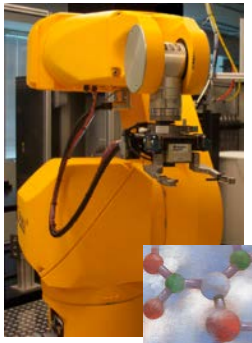

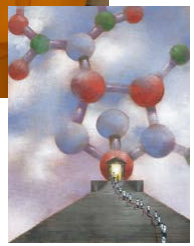

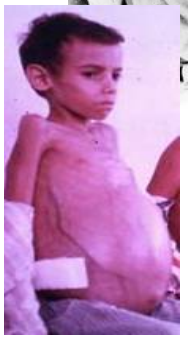

NCATS ICCVAM Update

Anton Simeonov, Ph.D.
Scientific Director, NCATS, NIH

ICCVAM Public Forum, Bethesda, May 25, 2016

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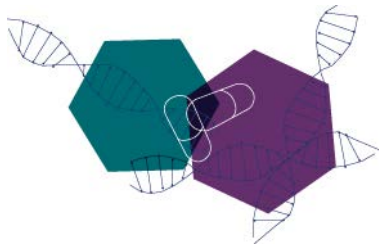


The Tox21 Program

Tox21 10K Compound Library

EPA

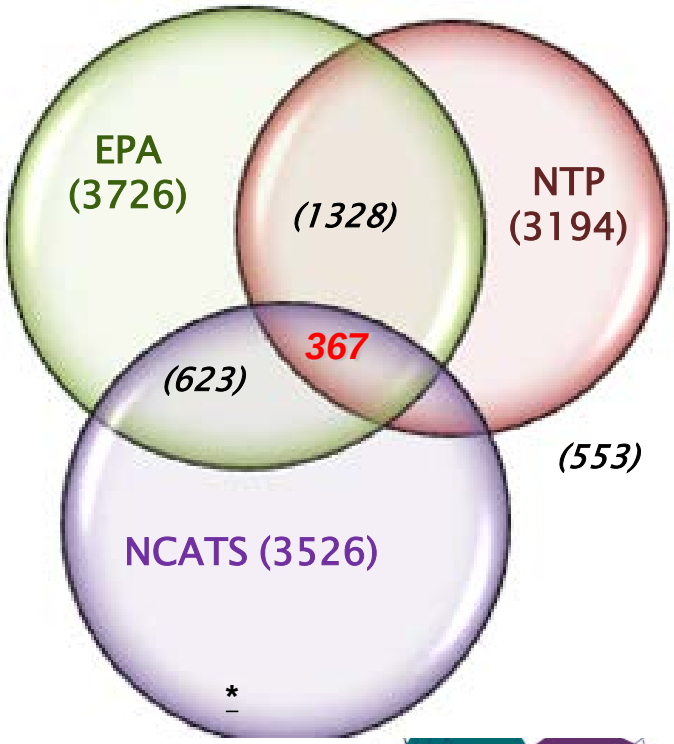
- ToxCast I and II compounds
- Antimicrobial Registration Program
- Endocrine Disruptor Screening Program
- OECD Molecular Screening Working Group
- FDA Drug Induced Liver Injury Project
- Failed Drugs

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
- Active pharmaceutical ingredients



- *88 single-sourced cmpds in duplicate on each plate*
- *Three replicates, cmpds positionally-varied*

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Entire-Library QC Project

- Multi-year undertaking using a range of LC- and GC-MS methods.
- >7000 analytical chromatograms in PDF format available through PubChem: http://www.ncbi.nlm.nih.gov/pcsubstance

