

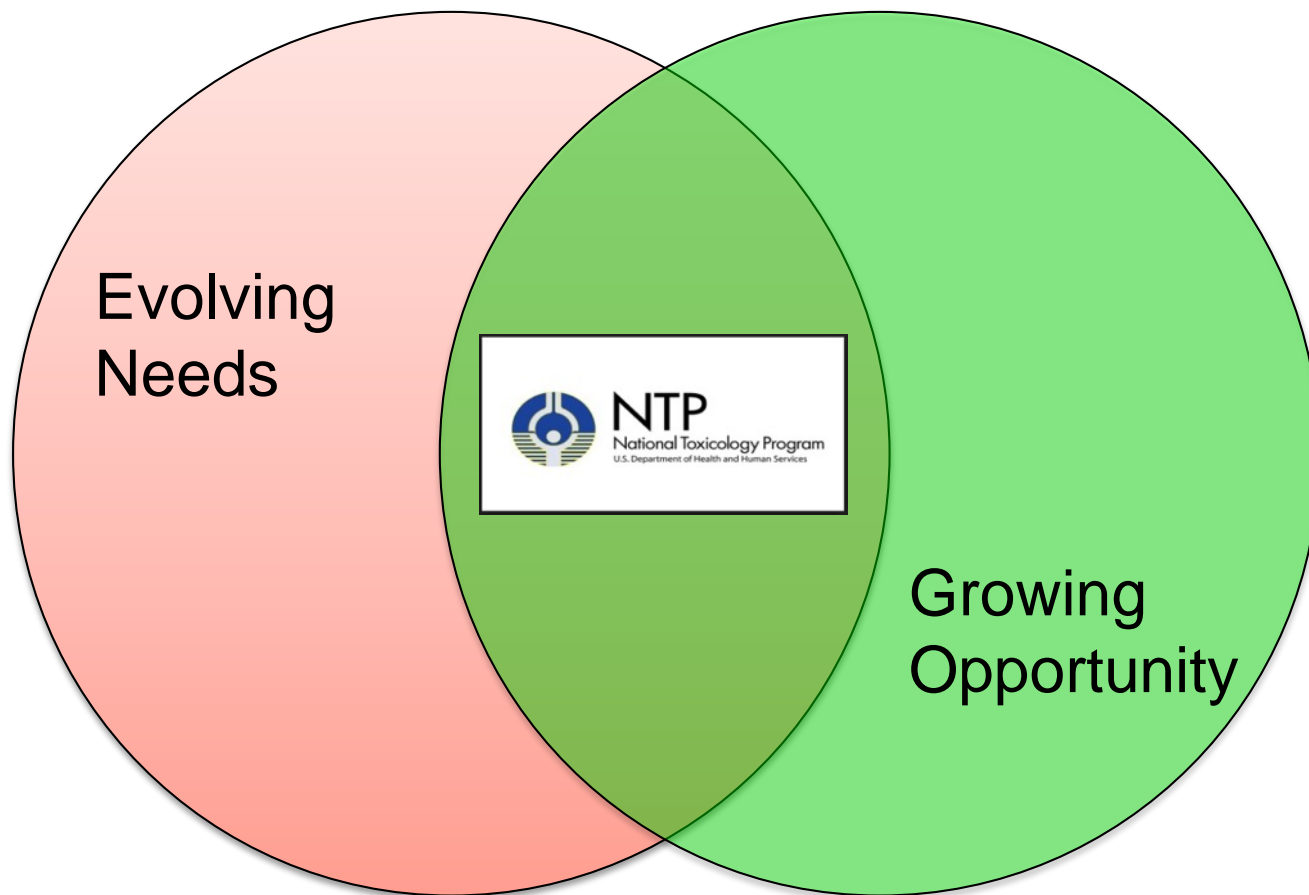
NTP Update on Implementing New Approaches to Evaluate the Safety of Chemicals and Medical Products

