JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Thomas Hartung & team

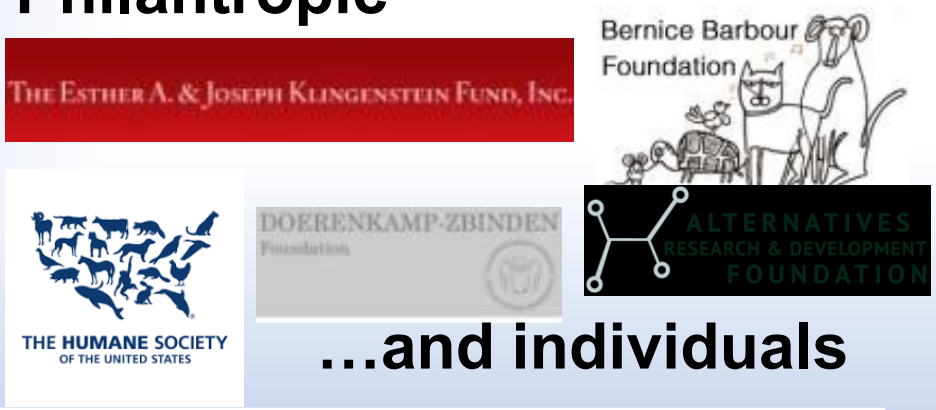
Slides available

Recent advances in the field

Thanking our sponsors

Current

Philantropic



Recent

frontiers in Artificial Intelligence

Editor

frontiers in Big Data

AstraZeneca

ATCC

AxoSim
Human Data, Faster.
VP, shareholder

MPS

insphero

Apellis

Pyrogen

MERCK MILLIPORE

BIOMÉRIEUX

A.I.

Consultant

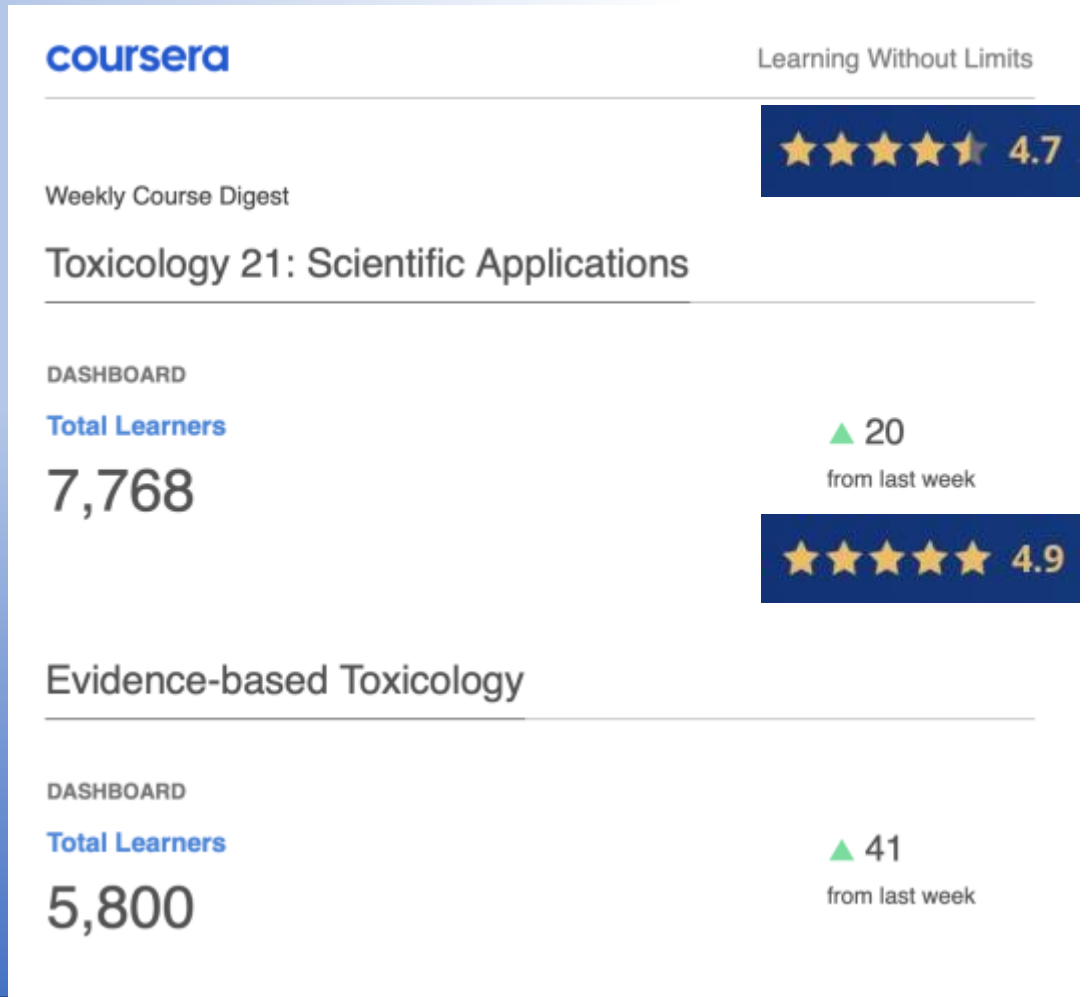
Green Chemistry Advisory Panel

TOXTRACK
Consultant, shareholder

In preparation: Insilica LLC

Working from home, Online meetings and teaching

Picture removed for copyright reasons



free

each 13 lectures

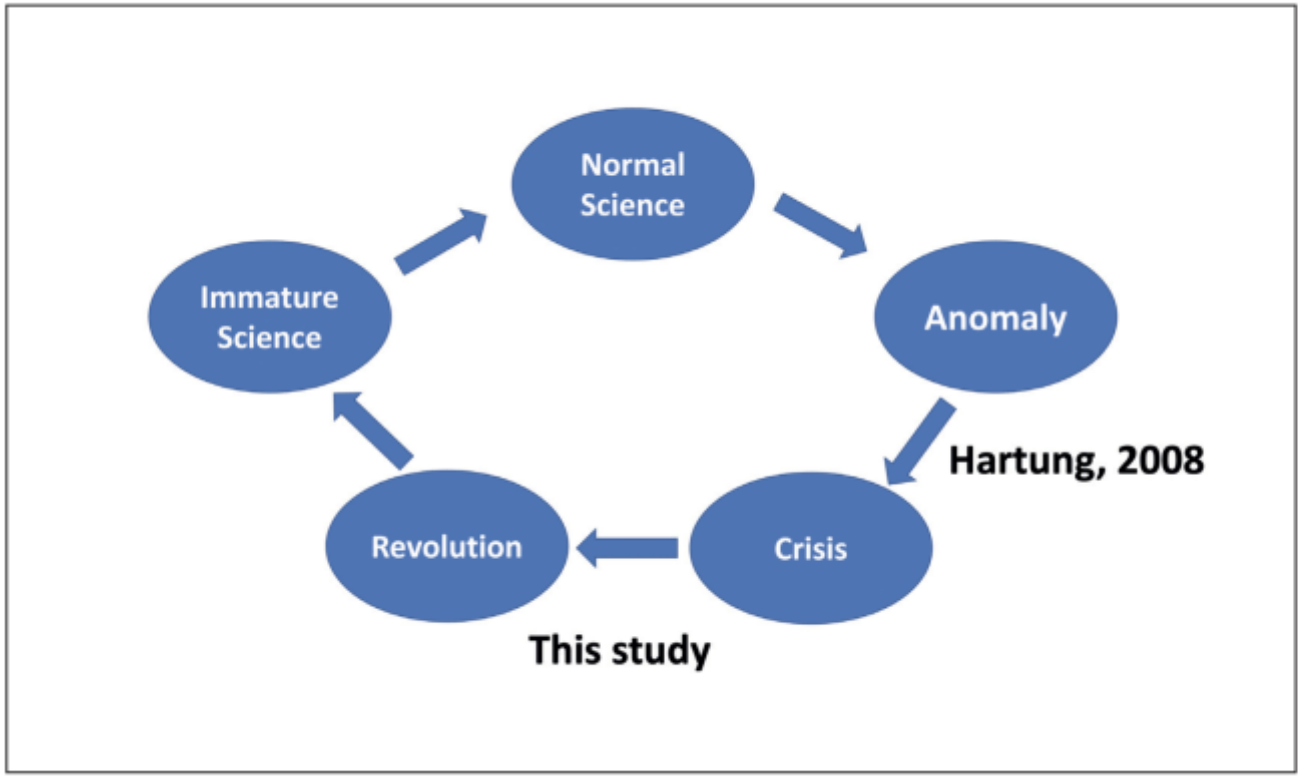


Fig. 1: Kuhn's Scientific Revolution Cycle (adapted from Kerry et al., 2008) and where the authors saw the state of regulatory toxicology in 2008 and now in 2021

Food for Thought ...

ALTEX 2021

The State of the Scientific Revolution in Toxicology

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

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]

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

Picture removed
for copyright reasons

Pressure is mounting

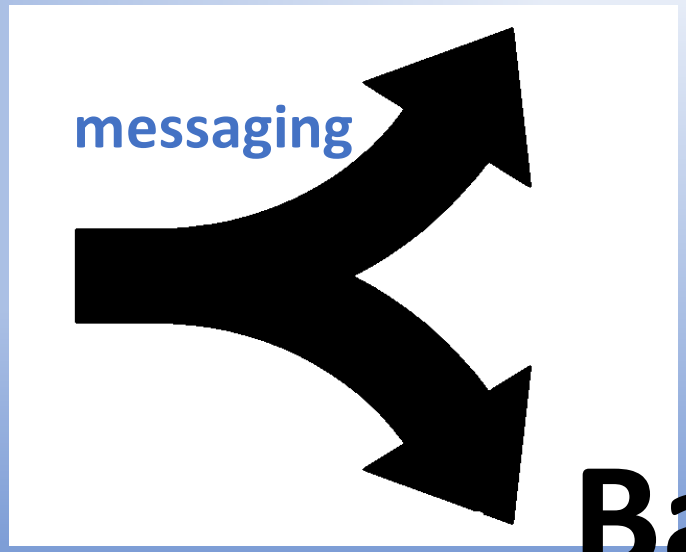
Picture removed
for copyright reasons

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

Change communication approach…
…and move from war of faith to an engineering challenge

Pictures removed for copyright reasons

Ethics



Bad Science

Lack of reproducibility and predictivity

Bad Economics

Economic consequences and opportunities

It is still good to be on the right side of ethics and history!

Food for Thought ...

ALTEX 2018, 35:275-305

Animal Testing and its Alternatives – the Most Important Omics is Economics

Lucy Meigs [1,2], Lena Smirnova [2], Costanza Rovida [3], Marcel Leist [3] and Thomas Hartung [2,3]

Picture removed for copyright reasons

Economic considerations are underestimated

They promote and hinder implementation of NAM

The value of animal tests is strongly overestimated

- For the 9 most common OECD tox tests (acute and topical, eco – n = 2,839), reproducibility is 81%, 69% for toxic substances
- Mice and rat predict each other ~60% for systemic tox

- Miss some human effects
- Too long, too expensive, too much substance need
- New hazards not covered
- New products not applicable
- Mixtures and individual susceptibility not adequately covered

Food for Thought...

ALTEX 2015, 32:79-100

The Human Whole Blood Pyrogen Test – Lessons Learned in Twenty Years

Thomas Hartung

Invented 1995, Validated 2006 PyroDetect (Merck-Millipore)
Accepted FDA 2009, European Pharmacopoeia 2010, USP 2017, ISO 2018

Implementation takes too long – little enforcement

Food for Thought ...

ALTEX 2021, 38:3-19

Pyrogen Testing Revisited on Occasion of the 25th Anniversary of the Whole Blood Monocyte Activation Test

Thomas Hartung[1,2]

Food for Thought ...

ALTEX 2020, 37:167-186

New European Union Statistics on Laboratory Animal Use – What Really Counts!

Francois Busquet[1,2#], Andre Kleensang[3#], Costanza Rovida[1,4#], Kathrin Herrmann[3], Marcel Leist[1] and Thomas Hartung[1,3]

Pyrogen testing

2005: ~160,000 rabbits
2008: ~170,000 rabbits
2015: 46,553
2016: 39,434
2017: 35,172

GOAL

News 2021: PharmEur will phase out rabbits within 5a!

Immunotoxicity - too much of a good thing…

- Inflammation
- Pyrogenicity
- Sensitization

Pictures removed for copyright reasons

- Immunosuppression
- Developmental ImmunoTox

= impaired or false response

Inflammation usually lacking *in vitro*

Food for Thought …

Immunotoxicology: Challenges in the 21st Century and *In Vitro* Opportunities

Thomas Hartung [1] and Emanuela Corsini [2]

Strong evidence, e.g., for involvement of immune cells likely activated by translocation of bacteria (Su, 2002; Nolan, 2010) in the effects of classic hepatotoxicants (Laskin and Pendino, 1995; Leist et al., 1998; Luster et al., 2001): paracetamol, cocaine, nitrosamine, galactosamine, lead withdrawal, thioacetamide, α-amanitin, actinomycin D, diethyl-dithiocabarmate, phalloidin, CCl4, cyproterone acetate, 1,2-dichlorobenzene, cadmium, allyl alcohol, heliotrine, ischemia-reperfusion, microcystine, and others.

