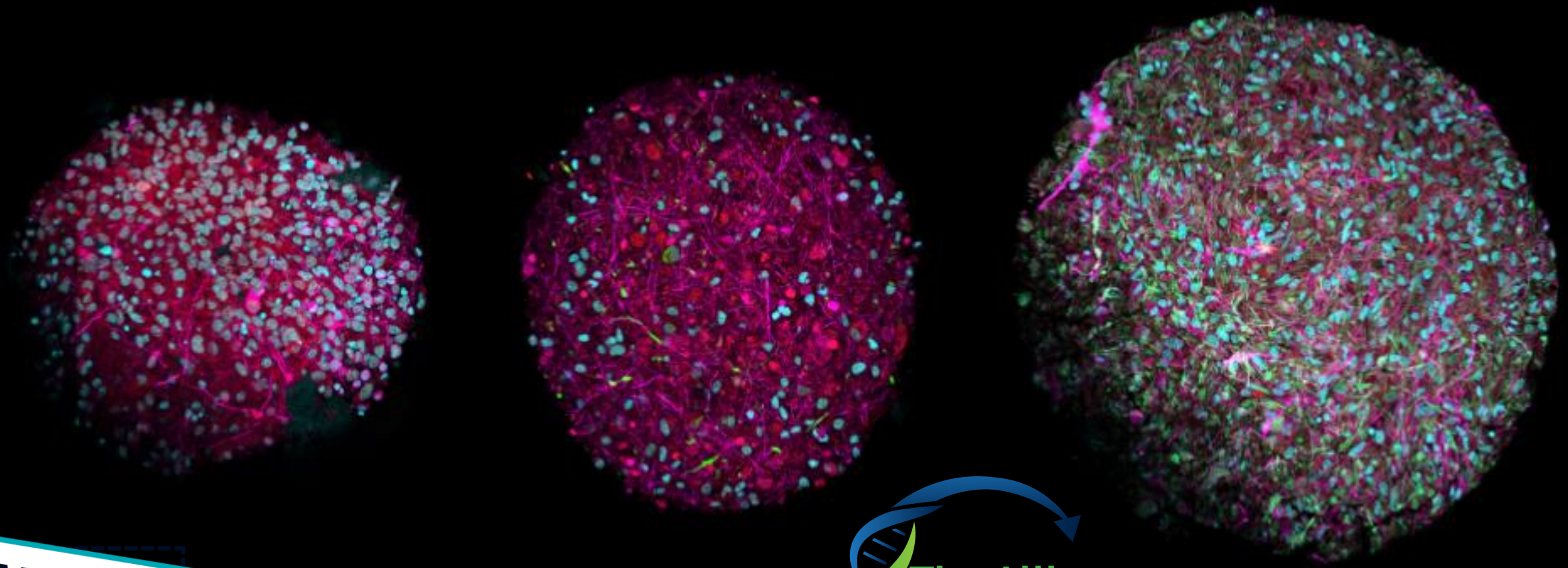
The Alliance Exchange

Talking Human Relevant Science

New Approach Methodologies (NAMs) and their relevance to human research and drug development