Identification

Depositor-Supplied Synonyms

DOLASETRON MESYLATE
DSSTox_CID_26827
DSSTox_RID_81939
DSSTox_GSID_46827
Tox21_112695
NCGC00181048-01
CAS-115956-13-3

... see more options

Substance Information

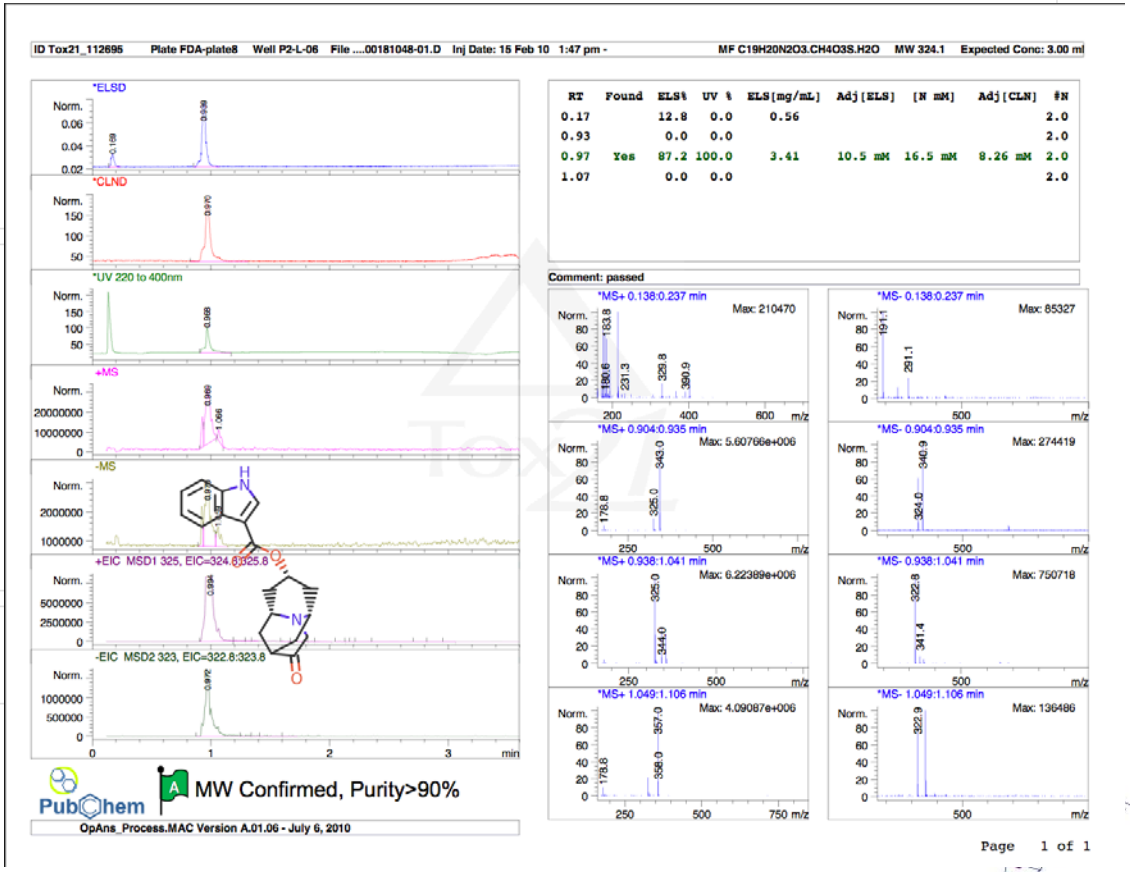
SID 144206248
Deposit Date: 2012-10-06
Modify Date: 2014-12-12
Substance Version: 2

Data Source:
Depositor: Tox21
External ID: NCGC00181048-01

Compound CID: 3033817

Depositor Comments

TOX21S_v5a



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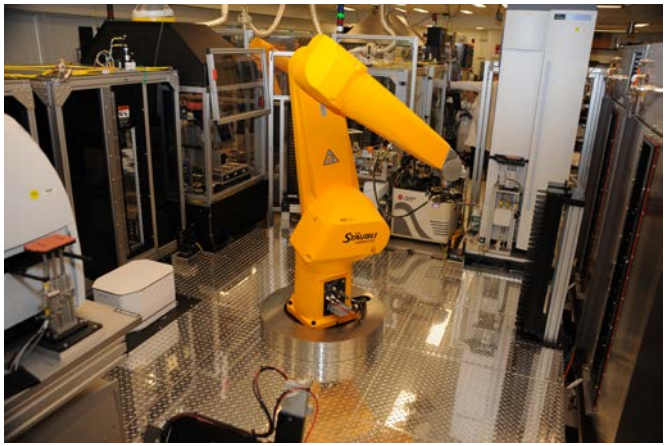
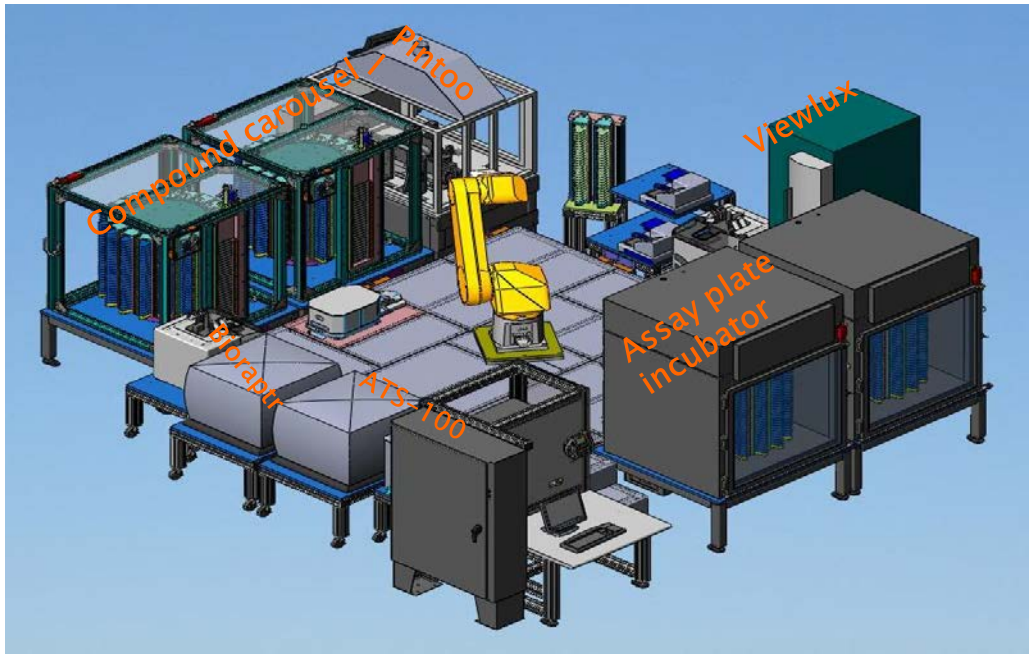
Tox21 Robot Platform





