

Evolving the Paradigm: In Vivo to In Vitro Extrapolation

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

Brian R. Berridge, DVM, PhD, DACVP

Scientific Director, Division of NTP

National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting

February 21, 2020





- 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

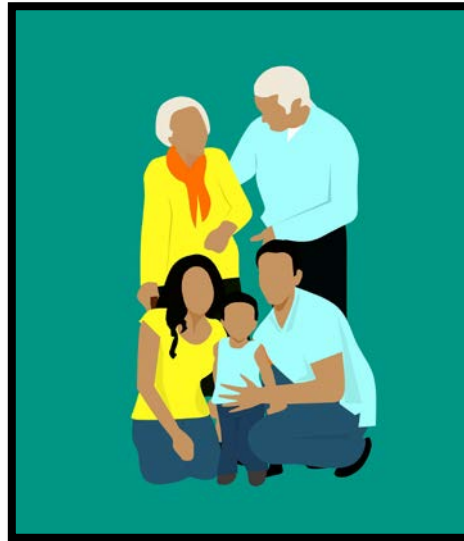


Primary stakeholder



Environmental public health interests

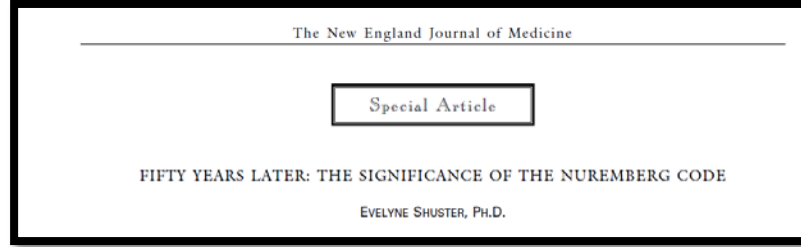
Personal interests



Pharma interests



Animal studies as human surrogates



- THE 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

The screenshot shows the EPA website's 'Pesticide Registration' section. The main heading is 'Data Requirements for Pesticide Registration'. On the left, there is a sidebar with links: 'Pesticide Registration Home', 'About Pesticide Registration', 'Electronic Submission of Applications', and 'Pesticide Registration Manual'. Below the main heading, there is a section titled 'On this page:' with links to 'Introduction', 'Guidance for EPA Staff', and 'Types of Studies Required'. To the right of this section is a green button labeled 'Related Information' with a link to 'Data requirements'.

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](#)."

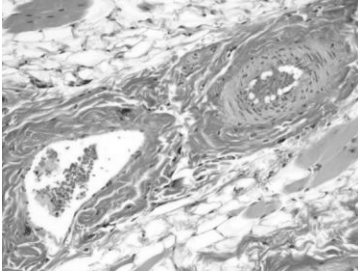
The image shows the cover of the ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, Step 5. The cover features the European Medicines Agency (EMA) logo at the top right, which includes the text 'EUROPEAN MEDICINES AGENCY' and 'SCIENCE MEDICINES HEALTH'. Below the logo, the date 'December 2009' and the reference number 'EMA/CPMP/ICH/286/1995' are listed. The main title of the guideline is centered on the page, and 'Step 5' is indicated at the bottom.

1.4. General principles

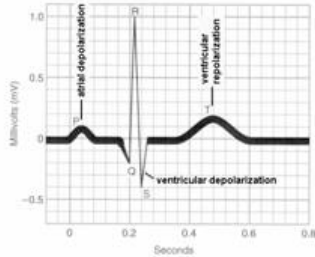
The development of a pharmaceutical is a stepwise process involving an evaluation of both animal and human efficacy and safety information. The goals of the nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship 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

