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BLOOMBERG SCHOOL of PUBLIC HEALTH

Understanding Neurotoxicity Assays and Interspecies Differences to Address Attrition in Drug Discovery

Thomas Hartung, MD, PhD

Doerenkamp-Zbinden Chair, Evidence-Based Toxicology

Molecular Biology & Immunology

Director, Centers for Alternatives to Animal Testing, CAAT JHU and CAAT-EU

Professor, Pharmacology & Toxicology, U. of Kostanz, Germany

Consulting VP of Scientific Affairs

AxoSim

AxoSim – Human Data, Faster.
Consulting VP shareholder

AstraZeneca
Consultant

ATCC

insphero

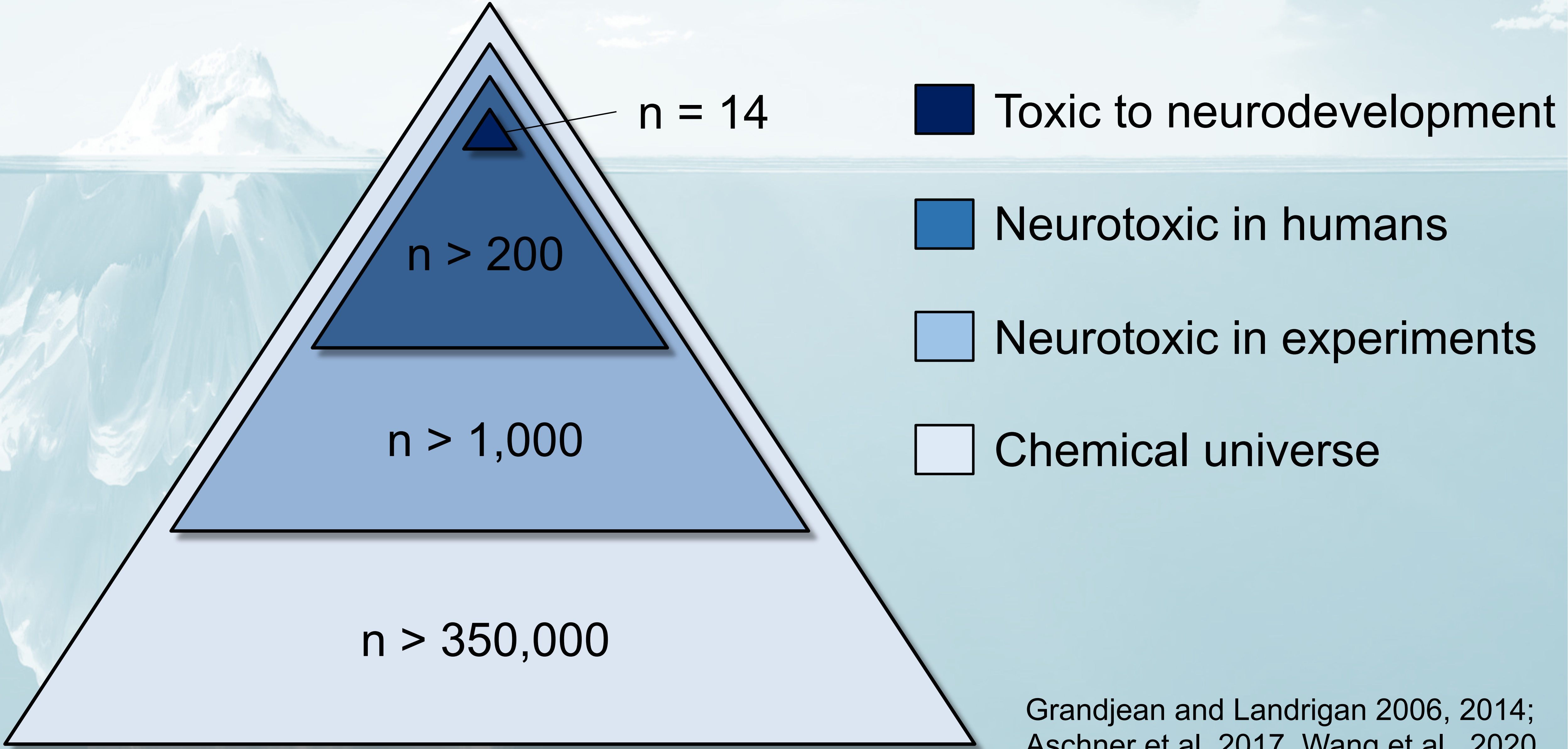
Merck Millipore
Licensed Pyrogen Test
Consultant

UL
Consultant Comp. Tox.

Green Chemistry Advisory Panel

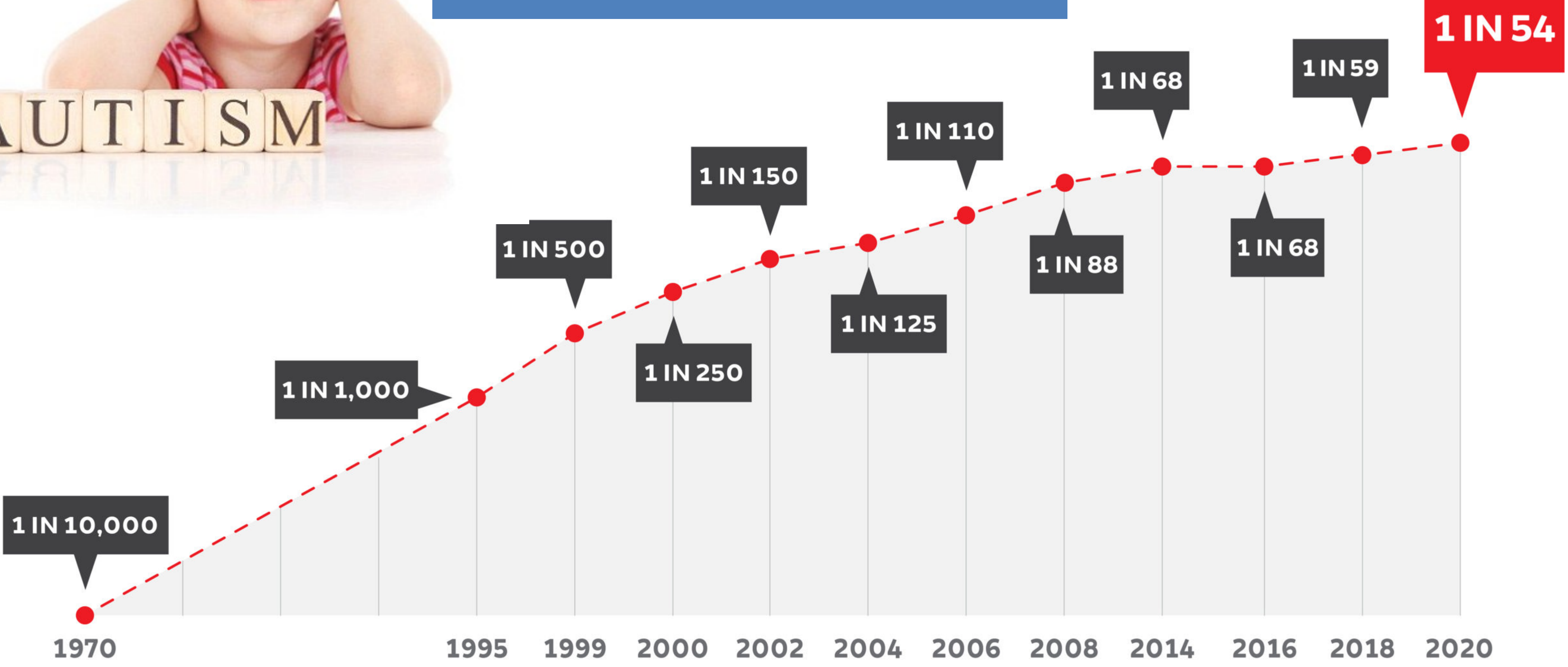
ToxTrack
Consultant, shareholder
In preparation: Insilica LLC

Limited knowledge of (developmental) neurotoxicity

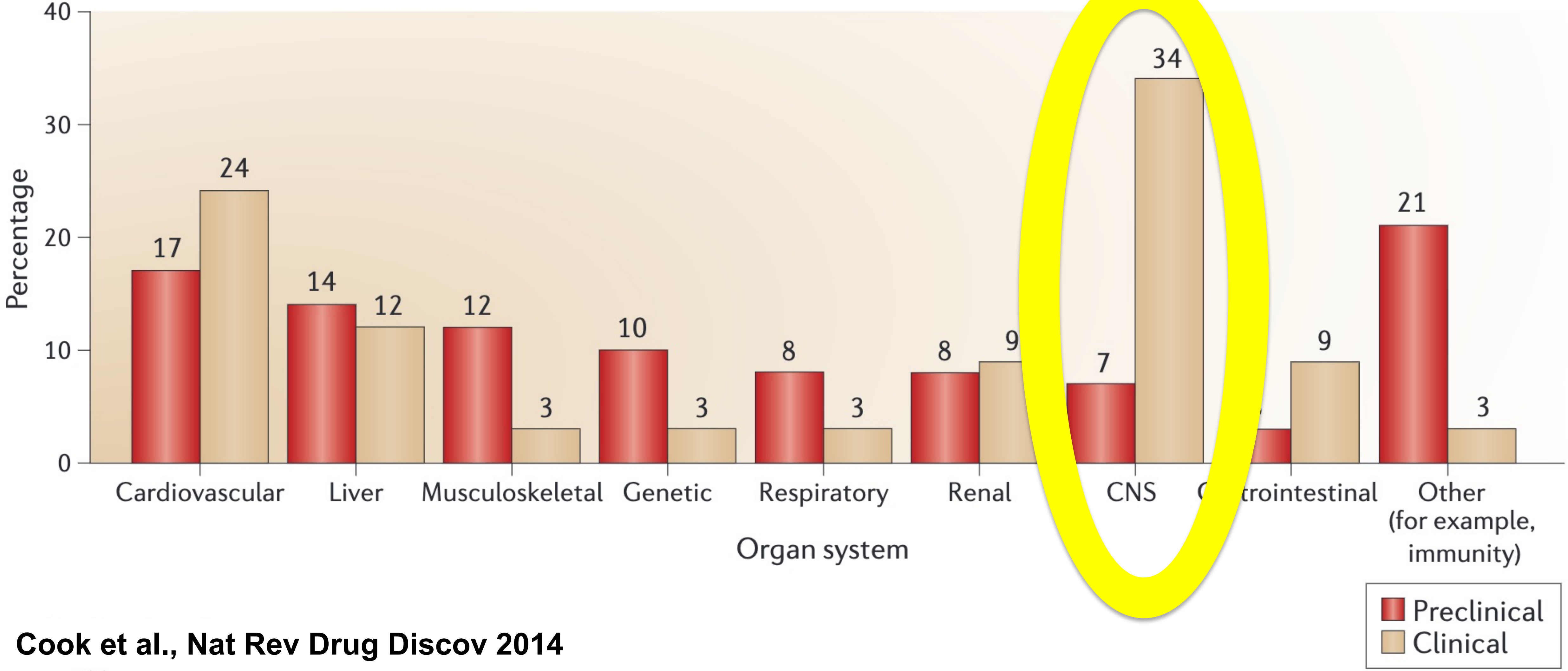


Grandjean and Landrigan 2006, 2014;
Aschner et al. 2017, Wang et al., 2020

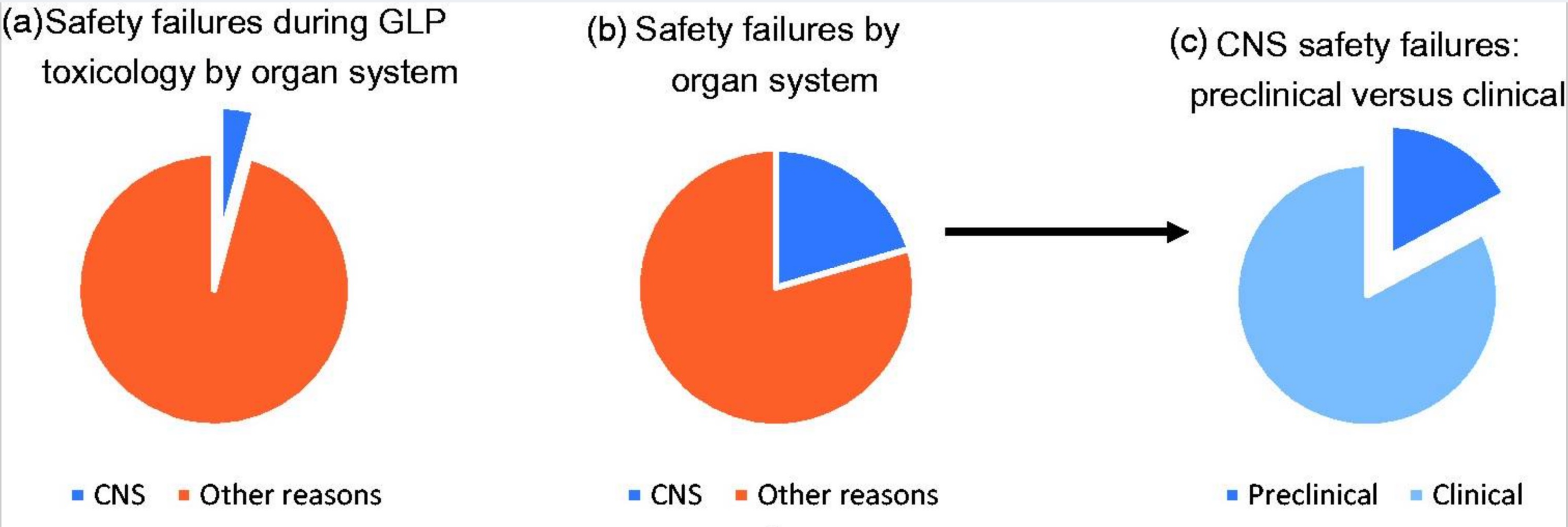
DEVELOPMENTAL NEUROTOXICITY



Organ systems involved in safety failures (AstraZeneca, 2005-2010)