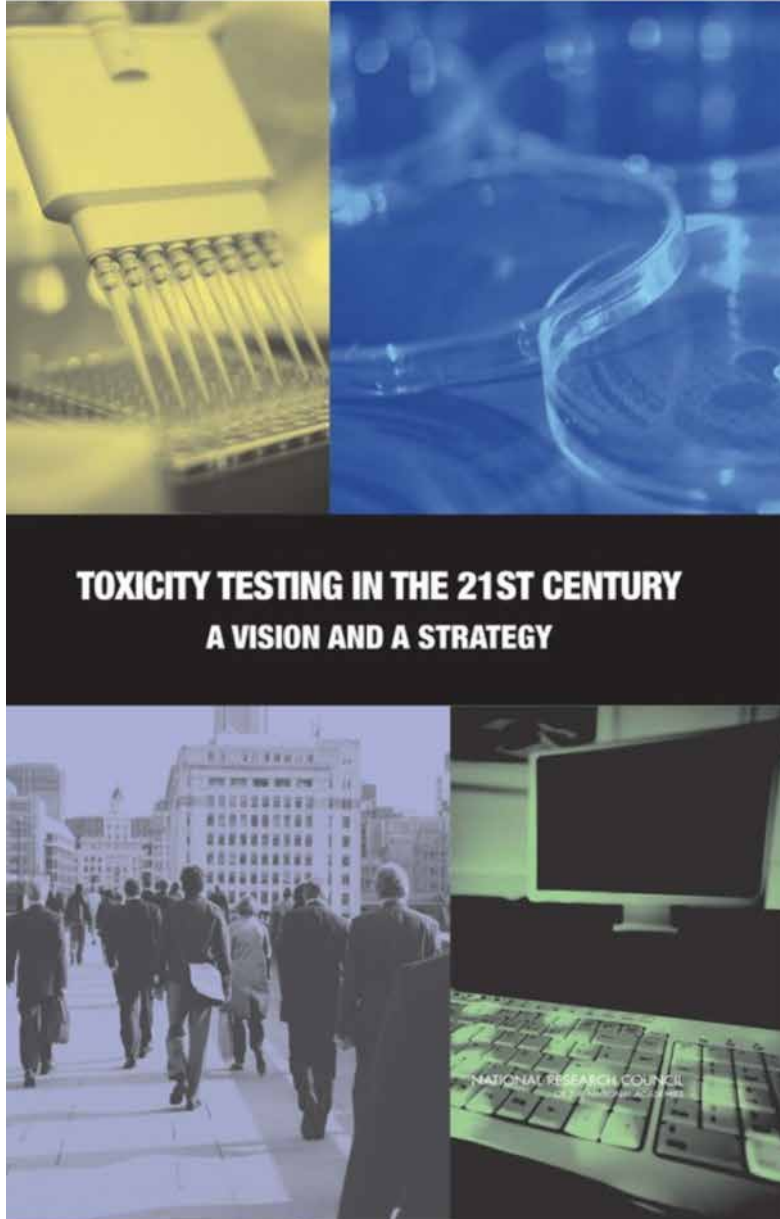
B. R. Berridge, DVM, PhD, DACVP

Associate Director, NTP

Scientific Director, NIEHS DNTP

11 Mar 2019





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.



Tox21: Chemical testing in the 21st century



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,*}

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

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^{6a}, Elizabeth A. Maul², Donna L. Mendrick⁷, B. Alex Merrick², Nisha S. Sipes², Daniel Svoboda¹, Richard S. Paules^{2,*}

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



Pathways



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

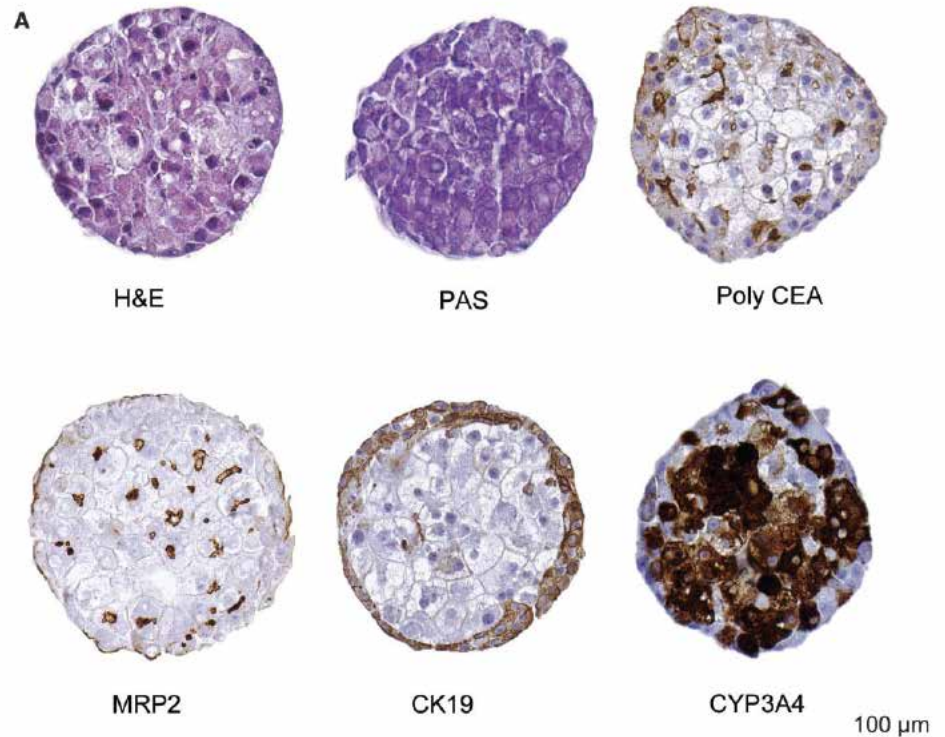
TOXICOLOGICAL SCIENCES, 167(1), 2019, 157–171



