NCATS Improving Health Through Smarter Science

Challenges and Opportunities in Disease and Toxicity Screening

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August 8, 2018

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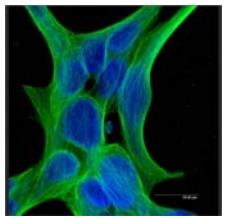
Therapeutic Discovery and Development

Identify disease mechanism → Create testing system → Test chemicals in system → Modify (chemistry) for human use → Test in animals → Test in humans

Basic Research

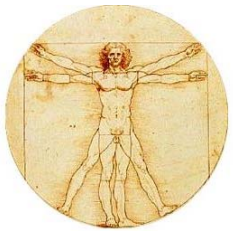


Assay Development

Screening

Medicinal Chemistry

Preclinical Development

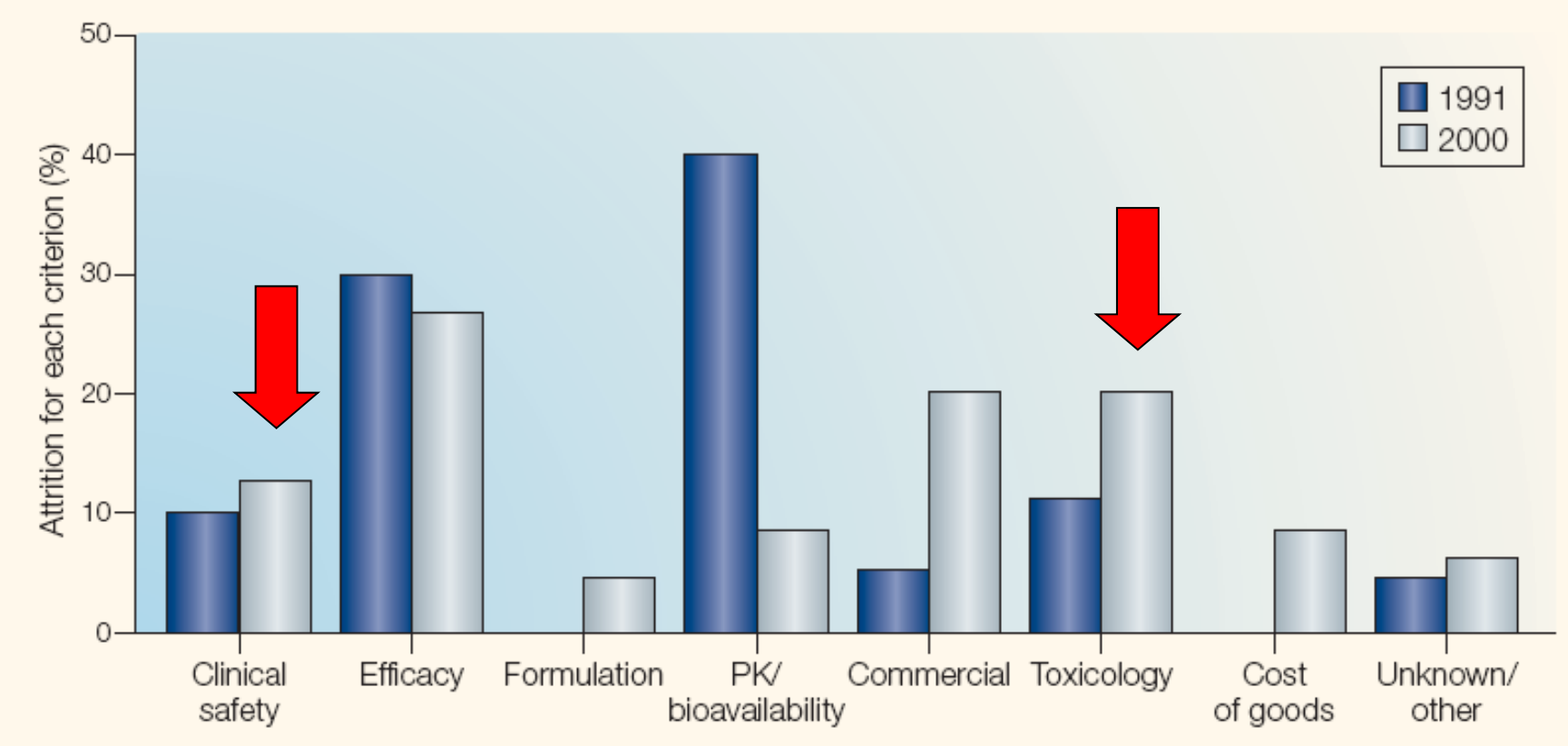


Clinical Development

The common causes of translational inefficiency are NCATS' focus

- Predicting safety and effectiveness of new drugs
- Scalable approaches to the >6000 untreatable diseases
- Data interoperability
- Biomarker qualification process
- Clinical trial networks
- Patient recruitment
- Electronic Health Records for research
- Harmonized IRBs
- Clinical diagnostic criteria
- Clinical outcome criteria (e.g., PROs)
- Adaptive clinical trial designs
- Shortening time of intervention adoption
- Methods to better measure impact on health (or lack thereof)
- Cross-sector collaborative structures
- Translational education/workforce development

