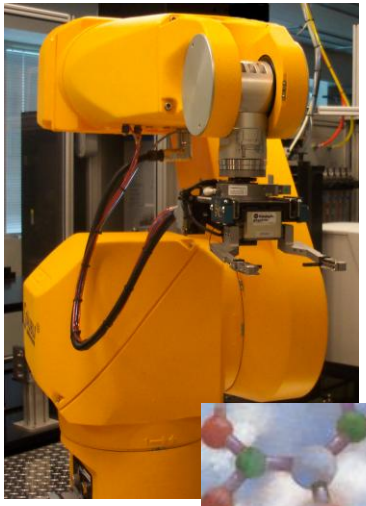
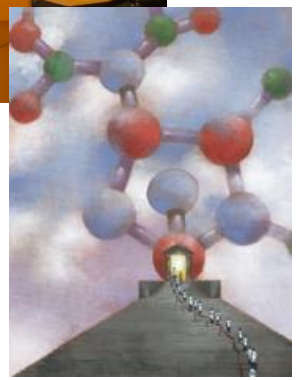
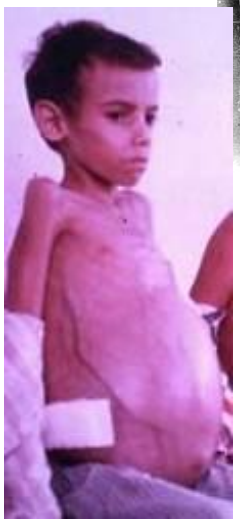




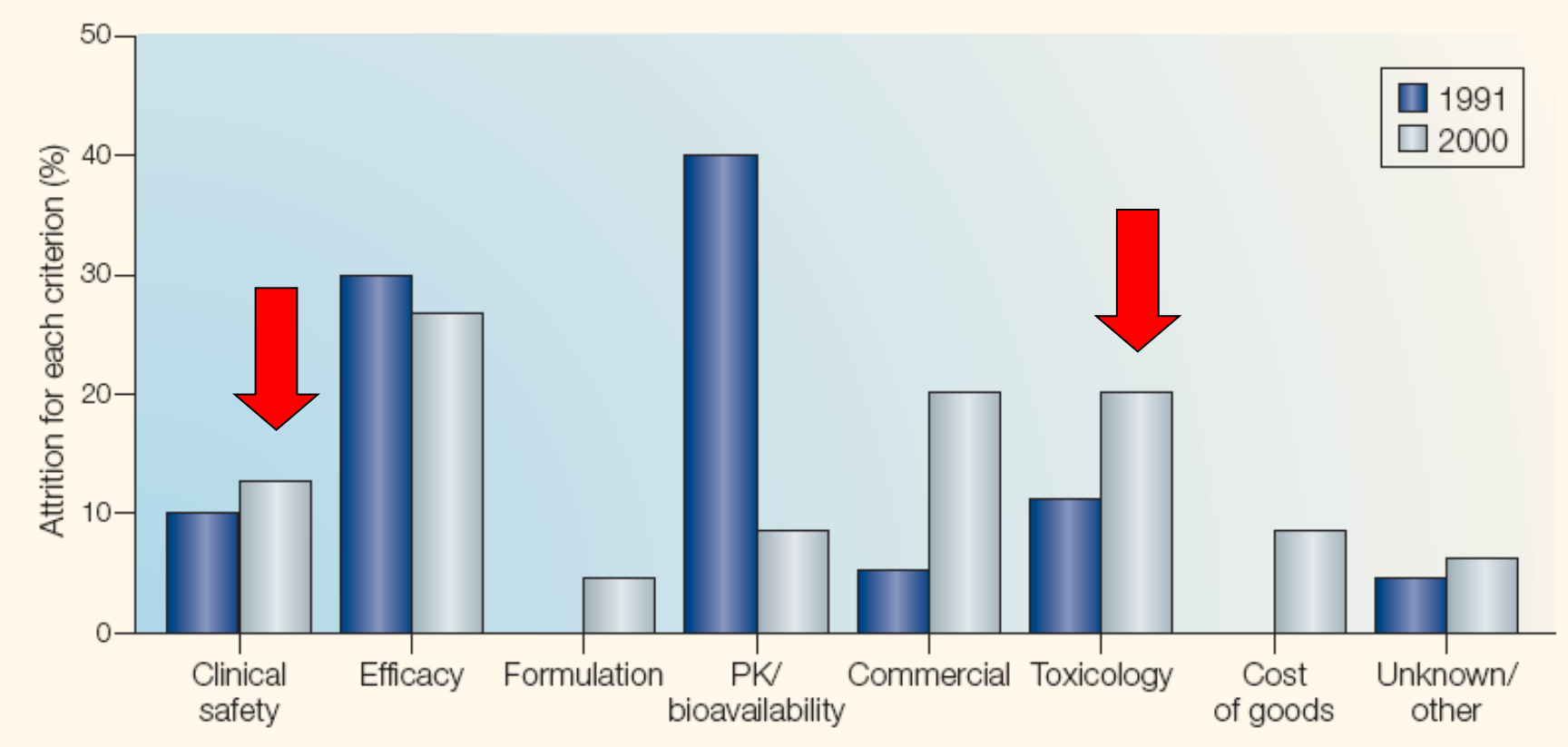
Development and Validation of New Technologies in Drug Discovery and Toxicology



Christopher P. Austin, M.D.
Director, Division of Preclinical Innovation
National Center for Advancing Translational Sciences
National Institutes of Health

AIMBE/NIH Summit on Validation and Qualification of New In Vitro Tools
March 19, 2012

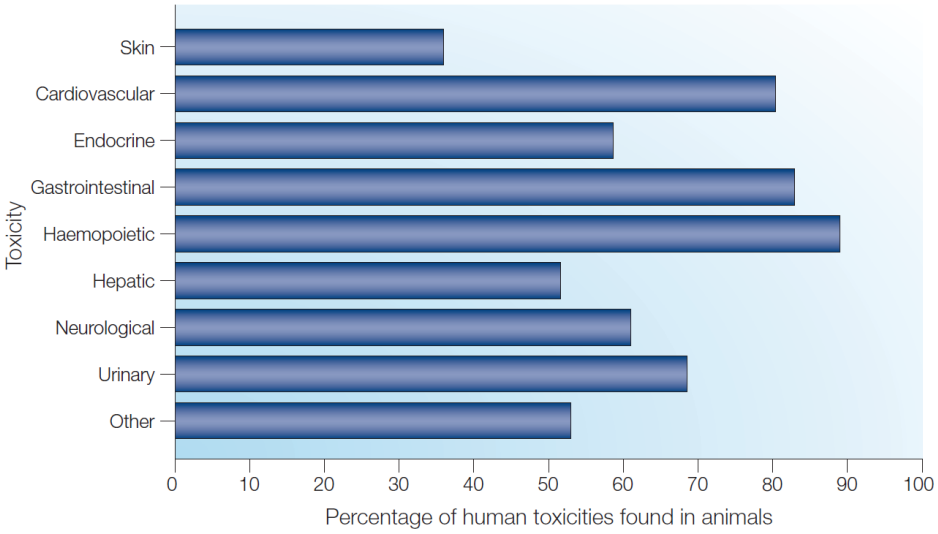
Toxicity is the Most Common Reason for Drug Development Failure

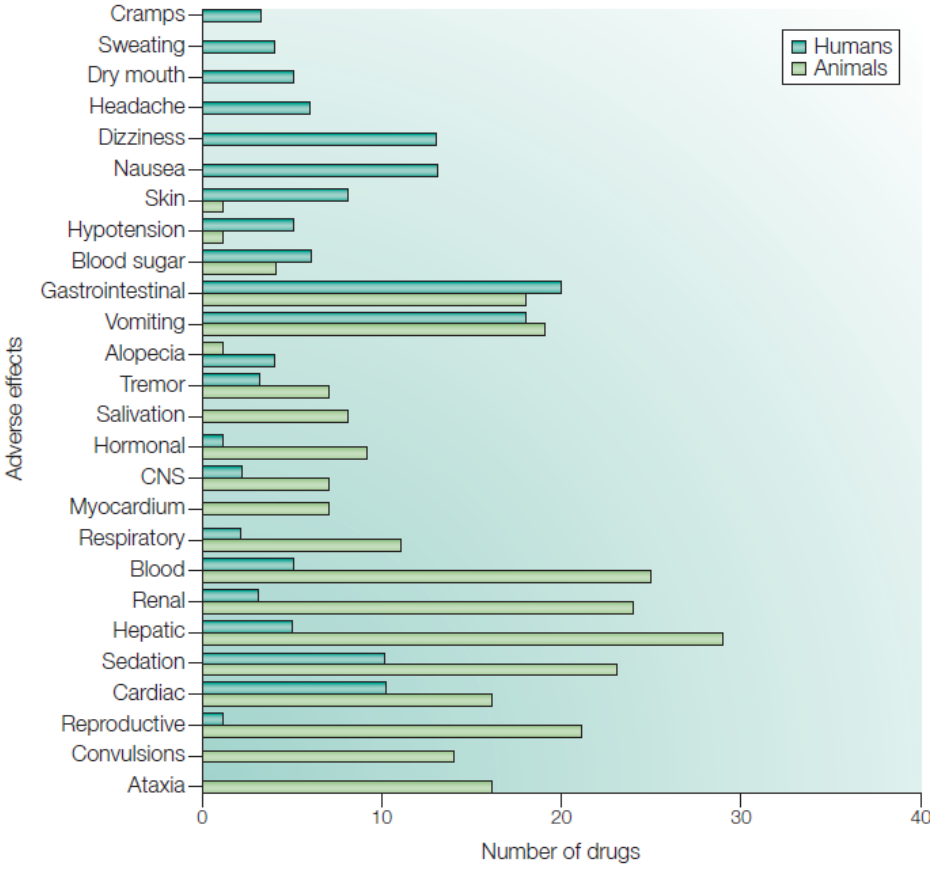


Preclinical (21%) + Clinical (12%) Tox = 33% of all failures

Kola and Landis, *Nature Reviews Drug Discovery* 3, 711-716, 2004.