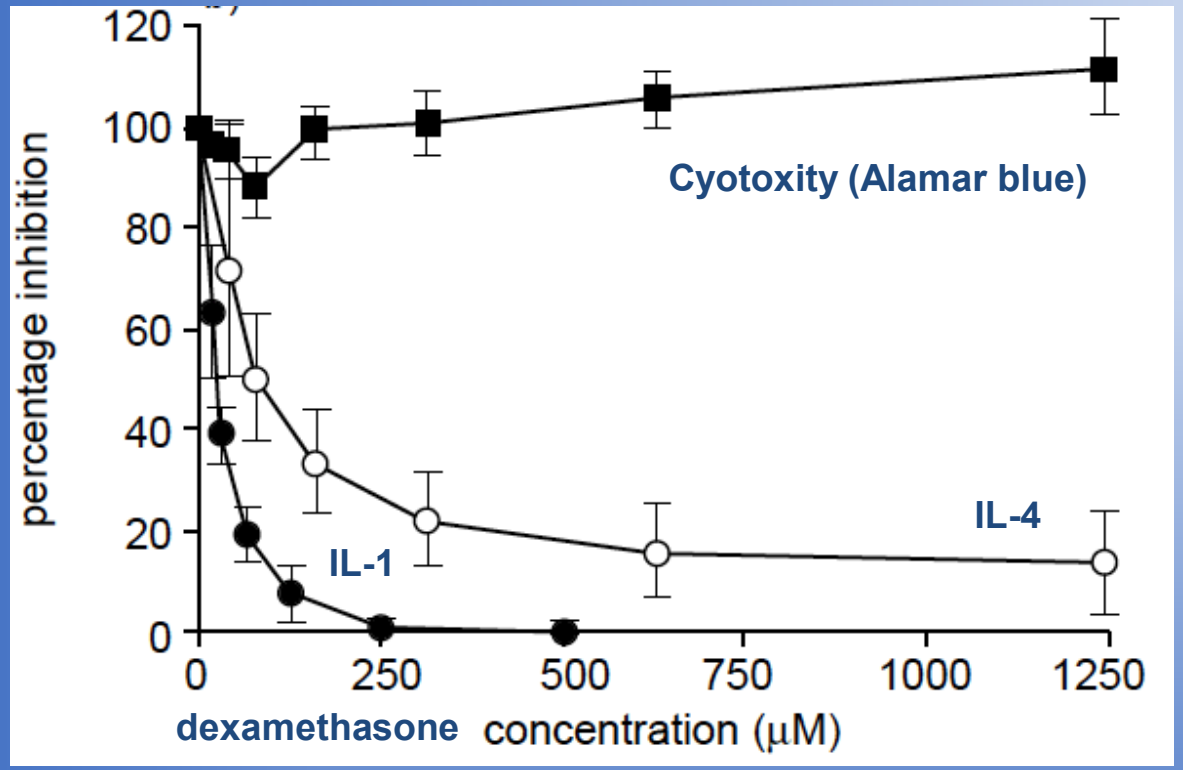
Picture removed for copyright reasons

https://www.gastroenterologyadvisor.com/liver/biomarkers-for-liver-damage-may-allow-for-early-identification-of-liver-toxicity-and-eventual-cancer/

ATLA 30, 581–595, 2002

Evaluation and Prevalidation of an Immunotoxicity Test Based on Human Whole-blood Cytokine Release

Ingrid Langezaal,[1,2,3] Sebastian Hoffmann,[2] Thomas Hartung[2,4] & Sandra Coecke[1]



Langezaal et al., ATLA 2002, 30:581-595

Immunotoxic disturbance of reaction to bacterial stimulation

Simple, robust test

Human primary cells

Lymphocyte and monocyte endpoints

Toxicol. In Vitro 2001, 15:313-318

Whole blood cytokine response as a measure of immunotoxicity

I. Langezaal[a,b], S. Coecke[b], T. Hartung[a,*]

ALTERNATIVES TO DEVELOPMENTAL IMMUNOTOXICITY TESTING (DIT) WORKING GROUP

- Fenna Sillé
- Helena Hogberg
- Katya Tsaioun

Academia / Research Institutes:

- Johanna Gostner, PhD (Biocenter, Medical University of Innsbruck)
- Emanuela Corsini, PhD (University of Milan)
- Dori R. Germolec, PhD (NTP/NIEHS)

Regulatory:

- Suzanne Fitzpatrick, PhD, DABT (FDA)
- Cameron Bowes, PhD (Health Canada - regulatory)
- David Lefebvre, PhD (Health Canada – Method development)
- O'hara, Shifawn (Health Canada)

Industry & End-users:

- Leigh Ann Burns-Naas, PhD, DABT, ERT, ATS (Magnolia Toxicology Consulting, LLC)
- Mark Collinge, PhD (Pfizer)
- Vic Johnson, PhD (BRT Labs)

Librarian:

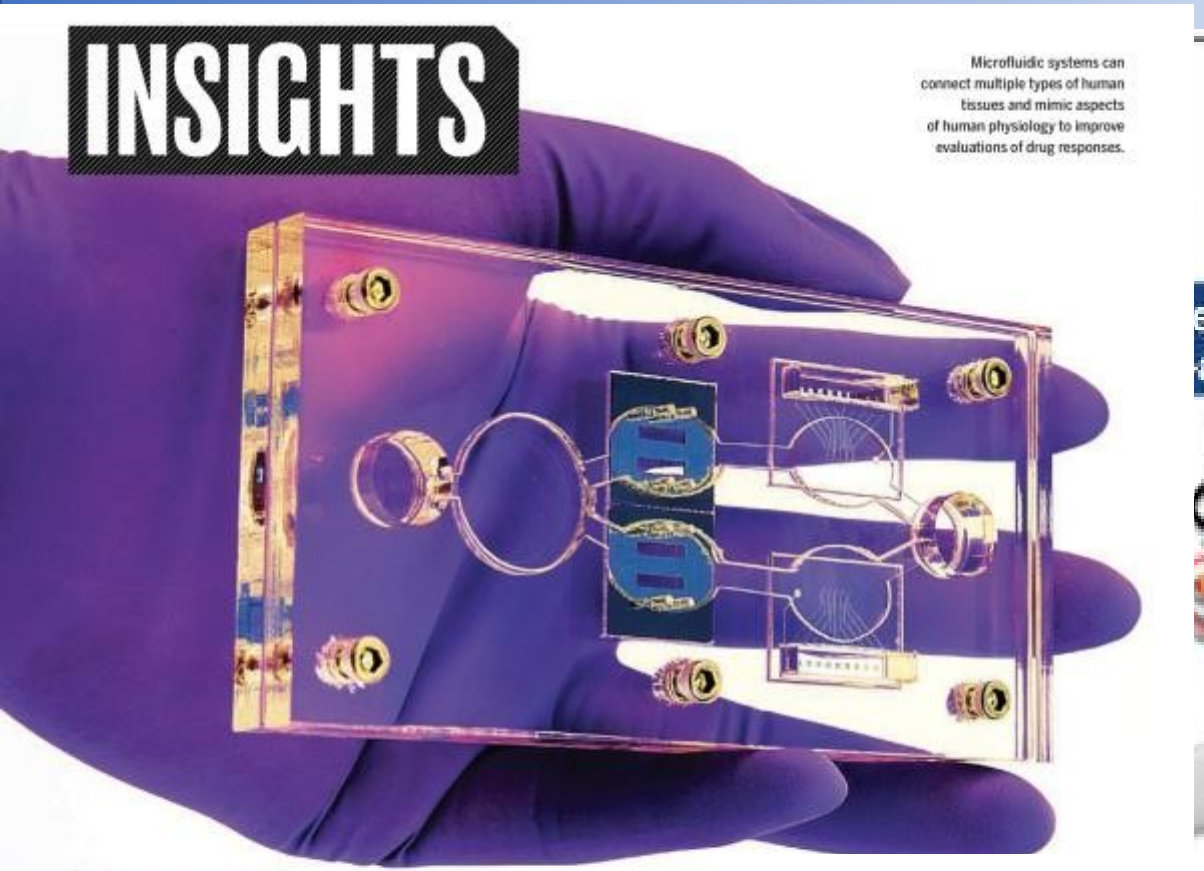
Robert Wright (JHU)

Picture removed for copyright reasons

- Opinion article
- Scoping review
- **May 4-5, 2021:** Virtual mini-workshop #1: "**Identification of Key Molecular and Biological events in Developmental Immunotoxicity**"
- **March 26-30, 2022: SOT** (San Diego): Workshop Session "Current Status and Future Outlook on Developmental Immunotoxicity Testing."

Call to Action

We have the tools 1
Evolution of Cell Culture - high-tech & business opportunity



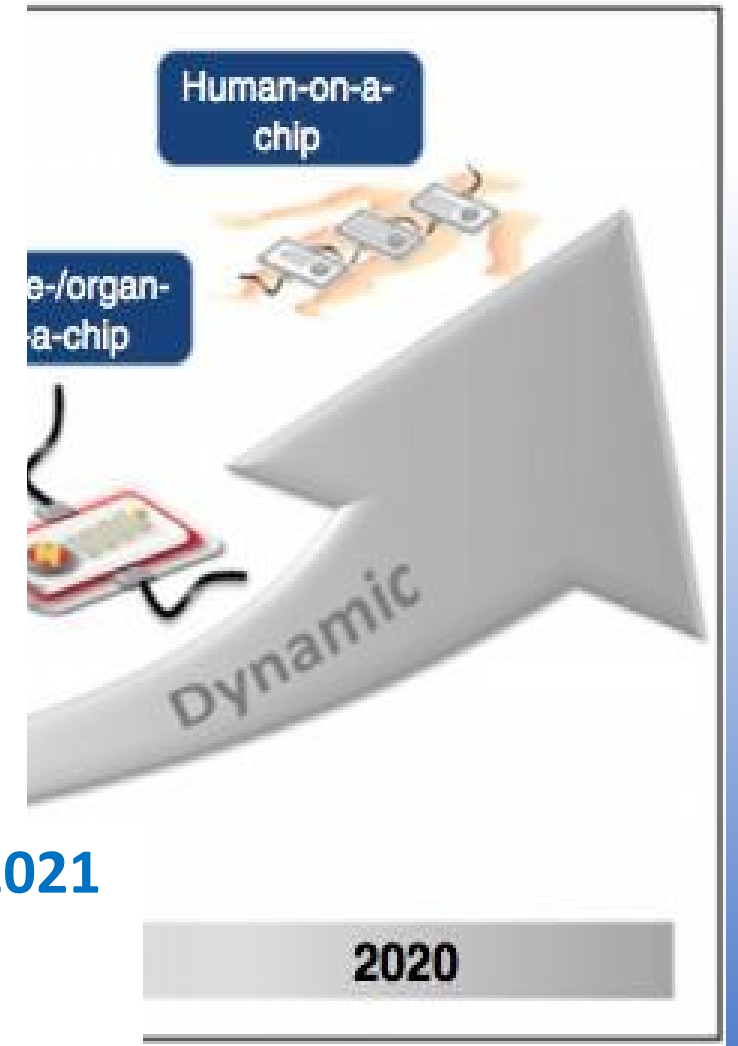
PERSPECTIVES

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

~45 organizations plus Scientific Advisory Board

$450k from NCATS

Forming an International Society and Conference Series

Virtual 24 Jun & 9 Dec ‘21

New Orleans 30 May-3 Jun ‘22

Hosts: Suzie Fitzpatrick, FDA

Thomas Hartung, Hopkins

Don Ingber, Harvard

https://mpsworldsummit.com

At ESTIV 2018 CAAT/ESTIV symposium

GCCP 2.0

Draft published

350 stakeholder comments integrated

- **ALTEX 1’2022**
- **Editor workshop 2022**
- **Funding bodies**

Letter

ALTEX 2020, 37: 490-492

Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0) – Draft for Stakeholder Discussion and Call for Action

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], Thomas Hartung[2,9] and Glyn Stacey[10,11,12]

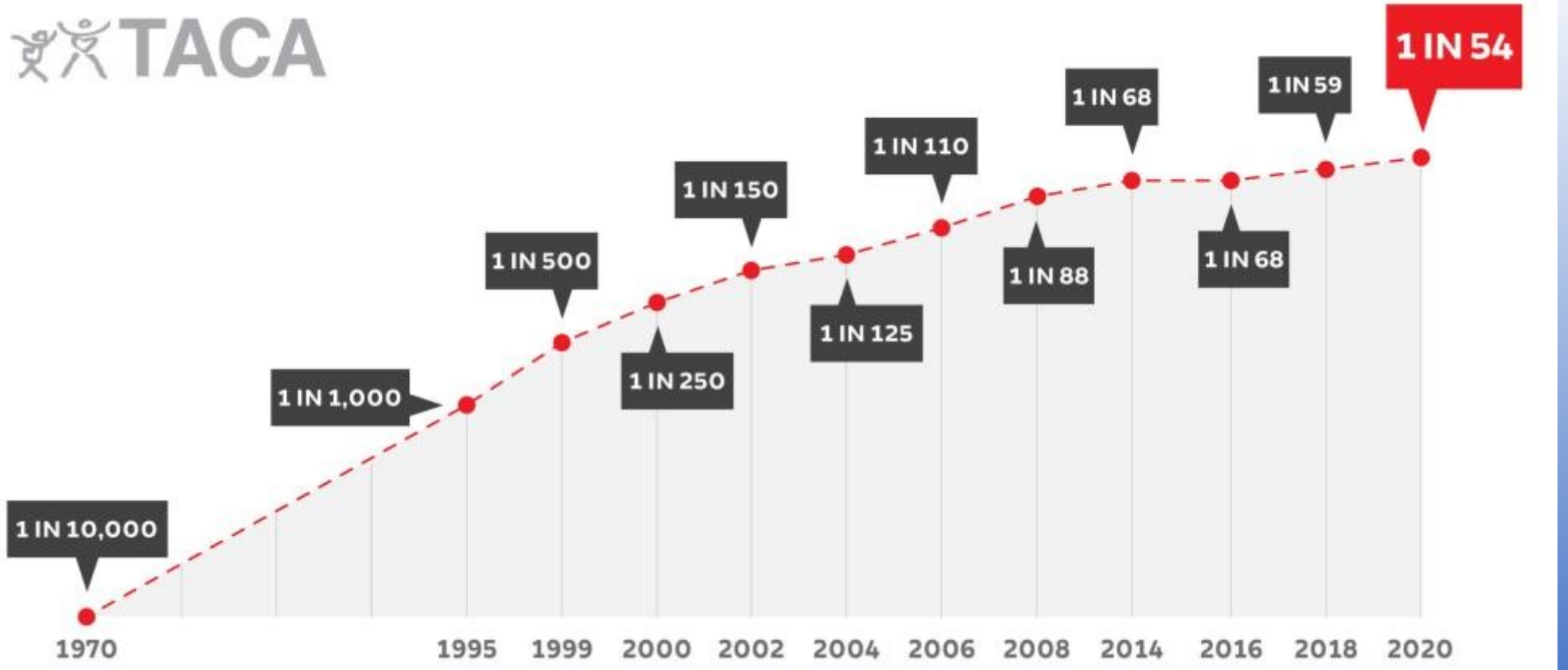
Register at:
CAAT@jhu.edu

Picture removed
for copyright reasons

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

Picture removed
for copyright reasons

DEVELOPMENTAL NEUROTOXICITY



DNT from *in vivo* towards *in vitro*

DNT3 Developmental Neurotoxicity

TestSmart DNT Developmental Neurotoxicity

efsa OECD

Expert Group on DNT

OECD

Guidance Document

ISTNET Workshop

2005 2010 2015 2020

TESTSMART DNT2 DEVELOPMENTAL NEUROTOXICITY

TESTSMART DNT4 DEVELOPMENTAL NEUROTOXICITY

transatlantic think tank for toxicology

Test Readiness

TESTSMART DNT5 DEVELOPMENTAL NEUROTOXICITY

STAR grant

FDA

transatlantic think tank for toxicology

DNT Reference Compounds

FDA

CERSI Johns Hopkins University

BrainSpheres: iPSC-derived human organotypic brain cultures

- All cell types but micro-glia
- 350 um diameter
- Reproducible in size and composition
- Myelination
- Genetic background from patient iPSC

