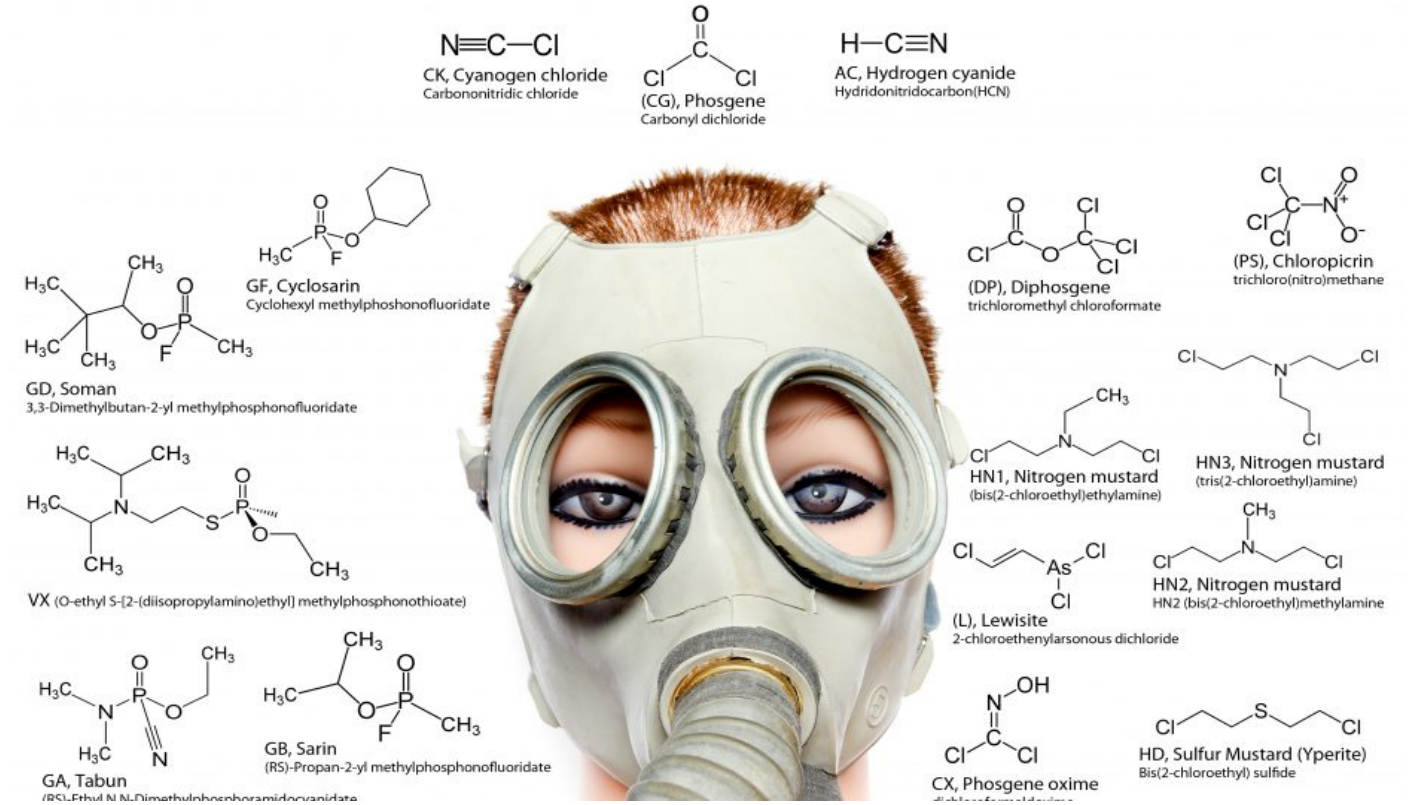
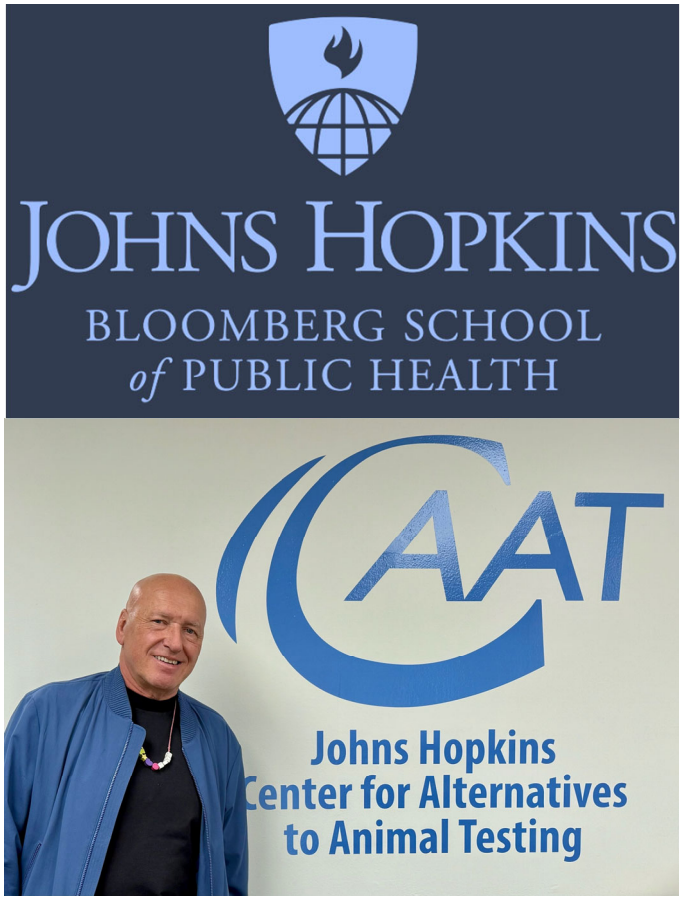
Computational methods for efficacy generation: how far are we?

