JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Toward Toxicology for the 21st Century 2.0

Slides available

Thomas Hartung & team

frontiers in Big Data

Chief Editor

frontiers in Artificial Intelligence

AstraZeneca

ATCC

AxoSim
Human Data, Faster.

VP, shareholder

MPS

inSphero

Apellis

A.I.

UL **Consultant**

Green Chemistry Advisory Panel

Pyrogen

MERCK MILLIPORE

BIOMÉRIEUX

ToxTrack

Consultant, shareholder

In preparation: Insilica LLC

Almost 16,000 active learners

Since 2018

Toxicology 21:
Scientific Applications

Johns Hopkins University

8500+ enrolled learners

Since 2019

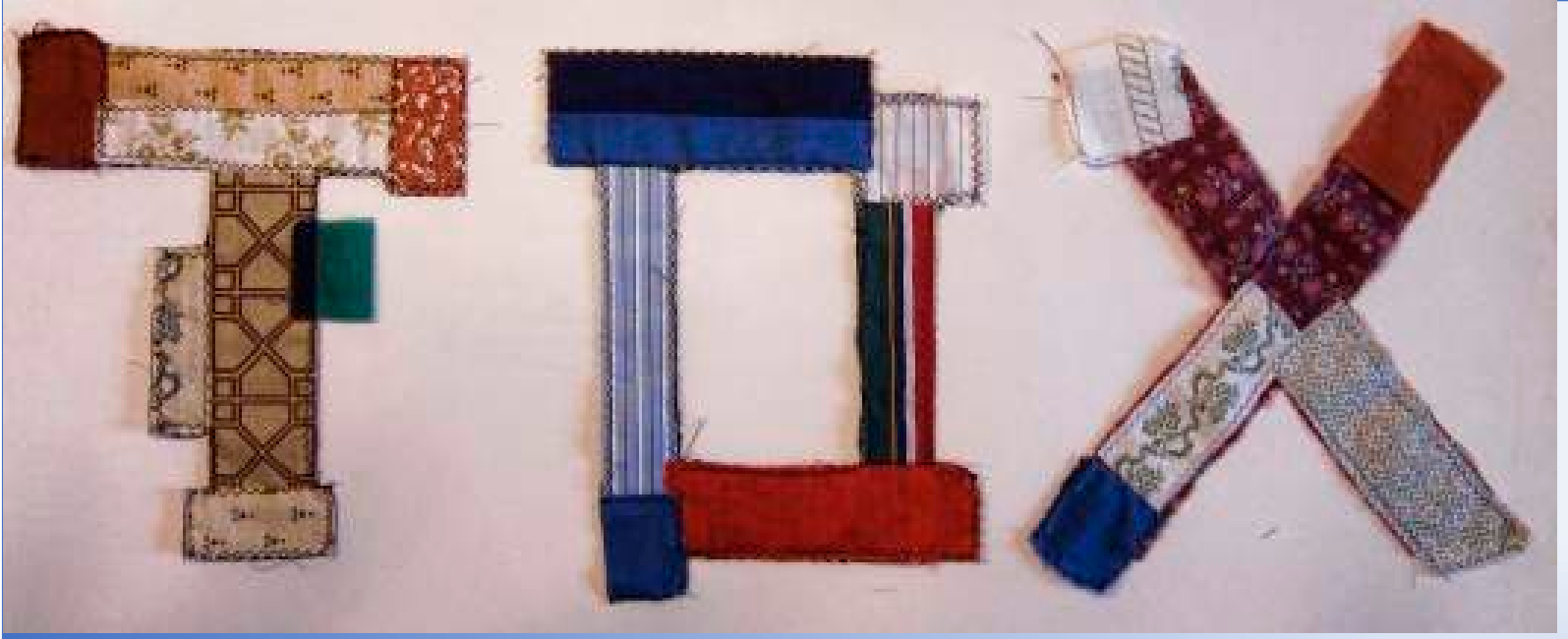
Evidence-based
Toxicology

Johns Hopkins University

7000+ enrolled learners

coursera

Massive Open Online Courses platform



The evolution of toxicology: patchwork

- Every scandal gives one patch
- Many patches are 50-80 years old
- No way to remove a patch
- Every patch is of its own appearance and workmanship
- Throughput, costs, reproducibility
- Public opinion

Food for Thought ...

The State of the Scientific Revolution in Toxicology

Thomas Hartung[1,2] and Aristides M. Tsatsakis[3]

No revolution in quite a while

Reproducibility

Six most frequent toxicity tests

Consuming 57% of animals in tox

Mice and rat predict each other ~60% for systemic tox

350-750 chemicals with repeat tests
(n = 2,839, up to ~100 repeats)

81% reproducible
69% reproducible for toxic chemicals

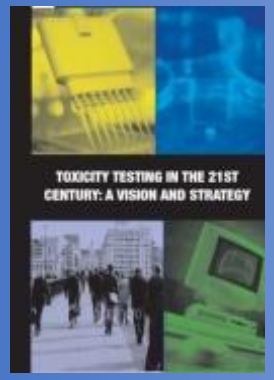
Luechtefeld et al., ToxSci 2018

Watershed moment
2007 NRC report

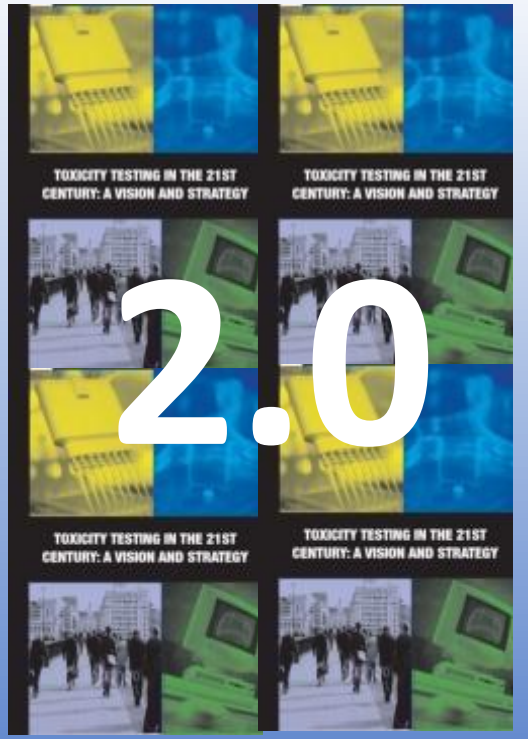
Toxicity testing in the 21st century: progress in the past decade and future perspectives

Arch Toxicol 2019

D. Krewski[1,2,4] · M. E. Andersen[3] · M. G. Tyshenko[2,4] · K. Krishnan[2,5] · T. Hartung[6,13] · K. Boekelheide[7] · J. F. Wambaugh[8] · D. Jones[9] · M. Whelan[10] · R. Thomas[8] · C. Yauk[11] · T. Barton-Maclaren[11] · I. Cote[12]