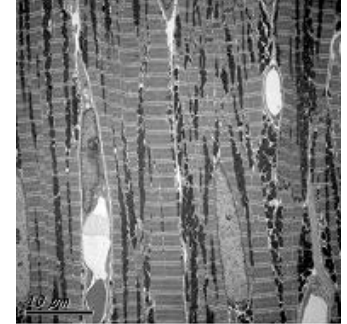
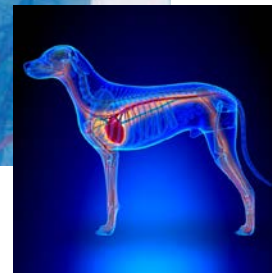
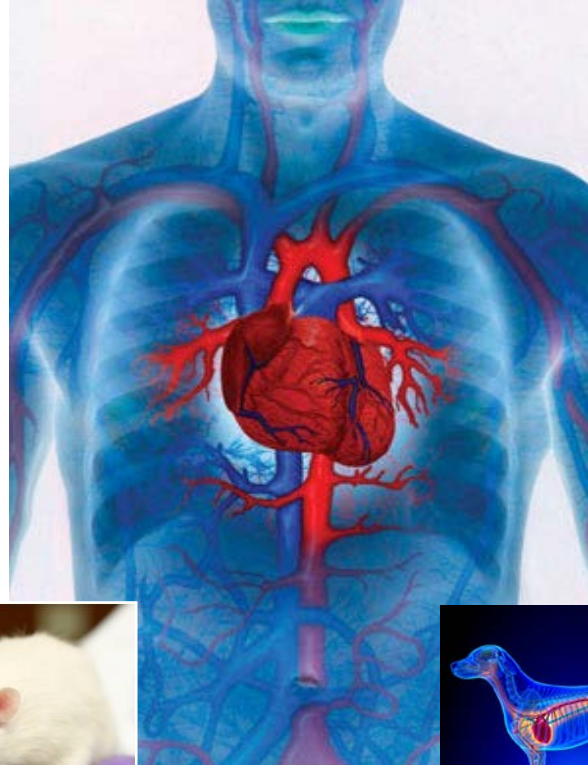


Blood vessels conduct blood to the heart itself as well as the rest of the body.



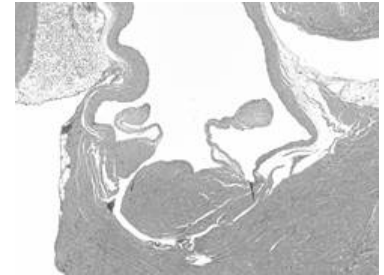
(b) Normal electrocardiogram of a single heartbeat

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



Richard M. Johnson, 2013

Cardiomyocytes are contractile cells with immense energy needs



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

ELSEVIER

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



Regulatory Toxicology and Pharmacology 96 (2018) 94–105



Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

ELSEVIER

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

581

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.



- 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



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?



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

Fundamental shifts

- Does this information be more broadly extrapolated to the complex human condition?
- What are the fundamental shifts?
- Uncertainty in biological systems is perturbed
- Is there a need for a shift?
- At what scale?
- What are the 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?
- Can this information be more broadly extrapolated to the complex human condition?

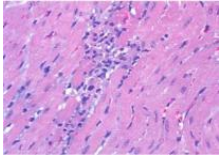


What current knowledge and capabilities might enable such a fundamental shift in how we model hazards?

