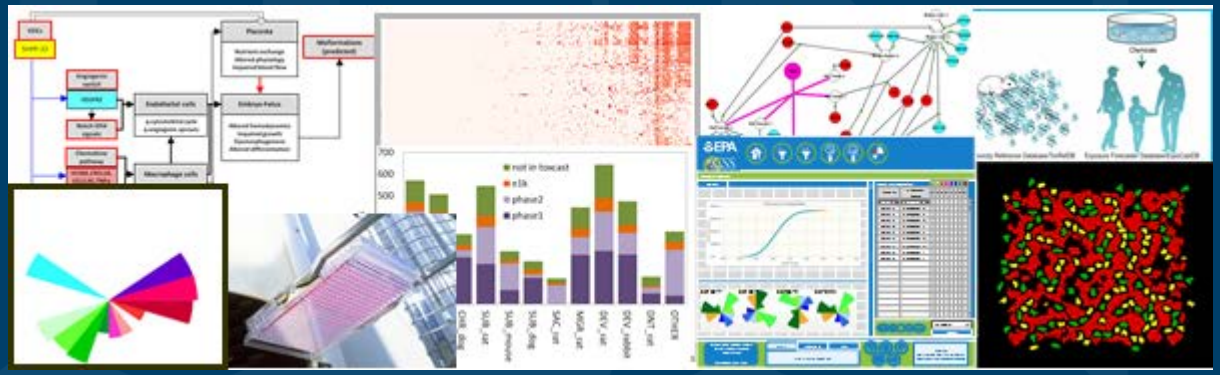
United States Environmental Protection Agency

EPA Activities for Integrating Genome Technology into High-Throughput Chemical Screening



GlobalChem
February 28, 2018

Rusty Thomas
Director
National Center for Computational Toxicology

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

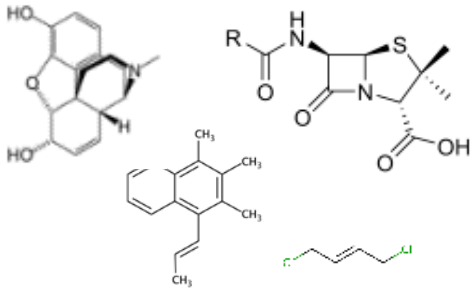
What Do Grandmothers and Toxicologists Have in Common?

http://talesfromthecircus.com/hissing-grandmother-roaming-hands/

Push To Use Alternative Methods Comes From Multiple Drivers

United States Environmental Protection Agency

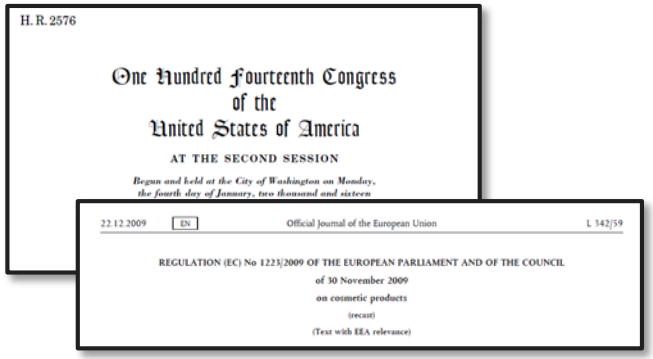
Number of Chemicals /Combinations



Can We Satisfy Grandma Too?