Doubling every seven years



Call for a Human Exposome Project, in press

Co-Chairs

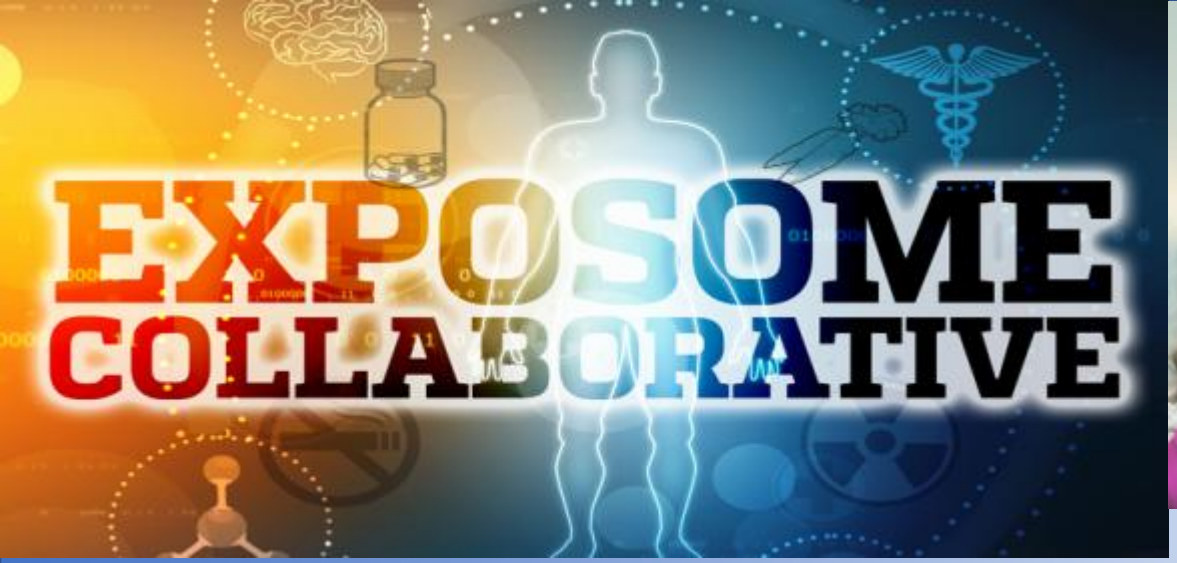
Ana Navas-Acien, Weihsueh A. Chiu & Thomas Hartung

What is emerging that can help us?

Exposure science (high throughput and untargeted exposomics, remote sensing, citizen science …)

Technologies (~omics, high-throughput, MPS, A.I.)

Evidence Integration (Evidence-based Tox, IATA, Green Tox Investigative Tox, Mechanistic Validation, Probabilistic Risk Assessment, Systems Toxicology, virtual experiments…)



Fenna Sillé

Johns Hopkins Discovery Awards

ALTEX 2020, 37, 3-23

"Progress is impossible without change, and those who cannot change their minds cannot change anything."
George Bernard Shaw (1856-1950)

"If you change the way you look at things, the things you look at change."
Wayne Dyer (1940-2015)

Food for Thought ...

The Exposome – a New Approach for Risk Assessment

Fenna Sillé[1], Spyros Karakitsios[2], Andre Kleensang[1], Kirsten Koehler[1], Alexandra Maertens[1], Gary W. Miller[3], Carsten Prasse[1], Lesliam Quiros-Alcala[1], Gurumurthy Ramachandran[1], Stephen M. Rappaport[4], Ana M. Rule[1], Denis Sarigiannis[2,5], Lena Smirnova[1] and Thomas Hartung[1,6]

Exposome & A.I. = E.I. (Exposome Intelligence)

What is emerging that can help us?

Exposure science (high throughput and untargeted exposomics, remote sensing, citizen science …)

Technologies (~omics, high-throughput, MPS, A.I.)

Evidence Integration (Evidence-based Tox, IATA, Green Tox Investigative Tox, Mechanistic Validation, Probabilistic Risk Assessment, Systems Toxicology, virtual experiments…)

A.I. = Making big sense of

Power of computers doubles every 2 years

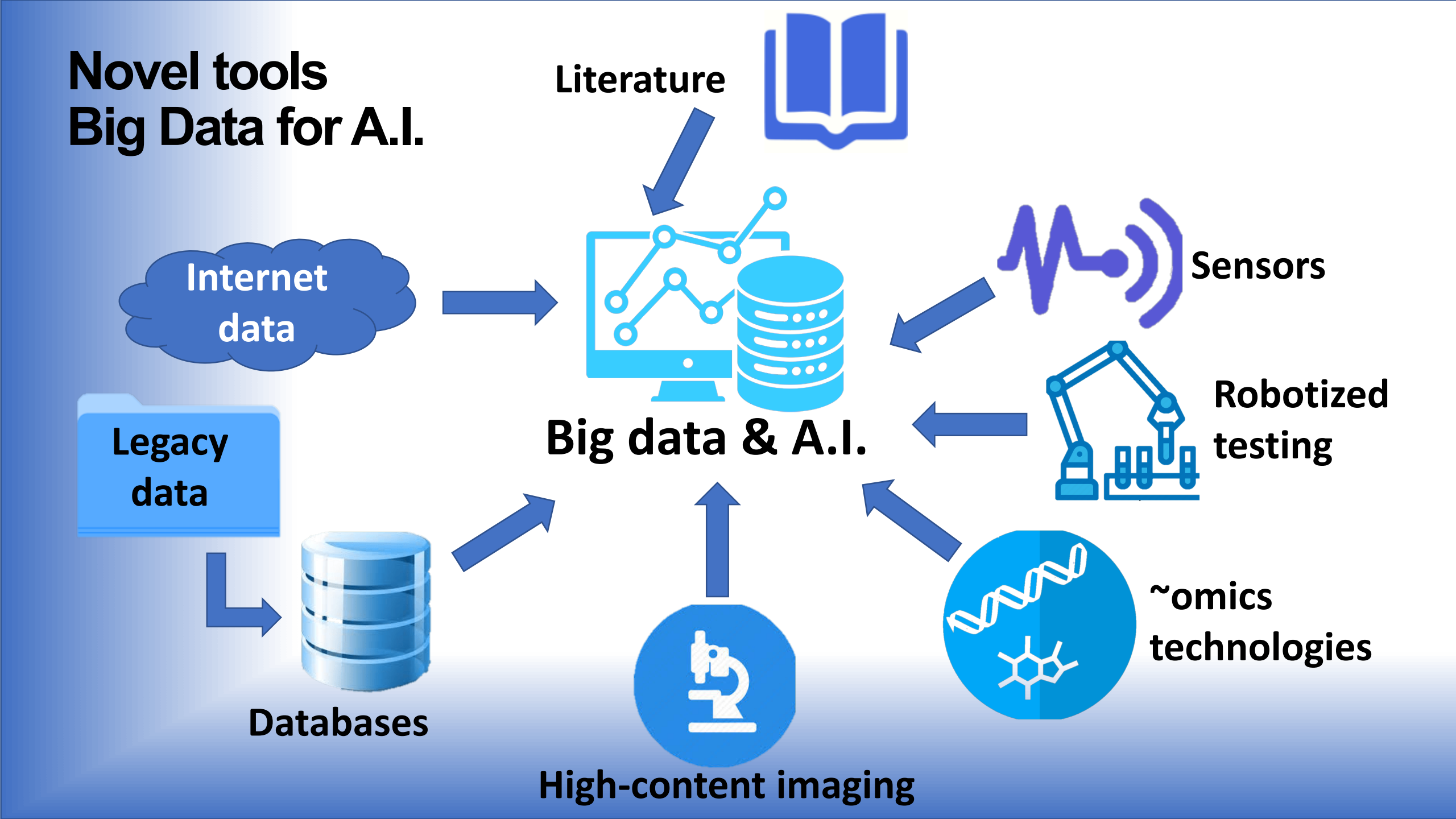
Power of AI doubles every 3 months

84% of all data produced last 6 years

Natural language processing

https://theamericangenius.com/editorials/big-data-is-watching-you-some-will-panic-others-will-rejoice/

Novel tools
Big Data for A.I.