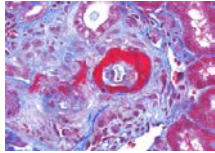


We know what failure looks like

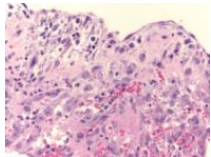
Structural injuries



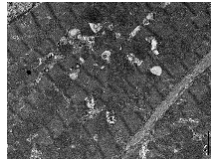
cardiomyocyte injury



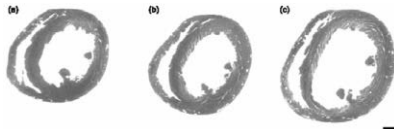
vascular injury



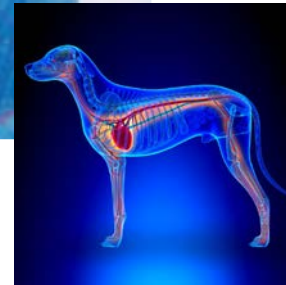
valvulopathy



organellar injury



Δ cardiac mass



Functional changes



Arrhythmia

Δ BP Δ HR

Δ contractility

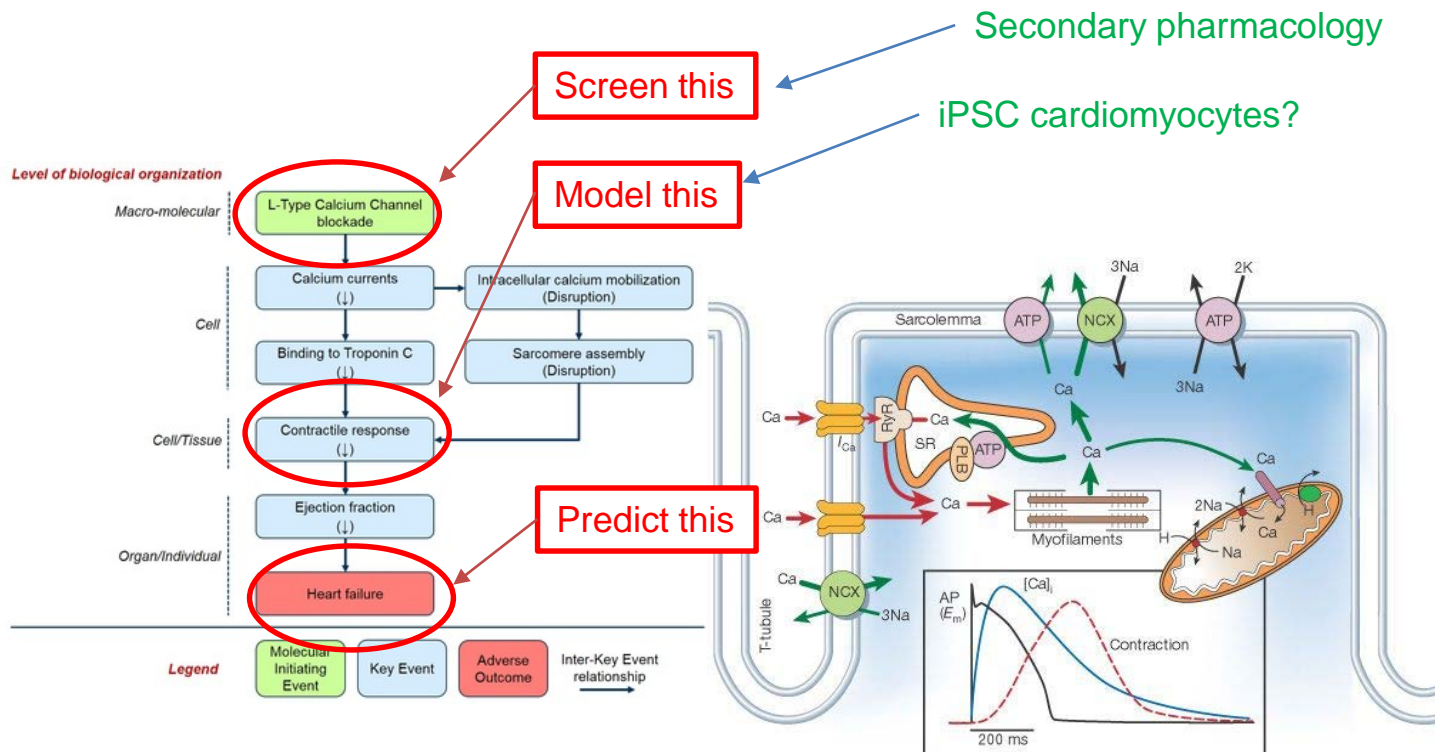
Changes in disease

- 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





We have experience with toxicity

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FDA Adverse Events Reporting System (FAERS) Public Dashboard

Home Demographics Reaction Group Reaction List of Cases Search by Product

IMATINIB (G) Total Cases: 3904 Serious Cases (Including Death): 345 Death Cases: 48