ViewLux Multilabel Reader

- Absorbance
- Fluorescence
- F.P.
- Luminescence
- TR-FRET
- Top reading

EnVision Multilabel Reader

- Absorbance
- Fluorescence
- F.P.
- Luminescence
- TR-FRET
- AlphaScreen
- Top/Bottom reading

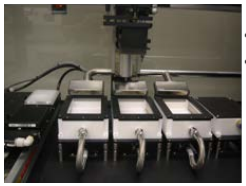
BioRAPTR FRD Workstation

- Transfer size: 0.2 - 10 ul
- 0.5 ml dead volume
- 4 reagents

Multidrop Combi

- Transfer size: 2 - 10 ul
- 10 ml dead volume
- 1 reagent

Pintool Station



- Transfer size: 20 nl
- Pins washed in 3 solvents

- Compound plate storage and assay plate incubator
- Pintool station and acoustic dispenser for nanoliter compound transfer
- Reagent dispensers (BioRPTR, Multidrop)
- Centrifuge (V-spin)
- Plate readers (ViewLux and EnVision)

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10K Screening Status (2014-2016)

SCREEN ORDER	ASSAY TARGET	CELL LINES	SPECIES	TISSUE OF ORIGIN	ASSAY READOUT	ASSAY PROVIDER	TOXICITY PATHWAY	SCREEN MODE	CYTOTOXICITY READOUT	DATE COMPLETED
1	EndoR (ESRE)	Hela	Human	Cervical carcinoma	beta-lactamase reporter	Invitrogen	Stress response	Agonist	CellTiter-Glo	Feb 28th, 2014
2	NFkB	ME-180	Human	Cervical carcinoma	beta-lactamase reporter	Invitrogen	Stress response	Agonist	CellTiter-Glo	Mar 15th, 2014
3	Retinol signaling pathway (RSP)	C3H10T1/2	Mouse	Embryonic connective tissue	CellTiter-Glo	FDA	Developmental Tox	Viability	CellTiter-Glo	April 3rd, 2014
4	Retinol signaling pathway (RSP)	C3H10T1/2	Mouse	Embryonic connective tissue	Luciferase reporter	FDA	Developmental Tox	Agonist		June 12th, 2014
5	RORr (Retinoid-related Orphan Receptor gamma)	CHO	Hamster	Chinese hamster ovary	CellTiter-Glo	NTP	NR signaling	Viability	CellTiter-Glo	July 25th, 2014
6	RORr (Retinoid-related Orphan Receptor gamma)	CHO	Hamster	Chinese hamster ovary	Luciferase reporter	NTP	NR signaling	Antagonist		Aug 15th, 2014
7	Retinoid X receptor alpha, LBD	HEK 293	Human	Embryonic kidney cells	beta-lactamase reporter	Invitrogen	NR signaling	Agonist	CellTiter-Glo	Aug 22nd, 2014
8	Retinol signaling pathway (RSP)	C3H10T1/2	Mouse	Embryonic connective tissue	CellTiter-Glo	FDA	Developmental Tox	Viability	CellTiter-Glo	Aug 29th, 2014
9	AP-1	ME-180	Human	Cervical carcinoma	beta-lactamase reporter	Invitrogen	Stress response	Agonist	CellTiter-Glo	Sept 17th, 2014
10	Retinol signaling pathway (RSP)	C3H10T1/2	Mouse	Embryonic connective tissue	Luciferase reporter	FDA	Developmental Tox	Antagonist		Sept 26th, 2014
11	Real time cytotoxicity and viability	HEK 293	Human	Embryonic kidney cells	Fluorescence/Luminescence	Promega	Stress response	Antagonist	CellTox-Green and Nanoluc	Jan 29th, 2015
12	Real time cytotoxicity and viability	HepG2	Human	Embryonic kidney cells	Fluorescence/Luminescence	Promega	Stress response	Antagonist	CellTox-Green and Nanoluc	Mach 6th, 2015