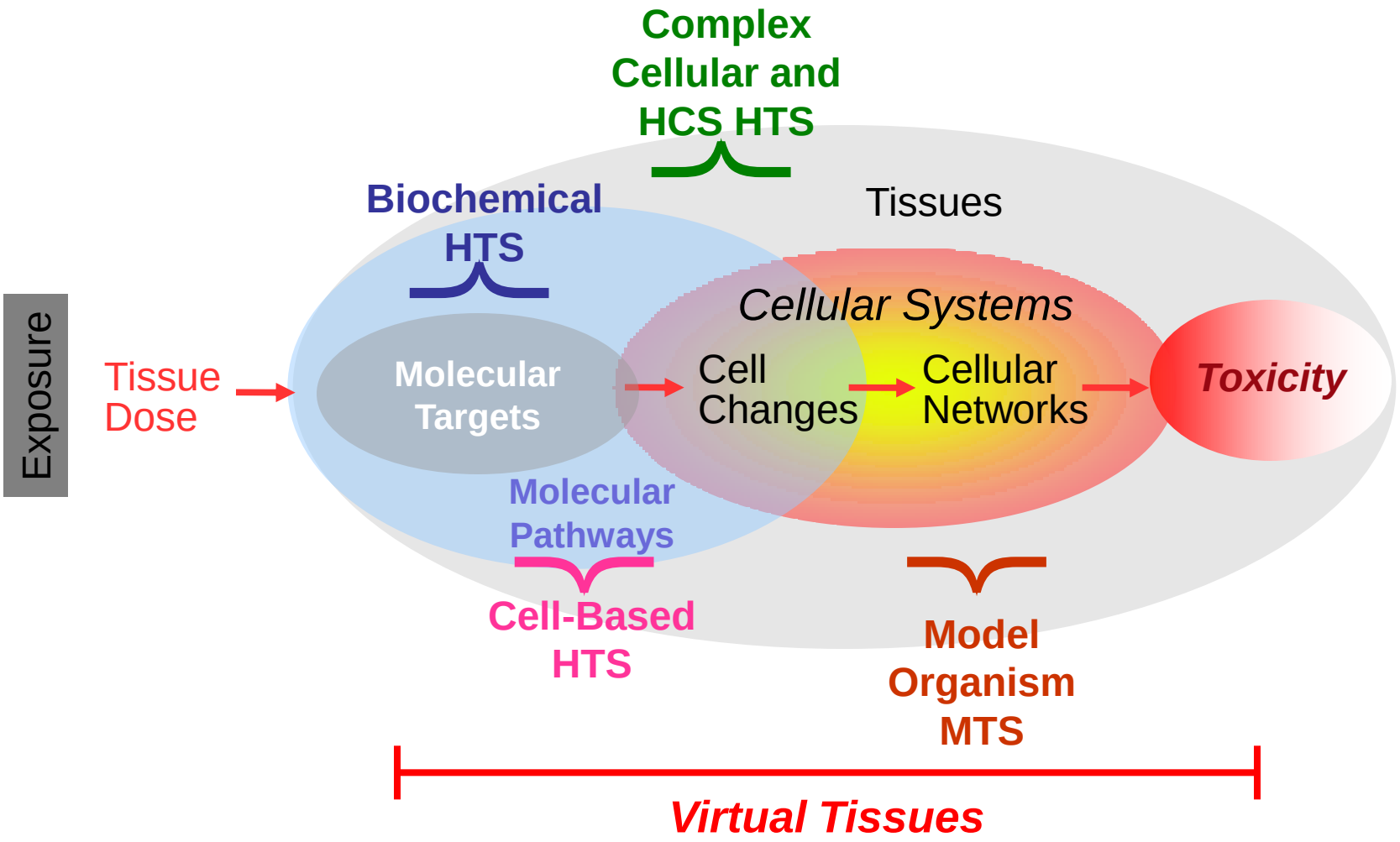
Poor concordance of human and animal drug toxicities



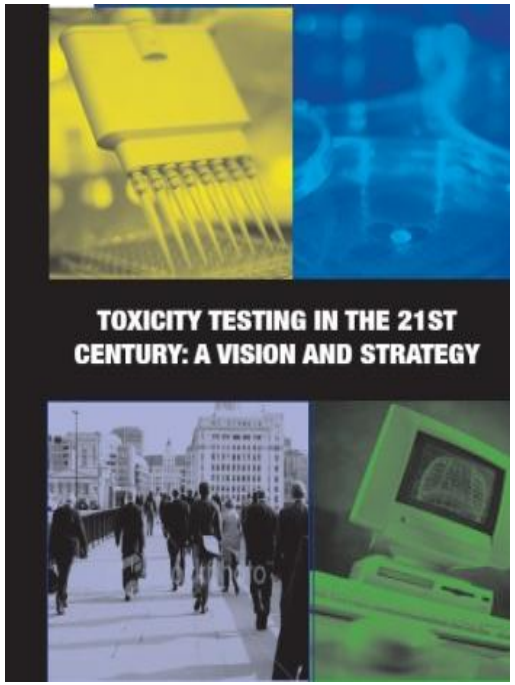


Greaves P, Williams A, Eve M. *Nat Rev Drug Disc* 3:226, 2004

Grand Challenge: Predicting Toxicity



NAS "Toxicology in the 21st Century"



"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."

TOXICOLOGY

Transforming Environmental Health Protection

We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments.

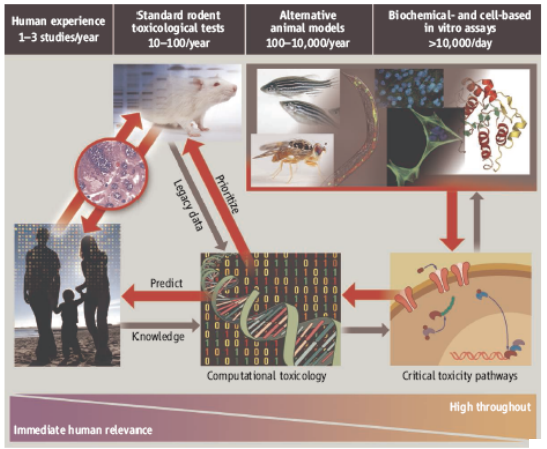
Francis S. Collins,*† George M. Gray,‡* John R. Bucher§*

In 2005, the U.S. Environmental Protection Agency (EPA), with support from the U.S. National Toxicology Program (NTP), funded a project at the National Research Council (NRC) to develop a long-range vision for toxicity testing and a strategic plan for implementing that vision. Both agencies wanted future toxicity testing and assessment paradigms to meet evolving regulatory needs. Challenges include the large numbers of substances that need to be tested and how to incorporate recent advances in molecular toxicology, computational sciences, and information technology; to rely increasingly on human as opposed to animal data; and to offer increased efficiency in design and costs (*1*–*5*). In response, the NRC Committee on Toxicity Testing and Assessment of Environmental Agents produced two reports that reviewed current toxicity testing, identified key issues, and developed a vision and implementation strategy to create a major shift in the assessment of chemical hazard and risk (*6*, *7*). Although the NRC reports have laid out a solid theoretical rationale, comprehensive and rigorously gathered data (and comparisons with historical animal data) will determine whether the hypothesized improvements will be realized in practice. For this purpose, NTP, EPA, and the National Institutes of Health Chemical Genomics Center (NCGC) (organizations with expertise in experimental toxicology, computational toxicology, and high-throughput technologies, respectively) have established a collaborative research program.

EPA, NCGC, and NTP Joint Activities

In 2004, the NTP released its vision and roadmap for the 21st century (*1*), which established initiatives to integrate high-throughput screening (HTS) and other automated screening assays into its testing program. In 2005, the EPA established the National Center for Computational Toxicology (NCCT). Through these initiatives, NTP and EPA, with the NCGC, are promoting the evolution of toxicology from a predominantly observational science at the level of disease-specific models in vivo to a predominantly predictive science focused on broad inclusion of target-specific, mechanism-based, biological observations in vitro (*1*, *4*) (see figure, below).

Toxicity pathways. In vitro and in vivo tools are being used to identify cellular responses after chemical exposure expected to result in adverse health effects (*7*). HTS methods are a primary means of discovery for drug development, and screening of >100,000 compounds per day is routine (*8*). However, drug-discovery HTS methods traditionally test compounds at one concentration, usually between 2 and 10 μM, and tolerate high false-negative rates. In contrast, in the EPA, NCGC, and NTP combined effort, all compounds are tested at as many as 15 concentrations, generally ranging from ~5 nM to ~100 μM, to generate a concentration-response curve (*9*). This approach is highly reproducible, produces significantly lower false-positive and false-negative rates than the traditional HTS methods (*9*), and facilitates multiassay comparisons. Finally, an informatics platform has been built to compare results among HTS screens; this is being expanded to allow comparisons with historical toxicologic NTP and EPA data (http://ncgc.nih.gov/pub/openhts). HTS data collected by EPA and NTP, as well as by the NCGC and other Molecular Libraries Initiative centers (http://mli.nih.gov/), are being made publicly available through Web-based databases [e.g., PubChem (http://pubchem.ncbi.nlm.nih.gov)]. In addition,



Transforming toxicology. The studies we propose will test whether high-throughput and computational to icology approaches can yield data predictive of results from animal toxicity studies, will allow prioritizatic of chemicals for further testing, and can assist in prediction of risk to humans.

[1]Director, National Human Genome Research Institute (NHGRI), National Institutes of Health, Bethesda, MD 20892; [2]Assistant Administrator for the Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460; [3]Associate Director, U.S. National Toxicology Program, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC 27709, USA.

