EPA
United States
Environmental Protection
Agency

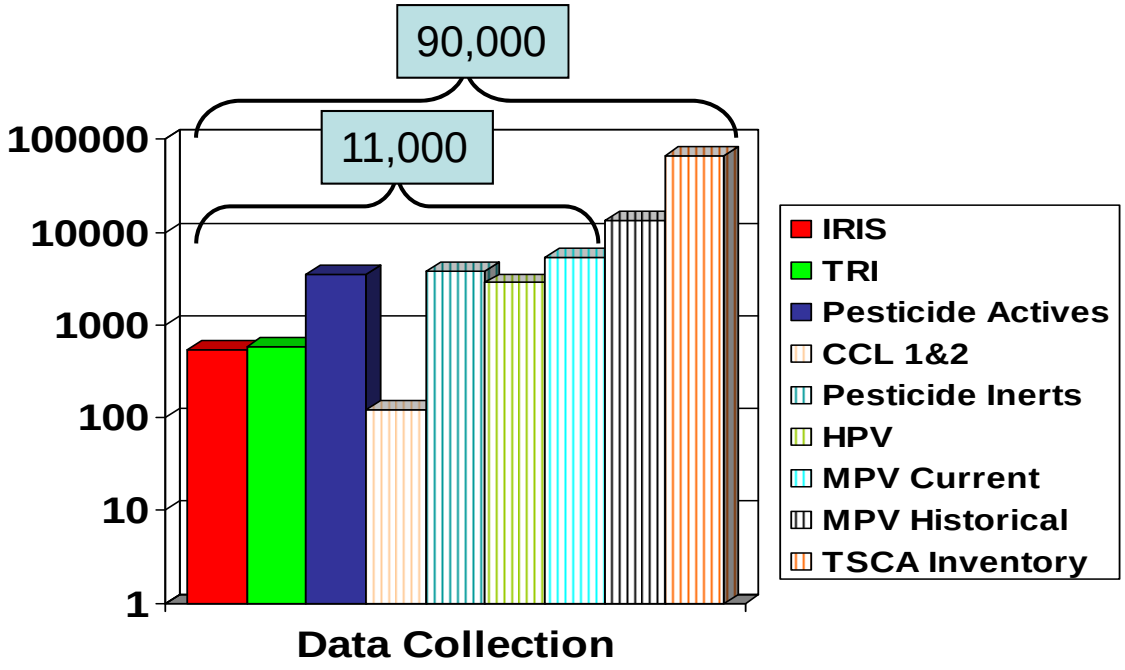
Update on: 2009 HESI Emerging Issue: Identification of Pharmaceuticals for Validation of ToxCast

Robert Kavlock
Director, National Center for Computational Toxicology, US EPA

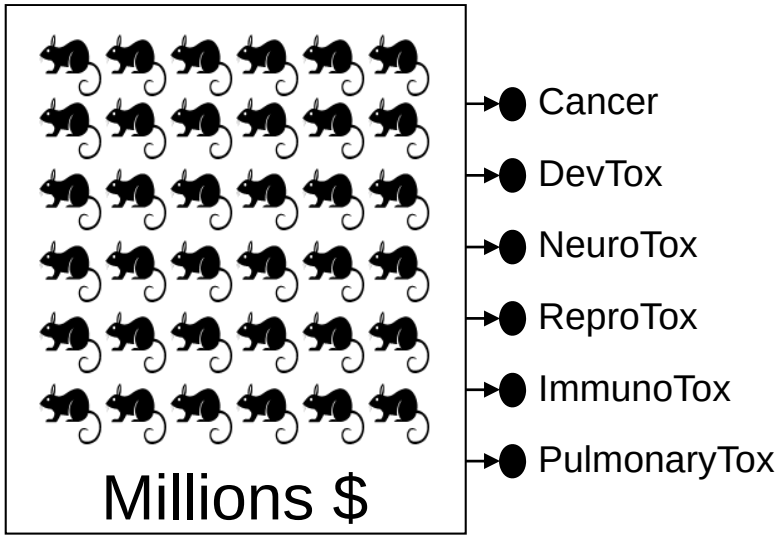
Robert Chapin
Pfizer

Change Needed Because …..