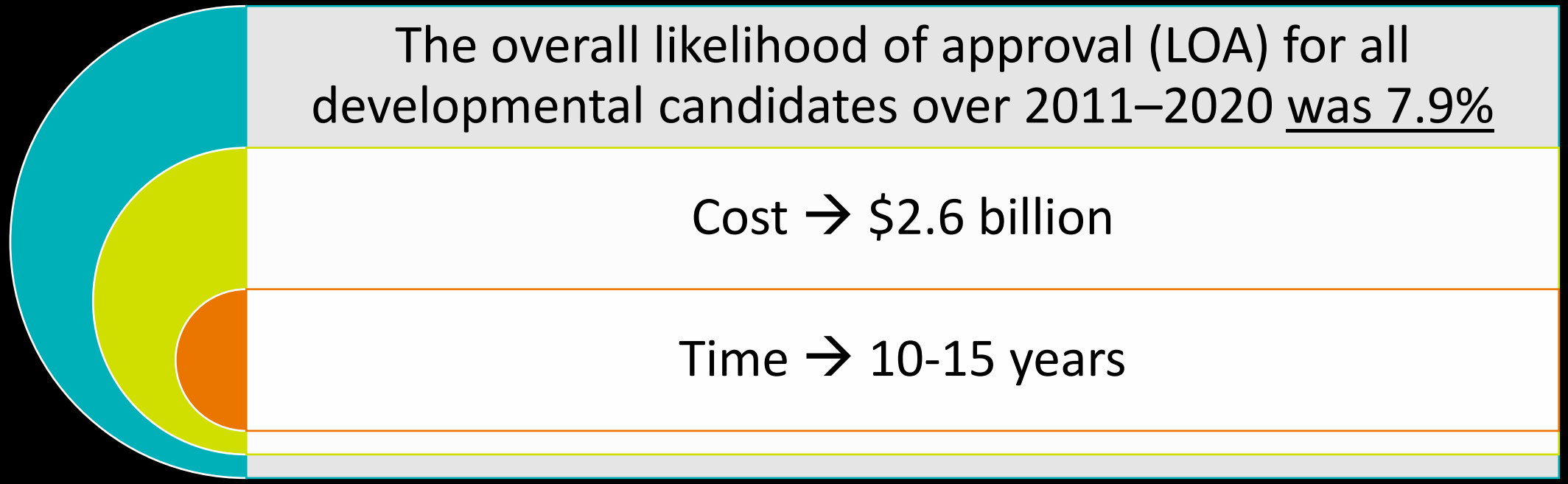


Dr Lilas Courtot

Science Manager

May 22nd 2023

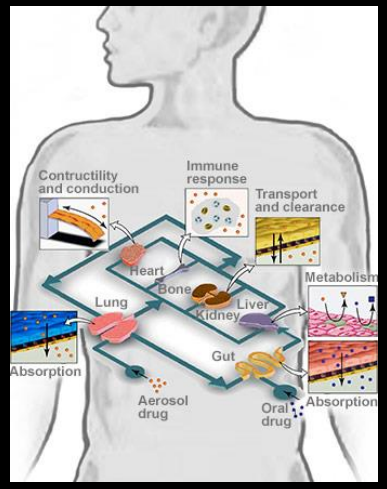
Drug Development: a ‘Business’ in Crisis



With over 90% failure rate, NO other sector has such figures and continues to exist with the bravado of business as usual...

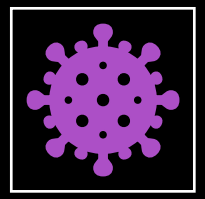
Source: https://pharmaintelligence.informa.com/resources/product-content/2021-clinical-development-success-rates

Presentation Outline



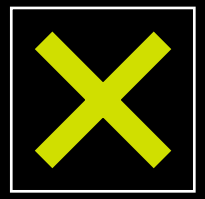
- Lost in translation – why animal studies are failing R&D
- Inertia towards New Approach Methodologies (NAMs)
- In vitro: from 2D cell model to Organ-On-Chip
- In silico: Big data, AI and computer modelling
- Current and Future Challenges and Opportunities