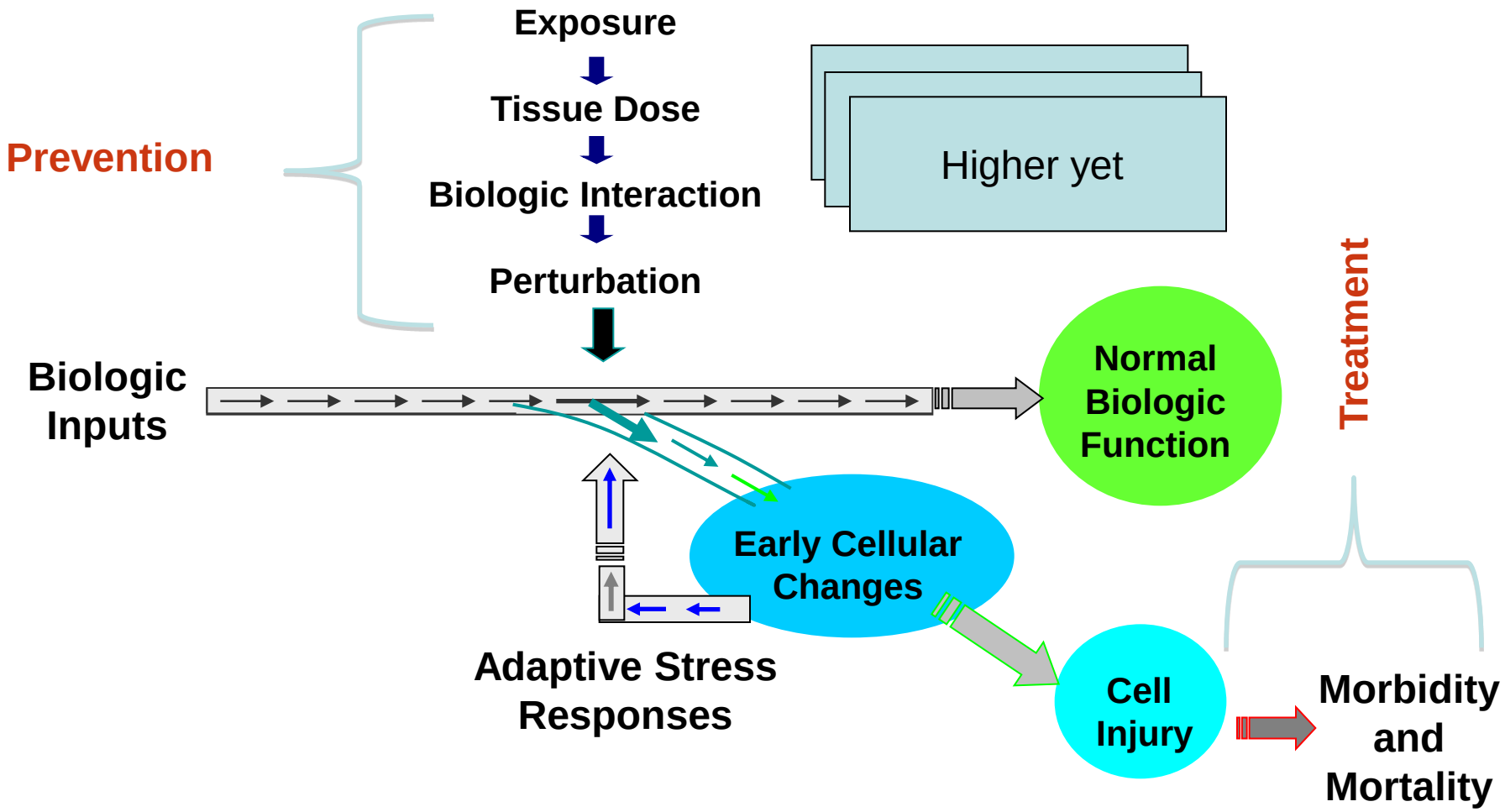
*The views expressed here are those of the individual authors and do not necessarily reflect the views and policies of their respective agencies.

†Author for correspondence. E-mail: francisc@mail.nih.gov

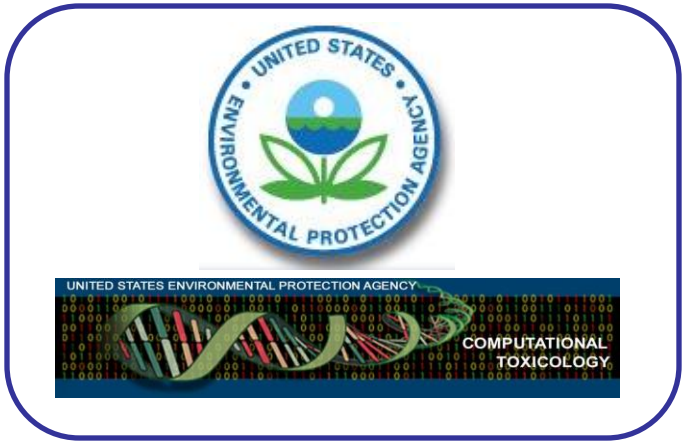
Tox21

Activation of a Toxicity Pathway

NAS Report, 2007



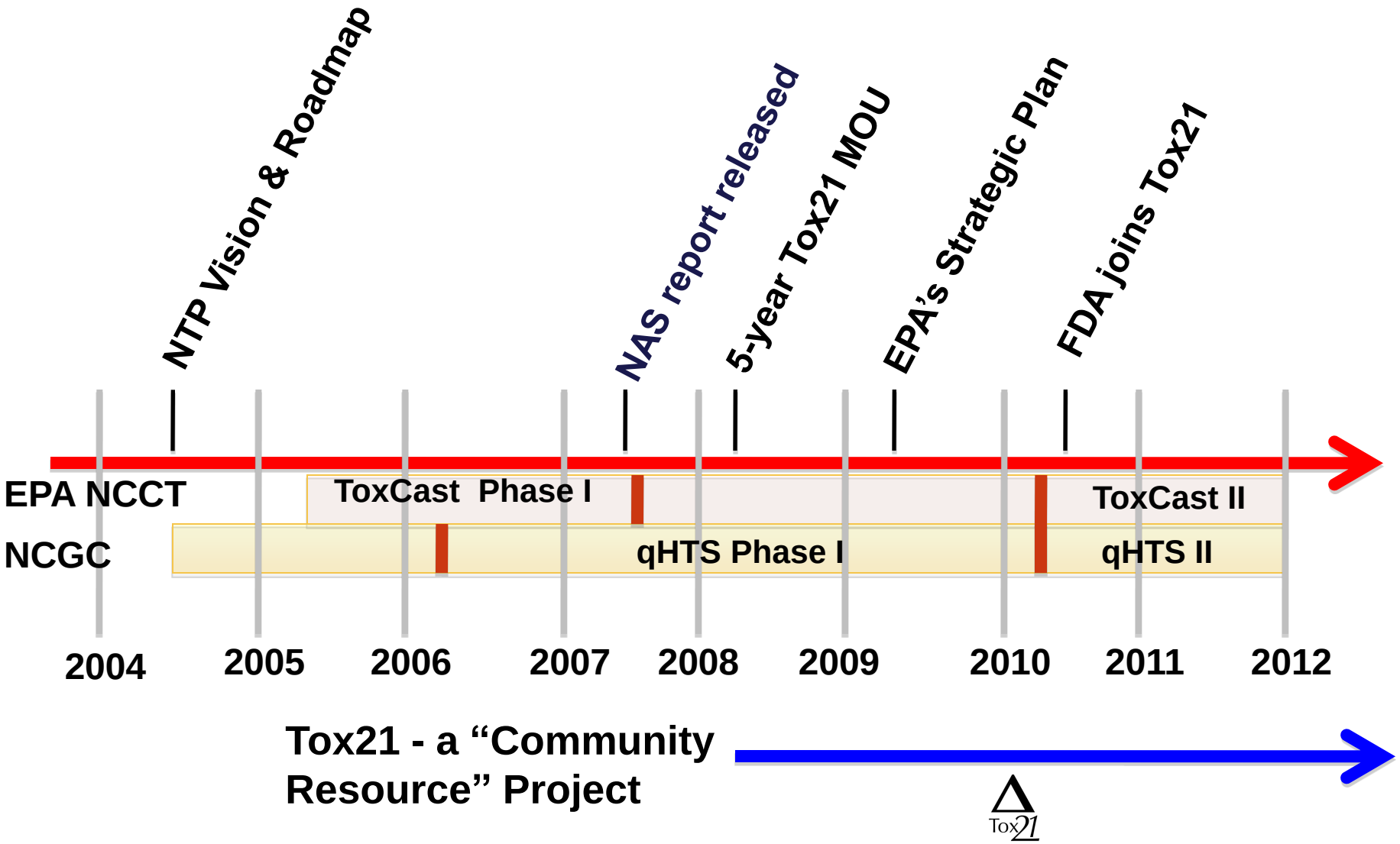
The Tox21 Community



NIH Chemical Genomics Center

National Institutes of Health
NATIONAL CENTER FOR ADVANCING
TRANSLATIONAL SCIENCES

Tox21 Timeline



Tox21 Partners have Complementary Expertises

Areas of Expertise	NIEHS/NTP	NCGC	EPA	FDA
Experimental Toxicology	✓		✓	✓
Human Toxicology				✓
qHTS		✓		
Epigenetics	✓	✓		
Low to Mid Throughput Assays	✓	✓	✓	✓
Lower Organism Systems	*C. elegans*		Zebrafish	Zebrafish/ *C. elegans*
In Vitro 3-D Model Systems	✓		✓	✓
Genetic Variability in Response	✓	✓		
Computational Toxicology	✓	✓	✓	✓
Human Exposure Assessment	✓		✓	
Validation Experience	✓		✓	✓

Operational Structure

Agency Points of Contact

Christopher Austin, M.D. (NCGC)
Tom Colatsky Ph.D. (FDA)
Robert Kavlock, Ph.D. (EPA)
Raymond Tice, Ph.D. (NTP)

Assays & Pathways Working Group

Co-Chairs
Kevin Gaido, Ph.D. (FDA)
Keith Houck, Ph.D. (EPA)
Kristine Witt, M.S. (NTP)
Menghang Xia, Ph.D. (NCGC)

- Identify toxicity pathways & corresponding assays
- Review nominated assays
- Prioritize assays for qHTS

Chemical Selection Working Group

Co-Chairs
William Leister, Ph.D. (NCGC)
Donna Mendrick, Ph.D. (FDA)
Ann Richard, Ph.D. (EPA)
Cynthia Smith, Ph.D. (NTP)

- Establish a 10K DMSO soluble compound library for qHTS
- Establish QC procedures
- Establish libraries of mixtures and aqueous soluble compounds for qHTS

Informatics Working Group

Co-Chairs
Ruili Huang, Ph.D. (NCGC)
Richard Judson, Ph.D. (EPA)
Jennifer Fostel, Ph.D. (NIEHS)
Weida Tong, Ph.D. (FDA)

- Characterize assay output and evaluate assay performance
- Develop prioritization schemes and prediction models
- Make all data publicly accessible via CEBS, PubChem, ACToR

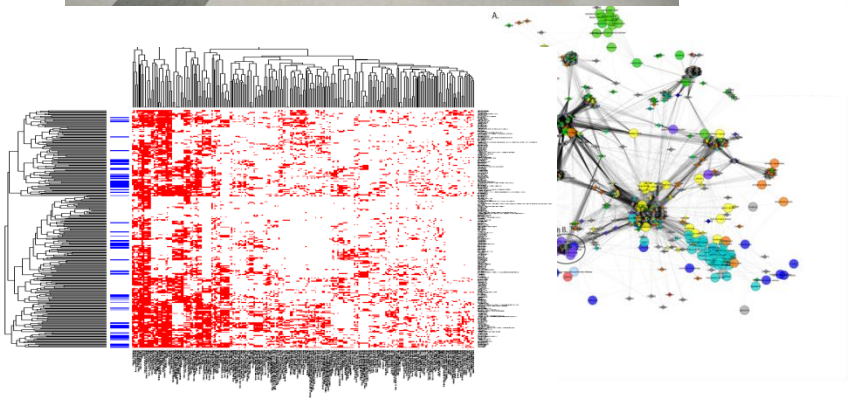
Targeted Testing Working Group

Co-Chairs
R. Daniel Benz, Ph.D. (FDA)
Kevin Crofton, Ph.D. (EPA)
Michael DeVito, Ph.D. (NTP)
David Gerhold, Ph.D. (NCGC)

