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National Toxicology Program

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

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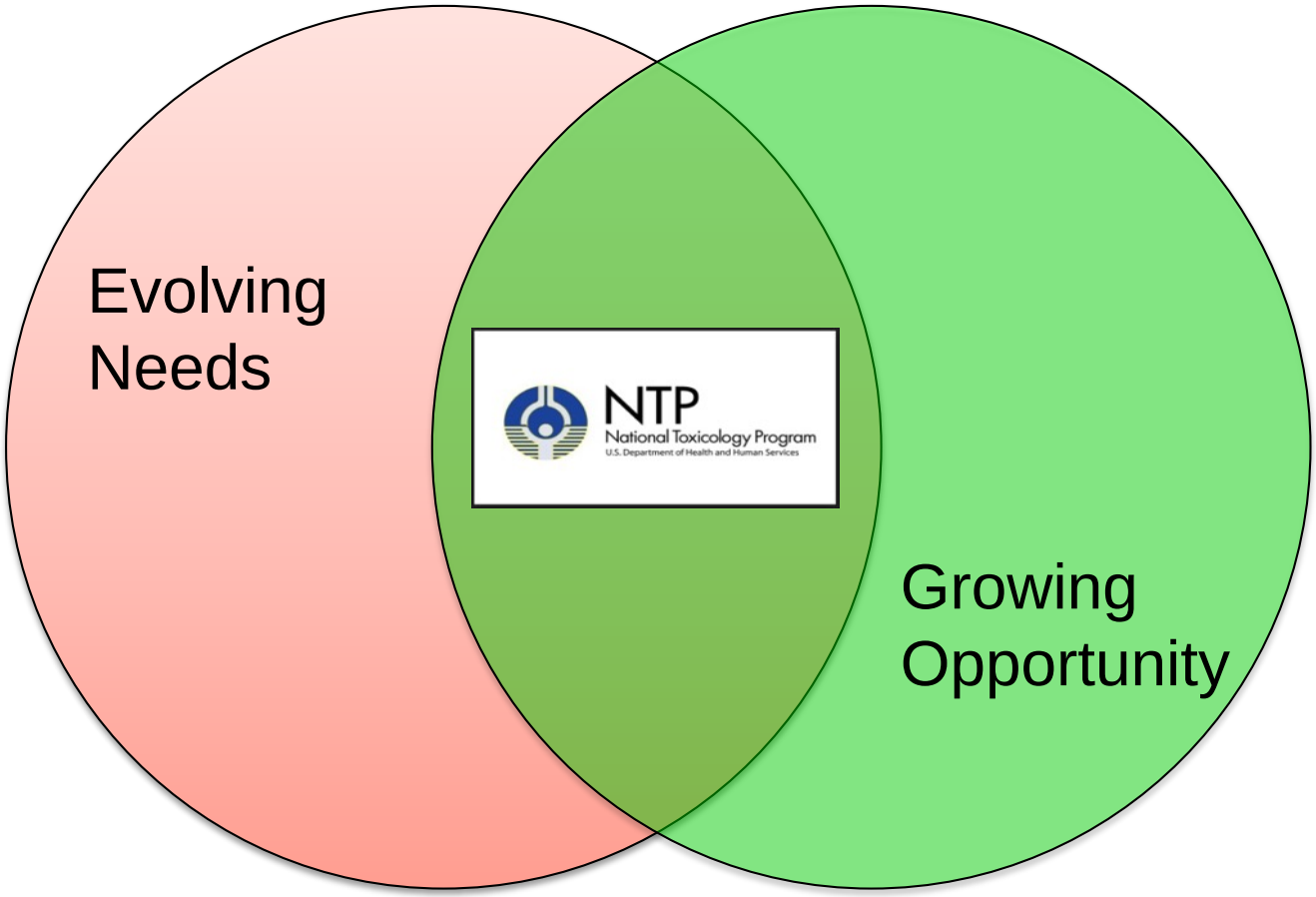
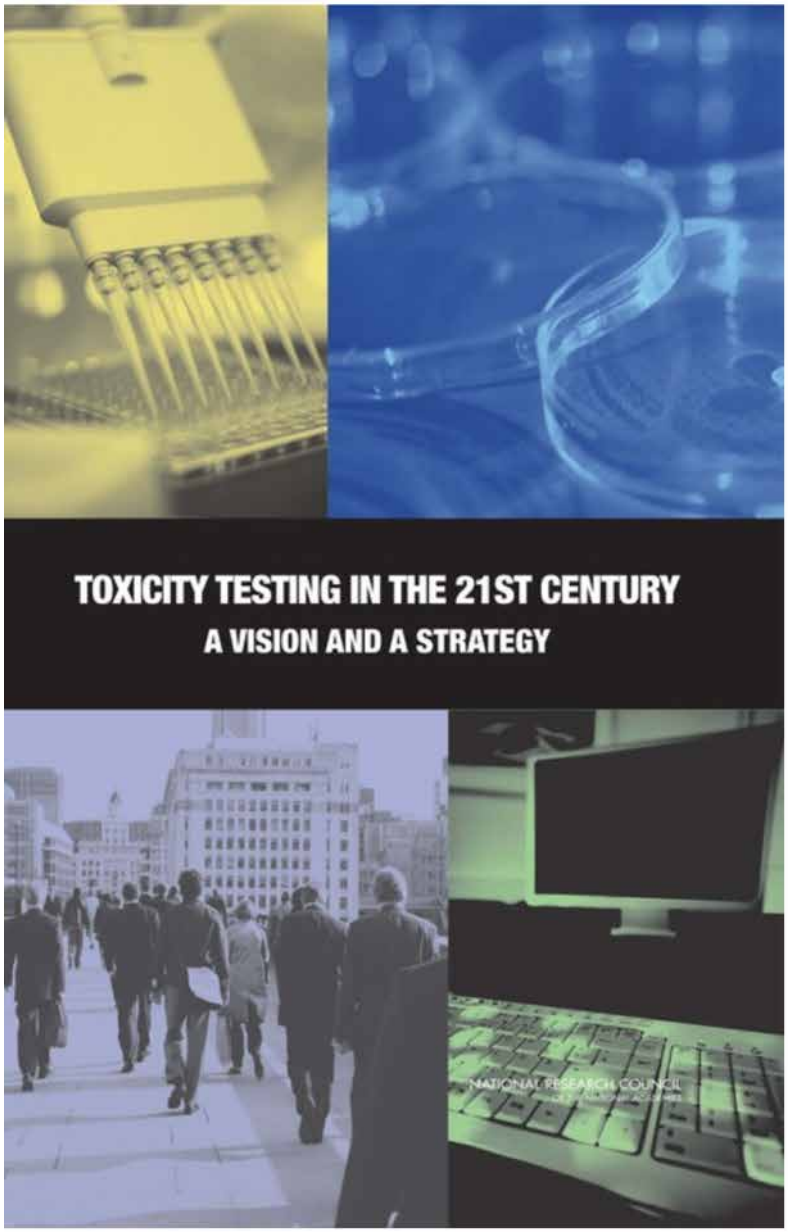
11 Mar 2019