Too Many Chemicals



Too High a Cost

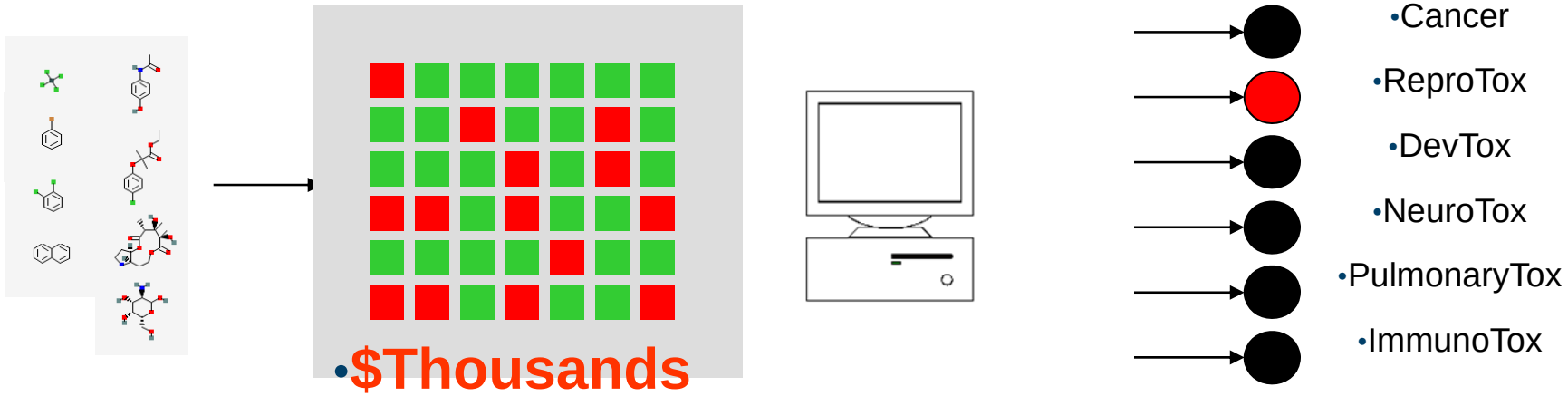


…and not enough data.