http://talesfromthecircus.com/hissing-grandmother-roaming-hands/

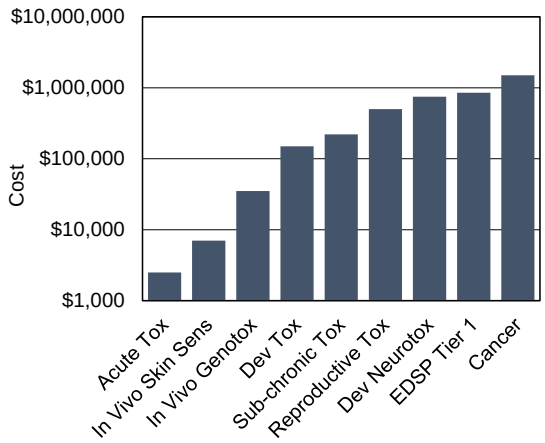
Legislative Mandates



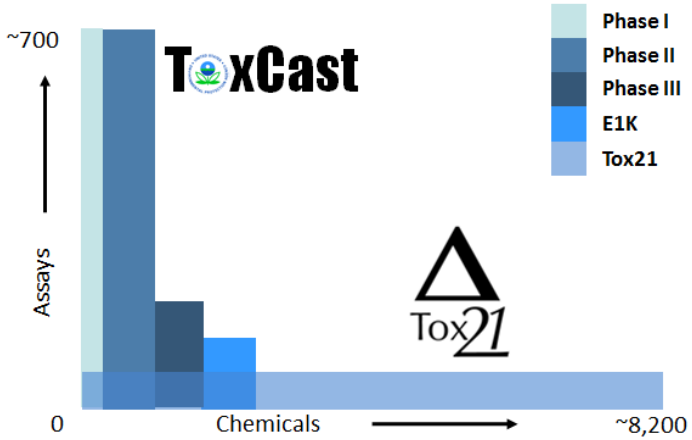
Ethics Concerns

http://www.victorpest.com

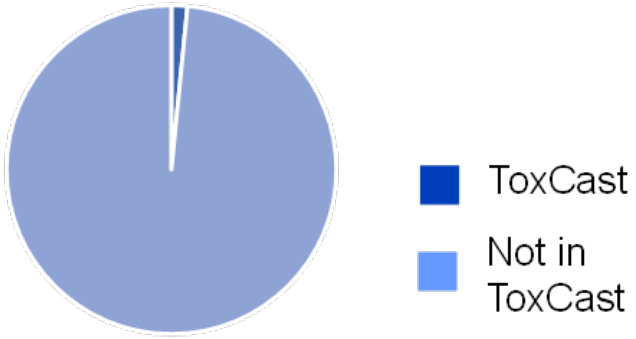
Economics



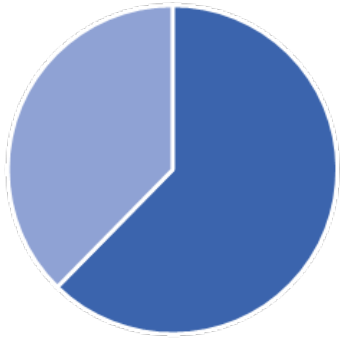
High-Throughput Screening Efforts Attempt to Address Worries, but…



Gene Coverage



Pathway Coverage*

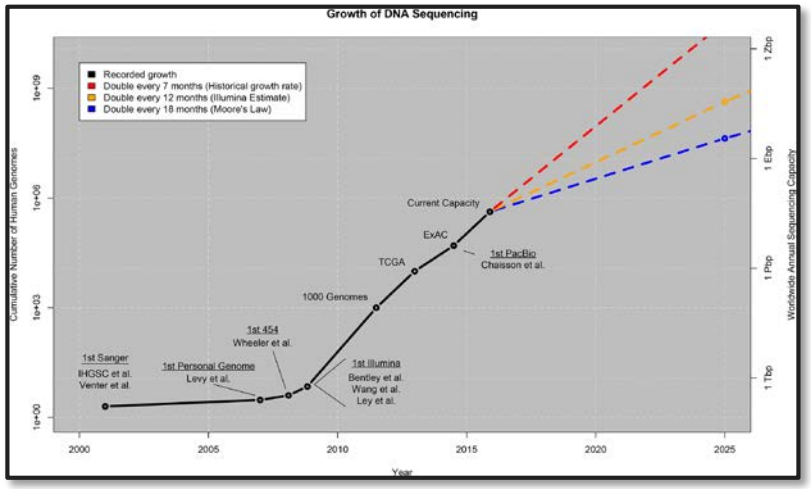


*At least one gene from pathway represented

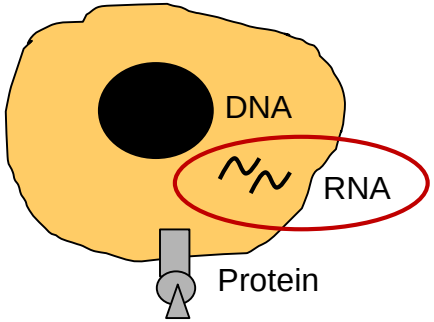
Using Technology from Genome Revolution to Increase Coverage