Revised Year	Case ID	Suspect Product Name	Suspect Product Active Ingredients	Reason for Use	Reactions	Serious	Outcomes
2017	17698214	Imatinib	Crift Versus Most Disease (C) Leaf	Off Label Use (Promotional)	Other Outcomes	Not S	Not S
2018	18067265	Imatinib	Acute Graft Versus Host Disease In L	Cardiomyopathy Pericarditis...	Serious	Other Outcomes	Other...
2018	17909818	Imatinib	Acute Lymphocytic Leukemia	Pneumonia Legionella L...	Serious	Other Outcomes	Other...
2018	17106206	Imatinib	Gastrointestinal Stromal Tumor	Hypertension (Diagnosis...	Serious	Other Outcomes	Other...
2018	17134249	Imatinib; Dasatinib	Chronic Myeloid Leukemia	Weight Decreased Adult...	Serious	Other Outcomes	Other...
2018	17170726	Imatinib; Nilotinib	Chronic Myeloid Leukemia Product...	Coronary Artery Stenosis...	Serious	Other Outcomes	Other...
2018	17257837	Imatinib	Imatinib	Product Size Issue	Non-Serious	Non-Serious	Non-Serious
2018	17270574	Imatinib	Chronic Myeloid Leukemia	Product Drug Discontinua...	Non-Serious	Non-Serious	Non-Serious
2018	17252928	Imatinib	Gastrointestinal Stromal Tumor	Fluorfenamicol (Surgical)	Non-Serious	Non-Serious	Non-Serious
2018	17252328	Imatinib	Imatinib	Product Storage Error (M...	Non-Serious	Non-Serious	Non-Serious
2018	17248136	Imatinib	Imatinib	Decreased Appetite (Sym...	Serious	Non-Serious	Non-Serious
2018	17194987	Imatinib	Chronic Myeloid Leukemia Product...	Electrocardiogram (E) Pr...	Serious	Other Outcomes	Other...
2018	78	Imatinib	Imatinib	Chemotherapy	Serious	Other Outcomes	Other...
2018	81	Imatinib	Imatinib	Disease Progression	Serious	Other Outcomes	Other...
2018	44	Imatinib	Imatinib	Surgery (Bleed Septic Op...	Non-Serious	Non-Serious	Non-Serious
2018	99	Imatinib	Imatinib	Discomfort (Peripheral S...	Non-Serious	Non-Serious	Non-Serious
2018	79	Imatinib	Imatinib	Gastrointestinal Neoplasia	Non-Serious	Non-Serious	Non-Serious
2018	18	Imatinib; Cytarabine; Docetaxel; Mitox...	Acute Lymphocytic Leukemia Prod...	Drug Resistance (Therap...	Serious	Other Outcomes	Other...
2018	37	Imatinib; Nilotinib	Chronic Myeloid Leukemia	Liver Function Test Abnor...	Serious	Other Outcomes	Other...
2018	17127861	Imatinib	Imatinib	Product Used For Unknown Indication	Serious	Other Outcomes	Other...
2018	17229266	Imatinib	Imatinib	Bleed Crisis In Myelogen...	Non-Serious	Non-Serious	Non-Serious

Photo as of December 31, 2019
To download data, Right-Click anywhere on the list and click on "Export". Then click "Export data".

Human Experience

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

Calendar & Events News & Media Get Involved Support

Search the NTP Website SEARCH

Chemical Effects in Biological Systems Help

Home > Chemical Effects in Biological Systems (CEBS)

Chemical Effects in Biological Systems

The **CEBS** database houses data of interest to environmental health scientists. **CEBS** is a public resource, and has received depositions of data from academic, industrial, and governmental laboratories. **CEBS** is designed to display data in the context of biology and study design, and permit data integration across studies for novel meta analysis.

All Search CEBS SEARCH CEBS

Example Searches

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,⁴ 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,⁹ Richard S. Paules,³ Raymond R. Tice,³ and Anton Simeonov¹

Modes of action

Environmental Health Perspectives 126(7) July 2018

molecules



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?



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. Mauli⁷, Donna L. Mendrick⁸, 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



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

DARPA DEFENSE ADVANCED RESEARCH PROJECTS AGENCY

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Microphysiological Systems (MPS)

Dr. Brad Ringeisen

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.