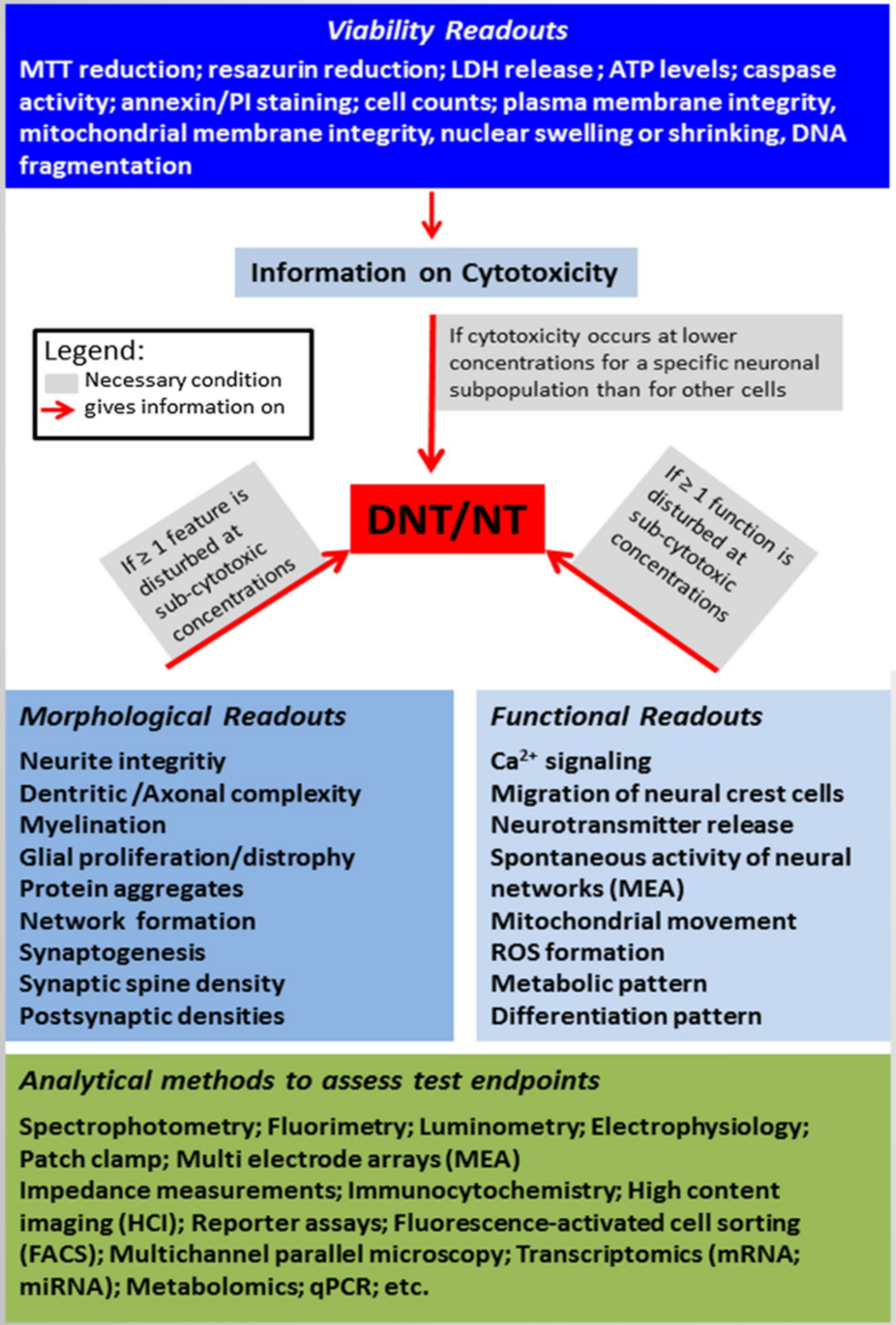


Cook et al., Nat Rev Drug Discov 2014



Walker et al., Exp Biol Med 2018

Fail earlier, fail cheaper



Arch Toxicol
DOI 10.1007/s00204-016-1805-9

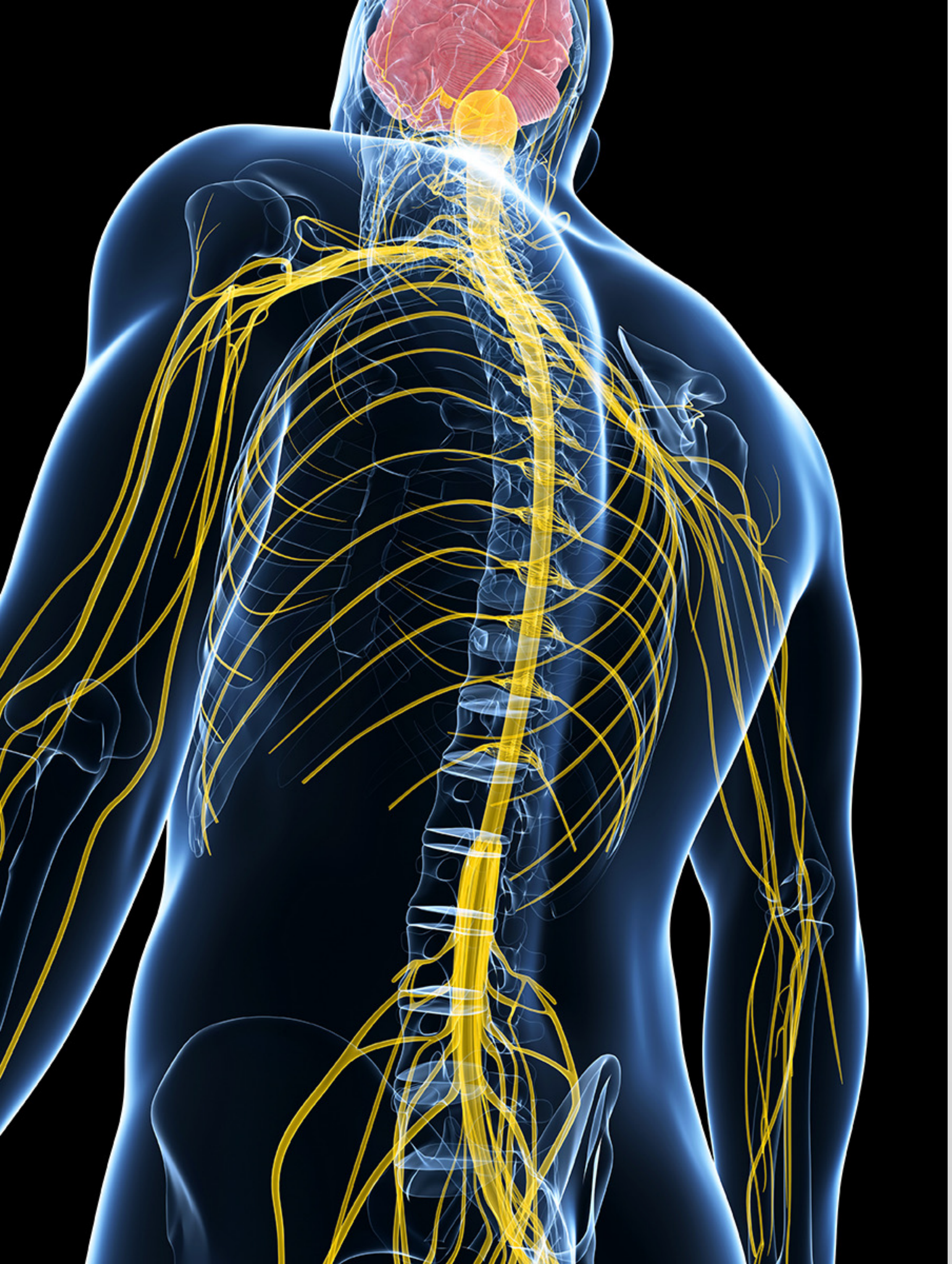
Schmidt et al. Arch. Toxicol. 2017, 91:1-33.

REVIEW ARTICLE

In vitro acute and developmental neurotoxicity screening: an overview of cellular platforms and high-throughput technical possibilities

Béla Z. Schmidt[1,2] · Martin Lehmann[1,3] · Simon Gutbier[4] · Erastus Nembo[1,3] · Sabrina Noel[5] · Lena Smirnova[6] · Anna Forsby[7,8] · Jürgen Hescheler[3] · Hasan X. Avci[1,9] · Thomas Hartung[6] · Marcel Leist[4] · Julianna Kobolák[1] · András Dinnyés[1,10]

"main cellular characteristics underlying neurotoxicity, present an overview of cellular platforms and read-out combinations assessing distinct parts of acute and developmental neurotoxicology, and highlight especially the use of stem cell-based test systems to close gaps in the available battery of tests"



Not only CNS !!!

Toxicity to the peripheral nerve system

https://ncats.nih.gov/sparc

Differentiation of hiPSC to DRG neurons

DRG: dorsal root ganglia

Marcel Leist

Universität Konstanz

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

STEM CELLS TRANSLATIONAL MEDICINE

CELL-BASED DRUG DEVELOPMENT, SCREENING, AND TOXICOLOGY

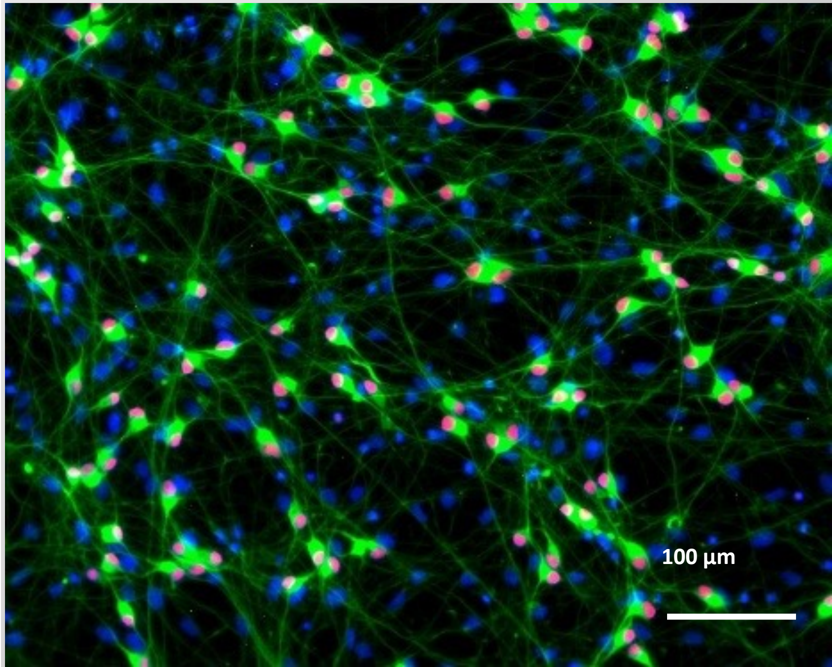
Stem Cell-Derived Immature Human Dorsal Root Ganglia Neurons to Identify Peripheral Neurotoxicants