April, 2003

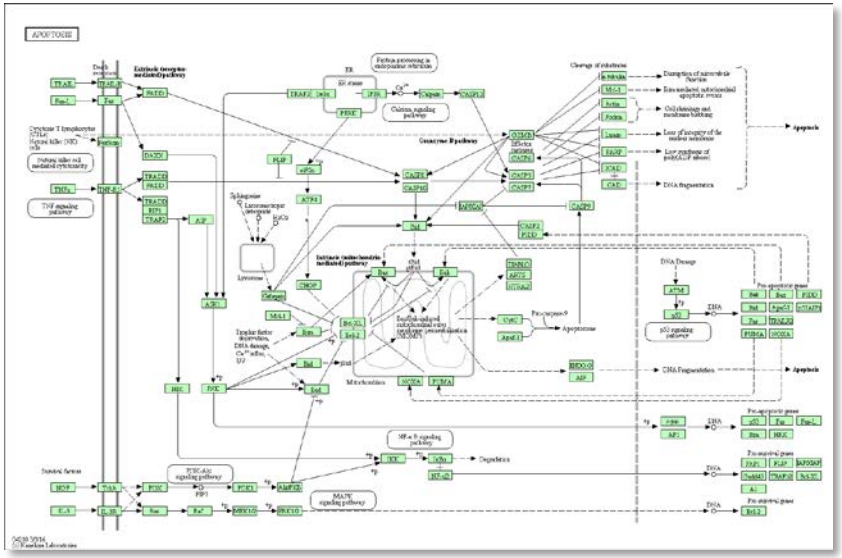
Dec, 2012



https://doi.org/10.1371/journal.pbio.1002195

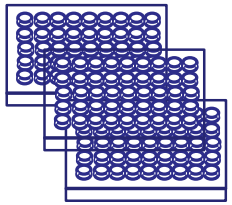


Pathway

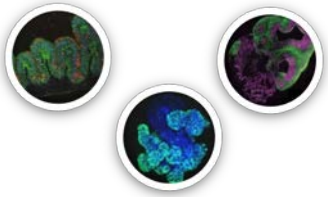


KEGG Pathway - hsa04210

Developing a High-Throughput Transcriptomic Toolbox



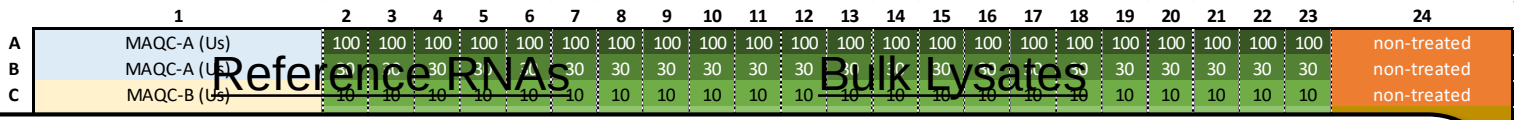
Thousands of Chemicals



Multiple Cell Types

High-Throughput Transcriptomic Screening Platform

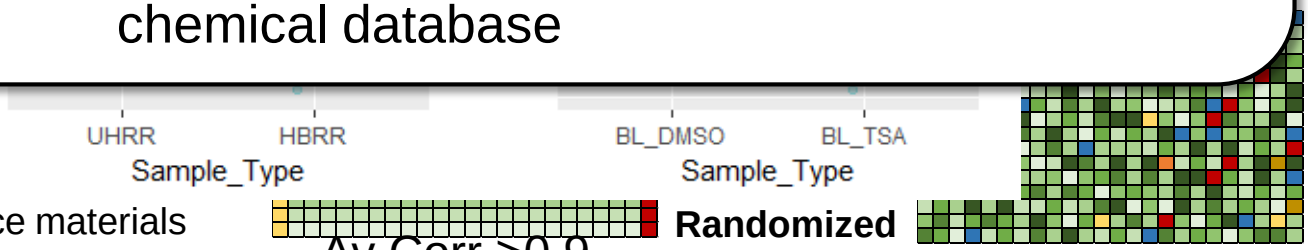
- Low cost, 384-well, cell lysate compatible
- Whole transcriptome
- Workflow integration of reference materials and controls, development of performance standards
- Portable platform/workflow for collaborative data generation