Toxicity is (still) a common reason for drug development failure

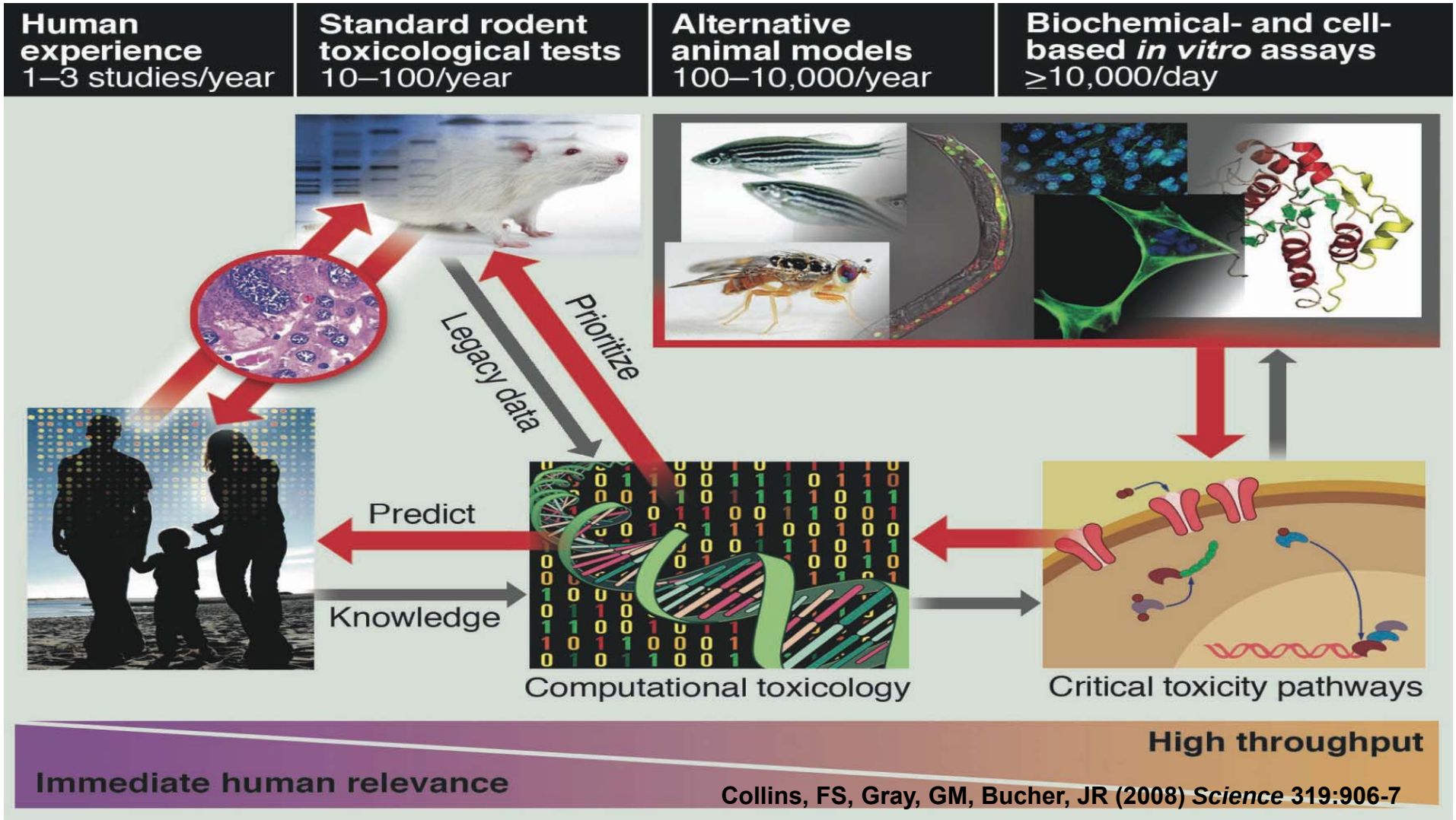


Preclinical (21%) + Clinical (12%) Tox = 33% of all failures

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

Why do we need to prioritize compounds for testing?

- There are over 80,000 chemicals in commerce, the majority with little to no toxicological data.
- We cannot solve the problem using laboratory animal tests only.



Collins, FS, Gray, GM, Bucher, JR (2008) *Science* 319:906-7

The Tox21 Collaborative

FDA

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U.S. Environmental Protection Agency

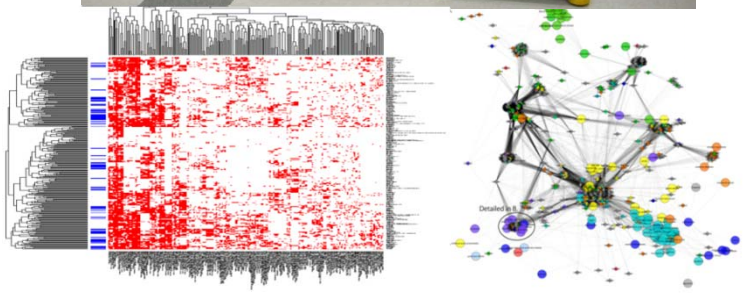
National Toxicology Program
Department of Health and Human Services

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
COMPUTATIONAL TOXICOLOGY

NIH National Institute of Environmental Health Sciences

Tox21

- Develop predictive models for biological response to new chemicals in humans, reducing use of animals
- Identify patterns of chemical-induced biological response to understand adverse effects
- Prioritize chemicals for more extensive toxicological evaluation, guide optimization



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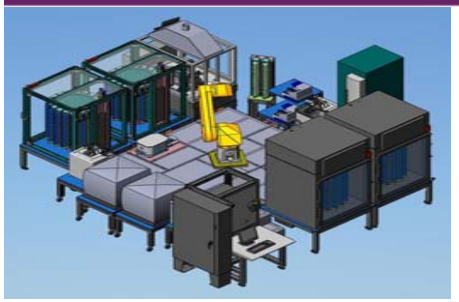


The Tox21 10K Library Screening Project

Collection of diverse chemicals

In vitro test methods, screening

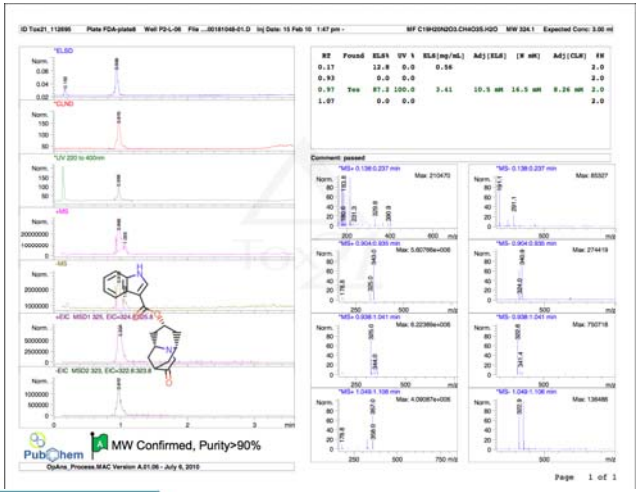
High quality bioactivity data

Predictive models

(of bioactivity of a new chemical *in vitro* and, one day, *in vivo*)

>50 screening campaigns of the 10K Collection

Tox21 10K Chemical Collection: ~10,000 chemicals (nominated and procured by EPA, NIEHS, and NCATS) comprising approved drugs, failed drugs, pesticides, industrial chemicals, etc. Extensive Quality Control →



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Tox21 10K Compound Library

EPA

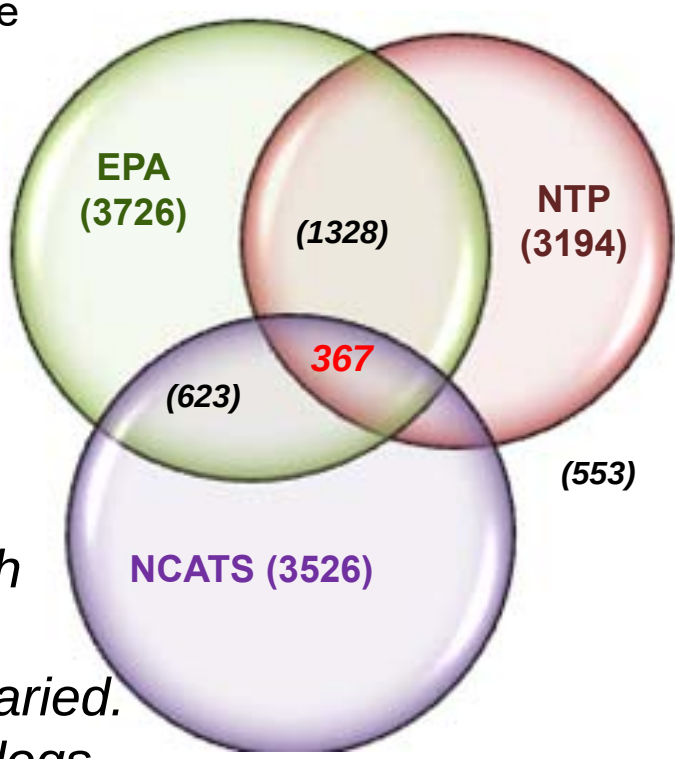
- ToxCast I and II compounds
- Antimicrobial Registration Program
- Endocrine Disruptor Screening Program
- OECD Molecular Screening Working Group
- FDA Drug Induced Liver Injury Project
- Failed Drugs