Judson, et al *EHP in press*

ToxCast Bioactivity Profiling

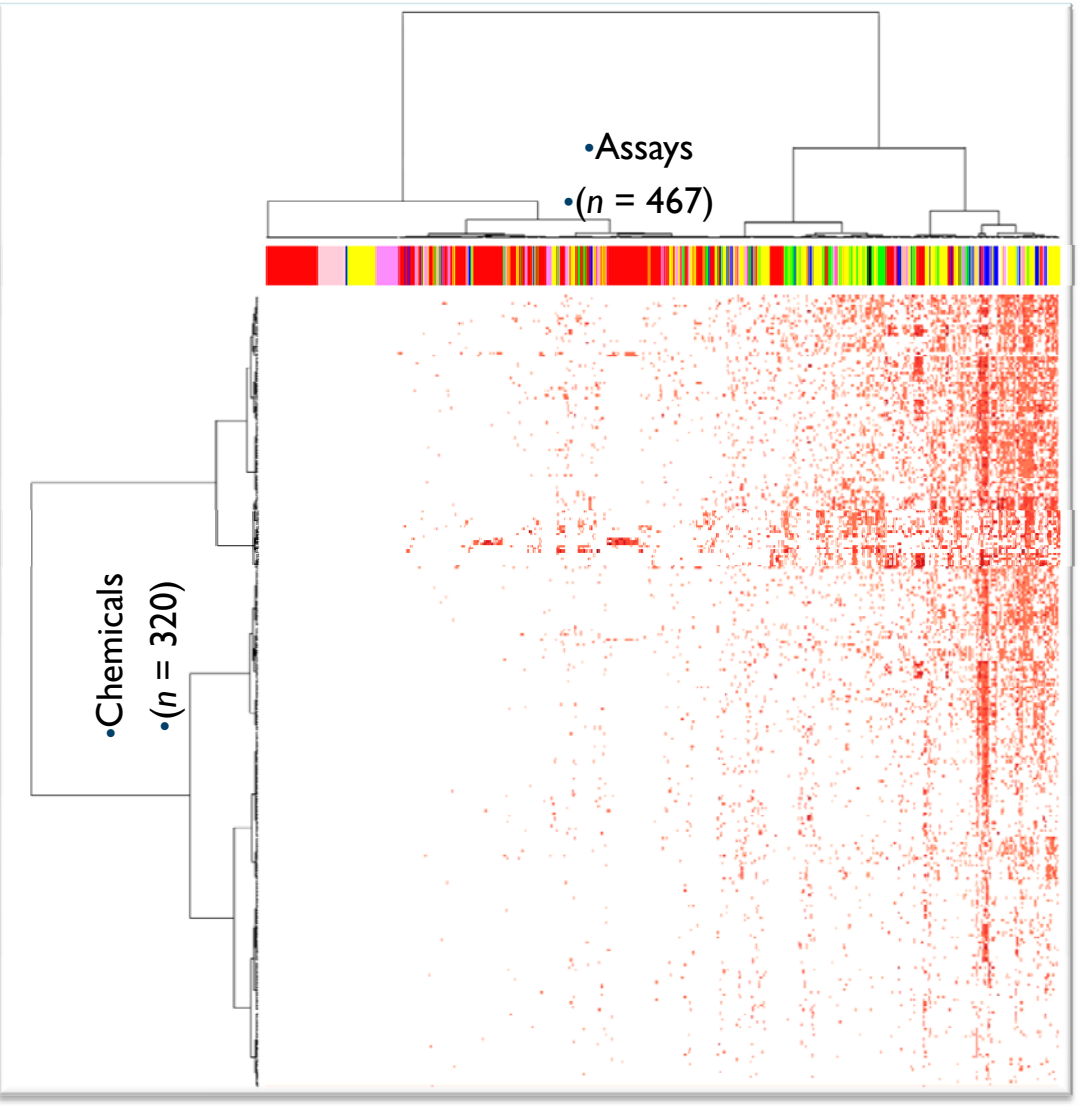
in vitro testing *in silico* analysis



HTS
-omics

Bioinformatics/
Machine Learning

ToxCast Phase I HTS Results



•Cellular Assays

- **Cell lines**
  - HepG2 human hepatoblastoma
  - A549 human lung carcinoma
  - HEK 293 human embryonic kidney
- **Primary cells**
  - Human endothelial cells
  - Human monocytes
  - Human keratinocytes
  - Human fibroblasts
  - Human proximal tubule kidney cells
  - Human small airway epithelial cells
- **Biotransformation competent cells**
  - Primary rat hepatocytes
  - Primary human hepatocytes
- **Assay formats**
  - Cytotoxicity
  - Reporter gene
  - Gene expression
  - Biomarker production
  - High-content imaging for cellular phenotype

•Biochemical Assays

- **Protein families**
  - GPCR
  - NR
  - Kinase
  - Phosphatase
  - Protease
  - Other enzyme
  - Ion channel
  - Transporter
- **Assay formats**
  - Radioligand binding
  - Enzyme activity
  - Co-activator recruitment

•Judson et al EHP (2010)

•http://www.epa.gov/ncct/toxcast/

Phased Development of ToxCast

Phase	Number of Chemicals	Chemical Criteria	Purpose	Number of Assays	Cost per Chemical	Target Date
Ia	320	Data Rich (pesticides)	Signature Development	>500	$20k	FY08
Ib	15	Nanomaterials	Pilot	166	$10K	FY09
IIa	>300	Data Rich Chemicals	Validation	>400	~$20-25k	FY09
IIb	>100	Known Human Toxicants	Extrapolation	>400	~$20-25k	FY09
IIc	>300	Expanded Structure and Use Diversity	Extension	>400	~$20-25k	FY10
IId	>12	Nanomaterials	PMN	>200	~$15-20K	FY09-10
III	Thousands	Data poor	Prediction and Prioritization	>300	~$15-20k	FY11-12

January 2009

Emerging Issues Proposal

- SPECIFIC ACTIONS
  - Coordinate Public-Private sector involvement in ToxCast predictions
  - Scoping meeting to articulate needs, timelines and boundaries of involvement by participants
- DESIRED OUTCOME
  - Successful deliberations and negotiations would result in:
    - Identification and provisioning of chemicals (~100mg) for screening
    - Sharing of relevant pre-clincal and clinical data
    - [Cost sharing of screening costs]
    - Co-publications on predictive models