Thomas Hartung





Slides available:https://share.zight.com/7Ku90L2Q

Chemicals

Pathogens

Terrorism & Warfare

Drugs & Countermeasures

… but no patients to test on.

NAS committee

Food for Thought ...
Alternative Approaches for Medical Countermeasures to Biological and Chemical Terrorism and Warfare

Thomas Hartung [1,2] *and Joanne Zurlo* [1]

[1]Johns Hopkins University, Bloomberg School of Public Health, CAAT, Baltimore, USA; [2]University of Konstanz, CAAT-Europe, Germany

ALTEX. 2012;29(3):251-60.

not warranted at this time … utilizing alternative methods to animal models”

CAS Registry Numbers: more than 200+ million unique organic and inorganic substances

APRIL 21, 2022 | 4 MIN READ

AI Drug Discovery Systems Might Be Repurposed to Make Chemical Weapons, Researchers Warn

SCI AM

A demonstration with drug design software shows the ease with which toxic molecules can be generated

BY REBECCA SOHN EDITED BY GARY STIX

alengo/Getty Images

AI can identify threat agents

Dual use of artificial-intelligence-powered drug discovery

An international security conference explored how artificial intelligence (AI) technologies for drug discovery could be misused for de novo design of biochemical weapons. A thought experiment evolved into a computational proof.

Fabio Urbina, Filippa Lentzos, Cédric Invernizzi and Sean Ekins

Nat Mach Intell **4**, 189–191 (2022).
https://doi.org/10.1038/s42256-022-00465-9

Big data and artificial intelligence allow now to identify toxic substances for bad or good...

Collaboration

2016:
Standardized Brain Organoids from induced pluripotent stem cells

Autism
COVID-19
Glioblastoma....