Massachusetts Institute of Technology

FDA

NIH National Center for Advancing Translational Sciences

NIH National Institute of Environmental Health Sciences

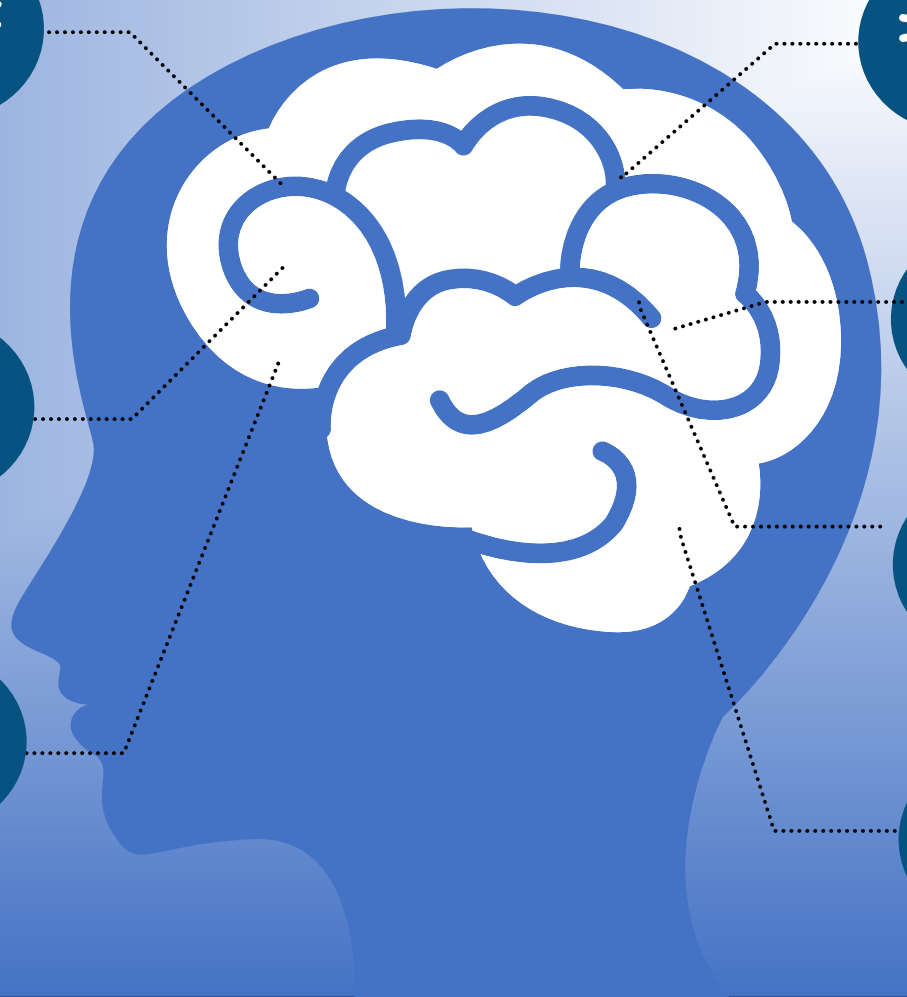
Pamies et al. ALTEX 2017, TAP 2018

BRAIN ORGANOIDS

STANDARDIZED HUMAN 3D DEVELOPMENT FROM IPSC

GLIA CELLS, MYELINATION +ADDED MICRO–GLIA

INFECTION CANCER GRAFTS TOXICITY



GENETIC BACKGROUNDS, + RISK GENES, REPAIR + REPORTER GENES

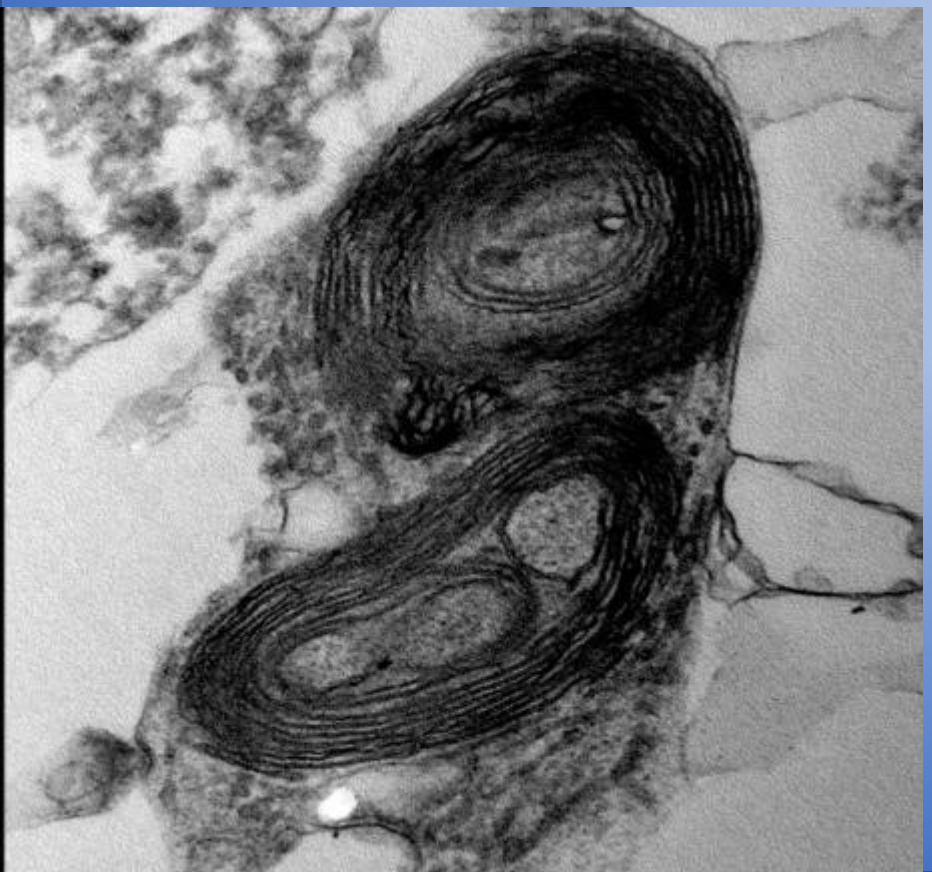
GENE X ENVIRONMENT MIXTURES

FUNCTIONAL ASSAYS: NEURITES, SYNAPSES, 3D ORGANOID EEG

INTELLIGENCE (O.I.)

Myelination

- 40% axons myelinated
- Allows studying de- and re-myelination



International Journal of *Molecular Sciences*

Int. J. Mol. Sci. 2021, 22, 9473

MDPI

Article

Human IPSC-Derived Model to Study Myelin Disruption

Megan Chesnut [1], Hélène Paschoud [2], Cendrine Repond [2], Lena Smirnova [1], Thomas Hartung [1,3], Marie-Gabrielle Zurich [2,4], Helena T. Hogberg [1,*] and David Pamies [1,2,4,*]

International Journal of *Molecular Sciences*

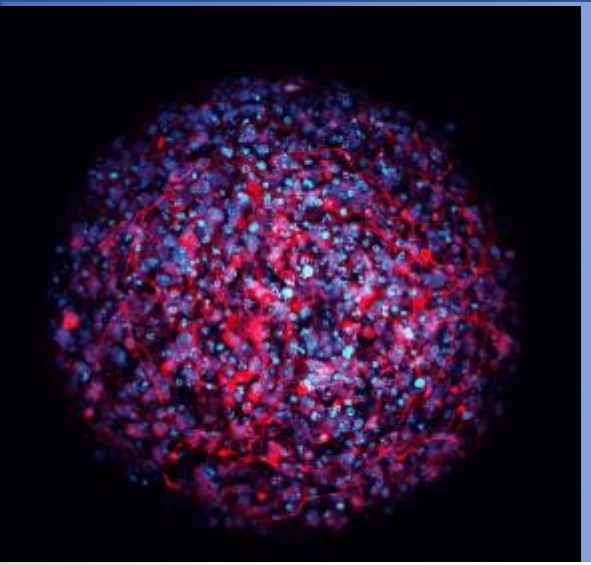
Int. J. Mol. Sci. 2021, 22, 7929

MDPI

Review

Human Oligodendrocytes and Myelin In Vitro to Evaluate Developmental Neurotoxicity

Megan Chesnut [1], Thomas Hartung [1,2], Helena Hogberg [1,*] and David Pamies [1,3,4,*]



DNT in human brain organoids

frontiers **Front Cell Neurosci 2020**

Antidepressant Paroxetine exerts developmental neurotoxicity in an iPSC-derived 3D human brain model

Xiali Zhong[1,2], Georgina Harris[1], Lena Smirnova[1], Valentin Zufferey[3], Rita Sa[4], Fabiele Baldino Russo[5], Patricia C. Baleeiro Beltrao Braga[5], Megan Chesnut[1], Marie-Gabrielle Zurich[3], Helena Hogberg[1], Thomas Hartung[6,7], David Pamies[3,1*]

Tox Appl Pharmacol 2018

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap

Rotenone exerts developmental neurotoxicity in a human brain spheroid model

David Pamies[a], Katharina Block[a], Pierre Lau[b], Laura Gribaldo[b], Carlos A. Pardo[c], Paula Barreras[c], Lena Smirnova[a], Daphne Wiersma[a], Liang Zhao[a,d], Georgina Harris[a], Thomas Hartung[a,e], Helena T. Hogberg[a,*]

Archives of Toxicology
https://doi.org/10.1007/s00204-020-02903-2

Arch Toxicol 2021

ORGAN TOXICITY AND MECHANISMS

Organophosphorus flame retardants are developmental neurotoxicants in a rat primary brainsphere in vitro model