13	pH2AX	CHO	Hamster	Chinese hamster ovary	HTRF*	Cisbio	Stress response	Agonist	N/A	Mach 25, 2015
14	pH2AX	CHO	Hamster	Chinese hamster ovary	CellTiter-Glo	Cisbio	Stress response	Viability	CellTiter-Glo	Apirl 3, 2015
15	Hypoxia/Hif-1	ME-180	Human	Cervical carcinoma	beta-lactamase reporter	Invitrogen	Stress response	Agonist	CellTiter-Glo	May 6th, 2015
16	Androgen receptor, full	MDA-kb-2	Human	Breast cancer line	Luciferase reporter	EPA	NR signaling	Antagonist	CellTiter-Fluor	May 20th, 2015
17	Constitutive androstane receptor (CAR), full	HepG2	Human	Hepatocellular carcinoma	Luciferase reporter	UMD	NR signaling	Antagonist	CellTiter-Fluor	June 10th, 2015
18	Constitutive androstane receptor (CAR), full	HepG2	Human	Hepatocellular carcinoma	Luciferase reporter	UMD	NR signaling	Agonist	CellTiter-Fluor	June 24th, 2015
19	Estrogen receptor alpha, full	BG1	Human	Ovarian adenocarcinoma	Luciferase reporter	UC Davis	NR signaling	Antagonist	CellTiter-Fluor	July 31th, 2015
20	Luciferase	None	otinus Pyralis		Luminescence	NCGC	Luciferase inhibition	Antagonist	N/A	Aug 28th, 2015
21	Estrogen related receptors (ERR) with PGC (coactivator)	HEK 293	Human	Embryonic kidney cells	Luciferase reporter	NTP	NR signaling	Agonist/Antagonist	CellTiter-Fluor	Oct 8th, 2015
22	Estrogen related receptors (ERR)	HEK 293	Human	Embryonic kidney cells	Luciferase reporter	NTP	NR signaling	Agonist/Antagonist	CellTiter-Fluor	Oct 30th, 2015
23	Thyroid stimulating hormone receptor (TSHR)	HEK 293	Human	Embryonic kidney cells	HTRF	NCGC /Cisbio	GPCR/cAMP signaling	Agonist	N/A	Nov 23th, 2015
24	Thyroid stimulating hormone receptor (TSHR)	HEK 293	Human	Embryonic kidney cells	HTRF	NCGC /Cisbio	GPCR/cAMP signaling	Antagonist	N/A	April 15th, 2016
25	HDAC I/II	HCT-116	Human	Colon cancer	HDAC-Glo I/II	Promega	Epigentics	Antagonist	N/A	April 27th, 2016
26	HDAC I/II	HCT-116	Human	Colon cancer	CellTiter-Glo	Promega	Viablility	Antagonist	CellTiter-Glo	May 5th, 2016
27	Sonic hedgehog/Gli signaling	3T3	Mouse	Embryonic connective tissue	Luciferase reporter	FDA	Developmental Tox	Agonist	CellTiter-Fluor	In progress
28	Non-specific cAMP signaling	HEK 293	Human	Embryonic kidney cells	HTRF*	NCGC /Cisbio	GPCR/cAMP signaling	Agonist	N/A	In queue
29	Sonic hedgehog/Gli signaling	3T3	Mouse	Embryonic connective tissue	Luciferase reporter	FDA	Developmental Tox	Antagonist	CellTiter-Fluor	In queue
30	Smad signaling pathway/SBE (SMAD Binding Element)	HEK 293	Human	Embryonic kidney cells	Beta-lactamase reporter	NCGC/Invitrogen	Developmental Tox	Agonist	CellTiter-Glo	In queue
31	Smad signaling pathway/SBE (SMAD Binding Element)	HEK 293	Human	Embryonic kidney cells	Beta-lactamase reporter	NCGC/Invitrogen	Developmental Tox	Antagonist	CellTiter-Glo	In queue