U.S. Department of Health & Human Services

NIH National Institutes of Health

NIH National Center for Advancing Translational Sciences

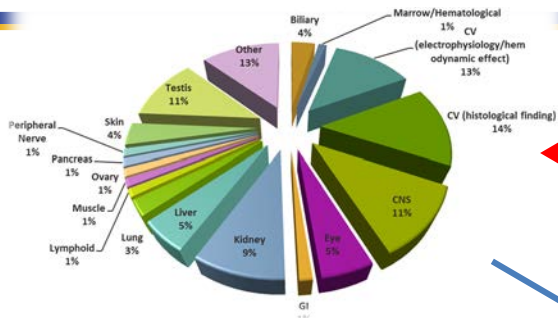
Tissue Chip Initiatives & Projects

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.

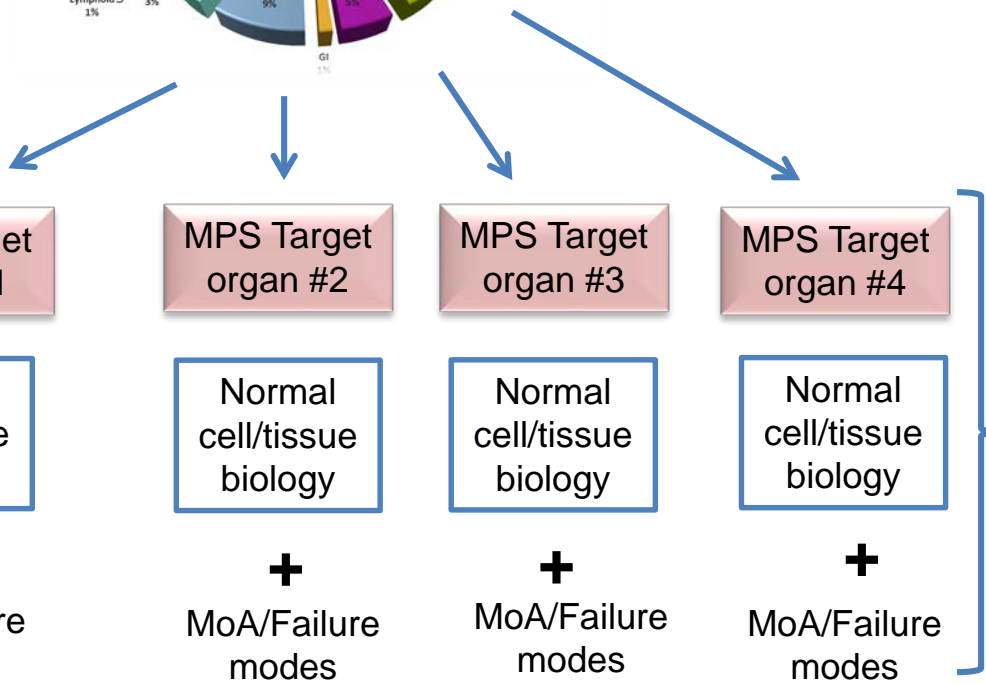
- [Tissue Chip Development](#)
- [Tissue Chip Testing Centers](#)
- [Tissue Chips in Space](#)
- [Tissue Chips for Disease Modeling and Efficacy Testing](#)
- [Tissue Chips for Pain, Opioid Addiction and Overdose \(a HEAL Initiative\)](#)



Strategic application - Think platform and paradigm!



