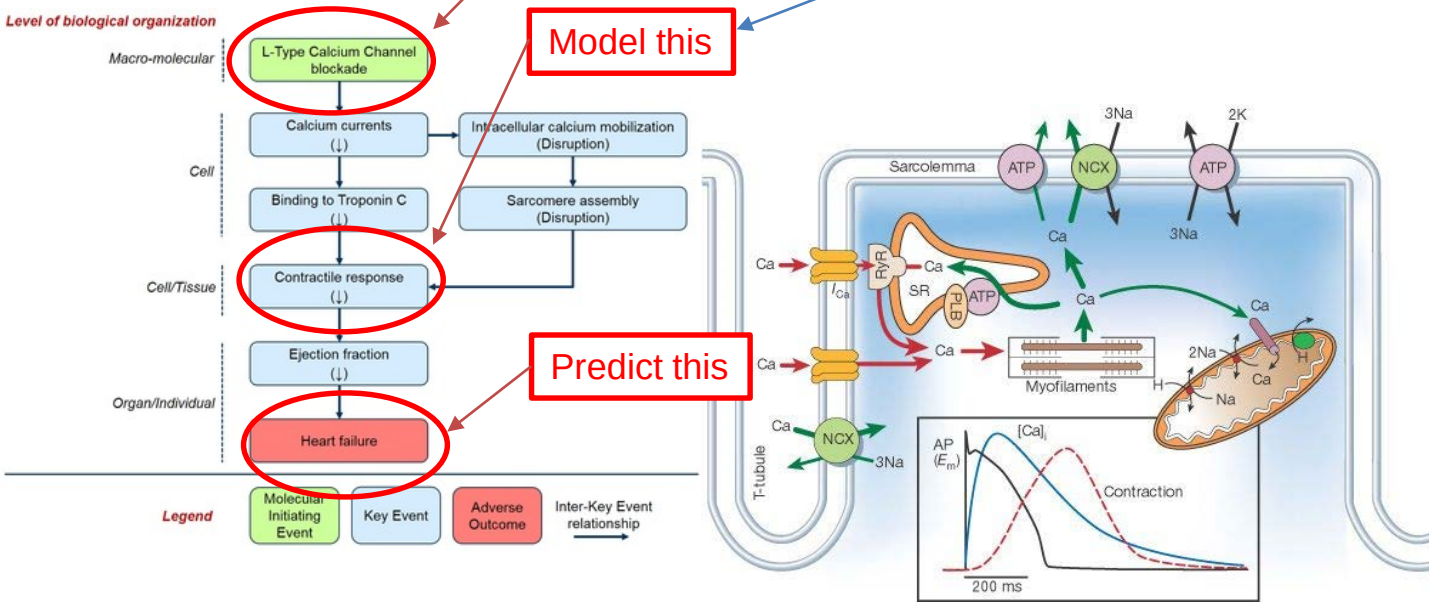
Secondary pharmacology

Screen this

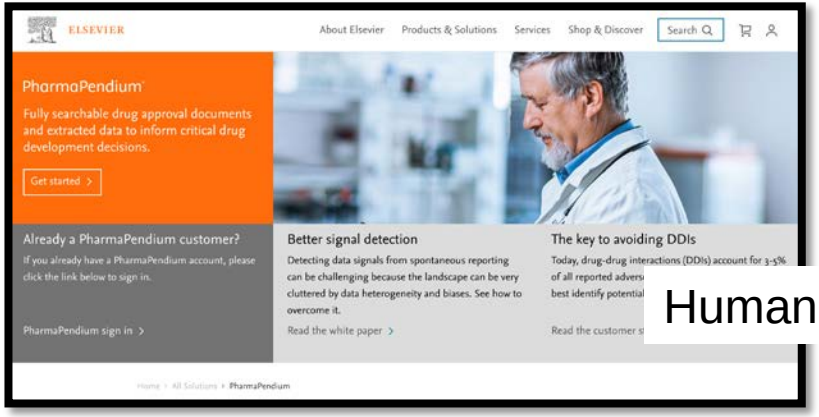
iPSC cardiomyocytes?