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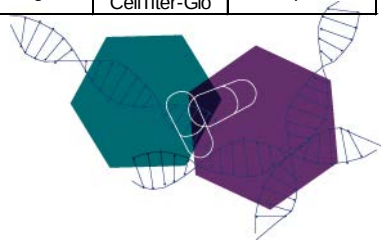
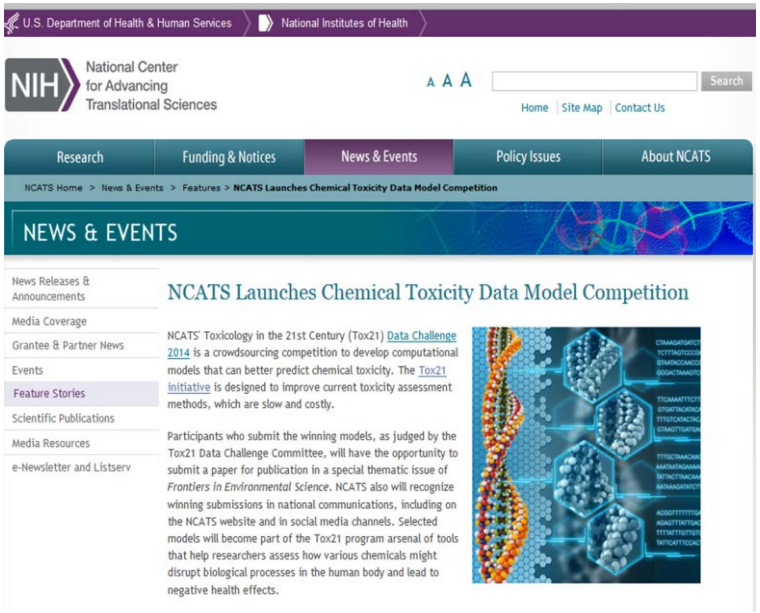
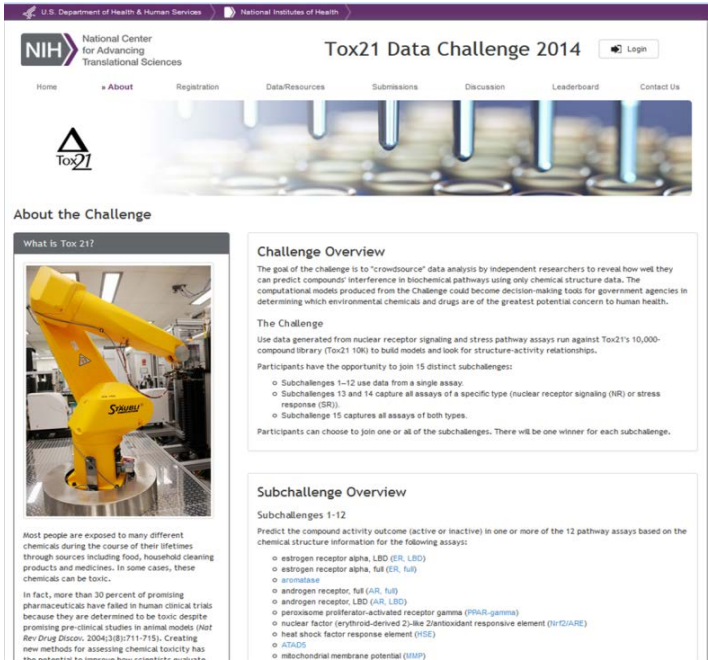


Model Building Based on Tox21 Data

- Data:
  - 30 nuclear receptor signaling and stress pathway assays
  - ~8,400 drugs and env chemicals
  - 50M data points (15 pt CRs)
- Goal: Models to predict toxicity assay response based on chemical structure
- 125 participants from 18 countries
- Winners announced 26 Jan 2015
- Papers now being published in *Frontiers in Environmental Science*





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Data Challenge Winners' Presentations at SOT 2016

Wednesday Morning, March 16
9:30 AM to 12:15 PM
CC Room R04

IS

Informational Session: Tox21 Challenge To Build Predictive Models of Nuclear Receptor and Stress Response Pathways As Mediated by Exposure to Environmental Toxicants and Drugs

- **Molecular Toxicology: Mechanistic Insights and Hazard Assessment**

Chairperson(s): *Menghang Xia, NCATS/NIH, Bethesda, MD; and Ruili Huang, NCATS/NIH, Bethesda, MD.*