Lost in Translation – Why animal studies are failing R&D



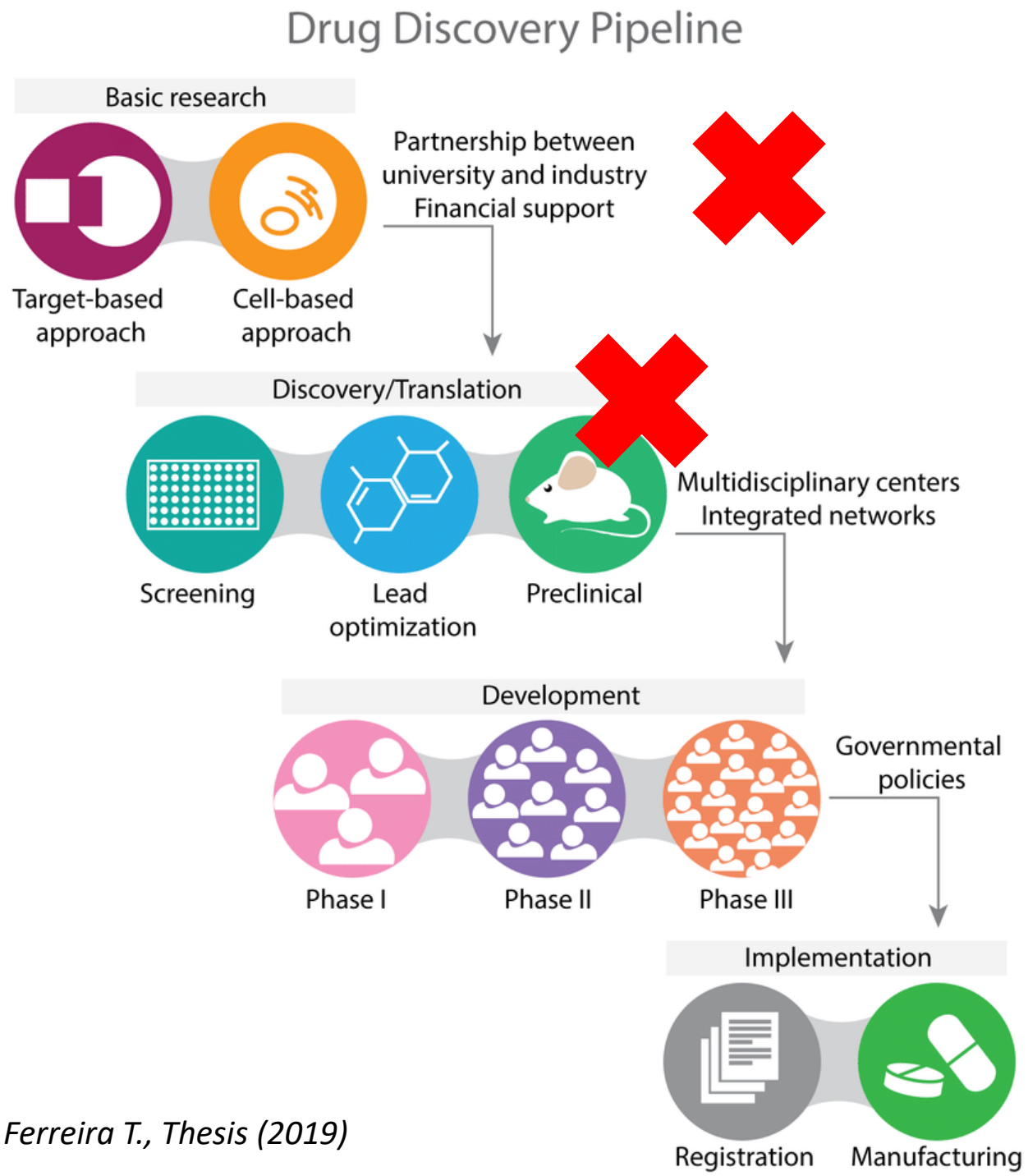
Several thousand human diseases, only ~500 have treatments available

Many years of high-cost failures (ethical and financial)



Translation failure due to inadequate preclinical models

Too much reliance on animals



Ferreira T., Thesis (2019)

Key issues with animal studies

- Low predictivity (>90% failure)
- No specificity (not humans)
- Low reproducibility
- Risk of missing targets
- Not ethical