Digital pathology

Many (pathologists) see toxicology as the pathology caused by chemicals

Image analysis
High-content imaging
Cloud storage
Standardized interpretation

Tom Luechtefeld

9 most common toxicity tests

190,000 chemical's hazard cross-validation:

87% correct

https://sfmagazine.com/technotes/february-2019-wipo-u-s-and-china-lead-the-world-in-ai-innovation/

ACCEPTED MANUSCRIPT

Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility

Thomas Luechtefeld, Dan Marsh, Craig Rowlands, Thomas Hartung

Toxicological Sciences, kfy152, https://doi.org/10.1093/toxsci/kfy152

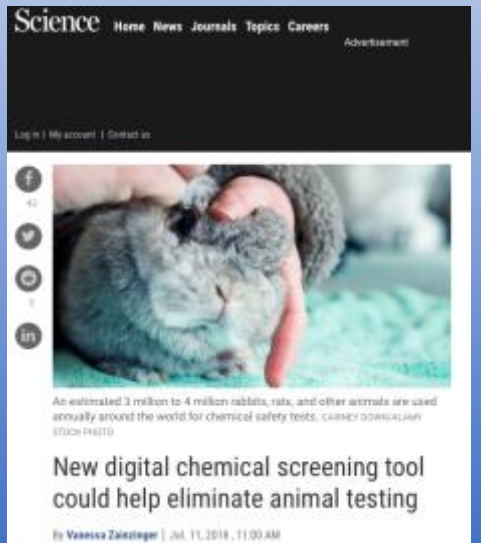
Published: 11 July 2018

Science, 12 Feb 2016

TOXICOLOGY

A crystal ball for chemical safety

By comparing new chemicals to known compounds, toxicologists seek early hazard warnings



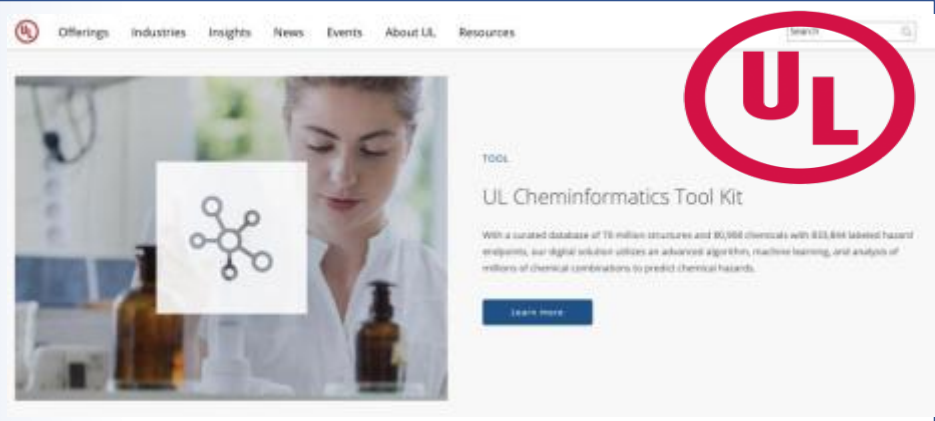
Ongoing RASAR developments

79% (n=131) and 80% (n=375) accuracy in predicting HUMAN skin sensitization (Golden et al., ALTEX, 2020)

38,250 predictions for 4,729 food-relevant substances
83% accurate (n=139) (Fu et al., 2022)

Preliminary (Luechtefeld et al., in preparation):
Reproductive Tox 82% accurate (n=1152)
Carcinogenicity 75% accurate (n=950)
Androgen effect 98% accurate (n=8492)
Estrogen transactivation 80% accurate (n=1660)

EU ONTOX project ($20 million, 2021-2026) to expand to liver, kidney and developing brain



Accepted for Australian Industrial Chemical Legislation 2020

https://www.dreamstime.com/photos-images/sky-limit.html

Green toxicology

– the toxicology aspects of green chemistry

Alex Maertens

Another use of alternatives methods

Green Chemistry Series

Green Toxicology

Making Chemicals Benign by Design

Alexandra Maertens

TOXICOLOGICAL SCIENCES, 161(2), 2018, 285–289

doi: 10.1093/toxsci/kfx243
Advance Access Publication Date: December 18, 2017
Editorial