Endorser(s):
American Association of Chinese in Toxicology Special Interest Group
Biological Modeling Specialty Section
***In Vitro* and Alternative Methods Specialty Section**

9:35	**Overview of *In Vitro* Assay Selection for the Tox21 HTS Program.** *M. Xia.* NCATS/NIH, Bethesda, MD.
10:00	**Overview of the Tox21 Phase II Data and the Modeling Challenge.** *R. Huang.* NCATS/NIH, Bethesda, MD.
10:25	**DeepTox: Toxicity Prediction Using Deep Learning.** G. Klambauer. Institute of Bioinformatics, Johannes Kepler University, Linz, Austria. Sponsor: *M. Xia.*
10:50	**Consensus Approach for Modeling HTS Assays Using *In Silico* Descriptors.** A.A. Sayed. Technical University of Munich, Munich, Germany. Sponsor: *M. Xia.*
11:15	**Identifying Biological Pathway-Interrupting Toxins Using Multi-Tree Ensembles.** G. Barta. Budapest University of Technology, and Economics, Budapest, Hungary. Sponsor: *M. Xia.*
11:40	**Construction of Discrimination Models for Identifying Compounds That Activate Toxicity-Related Proteins Based on the Rigorous Selection of Random Forest Models.** Y. Uesawa, Meiji Pharmaceutical University, Meiji, Japan. Sponsor: *M. Xia.*
12:05	**Panel Discussion/Q&A.**

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Dissemination of Models: Special Issue, Frontiers in Environmental Science

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Research Topic

Tox21 Challenge to Build Predictive Models of Nuclear Receptor and Stress Response Pathways as Mediated by Exposure to Environmental Toxicants and Drugs

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Submission closed.

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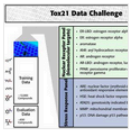
Articles

By Views | By Type | By Date



DeepTox: Toxicity Prediction using Deep Learning

Andreas Mayr, Günter Klambauer, Thomas Unterthiner and Sepp Hochreiter

Original Research The Tox21 Data Challenge has been the largest effort of the scientific community to compare computational methods for toxicity prediction. This challenge comprised 12,000 environmental chemicals and drugs which were measured for 12 different toxic ...

Published on 02 February 2016
Front. Environ. Sci. doi: 10.3389/fenvs.2015.00080

1,408 views Altmetric 1

Molecular similarity-based predictions of the Tox21 screening

Tox21Challenge to Build Predictive Models of Nuclear Receptor and Stress Response Pathways as Mediated by Exposure to Environmental Chemicals and Drugs

Ruili Huang, Menghang Xia, Dac-Trung Nguyen, Tongan Zhao, Srilatha Sakamuru, Jinghua Zhao, Sampada A. Shahane, Anna Rossoshek and Anton Simeonov

Original Research Tens of thousands of chemicals with poorly understood biological properties are released into the environment each day. High-throughput screening (HTS) is potentially a more efficient and cost-effective alternative to traditional toxicity tests. ...

2016
.3389/fenvs.2015.00085

Consensus Modeling for HTS Assays Using In silico Descriptors Calculates the Best Balanced Accuracy in Tox21 Challenge

Ahmed Abdelaziz, Hilde
Karl-Werner Schramm a

Original Research The need for filling informa reducing toxicity testing in animals is becomin in risk assessment. Recent legislations are acce approaches for predicting toxicological outcor describes the ...

Published on 04 February 2016
Front. Environ. Sci. doi: 10.3389/fenvs.2016.00

448 views Altmetric 1

Rigorous Selection of Random Forest Models for Identifying Compounds that Activate Toxicity-Related Pathways

Yoshihiro Uesawa

Original Research Random forest (RF) is a machine-learning ensemble method with high predictive performance. Majority voting in RF uses the discrimination results in numerous decision trees produced from bootstrapping data. For the same dataset, the bootstrapping ...