Three-Dimensional (3D) HepaRG Spheroid Model With Physiologically Relevant Xenobiotic Metabolism Competence and Hepatocyte Functionality for Liver Toxicity Screening

Sreenivasa C. Ramaiahgari, Suramya Waidyanatha, Darlene Dixon, Michael J. DeVito, Richard S. Paules, and Stephen S. Ferguson¹

TOXICOLOGICAL SCIENCES, 159(1), 2017, 124–136





Enabling Tools

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Computer Models of Chemical Activity

Using structural data to generate activity predictions for new or poorly characterized chemicals can help researchers and regulators make decisions about further testing needs.

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<https://ntp.niehs.nih.gov/research/chemistry>

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.	<ul style="list-style-type: none">Zeng 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):36-43.
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.	<ul style="list-style-type: none">Alves VM, et al. QSAR models of human data can match or exceed in vivo testing for human skin sensitization. <i>J Green Chem</i>. 2016 Oct;18(8):4535.

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

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In Vitro to In Vivo Extrapolation

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<https://ntp.niehs.nih.gov/in/vitro-to-in-vivo>

A workflow for conducting in vitro to in vivo extrapolation (IVIVE) analyses is now available in the [Integrated Chemical Environment](#).

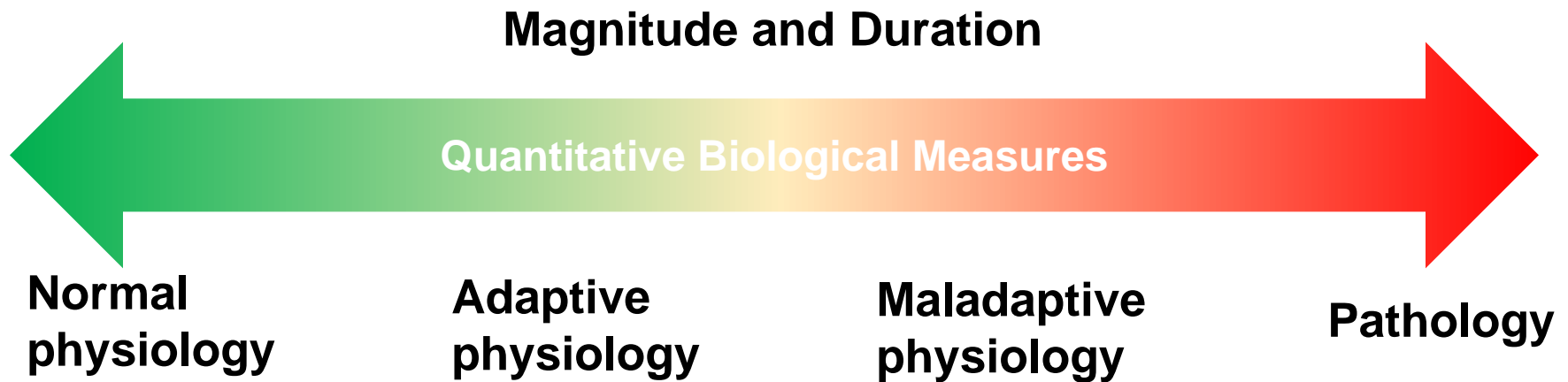
A key issue with high-throughput in vitro testing methods is how to accurately relate concentrations of substances that induce in vitro responses to in vivo exposure levels that could result in human or animal adverse effects. This relationship is established through [IVIVE](#), the focus of a [NICEATM webinar series and following workshop](#) during 2015 and 2016.