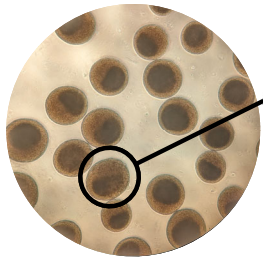
Lena Smirnova

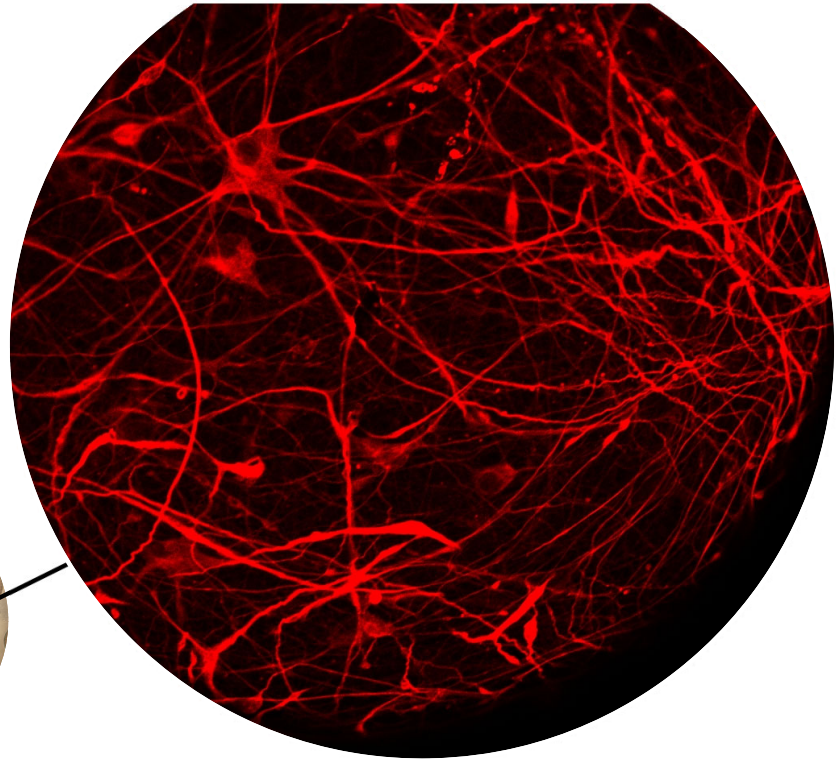
REVIEW

ADVANCED HEALTHCARE MATERIALS
www.advhealthmat.de

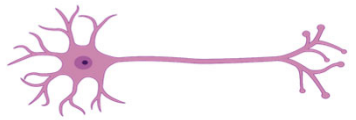
The Promise and Potential of Brain Organoids

Lena Smirnova and Thomas Hartung**

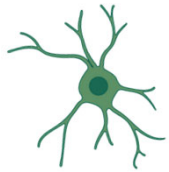




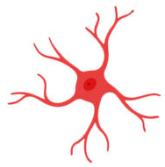
Neurons



Oligodendrocytes



Astrocytes



Standardized | Reproducible | Mass-produced | Genetic background of donor/patient

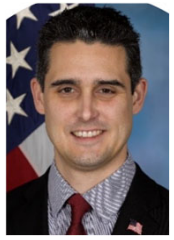
Seizurogenic model to study nerve agents and countermeasures