Published on 15 February 2016
Front. Environ. Sci. doi: 10.3389/fenvs.2016.00009

190 views Altmetric 1

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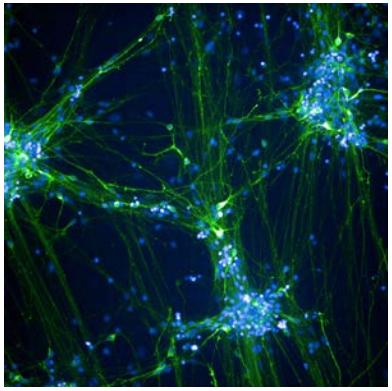
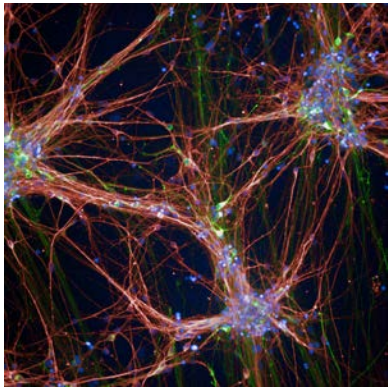
Towards Improved Models: Stem Cell Translation Laboratory (SCTL)

- Establish QC standards to define pluripotency and differentiated cell types.
- Develop methods to assess heterogeneity in iPSC-derived cells.
- Develop standardized methods to produce mature cells meeting the QC standards above.
- Discover, validate, and disseminate small molecule reagents to replace expensive recombinant proteins, xenogenic material, and undefined media components in cell differentiation protocols.
- Current status.
  - SCTL head recruited, team being formed, pilot experiments initiated.
  - Renovation of lab space for SCTL beginning shortly.

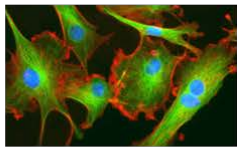




Towards Improved Models: 3D Bio-Printing

Gel

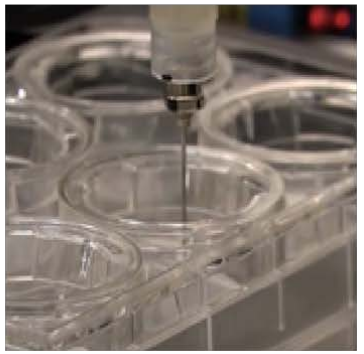
+



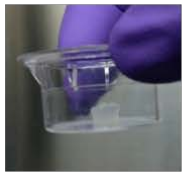
Cells

+

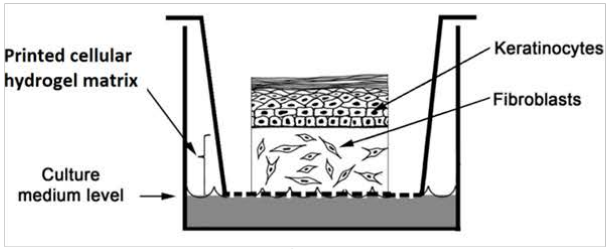
printer



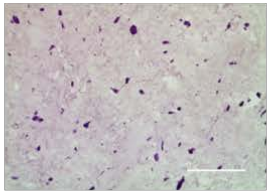
Hydrogel polymer is mixed with cells and loaded into syringe. The printer "3D prints" the cell/gel mixture in a layer by layer approach.



Construct



Incubation



Printed dermal region

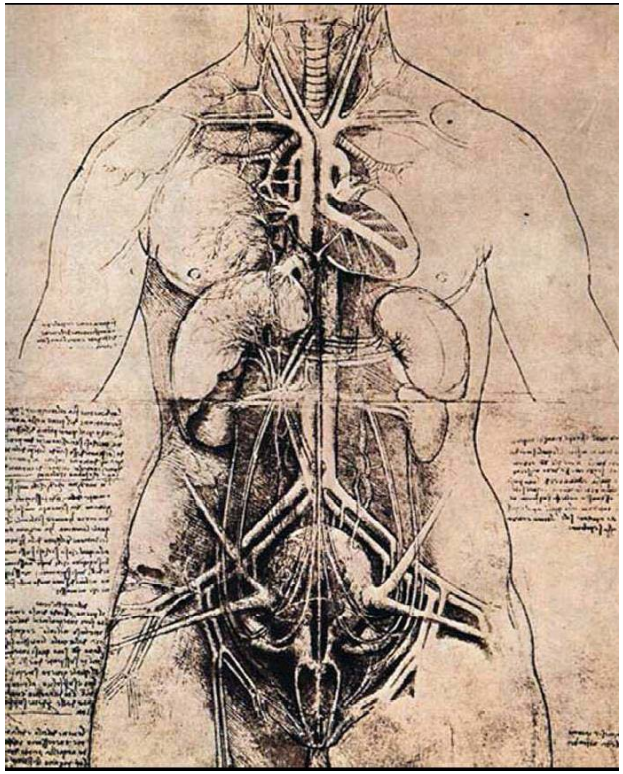
Native tissue

Tissue histology

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

Microphysiological Systems Program ("Tissue Chips")

GOAL: Develop an *in vitro* platform that uses <u>human</u> tissues to evaluate the efficacy, safety and toxicity of promising therapies.