- Evaluate the relevance of prioritization schemes and prediction models
- Prioritize substances for more complex testing
- Extrapolate *in vitro* conc to *in vivo* dose

Tox21 Goals

- Identify mechanisms of compound-induced biological activity in order to:
  - characterize toxicity/disease pathways
  - facilitate cross-species extrapolation
  - provide input to models for low-dose extrapolation
- Prioritize compounds for more extensive toxicological evaluation
- Develop predictive models for biological response in humans



Tox21 Implementation Strategy

- Develop
  - infrastructure to (1) support basic and applied research needed to develop the tests and pathway models, and (2) make all data/results available to scientific community
  - comprehensive suite of *in vitro* tests, preferably based on human cells, cell lines, or components
  - targeted animal tests to complement *in vitro* tests
  - computational models of toxicity pathways to support application of *in vitro* test results in hazard characterization and risk assessment
  - appropriate validation of tests and test strategies
  - evidence justifying that toxicity-pathway approach is adequately predictive of adverse health outcomes to use in decision-making

Tox21 Phase I: Proof of Principle

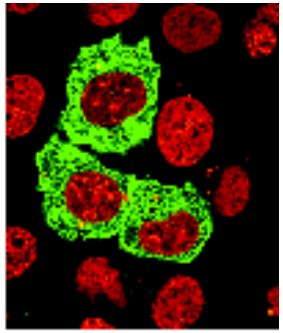
- NCGC screened 1408 compounds (1353 unique, 55 duplicates) from NTP and 1462 compounds (1384 unique, 78 duplicates) from EPA, with ~400 compound overlap in >100 qHTS assays.
- EPA via ToxCast™ screened 320 compounds (309 unique, 291 pesticide actives, 9 industrial, 56/73 proposed Tier 1 Endocrine Disruption Screening Program, 14 HPV, 11 HPV Challenge) in ~550 assays.
- Data released to the scientific community via:
  - EPA ACToR (Aggregated Computational Toxicology Resource; http://epa.gov/actor)
  - NLM PubChem (http://pubchem.ncbi.nlm.nih.gov/)
  - NTP CEBS (Chemical Effects in Biological Systems; http://www.niehs.nih.gov/research/resources/databases/cebs/index.cfm)

Range of screening assays performed

Extent of reductionism

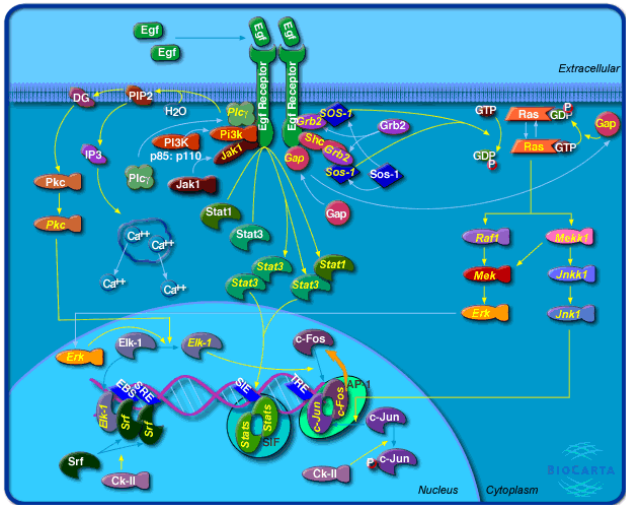
Phenotype

(Image-based HCS, GFP, etc)



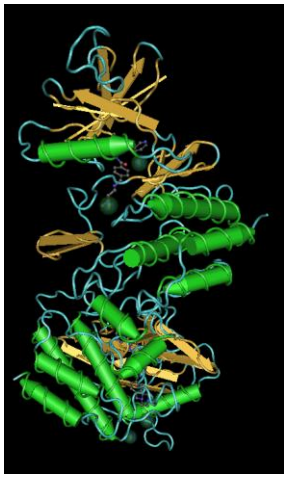
Pathway

(Reporters, e.g., luciferase, β-lactamase)



Protein

(Enzyme readouts, interactions, etc)



Quantitative High-Throughput Screening (qHTS)

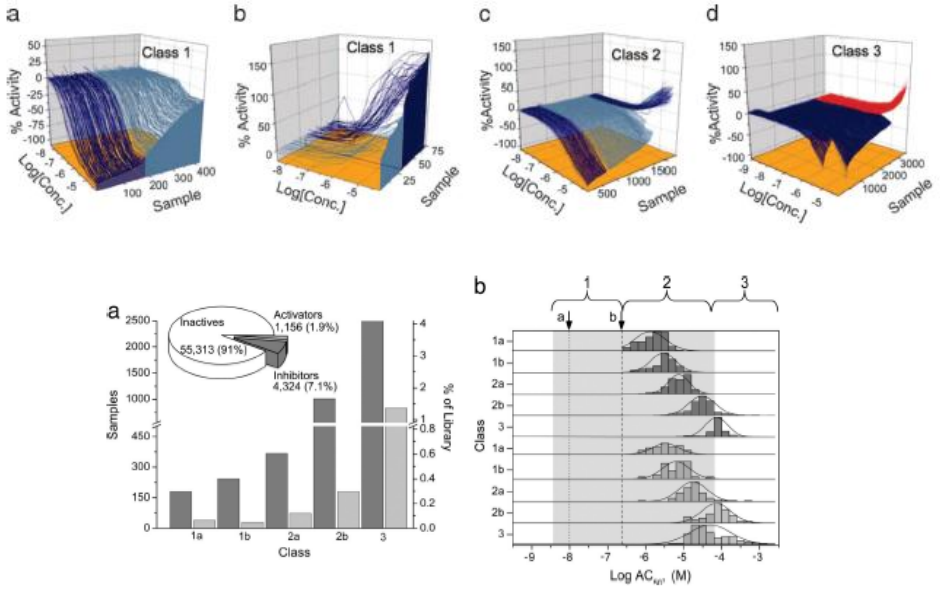
- Convhentional HTS done at single concentration
  - typically 10 μM
- qHTS assays compounds at multiple concentrations
  - Tox21 assays all screened at 15 concentrations
  - Range = 2 nM – 100 μM
  - 1536-well plate format, assay volume ~5 μL, ~1000 cells/well
  - Concentration-response curve generated for each compound from primary screen
- Produces robust ***activity profiles*** of all compounds
  - Dramatically reduced FP and FN
- Informatics pipeline for data processing, curve fitting & classification, extraction of SAR

Quantitative high-throughput screening: A titration-based approach that efficiently identifies biological activities in large chemical libraries

James Inglese*, Douglas S. Auld, Ajit Jadhav, Ronald L. Johnson, Anton Simeonov, Adam Yasgar, Wei Zheng, and Christopher P. Austin

NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892-3370

Communicated by Francis S. Collins, National Institutes of Health, Bethesda, MD, May 31, 2006 (received for review April 12, 2006)



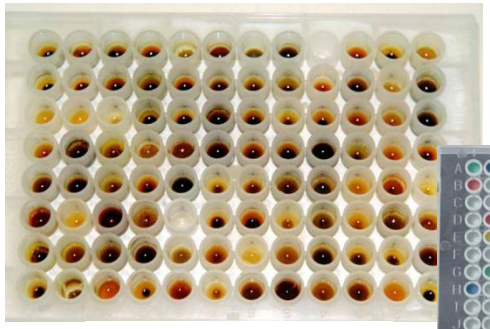
PNAS | August 1, 2006 | vol. 103 | no. 31 | 11473–11478

NIH Chemical Genomics Center

qHTS Screening Format

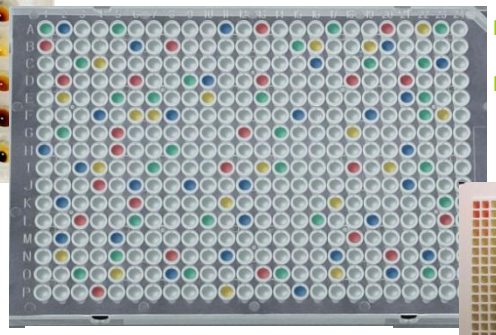
c

r



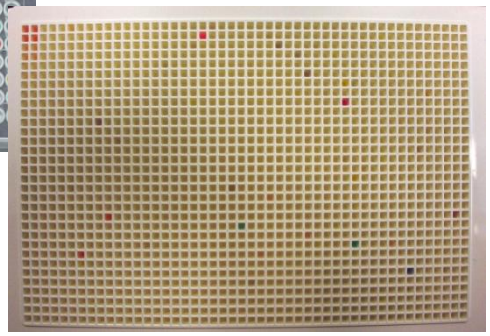
- 8 rows x 12 columns
- 88 test samples

96-well plate



- 16 rows x 32 columns
- 352 test samples

384-well plate
4 x 96-well plates



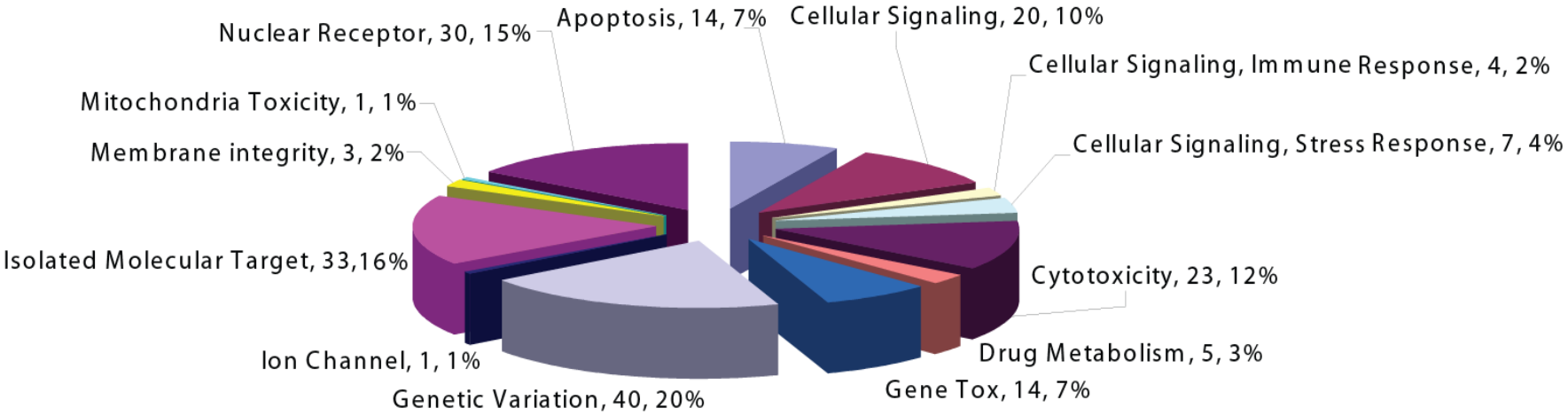
- 32 rows x 48 columns
- 1,408 test samples*