ly About and Avoid Toxic

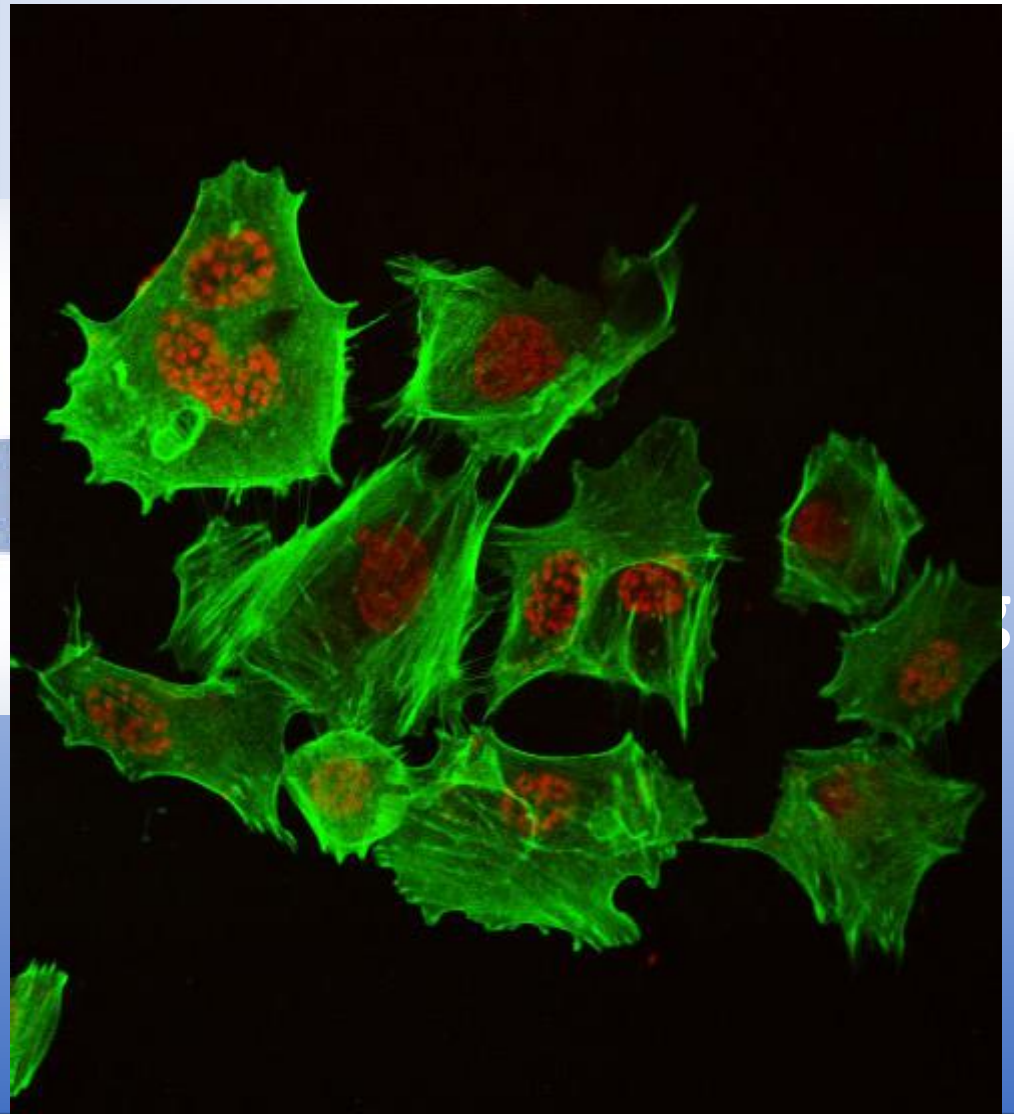
ng*,†,1

Human cell and tissue culture

Irreprodu-*ce*ll-bility

Primary cells of limited access, quality, and quantity

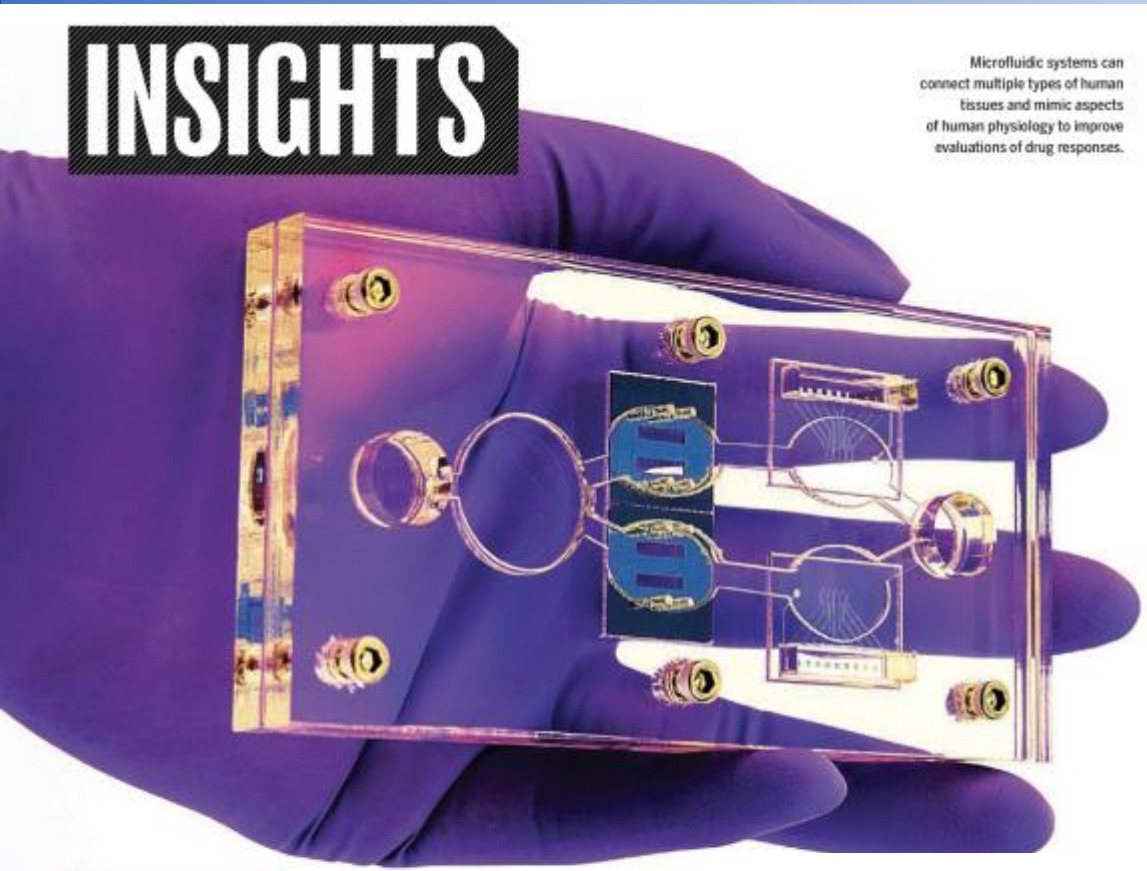
Tumor cell lines



gical

- **Ca. 25% of cell lines misidentified**
- **15-25% mycoplasma infected**
- **Genetic instability**
- **Culture artifacts**

Evolution of Cell Culture - high-tech & business opportunity



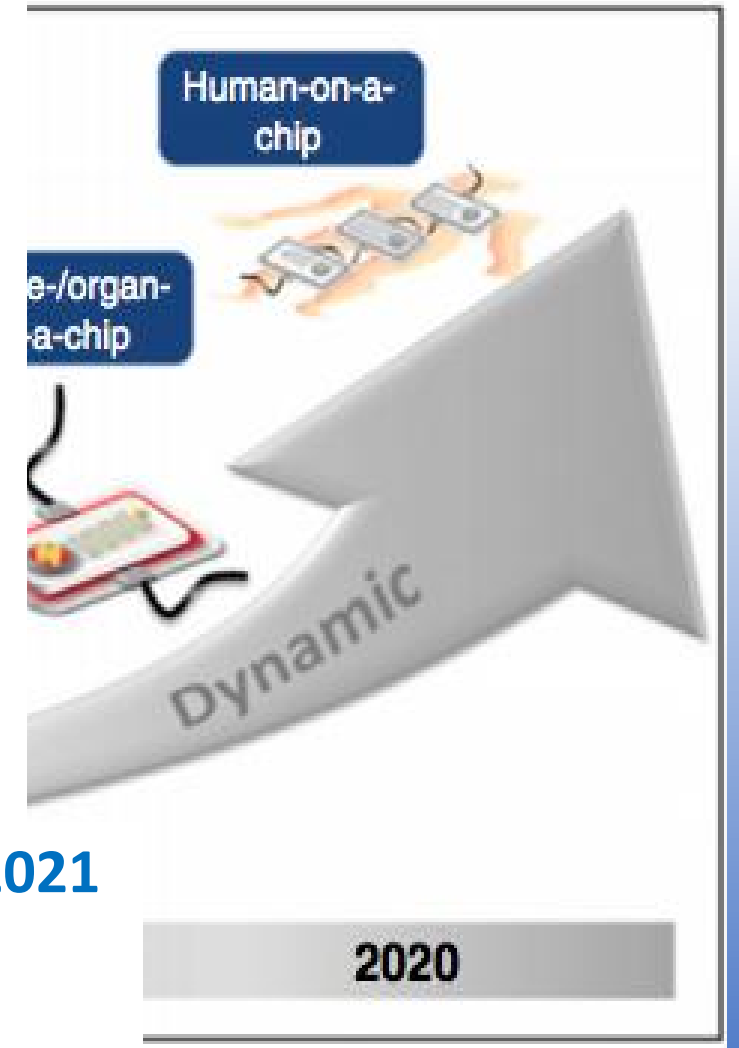
PERSPECTIVES

MEDICINE

Human microphysiological systems for drug development

Organs-on-chips could be used to assess drug efficacy and support personalized medicine