Model this

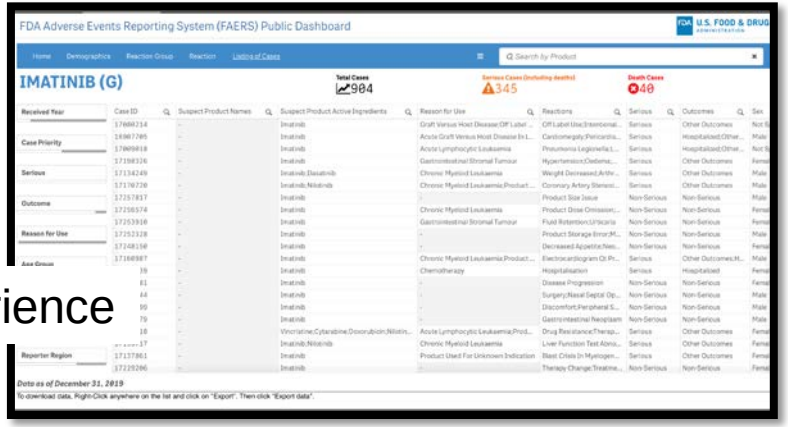
Predict this

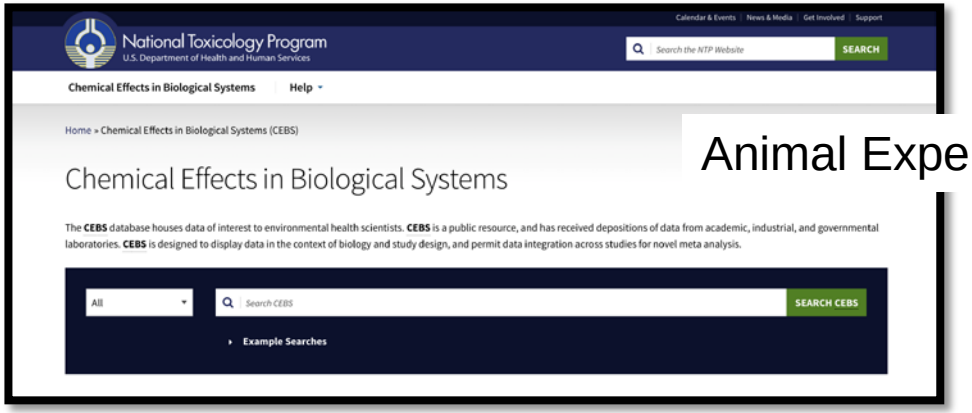


We have experience with toxicity



Human Experience





Animal Experience

Do these experiences enable us to target where we look for toxic bioactivity?

We've invested in mechanistic screening strategies

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 Simeonov[1]

Modes of action

Environmental Health Perspectives 126(7) July 2018

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,

Do these capabilities support a more evidence-based approach?

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. Maull[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

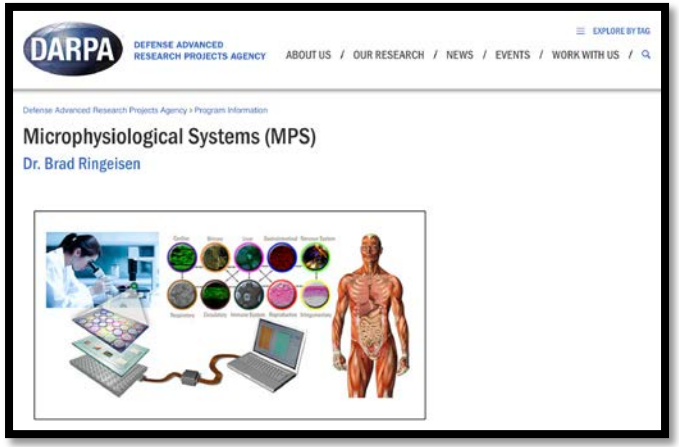
Identifying Attributes That Influence *In Vitro*-to-*In Vivo* Concordance by Comparing *In Vitro* Tox21 Bioactivity Versus *In Vivo* DrugMatrix Transcriptomic Responses Across 130 Chemicals

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]

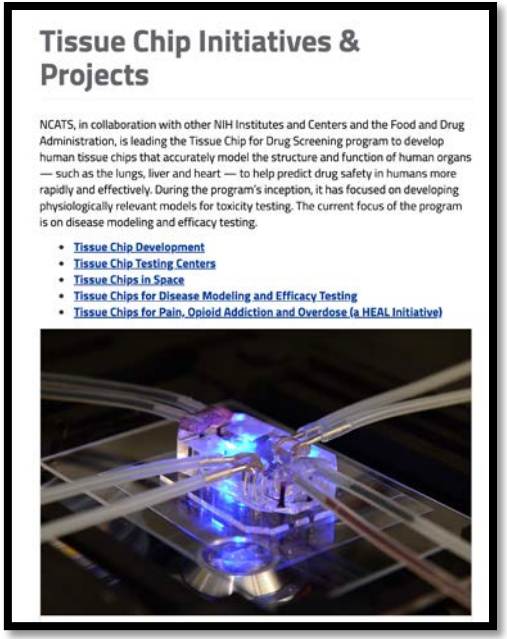
Predictive extrapolation

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

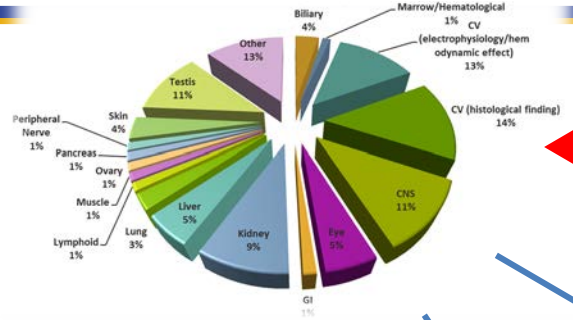
We've invested in human and physiologically-relevant modeling systems