1536-well plate
16 x 96-well plates

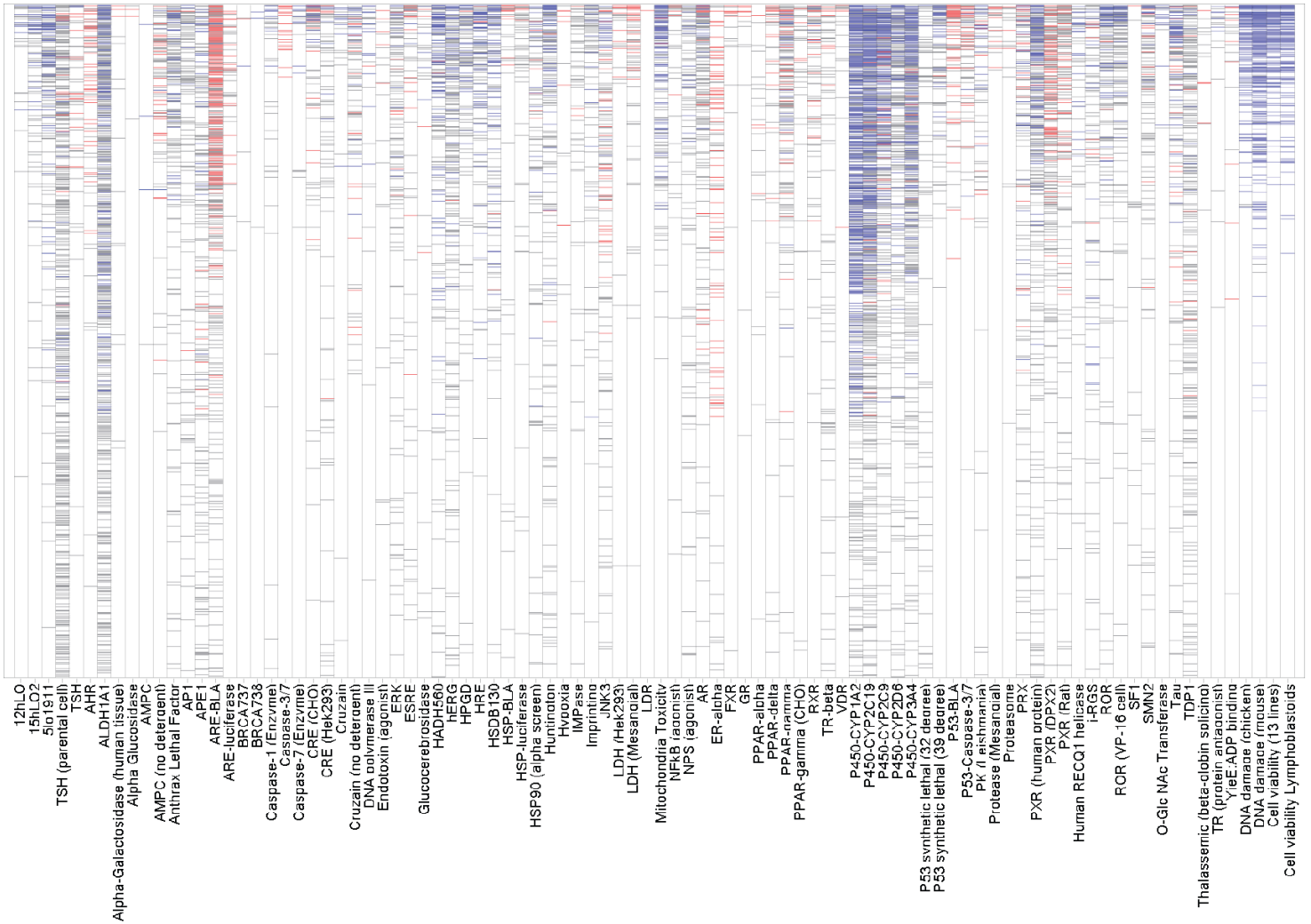
* wells remaining after subtraction of control wells; NCGC uses left 4 columns of 1536-well plate for controls

Phase I: NCGC qHTS Assays Screened

- Phenotypic readouts
  - Cytotoxicity
  - Apoptosis: caspase 3/7, 8, 9)
  - Membrane integrity: LDH, protease release
  - Mitochondrial toxicity (membrane potential)
  - Gene tox: p53, ELG1, DNA damage gene deficient lines (DT40 lines and mouse)
- Cell Signaling
  - Stress response: ARE, ESRE, HSP, Hypoxia, AP-1
  - Immune response: IL-8, TNFα, TTP
  - Other: AP-1, CRE, ERK, HRE, JNK3, NFkB, LDR
- Drug metabolism
  - CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4
- Target specific assays
  - Nuclear receptors: AR, AhR, ERα, FXR, GR, LXR, PPARα, PPARδ, PPARγ, PXR, RXR, TRβ, VDR, RORα, RORγ
  - hERG channel
  - Isolated molecular targets: 12hLO, 15hLO1, 15hLO2, ALDH1A1, HADH560, HPGD, HSD17b4, α-Glucosidase, α-Galactosidase, Glucocerebrosidase, APE1, TDP1, DNA polymerase III, RECQ1 helicase, RGS4, BRCA, IMPase, O-Glc NAc Transferase, Caspase-1/7, CBFβ-RUNX1, PK, Tau, Cruzain, β-Lactamase, PRX, YjeE , NPS, Proteasome, SF1, SMN2, beta-globin splicing, Anthrax Lethal Factor, TSHR
- Genetic variation: 87 HapMap lines

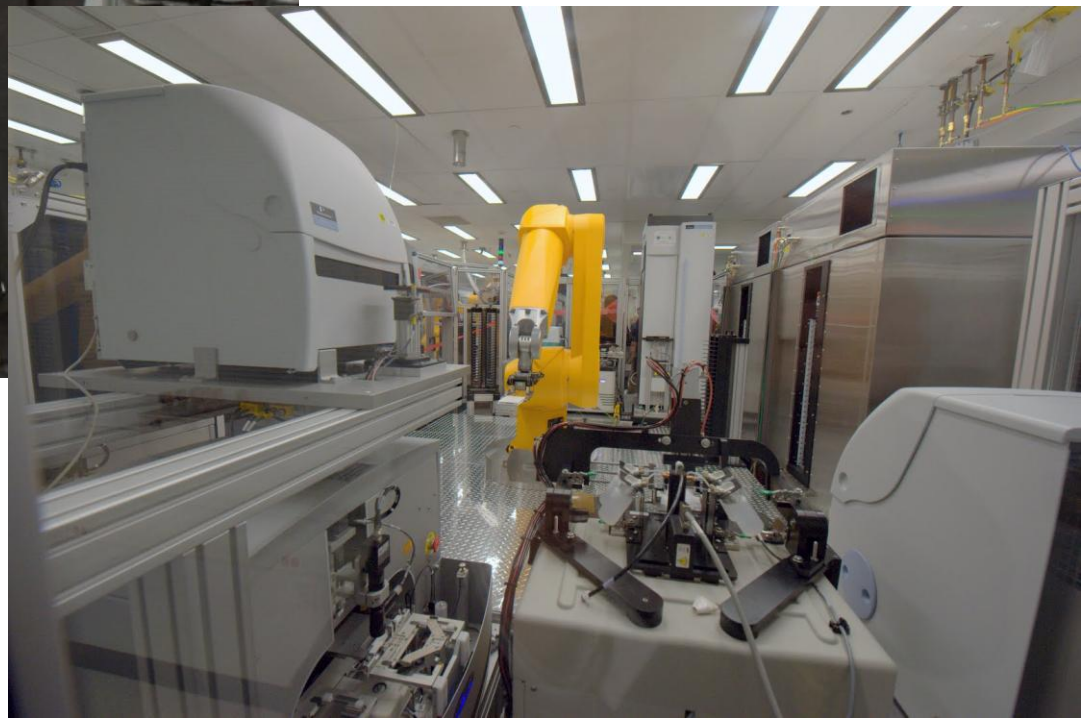


Phase I qHTS Compound Activity Profile



Compounds screened: NTP-1408 and EPA-1462

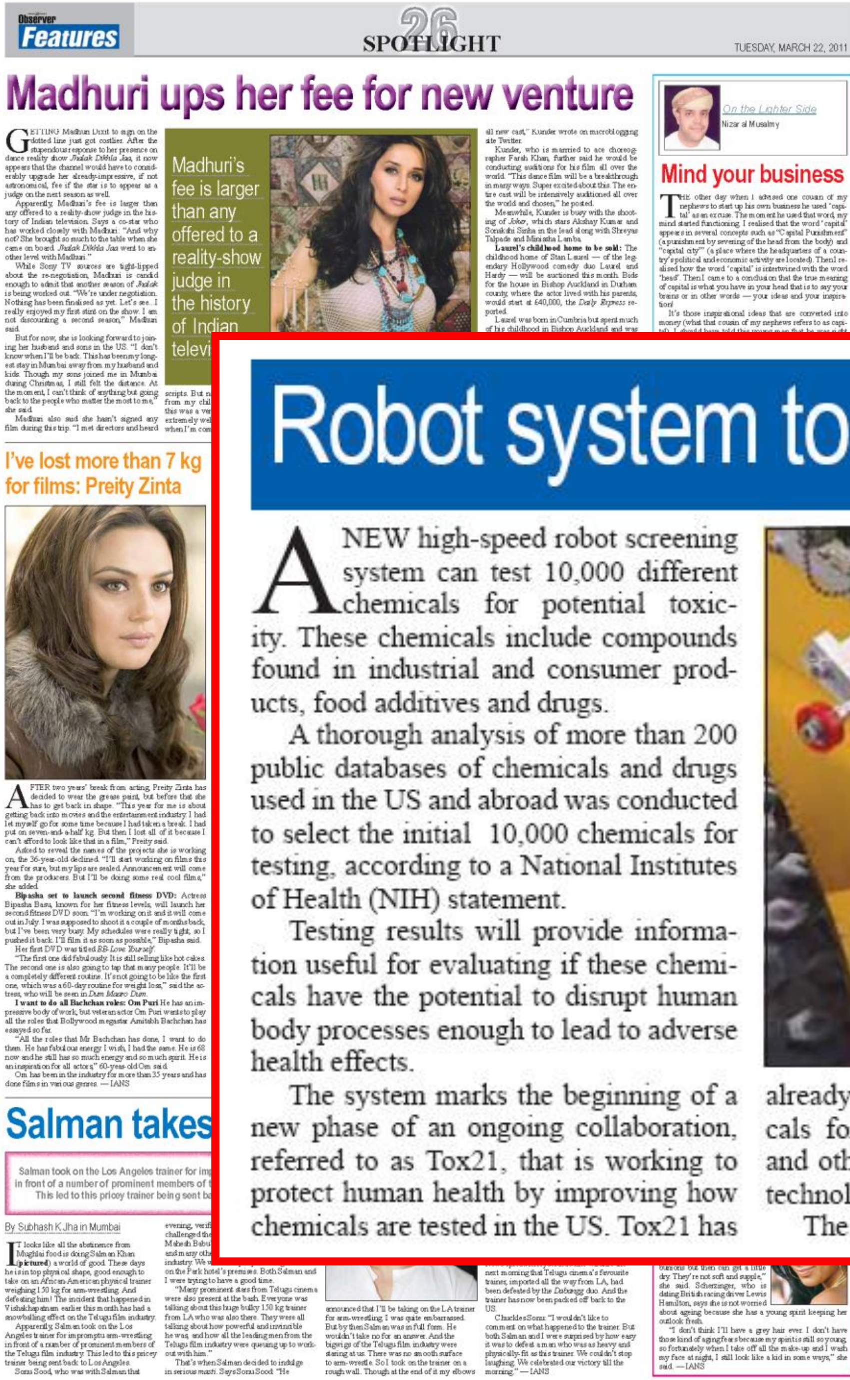
Tox21 Robot Ribbon-Cutting March 10, 2011