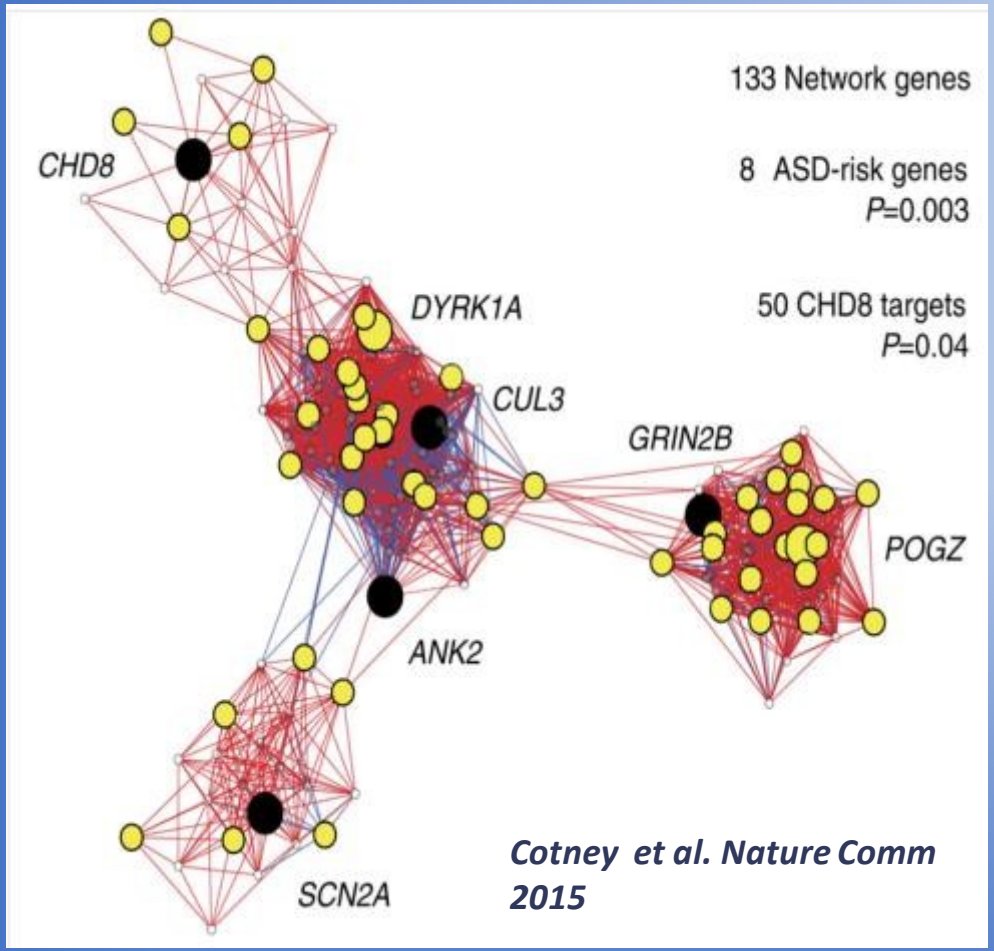
FDA

NTP National Toxicology Program
U.S. Department of Health and Human Services

CHD8 and chlorpyrifos functional synergy

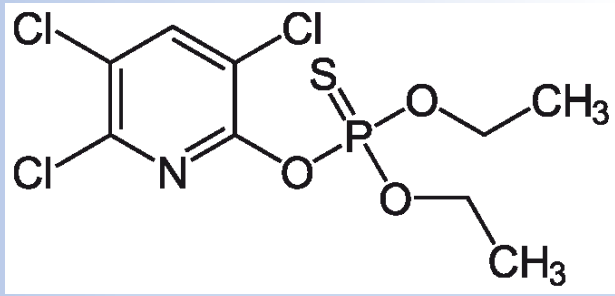
ALTERNATIVES RESEARCH & DEVELOPMENT FOUNDATION

AiR CHALLENGE



Cotney et al. Nature Comm 2015

CHLORPYRIFOS



CHLORPYRIFOS-OXON

GxE

Functional and Molecular signatures

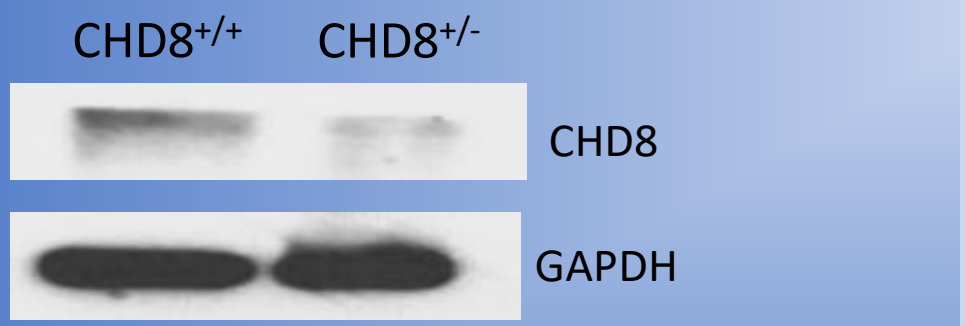
Lena Smirnova

CHD8 knockout BrainSpheres (CRISPR-CAS9) as disease model

Modafferi et al., EHP 2021

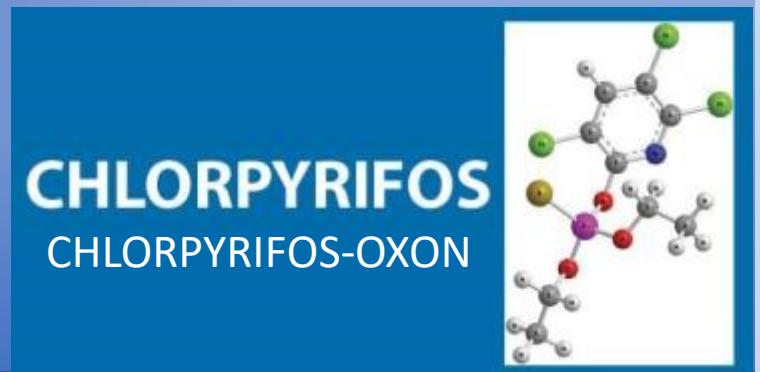
Gene–Environment Interactions in Developmental Neurotoxicity: a Case Study of Synergy between Chlorpyrifos and CHD8 Knockout in Human BrainSpheres

Sergio Modafferi,[1,2] Xiali Zhong,[1,3*] Andre Kleensang,[1] Yohei Murata,[1,4] Francesca Fagiani,[1,5,6] David Pamies,[1,7] Helena T. Hogberg,[1] Vittorio Calabrese,[2] Herbert Lachman,[8,9] Thomas Hartung,[1,10] and Lena Smirnova[1]*



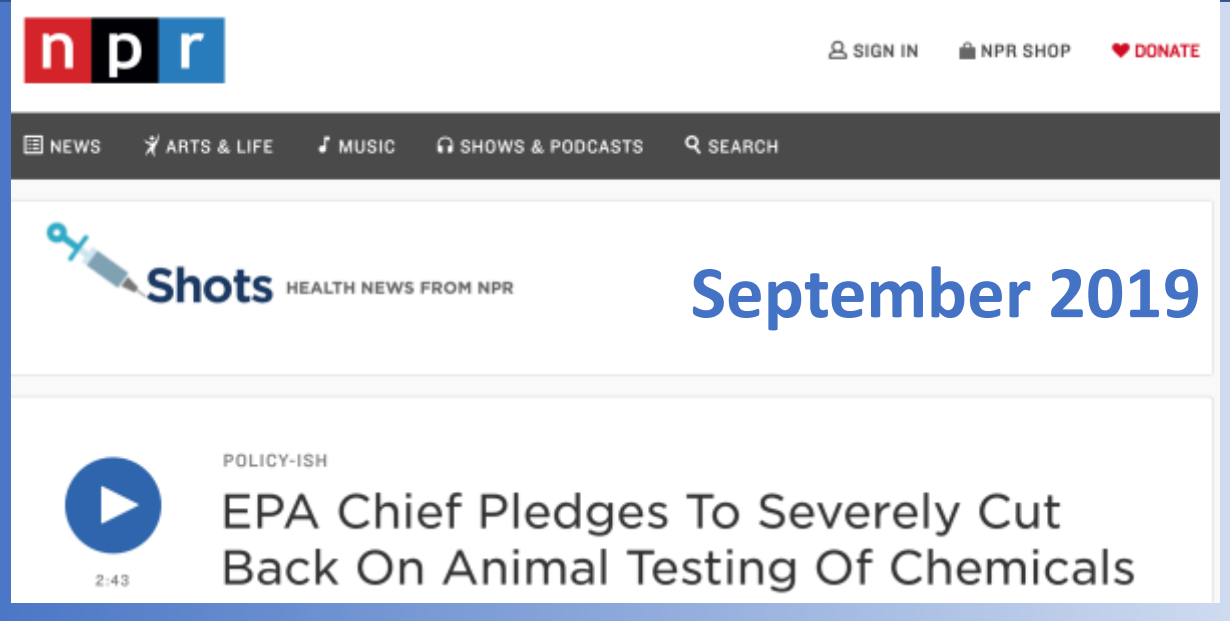

Lachman


Smirnova



CHD8/CPF synergy in perturbation of energy metabolism, one carbon metabolism, L-a-Hydroxyglutaric acid and tryptophan synthesis

	ASD patients			BrainSpheres		
	Blood	Urine	Brain	CHD8	CPF/CPO	Synergy
Dopamine			↓	↓	-	-
Choline			↓	↓	↓	↓↓
Tryptophan	-	↓↑	-			↑
Kynurenic acid	↓	-	-	↑		↑↑
Lactic acid	↑↓	↓				↑
L-Alanine					↑	
SAH	↑	↑		↑		↑
L-a-Hydroxyglutaric acid		↑				↑



Smirnova, Hartung, Berlinicke, Gracias

FDA

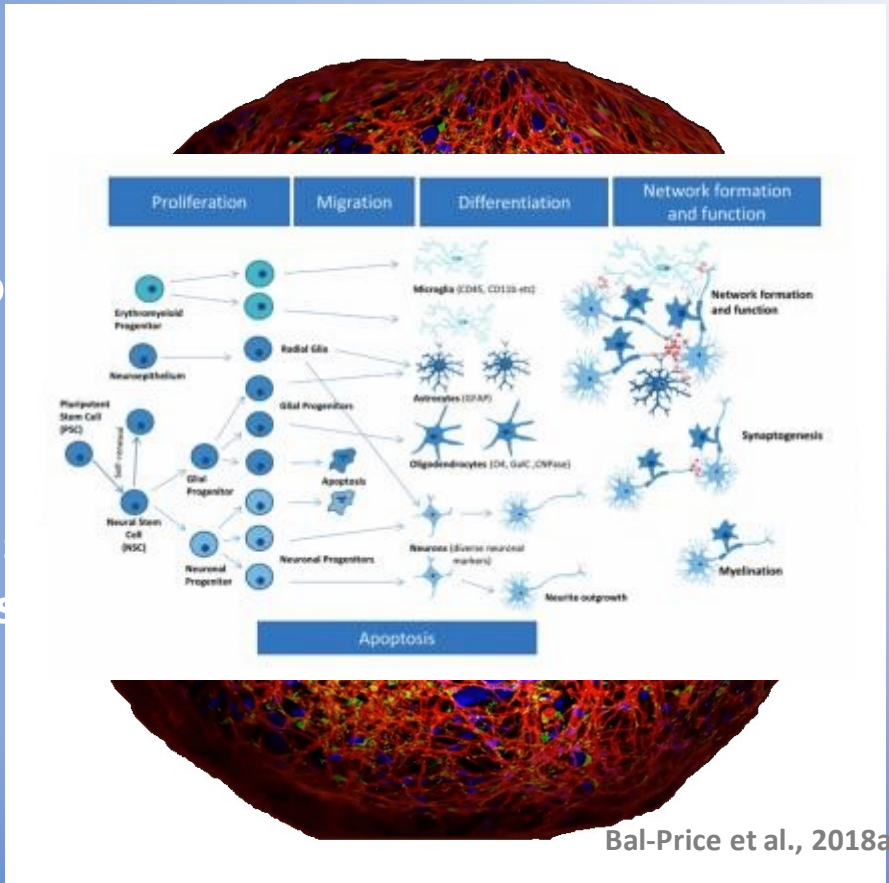
CERSI
Johns Hopkins University

Sep 2021

CAAT receives $300k grant from FDA for DNT-MPS (already funded by EPA) through the JH Center of Excellence in Regulatory Science and Innovation

6-in-1 BrainSphere assay to test Neurodevelopment

Neuronal differentiatio
Myelination
Neurite outgrowth
Synaptogenesis
Glia migration & Gliosi
Neural network (E-phys



Bal-Price et al., 2018a

CRISPR/C

Reporter/
Fusion
proteins

Mini- Brainbow

Neurons
Astrocytes
Oligodendrocytes
Synapses
3D electrophys

High content imaging
Toxicant/drug screening

Food for Thought ...

COVID-19 – Prime Time for Microphysiological Systems, as Illustrated for the Brain

Ian Kang[1], Lena Smirnova[1], Jens H. Kuhn[2], Helena T. Hogberg[1], Nicole C. Kleinstreuer[3] and Thomas Hartung[1,4]

ALTEX preprint
published June 26, 2020
doi:10.14573/altex.2006111

Short communication

Infectability of Human BrainSphere Neurons Suggests Neurotropism of SARS-CoV-2

C. Korin Bullen[1,#], Helena Therese Hogberg[2,#], Asli Bahadirli-Talbott[1], William R. Bishai[1], Thomas Hartung[2,3,4], Casey Keuthan[5], Monika M. Looney[1], Andrew Pekosz[4], July Carolina Romero[2], Fenna C. M. Sillé[2,6], Peter Um[1] and Lena Smirnova[2,#]

FINANCIAL TIMES

HOME WORLD US COMPANIES TECH MARKETS GRAPHICS OPINION WORK & CAREERS LIFE & ARTS HOW TO SPEND IT

CORONAVIRUS **BUSINESS UPDATE**
Get 30 days' complimentary access to our Coronavirus Business Update newsletter

Latest on Coronavirus treatment

Germany to take stake in Covid-19 vaccine hopeful CureVac

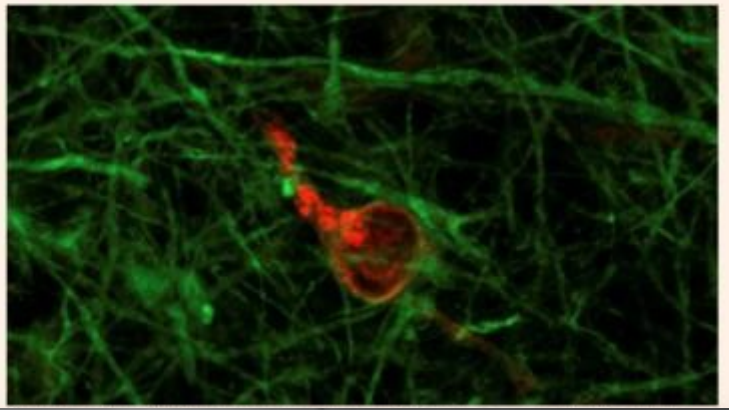
World economy's challenge laid bare by new data

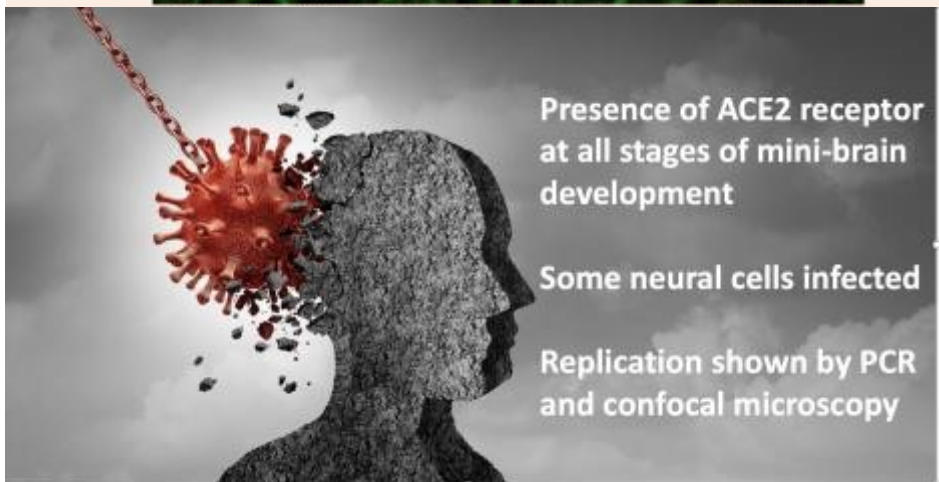
EU to spend billions of euros to secure coronavirus vaccine

Coronavirus treatment + Add to myFT

Coronavirus could infect human brain and replicate, US study shows

Johns Hopkins University research adds to concern about poorly understood neurological symptoms