A Crossroads



Needs



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.

National Academies Press, 2007

Opportunity

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,

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

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

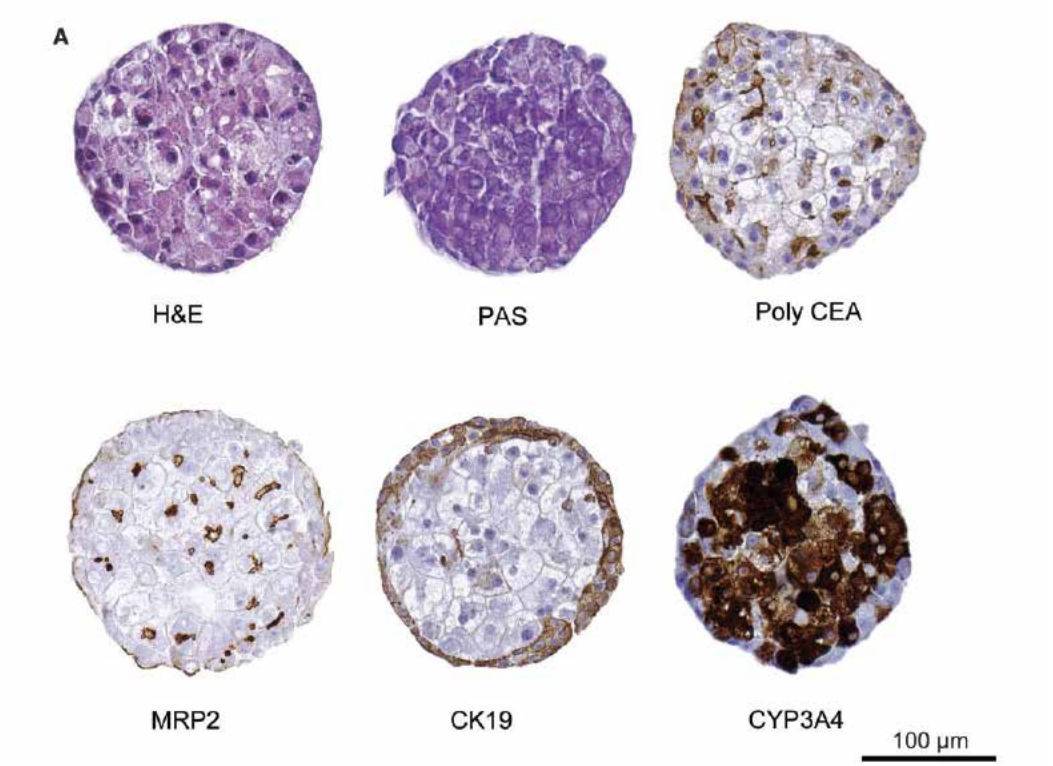
TOXICOLOGICAL SCIENCES, 167(1), 2019, 157–171