STEM CELLS TRANSLATIONAL MEDICINE 2016;5:476–487

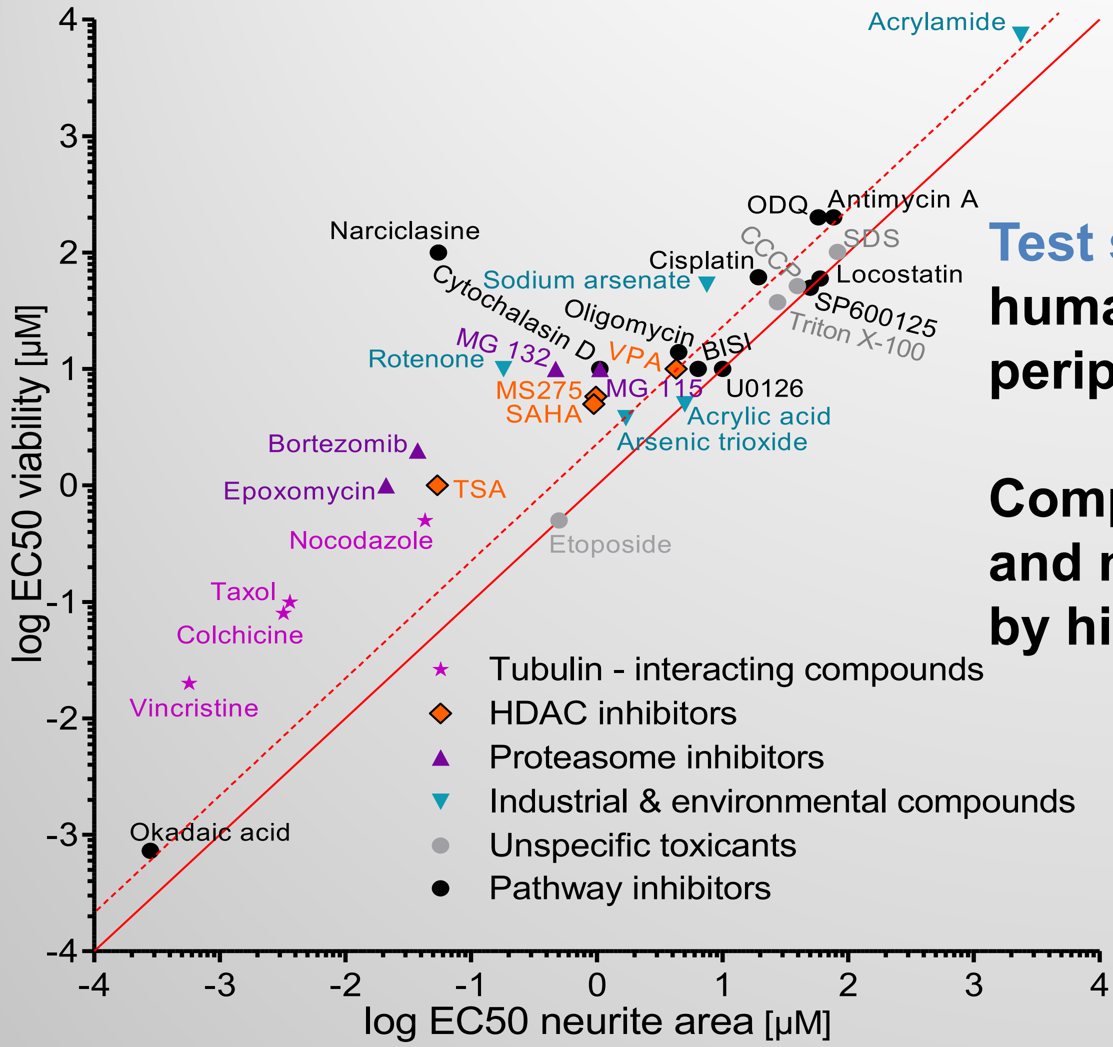
LISA HOELTING,[a,b] STEFANIE KLIMA,[a] CHRISTIAAN KARREMAN,[a] MARIANNA GRINBERG,[c] JOHANNES MEISIG,[d,e] MARGIT HENRY,[f] TAMARA ROTSHTEYN,[f] JÖRG RAHNENFÜHRER,[c] NILS BLÜTHGEN,[d,e] AGAPIOS SACHINIDIS,[f] TANJA WALDMANN,[a] MARCEL LEIST[a]

Peripherin (PRPH): marker of peripheral neurons

DNA PRPH ISL1



PeriTox assay: Specificity



Test system:

human iPSC derived peripheral neurons

Comparison of viability and neurite degeneration by high-content imaging

Comparison of peripheral neurons and central neurons (LUHMES)

Compound	PeriTox	LUHMES
Acrylamide	Specific neurite effect	No specific neurite effect
Bortezomib	Specific neurite effect	No specific neurite effect
Cisplatin	Specific neurite effect	No specific neurite effect
Cytochalasin D	Specific neurite effect	No specific neurite effect
MG 132	Specific neurite effect	No specific neurite effect
ODQ	Specific neurite effect	No specific neurite effect
Oligomycin	Specific neurite effect	No specific neurite effect
TSA	Specific neurite effect	No specific neurite effect
Blebbistatin	Specific neurite effect	Specific neurite effect
Colchicine	Specific neurite effect	Specific neurite effect
Narciclasine	Specific neurite effect	Specific neurite effect
Nocodazole	Specific neurite effect	Specific neurite effect
Rotenone	Specific neurite effect	Specific neurite effect
Vincristine	Specific neurite effect	Specific neurite effect
Y-27632	Specific neurite effect	Specific neurite effect
BIS I	No specific neurite effect	Specific neurite effect
U0126	No specific neurite effect	Specific neurite effect

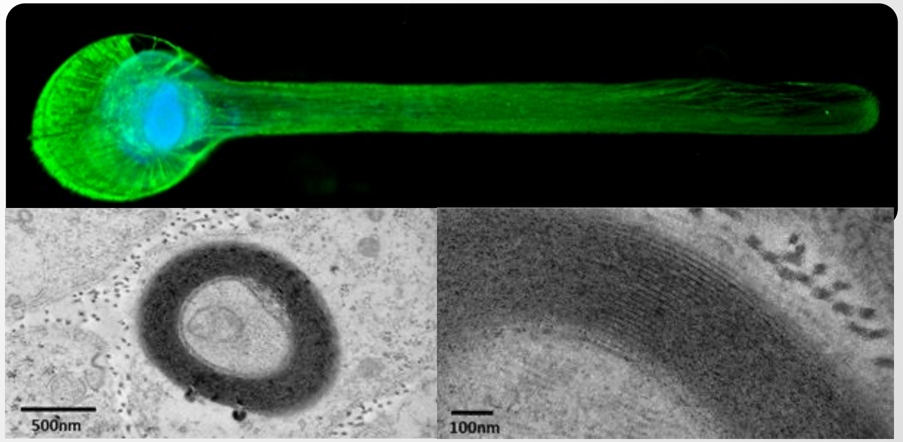
Specific neurite effect No specific neurite effect

NerveSim™ Platform

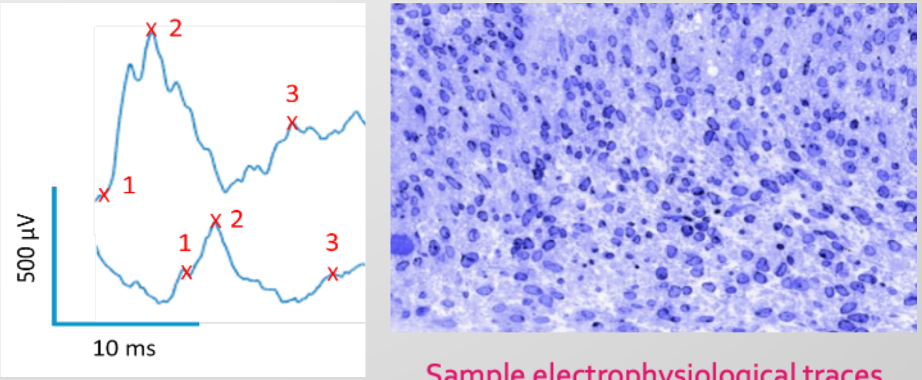
- **Differentiated:** First 3D nerve model to demonstrate two key characteristics of the peripheral nervous system
    - Schwann cell myelination
    - Nerve conduction studies

- **Applications:** Neurotoxicity, neuroprotection, and disease modeling

- **Multiple Species:** Available in human, rat, and mouse models



Mature compact myelin around nerve fibers



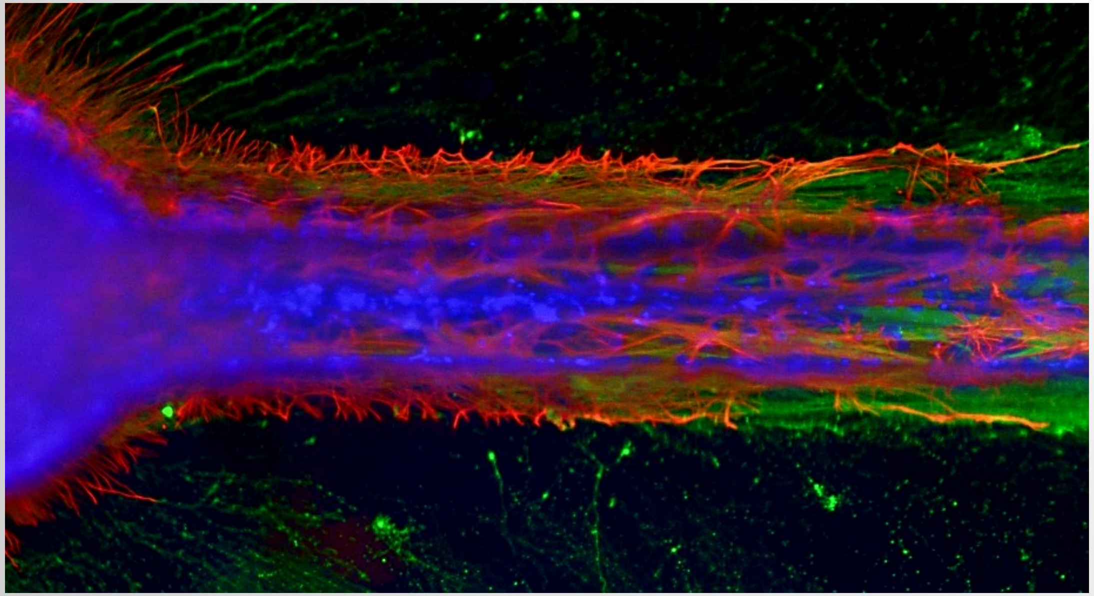
Sample electrophysiological traces and a cross section of Nerve-on-a-Chip

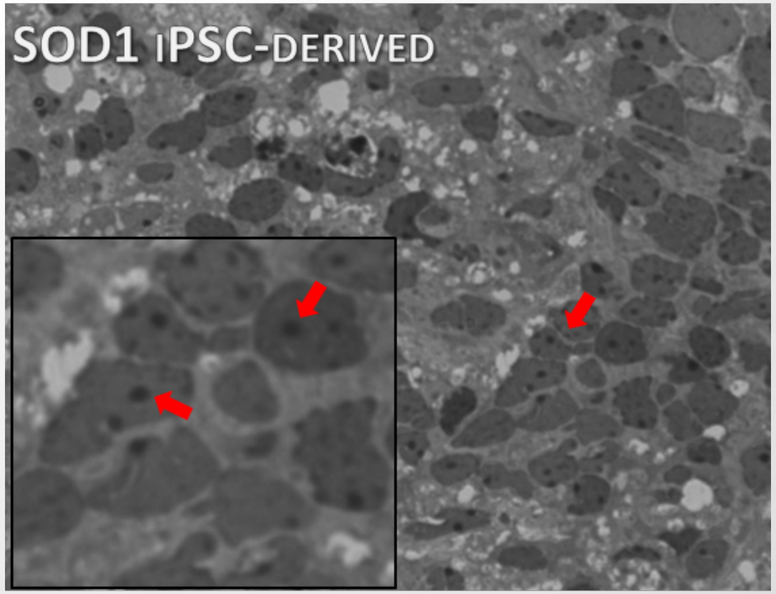
AxoSim

Khoshakhlagh, et al. J Neural Engineering (2018)

NerveSim™

Disease Modeling





ALS disease model showing protein inclusions

Ability to use the platform with patient-derived iPSC lines

Current 2 year grant from DoD to create ALS model with patient-derived cell line

- Early work showed protein inclusion suggestive of ALS pathology

CDMRP

Looking for opportunities to expand into neuroprotection and neuroregeneration among other peripheral and motor nerve diseases

FOOD FOR THOUGHT…
DEVELOPMENT NEUROTOXICITY – CHALLENGES IN THE 21ST CENTURY AND *IN VITRO* OPPORTUNITIES

ALTEX 2014, 31:129-156

Lena Smirnova[1], Helena T. Hogberg[1], Marcel Leist[2], and Thomas Hartung[1,2]