Benefits of Proposal

- Draws on unique position of HESI in bringing the public and private sectors together for progress in science
- Enables utilization of a unique private sector knowledge
- Builds on the experience of EPA in computational toxicology - note that the models that EPA develops will be publically available
- Brings direct human relevance to HTS screening on environmental and pharmaceutical chemicals, which already involves the use of many human protein targets and cell types
- HESI would be intimately associated and linked with progress at reaching the vision of toxicity testing in the 21st envisioned by the National Research Council

Maybe the Time has come …….

COMMENTARY

DRUG DISCOVERY

A Call for Sharing: Adapting Pharmaceutical Research to New Realities

Bernard H. Munos* and William W. Chin

Published 2 December 2009; Volume 1 Issue 9 9cm8

From the dawn of time, the sharing of knowledge has been one of the main forces driving science and innovation. Yet in recent decades, a proprietary culture, which wrongly posits that all intellectual property must be restricted, has spread across the pharmaceutical industry and threatens to stall the engine that has given us so many valuable treatments. This paper argues that pharmaceutical companies, together with universities and government agencies, stand to gain much from reversing that trend and engaging in widespread collaboration early in the research process to expand foundational knowledge and create a shared infrastructure to tap it.

The first scientific journals in the late 17th century transformed the practice of science, which until then had often been a secretive occupation shrouded in mystery, and ushered in a culture of sharing that made it easier for scientists to build on each other's been an engine of scientific progress through much of the modern age.

Sharing also fosters cross-pollination, an essential driver of creativity. Over a thousand new scientific papers enrich the life science literature every day. Turning that seldom have all the resources needed to approach a disease by the many avenues that can yield viable therapies. Take type 1 juvenile diabetes, for instance. It can potentially be treated with insulin, immunosuppressive drugs, vaccines, monoclonal antibodies, stem cells, tissue implants, gene therapy, allo- or xenotransplants, or a combination thereof. This combinatorial approach requires vast competencies across many fields that are unlikely to be found under one roof. Sharing addresses this challenge by bringing together people with complementary skills. Hollingsworth (*1*), who has studied breakthrough innovation across hundreds of biomedical research organizations, has observed that the most productive ones have numerous linkages to networks of scientists in diverse fields where the exchange of ideas takes place. When marshaled toward a common goal, these interacting innovation networks have been especially good at generating breakthrough solutions. They are also more efficient. Investing in a single or narrow set of options can lead to

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Citation
E. A. Zerhouni, Peer-to-peer sharing spurs scientific innovation. *Sci. Transl. Med.* **1**, 9ed2 (2009).

10.1126/scitranslmed.3000584

Peer-to-Peer Sharing Spurs Scientific Innovation

IN THIS ISSUE OF *SCIENCE TRANSLATIONAL MEDICINE*, BERNARD MUNOS AND William Chin, both of Eli Lilly and Company, present a timely and insightful analysis of the profound changes that the pharmaceutical industry must make to accelerate discoveries in the field of translational medicine. As I survey the issues facing the world of biomedical innovation, it is clear that no single organization or even country can muster all of the knowledge, talent, creativity, and resources required to decipher our continuously expanding knowledge about the complexity of biological systems and pathobiology that is evident today. Furthermore, human-made obstacles related to the natural tension between proprietary ownership for personal or institutional rewards versus the sharing of knowledge and ideas for collective benefits have grown to the point where competition becomes an impediment rather than an impetus to innovation. I cannot agree more with these authors about the need for creating a common precompetitive space in biomedical research that should facilitate intelligent, effective, and safe innovation for all.