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.



Strategic application - Think platform and paradigm!



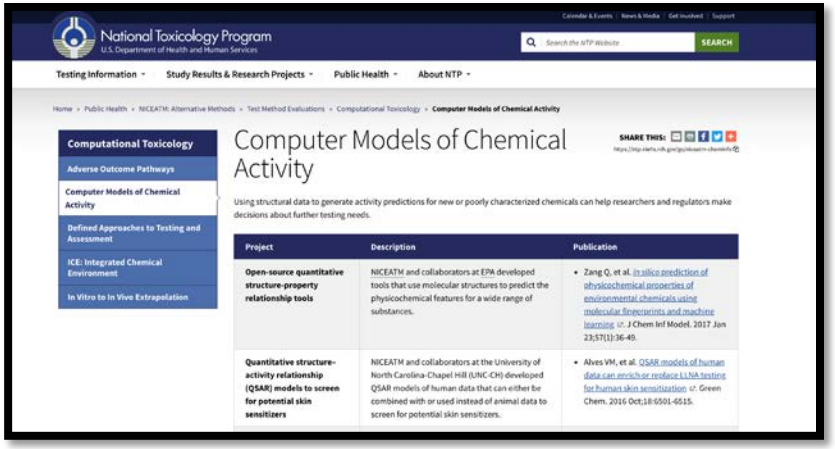
Prioritization of target organs

Organotypic Standards

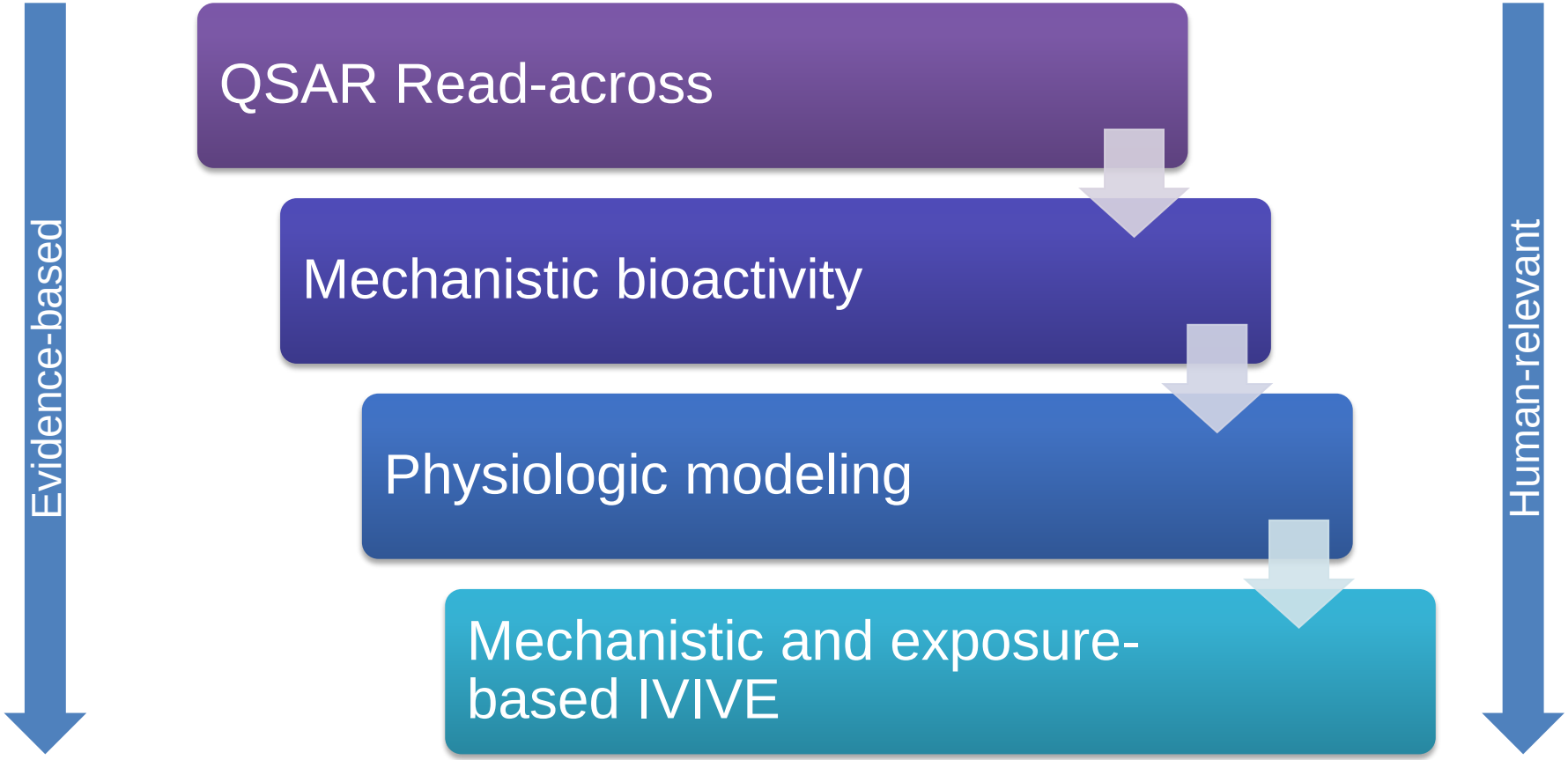
MPS Target organ #1	MPS Target organ #2	MPS Target organ #3	MPS Target organ #4
Normal cell/tissue biology	Normal cell/tissue biology	Normal cell/tissue biology	Normal cell/tissue biology
+	+	+	+
MoA/Failure modes	MoA/Failure modes	MoA/Failure modes	MoA/Failure modes