Animal test:
$1,4 million

1,400 animals

200 chemicals tested:
No regulatory consequence

https://commons.wikimedia.org/wiki/File:White_rat_on_table.jpg

DNT assessment from *in vivo* towards *in vitro*

ECVAM

TestSmart DNT – Developmental Neurotoxicity

DNT3 Developmental Neurotoxicity

ISTNET Workshop

efsa – OECD

Expert Group on DNT

OECD

Guidance Document

2005 2010 2015 2020

TESTSMART DNT2 DEVELOPMENTAL NEUROTOXICITY

TESTSMART DNT4 DEVELOPMENTAL NEUROTOXICITY

t4 transatlantic think tank for toxicology

DNT Reference Compounds

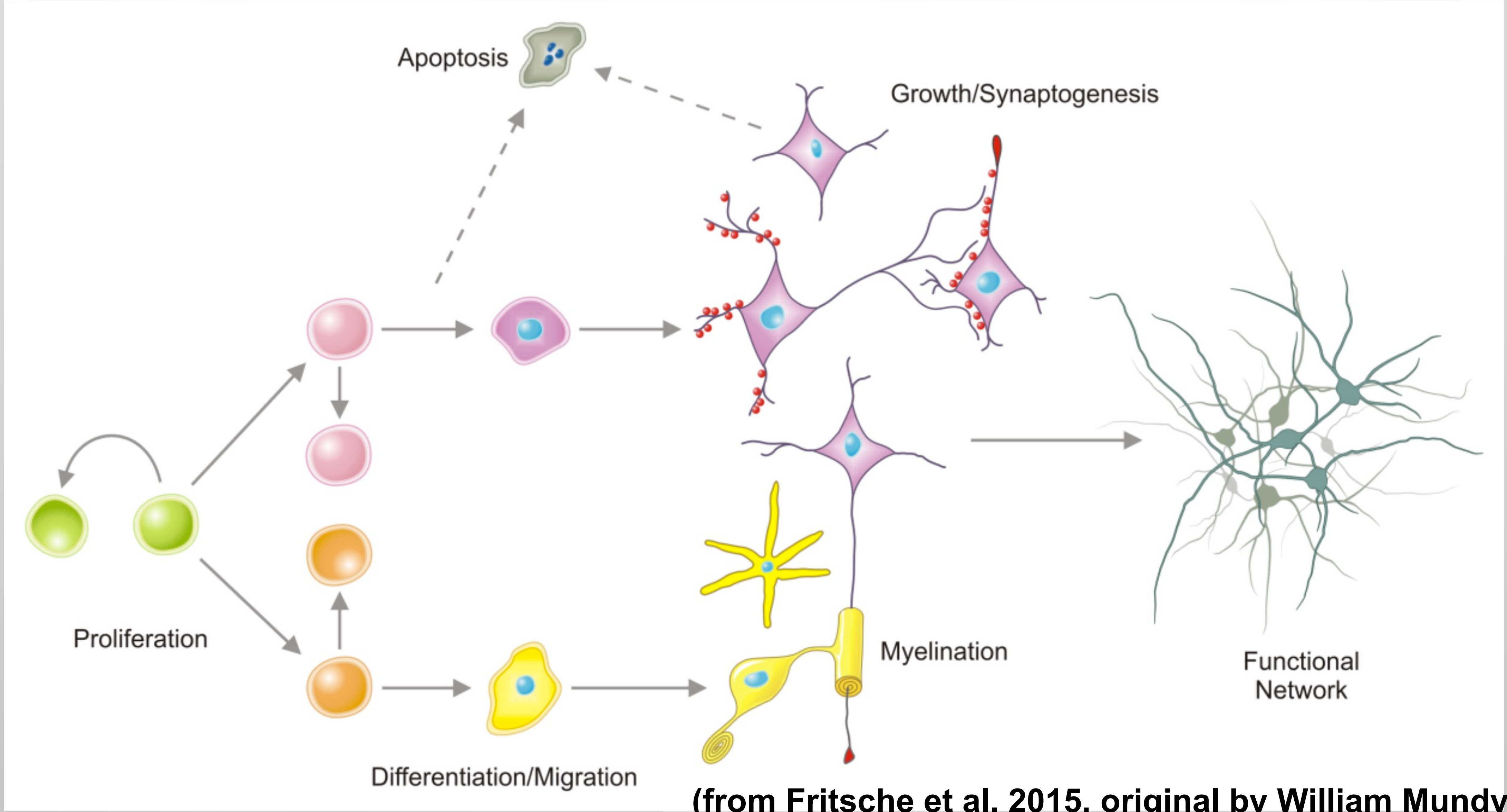
t4 transatlantic think tank for toxicology

Test Readiness

TESTSMART DNT5 DEVELOPMENTAL NEUROTOXICITY

FIFRA review NAMs for DNT

Key endpoints needed in a developmental neurotoxicity testing strategy



(from Fritsche et al. 2015, original by William Mundy, EPA)

transatlantic think tank for toxicology

ALTEX 2017, 34:49-74

t4 Workshop Report*

Reference Compounds for Alternative Test Methods to Indicate Developmental Neurotoxicity (DNT) Potential of Chemicals: Example Lists and Criteria for their Selection and Use

Michael Aschner[1], *Sandra Ceccatelli*[2], *Mardas Daneshian*[3], *Ellen Fritsche*[4], *Nina Hasiwa*[3], *Thomas Hartung*[3,5], *Helena T. Hogberg*[5], *Marcel Leist*[3,6,7], *Abby Li*[8], *William R. Mundy*[9], *Stephanie Padilla*[9], *Aldert H. Piersma*[10,11], *Anna Bal-Price*[12], *Andrea Seiler*[13], *Remco H. Westerink*[14], *Bastian Zimmer*[15] and *Pamela J. Lein*[16,17]

…a set of > 50 endpoint-specific control compounds was identified. For further test development, an additional "test" set of 33 chemicals considered to act directly as *bona fide* DNT toxicants is proposed, and each chemical is annotated to the extent it fulfills these criteria. A tabular compilation of the original literature used to select the test set chemicals provides information on statistical procedures, and toxic/non-toxic doses (both for pups and dams). Suggestions are provided on how to use the > 100 compounds (including negative controls) compiled here to address specificity, adversity and use of alternative test systems.

Unclassified **ENV/JM/MONO(2017)4**

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development **27-Jan-2017**

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2017)4
Unclassified

REPORT OF THE OECD/EFSA WORKSHOP ON DEVELOPMENTAL NEUROTOXICITY (DNT): THE USE OF NON-ANIMAL TEST METHODS FOR REGULATORY PURPOSES

Series on Testing and Assessment
No. 261

Workshop and Working Group for Test Guideline development

Table 6.3.1: Molecular Initiating Events and related key events of an DNT AOP – a literature review for the five established human DNToxicants lead (L), methymercury (M), PCB (P), arsenic (A) and toluene (T)

	Molecular Initiating Events/Key evenst	Cell Adverse Outcomes	In vivo correlate	Human (histo) pathology	Clinics
Oxidative Stress (clear evidence for L, M, P, A)	Inhibition delta-aminolevulinic acid dehydratase: L (1)	Oxidative Stress, ROS formation, lipid peroxidation of membrane (defense AP-1, NFkB): L (1,2,5,6), M (14)	Oxidative Stress and brain damage and impaired antioxidative defense (reduced GSH, induced defense AP-1, NFkB): L (1,2,5), M (14,15), P (17), A (18)	M is GSH-bound in erythrocytes, A leading to urinary 8 OHdG and plasma lipid peroxidation (21)	DNT (reduced intelligence, behavioral deficits, ADHD, fetal solvent syndrome): L (6,7,8), M (9,10), P (17), A (18), T (24)
	Inhibition of SOD, catalase, GSH peroxidase, GSH (via SH-binding) and Ca replacement at EF motifs abd C2 domains): L (2,6), M (11,13), P (17), A (18)				
	Mitochondrial accumulation and dysfunction: L (6), M (11,13)				
Membrane effects	Interaction with neg-charged membrane phospholipids: L (1)	Change membrane biophysics (leading to iron-mediated lipid peroxidation): L (1)	Changed myelin membrane fluidity: L (1)	Membrane rigidity (erythrocytes): L (1)	
Ca disturbation and replacement	Electronegativity, binding to Sulfur and Oxygen (substituting for	Changed calcium fluxes (also leading to ROS from			

...

Started to draft AOP for DNT based on 5 established human DNToxicants

ALTEX 2014, 31:129-156

"I have yet to see any problem, however complicated, which, when you look at it in the right way, did not become still more complicated."

Poul Anderson (1926-2001)

Food for Thought …
Developmental Neurotoxicity – Challenges in the 21st Century and *In Vitro* Opportunities

Lena Smirnova[1], *Helena T. Hogberg*[1], *Marcel Leist*[2], *and Thomas Hartung*[1,2]

Key Characteristics *Disturbed Process* *Adverse Outcome*

Agent (Chemical, Its metabolite, other) → BBB → ??? **Altered signaling, mutation, oxid. stress etc.** → Plasticity **Synapto-genesis, Myelination etc.** → ??? **Clinical manifest., Neurobehav. decrements** → **Neuro-tox DNT**

(Fetal) BBB
Placenta B.

Growth factors

Neuronal proliferation and migration

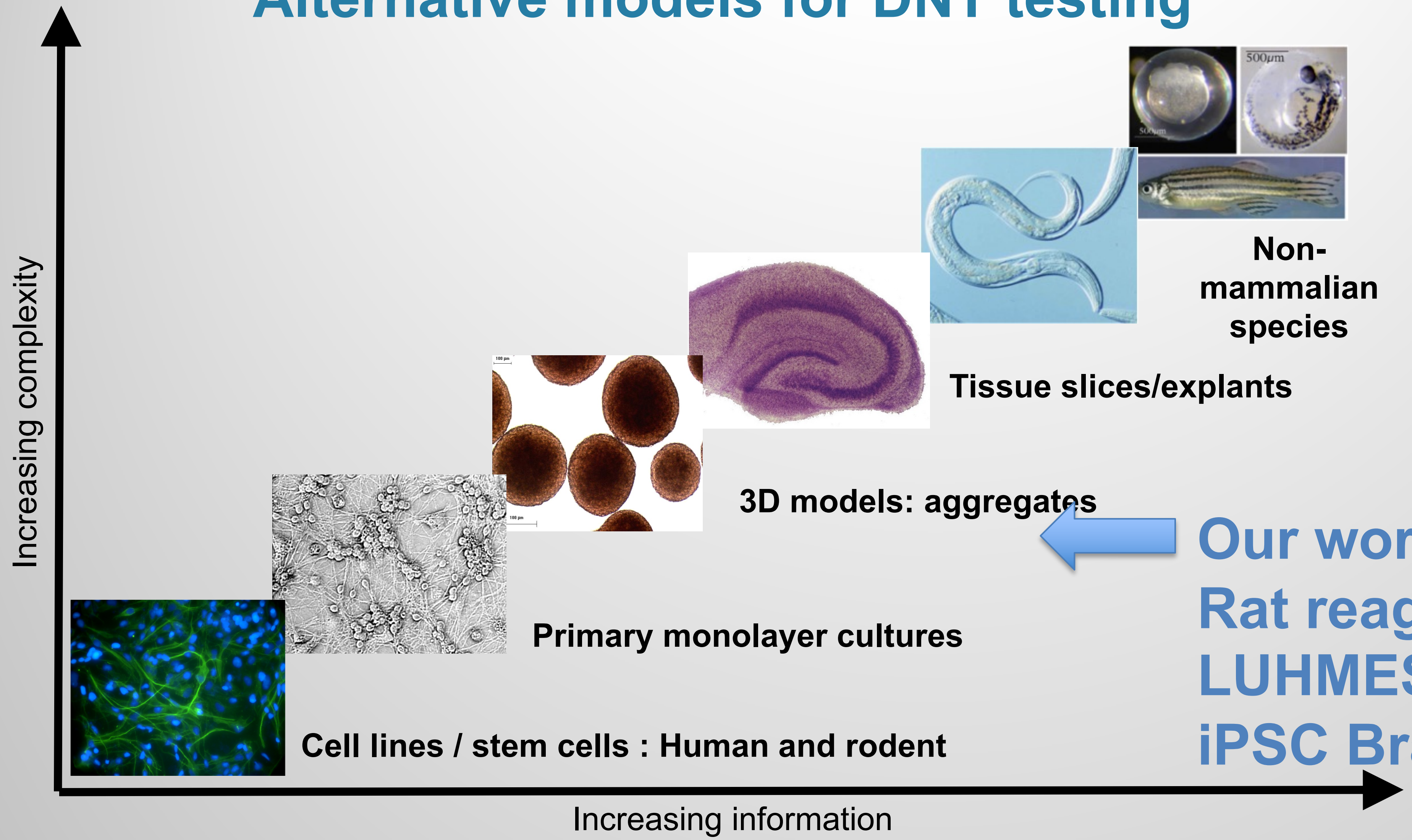
Changed brain developmen t, organization and function

Windows of vulnerability:

- *Spatial & temporal organization*
- *Functional integration*

Key characteristics
Workshop 9’19
Cohosted with
Martyn Smith
Pam Lein

Alternative models for DNT testing

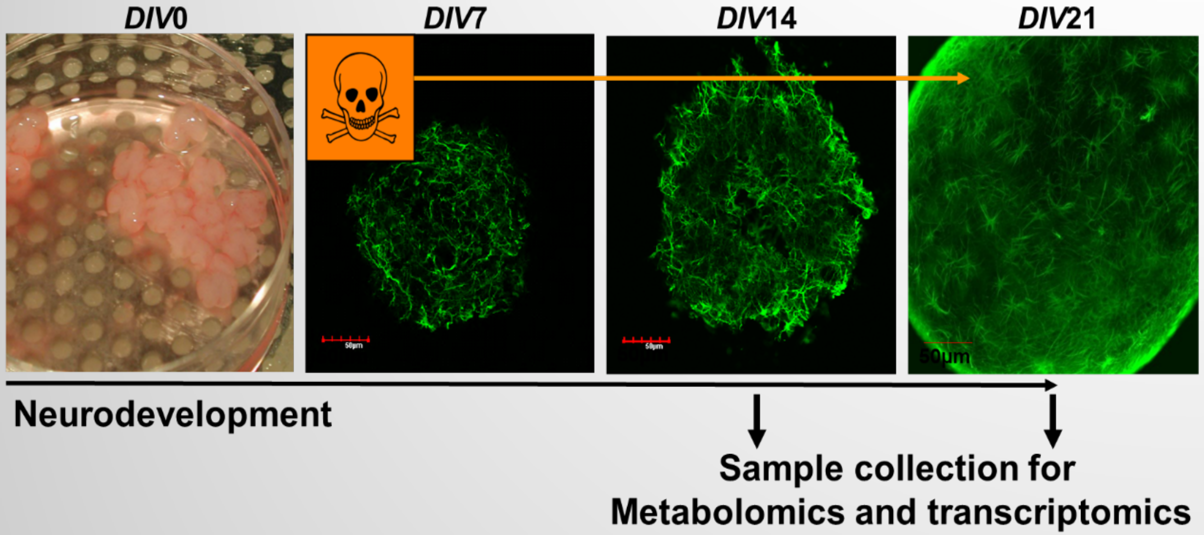


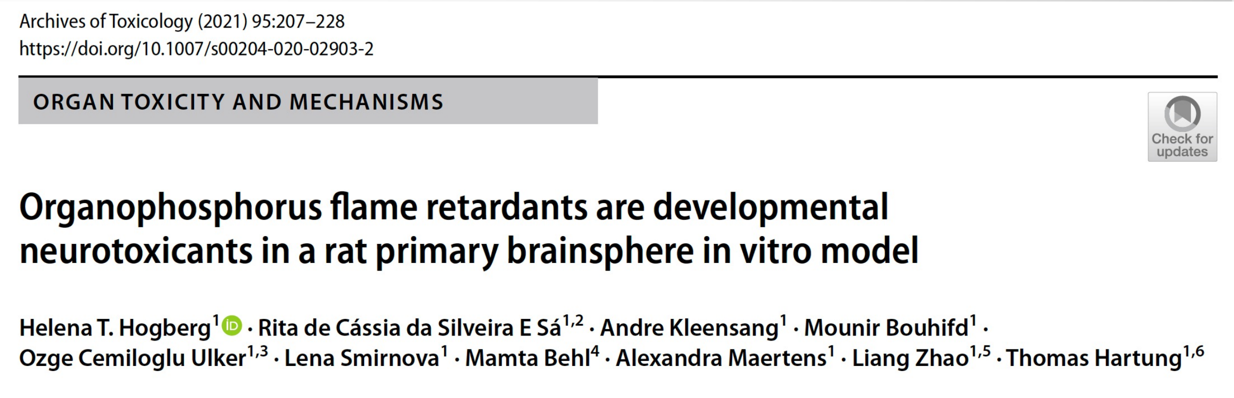
Our work:

Rat reaggregating culture
LUHMES 3D model
iPSC BrainSpheres

3D rat primary neural organotypic *in vitro* model

Experimental design





Archives of Toxicology (2021) 95:207–228
https://doi.org/10.1007/s00204-020-02903-2

ORGAN TOXICITY AND MECHANISMS

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

Helena T. Hogberg[1] · Rita de Cássia da Silveira E Sá[1,2] · Andre Kleensang[1] · Mounir Bouhifd[1] · Ozge Cemiloglu Ulker[1,3] · Lena Smirnova[1] · Mamta Behl[4] · Alexandra Maertens[1] · Liang Zhao[1,5] · Thomas Hartung[1,6]

Arch Toxicol 2021, 95:207–228

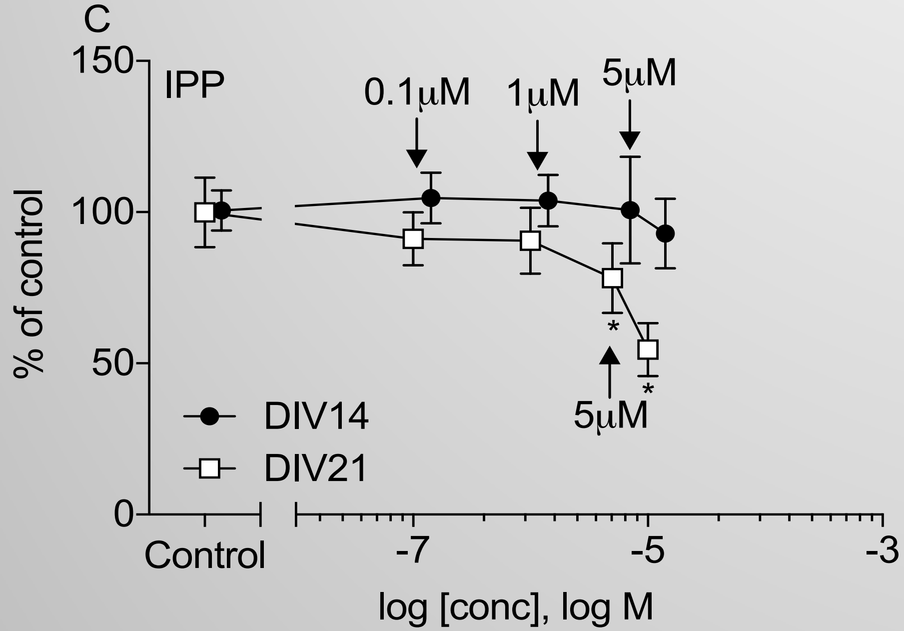
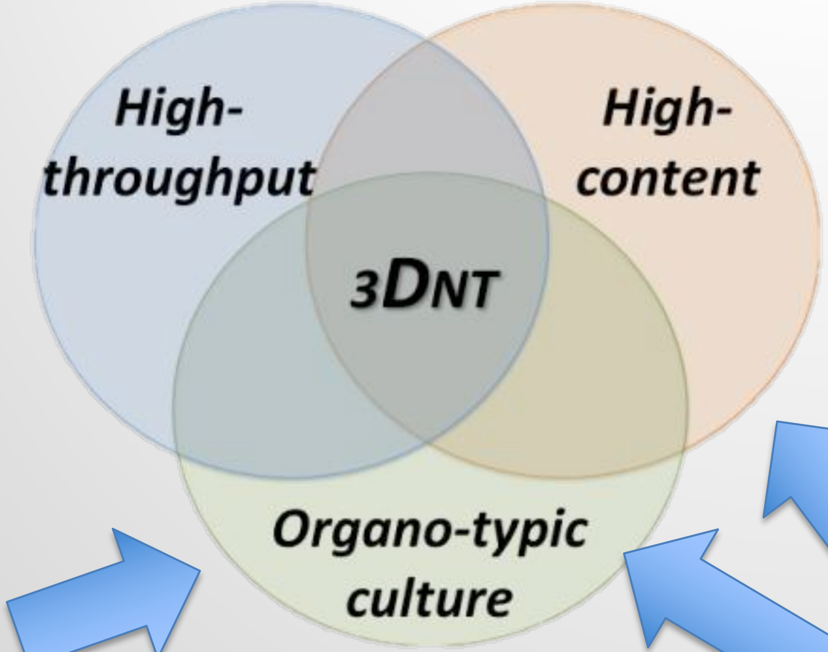


Table 1: Flame retardants (FR)

Flame Retardant	Conc. well
2,2'4,4'Tetrabromodiphenyl ether (BDE-47)	0.1-20μM
Triphenyl phosphate (TPHP)	0.1-20μM
Isopropylated phenol phosphate (IPP)	0.1-10μM
Isodecyl diphenyl phosphate (IDDP)	0.1-20μM
Tricresyl phosphate (TMPP)	0.1-20μM
Dimethyl sulfoxide (DMSO)	0.1% (v/v)

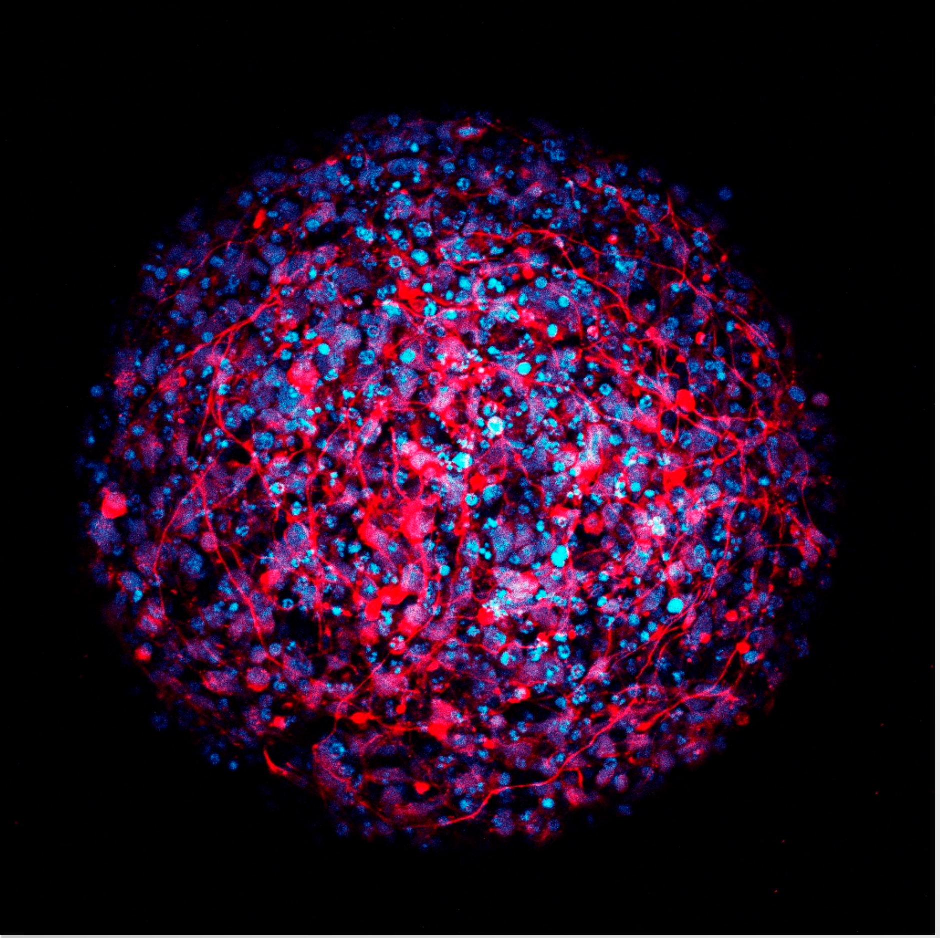
Our vision: paradigm shift

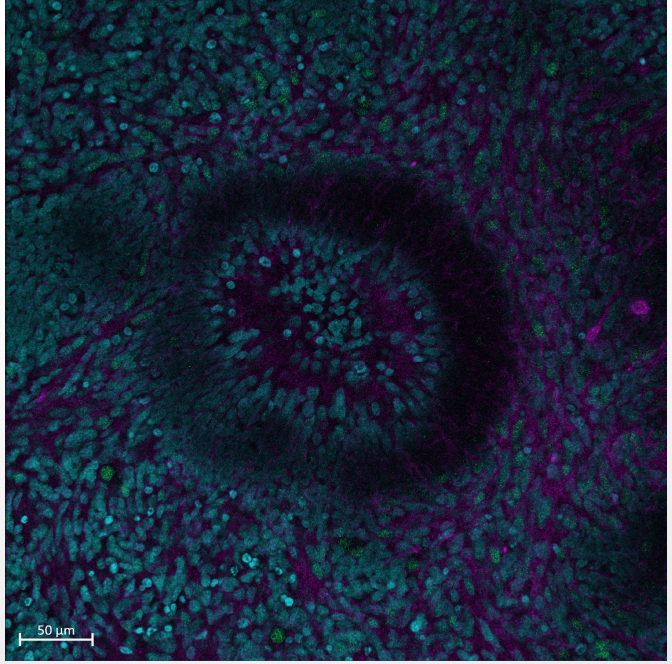


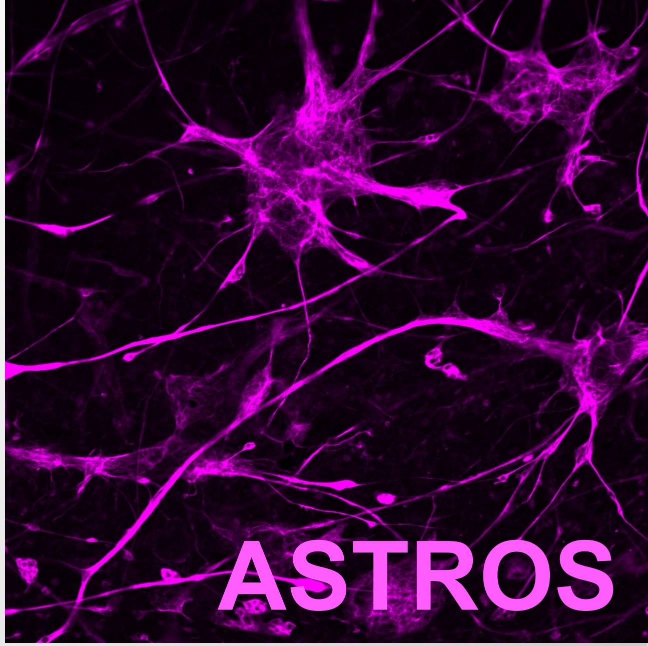
NIH: Human Toxome

NCATS: 3D iPSC (human)

FDA: DNTox-21c (rat)