Opportunity

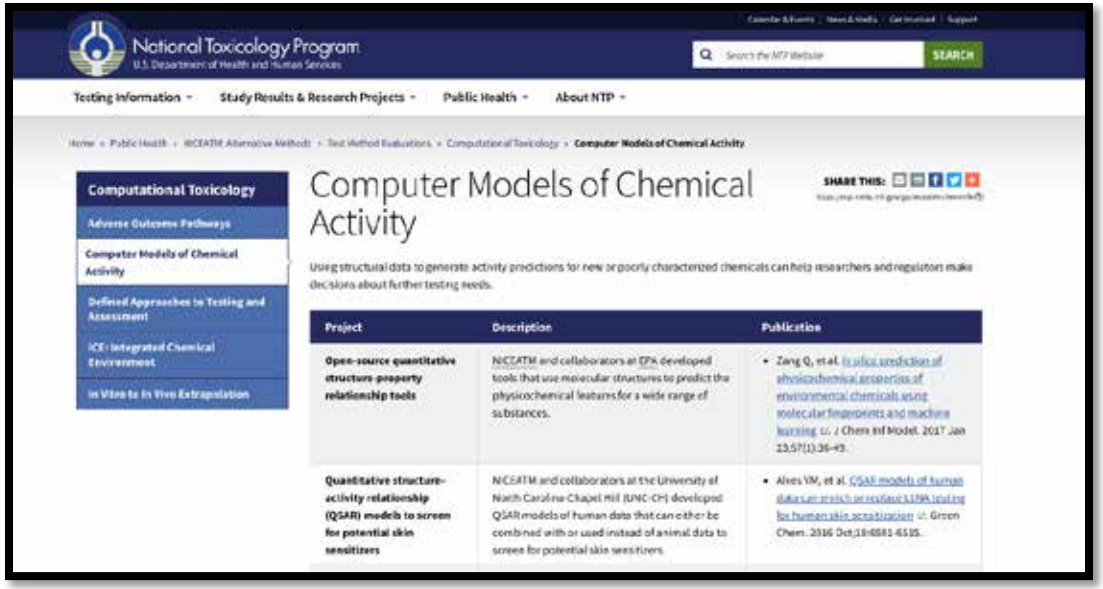
Three-Dimensional (3D) HepaRG Spheroid Model With Physiologically Relevant Xenobiotic Metabolism Competence and Hepatocyte Functionality for Liver Toxicity Screening

Sreenivasa C. Ramaiahgari, Suramya Waidyanatha, Darlene Dixon, Michael J. DeVito, Richard S. Paules, and Stephen S. Ferguson[1]

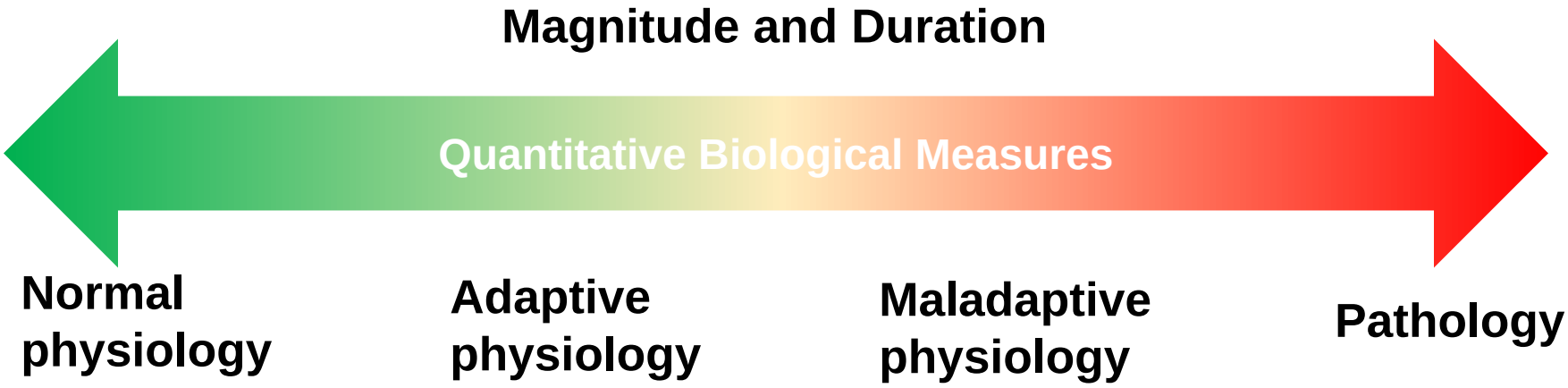
TOXICOLOGICAL SCIENCES, 159(1), 2017, 124–136