Reference RNAs Bulk Lysates

- Completed first large scale screen of 2,200 chemicals (ToxCast I/II/III) in single cell type
- Additional screens across multiple cell types/lines
- Tox21 cross-partner project to add reference chemical database

- characterized
- Concentration resp
- Parallel imaging/cy
- RNA and lysate reference materials
- Positive and negative controls

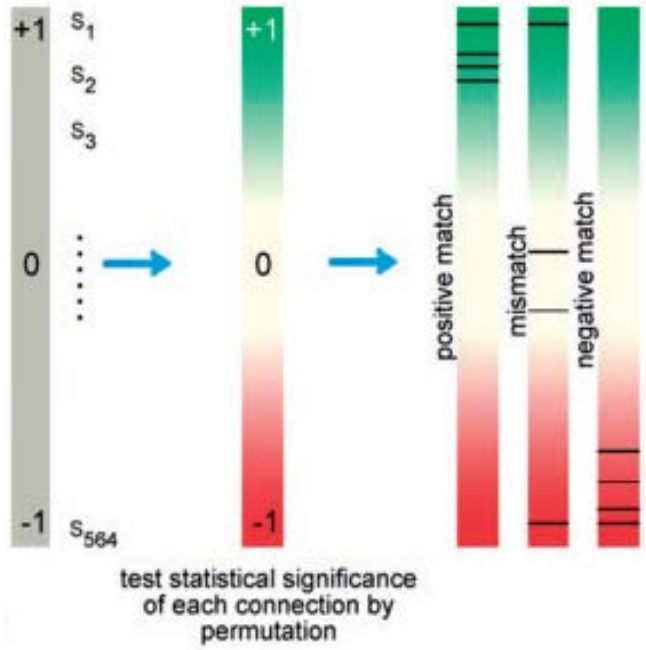


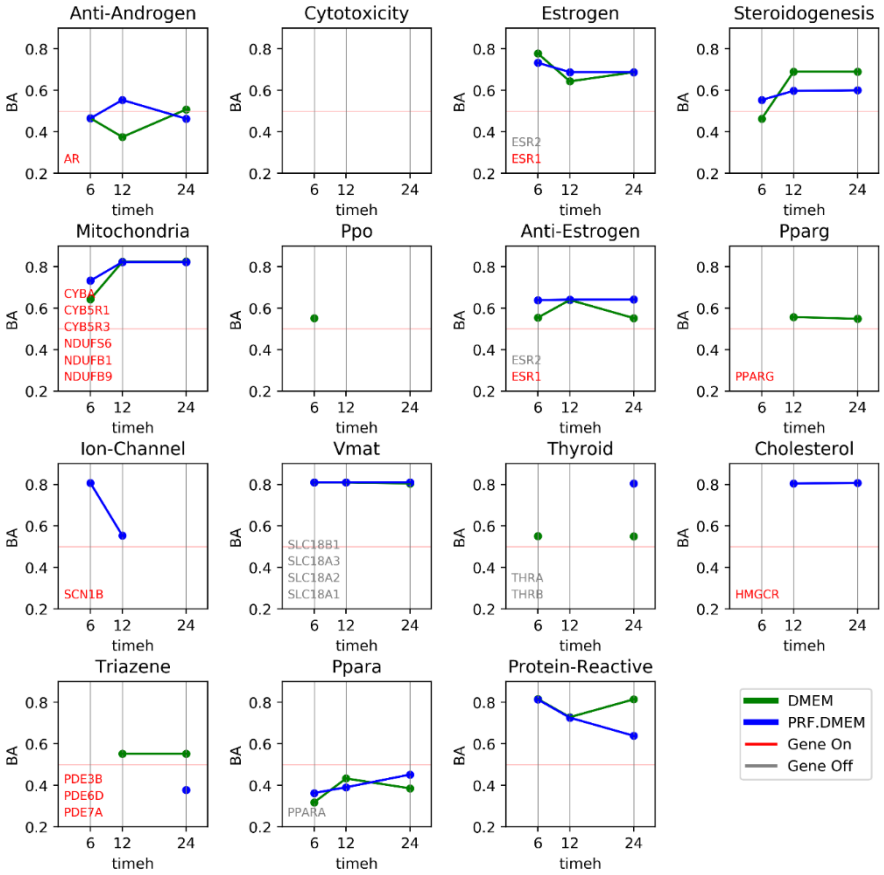
Josh Harrill, Unpublished

Developing a High-Throughput Transcriptomic Toolbox

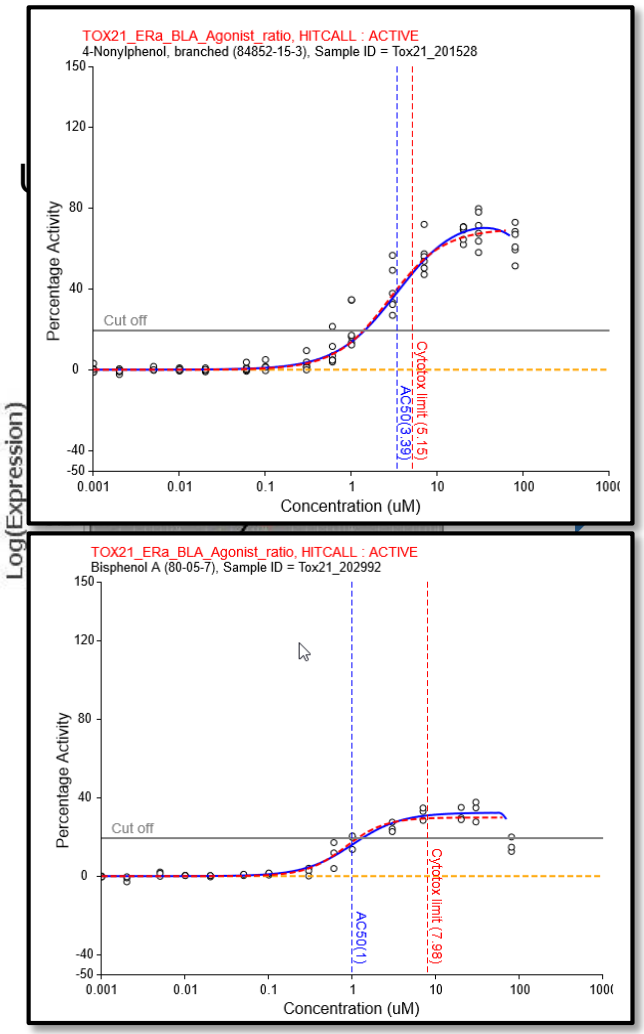
United States Environmental Protection Agency

