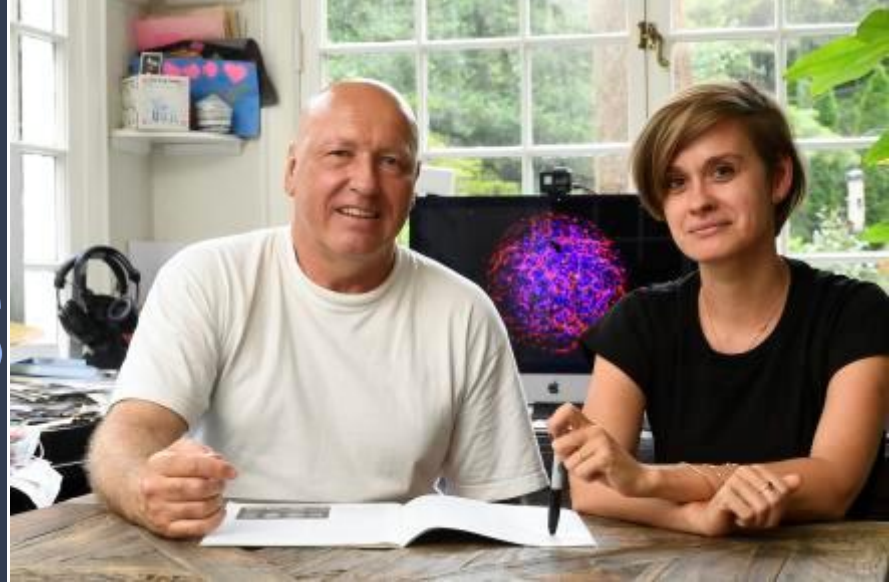
JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH



JOHNS HOPKINS UNIVERSITY
Center for Alternatives to Animal Testing

frontiers in Artificial Intelligence

**Thomas Hartung, Lena Smirnova & team**

# Organoid Intelligence, the new frontier in biocomputing and intelligence-in-a-dish

# frontiers in Artificial Intelligence

frontiers

We build the leading journals of the future
Frontiers in Artificial Intelligence

**13 sections**

**1034 articles (IF 4.0)**

**273 Research Topics**

Thomas Hartung
Field Chief Editor

## Sections

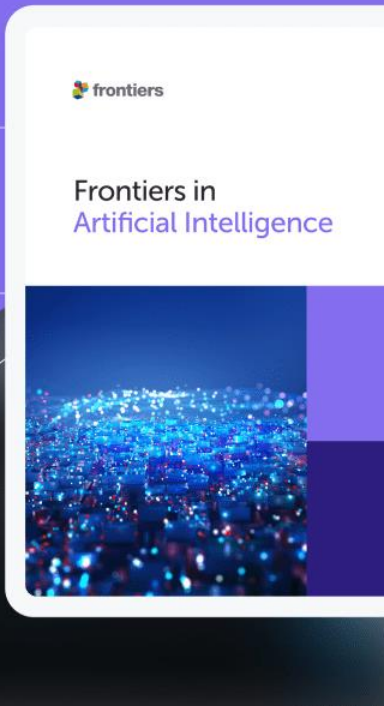
- AI for Human Learning and Behavior Change
- AI in Business
- AI in Food, Agriculture and Water
- Artificial Intelligence in Finance
- Big Data and AI in High Energy Physics
- Fuzzy Systems
- Language and Computation
- Machine Learning and Artificial Intelligence
- Medicine and Public Health
- Natural Language Processing
- Organoid Intelligence NEW
- Pattern Recognition
- Technology and Law

Frontiers (2023)
Journal Citation Reports (Clarivate, 2023)
Scopus (2023)

3.4M
article views and downloads

4.0
Journal Impact Factor

3.9
CiteScore™



KEYSTONE SYMPOSIA
Accelerating Life Science Discovery

50 YEARS 1972-2022

# AI in Biomedicine

**1-3 May 2024 (virtual)**

Thomas Hartung
Bloomberg School of Public Health, Johns Hopkins University
Baltimore, United States

Specialty Chief Editor
Medicine and Public Health

Weida Tong
National Center for Toxicological Research (FDA)
Jefferson, United States

Associate Editor
Medicine and Public Health

Yvonne Will
Janssen Pharmaceuticals, Inc.
Titusville, United States

Associate Editor
Medicine and Public Health

WORLD ECONOMIC FORUM

# 2024: AI/LLMs for Scientific Discovery

## AI for Scientific Discovery: Pioneering New Frontiers in Knowledge

**Andrew Maynard**
Professor, School for the Future of Innovation in Society, Arizona State University

**Sang Yup Lee**
Distinguished Professor of Chemical and Biomolecular Engineering, Korea Advanced Institute of Science & Technology

**Olga Fink**
Assistant Professor, Intelligent Maintenance and Operations Systems, EPFL

**Thomas Hartung**
Professor, Bloomberg School of Public Health, Johns Hopkins University

**Data**: double every 18month
= 90% in last three years

**Computer**: double every 24 months (Moore's law)

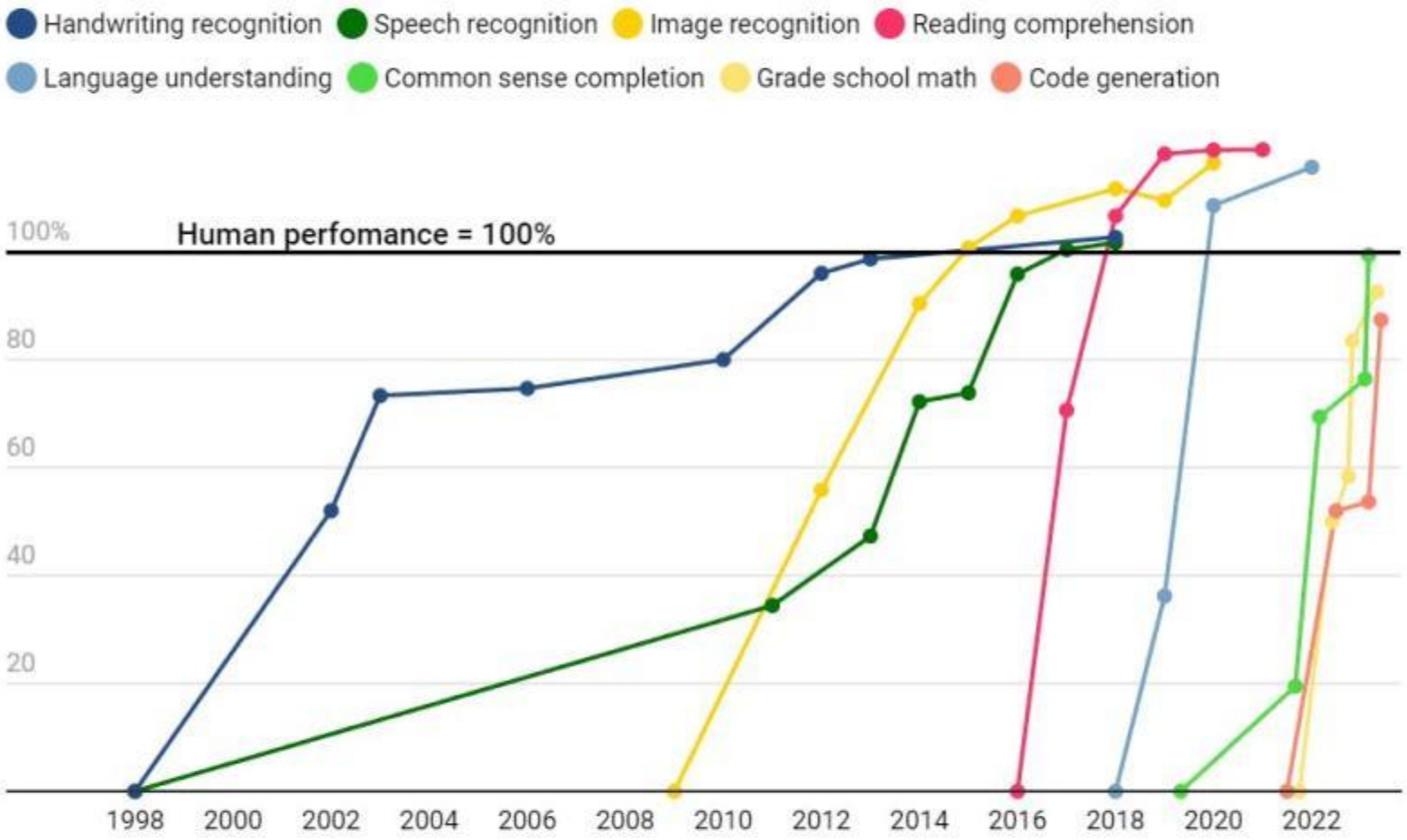
**AI**: double every 3 months since 2010

## Together increase >1 billion-fold

**(since we engaged in AI ten years ago)**

## AI has surpassed humans at a number of tasks and the rate at which humans are being surpassed at new tasks is increasing

State-of-the-art AI performance on benchmarks, relative to human performance




*For each benchmark, the maximally performing baseline reported in the benchmark paper is taken as the "starting point", which is set at 0%. Human performance number is set at 100%. Handwriting recognition = MNIST, Language understanding = GLUE, Image recognition = ImageNet, Reading comprehension = SQuAD 1.1, Reading comprehension = SQuAD 2.0, Speech recognition = Switchboard, Grade school math = GSK8k, Common sense completion = HellaSwag, Code generation = HumanEval.*

Chart: Will Henshall for TIME • Source: ContextualAI

TIME

# AI surpasses human performance, e.g., annotating scientific papers

2023


## BioGPT and human annotator have comparable performance in biomedical research test

Selected performances on PubMedQA, which tests biomedical language processing

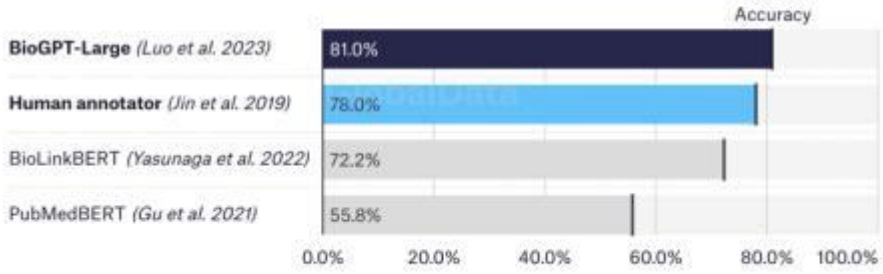



Chart: GlobalData • Source: PubMedQA

Plagiarism?

