



**NTP**  
National Toxicology Program



# The Tox21 Community – A U.S. Interagency Shared Vision and Coordinated Strategy

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- 2004 - NTP publishes a Vision and Roadmap for Toxicology in the 21<sup>st</sup> Century
  - NCGC founded
- 2005 - NTP and NCGC began HTS collaboration
  - EPA's NCCT established
- 2006 - NCGC begins qHTS testing with NTP 1408 compounds
  - EPA joins collaboration with 1462 compounds
- 2007 - EPA ToxCast™ Program started
  - NAS publishes *Toxicology in the 21<sup>st</sup> Century* -
- 2008 - Tox21 collaboration formally established**
- 2009 - ToxCast™ Phase I completed (320 compounds/>500 assays)
  - NCGC completes testing of >2800 compounds in >70 qHTS studies (e.g., cytotoxicity, apoptosis, 10 nuclear receptors)



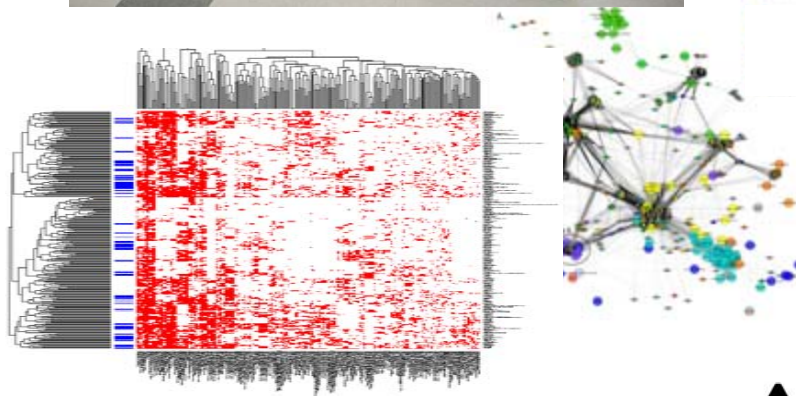
# Tox21 Community

- Memorandum of Understanding on “High-Throughput Screening, Toxicity Pathway Profiling and Biological Interpretation of Findings” (<http://ntp.niehs.nih.gov/go/28213>)
  - Signed February 14, 2008 by NIEHS, NHGRI, EPA
  - Status made publicly available through monthly meetings of the EPA CPCP (Chemical Prioritization Community of Practice)
- Leverage
  - Builds on existing expertise
  - Avoids the need to create a new administrative and support structure
  - By pooling resources, overcomes the resource limitations of a single agency



## Tox21 Goals

- Prioritize chemicals for more extensive toxicological evaluation
- Identify mechanisms of chemically-induced biological activity
  - characterize toxicity pathways
  - facilitate cross-species extrapolation
  - provide input to models for low-dose extrapolation
- Develop predictive models for biological response in humans





# Tox21 Working Groups

- **Pathways/Assays**

K. Houck (EPA), K. Witt (NTP), M. Xia (NCGC)

- **Compounds**

A. Richard (EPA), N. Southall (NCGC), C. Smith (NTP)

- **Bioinformatics**

R. Huang (NCGC), R. Judson (EPA), K. Shockley (NTP)

- **Targeted Testing**

J. Bucher (NTP), S. Edwards (EPA), J. Inglese (NCGC)



- Expand the current NCGC library of 2800 compounds to 10000 QC compounds (including ~3000 drugs), develop water-based and mixture compound libraries
- Identify and test main library in 100+ assays that assess “toxicity” pathways involved in human disease (e.g., Gohlke et al., 2009)
- Explore new platforms for HTS and HCS (high content screening) that use primary human cells and incorporate organ-specific metabolism
- Evaluate human and rodent genetic variability in response to toxicants
- Initiate ToxCast™ Phase II with >750 compounds and >400 assays
- Make all data publicly accessible and easily mineable (EPA ACToR, NTP CEBS, NLM PubChem)
- Expand the Tox21 community nationally and internationally



# Issues

- When is a “toxic” pathway excessively perturbed?
- How do we test for affects that are associated with chronic exposure conditions?
- How do we incorporate ADME into *in vitro* approaches?
- How do we account for compound, pathway, and cell-to-cell interactions?
- What is the standard for obtaining “fingerprints” - lab animal test data or human experience?
- What needs to be accomplished in order for this approach to be used for making regulatory decisions?