Enabling Tools



Key Challenges – Pathobiology Is a Continuum

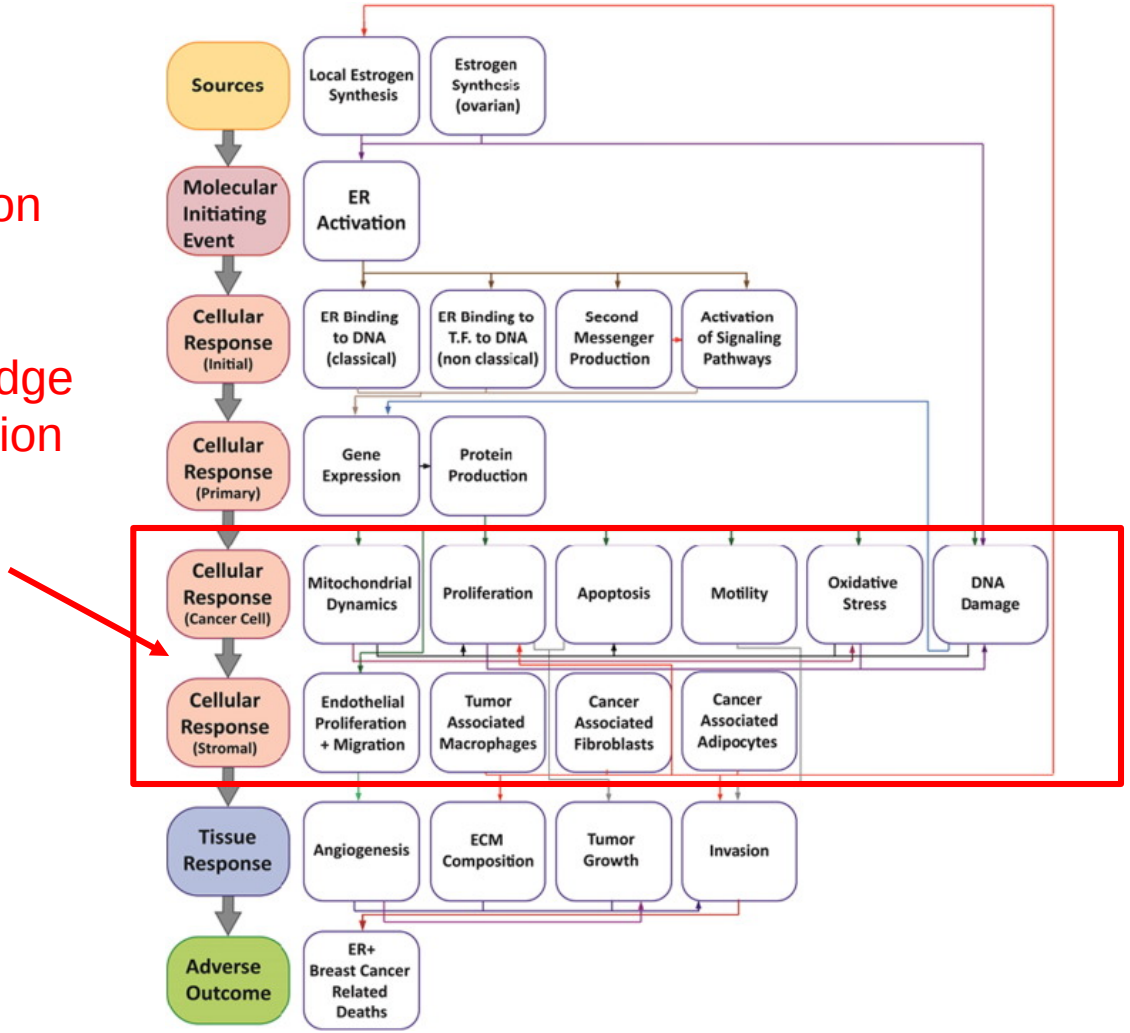


- Transition from normal to abnormal is generally not binomial.
- Thresholds of biological perturbation that represent ‘toxicity’ are difficult to define and not generally well understood mechanistically.
- Contextualizing those perturbations in a myriad of possible individual susceptibilities is even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



From Morgan et al., 2016, Pharmacology & Therapeutics 165: 79-92

Appreciation to Cynthia Rider for introducing me to this.