iPSC-derived microglia

Incorporation of microglia into brain organoids

Induction of Neuroinflammation

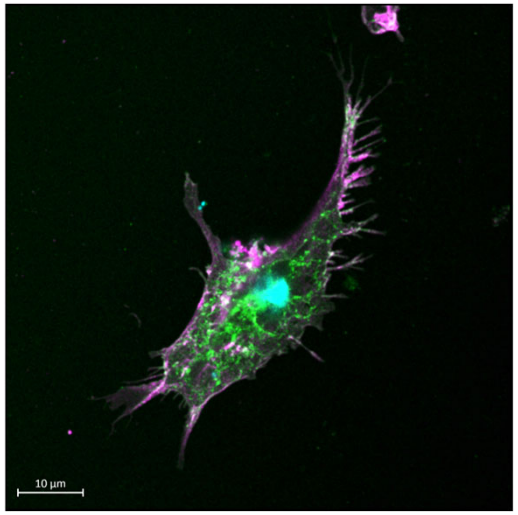
K. Glover



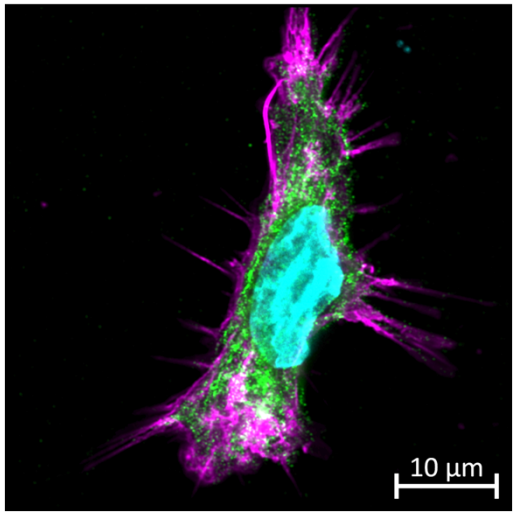
J. Plotkin

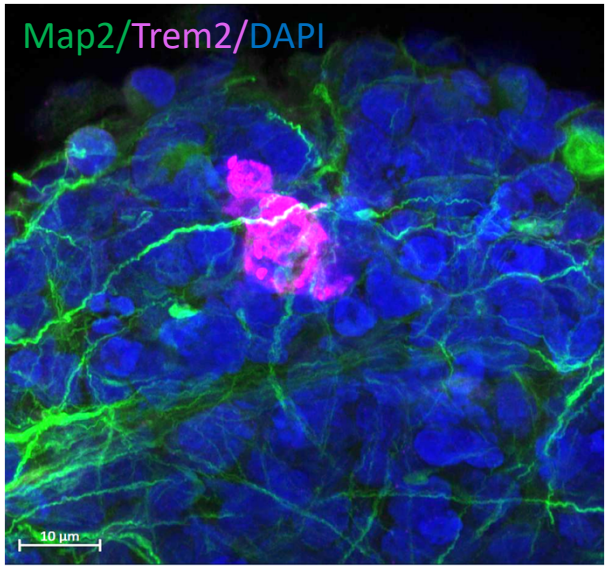
C. Krall

DAPI CD11b actin



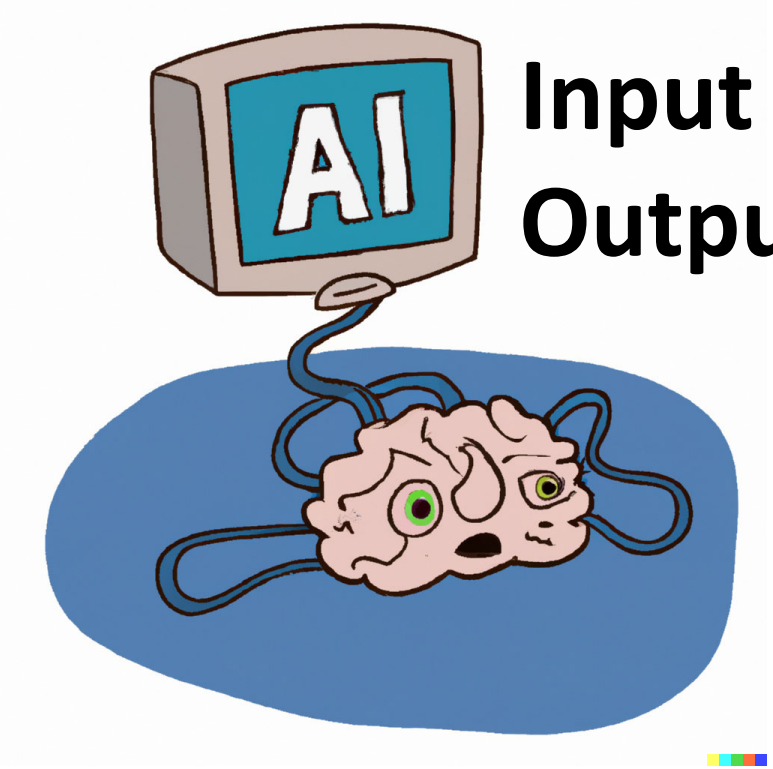
DAPI TREM2 actin



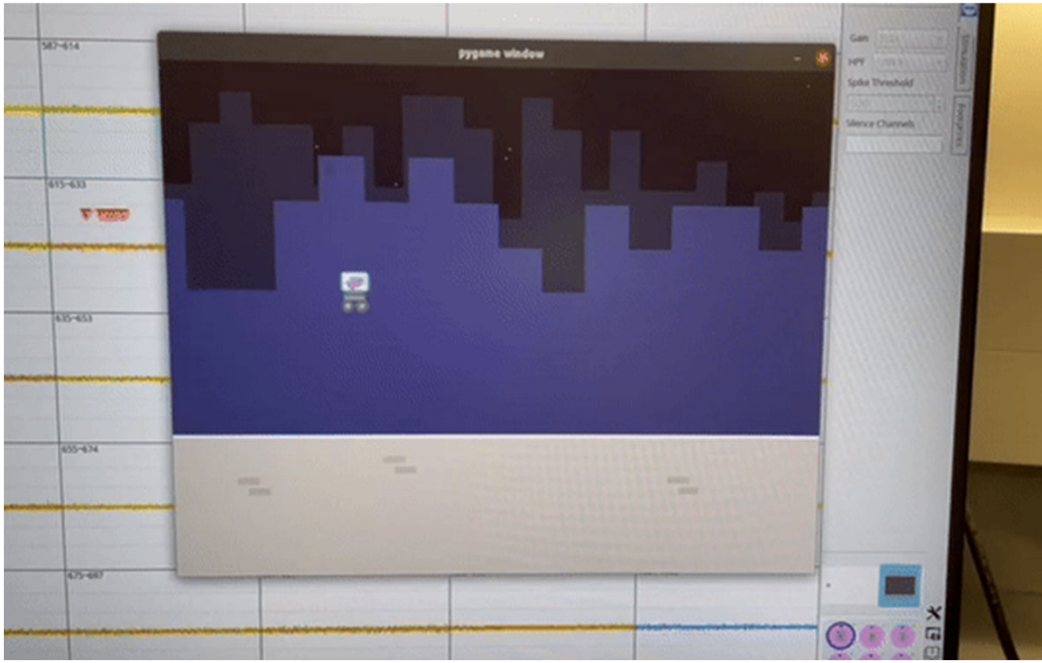


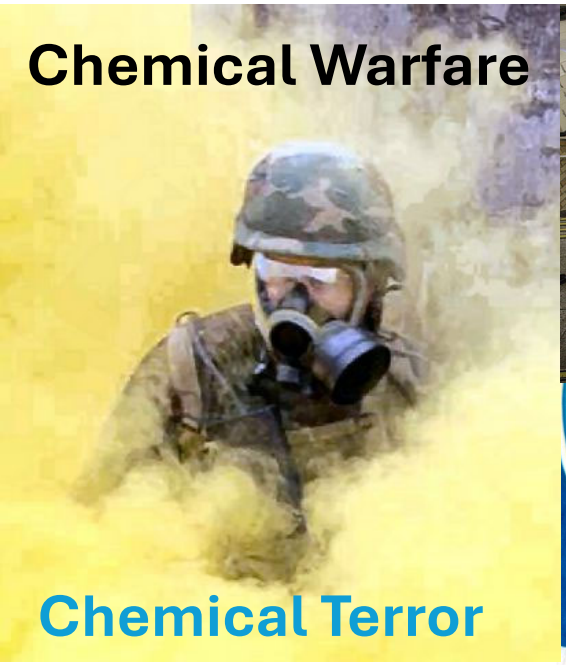
CRADA with CCDC, DoD

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



Input & Output





Tokyo
20 March 1995
Aum Sect

AI can predict toxicity
AI can help synthetize

On the positive side:

- AI can map toxicity space
- AI can identify chemicals used
- AI can trace synthesis efforts
- AI can help design medical countermeasures (w/o patients and good animal models)

ToxAIcology

Big Data

- High-content (~omics & imaging)
- High-throughput (Robotized testing, e.g., Tox21 & ToxCast)
- Sensors
- Literature, Internet
- Legacy studies

Big Computer

AI & Machine Learning

- Natural Language Processing (Large Language Models)

Big Sense

- Data retrieval
- Evidence integration (systematic reviews, risk assessments)
- Predictive toxicology
- Digital pathology
- Reporting

The NOW