Bias

Data gaps

Black box

Hallucination

Autonomous AI

Productivity

Information retrieval

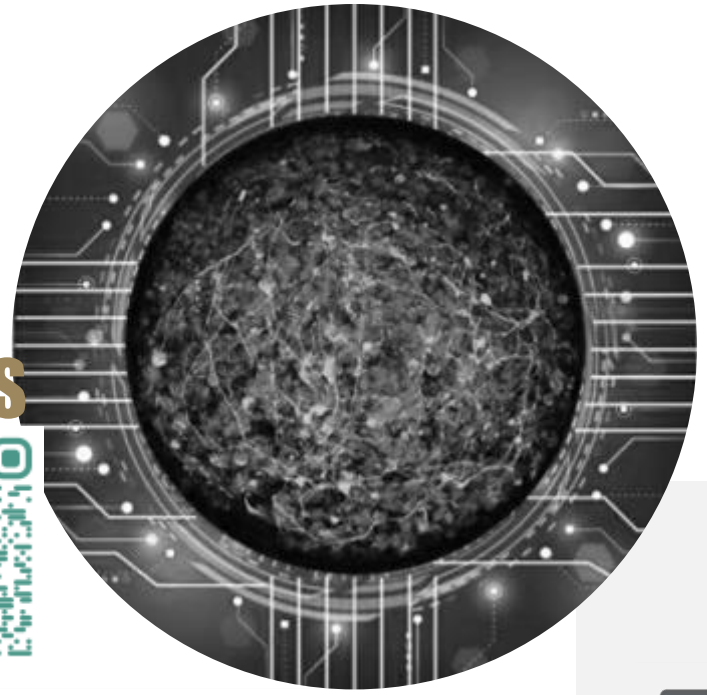
Evidence integration of Big Data

Multi-modal

Toward xAI

Human-in-loop

# Microphysiological systems (MPS)



JOIN US

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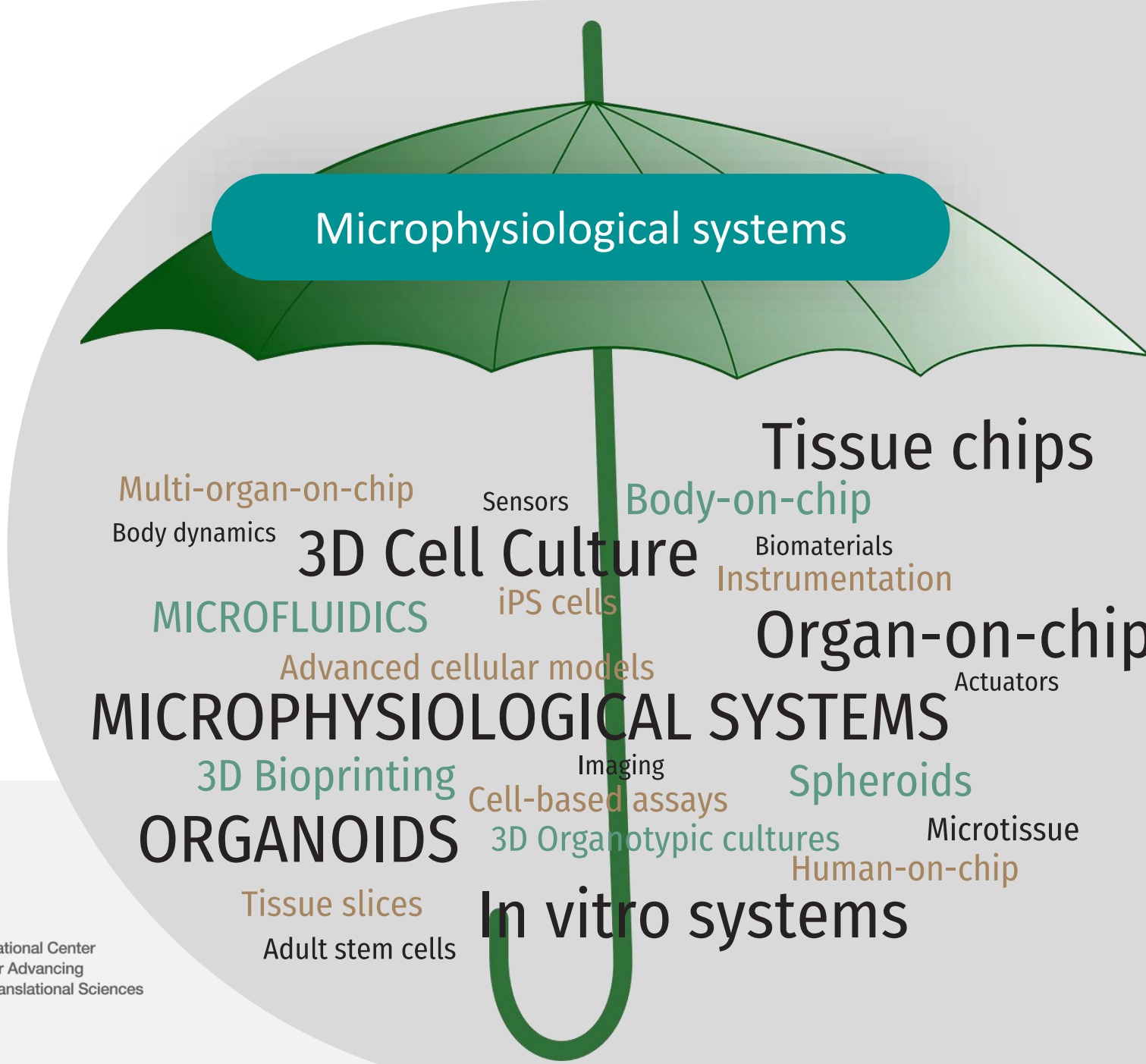
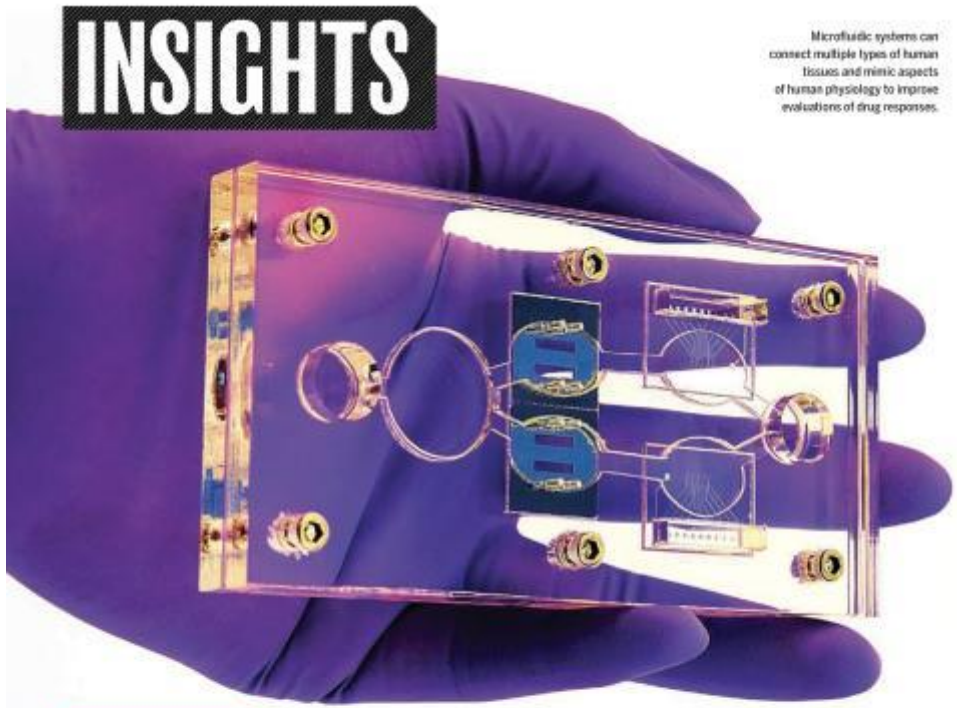
www.impss.org