In vivo-relevant endpoints

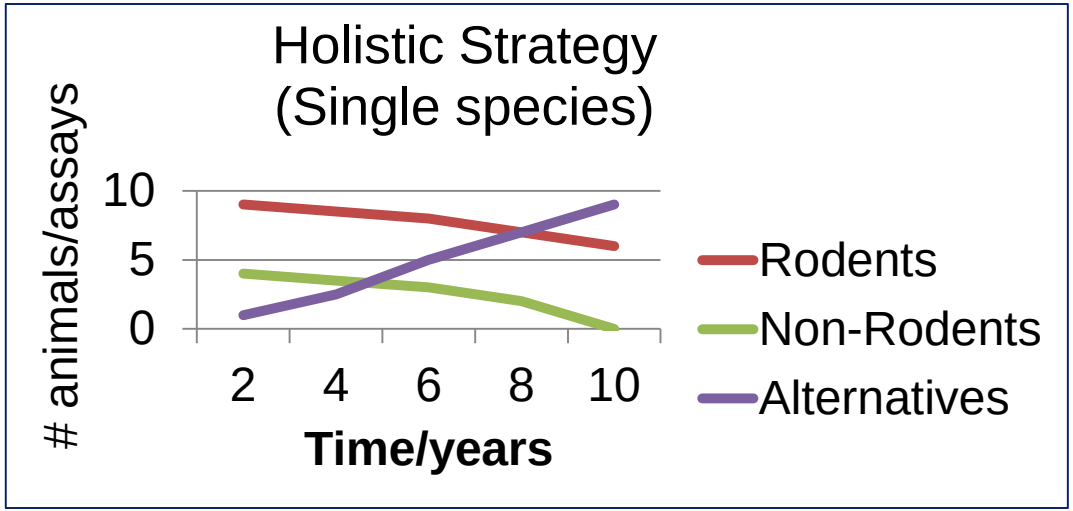
We've built enabling tools



Can we define a novel paradigm?



Enhancing value with aspiration - A BHAG Approach



Incentive-driven

Make it worth the effort!

Salient features

- Defined by a bold aspirational goal- i.e. single species safety package
- Alternatives development defined by the prioritized scope of in vivo assessments
- Improves human relevance and decreases animal use

Pros

- Deliberate innovation defined by current standards
- Significant alignment and complementarity of investment
- Significant decrease in animal studies- particularly for non-rodents
- Clinical predictivity could increase

Cons

- Requires Significant global coordination
- Regulatory acceptance required for full impact
- Structured development and qualification process
- Innovation directed

Acknowledgements

BSC Questions

- Are we asking the right questions? What's missing?
- Animal studies do not assess every possible biological effect. How do we know what scope of biology is most important to assess?
- How far down the temporal progression of pathogenesis do we need to model to predict an acute outcome? A chronic outcome?
- What is the tractability of a 'Virtual Human' hazard assessment platform?
- What technical capabilities would we need to develop to be successful?

Thank you

Questions?