(L to R): Eric Green (Director, NHGRI/NIH), Linda Birnbaum (Director, NIEHS/NIH), Janet Woodcock (Director, CDER/FDA), Lek Kadelli (Asst Administrator, ORD/EPA)

Tox21 Engineering makes it to the Fashion Page

Oman Observer, 22 March 2011



Robot system to test chemicals for toxicity

A NEW high-speed robot screening system can test 10,000 different chemicals for potential toxicity. These chemicals include compounds found in industrial and consumer products, food additives and drugs.

A thorough analysis of more than 200 public databases of chemicals and drugs used in the US and abroad was conducted to select the initial 10,000 chemicals for testing, according to a National Institutes of Health (NIH) statement.

Testing results will provide information useful for evaluating if these chemicals have the potential to disrupt human body processes enough to lead to adverse health effects.

The system marks the beginning of a new phase of an ongoing collaboration, referred to as Tox21, that is working to protect human health by improving how chemicals are tested in the US. Tox21 has already screened more than 2,500 chemicals for potential toxicity, using robots and other innovative chemical screening technologies.

The robot system, which is at the NIH Chemical Genomics Centre (NCGC) in Rockville, was purchased as part of the Tox21 collaboration. Tox21 was established in 2008 between the National Institute of Environmental Health Sciences National Toxicology Program (NTP), the National Human Genome Research Institute (NHGRI), and the US Environmental Protection Agency (EPA) with the addition of the US Food and Drug Administration (FDA) in 2010.

"Tox21 has used robots to screen chemicals since 2008, but this new robotic system is dedicated to screening a much larger compound library," said NHGRI Director Eric Green.

"Understanding the molecular basis of hazard is fundamental to the protection of human health and the environment," said Paul Anastas, assistant administrator of the EPA Office of Research and Development. — IANS

TEHRAN TIMES
IRAN'S LEADING INTERNATIONAL DAILY
Monday, February 18, 2008 | Volume: 10259

Latest News : India slump to Australia

View Rate : 103 # News Code : TTime- 163482 Print Date : Monday, February 18, 2008

Robots could reduce animal tests

U.S. scientists are taking the first step towards testing potentially hazardous chemicals on cells grown in a laboratory, without using live animals.

Two government agencies are looking into the merits of using high-speed automated robots to carry out tests.

Coverage of Tox21 engineering enthusiastic but not always scientifically accurate…

The Tox21 Phase II 10K Compound Library

NCGC

- Pharmaceutical Collection

EPA

- ToxCast I and II compounds
- Antimicrobial Registration Program
- Endocrine Disruptor Screening Program
- OECD Molecular Screening Working Group List
- FDA Drug Induced Liver Injury Project
- Failed Drugs from Pharma

NTP

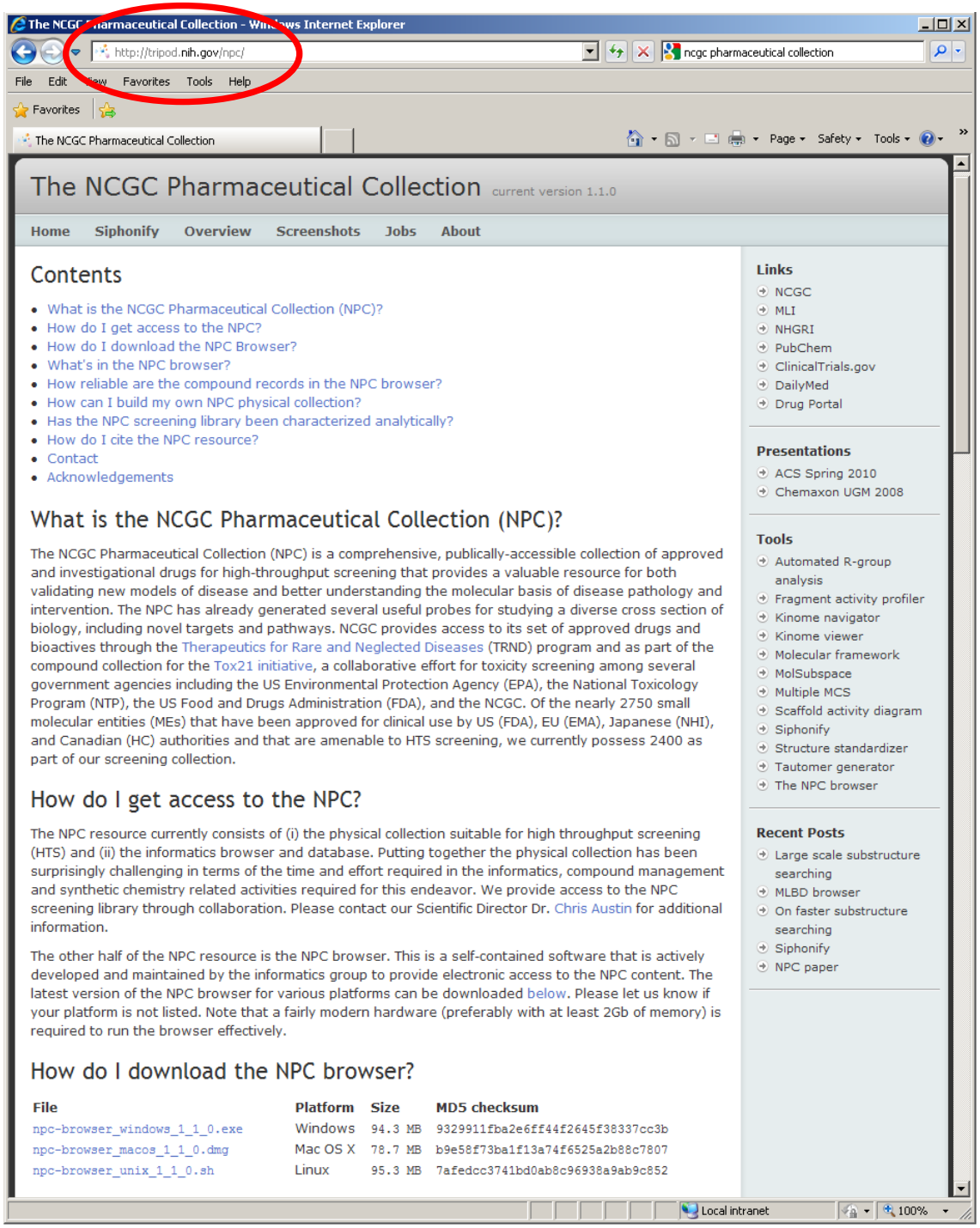
- NTP-studied compounds
- NTP nominations and related compounds
- ICCVAM/NICEATM validation and reference compounds
- External collaborators (e.g., Silent Spring Institute, U.S. Army Public Health Command)
- Defined mixtures

PHARMACOLOGY

The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

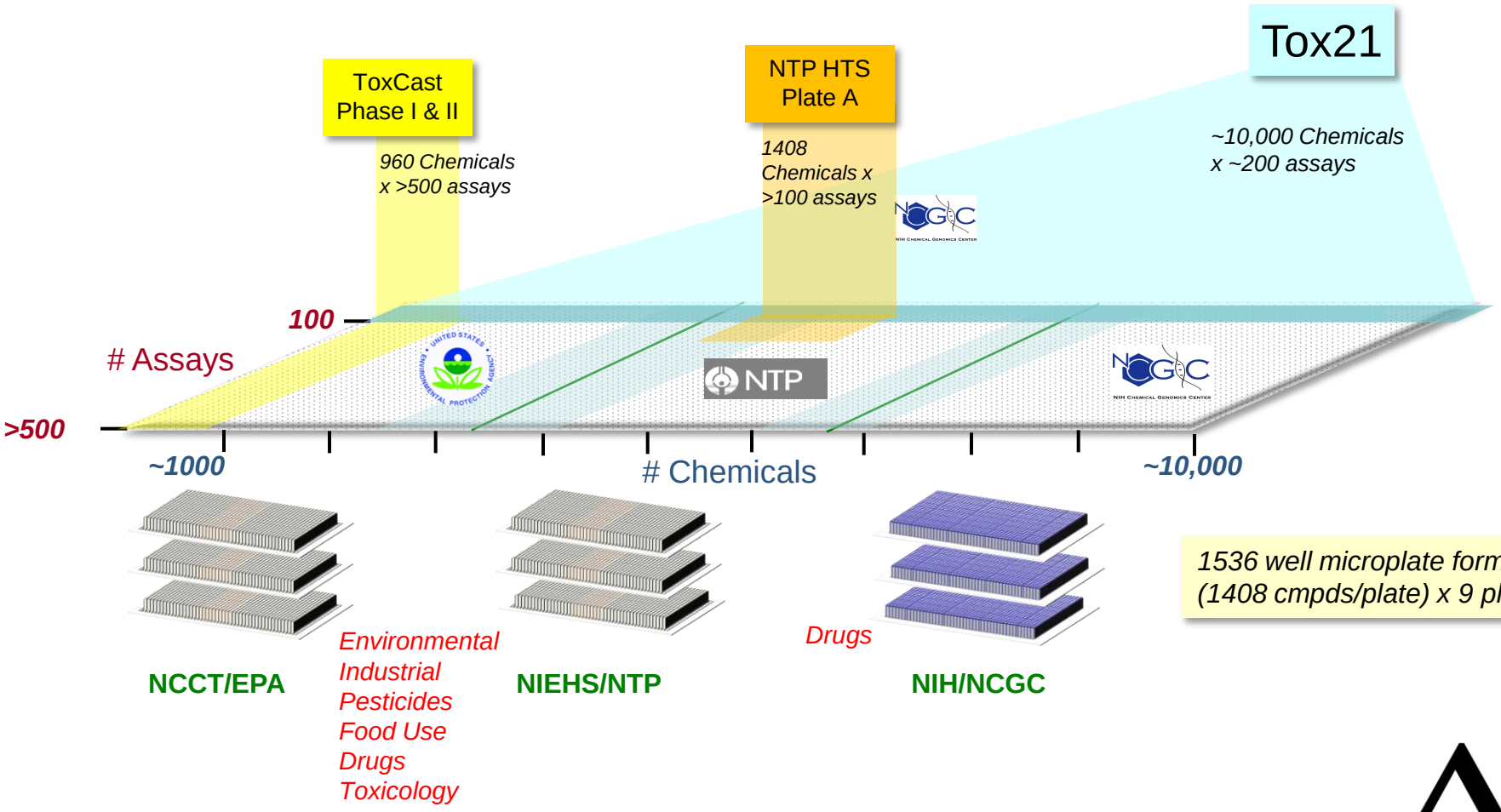
Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.