As in many human endeavors, the most difficult step is to figure out how to modify the existing culture and ethos of industry, academia, and government. Establishing the world of Science 2.0 as proposed by Munos and Chin will require leadership at all levels and a phased approach in areas in which the whole of the common good is greater than the sum of our specific interests. During my tenure as director of the U.S. National Institutes of Health (NIH), the leadership met at regular intervals with the heads of R&D at biotechnology and pharmaceutical companies as well as with active investigators in academia to identify and devise ways to reduce obstacles to innovation. The most commonly identified themes were as follows. First was the need to accumulate and share knowledge about human toxicology and adverse effects in order to improve predictive capabilities, avoid costly late-stage failures, and, most importantly, protect patients from untoward outcomes. At NIH, we launched many initiatives through pharmacogenomics and biomarkers consortia as well as data-sharing policies that included, as a matter of policy, public posting of as much experimental data as possible as a condition of grant receipt (exemplified by GenBank, genome-wise association studies, the PubChem Project, and other open-access databases). As indicated by the authors, others in

Key Events

- March 27th Invite to Membership

- April 20th Webinar
  - 19 participants (7 Pharmaceutical Companies)

- June 15th Response Date
  - Identification of failed agents
    - Pre- and clinical data
    - 100 mg of chemical
    - No financial exchange
    - MTA to cover property exchange
    - Public release of data and structure
      - Protection of pharmacology
    - Pre-publication access to data

Formal Partnerships

Company	Champion	Compounds	Comment
Pfizer	Bob Chapin Nigel Greene Larry Zaccaro	116	Prioritized 55
Sanofi-Aventis	Kevin Morgan Ernie Harpur	21 16	Pre & Clinical Clinical only
GSK	Neal Cariello Patrick Wier	13	Clinical and Pre-clinical
Merck	Frank Sistare James Monroe	11	Pre-clinical only

United States
Environmental Protection
Agency

Pfizer MTA March 27, 2009

MATERIALS TRANSFER AGREEMENT

EPA:

U.S. Environmental Protection Agenc
Office of Research and Development
National Center for Computational To

Pfizer:
Pfizer Inc, having a principal place of
("Pfizer") New York, 10017 and its Af

WHEREAS the EPA wishes to obtain
panels, and whereas Pfizer wishes to
panels, the parties agree as follows:

MATERIALS TRANSFER AGREEMENT

EPA:

U. S. Environmental Protection Agency (EPA)
Office of Research and Development (ORD)
National Center for Computational Toxicology (NCCT)

GSK:

SmithKline Beecham Corporation doing b
business at Five Moore Drive, Research T
Affiliates.

WHEREAS, the EPA wishes to obtain GS

DO NOT REMOVE ATTACHMENT MTA ID# 38799

MERCK

***AMENDED* - MATERIAL TRANSFER AGREEMENT-COMPOUNDS**

(For Tests In Vitro or in Laboratory Research Animals-Not for Use in Humans)

Return To: MERCK SHARP & DOHME CORP. ("Merck")
Merck Contact: John Obenchain
126 EAST LINCOLN AVE, RY70-100
RAHWAY, NEW JERSEY 07065-0900
Merck Telephone: 732-594-1396
Merck Fax: 732-594-3624

Re: Investigation of _____ Amount: 200mg 17 Jun 2010
Compound name and/or Compound number
(singly and collectively, "**Compound**")

1. In accordance with all applicable laws, rules and regulations relating to use of the Compound and, for Compound which is a new drug, in accordance with Sections 505 and 512 of the U.S. Federal Food, Drug and Cosmetic Act, as amended, and the regulations issued under such Act, Investigator and Entity (as defined below) hereby certify that:

   a. Investigator is regularly engaged in conducting tests in vitro or in laboratory research animals and is qualified by training and/or experience to conduct such tests on this Compound.

   b. Investigator has adequate facilities for the investigation of the Compound. (Complete the following with the name of Principal Investigator and location where work is to be done. **Please note: Compounds cannot be shipped to P.O. Box numbers; you must use a street address.)**

MATERIAL TRANSFER AGREEMENT

This **MATERIAL TRANSFER AGREEMENT** (this "***Agreement***"), is effective as of this 26 day of February, 2010 (the "***Effective Date***"), by and between **SANOFI-AVENTIS U.S. INC.**, with offices at 1041 Route 202-206, P.O. Box 6800, Bridgewater, NJ 08807-0800 ("***SANOFI-AVENTIS***") and the United States Environmental Protection Agency, Office of Research and Development, National Center for Computational Toxicology, with offices at 109 TW Alexander Dr., Research Triangle Park, NC 27711 ("***EPA***"). SANOFI-AVENTIS and EPA are each referred to herein as a "***Party***" and collectively as the "***Parties***."