Another scientific revolution

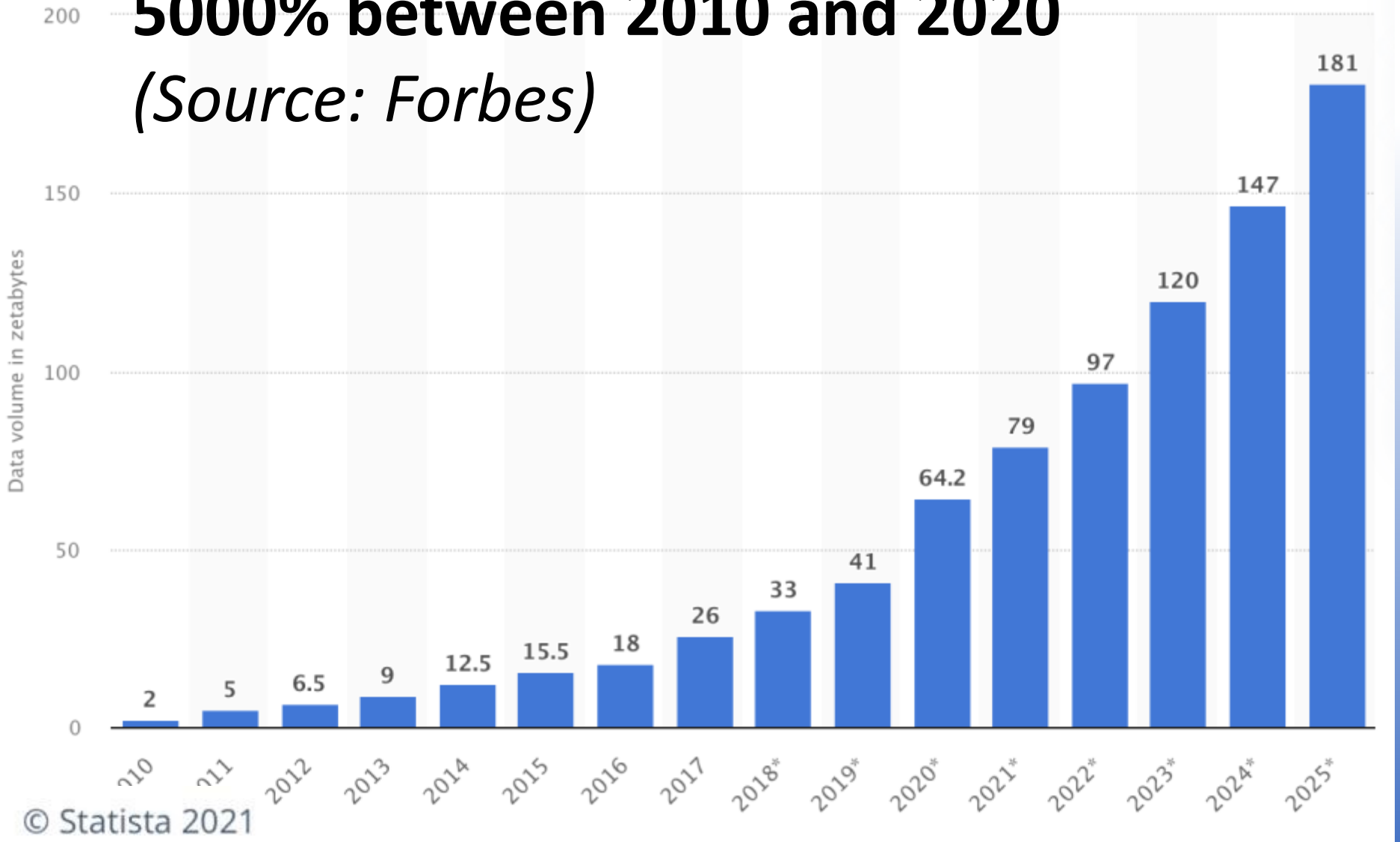
Picture removed
for copyright reasons

https://www.coe.int/en/web/commissioner/-/-we-need-to-act-now-and-put-human-rights-at-the-centre-of-artificial-intelligence-designs

Data produced world-wide

5000% between 2010 and 2020

(Source: Forbes)



84% of data in the world were created in the last 6 years

Volume of data/information created, captured, copied, and consumed worldwide from 2010 to 2025 *(in zettabytes)*

Machine Learning in Biology

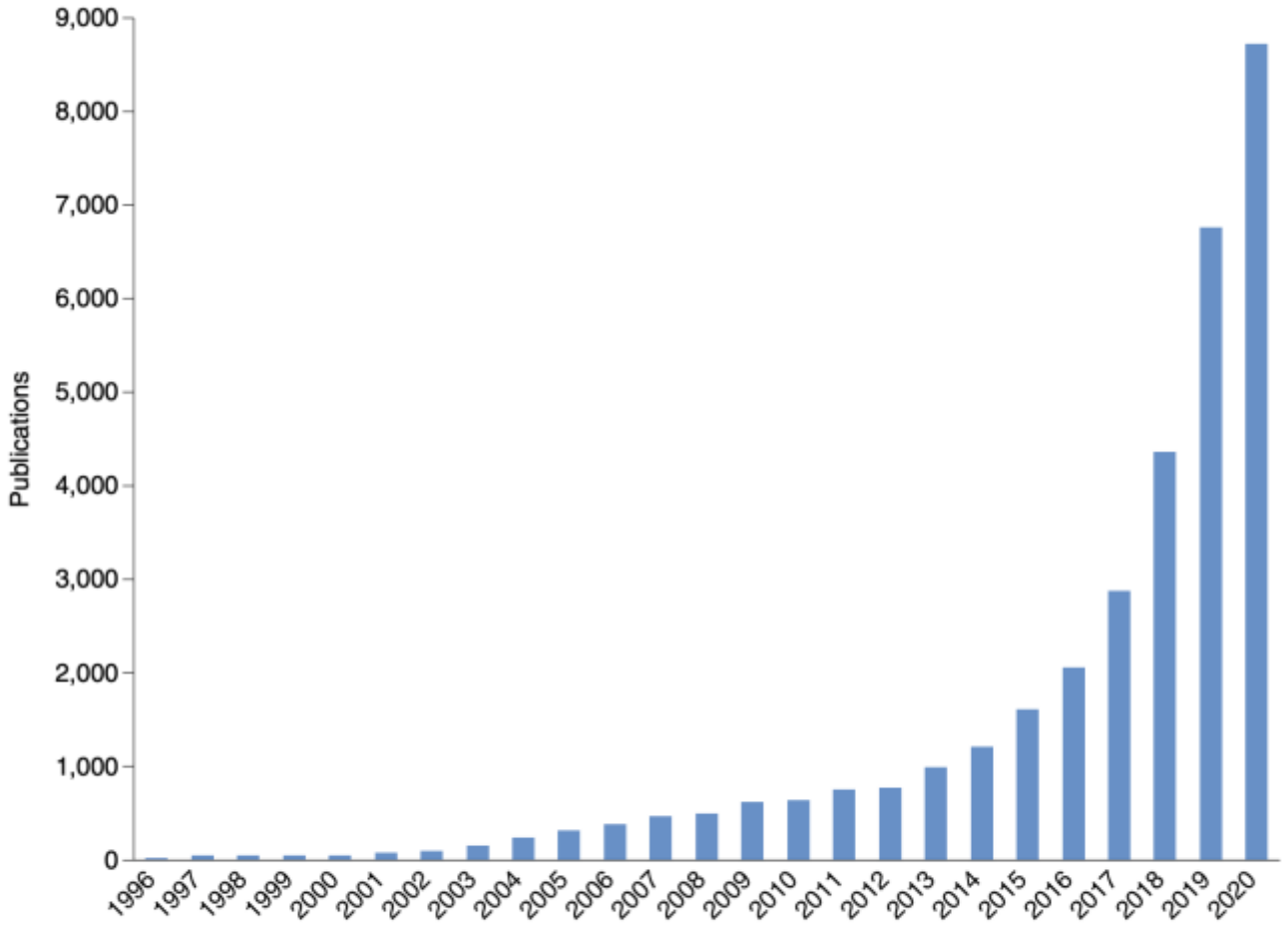


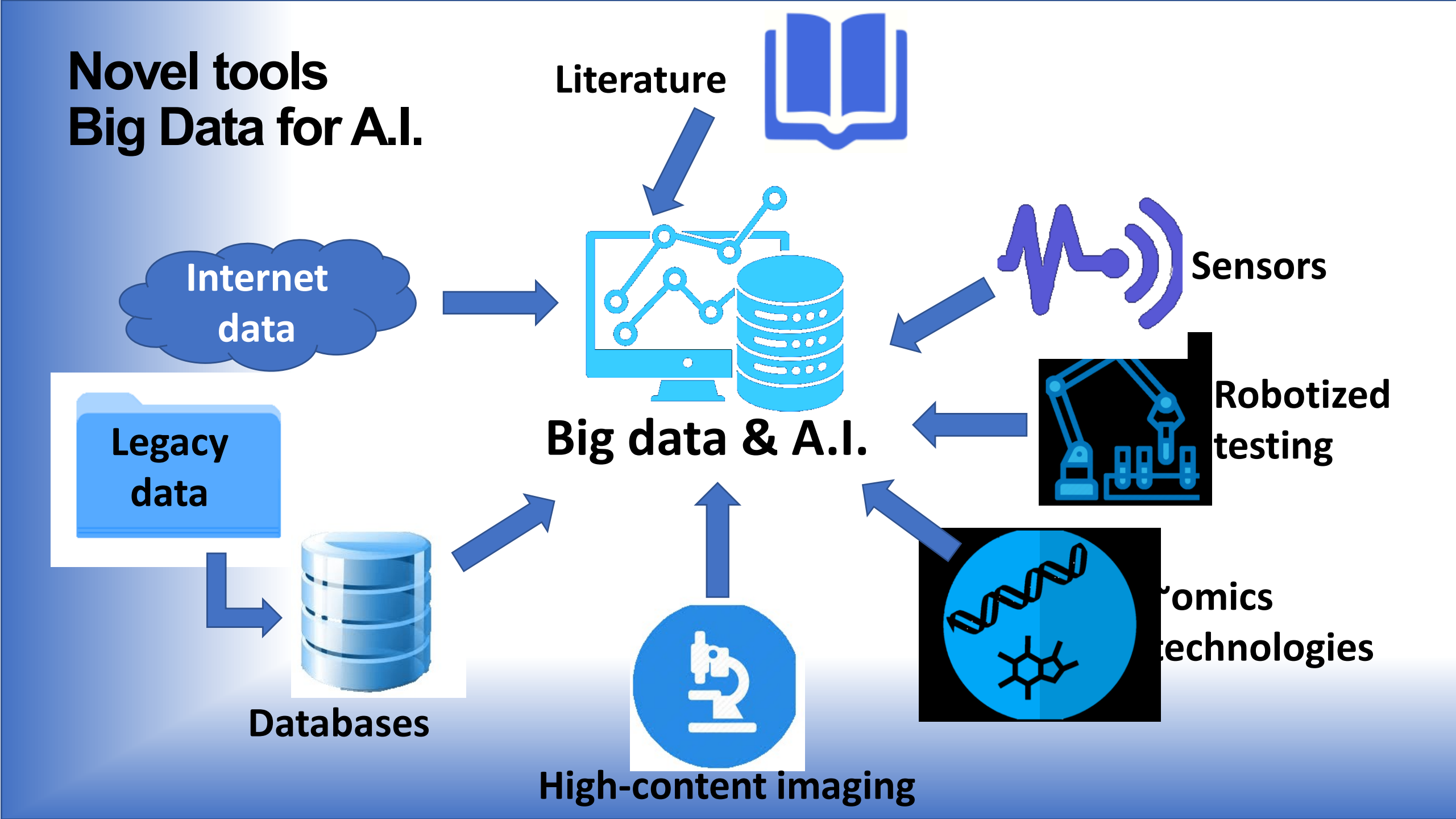
Fig. 1 | Exponential increase of ML publications in biology. The number of ML publications per year is based on Web of Science from 1996 onwards using the topic category for "machine learning" in combination with each of the following terms: "biolog*", "medicine", "genom*", "prote*", "cell*", "post translational", "metabolic" and "clinical".

Picture removed for copyright reasons

https://universitybusiness.com/revolutionary-ed-tech-creates-new-challenges-campus-leaders/attachment/artificial-intelligence-and-future-concept/

Walsh et al. Nat Meth 2021

Novel tools
Big Data for A.I.



A.I. = Making big sense of

BIG DATA

Picture removed
for copyright reasons

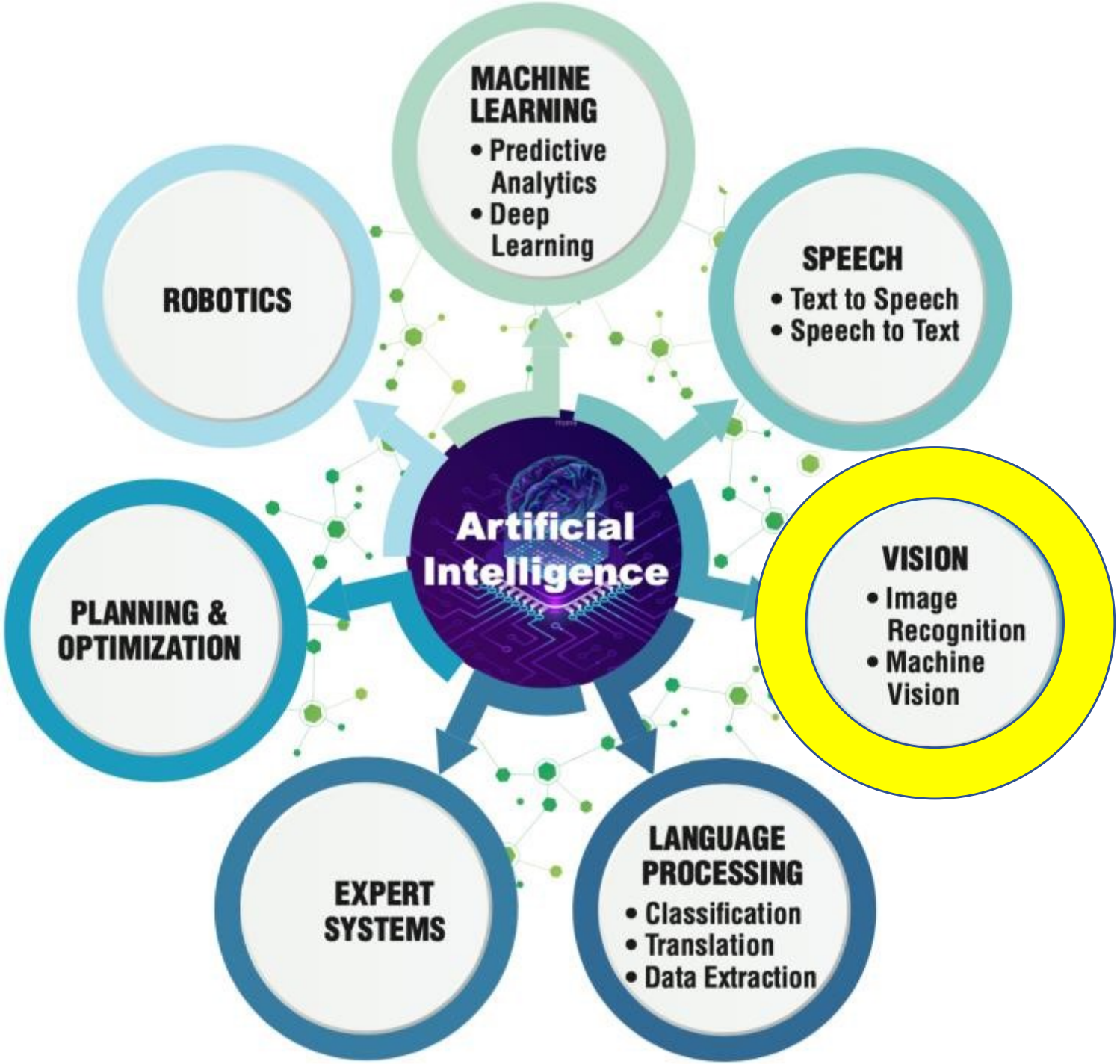
https://theamericangenius.com/editorials/big-data-is-watching-you-some-will-panic-others-will-rejoice/

Picture removed
for copyright reasons

Volume
Variety
Velocity

https://www.e-marketing.fr/Thematique/data-1091/big-data-2223/Breves/Tout-faut-savoir-big-data-363012.htm

...is more than a large EXCEL sheet!