NIH National Center for Advancing Translational Sciences



Science 16 Sep 2021




MPS WORLD SUMMIT
CONNECT, EXCHANGE, EDUCATE
2022, 2023, 2024

INTERNATIONAL MPS SOCIETY
CONNECT, EXCHANGE, EDUCATE
2023

MPS

3D workshop 2014

MPS workshops 2016, 2020, 2023 report to come

GCCP – MPS workshops 2015, 2016

GCCP 2.0 2022

Inv. Tox workshop 2019

# Since 2005: CAAT (Goldberg) & Hartung (then ECVAM)

## 9 workshops

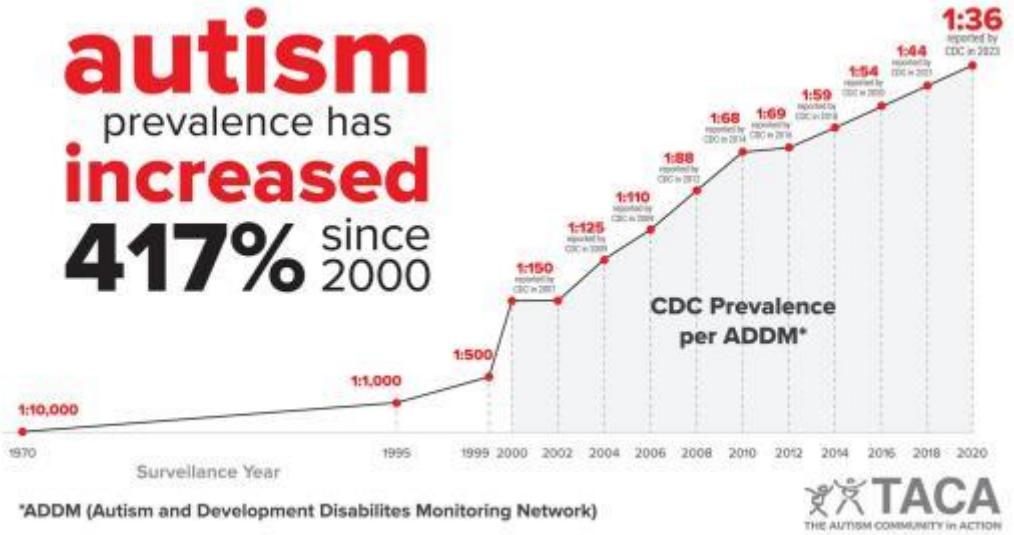
## 5 International conferences

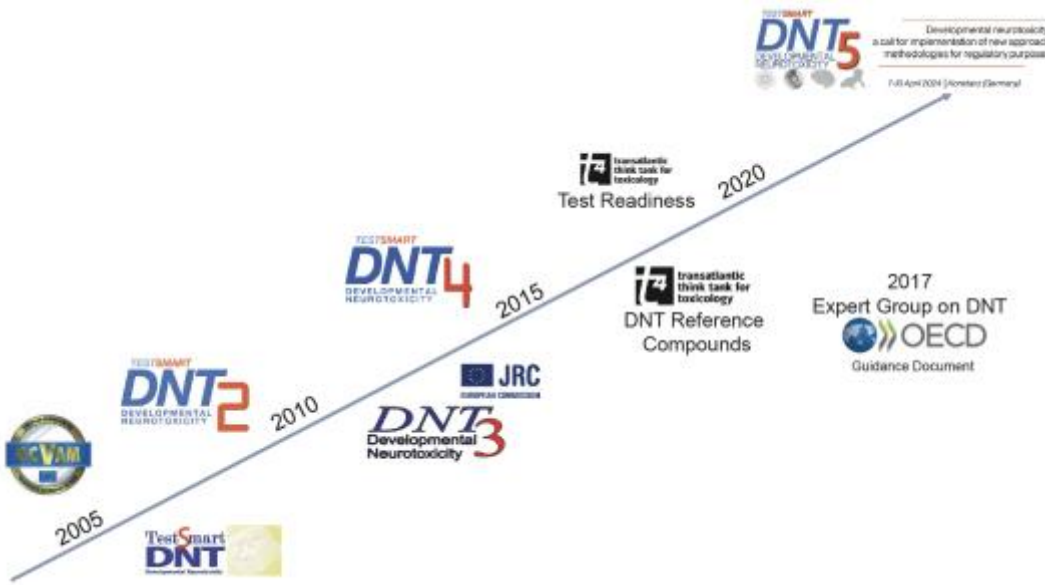
TESTSMART DNT5 DEVELOPMENTAL NEUROTOXICITY

**Expert Group on DNT**

OECD

**Guidance Document**



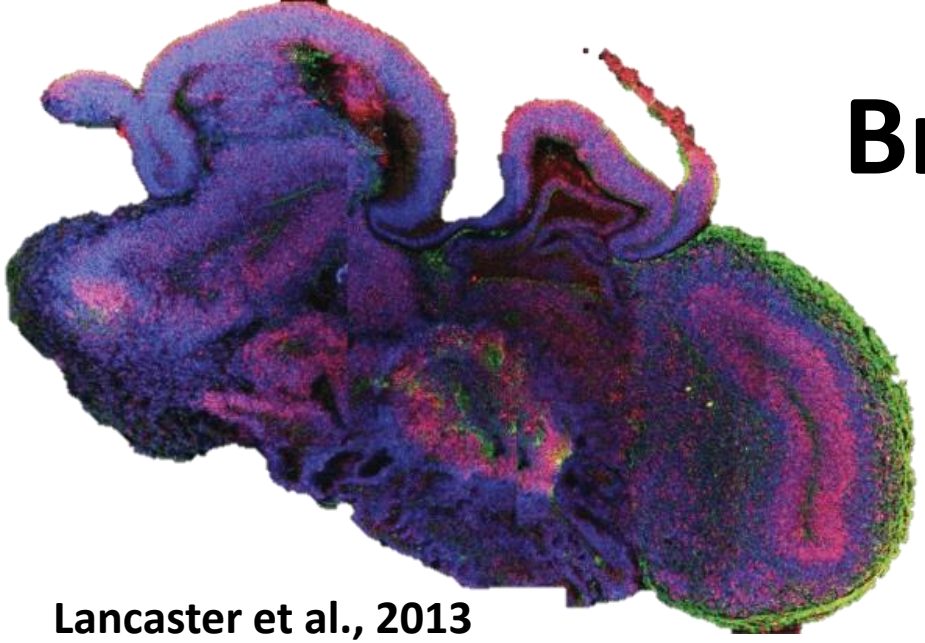




Food for Thought ...

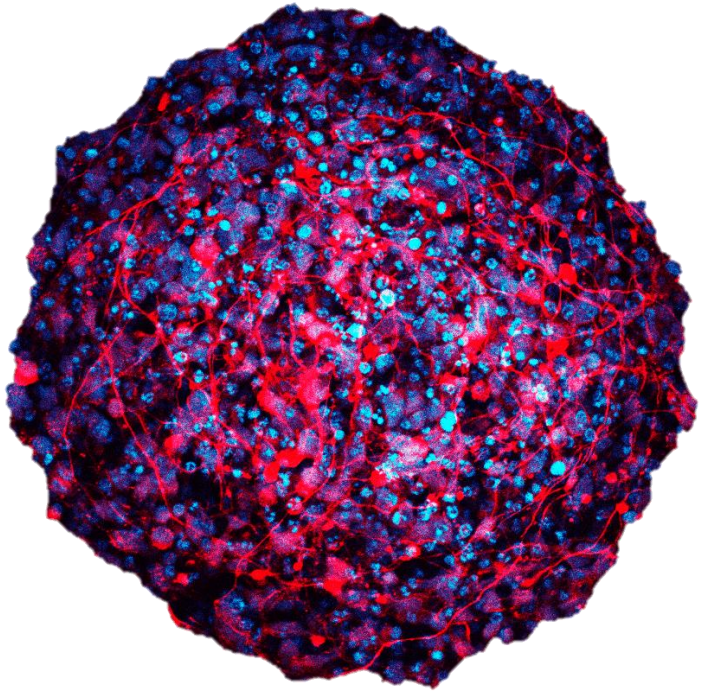
**Revolutionizing Developmental Neurotoxicity Testing – A Journey from Animal Models to Advanced *In Vitro* Systems** 2024

*Lena Smirnova[1], Helena T. Hogberg[2], Marcel Leist[3,4] and Thomas Hartung[1,3,5]*

# Brain Organoids



Lancaster et al., 2013



The truth about Myers-Briggs Personality types

Snow polo anyone? Inside the St Moritz property market

US edition

FT Weekend

Life & Arts Rhythm and booze | Diary On the US campaign trail | Person in the News Beyoncé

Mass-produced mini-brains to spark rethink over drug testing on animals

Autism

COVID-19

Glioblastoma

....