Lost in Translation – Why Animal Studies Are Failing R&D

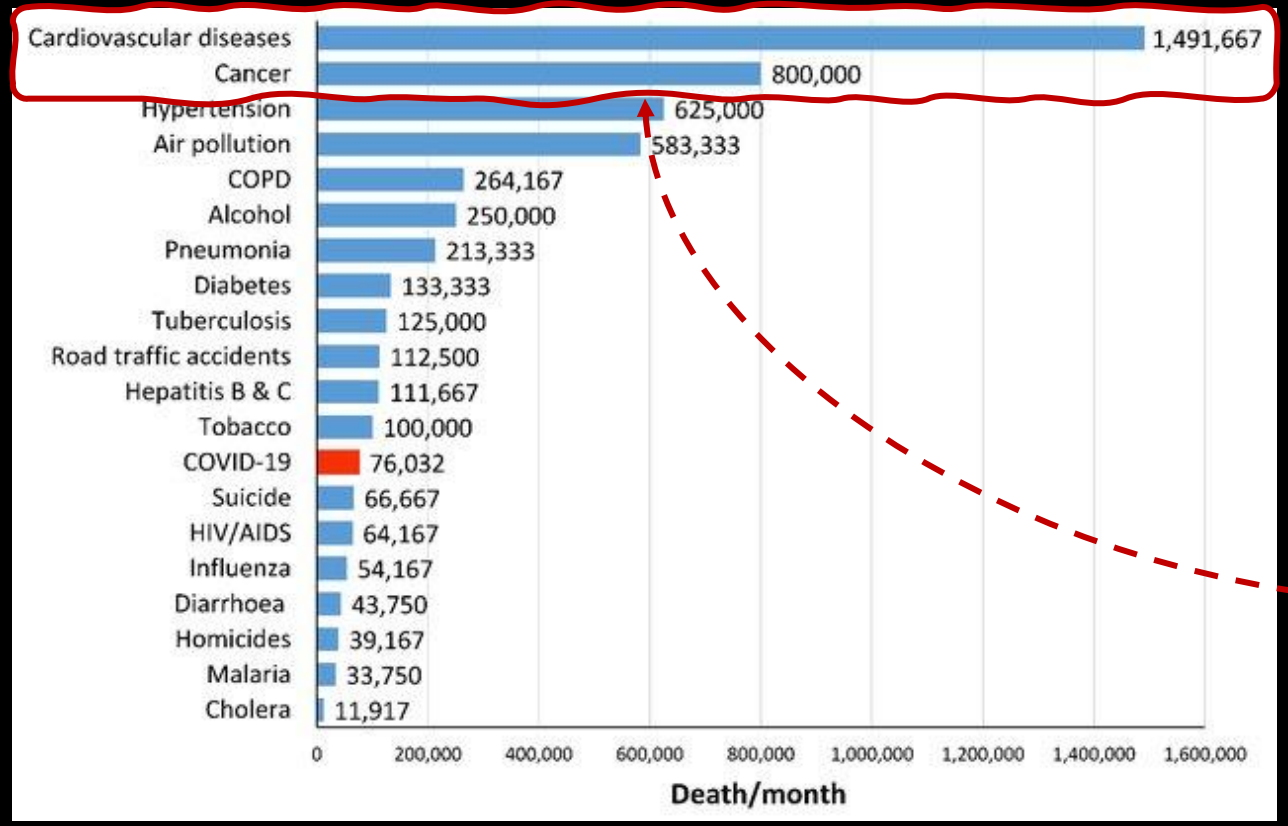
Key observations and facts
Only 1/3 of highly cited animal research tested in human trials
Overestimate by about 30% treatment effectiveness
41% to 89% differences in gene regulation between human and mouse
Significant metabolic difference between human and mouse
Other cells or mechanisms, leading to misinterpretation

Animal studies = poor science

- No best practice standards exist
- Lab environment (stress, food etc.)
- No gender or age balance
- Unpublished negative results
- Focusing on the wrong ‘whole organism’