MACHINE LEARNING
• Predictive Analytics
• Deep Learning
ROBOTICS
SPEECH
• Text to Speech
• Speech to Text
Artificial Intelligence
PLANNING & OPTIMIZATION
VISION
• Image Recognition
• Machine Vision
EXPERT SYSTEMS
LANGUAGE PROCESSING
• Classification
• Translation
• Data Extraction

A.I. use cases

IMAGE RECOGNITION: High-content Imaging, especially in pathology

transatlantic think tank for toxicology

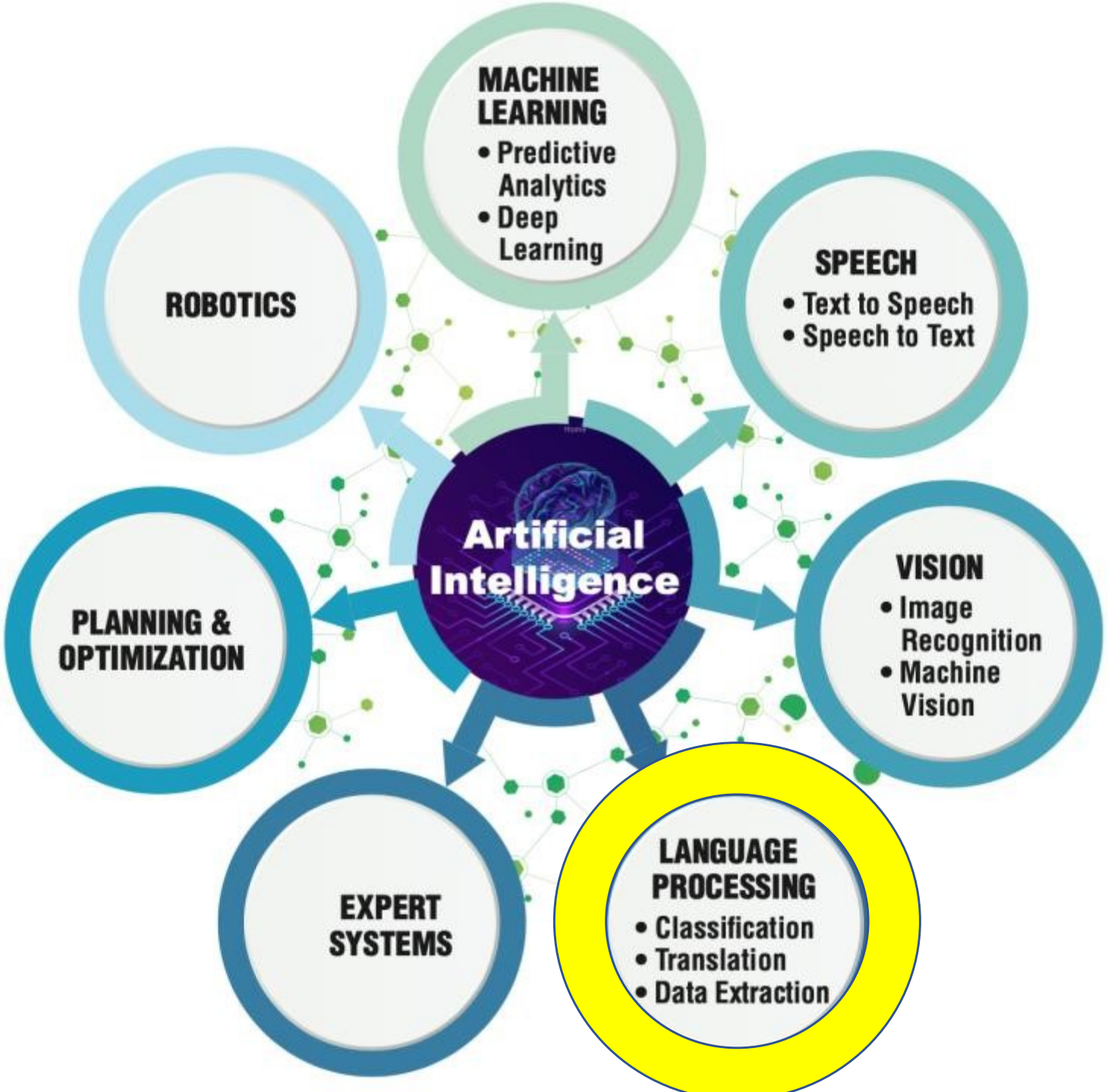
ALTEX 2014, 31:479-493

t⁴ Workshop Report*

Current Approaches and Future Role of High Content Imaging in Safety Sciences and Drug Discovery

Erwin van Vliet[1], *Mardas Daneshian*[2], *Mario Beilmann*[3], *Anthony Davies*[4], *Eugenio Fava*[5], *Roland Fleck*[6], *Yvon Julé*[7], *Manfred Kansy*[8], *Stefan Kustermann*[8], *Peter Macko*[9], *William R. Mundy*[10], *Adrian Roth*[8], *Imran Shah*[11], *Marianne Uteng*[12], *Bob van de Water*[13], *Thomas Hartung*[2,14] *and Marcel Leist*[2*]

Picture removed for copyright reasons


MACHINE LEARNING
• Predictive Analytics
• Deep Learning
ROBOTICS
SPEECH
• Text to Speech
• Speech to Text
Artificial Intelligence
PLANNING & OPTIMIZATION
VISION
• Image Recognition
• Machine Vision
EXPERT SYSTEMS
LANGUAGE PROCESSING
• Classification
• Translation
• Data Extraction

A.I. use cases

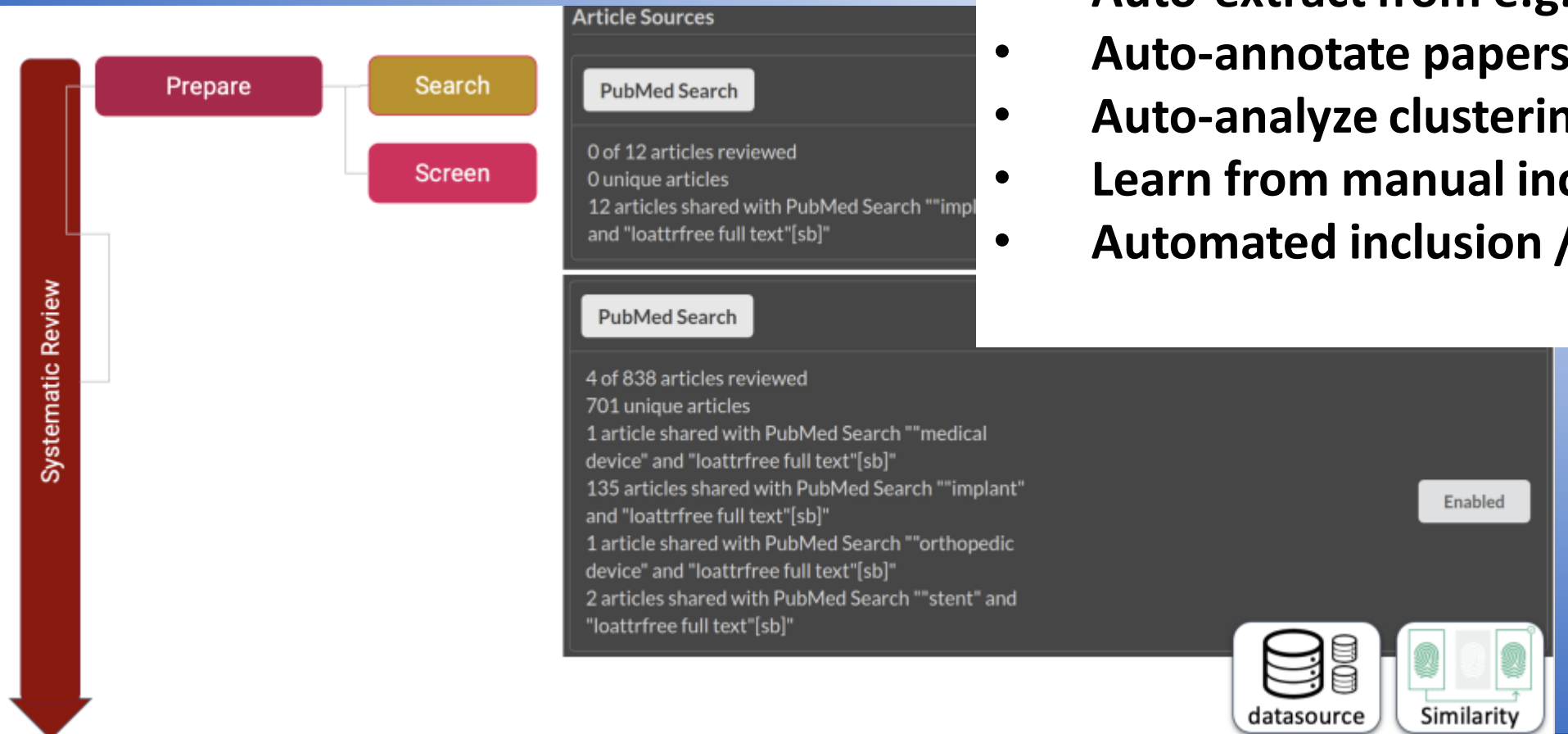
Mining publications

Sysrev.com

TOXTRACK

Semi-automated systematic review:

- **Auto-extract from e.g. PubMed**
- **Auto-annotate papers**
- **Auto-analyze clustering of papers**
- **Learn from manual inclusion / exclusion**
- **Automated inclusion / exclusion suggestions**



Alexandra Maertens

Making big sense of

Picture removed for copyright reasons

Research Article

Evaluation of the Global Performance of Eight *In Silico* Skin Sensitization Models Using Human Data

Emily Golden[1], Donna S. Macmillan[2], Greg Dameron[3], Petra Kern[3], Thomas Hartung[1,4] and Alexandra Maertens[1]

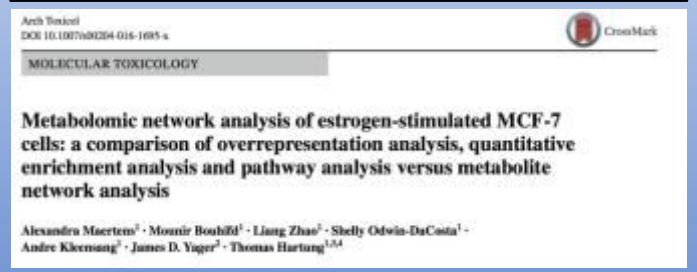
[1]Center for Alternatives to Animal Testing (CAAT), Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [2]Lhasa Limited, Leeds, UK; [3]Procter & Gamble NV, Beyer, Belgium; [4]CAAT-Europe, University of Konstanz, Konstanz, Germany

Chemical Research in Toxicology

Mapping Chemical Respiratory Sensitization: How Useful Are Our Current Computational Tools?

Emily Golden, Mikhail Maertens, Thomas Hartung, and Alexandra Maertens*

Cite This: https://dx.doi.org/10.1021/acs.chemrestox.0c00320 Read Online



Arch Toxicol
DOI 10.1007/s00204-016-1695-x

MOLECULAR TOXICOLOGY

Metabolomic network analysis of estrogen-stimulated MCF-7 cells: a comparison of overrepresentation analysis, quantitative enrichment analysis and pathway analysis versus metabolite network analysis

Alexandra Maertens[2] · Mounir Bouhifd[1] · Liang Zhao[2] · Shelly Odwin-DaCosta[1] · Andre Kleensang[2] · James D. Yager[3] · Thomas Hartung[1,2,4]

ACS Sustainable Chemistry & Engineering

Avoiding Regrettable Substitutions: Green Toxicology for Sustainable Chemistry

Alexandra Maertens, Emily Golden, and Thomas Hartung*

Cite This: https://doi.org/10.1021/acssuschemeng.8b04435 Read Online

frontiers in Genetics

ORIGINAL RESEARCH

Weighted Gene Correlation Network Analysis (WGCNA) Reveals Novel Transcription Factors Associated With Bisphenol A Dose-Response

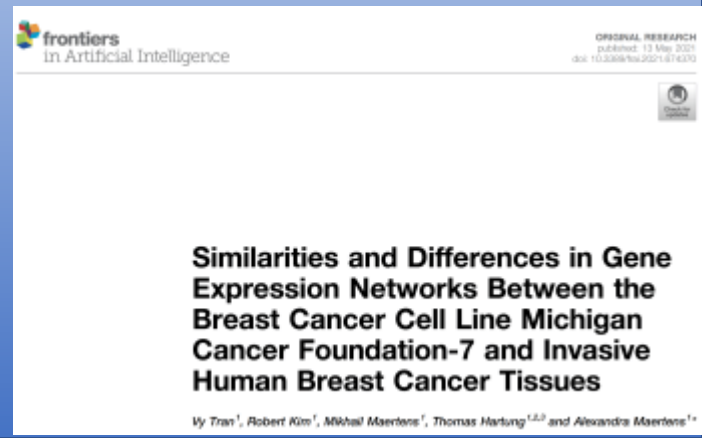
Alexandra Maertens[1], Vy Tran[1], Andre Kleensang[1] and Thomas Hartung[1,2,3]

SCIENTIFIC REPORTS
nature research

OPEN

Functionally Enigmatic Genes in Cancer: Using TCGA Data to Map the Limitations of Annotations