NIH Chemical Genomics Center

Tox21 Chemicals x Assays Landscape



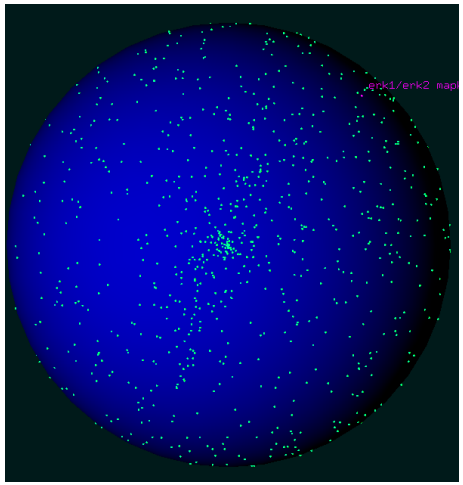
1536 well microplate format (1408 cmpds/plate) x 9 plates

Phase II qHTS Strategic Screening Strategy

- Assay selection based on
  - Phase I experience
  - Information from *in vivo* toxicological investigations
  - Advice of basic researchers and nominated assays
  - Maps of disease-associated cellular pathways
- Stage I
  - nuclear receptor activation or inhibition (AR, AhR, ER, FXR, GR, LXR, PPAR,, PXR, RXR, TR, VDR, ROR)
  - induction of stress response pathways (e.g., DNA damage, heat shock, hypoxia, inflammation, oxidative)
- Stage II
  - other disease-associated pathways (e.g., obesity/diabetes, autism) and move to HTS gene array assays applicable to all cell types

Facilitating Choice of Assays for Tox21: The NCGC BioPlanet of Pathways

- Hosts the universe of pathways
  - All pathway annotations from manually curated, public sources
  - Integrates ~1,100 unique human pathways from different data sources
  - Annotates pathways by source, species, biological function/process, disease/toxicity relevance, assay availability
  - Easy visualization, browsing, analysis of pathways
- Facilitates pathway assay selection/prioritization for Tox21 Phase 2
  - Disease, Toxicity pathways
  - Assay availability
    - Tox21/ToxCast/NCGC/PubChem
    - Commercial assays
  - Develop new assays for pathways with no coverage



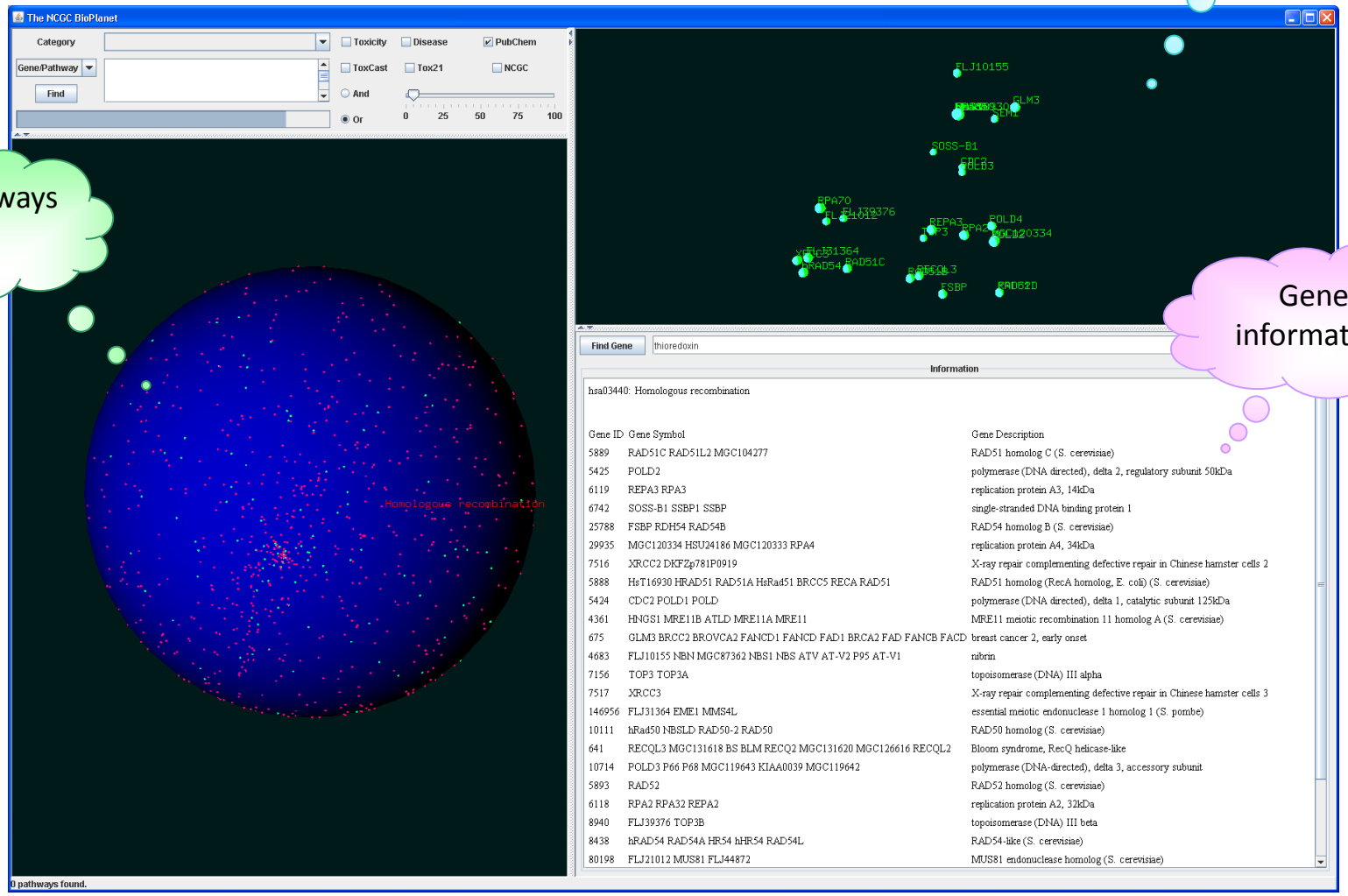
- Will be publicly available: http://spotlite.nih.gov/tox21/
- Future developments
  - Link compound activity data
  - Incorporate other data forms: sequence, gene/protein expression data, etc.
  - Other species: rat, mouse, etc.
  - Organize assays according to pathways/diseases/toxicity endpoints

