

Fourth anniversary
Gold Open Access
in the field of AI
[Open for submissions >](#)



Thomas Hartung & team



The Opportunities and Challenges for NAMs in Biomedical Research

Societal need:

~50% of Americans and
~60% of Europeans
object to animal testing

Pressure is
mounting

**PUBLIC
OPINION**



2002 EU cosmetics ban

2006 Goal of EU REACH

2016 Goal for US TSCA

2019 Deadline 2035 by US EPA

2021 Deadline 2027 by EFSA

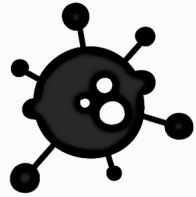
2021 EMA measures to reduce animal
testing

2022 FDA Modernization Act

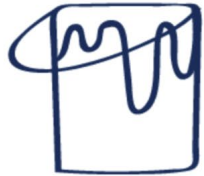
The primary societal need of biomedicine – understand, prevent and cure disease



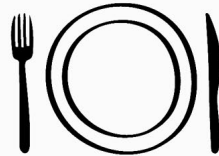
genetics



infections



toxic chemicals



dietary factors

Exposure



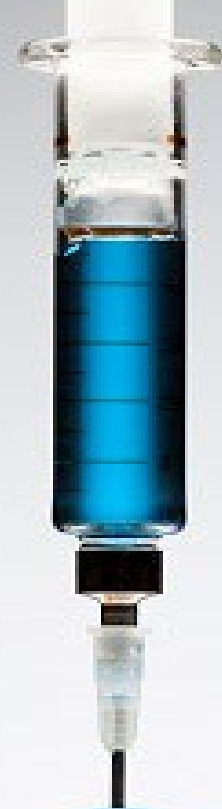
We are not 70kg rats!

Humans vs animals

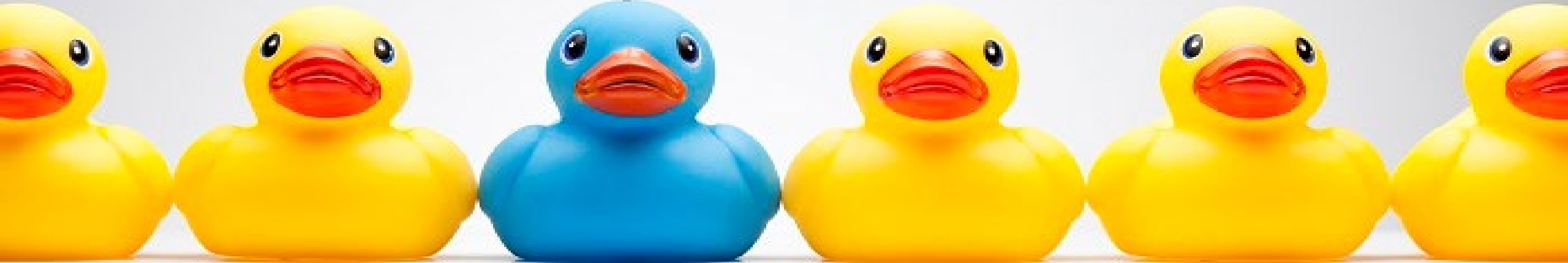


We need human models

**Traditional
Toxicology**



**Tox uses only 10%
of all animals,
but here 90% of
work on alternatives**





**Toxicology should be better than other areas:
Standardized tests (OECD TG), GLP, skilled performers,
maximum tolerated doses, no disease models on top
of substance effects**

