NTP
National Toxicology Program

Toxicology Testing: Perspective on How We Got Here
(NTP Centric View)

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Scientific Advisory Committee on Alternative Toxicological Methods
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Outline

- An historical perspective
  - Rodent cancer bioassay
  - Attempts to replace
- ICCVAM
  - 3Rs for many endpoints
- NTP Roadmap/ NRC Tox in 21st Century
  - Mechanism-based approaches
- Next steps- today's discussion
  - Scientific and technical
  - Social, political, regulatory, other


Nixon Signs $1.6 Billion Cancer Bill, Names Man to Head Fight

WASHINGTON (UPI)—President Nixon today signed into law a $1.6 billion program to find a cure for [illegible] the act was "a milestone in the long and difficult effort to find the cure and cures of cancer. While [illegible]

The Rodent Cancer Bioassay- A highly abridged history

- Original Intent
  - Screening assay
  - Confirm results by epidemiology

- Expansion for Risk Assessment
  - 2 doses plus control- high and low, to assure survival
  - 3 or more doses - provide a shape to the dose response curve
- Significant change in predictive expectation
  - From yes/no (dynamics) to,
  - yes/no and kinetics, meaning-
  - assumption of comparable sensitivity

The Rodent Cancer Bioassay- Attempted replacement

- Four widely used in vitro assays for genetic toxicity
  - Mutagenesis in Salmonella and mouse lymphoma cells
  - Chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells
- Compared to cancer bioassay findings from 83 studies
  - One test better than others, or combinations improve performance?
- Concordance of each assay ~ 60%,
  - No evidence of complementarity
  - Missed opportunity to recognize value
    - *Tennant et al. (1987) Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays, Science, 236:933-941.*

The Rodent Cancer Bioassay- A highly abridged history

- Transgenic mouse models
  - Shorten studies and use fewer animals
  - Used rudimentary mechanistic information, p53, Hras
  - Yes/no, but hopes for comparable sensitivity
  - Genetic background affected response
  - Missed known human carcinogens

- *Pritchard et al (2003) The role of transgenic mouse models in carcinogen identification Environ. Health Perspect. 111:444-454*.

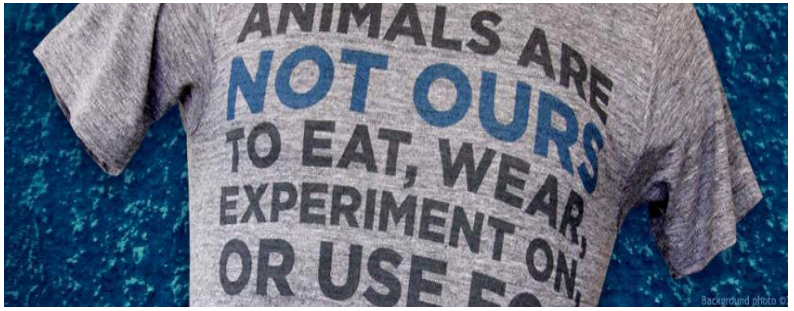
The Diversity Outbred mouse - reality check

- Diversity outbred (J:DO) male mice
- Exposure levels: 0, 1, 10, 100 ppm benzene, 28 days, 6 hr/day
- 600 mice total: 2 separate cohorts to assess reproducibility
- Endpoints for hematotoxicity and genetic damage
  - % reticulocytes and micronucleated reticulocytes in bone marrow and blood
- Variation in response was 9 fold greater than in isogenic B6C3Fi hybrid mice
- Calculated BMD was an ~ order of magnitude lower
- Associated with variable expression of sulfotransferase detoxification enzymes
- Who are we protecting?