frontiers | Frontiers in Artificial Intelligence

Artificial intelligence as the new frontier in chemical risk assessment

Thomas Hartung[1,2]*

Archives of Toxicology
https://doi.org/10.1007/s00204-023-03666-2

REVIEW ARTICLE

Artificial intelligence (AI)—it's the end of the tox as we know it (and I feel fine)*

Nicole Kleinstreuer[1] · Thomas Hartung[2,3]

Food for Thought ...

ToxAIcology – The Evolving Role of Artificial Intelligence in Advancing Toxicology and Modernizing Regulatory Science

Thomas Hartung[1,2]

The NEW

What's new?

AI =

Broad availability of LLM foundational models

Context and search capabilities

Big Data

AI reads scientific papers

Access to databases

Multi-modal

Unstructured

Big Computer

Cloud access to large models; local models

Federated learning

Price ⬇

Big Sense

Data retrieval from open access

Evidence-integration

Explainable AI

EVIDENCE-BASED TOXICOLOGY
2025, VOL. 3, NO. 1, 2520764
https://doi.org/10.1080/2833373X.2025.2520764

Taylor & Francis
Taylor & Francis Group

MEETING REPORT

OPEN ACCESS Check for updates

Present and future of AI, open science, and transparency in regulatory science

Katherine Tsaioun[a], Thomas Hartung[a], Sebastian Hoffmann[a,b], Ákos Bernard Jóźwiak[c,d] and Mathieu Vinken[e]