Reproducibility

Six most frequent **toxicity tests**

Consuming **57%** of animals in tox

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

81% reproducible

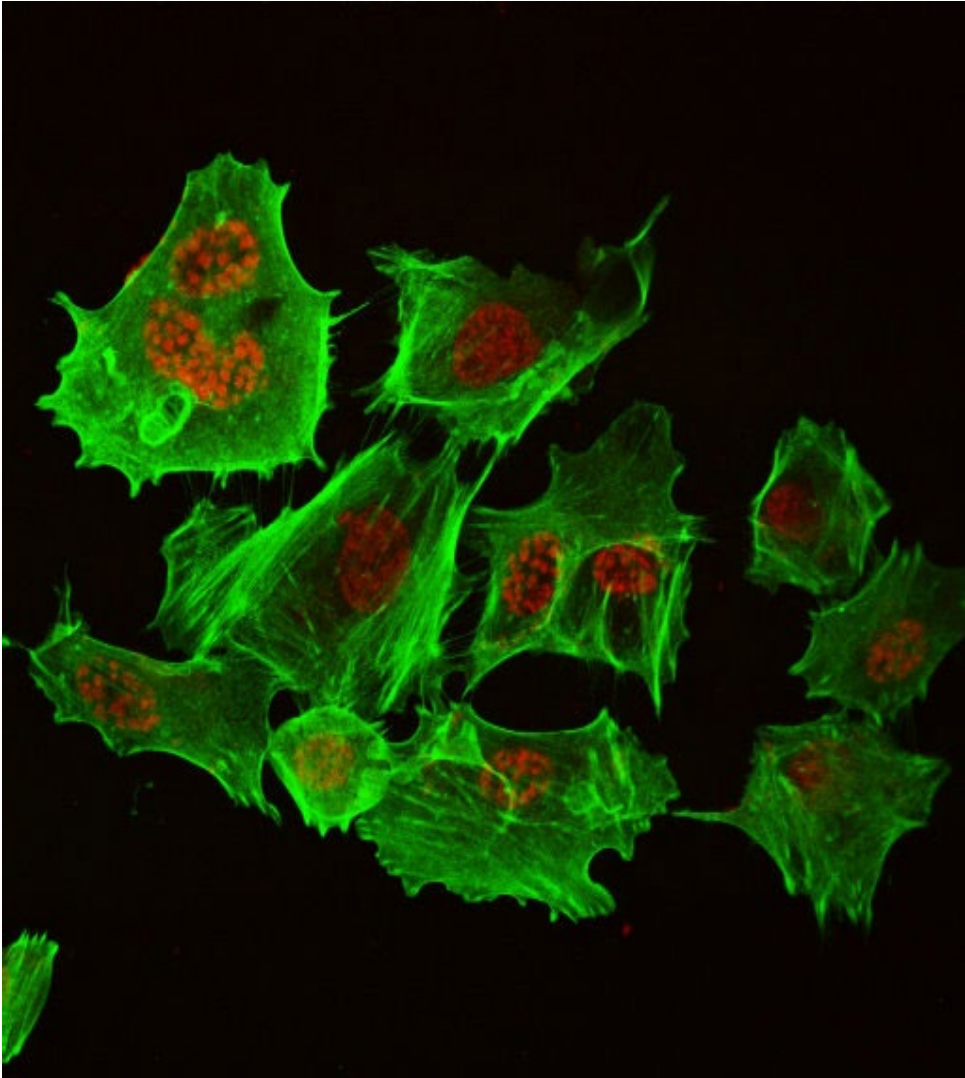
69% reproducible for toxic chemicals

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



Luechtefeld et al., ToxSci 2018

Irreprodu-cel/-bility



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

Human cell and tissue culture

Primary cells of
limited access,
quality, and
quantity

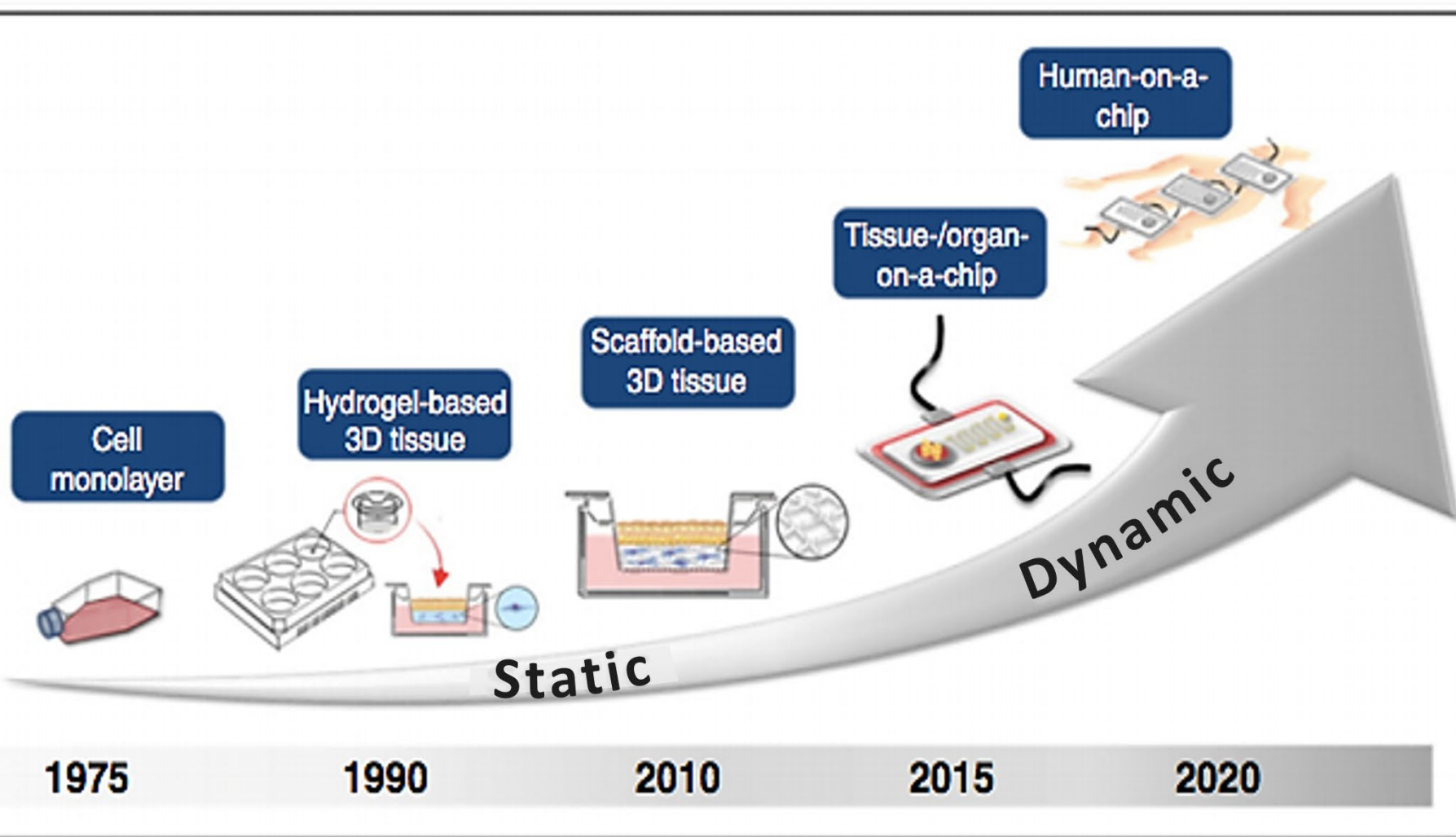
Tumor cell lines



Stem cells
&