NTP

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

NCATS

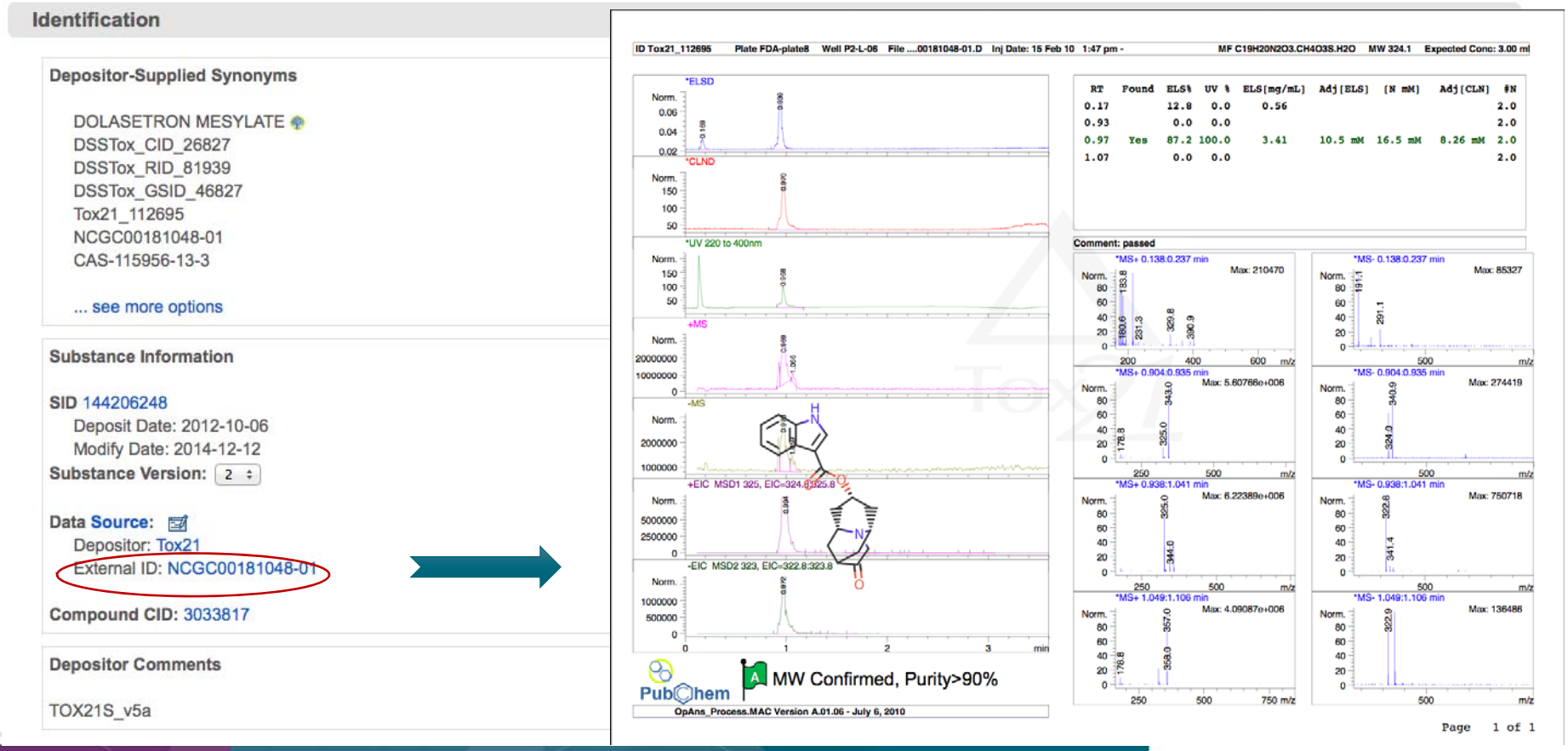
- Approved Drugs
- Investigational Drugs



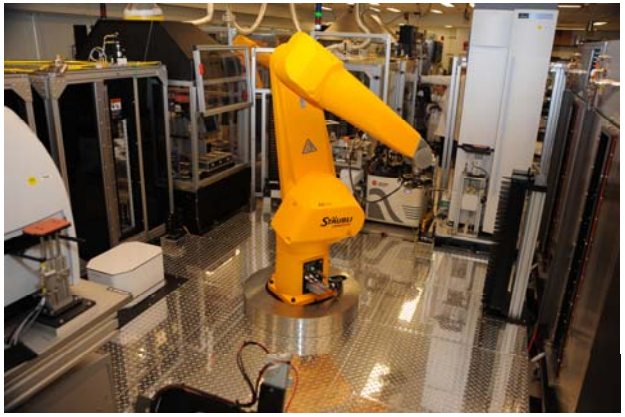
- *88 single-sourced compounds in duplicate on each plate.*
- *Three library replicates, compounds positionally-varied.*
- *Each sample arrayed in 15 concentrations over 4 logs.*

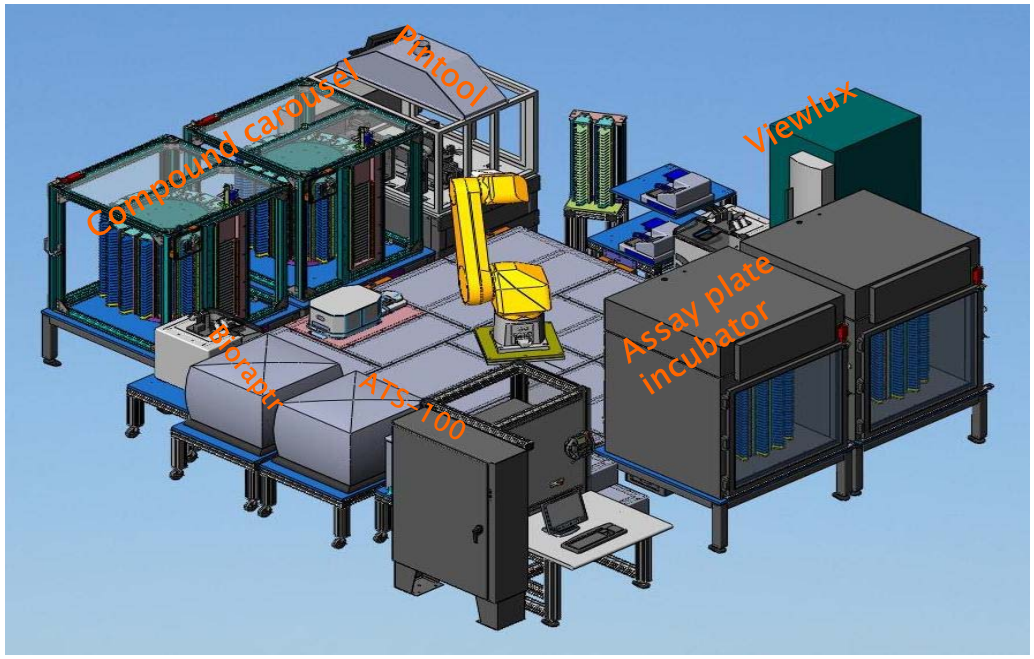
Entire-Library QC Project

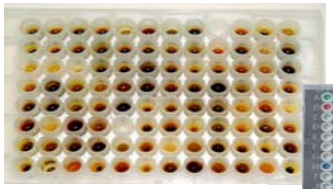
- Multi-year undertaking using a range of LC-/GC-MS and NMR methods.
- >10,000 analytical chromatograms in PDF format available through PubChem: http://www.ncbi.nlm.nih.gov/pcsubstance



Tox21 Robot Platform





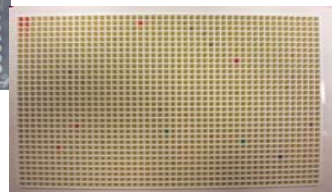


- 8 rows x 12 columns
- 88 test samples

96-well plate

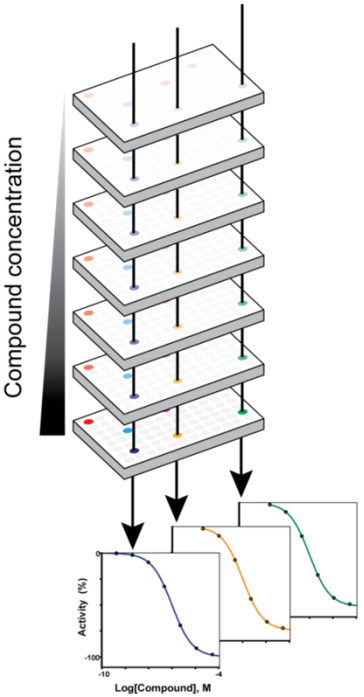
- 16 rows x 32 columns
- 352 test samples