Scaling of our own work 2015-2025

	2015	2016	2018	2020	2022	2023	2025
Hazards	One hazard			to		all properties	
Data	~1000			to		~260 million	
Chemicals predicted	~150			to		~120 million	
Accuracy	~65%			to		~90%	
Method	Random Forrest	KNN		Random Forrest	Random Forrest	Random Forrest	Transformer
	Luechtefeld et al. 2015	Luechtefeld et al. 2016	Luechtefeld et al. 2015	Golden et al. 2016	Fu et al., 2022	Luechtefeld et al. 2023 (poster)	In preparation

BioBricks.ai
Faster Informatics

```
$ biobricks install tox21
$ python
>>> import biobricks, pandas
>>> tx21 = biobricks.load('tox21')
>>> tx21.tox21.read().load()
#        SAMPLE_ID  PROTOCOL_NAME  ...                SMILES  ...
# NCGC00256074-01  tox21-ache-p3  ...          OCC(=O)OCCCC  ...
# NCGC00255047-01  tox21-ache-p3  ...  Nc1ccc(cc1)C(=O)OCC  ...
# [2075022 rows x 19 columns]
```

frontiers | Frontiers in Artificial Intelligence

TYPE Original Research
PUBLISHED 13 August 2025
DOI 10.3389/frai.2025.1599412

Check for updates

OPEN ACCESS

ilth

dom

BioBricks.ai: a versioned data registry for life sciences data assets

Yifan Gao[1], Zakariyya Mughal[2], Jose A. Jaramillo-Villegas[3,4], Marie Corradi[5], Alexandre Borrel[6†], Ben Lieberman[2], Suliman Sharif[2], John Shaffer[2], Karamarie Fecho[7,8], Ajay Chatrath[9], Alexandra Maertens[1], Marc A. T. Teunis[5], Nicole Kleinstreuer[10], Thomas Hartung[1,11] and Thomas Luechtefeld[1,2*]

ONTOX

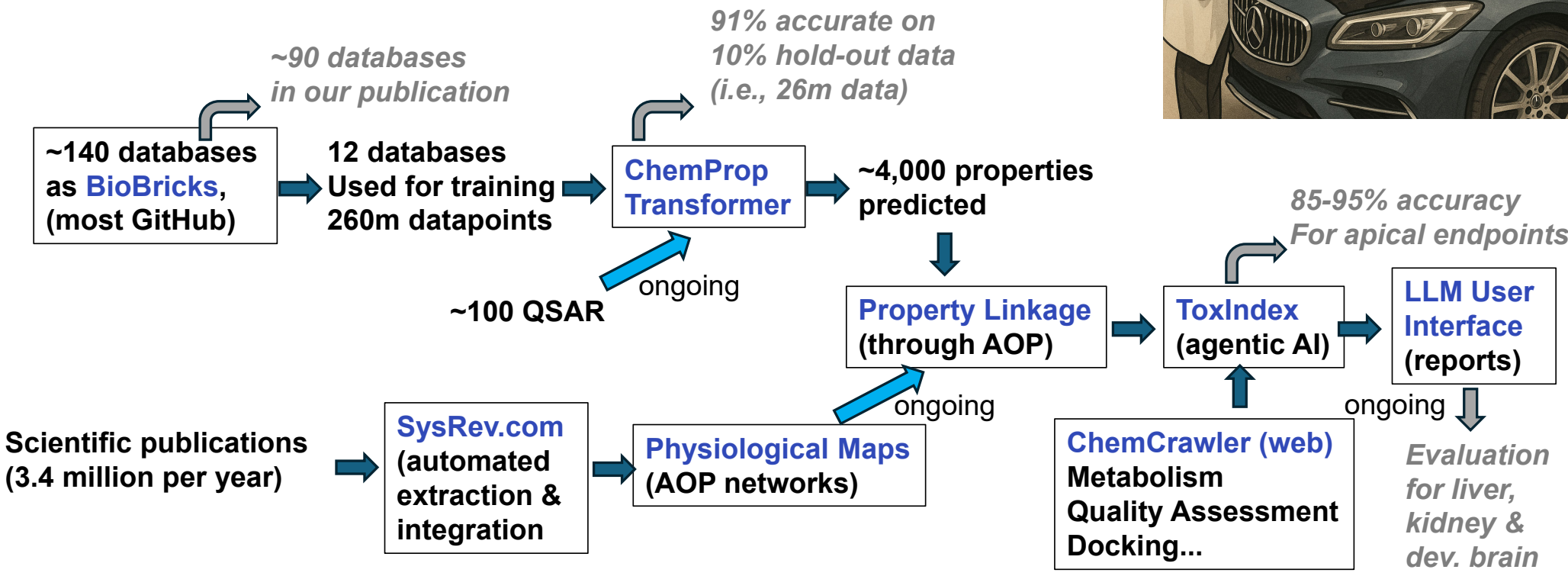
Current model

~140 databases made importable (BioBrick.ai)
12 of these:

- **117 million chemicals**
- **254 million chemical activities**
- **4026 'big properties' with 1000+ activities**

Prediction accuracy 91%

Data and & AI are at the core of ONTOX - let's look a bit under the hood!