The NCGC Universe of Human Pathways

Detailed view of a pathway

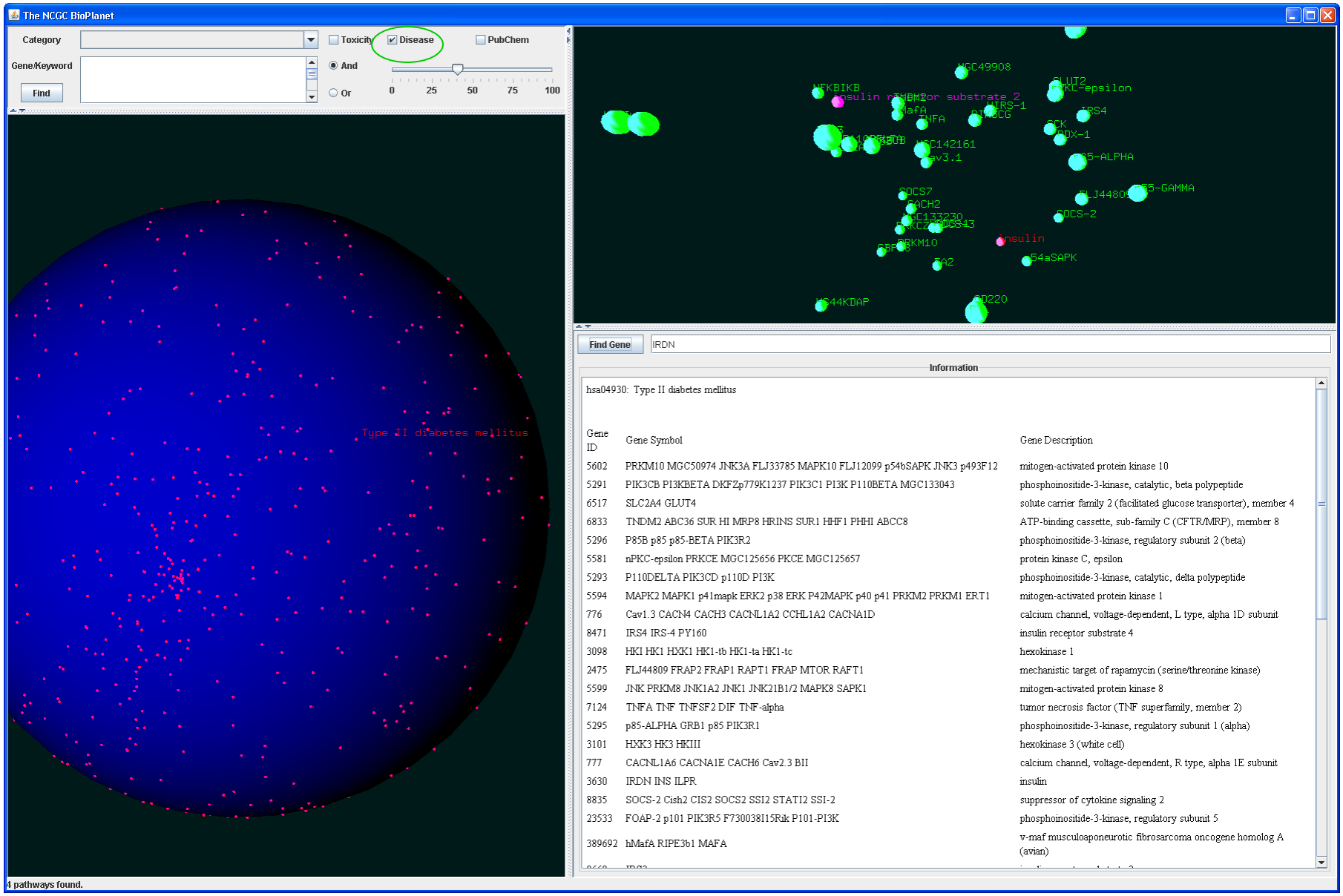
Pathways

Gene information

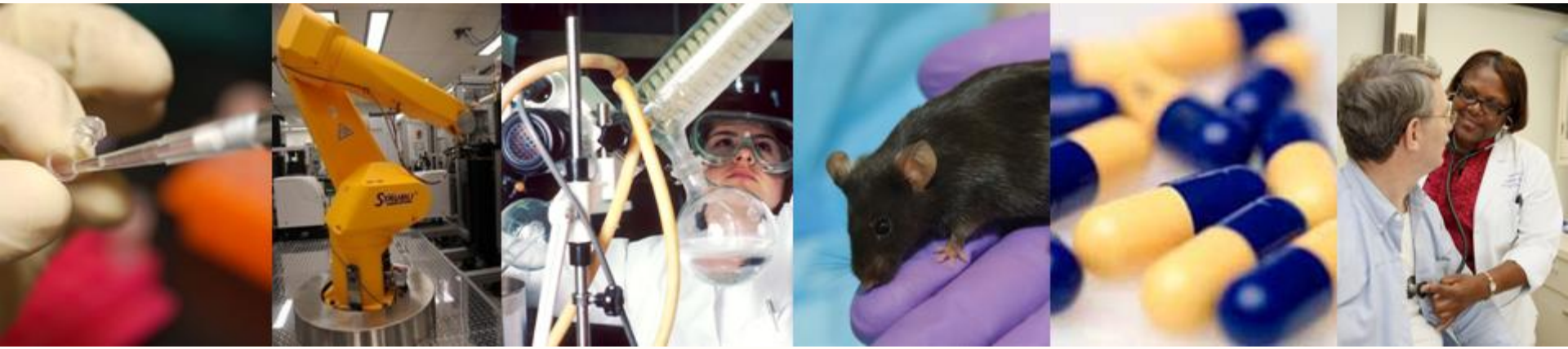


~1100 human pathways mapped to the pathway globe

“Disease” pathways (per OMIM)



NCATS: Pursuing Opportunities for Disruptive Innovation



To catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

NCATS Catalyzing Innovation
National Institutes of Health
NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

NCATS: Programs & Initiatives

Clinical and Translational Science Activities

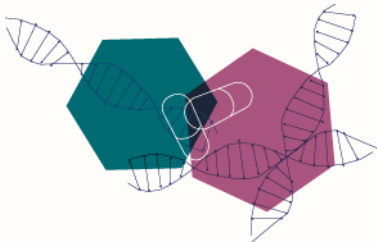
- Clinical and Translational Science Awards

Rare Diseases Research and Therapeutics

- Therapeutics for Rare and Neglected Diseases
- Office of Rare Diseases Research

Re-engineering Translational Sciences

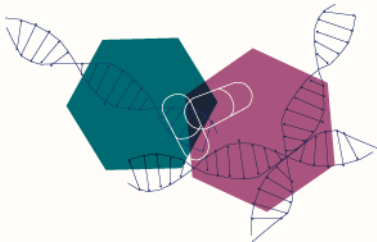
- NIH Chemical Genomics Center
- Bridging Interventional Development Gaps
- Toxicology in the 21st Century



NCATS: Fostering Collaboration

NIH–FDA–DARPA Collaboration for Tissue Chip

- Aims to develop a tissue chip that mimics human physiology to screen for safe, effective drugs
  - Liver, heart, lung, other cell types
  - Designed for multiple types of readouts
- NIH and Defense Advanced Research Projects Agency (DARPA) contribute $70M over 5 years; FDA provides guidance
- Received first proposals in late January 2012
  - Seeking best ideas in engineering, biology, toxicology



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Program Snapshot

The NIH is partnering with the U.S. Food and Drug Administration (FDA) and the Defense Advanced Research Projects Agency (DARPA) to advance the field of regulatory science, a specialized research area that aims to improve assessment of experimental therapies, preventives, and diagnostics. The Common Fund's **Regulatory Science** program is fostering the development, evaluation and availability of new or improved tools, methods, standards, and applied science that support a better understanding and improved evaluation of product safety, quality, effectiveness, and manufacturing throughout the product life cycle.

During the initial phase of the program, launched in fiscal year 2010, four new research awards in high priority areas of regulatory science were supported. Expansion of the program in FY 2012 focuses on developing new cell-based technologies, called microsystems, to predict more accurately drug safety and efficacy in humans.

Read more...

Program Highlights

In 2010, in partnership with the U.S. Food and Drug Administration (FDA), the Common Fund awarded four new grants in the Regulatory Science program. The awards address four distinct,

New collaboration and funding announcement to accelerate therapeutics development

The NIH announces a new collaboration and funding opportunity through the Common Fund's Regulatory Science program, and involving NIH, DARPA, and the FDA, to advance the development of new technologies aimed at streamlining the drug development pipeline. The initiative will support the development of human microsystems, or organ "chips," that can be used to screen for safe and effective drugs far more swiftly and efficiently than current methods, and before they are tested in humans. These microsystems will use specific cell types that reflect the biology of several different organs and tissues, and will be integrated together to model the connection between different organ systems in the human body. This integration will allow researchers to assess how drugs metabolized by one organ affect other organs or systems. It is hoped that the development of such microsystems will allow faster and more accurate measures of drug toxicology and efficacy, thereby reducing the time and cost associated with new therapeutics development.

View the funding opportunity
Read Frequently Asked Questions (FAQs) for the funding opportunity
Read the press release from NIH Director announcing NIH-DARPA-FDA collaboration

NCATS Catalyzing Innovation

National Institutes of Health
NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

NIH Office of the Director (OD)

For Immediate Release
Friday, September 16, 2011

Contact:
NIH Communications
301-496-5787

NIH, DARPA and FDA collaborate to develop cutting-edge technologies to predict drug safety

President Obama announced today that the National Institutes of Health will collaborate with the Defense Advanced Research Projects Agency (DARPA), and the U.S. Food and Drug Administration to develop a chip to screen for safe and effective drugs far more swiftly and efficiently than current methods, and before they are tested in humans. The chip will be loaded with specific cell types that reflect human biology. It will be designed to allow multiple different readouts that can indicate whether a particular co
run separate and independent programs, but they
example, DARPA and NIH will facilitate collaborati
programs. This fall, the two agencies, in coordina
academic institutions, and other research organiz
advances in engineering, biology, and toxicology

"Drug toxicity is one of the most common reasons
director said. "We need to know which ones are s
unprecedented opportunity to speed developmen

Over the next five years, the NIH plans to commit
effort. This groundbreaking effort is an example o
National Center for Advancing Translational Scier
provide science-based solutions to reduce costs
help determine how this new technology can be u
studies.

"We know the development pipeline has bottlened
"What we need are entirely novel approaches to t
biomedical discoveries that have been made in re

As proposed, NCATS will study the steps in the pi
bottlenecks, and experiment with innovative methods to streamline the process. By focusing on developing innovative new tools and methods for therapeutics development, as opposed to developing therapeutics themselves, NCATS will enable others to bring safer and more effective medical products to market in less time. In this way, NCATS will complement, and not compete with, the work of the private sector and other NIH translational science efforts.

About the National Institutes of Health (NIH): NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov.

NIH...Turning Discovery Into Health

Current Funding Opportunities

Title	NIH Guide	RFA Number	Common Fund Contact	Application Receipt Date
Pre-Application Teleconference for RFA-RM-11-022 - Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing in Human Health and Disease (UH2/UH3) and RFA-RM-12-001 Stem/Progenitor Cell-Derived Human Micro-organs and -tissues (U18) ▪ Read Frequently Asked Questions (FAQs) for the funding opportunity ▪ View slides from the December 16, 2011 Pre-Application Teleconference	12/5/11	NOT-RM-12-007	Margaret Sutherland sutherlandm@ninds.nih.gov 301 496-5680	N/A
Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing in Human Health and Disease (UH2/UH3)	11/22/11	RFA-RM-11-022	Danilo A. Tagle tagled@ninds.nih.gov 301 496-5745	1/26/12
Stem/Progenitor Cell-Derived Human Micro-organs and -tissues (U18))	11/23/11	RFA-RM-12-001	Margaret Sutherland sutherlandm@ninds.nih.gov 301 496-5680	1/26/12

Related/Coordinated Initiatives

- ICCVAM, NICETAM, ECVAM
- REACH: European Community Regulation on chemicals and their safe use
  - **R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emical substances
- IMI eTox: drug safety database from the pharmaceutical industry legacy toxicology reports and public toxicology data
- OECD Molecular Screening project: internationally collaborative efforts to define screening applications in a regulatory context

Take-home points

- Opportunity and imperative now exists to transform preclinical toxicology from an empirical animal-based exercise to a predictive mechanism-based science
- Tox21 and the DARPA-NIH toxicology initiative are two of the initiatives driving this vision forward
- All data and results from both initiatives are being made public for all researchers to use/compute on
- U.S. efforts are being coordinated with related international initiatives including REACH, eTox, OECD
- For the most part these are research initiatives so far, not broadly applied in regulatory contexts

Further Information

NCATS.nih.gov

austinc@mail.nih.gov

Tox21: http://www.epa.gov/ncct/Tox21/

ICCVAM/NICETAM: http://iccvam.niehs.nih.gov/

REACH: http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm

eTox: http://www.etoxproject.eu/

OECD Molecular Screening project: http://www.oecd.org/document/14/0,3746,en_2649_34377_48906062_1_1_1_1,00.html