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



Dose-response-based screening
Proc Natl Acad Sci 103:11473

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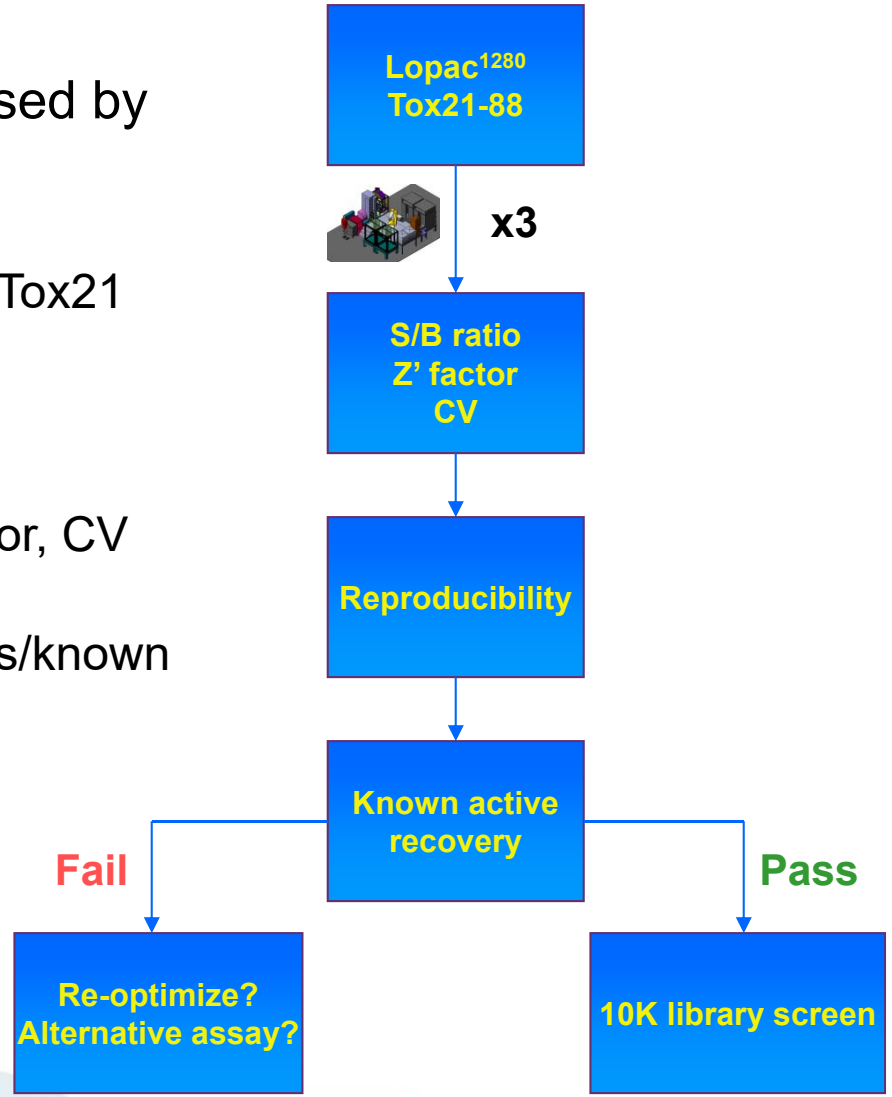
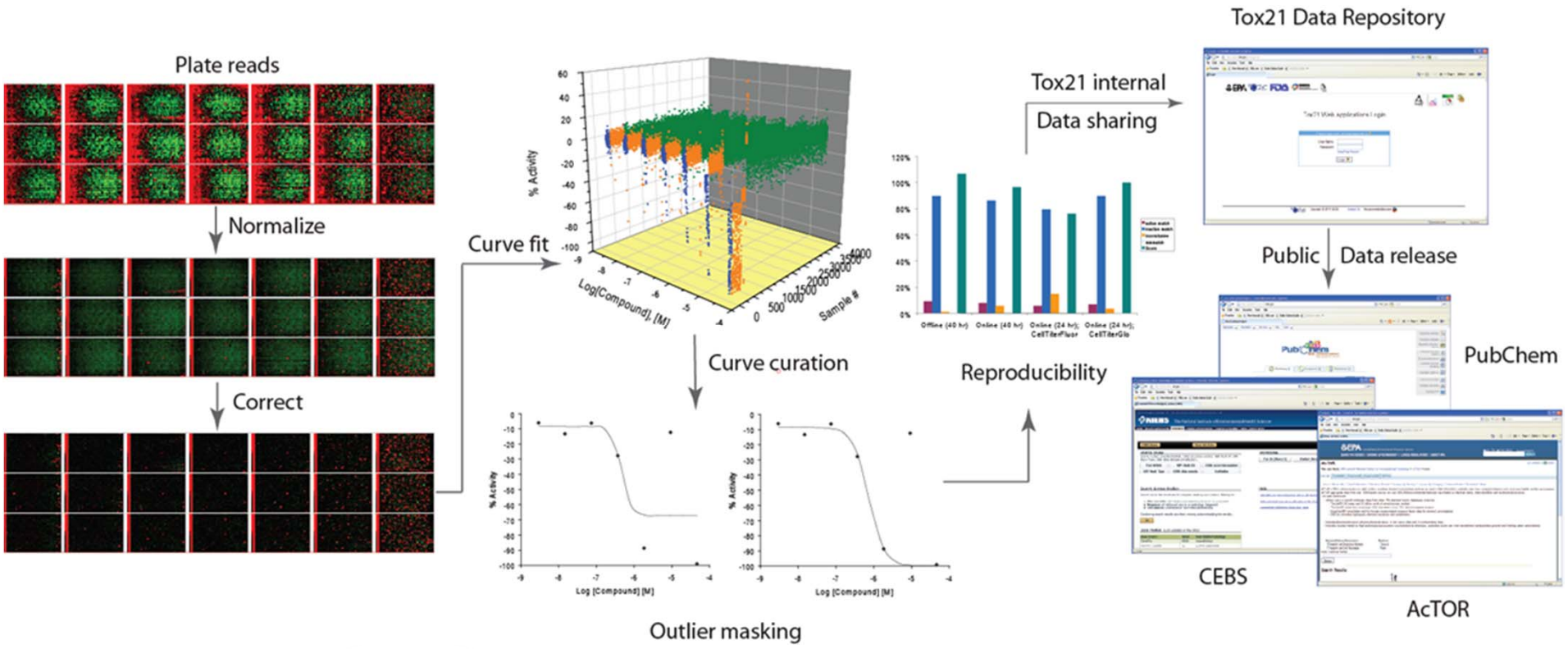
Assay Nomination and Validation Process

- Screening assay proposed and discussed by Assays and Pathways WG.
- Online validation on Tox21 Robot
  - Tox21 validation plate: Lopac^{1280} + 88 Tox21 replicates
  - Triplicate runs
- Acceptance criteria
  - Performance metrics: S/B ratio, Z' factor, CV
  - Reproducibility
  - Ability to recover reference compounds/known actives
- Pass
  - Proceed to 10K library screening
- Fail
  - Go back to optimization?
  - Select alternative assay?



Informatics Analysis Process



Tox21 Screening Outcomes

- Rapid testing of chemicals enabled through robotic screening, largest collection of environmental chemicals and drugs assembled, multiple Quality Control (QC) measures in place.
- Deposition into the public domain of the largest-ever toxicology dataset (>90M datapoints).
- Using crowdsourcing to move from data to knowledge.
- Estrogen receptor *in vitro* data being used by the EPA for regulatory purposes (https://www.epa.gov/endocrine-disruption/use-high-throughput-assays-and-computational-tools-endocrine-disruptor).
- Multiple organizations and consortia worldwide using Tox21 data (*e.g.*, eTox/IMI, Tiley *et al. Environ Int* 101:19-26 used Tox21 data to rank chemicals of concern at Superfund sites).