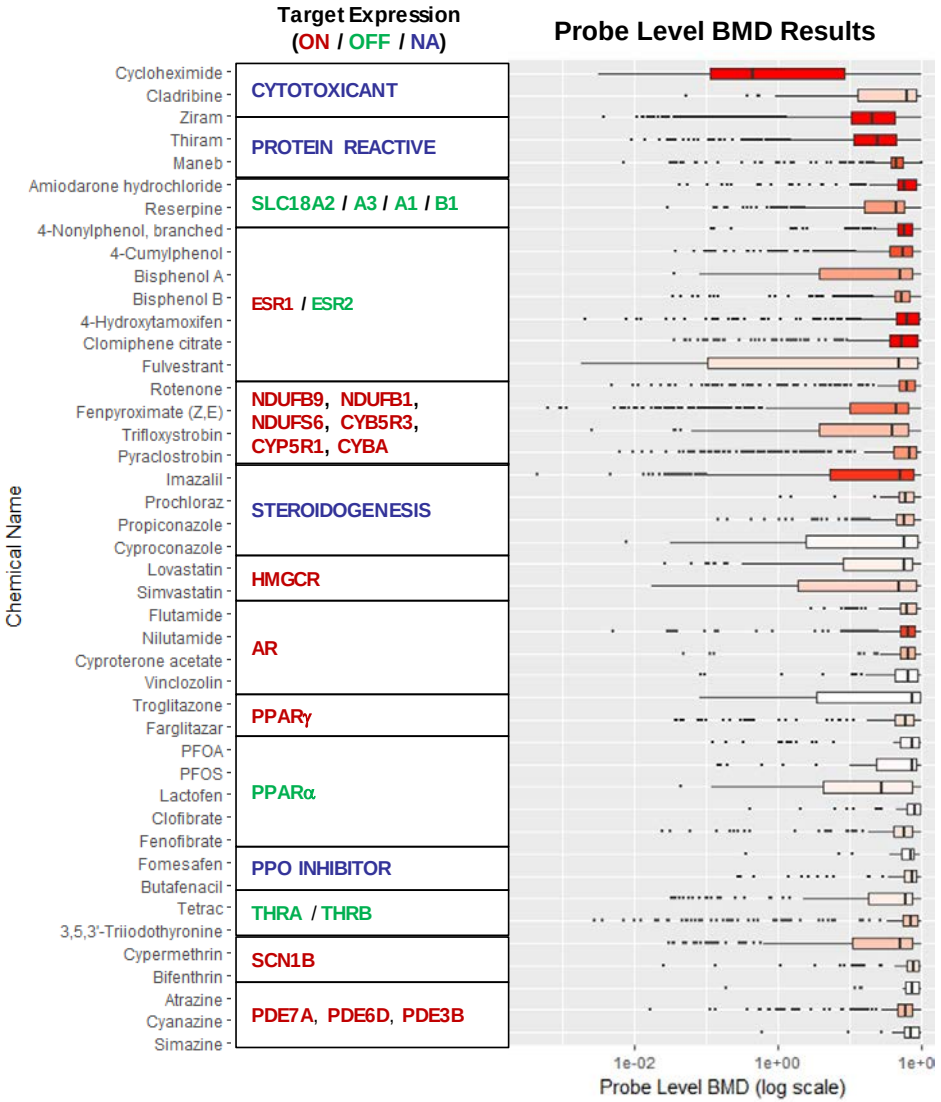
Using Connectivity Map to Identify Potential MOAs/MIEs