Developing new drugs is an Emergency

Leading causes of death worldwide in 2018



Overall Likelihood of Drug Approval by Disease Area

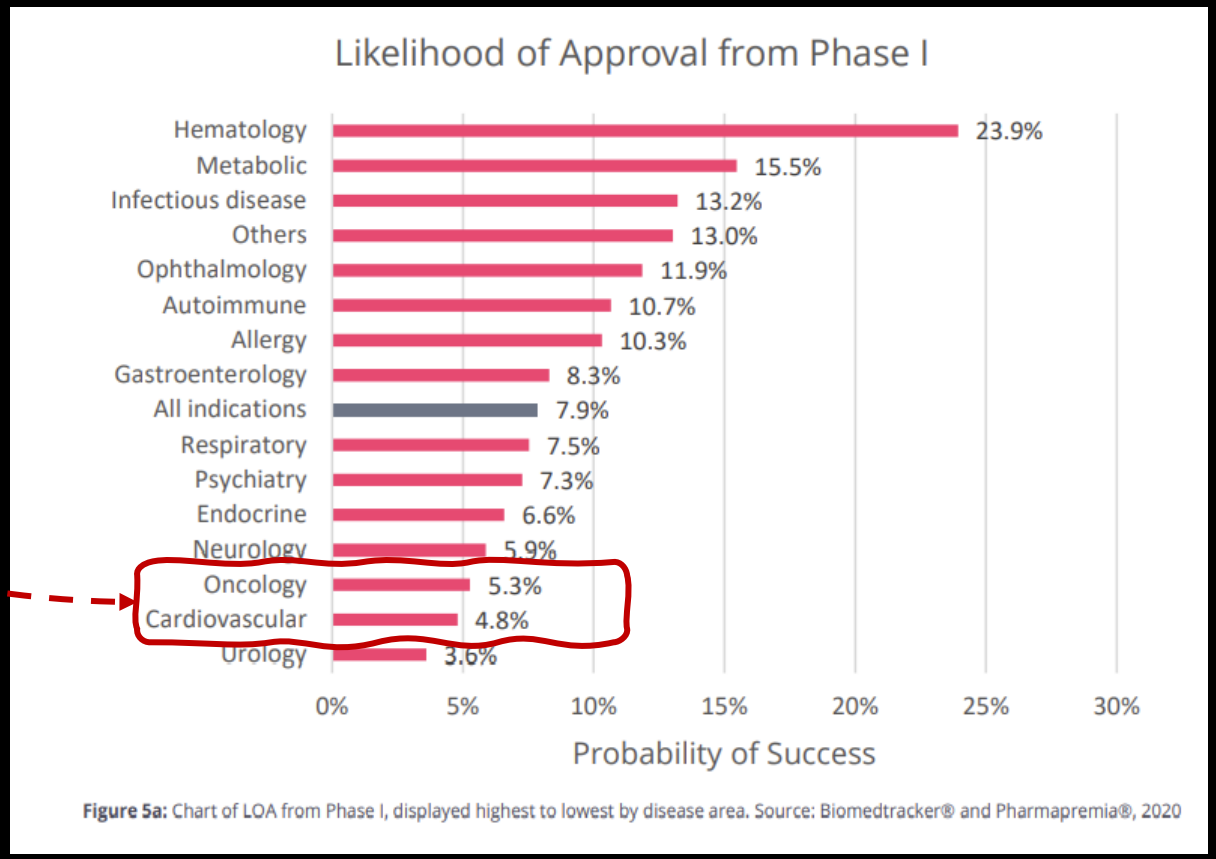


Figure 5a: Chart of LOA from Phase I, displayed highest to lowest by disease area. Source: Biomedtracker® and Pharmapremia®, 2020