Scientists interested in the use of IVIVE 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](#) ¹).

NICEATM's computational toxicologists developed methods for conducting IVIVE analyses, described in a publication in the journal *Applied In Vitro Toxicology* ([Chang et al. 2014](#) ²). 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. 2016](#) ³).



Key Challenges – Pathobiology Is a Continuum



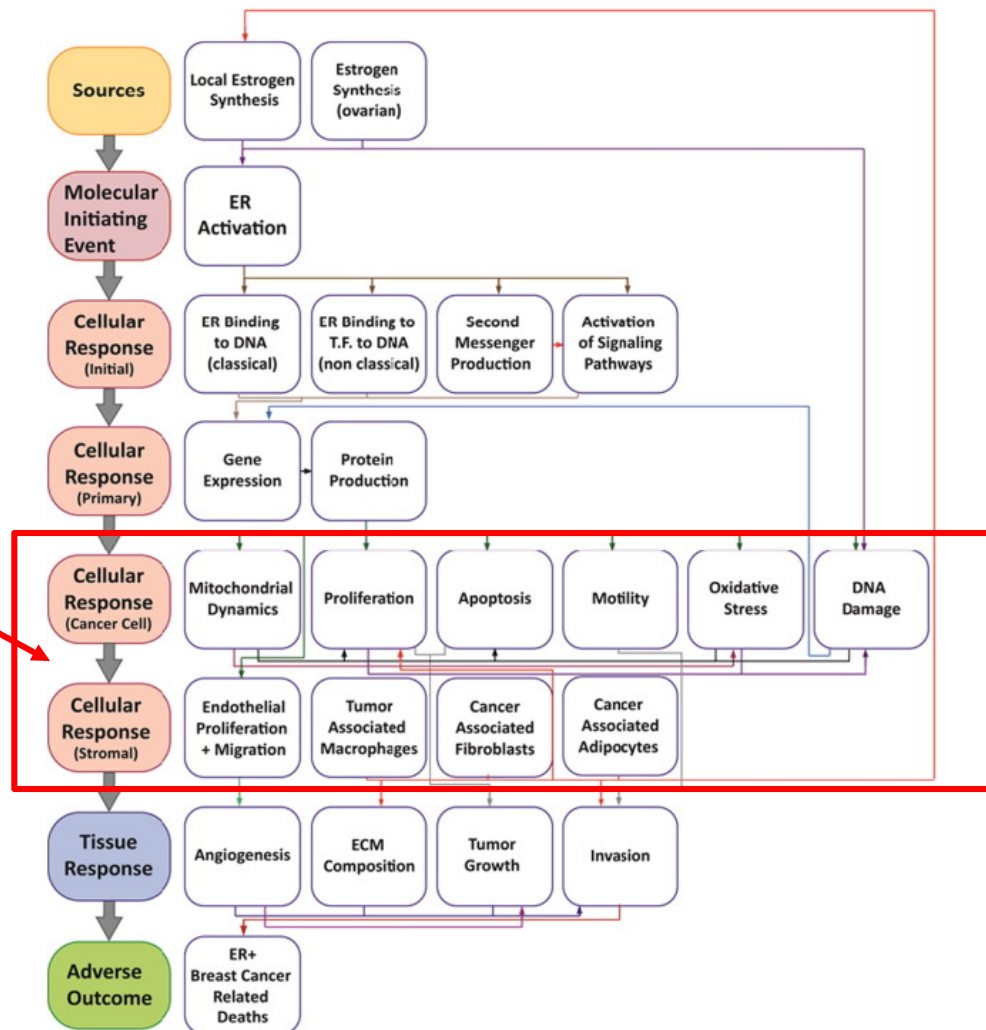
- Transition from normal to abnormal is generally not binomial.
- Thresholds of biological perturbation that represent ‘toxicity’ are difficult to define and not generally well understood mechanistically.
- Contextualizing those perturbations in a myriad of possible individual susceptibilities is even more difficult.