Key Challenges – Validation-Qualification Continuum

Building confidence

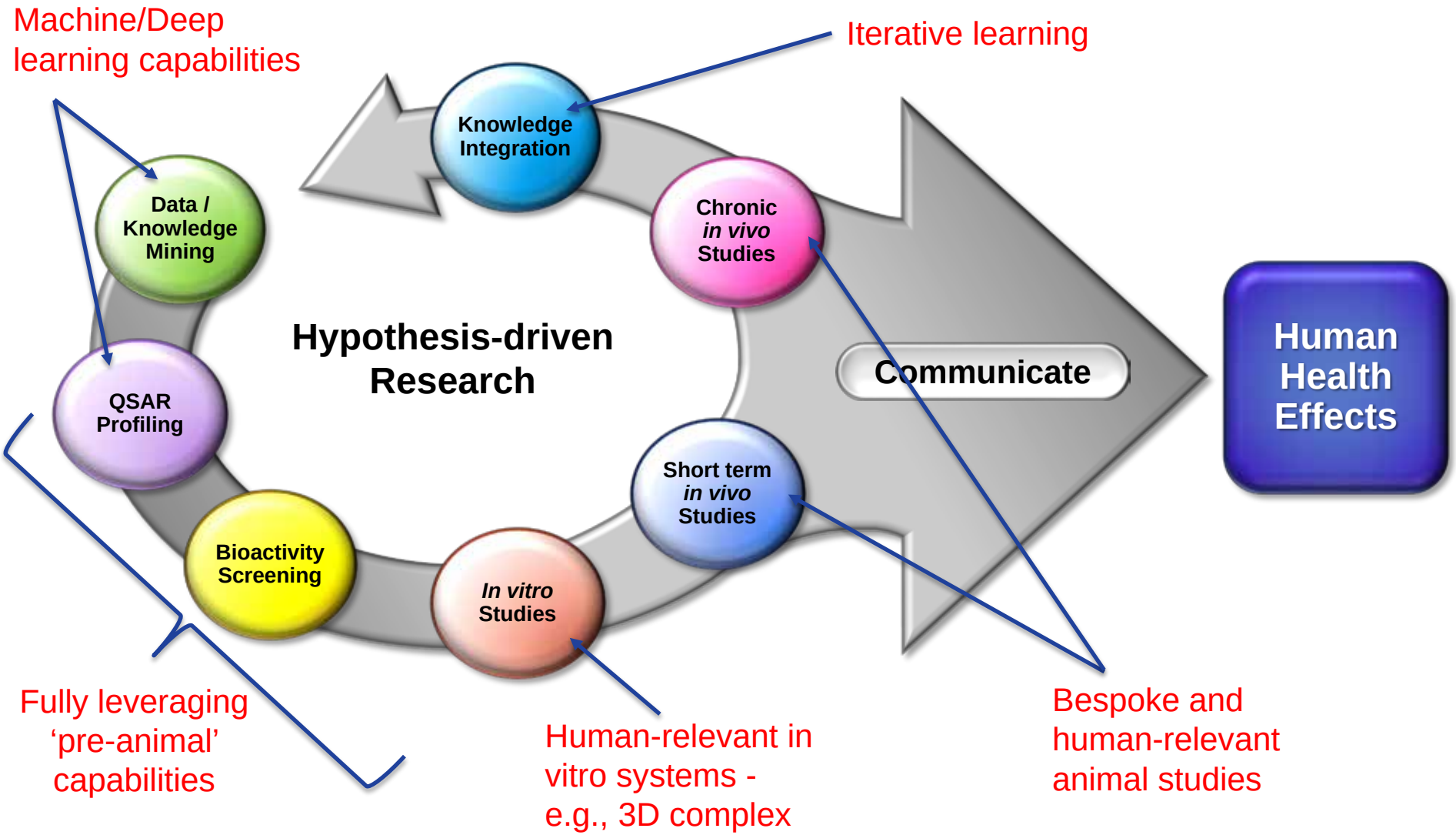
Analytical validation

Translational qualification

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 Toxicology Pipeline



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Questions?