Prioritization of target organs





We've built enabling tools

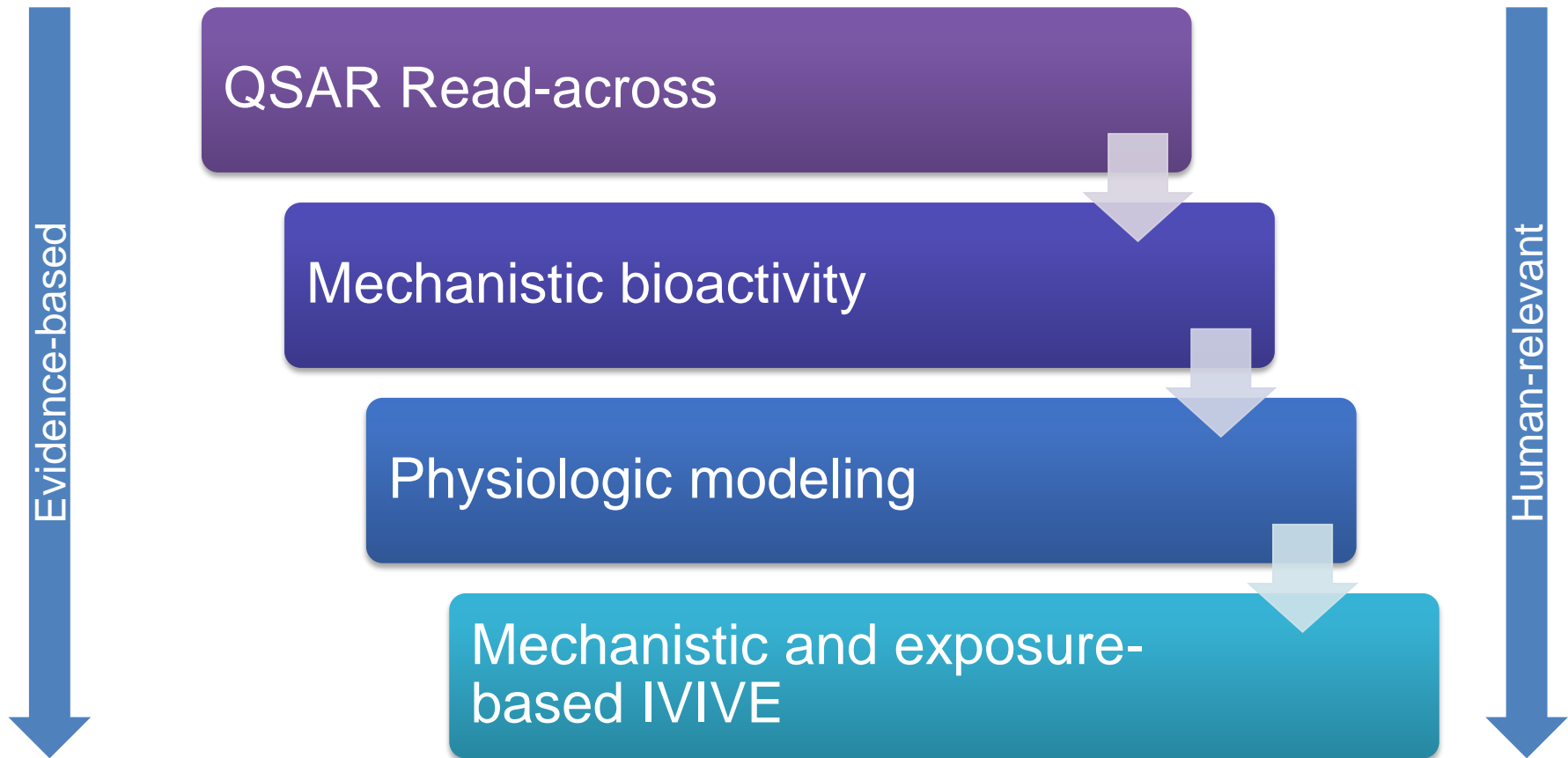
The screenshot shows the National Toxicology Program website. The header includes the logo, the text 'National Toxicology Program U.S. Department of Health and Human Services', and a search bar. The main navigation menu has 'Testing Information', 'Study Results & Research Projects', 'Public Health', and 'About NTP'. The breadcrumb trail is 'Home > Public Health > NICEATM: Alternative Methods > Test Method Evaluations > Computational Toxicology > Computer Models of Chemical Activity'. The page title is 'Computer Models of Chemical Activity'. A sidebar on the left lists '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 has a sub-header '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 columns: 'Project' and 'Description'. The first row is 'Open-source quantitative structure-property relationship tools' with a description of tools developed by NICEATM and EPA. The second row is 'Quantitative structure-activity relationship (QSAR) models to screen for potential skin sensitizers' with a description of QSAR models developed by NICEATM and the University of North Carolina-Chapel Hill. A 'Publication' column on the right lists two articles: 'Zang Q, et al. In silico prediction of physicochemical properties of environmental chemicals using molecular fingerprints and machine learning.' and 'Ahnes VM, et al. QSAR models of human data can predict or improve IIVX tests for human skin sensitization.'