Bioengineering

Microphysiological
Systems

Evolution of Cell Culture - high-tech & business opportunity



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



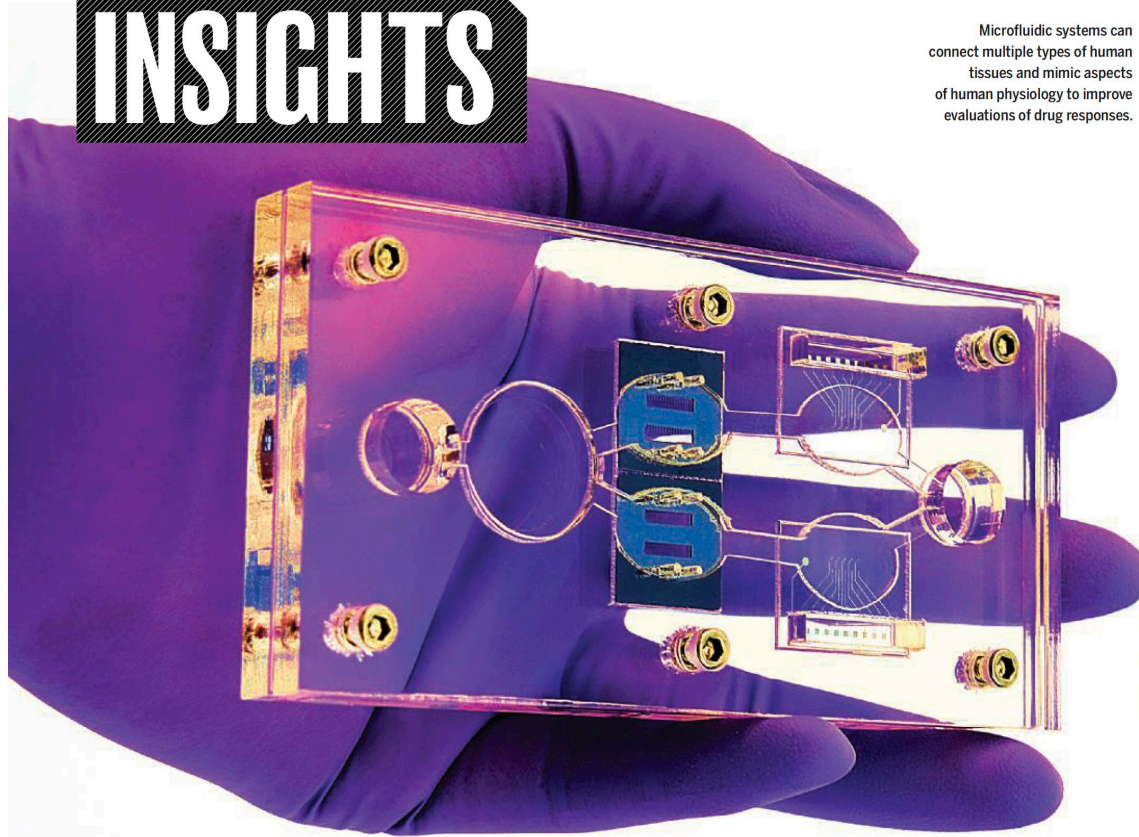
Marx et al., Biology-inspired microphysiological systems to advance medicines for patient benefit and animal welfare. *ALTEX* 2020, 37:365-394.



Evolution of Cell Culture - high-tech & business opportunity (continued)

INSIGHTS

Microfluidic systems can connect multiple types of human tissues and mimic aspects of human physiology to improve evaluations of drug responses.