Key Challenges – Predictive Toxicology Conundrum

ER pathway to breast cancer

This is the inflection point we need to model since it represents the bridge between observation and prediction





Building confidence



Analytical
validation

Key Enablers

- Replicate biology
- Demonstrate pharmacology and toxicology
- Test for analytical reproducibility
- Conduct comparative studies
- Evolve use
- Learn to make decisions
- Understand clinical outcomes
- Build experience

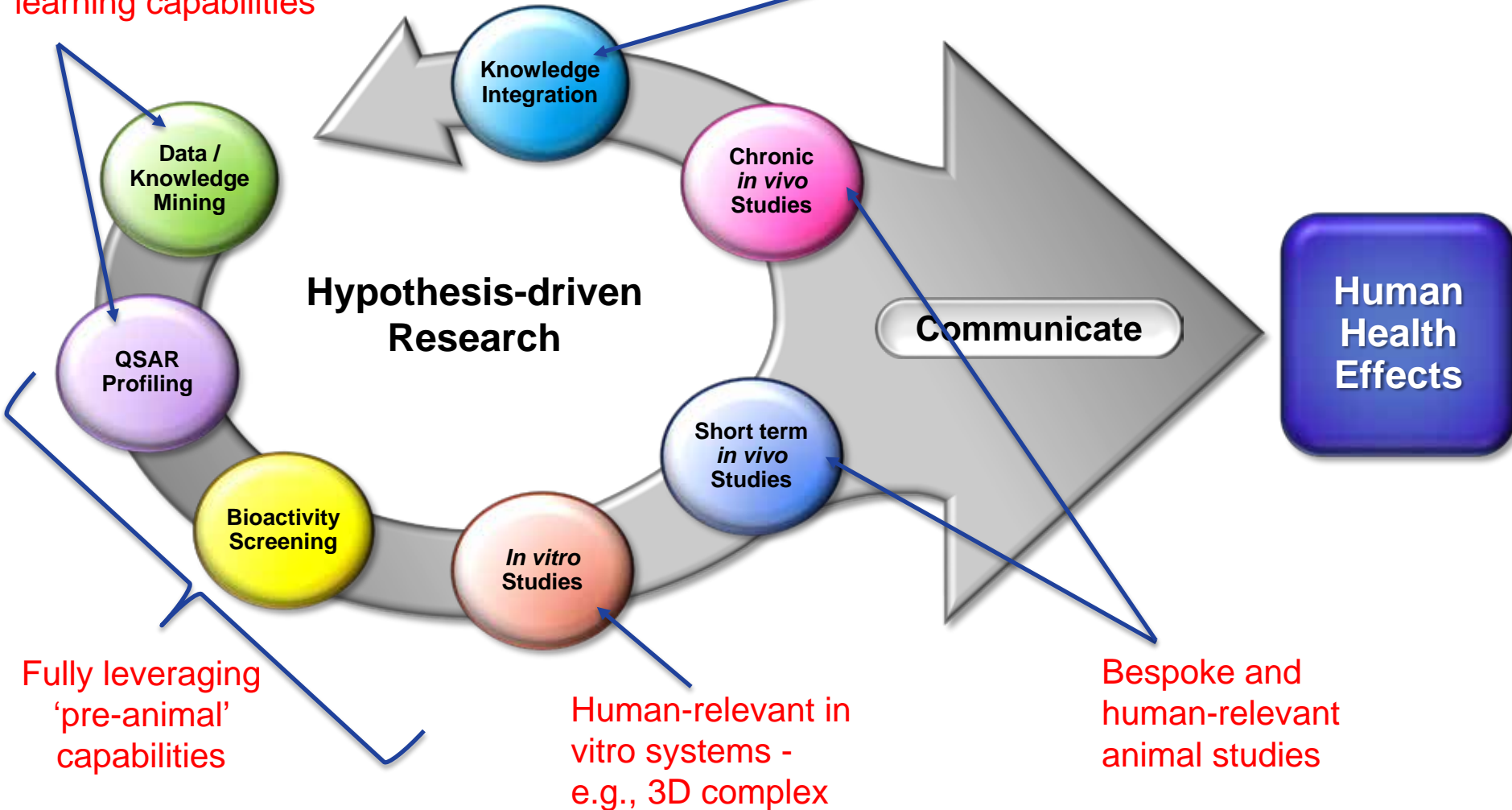
Translational
qualification



Translational Toxicology Pipeline

Machine/Deep learning capabilities

Iterative learning



Questions?