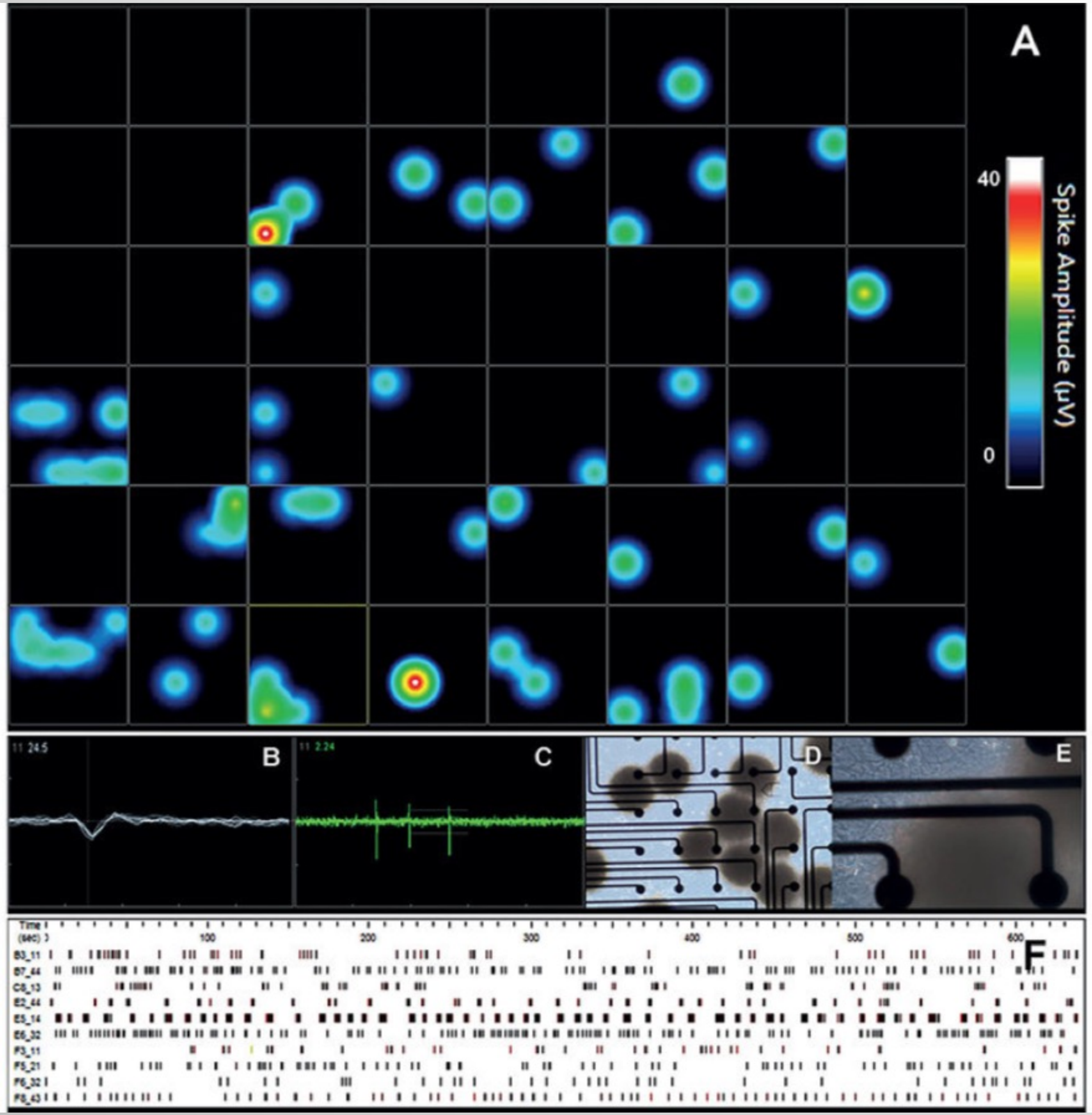




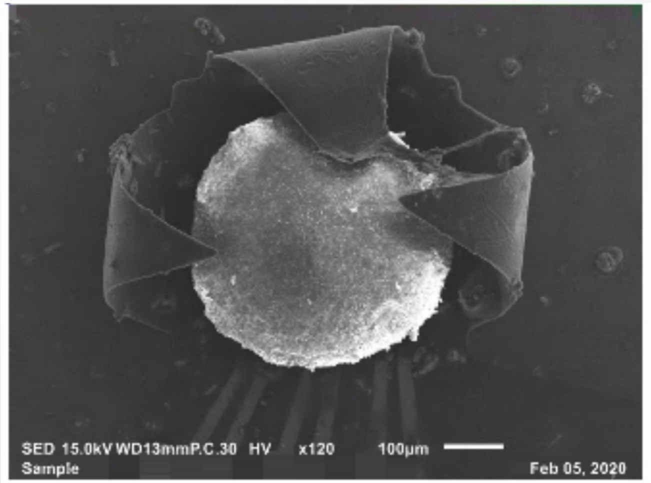
OUR MINI-BRAIN PROJECT

- FROM SKIN OF DONORS, INDIVIDUAL STEM CELLS
- IN 3 MONTHS THOUSANDS OF IDENTICAL ORGANOIDS
- NEURONS COMMUNICATING
- SOME BRAIN FUNCTIONALITY

BrainSphere functionality

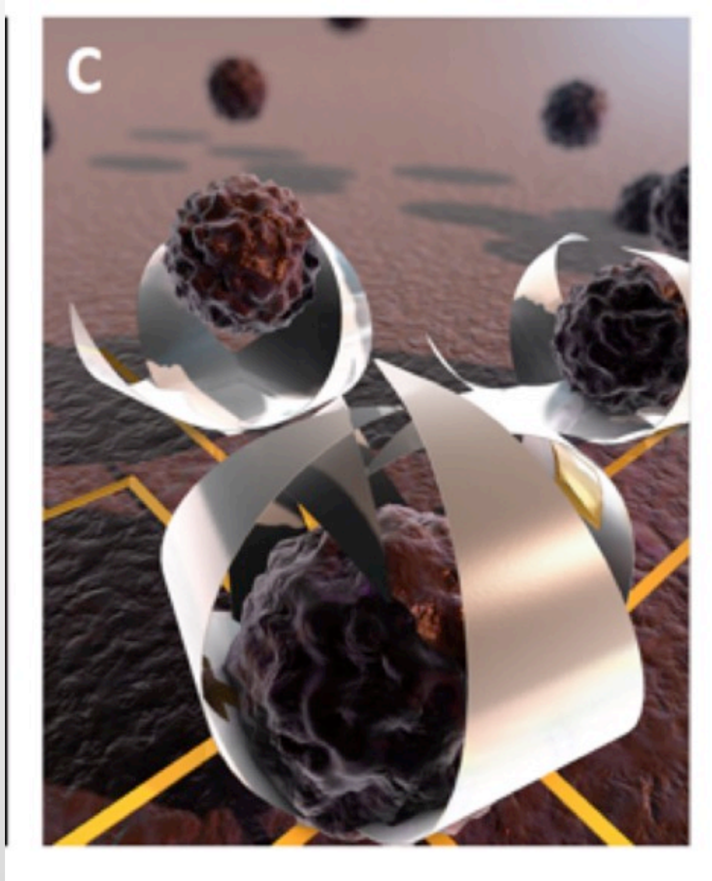


Pamies et al., ALTEX 2017



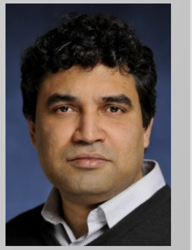
unpublished

3D spatiotemporal recording from a multi-electrode shell



Multi-electrode arrays

D Gracias



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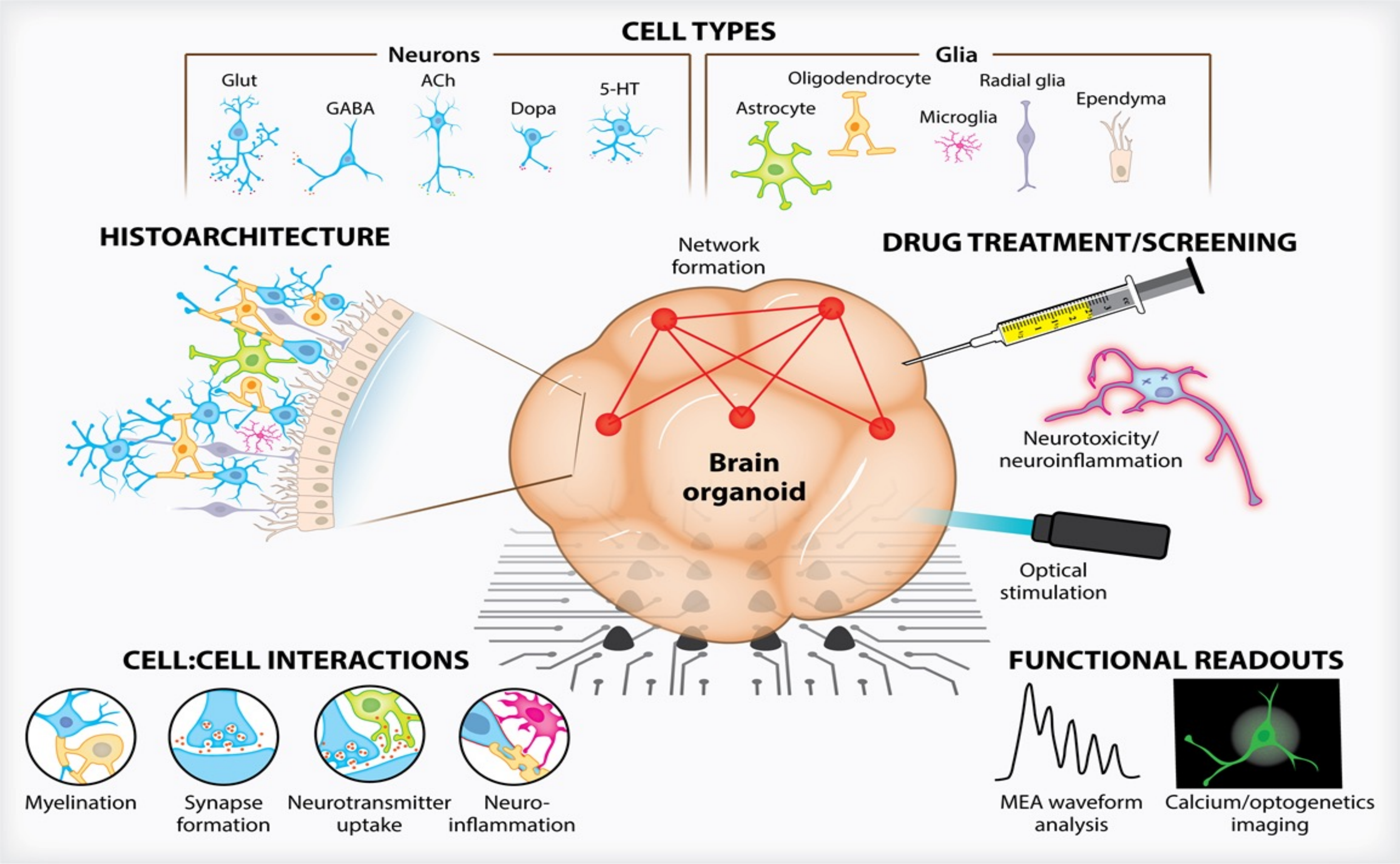
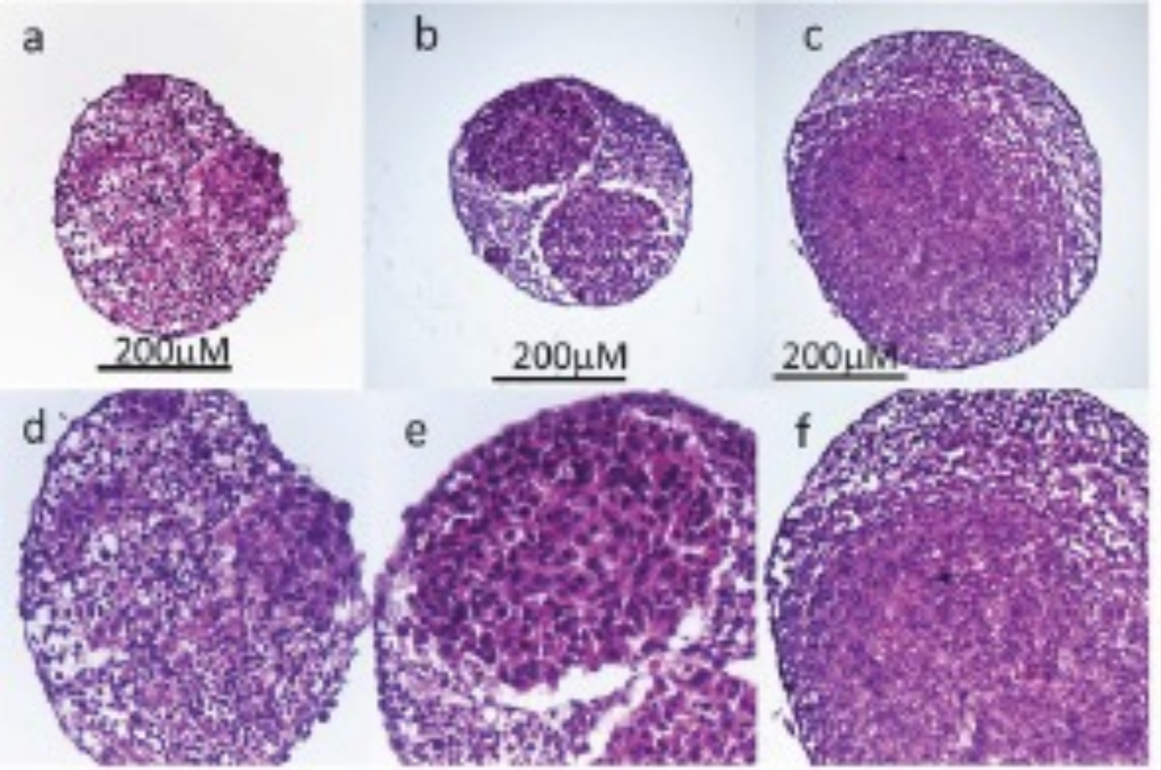
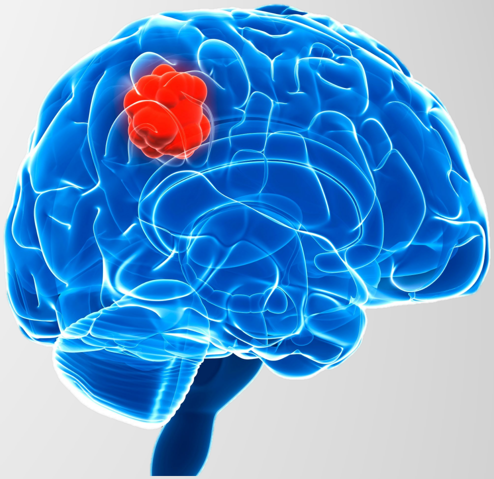