2016

# Brain Organoid Research

**Lena Smirnova**

Molecular Psychiatry www.nature.com/mp

ARTICLE

Blood extracellular vesicles carrying brain-specific mRNAs are potential biomarkers for detecting gene expression changes in the female brain

Lena Smirnova[1], Sergio Modafferi[1], Charlotte Schlett[1], Lauren M. Osborne[2], Jennifer L. Payne[3] and Sarven Sabunciyan[4,5]

**Novel biomarkers**

Oligodendrogenesis and myelination tracing in a CRISPR/Cas9-engineered brain microphysiological system

July Carolina Romero[1], Cynthia Berlinicke[2], Sharon Chow[1], Yukan Duan[2], Yifei Wang[1], Xitiz Chamling[2] and Lena Smirnova[1]*

**Reporter lines**

**Freezing protocol developed (to be published)**

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

**18 centers**
**175,000 children**
**+ organoid GxE**

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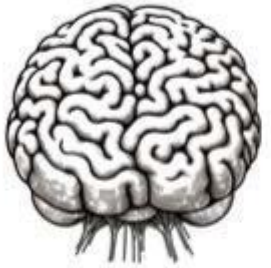
# The Promise and Potential of Brain Organoids

*Lena Smirnova* and Thomas Hartung**

**Lena Smirnova**

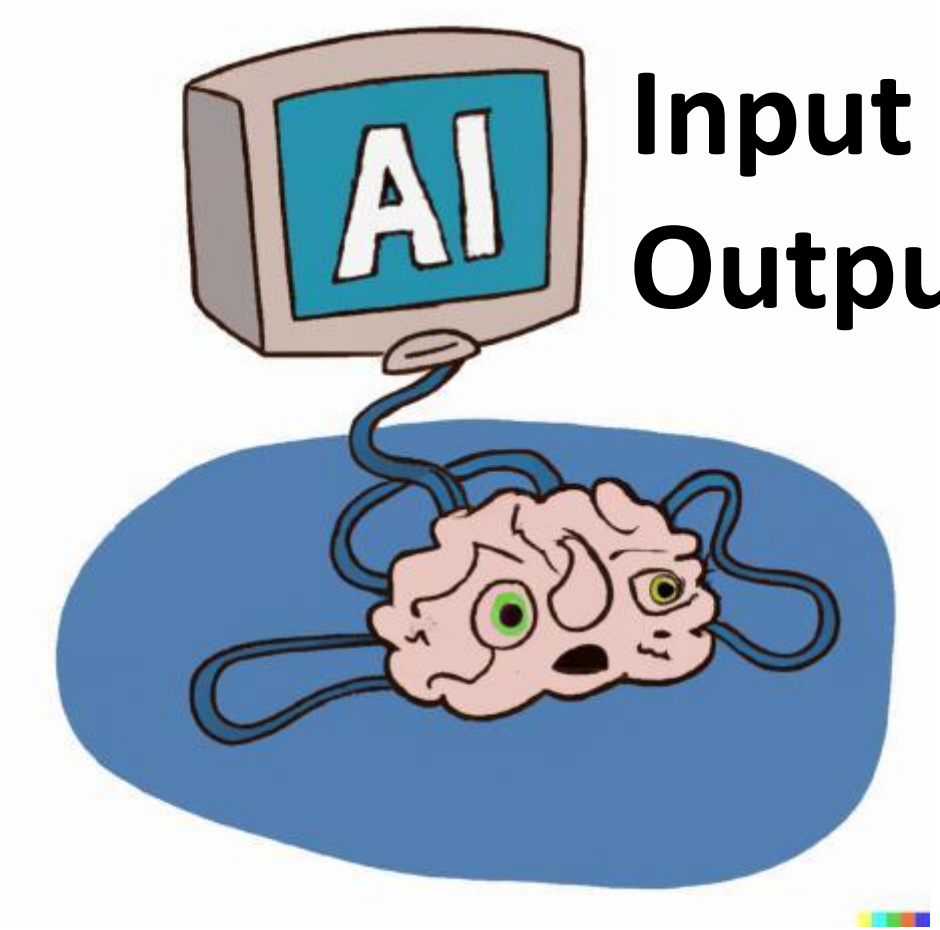
## BRAIN ORGANOID OPPORTUNITIES


## BRAIN ORGANOID AND BRAINSPHERE VARIANTS



- Different species; patient-derived or healthy; genetically modified or not
- Reaggregation of tissue-derived cell suspension or stem cell-derived (embryonic stem cells or iPSC)
- Use of extracellular matrix, hydrogels or none
- Scaffold or none; possible electrode integration
- Use of growth factors to induce differentiation or not; addition of cell types (micro-glia)
- Gravity-based aggregation (e.g., hanging drop or microtiter plates) or bioreactor (e.g., spinner or shaker)
- Brain region-specific organoids; addition of blood-brain-barrier
- Fusion and assembloids of different brain regions or organs (cell lineages)
- Use of microfluidics and vascularization for perfusion or not

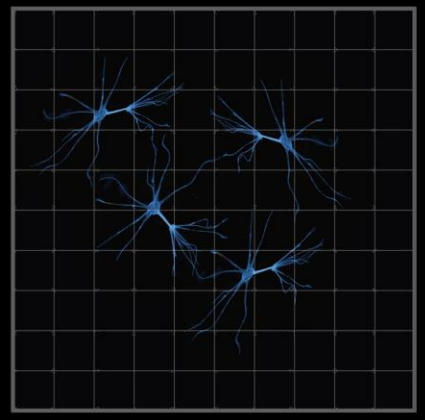
# Combining MPS, sensors and AI = Organoid Intelligence (OI)




**Input & Output**

- **Physiology of learning**
- **Brain Machine Interfaces**
- **Tox & Drug Development**
- **Biological Computing**

2D culture



Neuron

CellPress
OPEN ACCESS

CORTICAL LABS

Article

# *In vitro* neurons learn and exhibit sentience when embodied in a simulated game-world

Brett J. Kagan,[1,11,*] Andy C. Kitchen,[1] Nhi T. Tran,[2] Forough Habibollahi,[9] Moein Khajehnejad,[10] Bradyn J. Parker,[3] Anjali Bhat,[4] Ben Rollo,[5] Adeel Razi,[4,6,7,8] and Karl J. Friston[4]

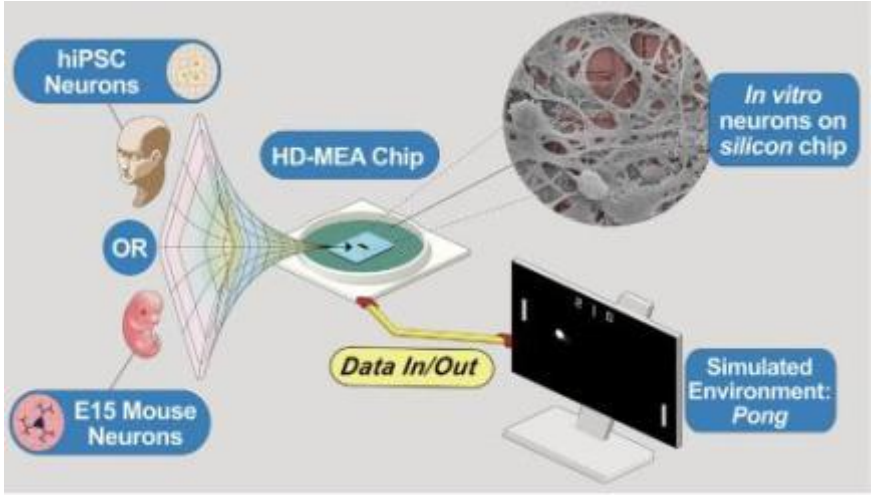
Neuron
Previews

CellPress

# Neuronal cultures playing Pong: First steps toward advanced screening and biological computing

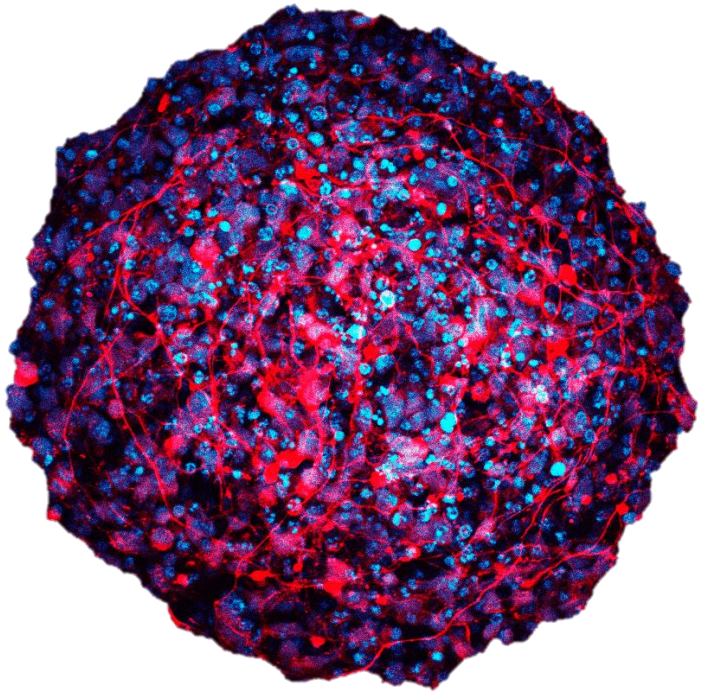
Lena Smirnova[1] and Thomas Hartung[1,*]