Science 16 Sep 2021



Marx et al., Biology-inspired micro-physiological system approaches to solve the prediction dilemma of substance testing using animals. ALTEX 2016, 33:272-321.

Marx et al., Biology-inspired microphysiological systems to advance medicines for patient benefit and animal welfare. ALTEX 2020, 37:365-394 .

MPS WORLD SUMMIT

CONNECT, EXCHANGE, EDUCATE

New Orleans 30 May-3 Jun ‘22

Hosts: Suzie Fitzpatrick, FDA

Thomas Hartung, Hopkins

Don Ingber, Harvard

https://mpsworldsummit.com

52 organizations

34 Scientific Advisory Board

665 Registered (215 Online, 65 FDA)

26 Countries

142 speakers, 189 posters

$450k from NCATS

Forming the International MPS Society and Conference Series

2nd MPS world Summit: June 26-30th 2023

Guidance Document on Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0)

ALTEX 2022, 39:30-70

David Pamies[1], Marcel Leist[2,3], Sandra Coecke[4], Gerard Bowe[4], Dave Allen[5], Gerhard Gstraunthaler[6], Anna Bal-Price[4], Francesca Pistollato[4], Rob deVries[7,8], Helena T. Hogberg[9], Thomas Hartung[2,9] and Glyn Stacey[10,11,12]

- **Quality of cell model (GCCP)**
- **Quality of reporting (GIVReSt)**
- **Quality of results (validation)**

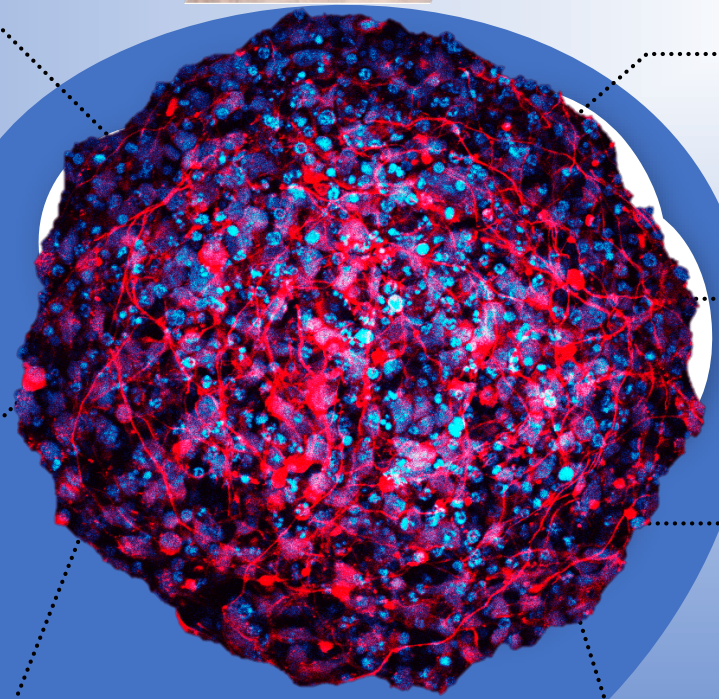
BRAIN ORGANOIDS

Lena Smirnova

STANDARDIZED
HUMAN 3D
DEVELOPMENT
FROM IPSC

GLIA CELLS,
MYELINATION
+ADDED MICRO-GLIA

INFECTION
CANCER GRAFTS
TOXICITY
DNT
NEURODEGENERATION



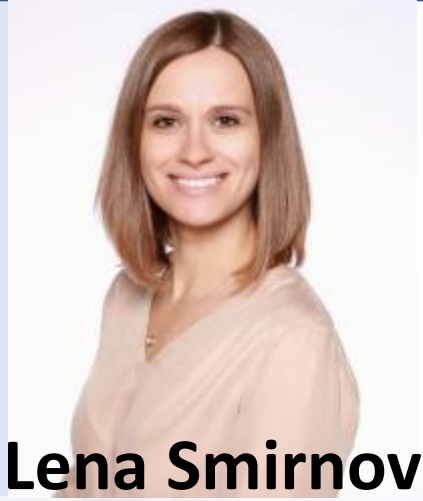
GENETIC
BACKGROUNDS,
+ RISK GENES, REPAIR
+ REPORTER GENES

GENE X ENVIRONMENT
MIXTURES

FUNCTIONAL
ASSAYS: NEURITES,
SYNAPSES, 3D EEG

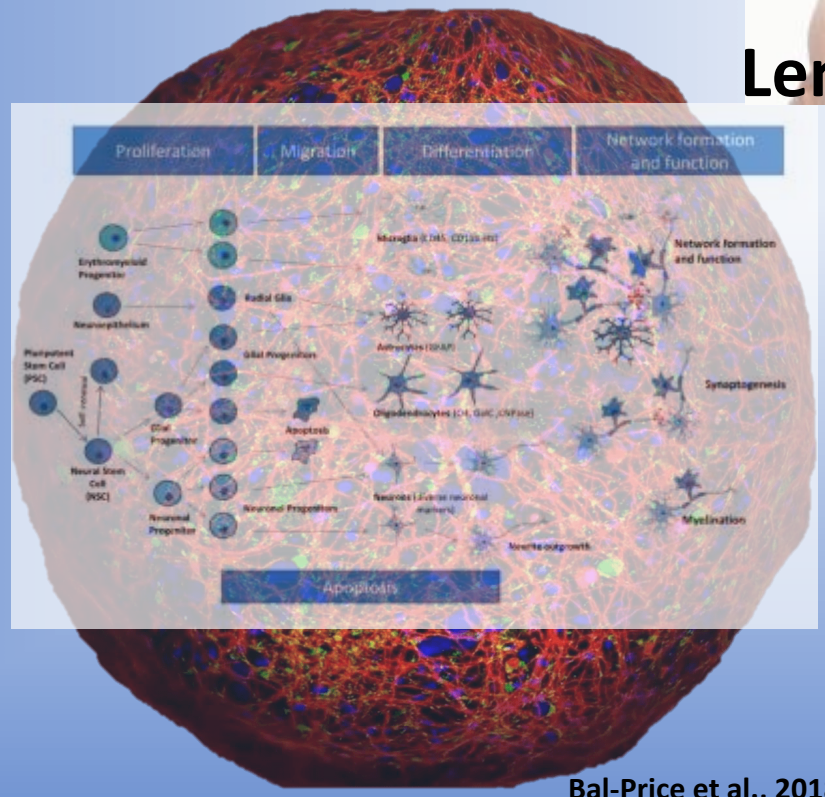
ORGANOID
INTELLIGENCE (O.I.)