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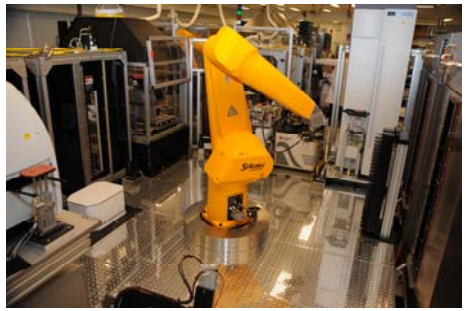
Tox21 Rapid Response to a Public Health Emergency: the EPA Oil Spill Dispersants Project

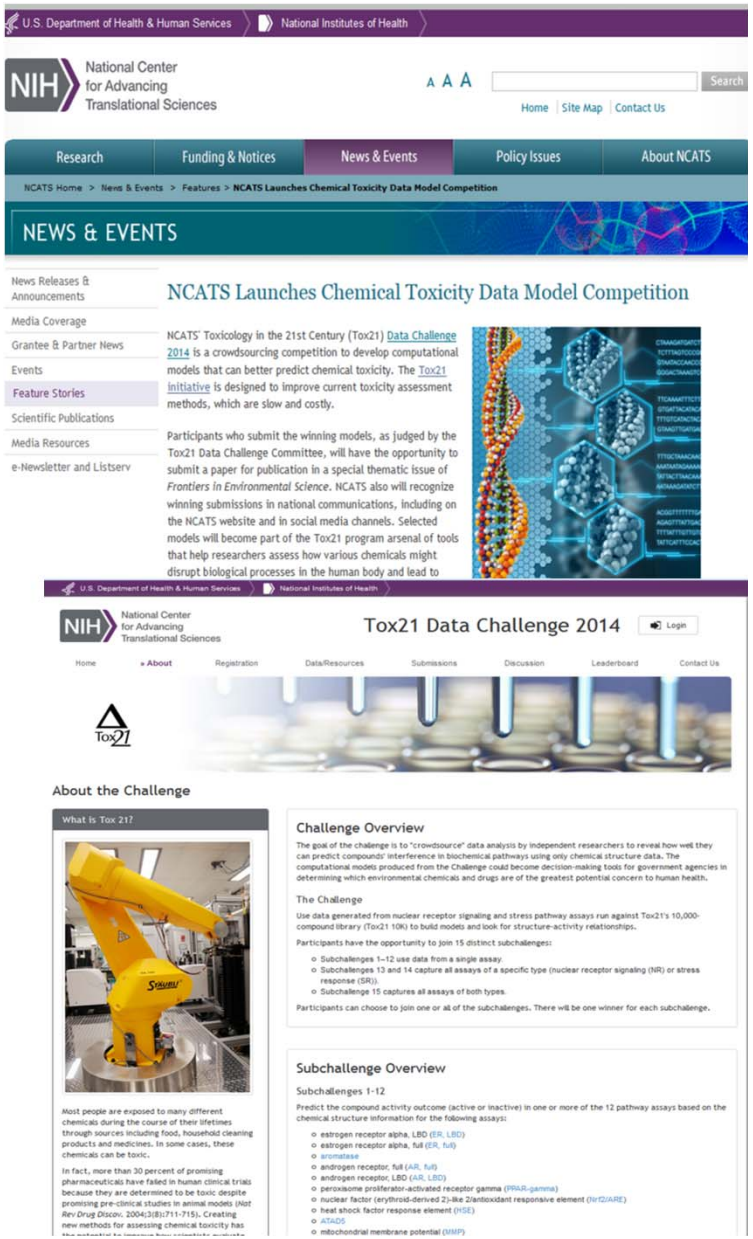
Task: using *in vitro* tests, evaluate as rapidly as possible the potential toxicities of dispersants to use in cleaning the Deepwater Horizon oil spill

- Project completed in 30 days from start to finish, including preparation of tests and dispersants, carrying out the tests, data analysis, and reporting.
- Corexit 9500, ultimately used for cleaning the oil spill in the Gulf of Mexico, did not show estrogenic and androgenic activity.
- Team received an Appreciation Award from the EPA.



Dissemination and utilization of data: model-building through “challenge” competitions

- Data:
  - 30 nuclear receptor signaling and stress pathway assays
  - 50M data points (15 pt CRs)
- Goal: models to predict toxicity assay response based on chemical structure
- 125 participants from 18 countries
- Winners announced Jan 2015, presentations at SOT2016
- Papers describing top models published in *Frontiers in Environmental Science*
- >80% accuracy of prediction for most top-scoring models



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Tox21 Limitations Being Addressed in the Next Phase

- Focus on the use of reporter gene assays using immortal cell lines
- Extent of chemical coverage, focus on single compounds
- Limited capability for xenobiotic metabolism
- Limited to acute exposure scenarios

ALTEX 2018 Mar 8; 35(2): 163-168. doi: 10.14573/altex.1803011

TRANSFORM TOX TESTING CHALLENGE: INNOVATING FOR METABOLISM

Key Development: Three federal agencies are offering toxicity test developers up to $1 million to modify high-throughput screens to predict the toxicity of chemical metabolites.

Potential Impact: If successful, the Tox Testing Challenge will improve the relevance and predictive capacities of automated tests that can quickly and simultaneously evaluate hundreds, even thousands, of chemicals.

http://www.transformtoxtesting.com/

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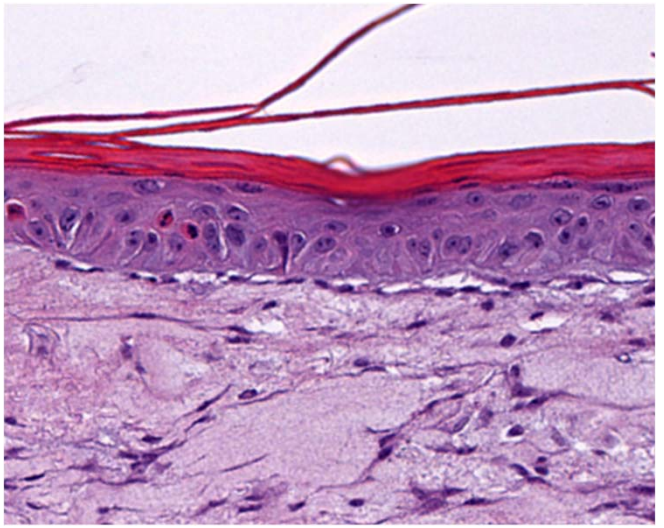
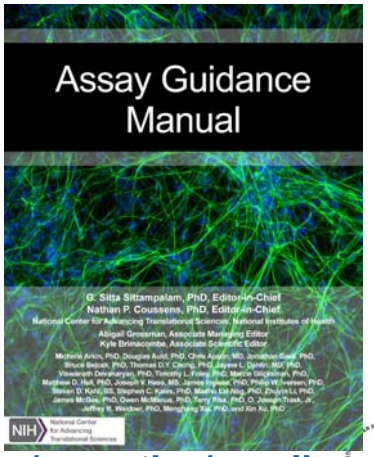
Tox21 Next Phase Focus Areas for NCATS

- Work with partners on the continuing evolution of the chemicals test set(s).
- Maintain supply of the approved-drugs (NPC) portion of the screening library.
- Increased use of physiologically relevant cells (*e.g.,* primary and iPS-derived) in HTS.
- Collaboration with EPA and NTP on improving the metabolic competence of HTS assays.
- Introduction and use of 3D models, such as those derived through 3D bioprinting.
- Continue building predictive models using Tox21 datasets.
- Dissemination: improved web site, AGM.