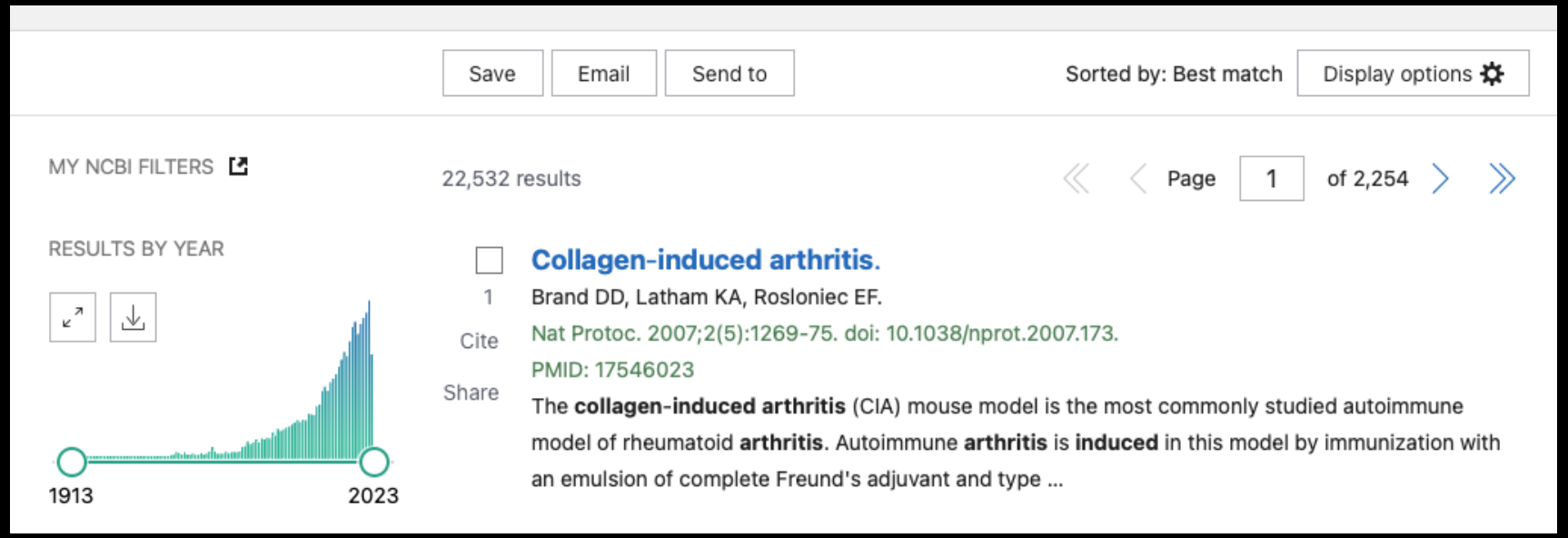
Based on the World Health Organization (WHO) report 2018

The Case of Rheumatoid Arthritis

Over the last 10 years…

9,665 papers + **Almost 1M mice** = **Zero available drug**

Time to switch to new and more human-focused models



Inertia towards New Approach Methodologies (NAMs)