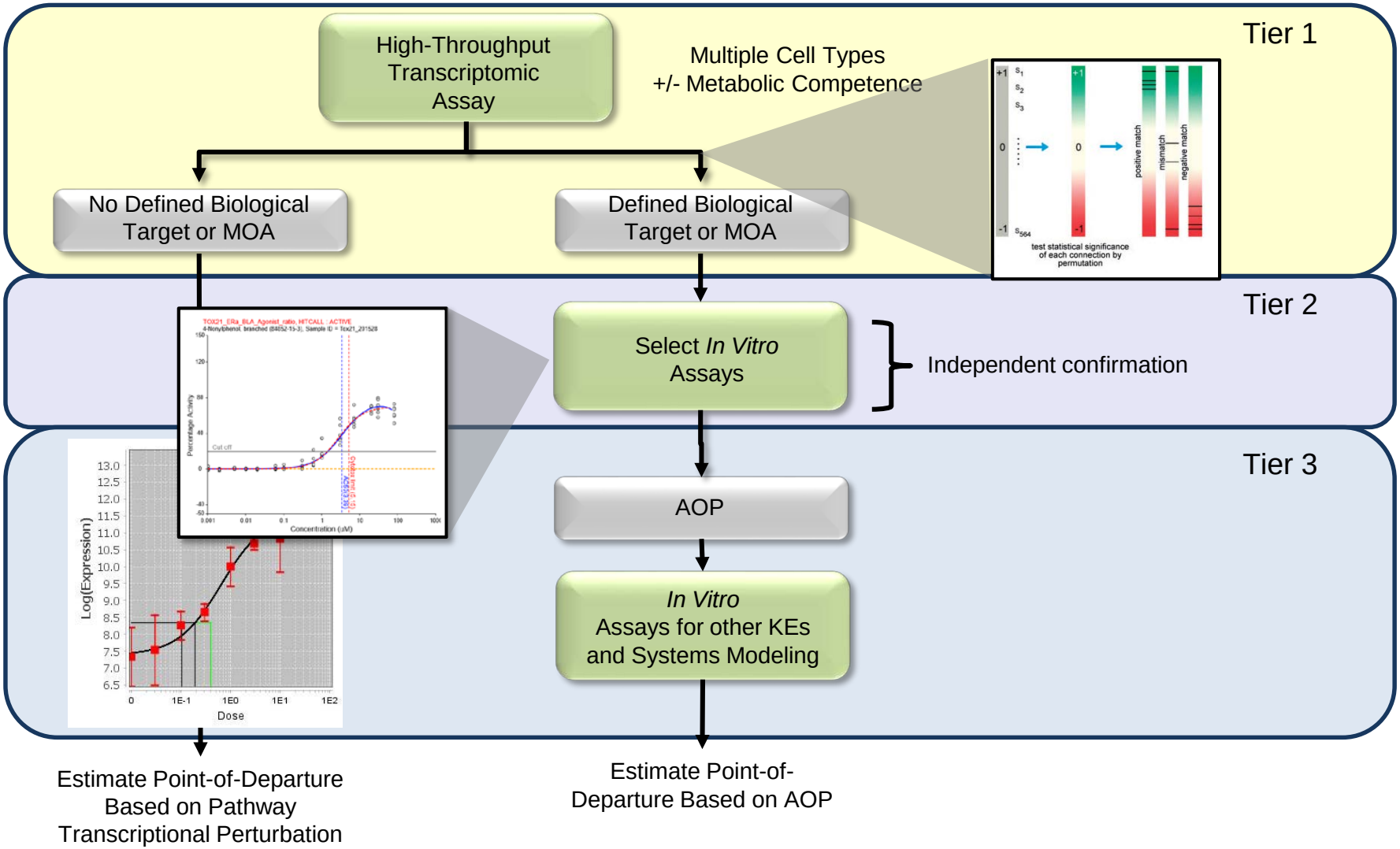


Developing a High-Throughput Transcriptomic Toolbox

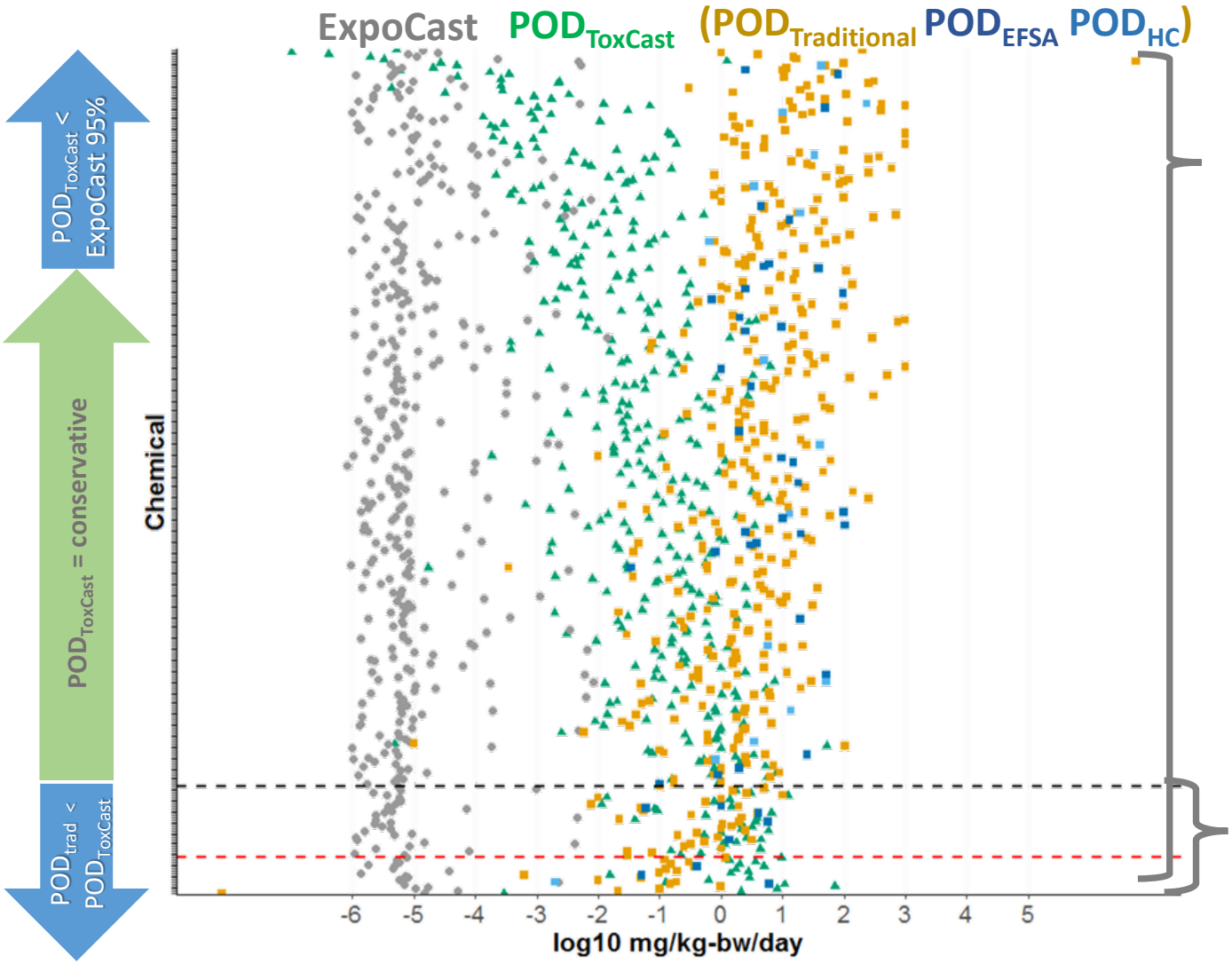




Integrating Components Into a Tiered Testing and Assessment Strategy



Bioactivity Provides a Conservative Estimate of a NOAEL/LOAEL



Total =

380 chemicals

httk, ToxCast data, and POD value(s) currently available

For ~91.3% of the chemicals, $POD_{ToxCast}$ was conservative.

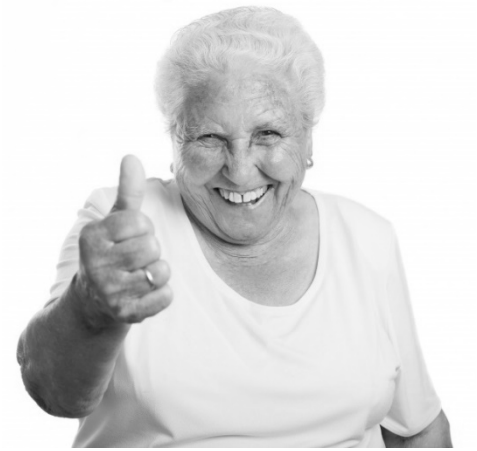
(~130-fold with human HTTK

~40-fold with rat HTTK)

Missing an important component of biology?

Take Home Messages…

Grandma Approved



https://www.freepik.com/free-photo/senior-woman-with-a-thumbs-up_1014676.htm

- Using advances from the genome revolution to broadly capture chemical perturbations in biological pathways and processes
- High-throughput transcriptomic platform is being designed to include performance standards and as a portable platform/ workflow for collaborative data generation
- Integrating bioinformatic tools to identify potential MOAs/MIEs and potency estimates
- The new transcriptomic platform is part of a larger tiered testing strategy for priority setting an other risk-based decisions

Acknowledgements and Questions

Tox21 Colleagues:
- NTP
- FDA
- NCATS

EPA Colleagues:
- NERL
- NHEERL
- NCEA

Collaborative Partners:
- Unilever
- A*STAR
- ECHA
- EFSA
- Health Canada

EPA's National Center for Computational Toxicology