3D-bioprinted skin produced at NCATS



https://ncats.nih.gov/expertise/preclinical/agm

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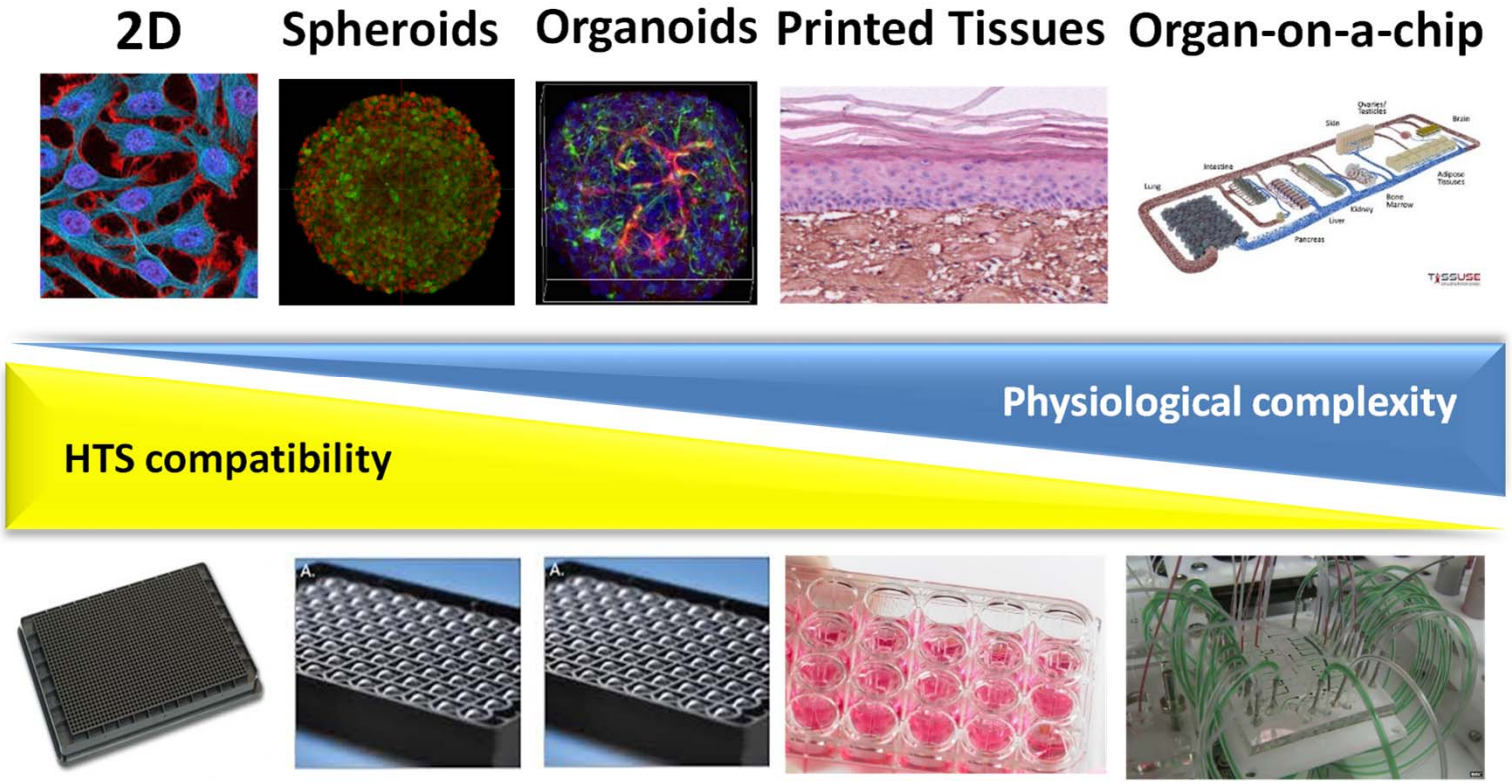
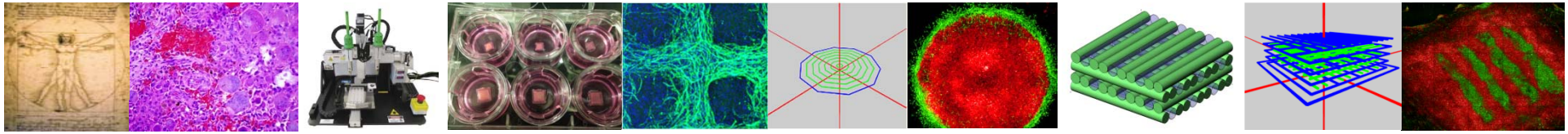
Increasing the predictivity of HTS: a continuum of 3D models of healthy and diseased tissues

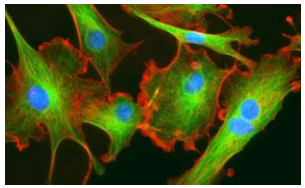


3D Tissue Bioprinting

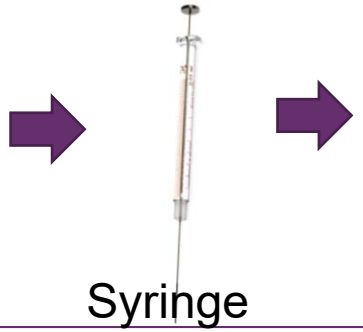


Gel

+



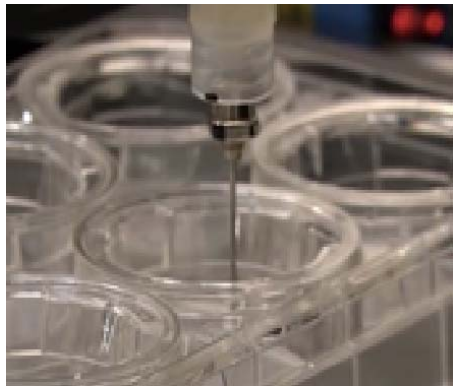
Cells



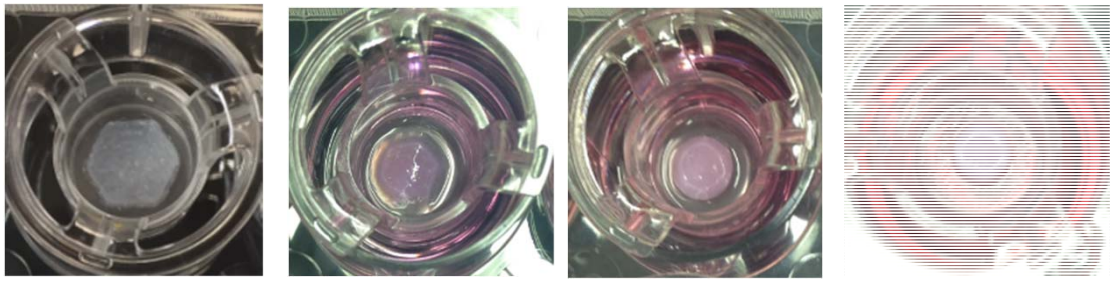
Syringe

Printer

Hydrogel polymer is mixed with cells and loaded into syringe.



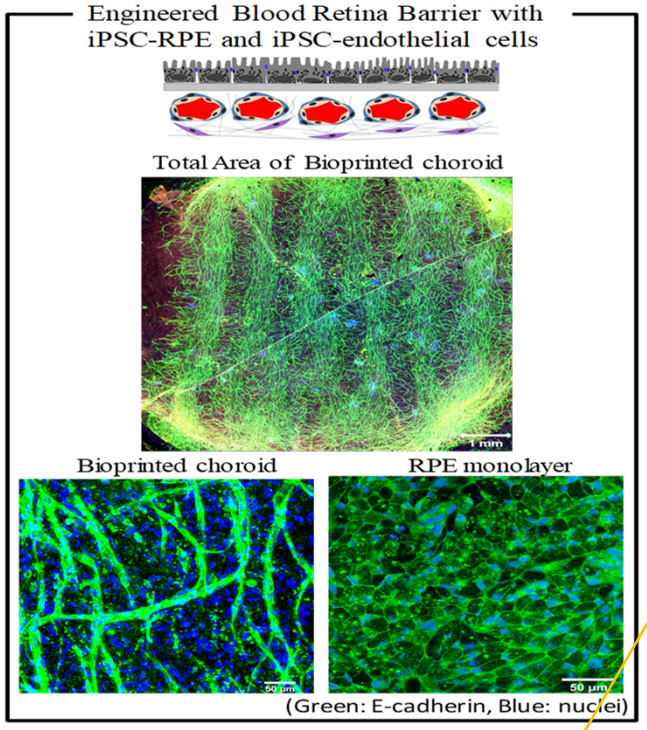
The printer “3D prints” the cell/gel mixture in a layer by layer approach.