PERSPECTIVES

MEDICINE

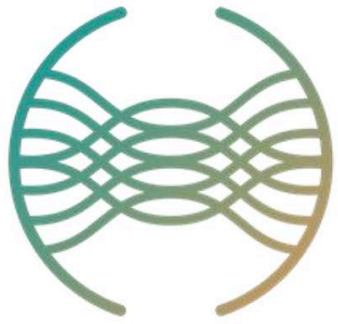
Human microphysiological systems for drug development

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

interconnections with other organs (4, 5). They add to the toolbox of assays to identify potential therapeutics for diseases, including COVID-19 (6). These features enable human multi-cell-type systems that can better replicate complex tissue and organ functions than conventional cell culture. Consequently, MPS have gained broader attention as a tool to improve the prediction of human efficacy and potential undesired effects of drugs before patients are exposed

Science 16 Sep 2021





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)

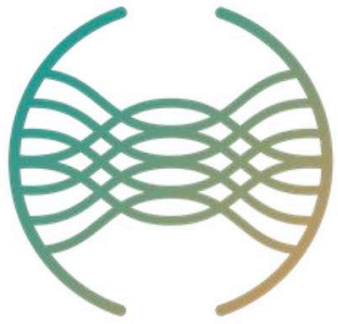
26 Countries

142 speakers, 189 posters

\$450k from NCATS

Forming the International MPS

Society and Conference Series



MPS WORLD SUMMIT
CONNECT, EXCHANGE, EDUCATE

2nd MPS World Summit

Berlin, June 26-30th 2023

Berlin 26-30 June'23

Hosts: Uwe Marx, Tissue
Marcel Leist, Univ Konstanz
Peter Loskill, EUROoCS



60 organizations
29 Scientific Advisory Board
1200+ Registered
(recorded, not online)
200+ speakers, 700+ posters

<https://mpsworldsummit.com>

Guidance Document on Good Cell and Tissue Culture

Practice 2.0 (GCCP 2.0)

ALTEX 2022, 39:30-70



David Pamies¹, Marcel Leist^{2,3}, Sandra Coecke⁴, Gerard Bowe⁴, Dave Allen⁵, Gerhard Gstraunthaler⁶, Anna Bal-Price⁴, Francesca Pistollato⁴, Rob deVries^{7,8}, Helena T. Hogberg⁹, Thomas Hartung^{2,9} and Glyn Stacey^{10,11,12}

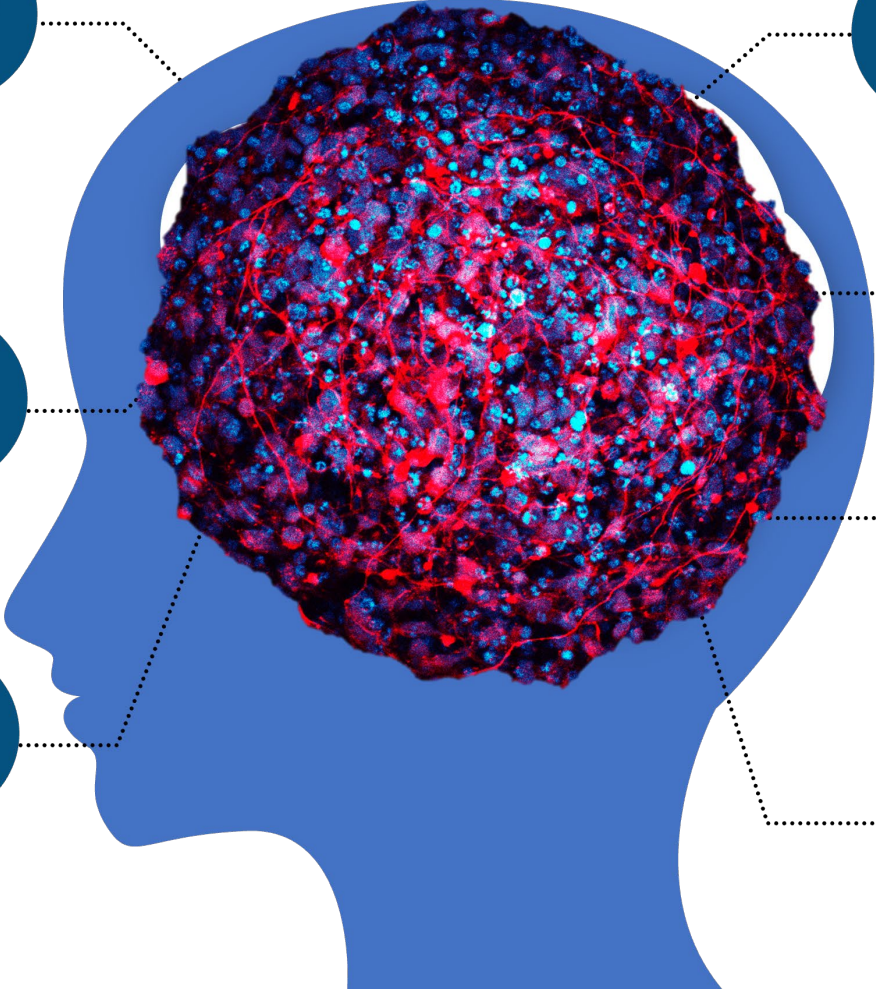


- **Quality of cell model**
(GCCP)
- **Quality of reporting**
(GIVReSt)
- **Quality of results**
(validation)