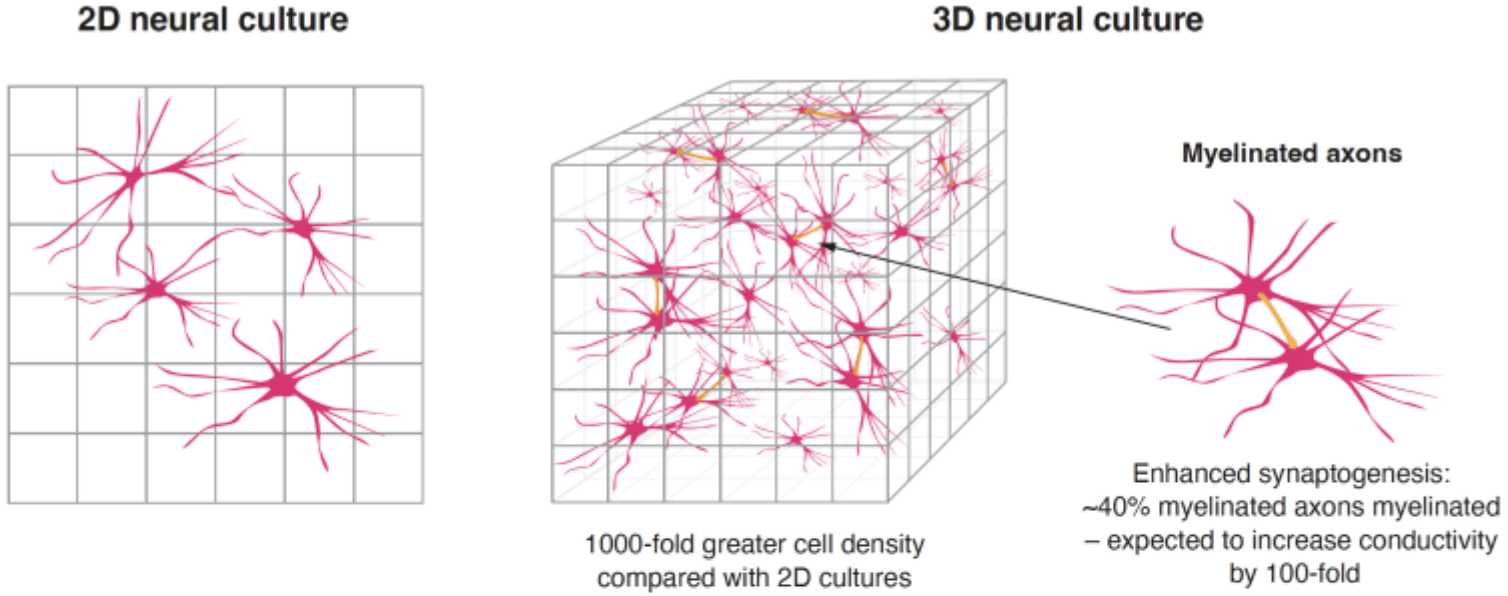
## The *DishBrain* system embodies *in vitro* neurons in a virtual world



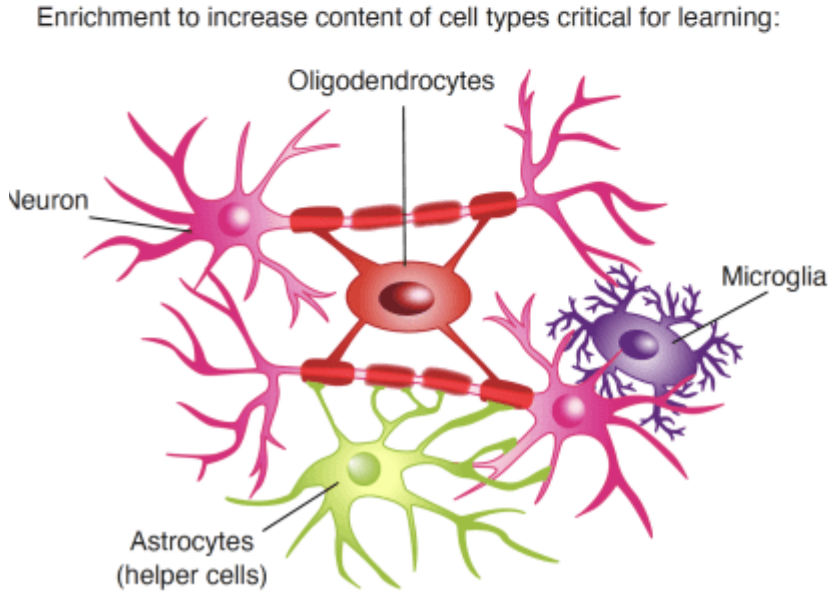
# Brain microphysiological systems

**Providing the cellular architecture and physiology for cognition**






**1,000x cell density**
**= more synapses**
**Myelination**
**= 100x conductivity**
**Glial cells**
**= synapse pruning for long-term memory**



frontiers | Frontiers in Science

TYPE Frontiers in Science Lead Article
PUBLISHED 28 February 2023
DOI 10.3389/fsci.2023.1017235



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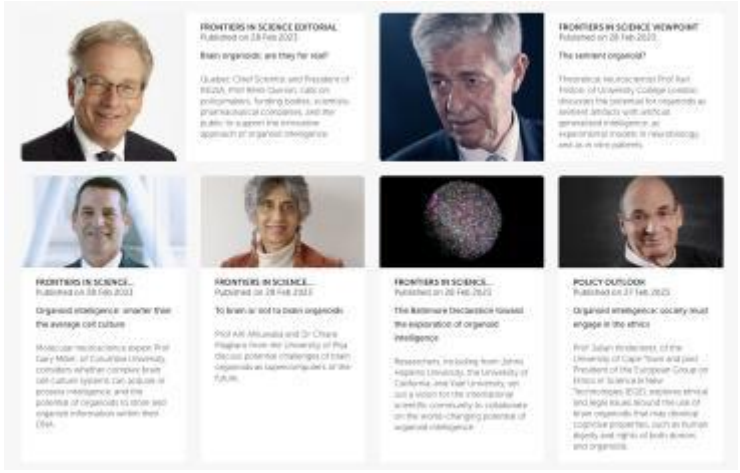
RECEIVED 11 August 2022
ACCEPTED 07 February 2023
PUBLISHED 28 February 2023

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

Lena Smirnova[1], Brian S. Caffo[2], David H. Gracias[3,4,5,6,7,8], Qi Huang[3], Itzy E. Morales Pantoja[1], Bohao Tang[2], Donald J. Zack[9], Cynthia A. Berlinicke[10], J. Lomax Boyd[11], Timothy D. Harris[12,13], Erik C. Johnson[14], Brett J. Kagan[15], Jeffrey Kahn[16], Alysson R. Muotri[17,18], Barton L. Paulhamus[19], Jens C. Schwamborn[20], Jesse Plotkin[1], Alexander S. Szalay[21,22,23], Joshua T. Vogelstein[12], Paul F. Worley[24] and Thomas Hartung[1,25*]

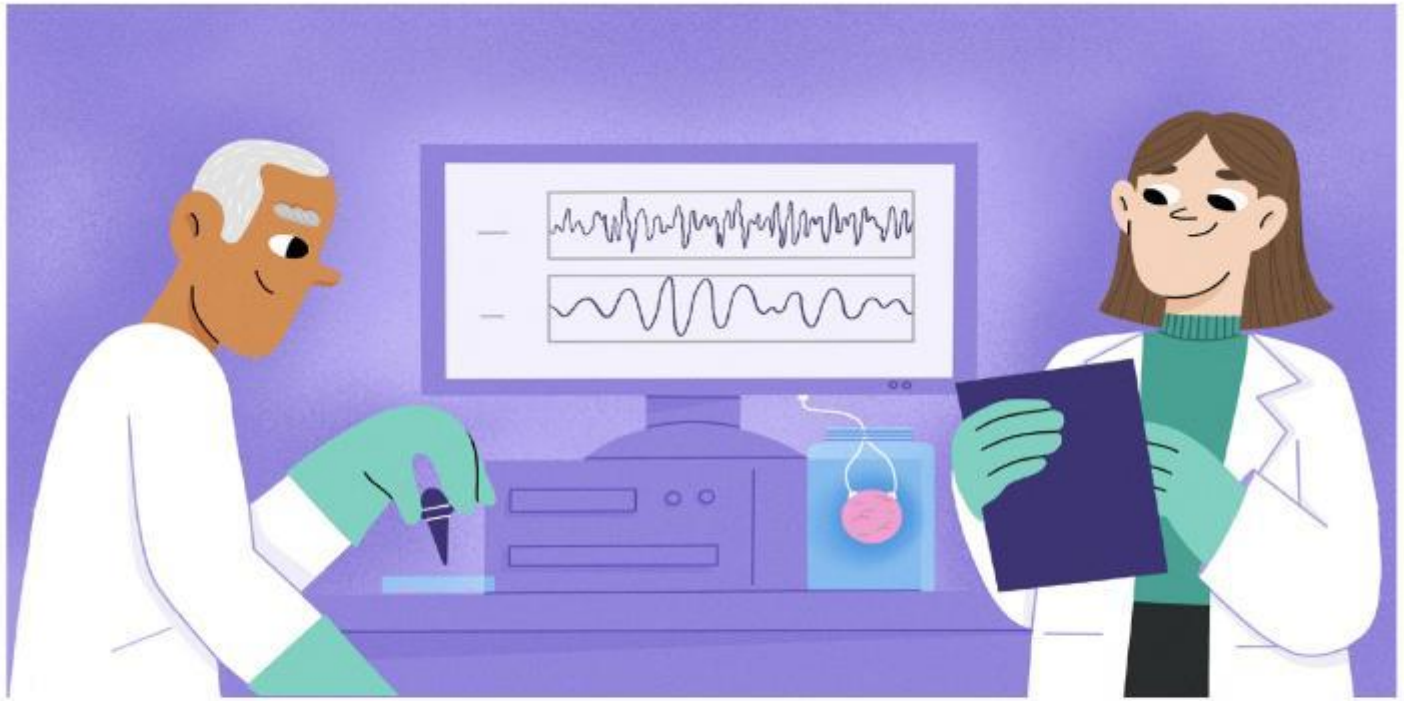


## Forming a community

- Dissemination (kid and lay versions, 600+ press hits)
- Workshop report
- US White House Bold Biotechnology Goals 3’23
- NSF “Engineering OI”