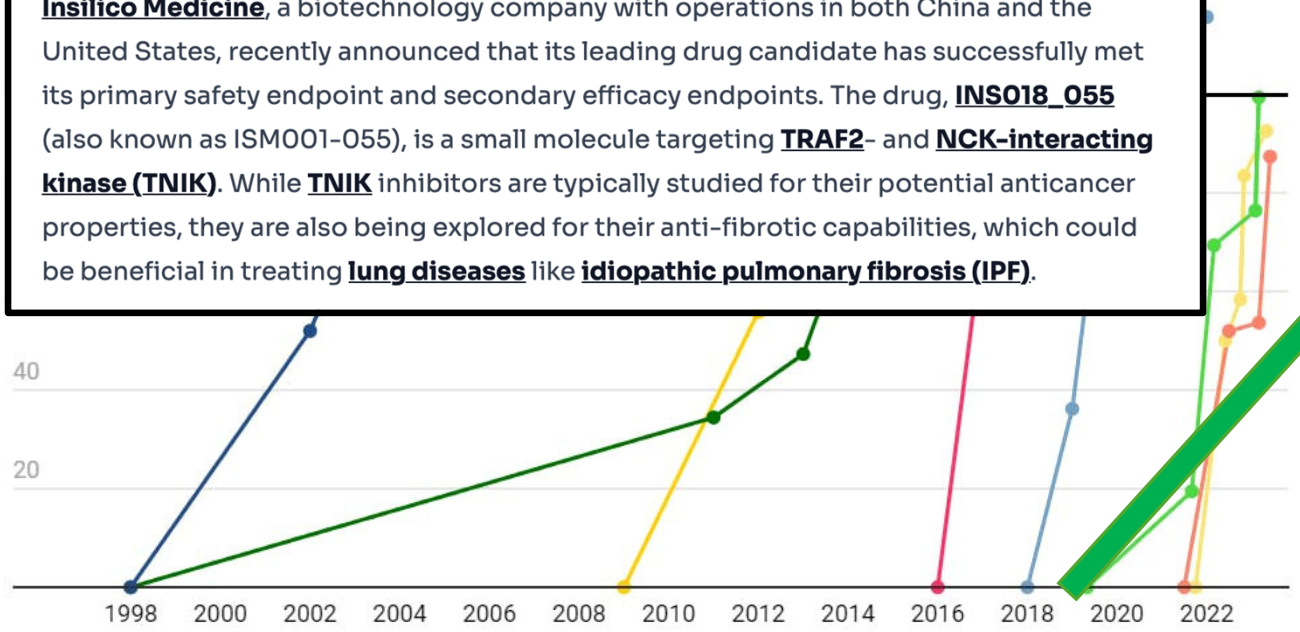
Insilico Medicine announces phase 2 success for AI-designed drug

26 September 2024 |

Insilico Medicine, a biotechnology company with operations in both China and the United States, recently announced that its leading drug candidate has successfully met its primary safety endpoint and secondary efficacy endpoints. The drug, **INS018_055** (also known as ISM001-055), is a small molecule targeting **TRAF2**- and **NCK-interacting kinase (TNIK)**. While **TNIK** inhibitors are typically studied for their potential anticancer properties, they are also being explored for their anti-fibrotic capabilities, which could be beneficial in treating **lung diseases** like **idiopathic pulmonary fibrosis (IPF)**.