BRAIN ORGANOIDS



Lena Smirnova



**STANDARDIZED
HUMAN 3D
DEVELOPMENT
FROM IPSC**



**GENETIC
BACKGROUNDS,
+ RISK GENES, REPAIR
+ REPORTER GENES**



**GLIA CELLS,
MYELINATION
+ADDED MICRO-GLIA**



**GENE X ENVIRONMENT
MIXTURES**



**INFECTION
CANCER GRAFTS
TOXICITY
DNT
NEURODEGENERATION**



**FUNCTIONAL
ASSAYS: NEURITES,
SYNAPSES, 3D EEG**



**ORGANOID
INTELLIGENCE (O.I.)**

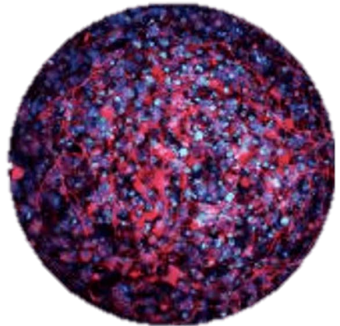


AI & *in vitro*

Organoid Intelligence

(O.I.)

- Physiology of learning
- Tox & Drug Development
- Biological Computing



Brain Organoid

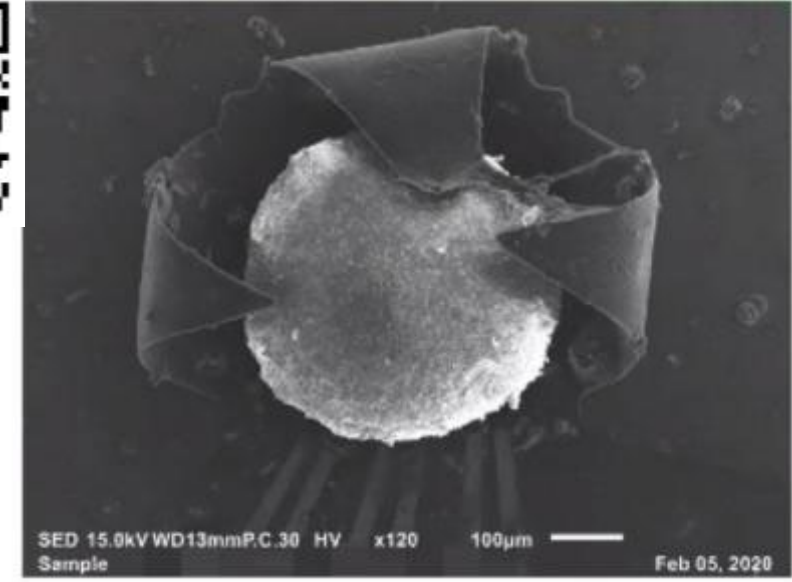
O.I.



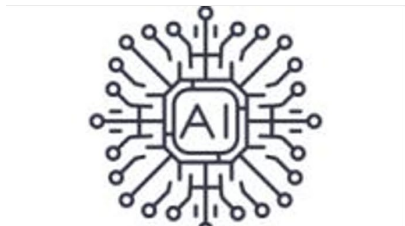
Input

Output

A.I.



Human brain organoid caged in shell electrodes





OPEN ACCESS

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Organoid intelligence (OI): the new frontier in biocomputing and intelligence-in-a-dish

Lena Smirnova¹, Brian S. Caffo², David H. Gracias^{3,4,5,6,7,8}, Qi Huang³, Itzy E. Morales Pantoja¹, Bohao Tang², Donald J. Zack⁹, Cynthia A. Berlinicke¹⁰, J. Lomax Boyd¹¹, Timothy D. Harris^{12,13}, Erik C. Johnson¹⁴, Brett J. Kagan¹⁵, Jeffrey Kahn¹⁶, Alysson R. Muotri^{17,18}, Barton L. Paulhamus¹⁹, Jens C. Schwamborn²⁰, Jesse Plotkin¹, Alexander S. Szalay^{21,22,23}, Joshua T. Vogelstein¹², Paul F. Worley²⁴ and Thomas Hartung^{1,25*}