frontiers | Frontiers for Young Minds

# Next-Next-Generation Education



## BRAIN-CELL CULTURES: THE FUTURE OF COMPUTERS AND MORE?

*Lena Smirnova*, Itzy Erin Morales Pantoja and Thomas Hartung*

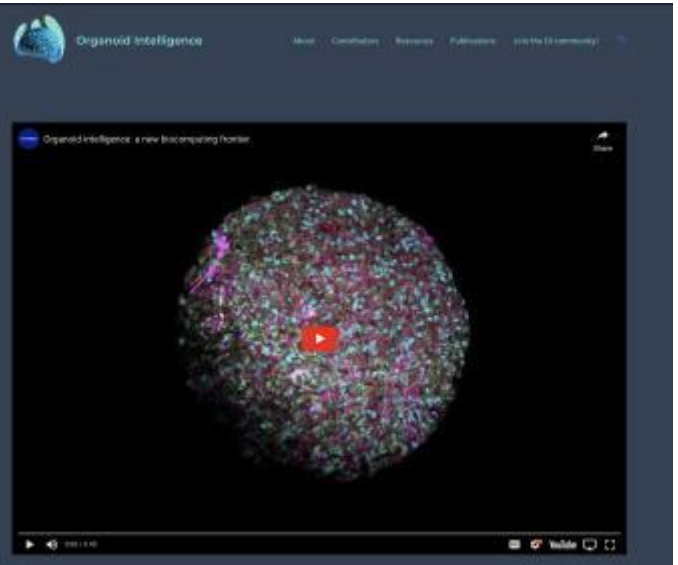
doi: 10.3389/frym.2023.1049593

*The Official News Bulletin of the Organoid Intelligence Community*

Welcome to the first official newsletter of the OI community!

## Newsletter

## Website (shortly)

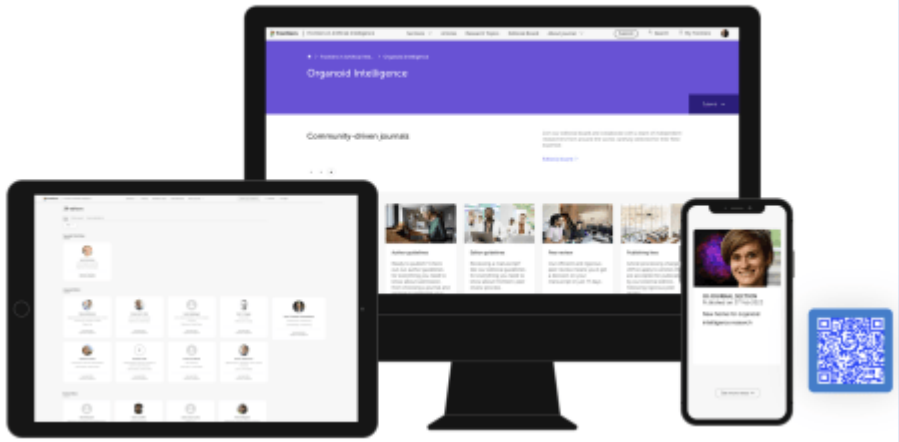



organoidintelligence.org

# First Organoid Intelligence (OI) workshop to form an OI community

Itzy E. Morales Pantoja[1], Lena Smirnova[1], Alysson R
Karl J. Wahlin[4], Jeffrey Kahn[5], J. Lomax Boyd[5],
David H. Gracias[6,7,8,9,10,11], Timothy D. Harris[12,13],
Tzahi Cohen-Karni[14,15], Brain S. Caffo[16], Alexander S. Szalay[17,18,19],
Fang Han[20], Donald J. Zack[21,22,23,24], Ralph Etienne-Cummings[25],
Akwasi Akwaboah[25], July Carolina Romero[1],
Dowlette-Mary Alam El Din[1], Jesse D. Plotkin[1],
Barton L. Paulhamus[26], Erik C. Johnson[26], Frederic Gilbert[27],
J. Lowry Curley[28], Ben Cappiello[28], Jens C. Schwamborn[29],
Eric J. Hill[30], Paul Roach[31], Daniel Tornero[32,33], Caroline Krall[1,34],
Rheinallt Parri[35], Fenna Sillé[1], Andre Levchenko[36],
Rabih E. Jabbour[37], Brett J. Kagan[38], Cynthia A. Berlinicke[21],
Qi Huang[6], Alexandra Maertens[1], Kathrin Herrmann[1],
Katya Tsaioun[1], Raha Dastgheyb[39], Christa Whelan Habela[39],
Joshua T. Vogelstein[12] and Thomas Hartung[1,40*]

**New journal:** Frontiers in Organoid Intelligence




# Engineering Organoid Intelligence

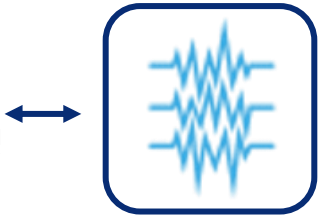

# The Baltimore declaration toward the exploration of organoid intelligence

Thomas Hartung[1,2*], Lena Smirnova[1], Itzy E. Morales Pantoja[1],
Akwasi Akwaboah[3], Dowlette-Mary Alam El Din[1],
Cynthia A. Berlinicke[4], J. Lomax Boyd[5], Brian S. Caffo[6],
Ben Cappiello[7], Tzahi Cohen-Karni[8,9], J. Lowry Curley[7],
Ralph Etienne-Cummings[3], Raha Dastgheyb[10],
David H. Gracias[11,12,13,14,15,16], Frederic Gilbert[17],
Christa Whelan Habela[10], Fang Han[18], Timothy D. Harris[19,20],
Kathrin Herrmann[1], Eric J. Hill[21], Qi Huang[11],
Rabih E. Jabbour[22], Erik C. Johnson[20], Brett J. Kagan[23],
Caroline Krall[1], Andre Levchenko[24], Paul Locke[1],
Alexandra Maertens[1], Monica Metea[25], Alysson R. Muotri[26,27],
Rheinallt Parri[28], Barton L. Paulhamus[20], Jesse D. Plotkin[1],
Paul Roach[29], July Carolina Romero[1], Jens C. Schwamborn[30],
Fenna Sillé[1], Alexander S. Szalay[31,32,33], Katya Tsaioun[1],
Daniel Tornero[34,35], Joshua T. Vogelstein[36], Karl J. Wahlin[37]
and Donald J. Zack[38,39,40,41]

# SURPASS project

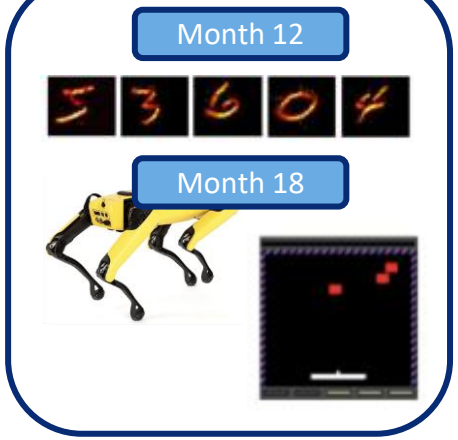
Track 1- Organoids

Track 4- Ethics



Track 2- Interfacing

Track 3- Data Analysis




Track 5- AI Demonstrations

## Organoids

## Data Analysis

## AI Demonstrations

## Interfacing

## Ethics

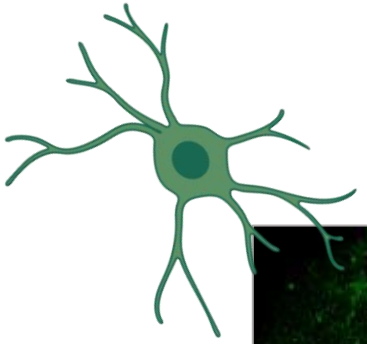
Johns Hopkins Whiting School of Engineering

Johns Hopkins Berman Institute of Bioethics

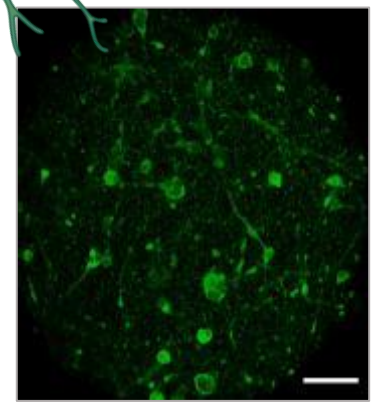
Johns Hopkins Applied Physics Laboratory