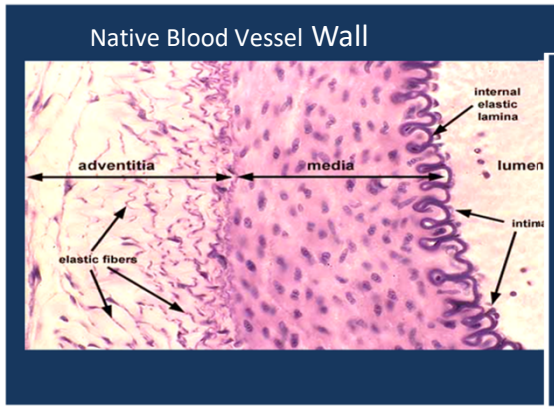


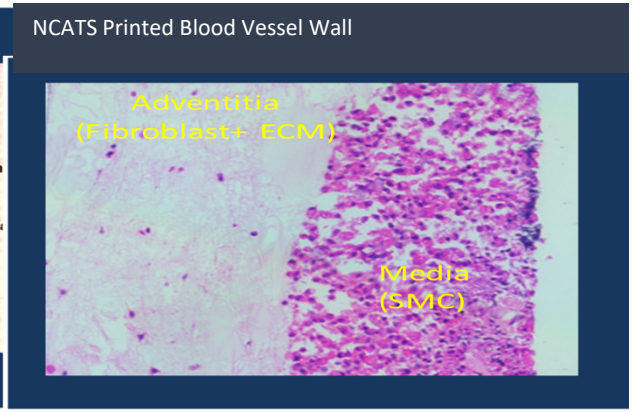
Printed construct 1 day 1 week 2 weeks

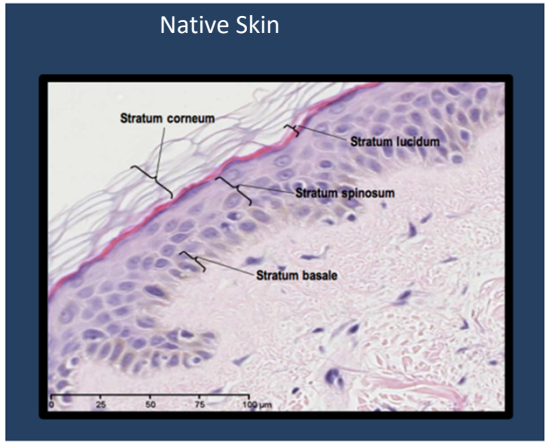
The printed construct is incubated to allow the cells to form a tissue, and to enable proper cell differentiation.

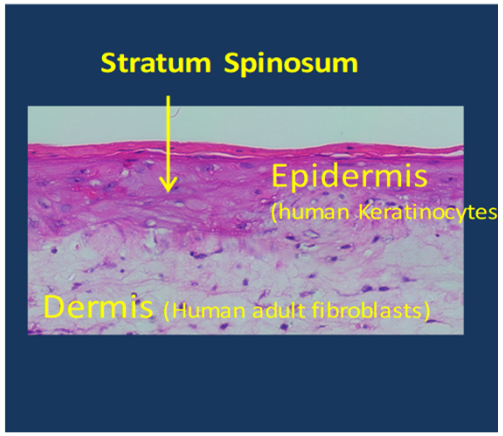
3D Bioprinting Pilot Projects











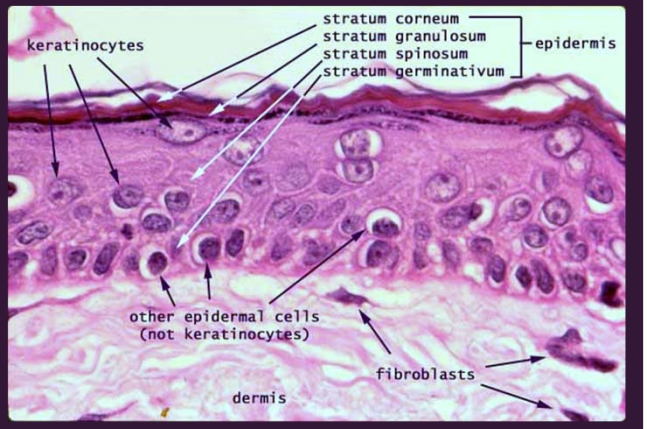
Blood vessel wall (Kan Cao, U of Maryland)

Retina (Kapil Bharti, National Eye Institute)

Skin (Angela Christiano, Columbia University)

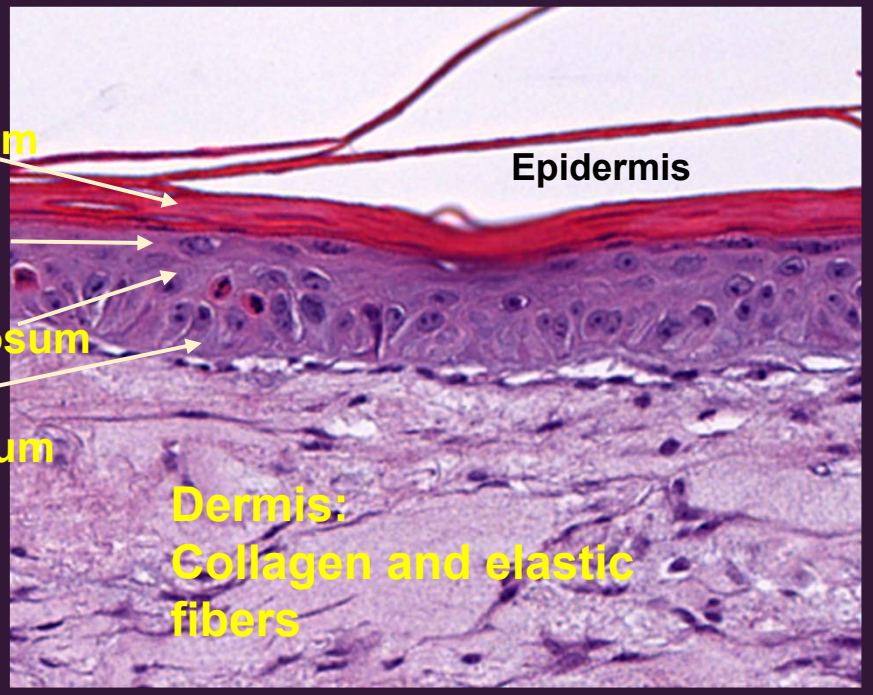
Layers of the Epidermis: native skin *versus* 3D-bioprinted skin