600+ press hits

Forming a community







- 1st workshop report

- New journal Frontiers in OI

US White House Bold Biotechnology Goal

National Science Foundation Program



 <p>FRONTIERS IN SCIENCE EDITORIAL Published on 28 Feb 2023</p> <p>Brian Engel, <i>are they for real?</i></p> <p>London, Chief Science and President of REEDA, Prof. Brian Engel calls on policymakers, funding bodies, scientists, pharmaceutical companies, and the public to support the innovative approach of organoid intelligence.</p>	 <p>FRONTIERS IN SCIENCE HIGHLIGHT Published on 28 Feb 2023</p> <p>The latest organoid?</p> <p>Theoretical neuroscientist Prof. Bartlett of University College London, discusses the potential for organoid intelligence in artificial intelligence, as well as its implications for neurobiology and its applications.</p>
 <p>FRONTIERS IN SCIENCE Published on 28 Feb 2023</p> <p>Organoid intelligence: smarter than the average cell culture</p> <p>Molecular neuroscientist David Plotkin, MD, PhD, of Columbia University, considers whether complex brain cell culture systems can achieve in vivo intelligence, and the potential of organoids to drive and engage information within them (OI).</p>	 <p>FRONTIERS IN SCIENCE Published on 28 Feb 2023</p> <p>To learn or not to learn: organoids</p> <p>Dr. Ari Adoniou and Dr. Chris Higgins from the University of Pittsburgh discuss the challenges of training organoids as computational units (AI).</p>
 <p>FRONTIERS IN SCIENCE Published on 28 Feb 2023</p> <p>The Baltimore Declaration toward the exploration of organoid intelligence</p> <p>Researchers, including from Johns Hopkins University, the University of California, and Yale University, set out a vision for the interdisciplinary scientific community to collaborate on the world-changing potential of organoid intelligence.</p>	 <p>POLICY OUTLOOK Published on 27 Feb 2023</p> <p>Organoid intelligence: society must engage in the ethics</p> <p>Prof. John Winkler, of the University of Cape Town and past President of the European Council on Ethics of Science in Italy, discusses OI, including what it might mean, around the use of brain organoids that may develop cognitive processes, such as human thought, and rights of body donors, and organoids.</p>

DATA



COMPUTING POWER

AI MODELS

Data: +60% per year
= 90% in last three years

Computer: +40% per year
(Moore's law)

AI: +700% per year since 2010

Together increase
>1 billion-fold
over last 60 years

DISRUPTIVE
TECHNOLOGY

A 3D rendering of shattered, translucent white glass or plastic. The shards are jagged and layered, creating a sense of depth and movement. The text 'DISRUPTIVE TECHNOLOGY' is superimposed in the center in a bold, red, sans-serif font with a slight shadow effect.

R.E.M.

**IT'S THE END
OF THE WORLD
AS WE KNOW IT
(AND I FEEL FINE)**



2018:
9 most common toxicity tests
190,000 chemical's hazard
cross-validation:
87% correct

WIPO: U.S. and China Lead the World in AI Innovation

<https://www.sfmagazine.com/technotes/2019/february/wipo-us-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



2020: Better than animals for human skin allergy
2022: Mass prediction for 4,700 food chemicals,
83% correct
~38,000 animal studies at \$250+ million
2023: Cancer 75% correct, reproductive tox 82%
correct

Animal Replacement

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



SOT | Society of
Toxicology
www.toxsci.oxfordjournals.org



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

doi: 10.1093/toxsci/kfx243

Advance Access Publication Date: December 18, 2017

Editorial

EDITORIAL

Green Toxicology—Know Early About and Avoid Toxic Product Liabilities

Alexandra Maertens* and Thomas Hartung^{*,†,1}

The Future of Toxicology



Future Directions Workshop:
Advancing the Next Scientific Revolution in Toxicology

Office of the Under Secretary of Defense for Research and Engineering OUSD(R&E)

April 28–29, 2022

Arlington, VA

Co-Chairs

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

Call for a Human Exposome Project



Future Directions
Workshop: Advancing
the Next Scientific
Revolution in
Toxicology

April 28-29, 2022

Thomas Hartung, Johns Hopkins University, University of Konstanz,
and Georgetown University

Ana Navas-Acien, Columbia University

Weihseh Chiu, Texas A&M University

Prepared by:
Kata Klami, Virginia Tech Applied Research Corporation
Matthew Peters, Virginia Tech Applied Research Corporation
Shawn Silberberg, Office of the Under Secretary of Defense
(Research & Engineering), Basic Research Office

Future Directions Workshop series
Workshop sponsored by the Basic Research Office, Office of
the Under Secretary of Defense for Research & Engineering



Releasable to the US Government Only and its Contractors | Unclassified



1. Exposure-driven
2. Technology-enabled
3. Evidence-integrated

Food for Thought ...

A Call for a Human Exposome Project

Thomas Hartung^{1,2}

ALTEX 2023



Etiology of Diseases

Genetic

Genome

**Suscept-
ibility**

**Epigenetic
GxE**

Disease



Infection

incl. microbiome

Exposure

incl. physical &
social

Exposome

**Suscept-
ibility**



Fenna Sillé



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)

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

Food for Thought ...