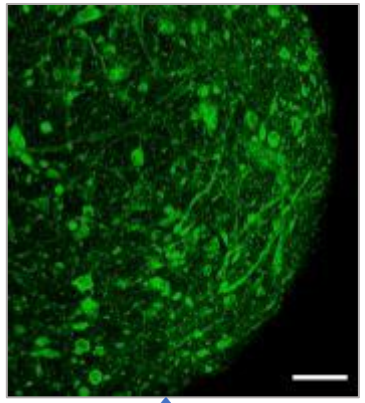
# Physiological Glia Numbers

## Adv. Biol. 2024



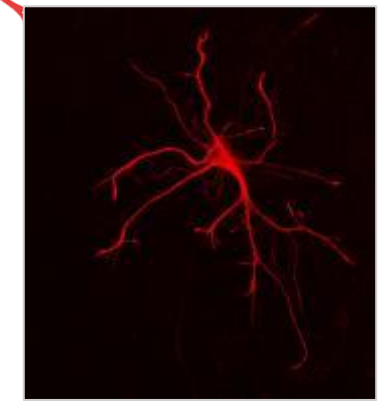
Astrocytes ⬆

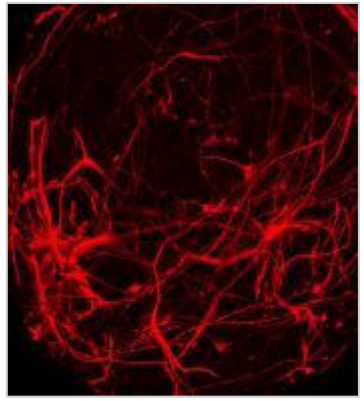


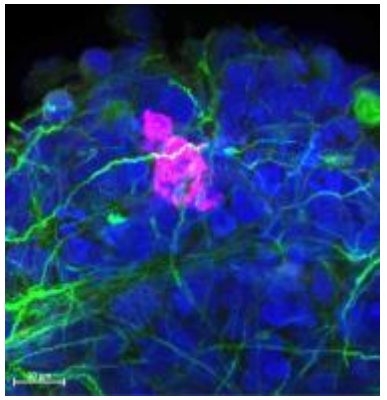


Added microglia


Oligodendrocytes ⬆

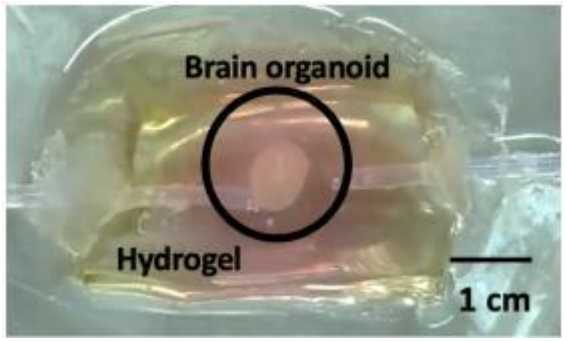






**Itzy Morales Pantoja**

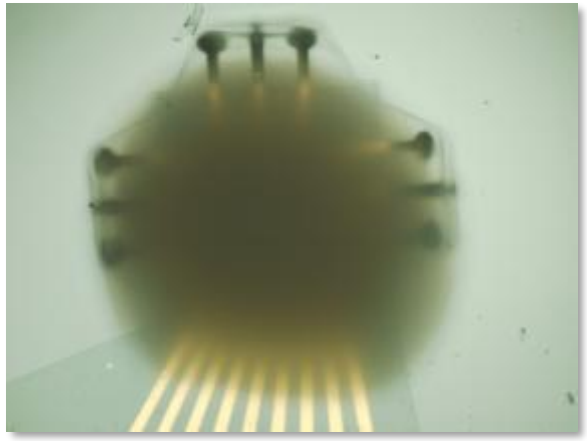
COLGATE-PALMOLIVE




- Scaling & perfusion

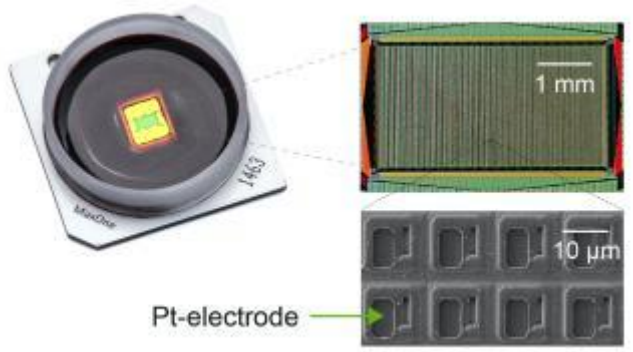
ongoing

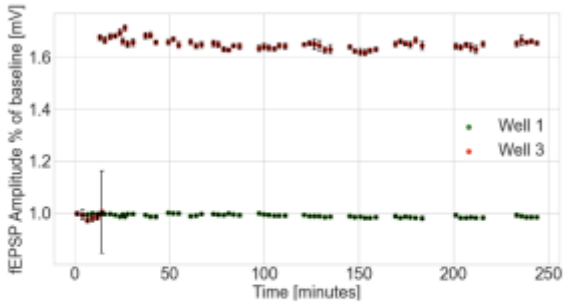
- Physiological glia ratio + micro-glia



- Electro-Physiology
- Ca-flux

maxwell BIOSYSTEMS

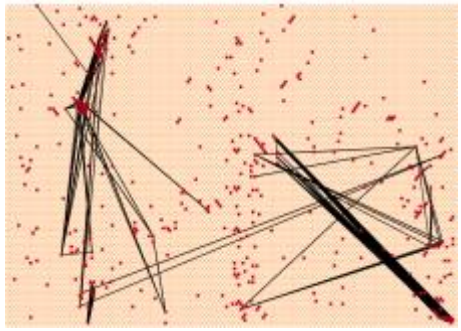


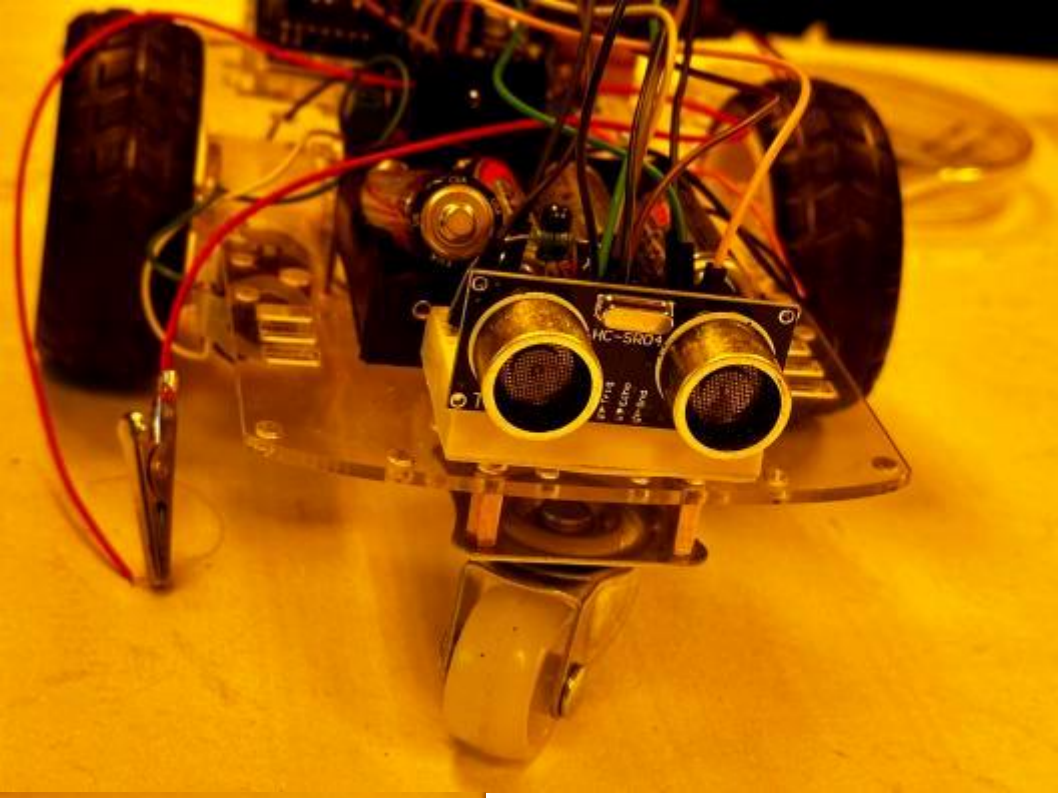



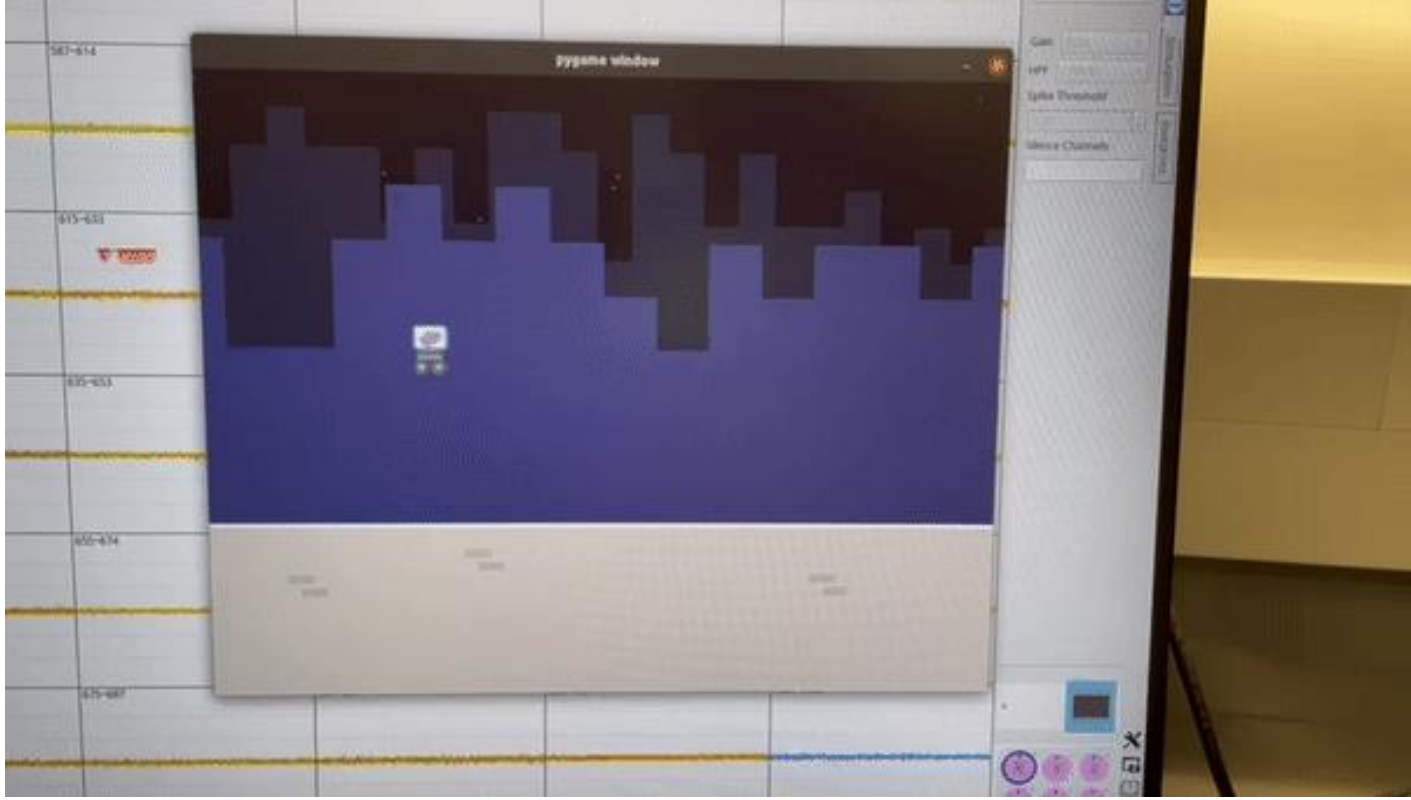

fEPSP – Excitatory Postsynaptic Potential

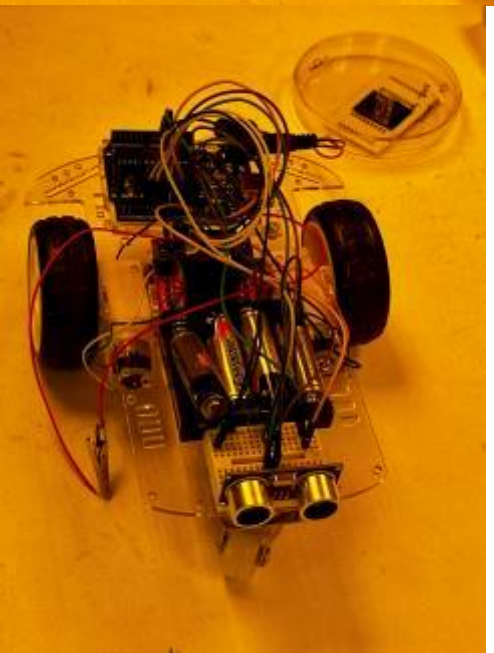
evoked not stimulated

- Long-term Potentiation
- Criticality
- Early genes ⇧
- Modulated by drugs





**Bluetooth-controlled by Brain Organoid**

**Brain Organoid playing video game over the internet**


# Renewal SURPASS
# Jul 2024 to Dec 2025

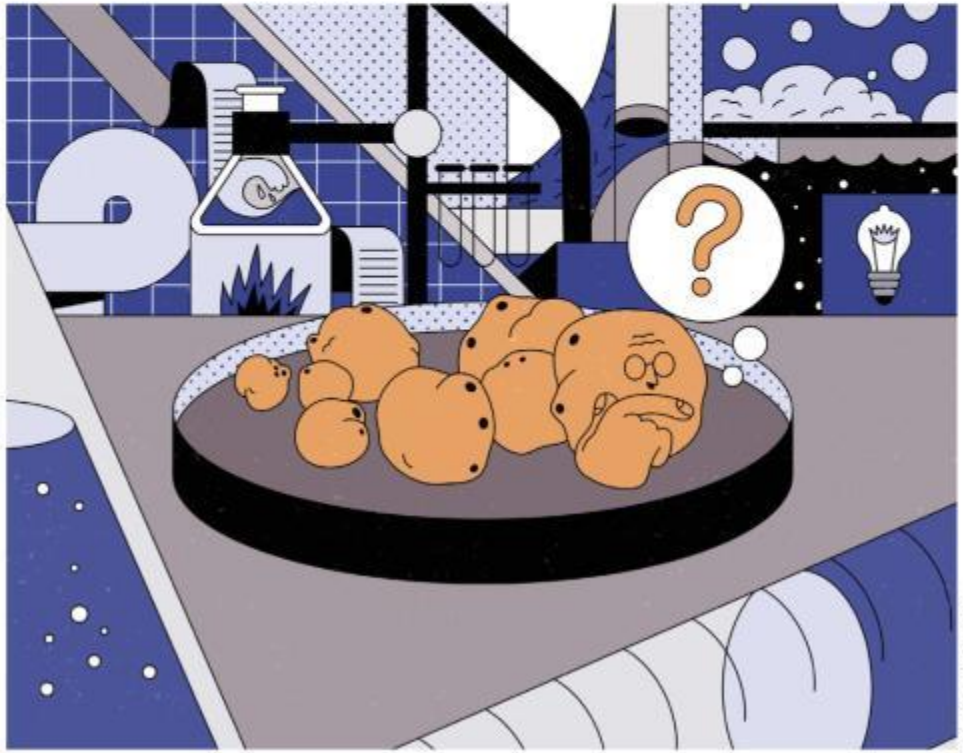
**Continuation scaling the model**
**Publication long-term learning**
**Incorporation of a reward center / zonation**
**Dissemination and fund raising**

Nature 20 Oct 2020

Feature

# Can lab-grown brains become conscious?

A handful of experiments are raising questions about whether clumps of cells and disembodied brains could be sentient, and how scientists would know if they were. **By Sara Reardon**







