NIEHS Update

Tox21: A U.S. Federal Collaboration to Improve the Human Hazard Characterization of Chemicals

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Formation of the U.S. Tox21 Community

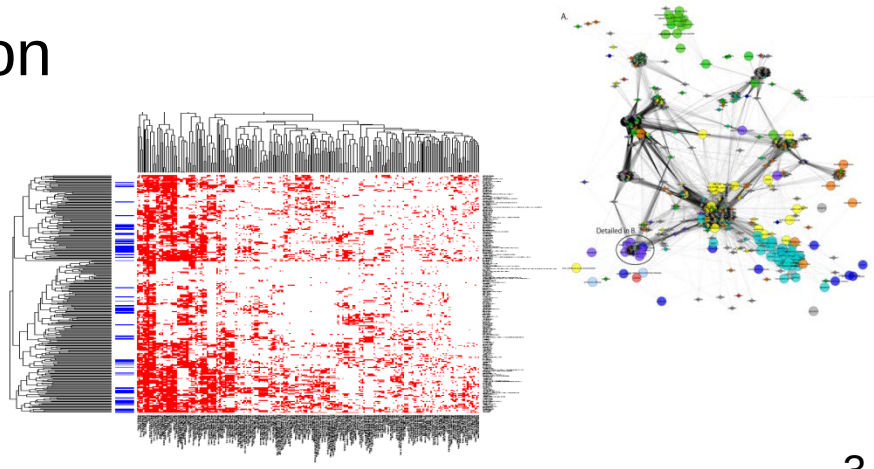
- 5-year Memorandum of Understanding (MoU) on "High-Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings" released on Feb 14, 2008 signed by NHGRI (F.S. Collins), NIEHS/NTP (S.H. Wilson), and EPA (G.M. Gray).

- Revised 5-year MoU to add FDA signed on July 19, 2010 http://ntp.niehs.nih.gov/go/28213) by NHGRI (E.D. Green), NIEHS/NTP (L.S. Birnbaum), EPA (P.T. Anastas), and FDA (J. Woodcock).

- Known informally as Tox21 for Toxicology in the 21st Century

Tox21 Goals

- Identify patterns of compound-induced biological response in order to:
  - Characterize toxicity/disease pathways
  - Facilitate cross-species extrapolation
  - Model low-dose extrapolation
- Prioritize compounds for more extensive toxicological evaluation
- Develop predictive models for biological response in humans



Tox21 Quantitative High Throughput Screening

Phase I - Proof of Principle (2005-2010)

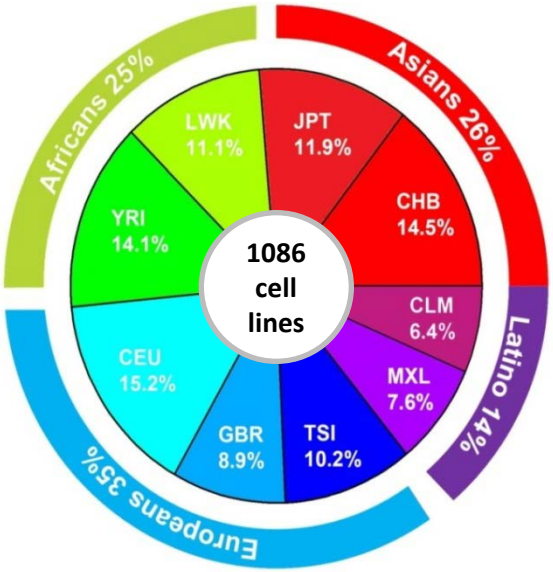
- NCGC screened 1408 compounds (1353 unique) from NTP and 1462 compounds (1384 unique, includes ToxCast Phase I compounds) from EPA at 15 concentrations in 140 qHTS assays representing 77 predominantly cell-based reporter gene endpoints.
  - Data made public via PubChem (http://pubchem.ncbi.nlm.nih.gov/) and CEBS (Chemical Effects in Biological Systems; http://www.niehs.nih.gov/research/resources/databases/cebs/)