6-in-1 BrainSphere assay to test Neurodevelopment



Lena Smirnova

Neuronal differentiation
Myelination
Neurite outgrowth
Synaptogenesis
Glia migration & Gliosis
Neural network (E-phys)



Bal-Price et al., 2018a

CRISPR/CAS9

Reporter/
Fusion
proteins

Mini- Brainbow

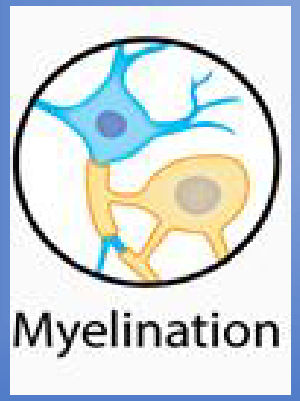
Neurons
Astrocytes
Oligodendrocytes
Synapses
3D electrophys

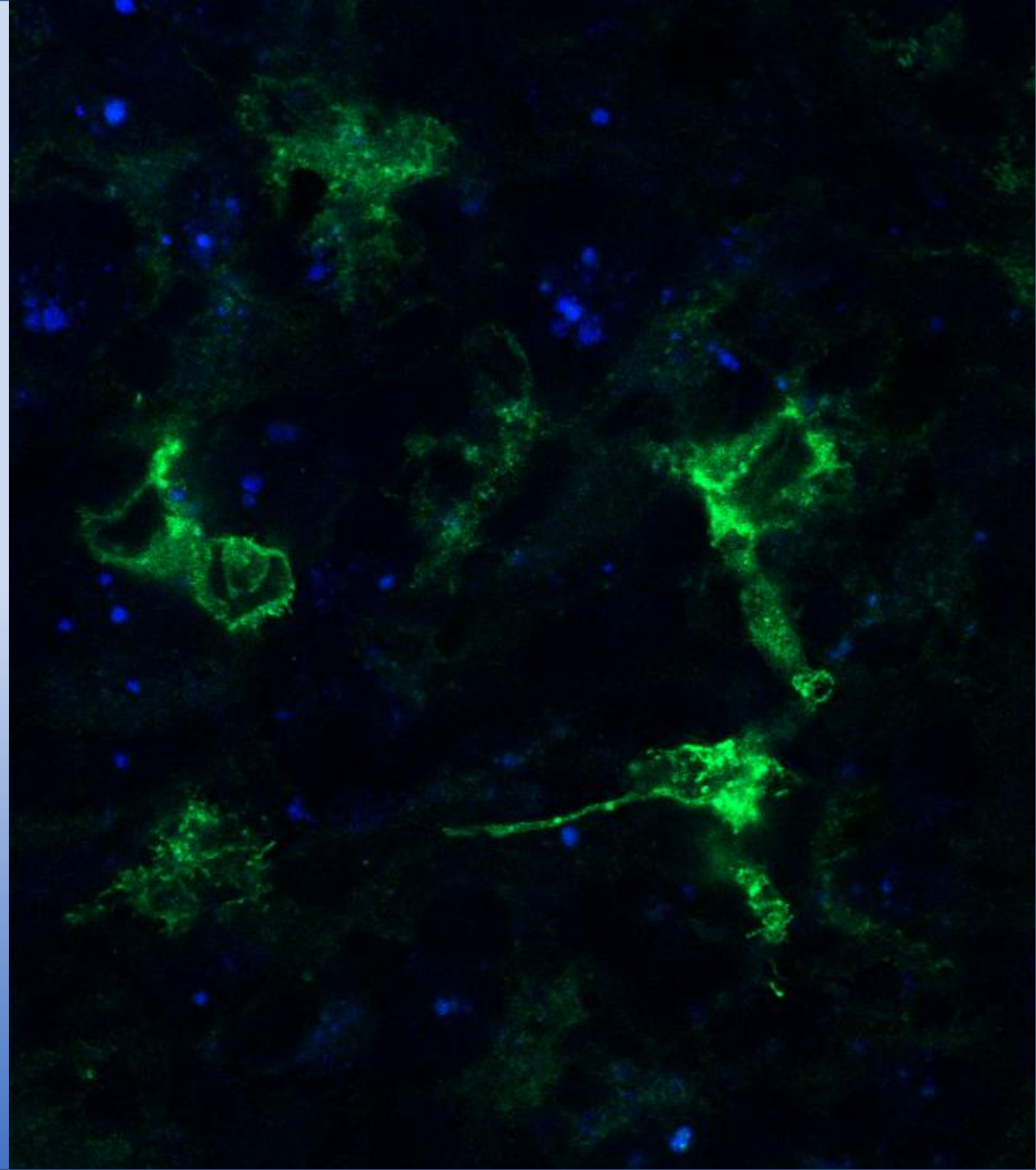
High content imaging
Toxicant/drug screening

CRISPR/Cas9 Knock-Ins

Oligodendrocytes (PLP-GFP)

Synapsis (Synaptophysin-BFP)



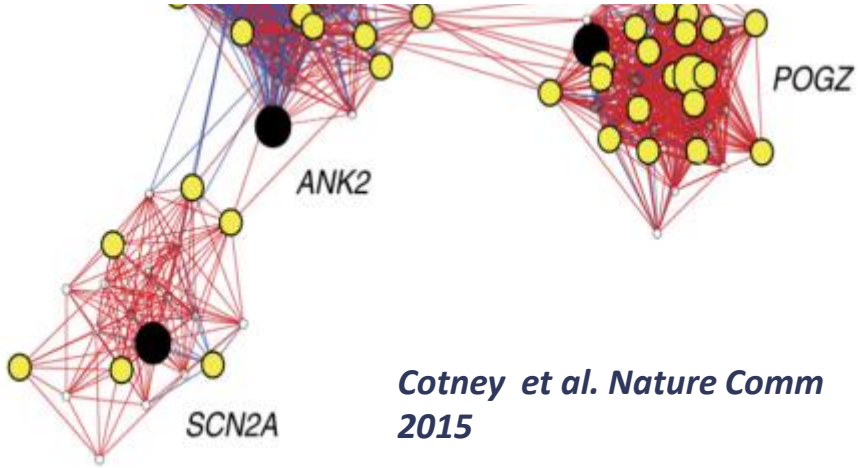


Bloomberg School Researchers Awarded $11.7 Million Five-Year NIH Grant to Build and Lead Autism Center of Excellence Network

Published **September 08, 2022**

DISABILITY

Network will aggregate global research projects studying gene-environment interaction to understand autism's causes and to improve quality of life among autistic individuals



Cotney et al. Nature Comm 2015

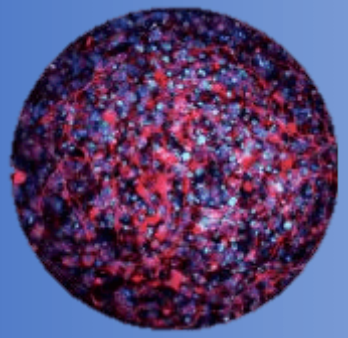
Functional and Molecular signatures

Lena Smirnova

Organoid Intelligence (O.I.)