# Embedded Ethics

- **Criteria for physiological conditions of consciousness**
- **Rudimentary pain and suffering?**
- **Privacy concerns for iPSC donors**
- **Intellectual property**
- **Perception by public**

## Brain organoids and organoid intelligence from ethical, legal, and social points of view

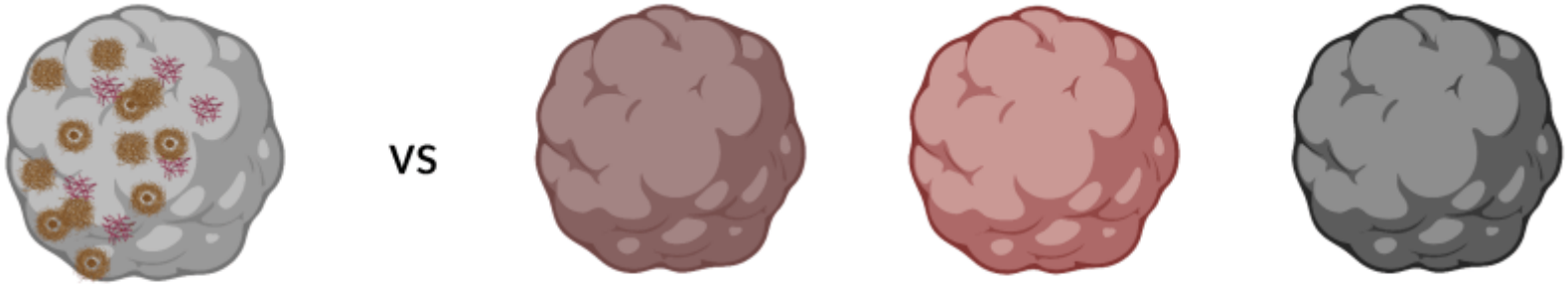
Thomas Hartung[1,2*], Itzy E. Morales Pantoja[1] and Lena Smirnova[1]

# Understand similarities and differences across types of dementia

Food for Thought ...

**Organoid Intelligence (OI) – The Ultimate Functionality of a Brain Microphysiological System**

*Lena Smirnova[1], Itzy E. Morales Pantoja[1] and Thomas Hartung[1,2]*



Alzheimer's organoid

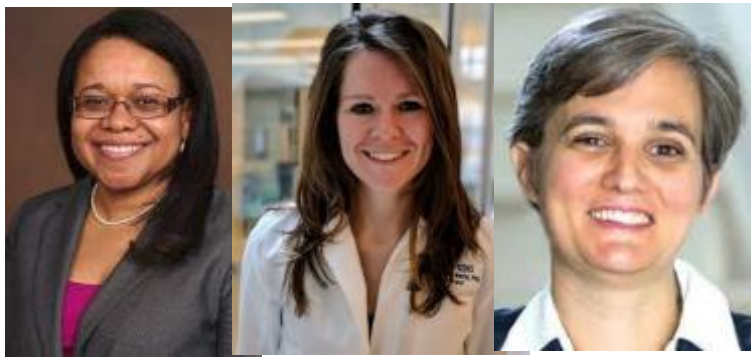
vs

Other types of dementia and neurodegenerative diseases

Vasiliki Machairaki
Kostas Lyketsos
AD

Jiou Wang
ALS

Christine Ladd-Acosta
& Heather Volk
Autism



Constance Smith-Hicks
Christina Nemeth Mertz
Adeline Vanderver
Leukodystrophies

Dementia OI Research Initiative

UNDER CONSTRUCTION

Generated with DALL-E and LeiaPix

- Integrate Disruptive Technologies with Existing Knowledge
- Accelerate Drug Development
- Optimize Prevention and democratize Healthcare Access

The Smart Path Forward

- Open access, machine readable
- Identify bias in data, explainable AI
- Mechanistic MPS and evidence-based approaches
- Organoid Intelligence (OI)

**Slides available:**