- All ten human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Integumentary
  - Musculoskeletal
  - Nervous
  - Reproductive
  - Respiratory
  - Urinary
- Physiologically relevant, genetically diverse, and pathologically meaningful.
- Modular, reconfigurable platform.
- Tissue viability for at least 4 weeks.
- Community-wide access.

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Program Director: Danilo Tagle, Ph.D.
danilo.tagle@nih.gov

Tissue Chip Program Status

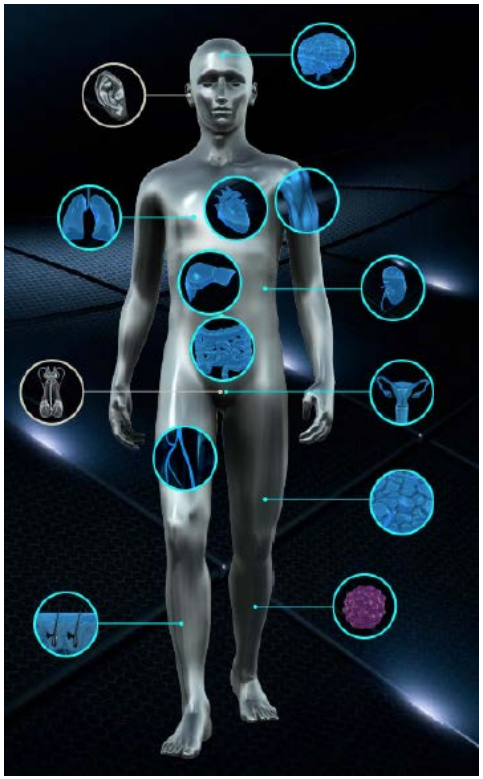
National Institutes of Health

Phase 1: Development

Phase 2: Cell incorporation & organ integration

2012–13 | 2013–14 | 2014–15 | 2015–16 | 2016–17

DARPA base periods: Organ integration



**FDA provides insight and expertise throughout the program

National Institutes of Health

Current Goals:

- Integration
- Compound testing
- Validation
- Partnerships
- Adoptions of the tech by the community

National Center for Advancing Translational Sciences

Future Directions in Tissue-on-chips Technology

Human Fibroblasts

Genetic reprogramming

iPSCs

Differentiation/maturation into all major organs

Druggable Genome
- Gene Editing on isogenic background for physiological differences among diverse populations:
- Genetic variation
- Examine various demographics
- Gender or age variation

FY16 **Tissue-Chips Testing Centers**

Rare disease research and therapeutics

Precision Medicine (you-on-chip)
- Drug response in individuals
- Individualized medicine and therapeutics

Disease Modeling

FY17
- Disease pathogenesis
- Dissecting mutations in isogenic background

Human-on-a-Chip

Clinical Trials on Chips

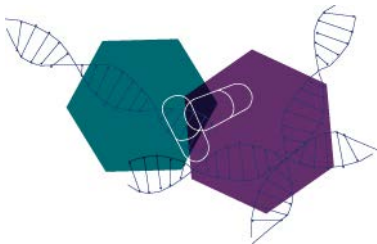
FY17 **Tissue Chips in Space**

Microbiome

Environmental Toxins

Infectious disease

Countermeasure Agents



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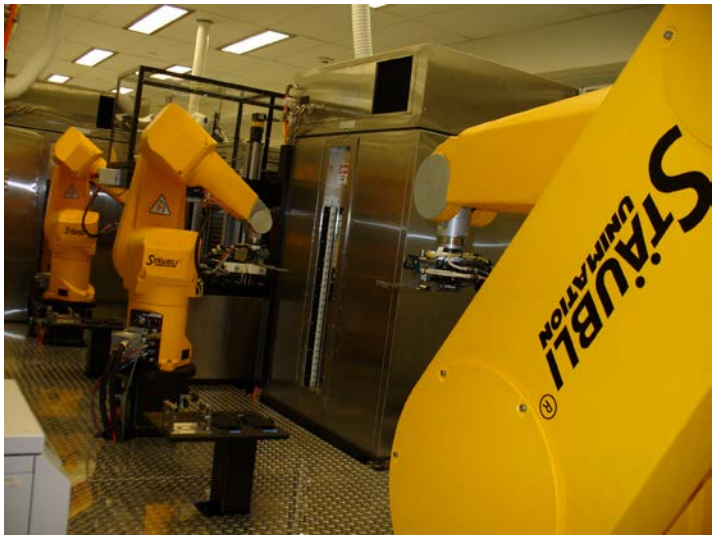
Additional Information



asimeono@mail.nih.gov