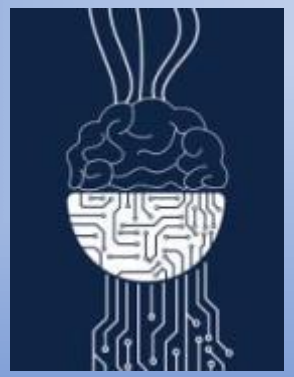
Discovery Grant

JOHNS HOPKINS UNIVERSITY



Brain Organoid

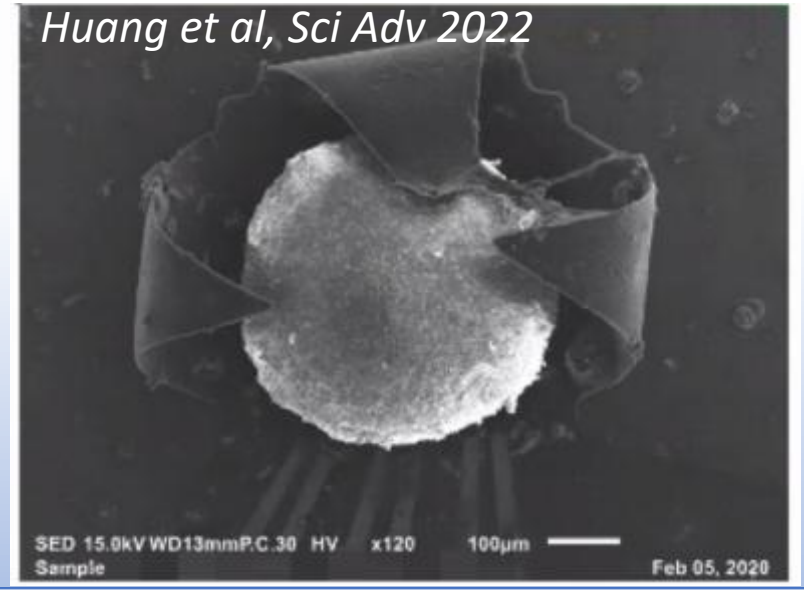
O.I.



Input

Output

A.I. ⟵



Human brain organoid caged in shell electrodes

Workshop 2022

Baltimore Declaration Toward OI

What is emerging that can help us?

Exposure science (high throughput and untargeted exposomics, remote sensing, citizen science …)

Technologies (~omics, high-throughput, MPS, A.I.)

Evidence Integration (Evidence-based Tox, IATA, Green Tox Investigative Tox, Mechanistic Validation, Probabilistic Risk Assessment, Systems Toxicology, virtual experiments…)

The challenge

https://www.loopclosed.com.au/program_services/data_integration_and_analysis.html

Similar for

- Systematic reviews
- Risk assessments
- Integrated Testing Strategies

http://phd.dia.uniroma3.it/multi-source-data-integration-with-humans-in-the-loop/

In vivitrosi

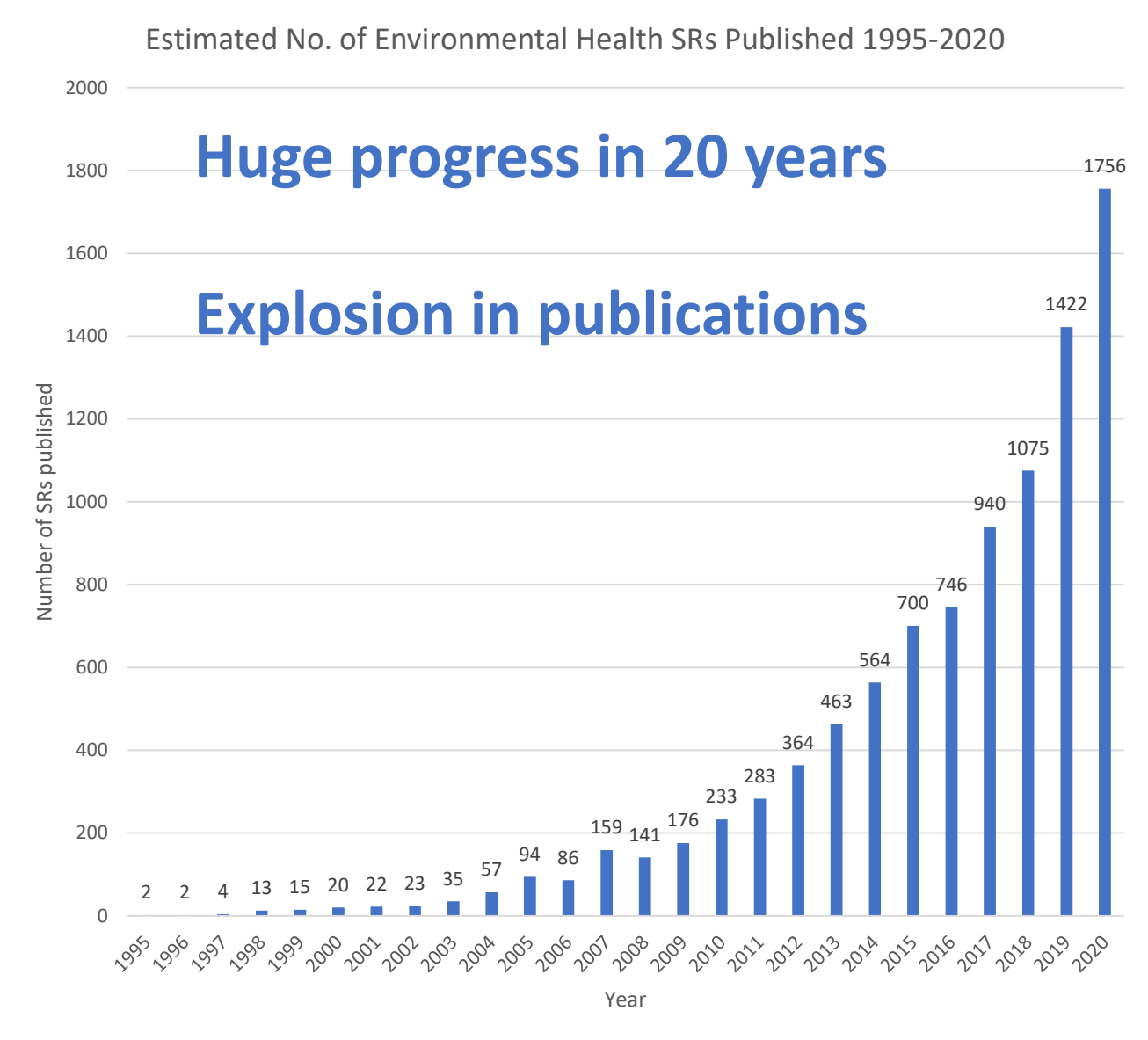
Replacement of animal testing by integrated approaches to testing and assessment (IATA): a call for in vivitrosi