Anderson et al., In Vitro Cellular & Developmental Biology 2021, Published online. Doi: 10.1007/s11626-020-00532-8

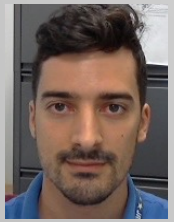
Glioblastoma in BrainSpheres



Effect of Temozolomide and Doxorubicin treatment



- ► **DEVELOP DRUGS**
- ► **OPTIMIZE CHOICE OF DRUG**



SCIENTIFIC REPORTS

OPEN

A Human iPSC-derived 3D platform using primary brain cancer cells to study drug development and personalized medicine

: 22 August 2018
: 19 December 2018
d online: 05 February 2019

Simon Plummer[1], Stephanie Wallace[1], Graeme Ball[2], Roslyn Lloyd[3], Paula Schiapparelli[4], Alfredo Quiñones-Hinojosa[4], Thomas Hartung[5,6] & David Pamies[5,7]

iScience 2020, 23:101633

CellPress OPEN ACCESS

Review

Organotypic Models to Study Human Glioblastoma: Studying the Beast in Its Ecosystem

David Pamies,[1,2,*] Marie-Gabrielle Zurich,[1,2] and Thomas Hartung[3,4]

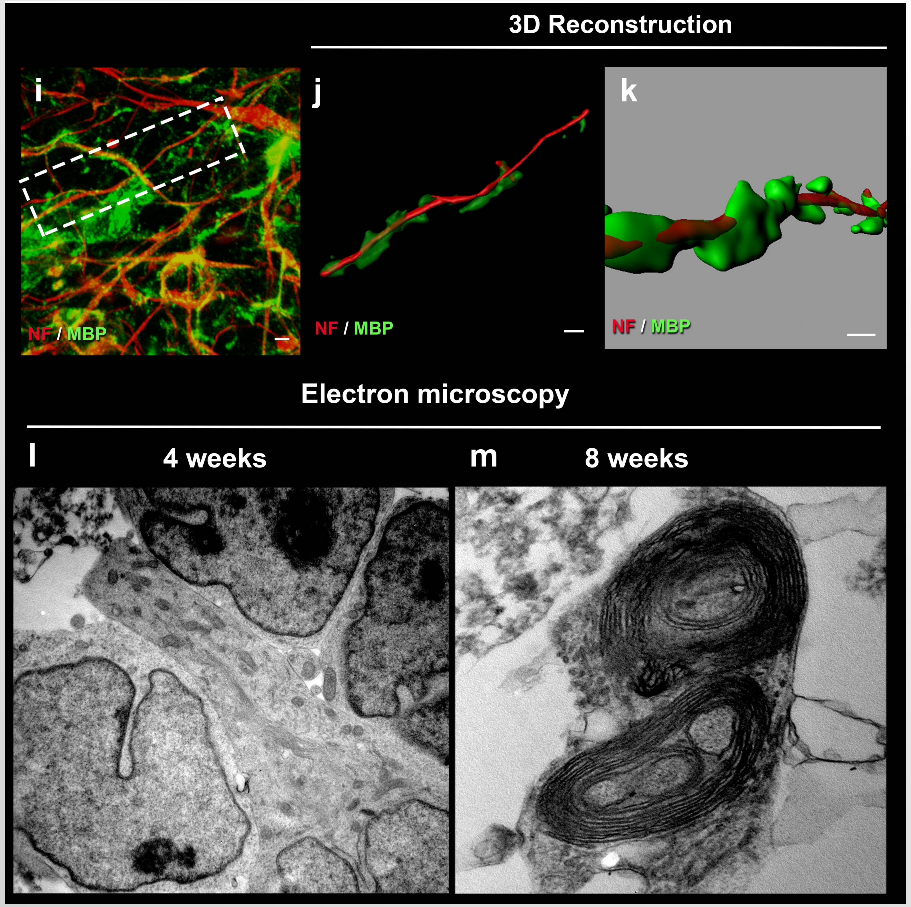
Myelination

Megan Chesnut

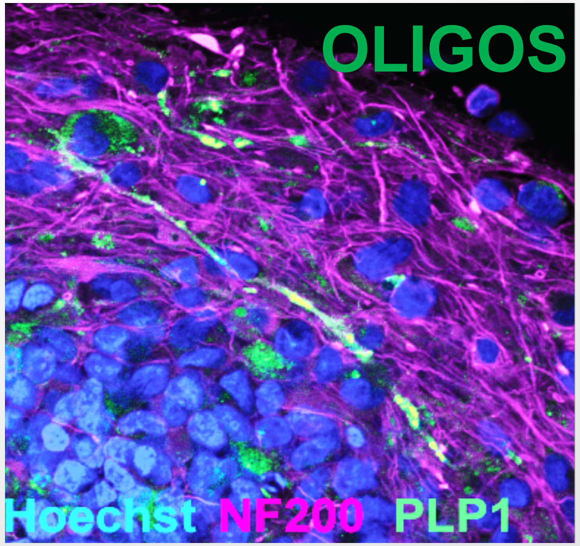
I Scarisbrick, MAYO

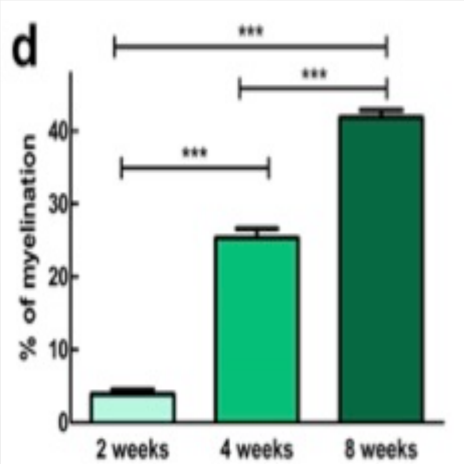
COLGATE-PALMOLIVE

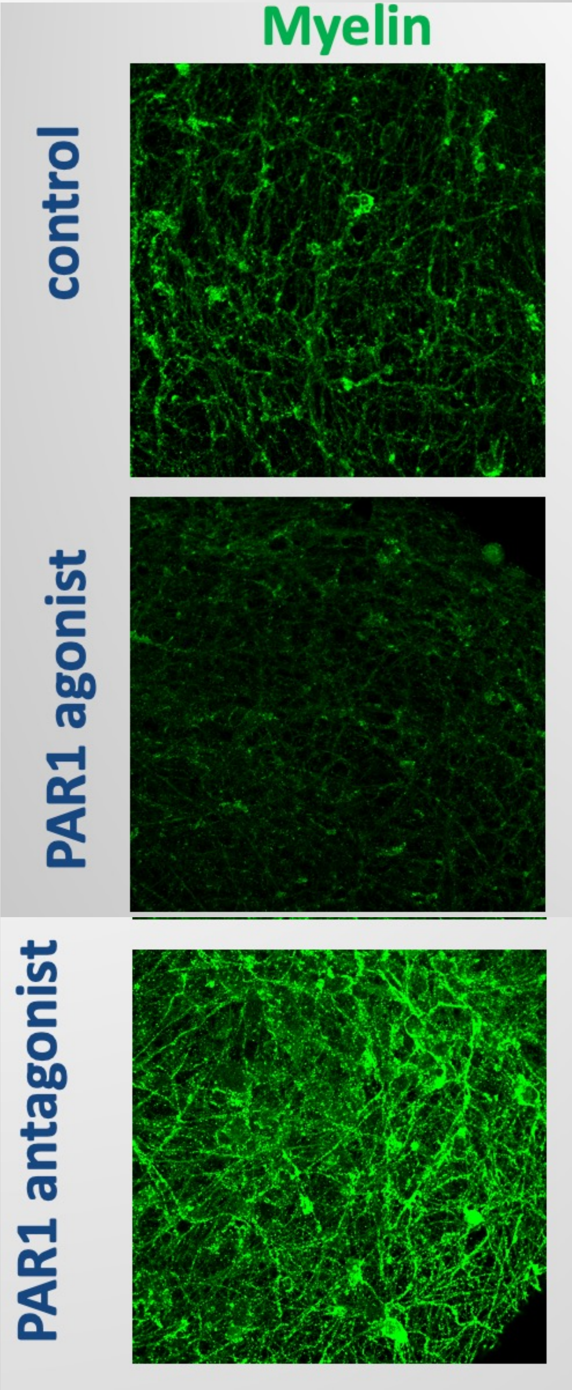
Roche

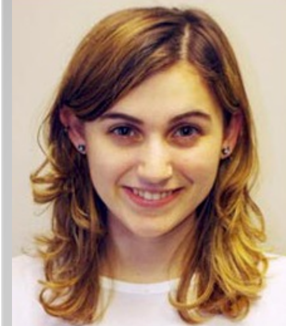


Pamies et al., Altex 2017



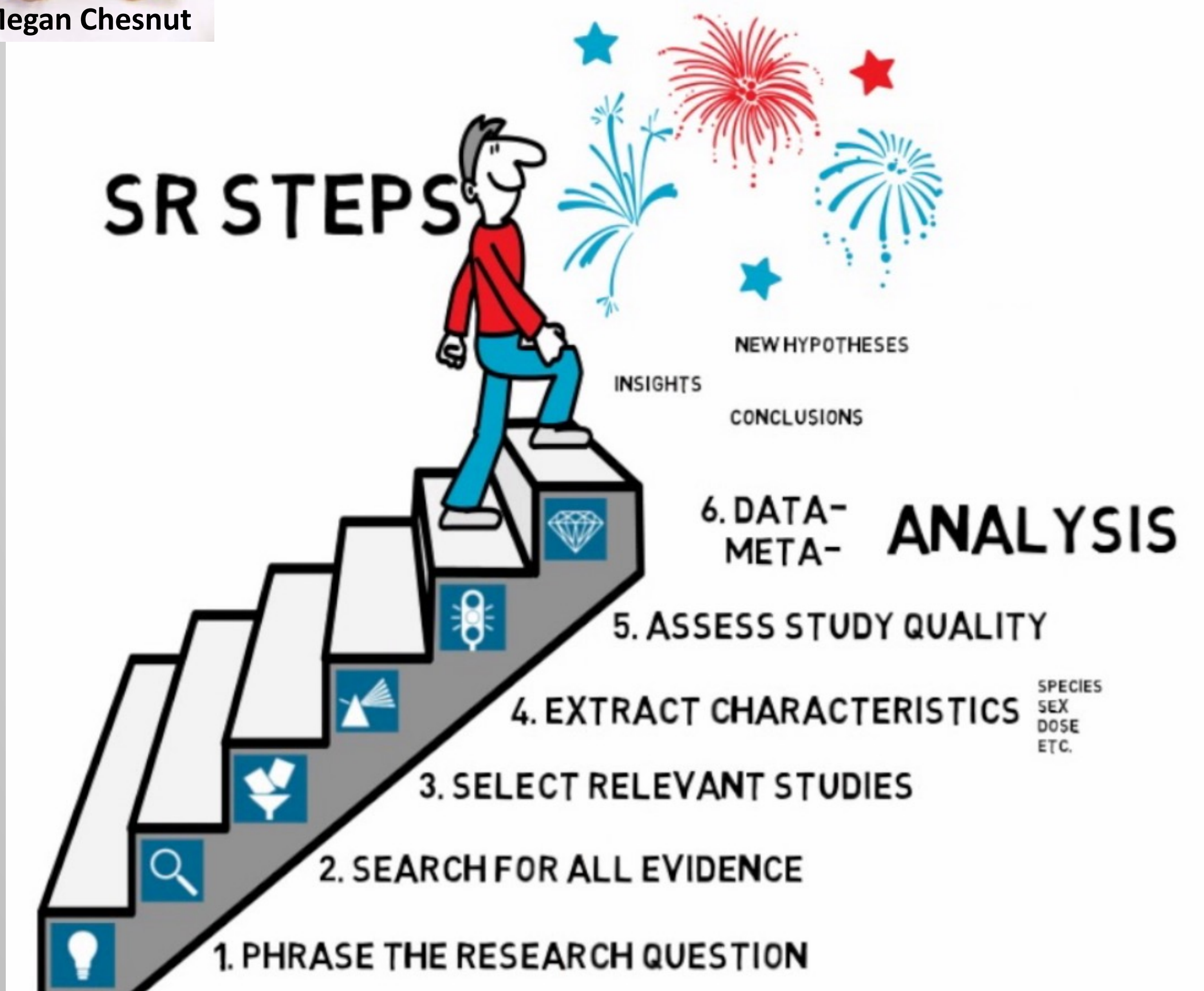


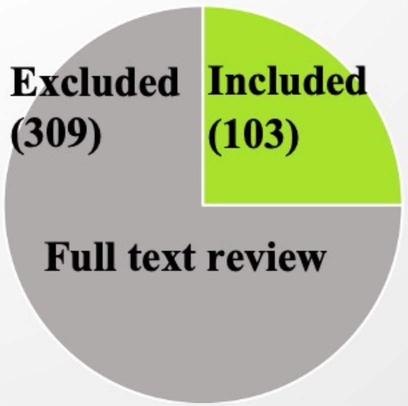




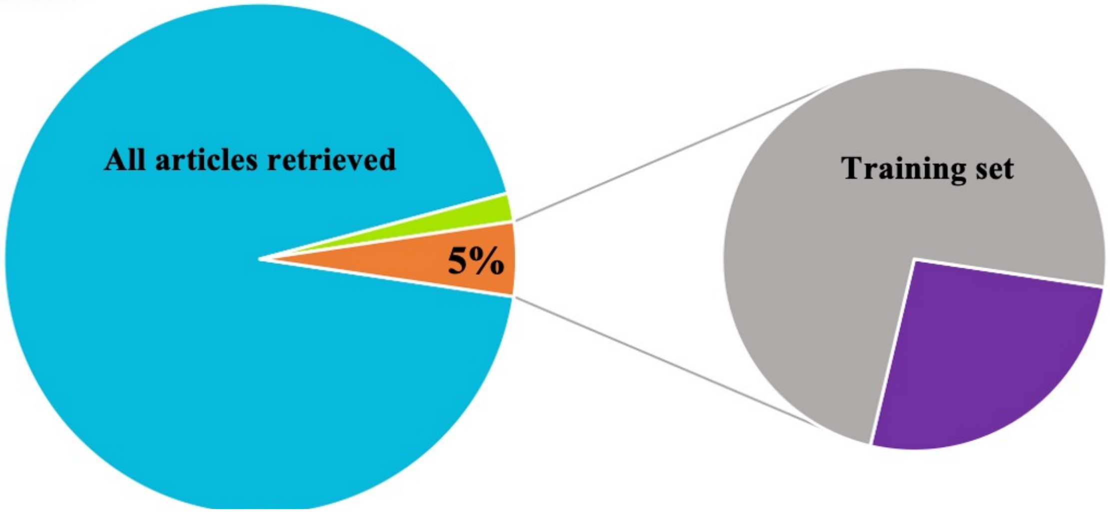
Megan Chesnut

Systematic review of compounds for myelination assay





1 Standard (cuprizone)
16 drugs
6 illicit drugs
22 environ. toxicants



SWIFT REVIEW

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2 articles shared with PubMed Search ""stent" and "loattrfree full text"[sb]"

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Semi-automated systematic review:

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Inclusion Criteria

Medical Device is primary subject

datasource

Similarity

The model identifies suspected developmental neurotoxicants and models various diseases

Toxicology and Applied Pharmacology 354 (2018) 101–114

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

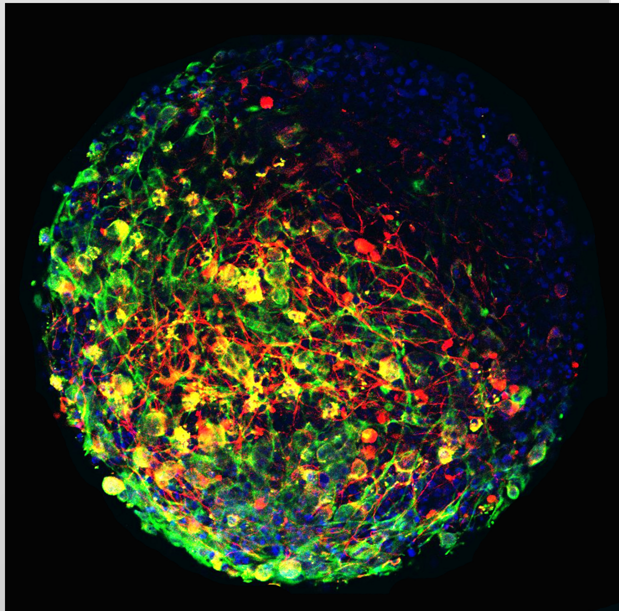
David Pamies[a], Katharina Block[a], Pierre Lau[b], Laura Gribaldo[b], Carlos A. Pardo[c], Paula Barreras[c], Lena Smirnova[a], Daphne Wiersma[a], Liang Zhao[a,d], Georgina Harris[a], Thomas Hartung[a,e], Helena T. Hogberg[a,*]

In conclusion, our BrainSpheres model has shown to be a reproducible and novel tool to study neurotoxicity and developmental neurotoxicity. Results presented here support the idea that rotenone can potentially be a developmental neurotoxicant.

frontiers

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*]



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EPA Awards Nearly $850,000 to Johns Hopkins University to Advance Research on Alternative Methods to Animal Testing

Multiplexed human BrainSphere Developmental Neurotoxicity test for six key events of neural development

Smirnova, Hartung, Berlinicke, Gracias

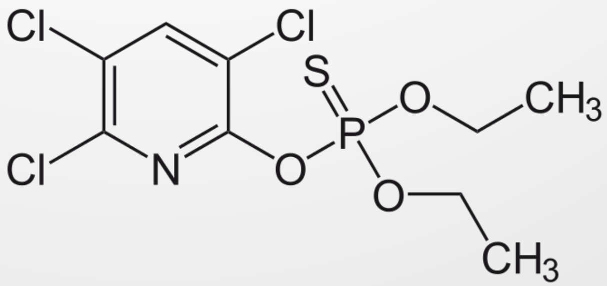
Romero, Morales, Plotkin, Modafferi

CHD8 and chlorpyrifos functional synergy

EHP, revised

CRISPR-CaS9 introduction of risk / reporter genes of interest

CHLORPYRIFOS

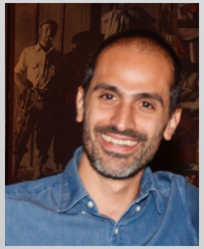


CHLORPYRIFOS-OXON

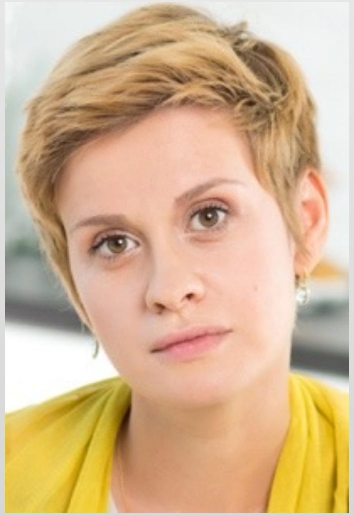
GxE

Functional and Molecular signatures





Herbert Lachman,
Xiali Zhong,
Sergio Modafferi