The Exposome – a New Approach for Risk Assessment

Fenna Sillé¹, Spyros Karakitsios², Andre Kleensang¹, Kirsten Koehler¹, Alexandra Maertens¹, Gary W. Miller³, Carsten Prasse¹, Lesliam Quiros-Alcala¹, Gurusurthy Ramachandran¹, Stephen M. Rappaport⁴, Ana M. Rule¹, Denis Sarigiannis^{2,5}, Lena Smirnova¹ and Thomas Hartung^{1,6}



The challenge

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

Similar for

- **Systematic reviews**
- **Risk assessments**
- **Integrated Testing Strategies**



<https://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 Caloni¹  · Isabella De Angelis² · Thomas Hartung^{3,4}

Arch Toxicol 2022



**Aka Integrated
Testing Strategies,
IATA, Defined
Approaches...**



EVIDENCE INTEGRATION: Evidence-based Toxicology

2006 Article

Human & Experimental Toxicology (2006) 25: 497–513
www.sagepublications.com

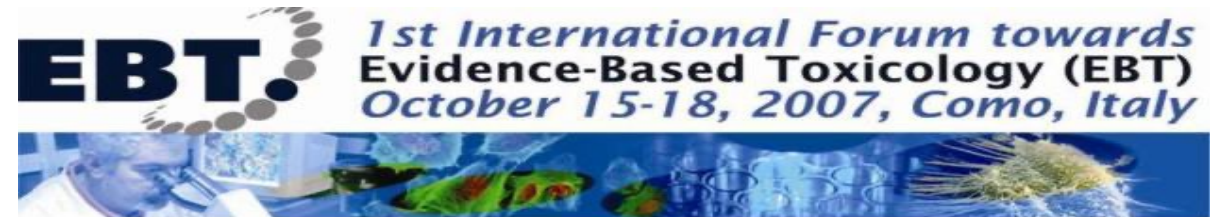
Toward an evidence-based toxicology

S Hoffmann* and T Hartung

European Commission, JRC – Joint Research Centre, Institute for Health & Consumer Protection, ECVAM – European Centre for the Validation of Alternative Methods, 21020 Ispra (VA), Italy