Francesca Caloni[1] · Isabella De Angelis[2] · Thomas Hartung[3,4]

Arch Toxicol 2022

Aka Integrated Testing Strategies, IATA, Defined Approaches…

The explosion of systematic reviews



ebtc
Evidence-based Toxicology Collaboration

Katya Tsaioun

- **~1000 people engaged with EBTC in 12 years**
- **Stakeholders at every level, everywhere**
- **EBT journal from 2023**
- **EBT association forming**

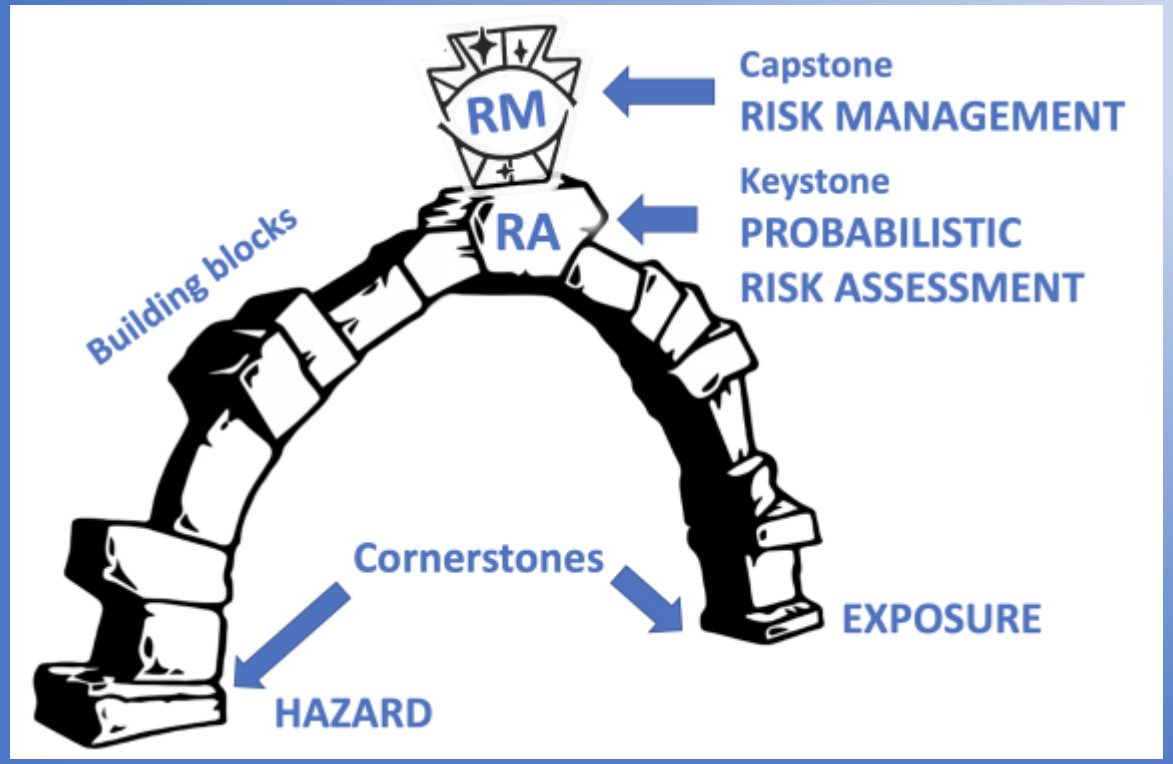
ALTEX 2022

"Probability is the very guide of life."
Cicero (106 – 43 B.C.)

Food for Thought …

Probabilistic Risk Assessment – the Keystone for the Future of Toxicology

Alexandra Maertens[1], Emily Golden[1], Thomas H. Luechtefeld[1,2], Sebastian Hoffmann[1,3], Katya Tsaioun[1] and Thomas Hartung[1,4]



transatlantic think tank for toxicology

ONTOX

Workshop 4-6 July 2022
Ranco, Italy

Chemicals
Mixtures /products
Metabolites

X

Humans
Animals
Ecosystems

X

Uses

X

Industries
= legislations

X

Countries
Regions

=

Tons of test needs
Tons of discrepancies
= Mission Impossible

Mixture Tox

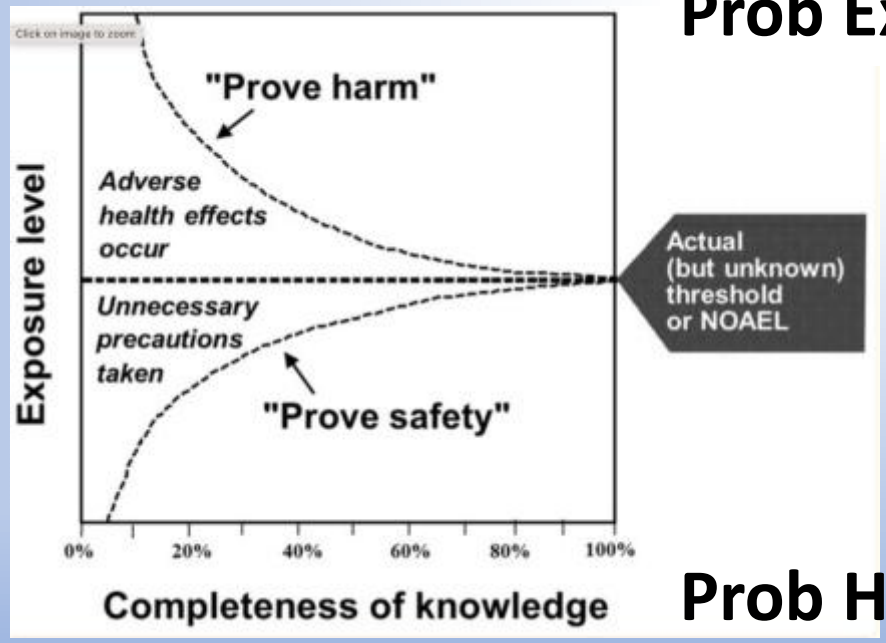
One Health

Cumulative Exposure

OSOA

Harmonization

Exposomics, EI
Exposure science, HT exposure



Prob Exposure

Prob Hazard

ProbRA

Evidence generation

Evidence integration

Legacy data

MPS, AI, HTS

Evid-based Tox Test strategies, AI

The difficulty lies not in the new ideas,

but in escaping from the old ones.

JM Keynes

Slides available:

Current Sponsors:

+philantropy

BASF
RIFM
IFRA INTERNATIONAL FRAGRANCE ASSOCIATION
SENZA GEN
ESTĒE LAUDER
CORTEVA
DANONE
Agilent Technologies
Boehringer Ingelheim
PEPSICO
CLOROX
Pfizer
P&G
ExxonMobil
Roche
UL
BAYER
Coca-Cola
Johnson & Johnson

Space for You!