Lena Smirnova

GCCP 2.0
Draft published

- Stakeholder discussion
- Editor workshop
- 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

"In God we trust.
All others must bring data."
W. Edwards Deming
(1900-1993)
Professor and author

ALTEX 2019, 36:3-17

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]

Bench Marks!

ALTEX 2019, 36:682-699

Template for the Description of Cell-Based Toxicological Test Methods to Allow Evaluation and Regulatory Use of the Data

Alice Krebs[1,2], Tanja Waldmann[1], Martin F. Wilks[3], Barbara M. A. van Vugt-Lussenburg[4], Bart van der Burg[4], Andrea Terron[5], Thomas Steger-Hartmann[6], Joelle Ruegg[7], Costanza Rovida[8], Emma Pedersen[9], Giorgia Pallocca[1,8], Mirjam Luijten[10], Sofia B. Leite[11], Stefan Kustermann[12], Hennicke Kamp[14], Julia Hoeng[14], Philip Hewitt[15], Matthias Herzler[16], Jan G. Hengstler[17], Tuula Heinonen[18], Thomas Hartung[8,19], Barry Hardy[20], Florian Gantner[21], Ellen Fritsche[22], Kristina Fant[9], Janine Ezendam[10], Thomas Exner[20], Torsten Dunkern[23], Daniel R. Dietrich[24], Sandra Coecke[11], Francois Busquet[8,25], Albert Braeuning[26], Olesja Bondarenko[27], Susanne H. Bennekou[28], Mario Beilmann[29] and Marcel Leist[1,2,8]

https://zeenea.com/data-quality-management-the-ingredients-to-improve-the-quality-of-your-data/

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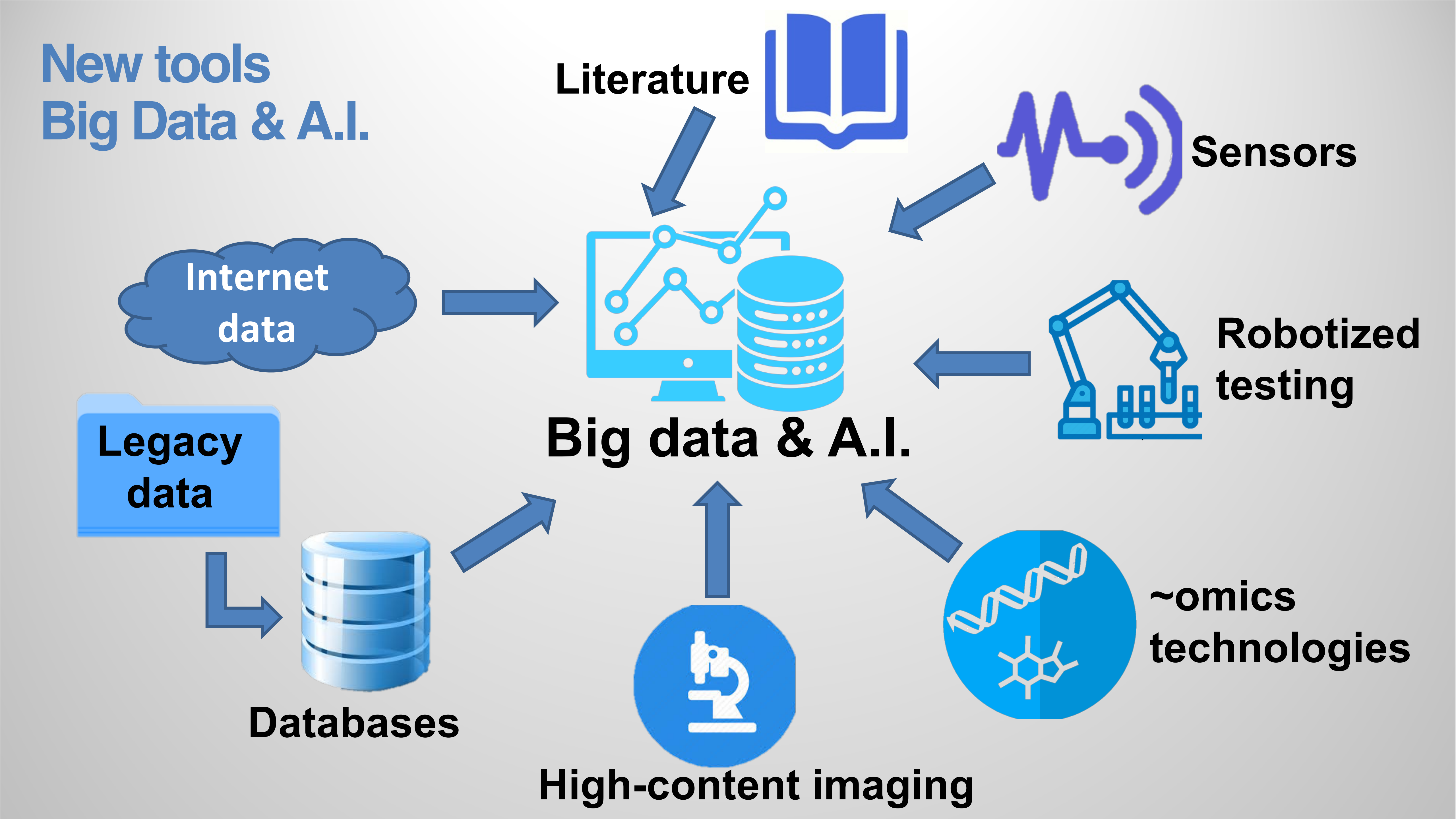
New tools
Big Data & A.I.
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Legacy data
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Databases
~omics technologies
High-content imaging

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

An estimated 3 million to 4 million rabbits, rats, and other animals are used annually around the world for chemical safety tests. CAIRNEY DOWN/ALAMY STOCK PHOTO

New digital chemical screening tool could help eliminate animal testing

By Vanessa Zainzinger | Jul. 11, 2018 , 11:00 AM

NEWS · 11 JULY 2018

Software beats animal tests at predicting toxicity of chemicals

Machine learning on mountain of safety data improves automated assessments.

A.I. use for (developmental) neurotox is starting

Journal of AppliedToxicology

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Quantitative neurotoxicology: Potential role of artificial intelligence/deep learning approach

Anshul Srivastava, Joseph P. Hanig

2019 18th IEEE International Conference on Machine Learning and Applications (ICMLA)

Machine learning to predict developmental neurotoxicity with high-throughput data from 2D bio-engineered tissues

Finn Kuusisto[1,*], Vitor Santos Costa[2], Zhonggang Hou[1,+], James Thomson[1,3,4], David Page[5], and Ron Stewart[1]

Machine learning-assisted neurotoxicity prediction in human midbrain organoids

Anna S. Monzel[a], Kathrin Hemmer[a], Tony Kaoma[b], Lisa M. Smits[a], Silvia Bolognin[a], Philippe Lucarelli[a], Isabel Rosety[a], Alise Zagare[a], Paul Antony[c], Sarah L. Nickels[a], Rejko Krueger[c, d, e], Francisco Azuaje[b, f], Jens C. Schwamborn[a]*

ONTOX

Under negotiation
To start 1 May 2021

~ $20 million
18 partners
Incl. CAAT-US, ToxTrack, AlterTox
5 years

Figure 3.3a: Geographical location of the ONTOX partners.

The difficulty lies, not in the new ideas, but in escaping from the old ones.

John Maynard Keynes

(1883 - 1946)