ICCVAM- NICEATM- ICATM

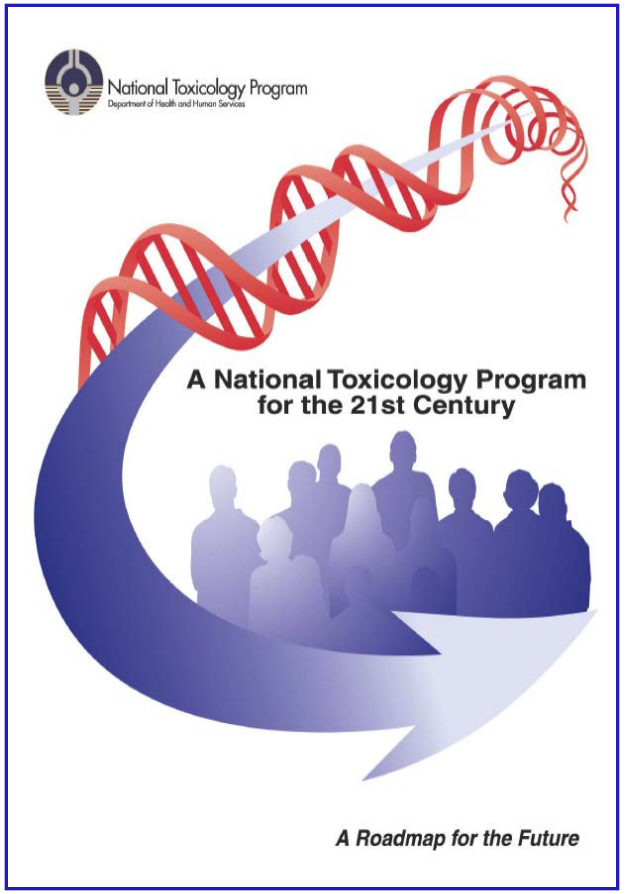
- 1997- 2000 authorization- 2016

- Acute Dermal Systemic Toxicity
- Acute Oral Systemic Toxicity
- Acute Inhalation Toxicity
- Biologics Testing
- Dermal Corrosivity and Irritation
- Dermal Phototoxicity
- Ecotoxicity
- Endocrine Disruptors
- Genetic Toxicity
- Immunotoxicity: Allergic Contact Dermatitis
- Ocular Corrosivity and Irritation
- Pyrogen Testing
- Reproductive and Developmental Toxicity



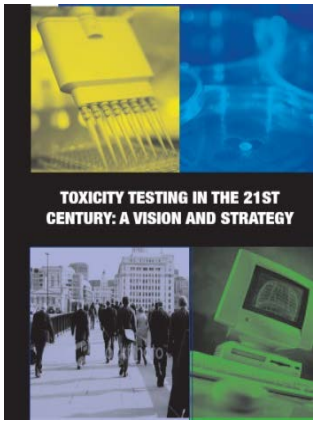
NTP Roadmap- 2004

- Review and refine traditional toxicology assays
- Develop rapid, mechanism-based screens for environmentally induced toxicity and disease
- Improve the utility of NTP products for public health decisions



The Tox21 Community - Origins……

This 2007 National Academy of Science report envisions a not-so-distant future in which virtually all routine toxicity testing would be conducted *in vitro* in human cells or cell lines by evaluating perturbations of cellular responses in a suite of toxicity pathway assays using high throughput robotic assisted methodologies.



Memorandum of Understanding: "High-Throughput Screening, Toxicity Pathway Profiling and Biological Interpretation of Findings"

- Signed February 14, 2008, as an agreement between:
  - National Institute of Environmental Health Sciences/National Toxicology Program
  - NIH National Human Genome Research Institute/ Chemical Genomics Center (now NCATS)
  - US Environmental Protection Agency/ Office of Research and Development

The Tox21 Community

Tox21

NIEHS
National Institute of Environmental Health Sciences

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

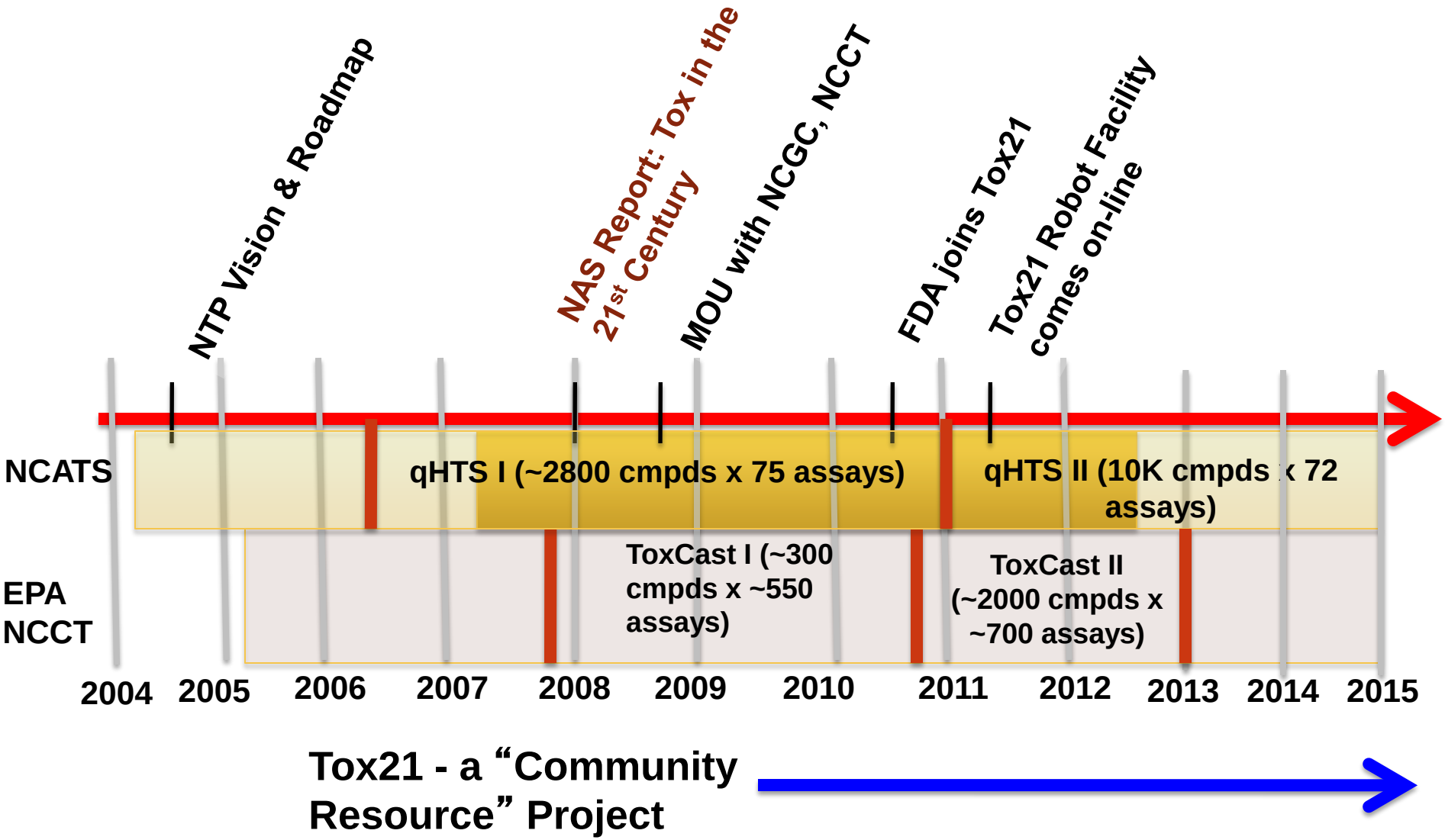
NIH National Center for Advancing Translational Sciences