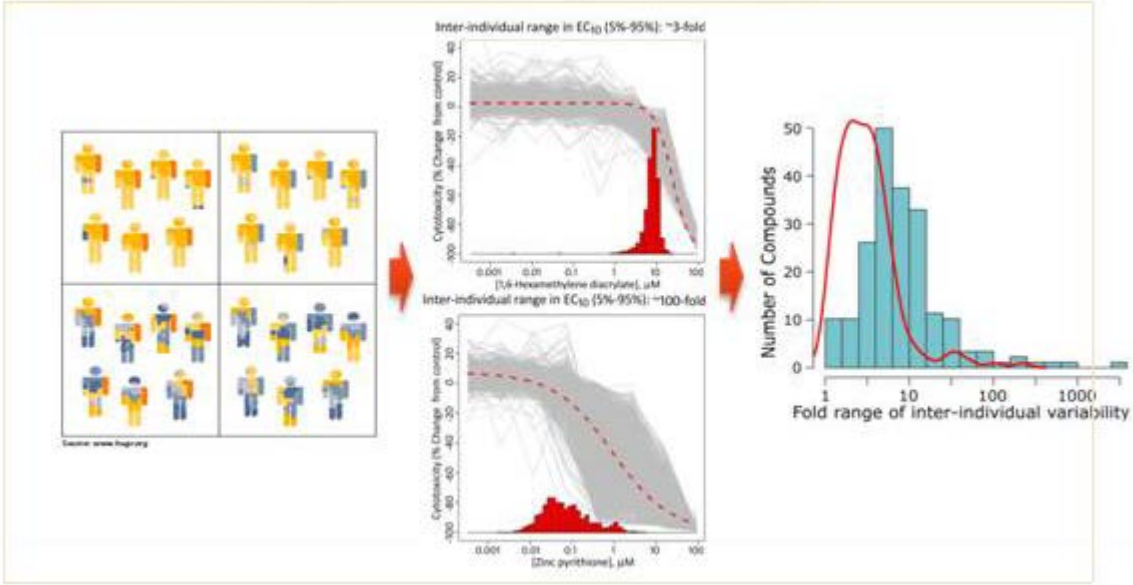
Phase II – Expanded Compound Screening (2010-2014)

- 10K compound library screened 3 x at 15 concentrations in qHTS assays that focused on:
  - Nuclear receptor activation or inhibition
  - Induction of cellular stress response pathways
  - Data released in PubChem (88 entries to date at https://www.ncbi.nlm.nih.gov/pcassay?term=tox21)
- The 1000 genomes project

The 1000 Genomes qHTS Toxicity Screening Project

Population-wide study design (Collaboration with I. Rusyn at UNC-CH)





1086 Human lymphoblastoid cell lines representing 9 racial groups

179 compounds **(9 duplicates)**

8 concentrations (0.33 nM - 92 µM)

1-3 plate replicates

1 assay (CellTiterGLO® - ATP production)

= ~2,400,000 data points + 2-5x10^6 SNPs

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

National Institute of Environmental Health Sciences

National Center for Advancing Translational Sciences

NIEHS-NCATS-UNC DREAM *Toxicogenetics Challenge*

(June 10 – September 16, 2013)

Sage BIONETWORKS

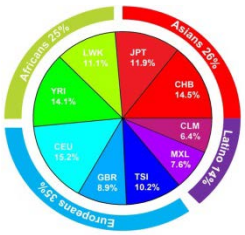
Goal: Use crowdsourcing to better predict the toxicity of chemicals

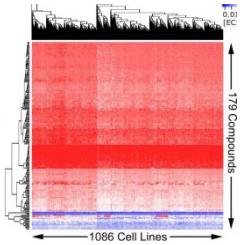
(1) Use the biological data (SNPs, basal gene expression) to develop a model that accurately predicts ***individual responses*** to compound exposure

(2) Use the intrinsic chemical properties to develop a model that accurately predicts how a particular ***population*** will respond to ***certain types of chemicals***

How it works:

Data set: genomic, cytotoxicity and chemical properties data from ~1000 cell lines and ~200 chemicals



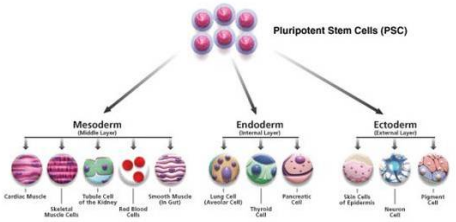


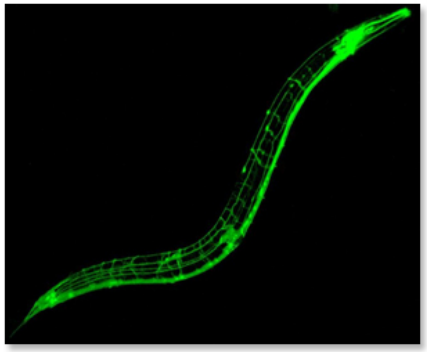
Subchallenge 1: 34 teams submitted 99 prediction models
Subchallenge 2: 24 teams submitted 85 prediction models

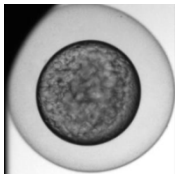
Winner: Quantitative Biomedical Research Center
(UT Southwestern Medical Center, Dallas, TX)

Tox21 Phase III – Improving on Biological Coverage and Relevance (2013 - ?)

- Focus on more physiologically-relevant *in vitro* cell systems (e.g., human stem cell derived differentiated cell populations).
- Include cell types (e.g., HepaRG in 2D and 3D models) that incorporate xenobiotic metabolism/allow for longer-term exposures.
- Increase the use of computational models to predict metabolism/toxicity.
- Increase the testing of compounds in alternative animal models.
- Develop and implement a high throughput transcriptomics platform for human, rat, mouse, zebrafish, and *C. elegans.*







5 days