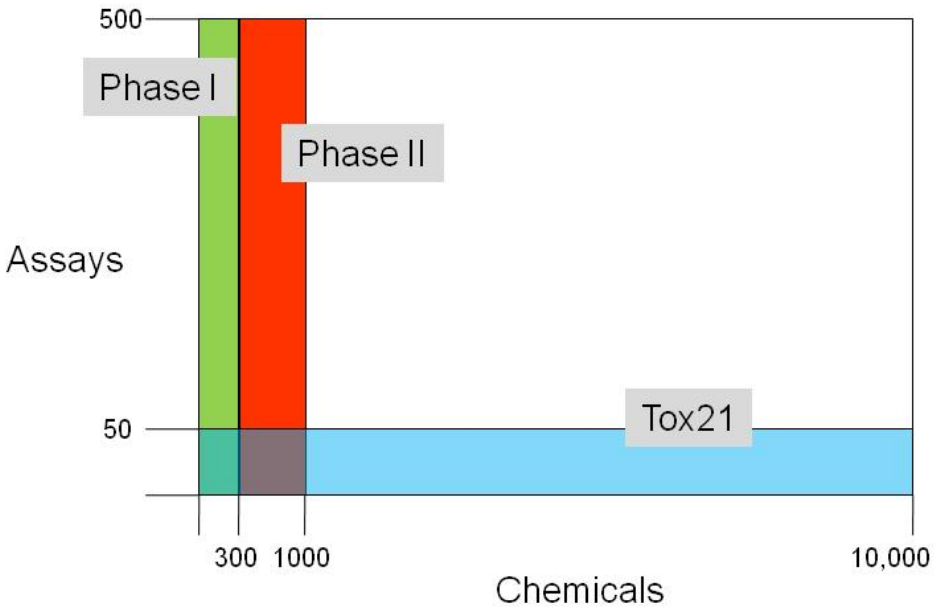
RECITALS:

WHEREAS, SANOFI-AVENTIS is in possession of certain proprietary compounds, more fully described in Exhibit A (which, in any form or any of its intermediates and derivatives, shall comprise the "***SANOFI-AVENTIS COMPOUNDS***") and certain INFORMATION (as defined in **Section 4** below);

WHEREAS, EPA desires to receive INFORMATION and SANOFI-AVENTIS COMPOUNDS solely for the purpose of conducting research activities as more fully described in Exhibit B attached hereto (the "***ToxCast™ PROGRAM***");

From Phase I to Phase II and Tox21

	Phase I	Phase II	Tox21
Actives	272	120	700
Inerts	24	100	1000
Antimicrobials	33	100	500
HPV	35	170	1300
MPV	7	60	1500
Green	4	60	500
PCCL	73	150	500
Pharmaceuticals	0	100	2500
Consumer Products /Food additives	0	0	1500
Total	**309**	**~700**	**~10000**



Additional Offer From GSK

- Rat Hepatoxicity Database
- ~140 Non-GSK hepatotoxic compounds. These are publically available and there is literature. Short term exposures, single dose level, dosing for 4 days, sacrifice on day 5
- Annotations on modes and mechanisms of toxicity
- Clinical chemistry, and liver histopathology
  - May be used for computational modelling
- Building selected chemicals in Phase 2

Biggest Challenges

- Having an internal champion
- Getting corporate buy in for transparency
- Locating the preclinical and clinical data
- Mergers, legacy data systems
- Limitations of adverse phenotypes
- Persistence
- Loading data in ToxRefDB

Next Steps

- Final selection of ToxCast Phase II Chemicals
  - 700 total; ~100 pharmaceuticals
  - Subset of 10,000 in Tox21 library
- Analytical chemistry on collection
  - Mother plate, Time 0 and ~3 months
- Distribution to HTS Contractors & Collaborators
- Early data sharing with contributors
- Bioactivity signature development
- Publication and release of results

Acknowledgements

- HESI and Nancy Doerrer
- Pfizer for breaking the Ice
- GSK, Sanofi-Aventis and Merck for forward thinking
- US EPA for continued support of ToxCast