Neuroethics and

Th

L. Syd

Pound and Ritskes-Hoitinga *J Transl Med* (2018) 16:304

Journal of cine

Limitations of Animal Studies for

F

Is

animals

MDPI

Commentary

Modernizing Medical Research to Benefit People and Animals

Review Article

Lost in translation: a cancer treatment

Special Section: Moving Fo

The Flaws and Humai
Experimentation

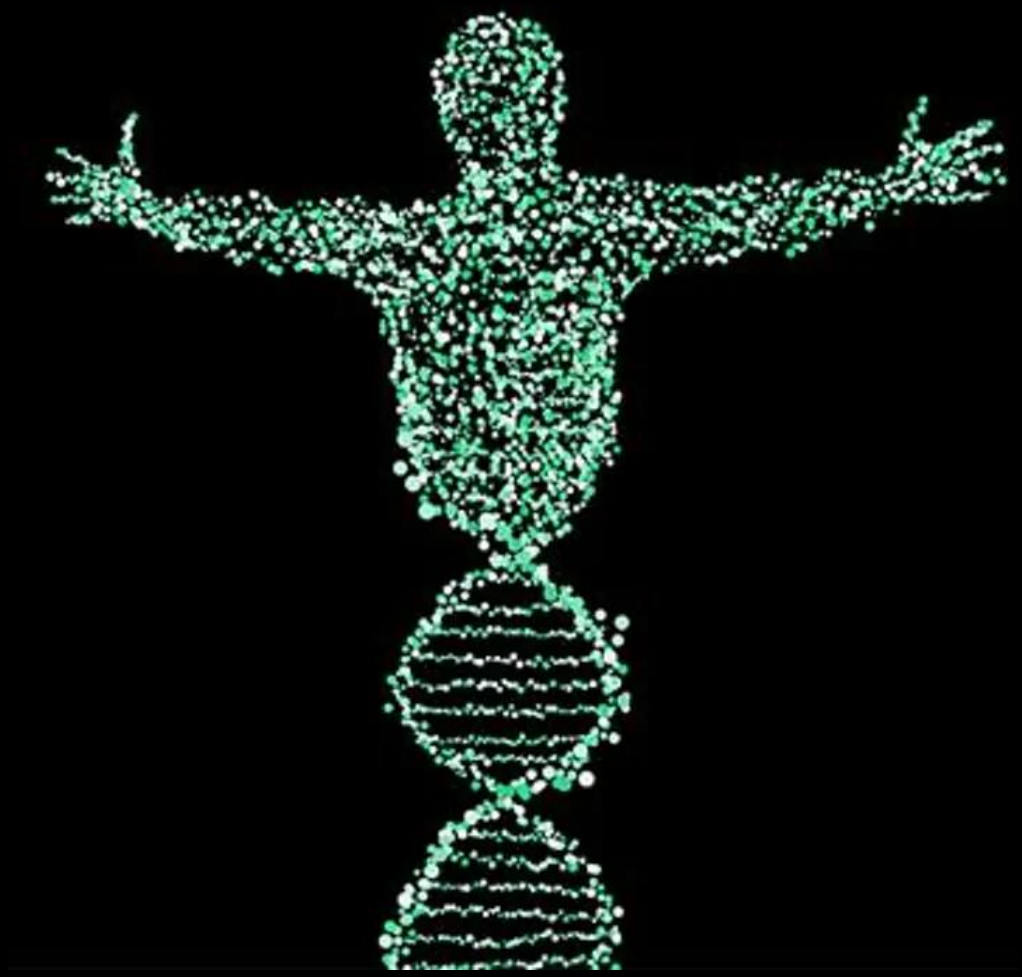