Alexandra Maertens[1,2], Vy H. Tran[1,2], Mikhail Maertens[1], Andre Kleensang[1], Thomas H. Luechtefeld[1,2], Thomas Hartung[1,2] & Channing J. Paller[3*]

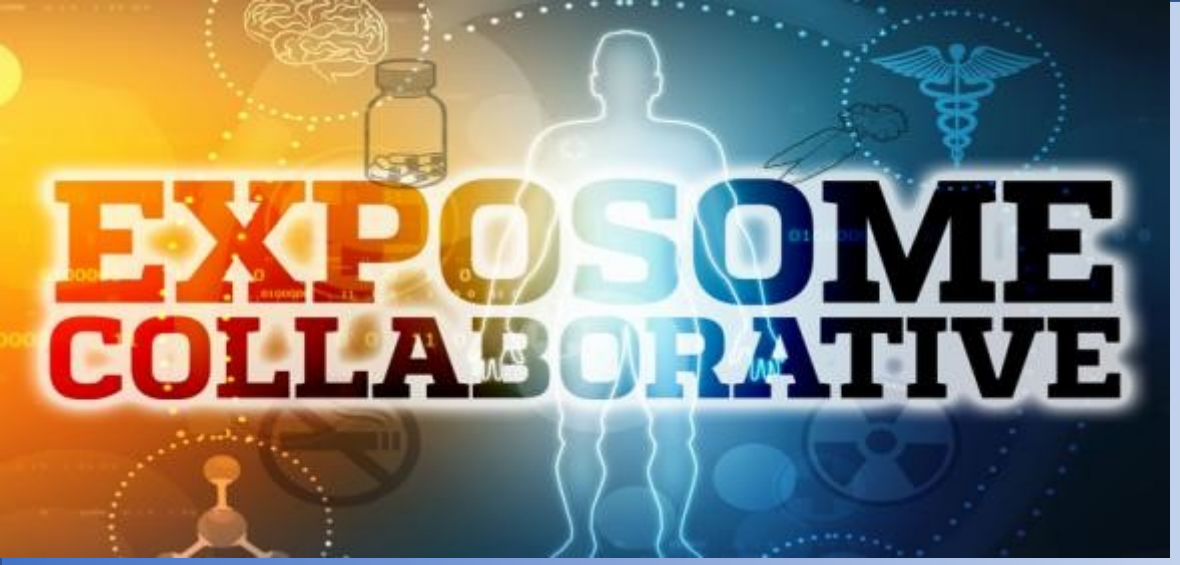


frontiers in Artificial Intelligence

ORIGINAL RESEARCH

Similarities and Differences in Gene Expression Networks Between the Breast Cancer Cell Line Michigan Cancer Foundation-7 and Invasive Human Breast Cancer Tissues

Vy Tran[1], Robert Kim[1], Mikhail Maertens[1], Thomas Hartung[1,2,3] and Alexandra Maertens[1]



Example Big Data and making sense of it

ALTEX 2020, 37, 3-23

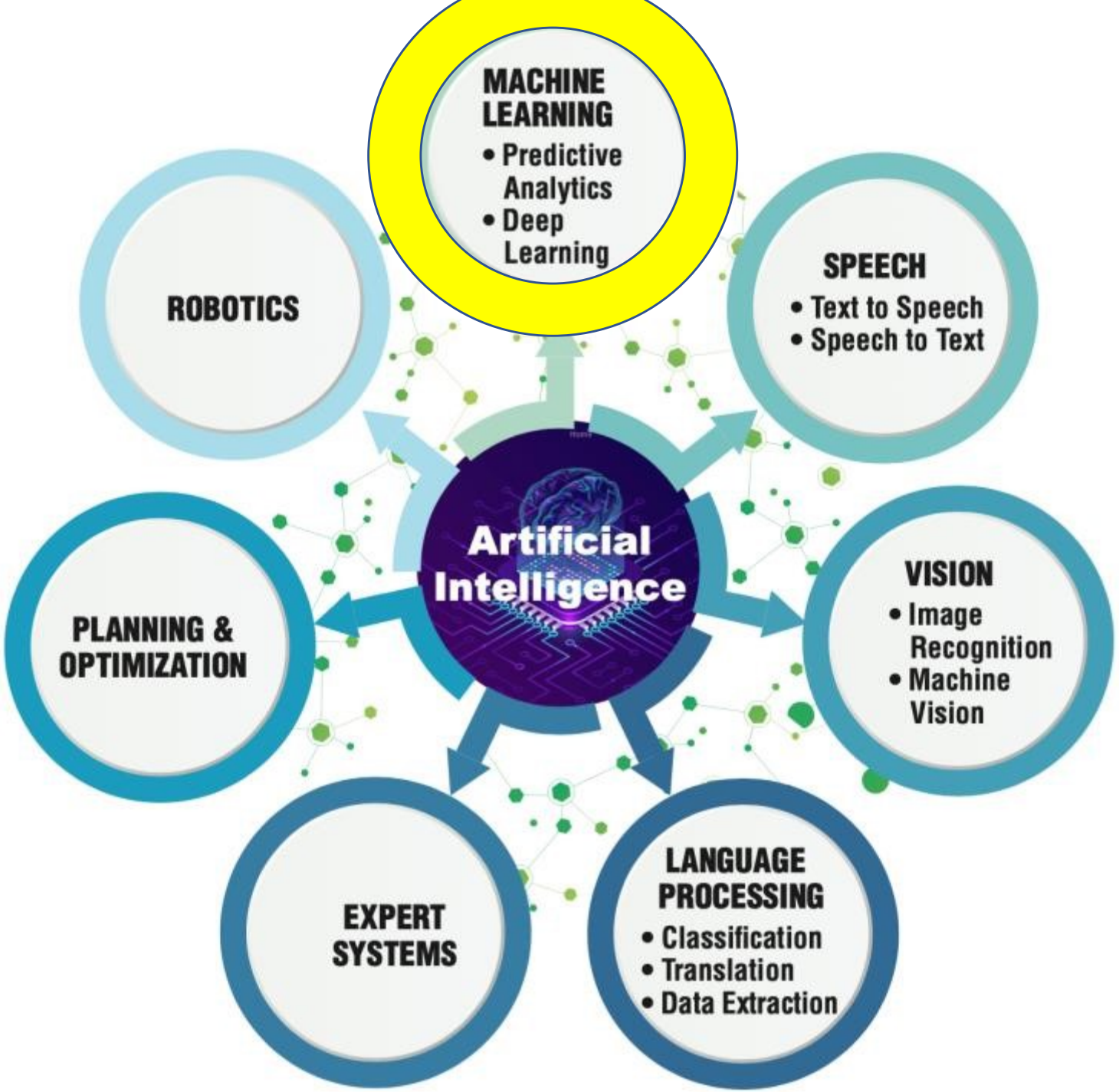
"Progress is impossible without change, and those who cannot change their minds cannot change anything."
George Bernard Shaw (1856-1950)

"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]


MACHINE LEARNING
• Predictive Analytics
• Deep Learning
ROBOTICS
SPEECH
• Text to Speech
• Speech to Text
Artificial Intelligence
PLANNING & OPTIMIZATION
VISION
• Image Recognition
• Machine Vision
EXPERT SYSTEMS
LANGUAGE PROCESSING
• Classification
• Translation
• Data Extraction

A.I. use cases

The map of the chemical universe

Similarity = proximity

ARTIFICIAL INTELLIGENCE

10 million structures
74 properties
600k chemicals with data

Picture removed
for copyright reasons

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

9 most common toxicity tests

190,000 chemical's hazard cross-validation:

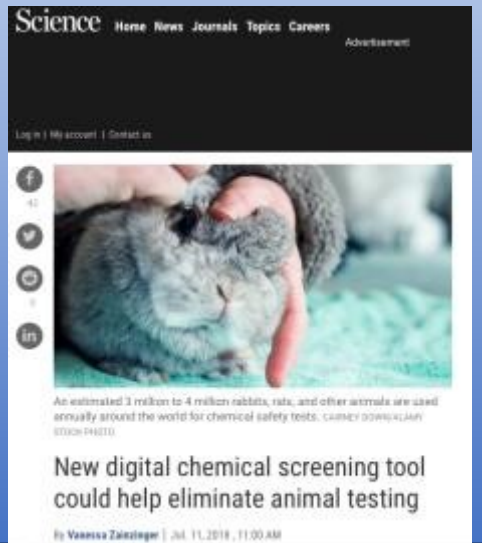
87% correct

Science, 12 Feb 2016

TOXICOLOGY

A crystal ball for chemical safety

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



Pictures removed
for copyright reasons

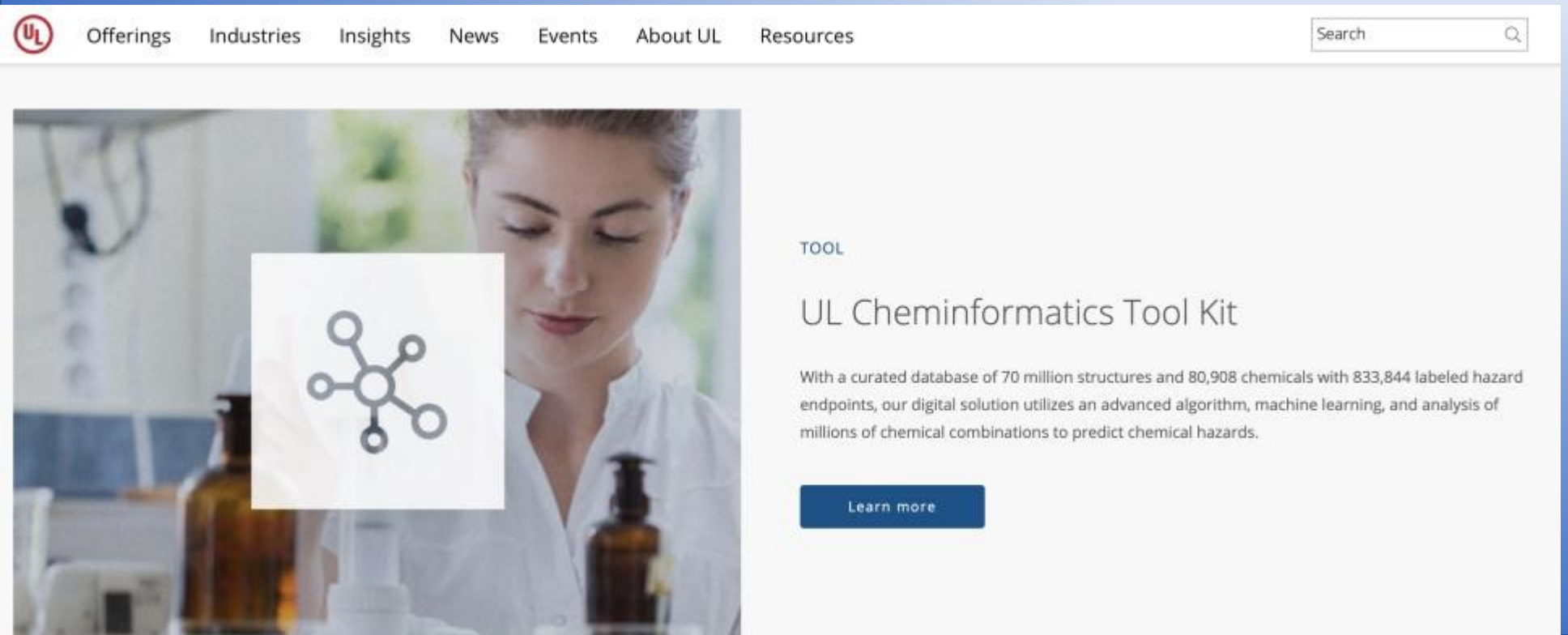
Uses chemical similarity (network effect)
Uses transfer learning (74 labels)

Boosted accuracy by ~10%

- Combining read-across with machine-learning
- Very large database
- Nine OECD test predicted
- 87% accuracy for 190,000 chemicals with known classifications
- 81% reproducibility of respective animal tests

The implementation: Version 2.0 released 2020 - deep learning, applicability domains, certainty, potency

- **Accepted for Australian Industrial Chemical Legislation 2020**
- **Under evaluation by FDA**



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., submitted)

Preliminary (Luechtefeld et al., unpublished):
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

Picture removed for copyright reasons

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

Green toxicology

– the toxicology aspects of green chemistry

Picture removed for copyright reasons

Another use of alternatives methods

OXFORD
SOT | Society of Toxicology
www.toxsci.oxfordjournals.org
ToxSci 20 Years

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 dark side of A.I.

Picture removed
for copyright reasons

- Data and energy need
- You always get a result, whether the information is in the data or not
- Challenges: Explainable A.I., Causality, Validation, Bias in data = bias in results

Human-in-the-loop

Pictures removed
for copyright reasons

Same approach as self-driving cars….
…but A.I. is far safer than humans!