Native Skin



http://www.siumed.edu/~dking2/intro/IN005b.htm

3D-Bioprinted Skin



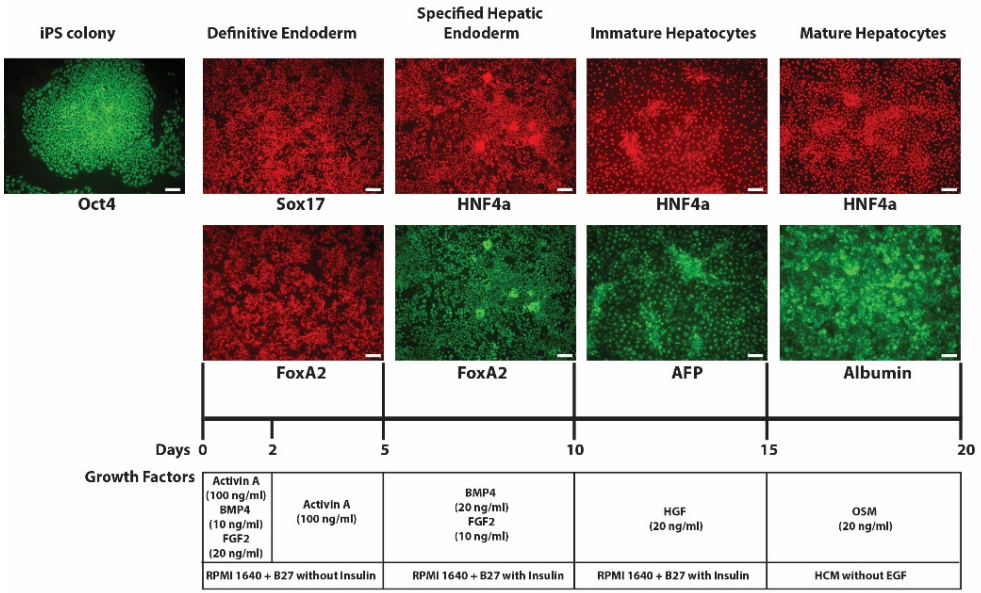
Improving chemical testing models to better predict effect in humans

Addressing roadblocks to utilization of induced pluripotent stem cells (iPSC)

- Problem: present methods for production of cells for drug screening and regenerative medicine are not cheap, standardized, and scalable.

- Solution: create a Stem Cell Translation Laboratory that uses cutting-edge technologies (single-cell proteomics, next-gen sequencing, screening technologies and chemistry) in order to:
  - Derive and disseminate Quality Control standards.
  - Dramatically improve methods for cell production by making them cheaper and more efficient, and demonstrating scalability, reproducibility, and transferability.

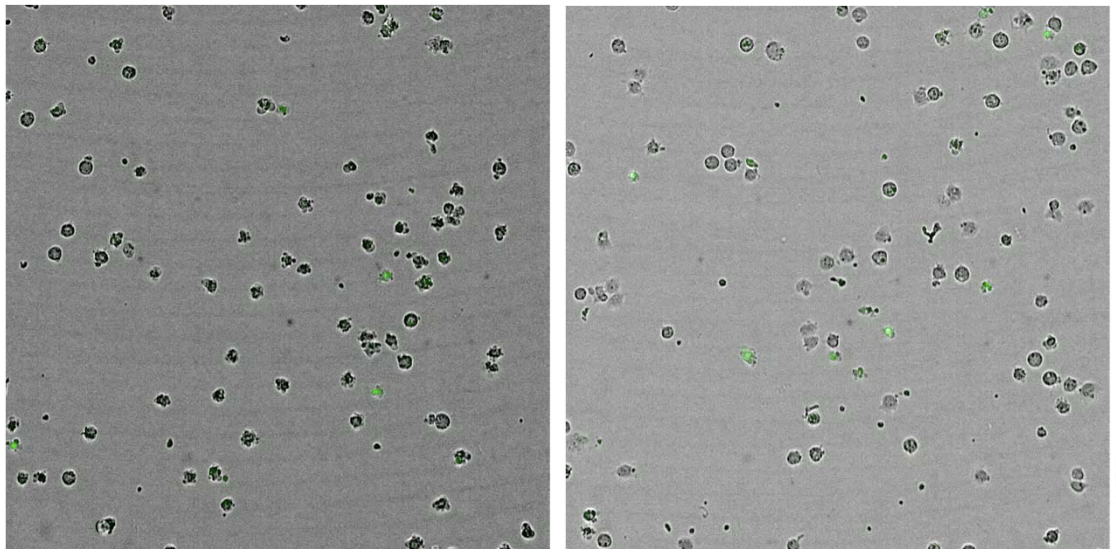
Example: *Fully-automated production of drug screen-ready liver cells from iPSCs*



Example: *A novel small molecule combination to promote stress-free scale-up of iPS cells*

Culturing of cells using the current methods:

Green=stress



Culturing of cells using the novel reagent combination to minimize stress.

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Sharing internal know-how: Assay Guidance Manual (47 chapters/ 1,338 printed pages)

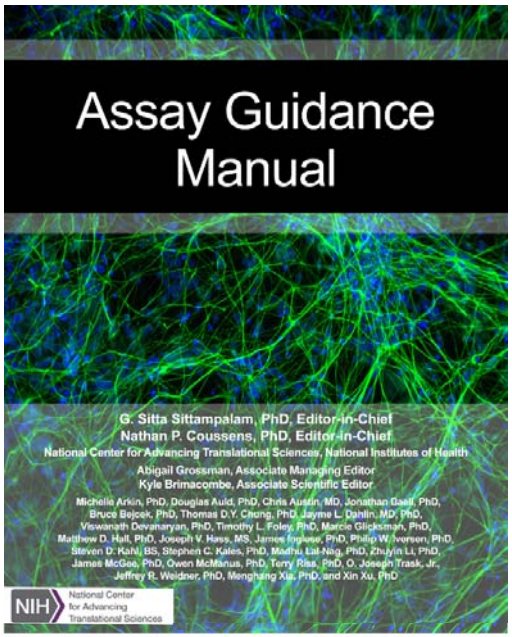
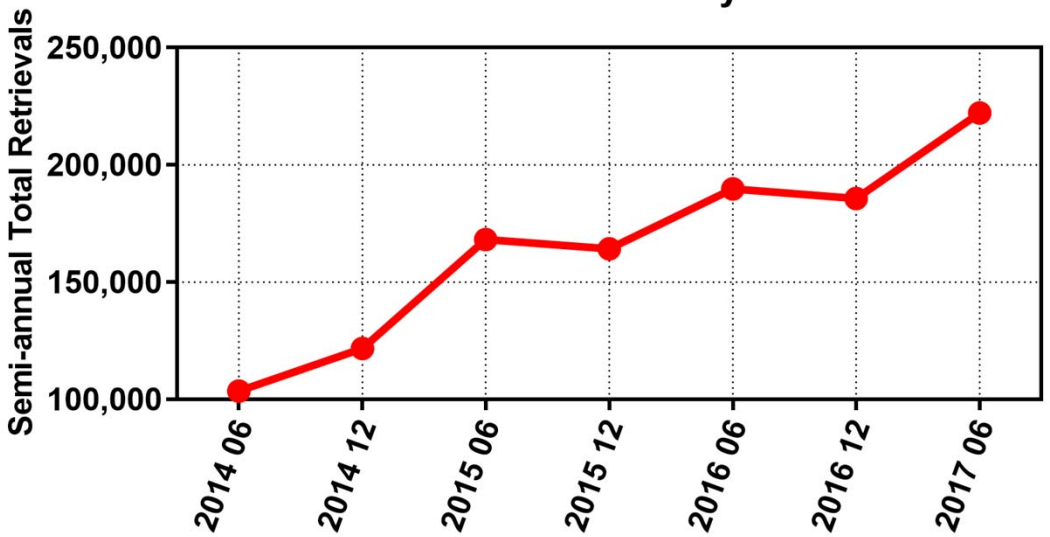


Table of Contents

Retrieval Statistics for the Assay Guidance Manual



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Q-State Biosciences
Promega Corporation
PerkinElmer, Inc.
QualSci Consulting, LLC
Merck Research Laboratories
Novartis Institute for Biomedical Research
NCATS

Lectures/Workshops to bring AGM to the community:

2017- October 23
University of North Carolina Chapel Hill, NC

2018- February 3
Society for Laboratory Automation and Screening Annual Conference
San Diego, CA

2018- March 26 and September 10
William F. Bolger Center
Potomac, MD

2019- February
Society for Laboratory Automation and Screening Annual Conference
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