2007 Conference



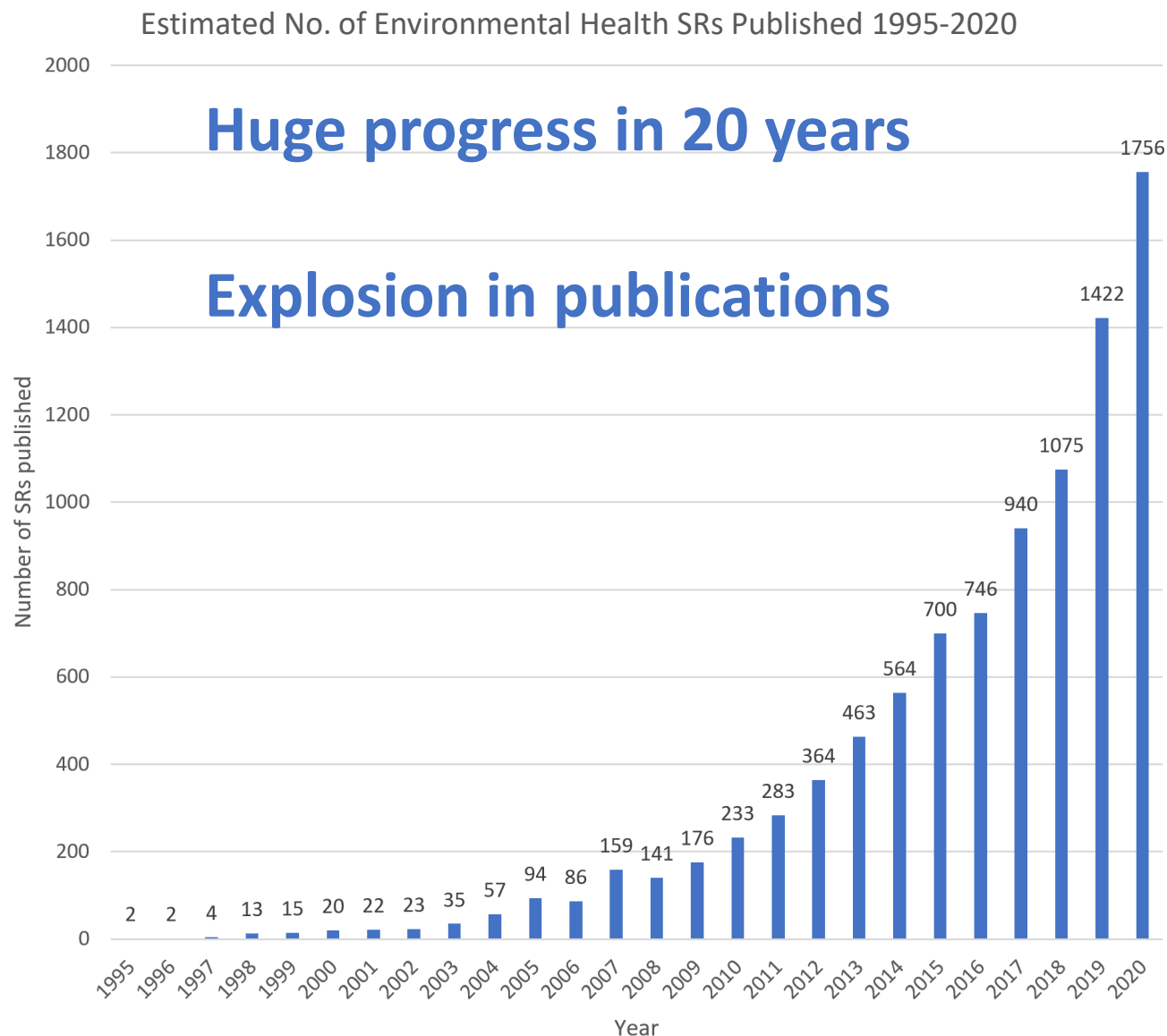
2009 Chair Hopkins

2011 Organization

www.ebtox.org

ebotc
Evidence-based Toxicology Collaboration

The explosion of systematic reviews



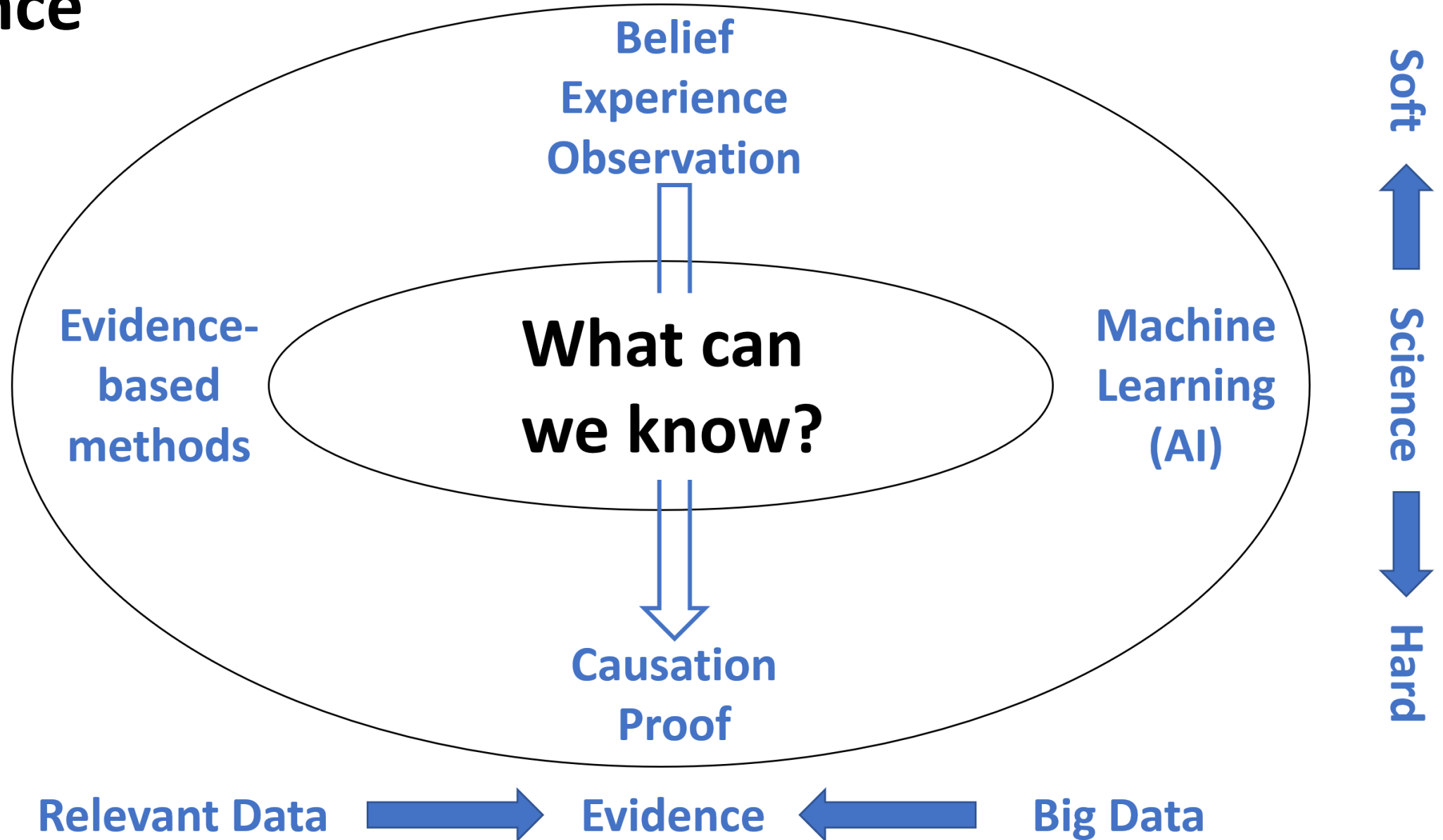
ebtc
Evidence-based Toxicology Collaboration



Katya Tsaion

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

Science





- AI
- Microphysiological Systems
- Green Toxicology
- Integrated Testing
- Evidence-based approaches

The Smart Path Forward

- Open access publishing and FAIR data
- Explainable AI
- Mechanistic Validation
- Human Exposome