“AI will not replace toxicologists, but those who don’t use AI will be replaced by those who do”

Stefan Platz, AstraZeneka
Senior Vice President of Clinical Pharmacology and Safety Sciences

EVIDENCE INTEGRATION

Food for Thought …
Integrated Testing Strategies for Safety Assessments

Thomas Hartung [1,2], Tom Luechtefeld [1], Alexandra Maertens [1], and Andre Kleensang [1]

In vivitrosi

Aka Integrated Testing Strategies, IATA, Defined Approaches…

1 + 1 > 2

Picture removed for copyright reasons

A cultural problem in science

Nobody likes to criticize their tools

This holds especially for the regulating and the regulated community.

https://www.inc.com/minda-zetlin/7-reasons-being-self-critical-can-make-you-more-successful.html

EVIDENCE INTEGRATION 2: Evidence-based Toxicology, systematic reviews, risk assessment…

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

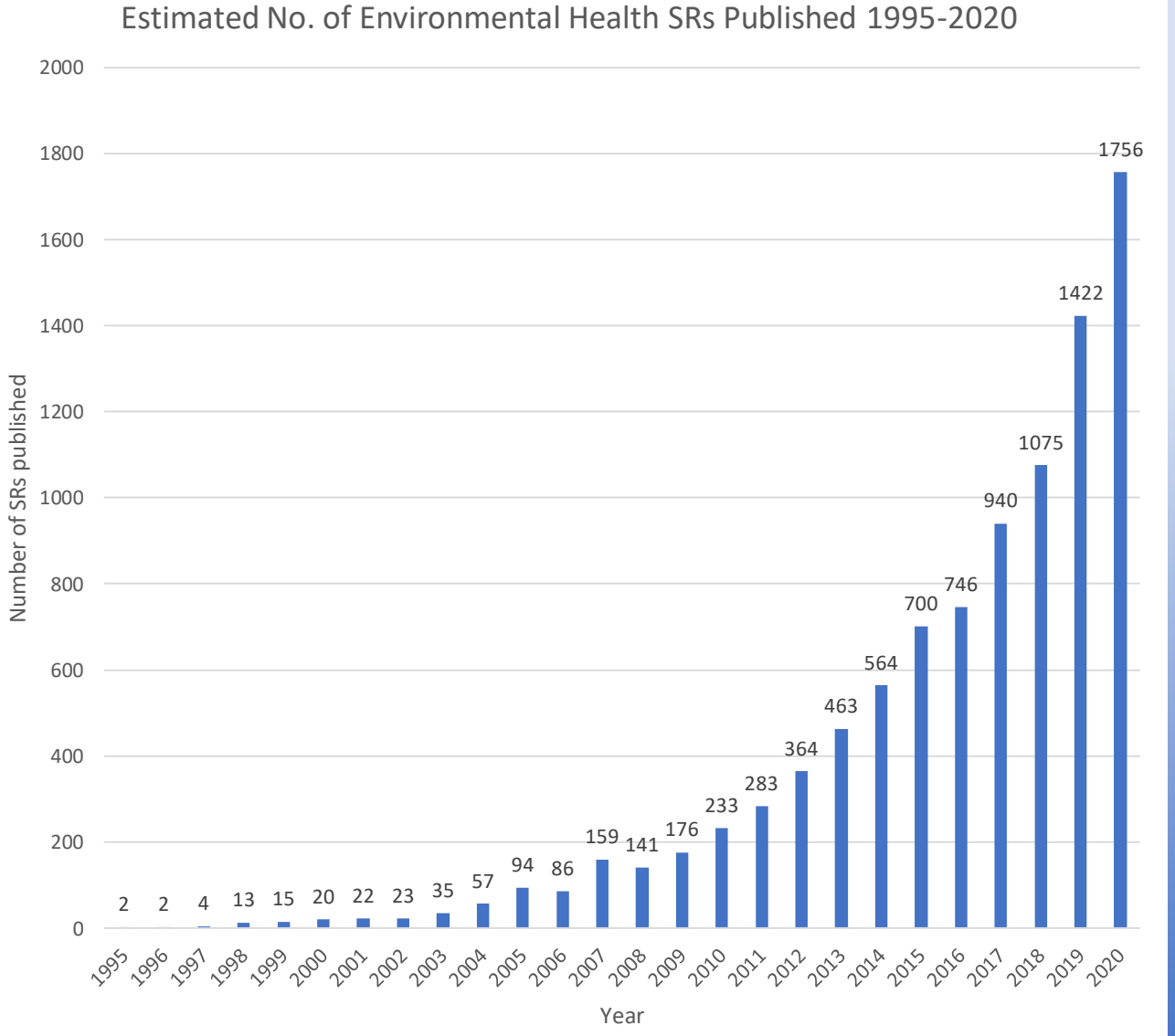
2009 Chair Hopkins

2011 Organization

www.ebtox.org

ebtc
Evidence-based Toxicology Collaboration

The explosion of systematic reviews



- Huge progress from almost nothing in the 90s
- Explosion in publications
- Thousands of people now engaged in EBT
- Stakeholders at every level, everywhere

Main steps

Guidance on assessing the methodological and reporting quality of toxicologically relevant studies: A scoping review

EBTC workshop: EBT for the 21st Century: Opportunities and Challenges

publication

SOT 2011 EBTC kick-off

UCSF Navigation Guide

NTP OHAT

EFSA / EBTC Colloquium on Evidence Integration

EPA TSCA

uOttawa / EBTC workshops 1 & 2

Zebrafish Systematic Review

WHO ILO Joint Estimates are SR-based

2007 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021

US NRC recommends SR

The 1st int. forum towards an EBT

US EPA SR Workshop

Lautenberg Act

EU stipulates SR methods for EDC

NAS Work

EBTC/GRADE workshop: Integrating Mechanistic Evidence into Toxicology Systematic Reviews

EBTC/EFSA workshop: EB methods to construct mechanism-driven chemical assessment frameworks

EBTC Journal Editors Workshop

SR Primer

AN SR for CRA

EBTC workshop: The Emergence of Systematic Review and Related EB Approaches in Toxicology

Key publications

A primer on systematic reviews in toxicology

Sebastian Hoffmann[1,13] · Rob B. M. de Vries[2] · Martin L. Stephens[1] · Nancy B. Beck[3] · Hubert A. A. M. Dirven[4] · John R. Fowle III[5] · Julie E. Goodman[6] · Thomas Hartung[7] · Ian Kimber[8] · Manoj M. Lalu[9] · Kristina Thayer[10] · Paul Whaley[11] · Daniele Wikoff[12] · Katya Tsaioun[1]

Guidance on assessing the methodological and reporting quality of toxicologically relevant studies: A scoping review

Gbeminiyi O. Samuel [a], Sebastian Hoffmann [b], Robert A. Wright [c], Manoj Mathew Lalu [d], Grace Patlewicz [e,1], Richard A. Becker [f], George L. DeGeorge [g], Dean Fergusson [d], Thomas Hartung [a], R. Jeffrey Lewis [h], Martin L. Stephens [a,*]

A Systematic Review to Compare Chemical Hazard Predictions of the Zebrafish Embryotoxicity Test With Mammalian Prenatal Developmental Toxicity

Sebastian Hoffmann,[*,†,1] Bianca Marigliani,[‡] Sevcan Gül Akgün-Ölmez,[§] Danielle Ireland,[¶] Rebecca Cruz,[‖] Francois Busquet,[|||] Burkhard Flick,[||||] Manoj Lalu,[#] Elizabeth C. Ghandakly,[**] Rob B.M. de Vries,[*,††] Hilda Witters,[‡‡] Robert A. Wright,[§§] Metin Ölmez,[¶¶] Catherine Willett,[##] Thomas Hartung,[***] Martin L. Stephens,[*] and Katya Tsaioun[*]

TOXICOLOGICAL SCIENCES 109(1), 18–23 (2009)
doi:10.1093/toxsci/kfp059
Advance Access publication April 8, 2009

FORUM SERIES, PART III

A Toxicology for the 21st Century—Mapping the Road Ahead

Thomas Hartung[1]

Johns Hopkins University, Bloomberg School of Public Health, Department for Environmental Health Sciences, Center for Alternatives to Animal Testing, Chair for Evidence-based Toxicology, Baltimore, MD 21231

Received February 19, 2009; accepted March 13, 2009

The landmark publication …toxicology for the 21st century in 2007 has created an atmosphere of departure in our field. The alliances formed, symposia and meetings held and the articles following are remarkable, indicating that this is an idea whose time has come. Most of the discussion centers on the technical opportunities to map pathways of toxicity and the financing of the program. Here, the other part of the work ahead shall be discussed, that is, the focus is on regulatory implementation once the technological challenges are managed, but we are well aware that the technical aspects of what the National Academy of Science report suggests still need to be addressed: A series of challenges are put forward which we will face in addition to finding a technical solution (and its funding) to set this vision into practice.

PoT / AoP

CHALLENGES

TESTING STRATEGIES INSTEAD OF INDIVIDUAL TESTS

- ITS, IATA, Defined Approaches

STATISTICS AND MULTIPLE TESTING

- A.I. evidence Integration

THRESHOLD SETTING

- TTC, safety vs. adversity

WHAT TO VALIDATE AGAINST?

- Mechanistic validation

HOW TO OPEN UP REGULATORS FOR CHANGE?

- Evidence-based Toxicology

THE GLOBAL DIMENSION

- Ongoing (World Conferences, PanAmerican, MPS-WS)

QUALITY ASSURANCE FOR THE NEW APPROACH

- GCCP 2.0, Good In Vitro Reporting Standards, Good Read-Across Practice

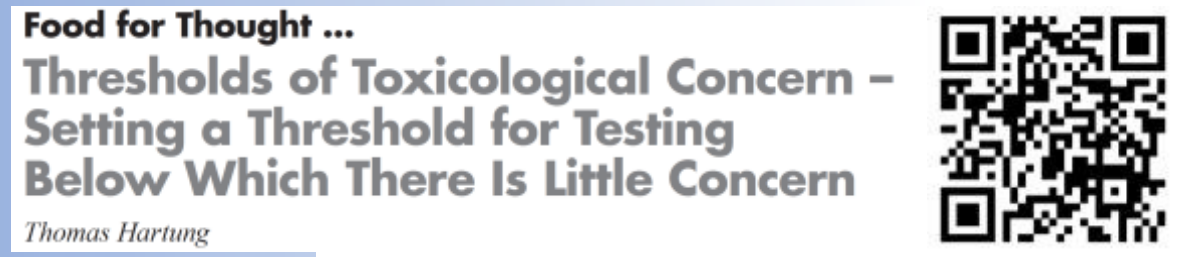
HOW TO CHANGE WITH STEP BY STEP DEVELOPMENTS BECOMING NOW AVAILABLE?

- Probabilistic Risk Assessment (Workshop Italy 4-6 Jul 2022)

CHALLENGES TO BE TACKLED

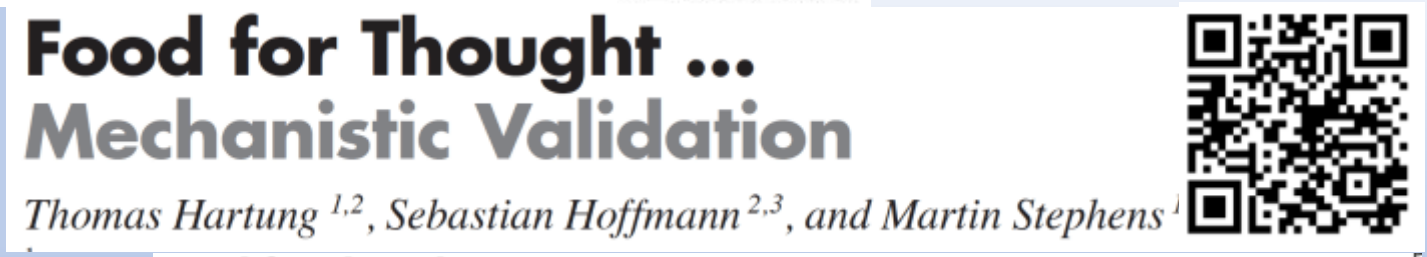
HOW TO ORGANIZE TRANSITION?

MAKING IT A WIN/WIN/WIN SITUATION


Food for Thought ...

Thresholds of Toxicological Concern – Setting a Threshold for Testing Below Which There Is Little Concern

Thomas Hartung


Food for Thought ...

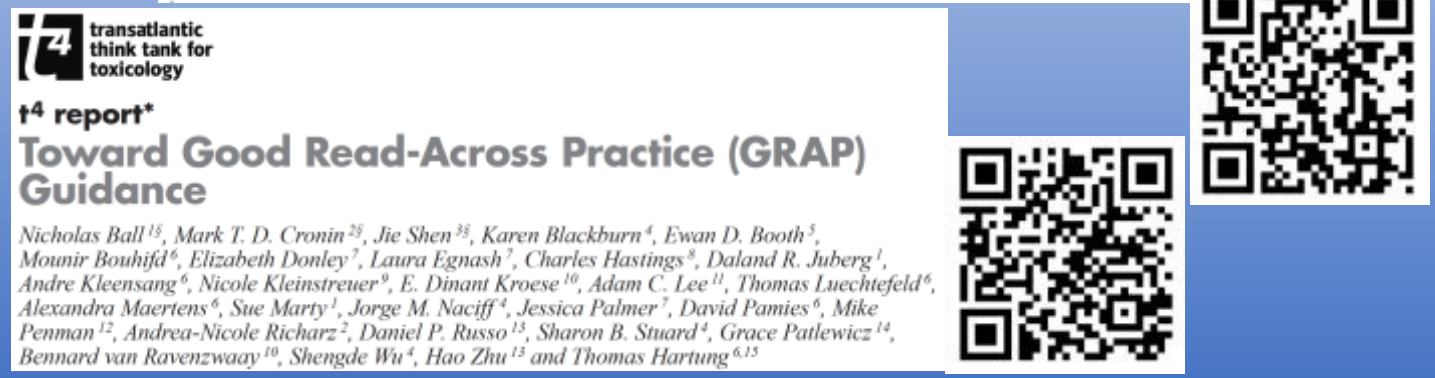
Mechanistic Validation

Thomas Hartung [1,2], Sebastian Hoffmann [2,3], and Martin Stephens [1]


Food for Thought ...

Toward Good *In Vitro* Reporting Standards

Thomas Hartung [1,2], Rob de Vries [3], Sebastian Hoffmann [4], Helena T. Hogberg [1], Lena Smirnova [1], Katya Tsaioun [1], Paul Whaley [5] and Marcel Leist [2]


transatlantic think tank for toxicology

t4 report*

Toward Good Read-Across Practice (GRAP) Guidance

Nicholas Ball [1§], Mark T. D. Cronin [2§], Jie Shen [3§], Karen Blackburn [4], Ewan D. Booth [5], Mounir Bouhifd [6], Elizabeth Donley [7], Laura Egnash [7], Charles Hastings [8], Daland R. Juberg [1], Andre Kleensang [6], Nicole Kleinstreuer [9], E. Dinant Kroese [10], Adam C. Lee [11], Thomas Luechtefeld [6], Alexandra Maertens [6], Sue Marty [1], Jorge M. Naciff [4], Jessica Palmer [7], David Pamies [6], Mike Penman [12], Andrea-Nicole Richarz [2], Daniel P. Russo [13], Sharon B. Stuard [4], Grace Patlewicz [14], Bennard van Ravenzwaay [10], Shengde Wu [4], Hao Zhu [13] and Thomas Hartung [6,15]

Pictures removed
for copyright reasons

We have most tools but we do not know how to change.

The roadblocks are not scientific but economic & legal.

Validation is as much a hurdle as it is enabling.

Change is more likely to come from politics than science

The difficulty lies not in the new ideas,

but in escaping from the old ones.

John Maynard Keynes

(1883 - 1946)

Slides available

Pictures removed for copyright reasons