NCGC
NIH Chemical Genomics Center

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
COMPUTATIONAL TOXICOLOGY

FDA U.S. FOOD & DRUG ADMINISTRATION

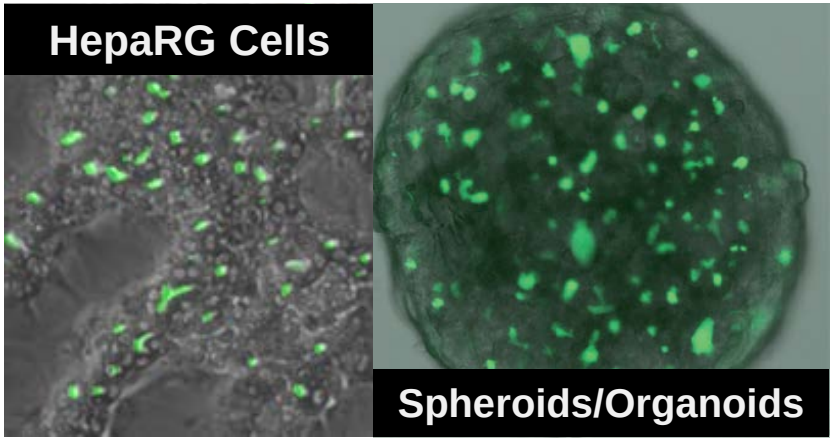
The Tox21 timeline

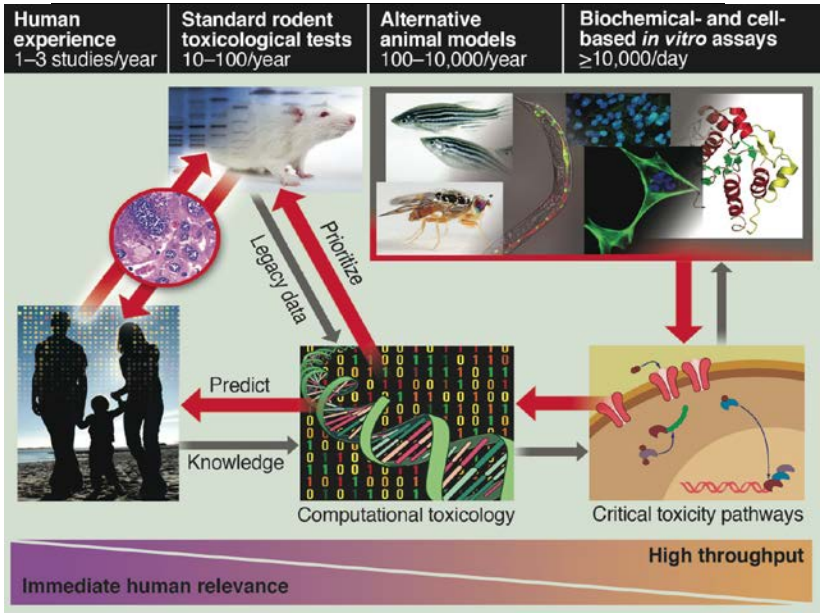


Tox21 - a "Community Resource" Project

Tox21 Phase III – Improving biological coverage

- Develop more physiologically-relevant in vitro models and assays
- Incorporate xenobiotic metabolism & longer-term exposures
- Increase use of in silico models (e.g. xenobiotic metabolism, toxicity)
- Integrate data-rich transcriptomic assessments into routine screening
- Assess Adverse Outcome Pathways as an organizing principle
- Develop in vivo/in vitro kinetic models
- Expand collaborations and interactions
- Identify technical *<u>and other obstacles</u>* to greater use and utility





Questions?