2022: 18 AI-first into human trials
2023: InSilico Med into phase 2a
2024: phase 2b

Drug Devlopment

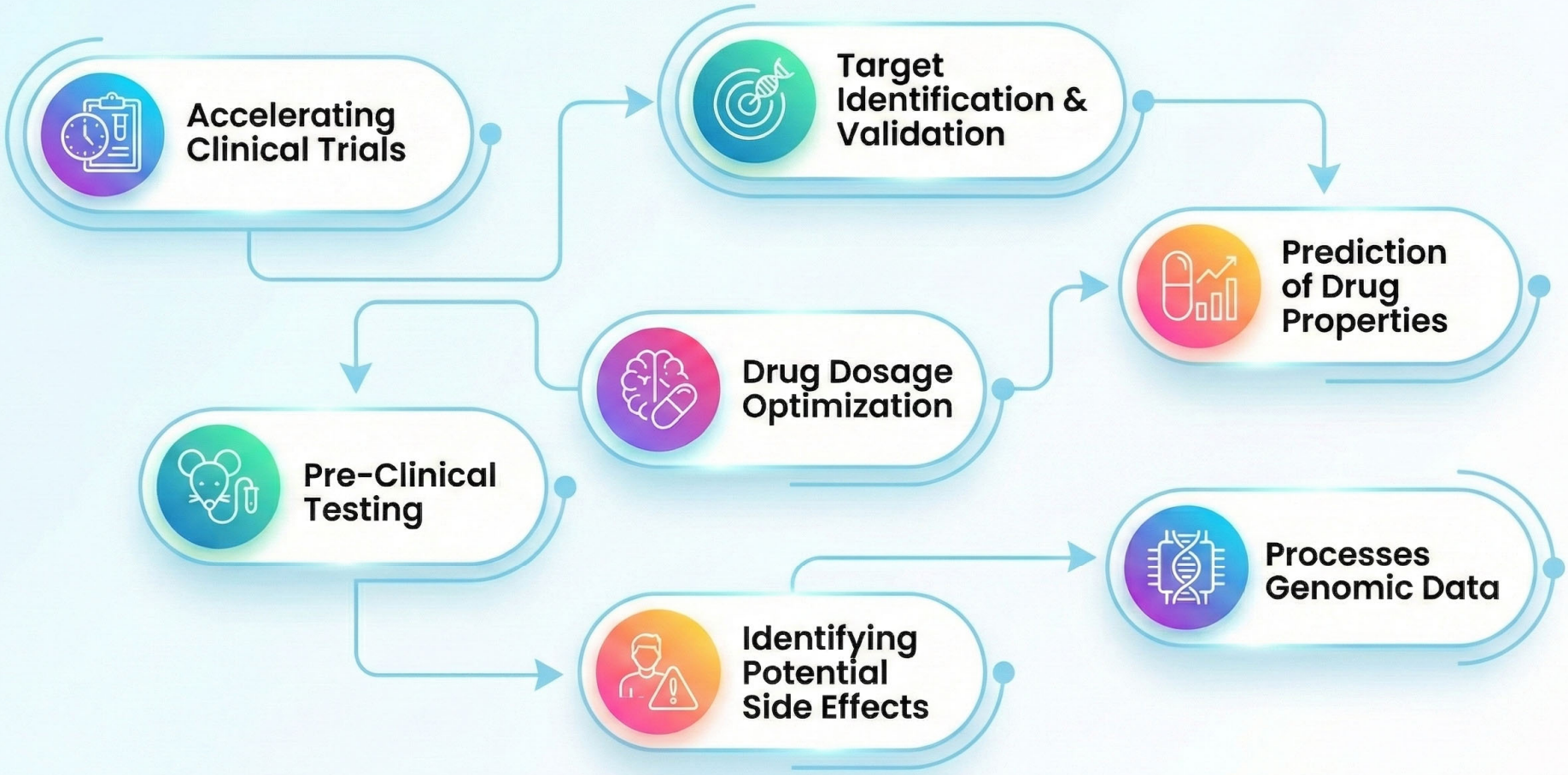


For each benchmark, the maximally performing baseline reported in the benchmark paper is taken as the "starting point", which is set at 0%. Human performance number is set at 100%. Handwriting recognition = MNIST, Language understanding = GLUE, Image recognition = ImageNet, Reading comprehension = SQuAD 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

7 WAYS AI IS TRANSFORMING DRUG DEVELOPMENT



The Next
- Building trust
- Deploy ToxAIcology

npj | digital medicine

Perspective

Published in partnership with Seoul National University Bundang Hospital

https://doi.org/10.1038/s41746-025-01596-0

Is regulatory science ready for artificial intelligence?

Check for updates

Thomas Hartung[1,2], Maurice Whelan[3], Weida Tong[4] ✉ & Robert M. Califf[5]

See evil, hear evil, and speak about evil!

Thartung@jhu.edu

Slides available:https://share.zight.com/7Ku90L2Q