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. <i>In silico prediction of physicochemical properties of environmental chemicals using molecular fingerprints and machine learning.</i> <i>J Chem Inf Model.</i> 2017 Jun 23;57(11):36-46.
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.	Ahnes VM, et al. <i>QSAR models of human data can predict or improve IIVX tests for human skin sensitization.</i> <i>Green Chem.</i> 2016 Oct;18:6501-6515.

The screenshot shows the National Toxicology Program website. The header includes the logo, the text 'National Toxicology Program U.S. Department of Health and Human Services', and a search bar. The main navigation menu has 'Testing Information', 'Study Results & Research Projects', 'Public Health', and 'About NTP'. The breadcrumb trail is 'Home > Public Health > NICEATM: Alternative Methods > Test Method Evaluations > Computational Toxicology > In Vitro to In Vivo Extrapolation'. The page title is 'In Vitro to In Vivo Extrapolation'. A sidebar on the left lists '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 has a sub-header 'A workflow for conducting in vitro to in vivo extrapolation (IIVX) analyses is now available in the Integrated Chemical Environment.' Below this is a paragraph: 'A key issue with high-throughput in vitro testing methods is how to accurately relate concentrations of substances that induce in vitro responses to in vivo exposure levels that could result in human or animal adverse effects. This relationship is established through IIVX, the focus of a NICEATM webinar series and following workshop during 2015 and 2016.' Another paragraph follows: 'Scientists interested in the use of IIVX for substance screening and risk decision-making met at the 2016 workshop to develop best practices and identify areas for further research. The workshop, co-organized by NICEATM and the U.S. Environmental Protection Agency, was summarized in a 2018 publication in the journal Toxicology in Vitro (Bell et al. 2018).' A final paragraph states: 'NICEATM's computational toxicologists developed methods for conducting IIVX analyses, described in a publication in the journal Applied in Vitro Toxicology (Chang et al. 2018). Subsequent work focused on understanding the impact of various parameters, such as using free plasma concentration as a surrogate for total plasma concentration, and comparing multiple modeling approaches. This work is described in a publication in Environmental Health Perspectives (Casey et al. 2018).'

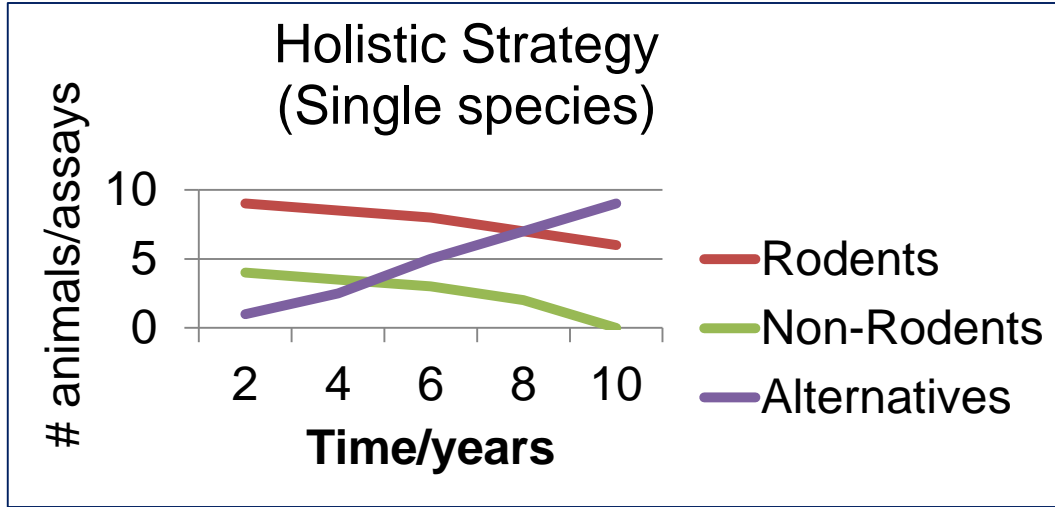


Can we define a novel paradigm?





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





- 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?