th Animal Models

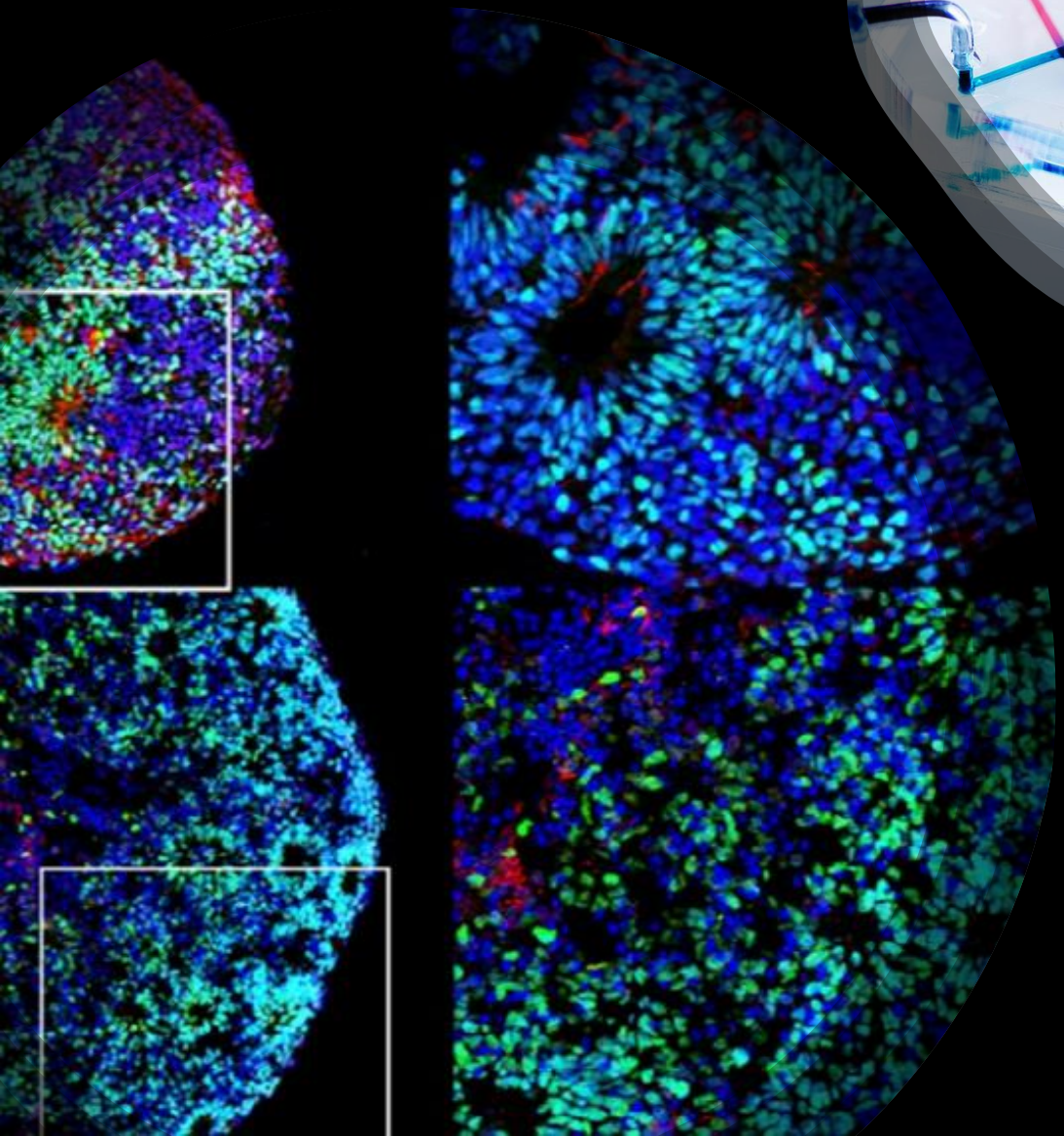
Anais da Academia Brasileira de Ciências (2019) 91(Suppl. 1): e20170238
(Annals of the Brazilian Academy of Sciences)
Printed version ISSN 0001-3765 / Online version ISSN 1678-2690
http://dx.doi.org/10.1590/0001-3765201720170238
www.scielo.br/aabc | www.fb.com/aabcjournal

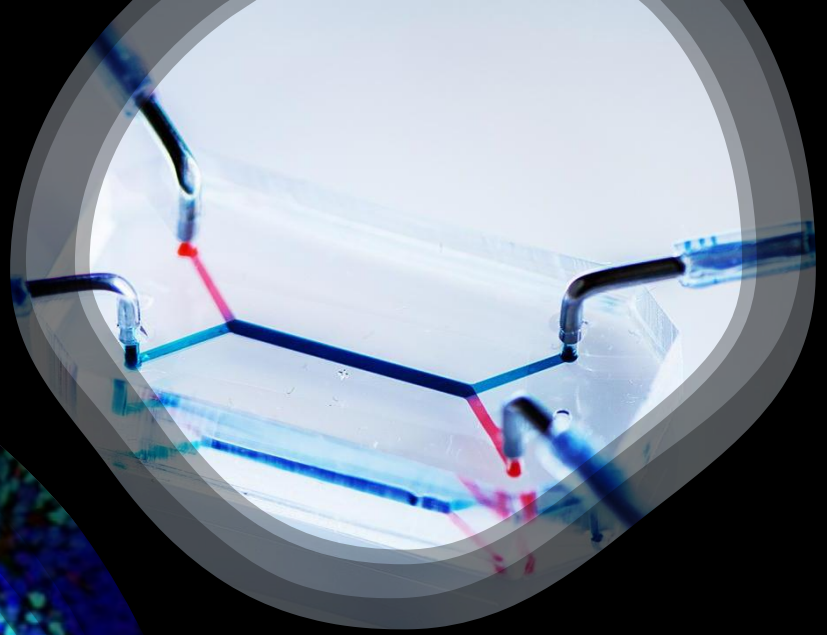
ACADEMIA BRASILEIRA DE CIÊNCIAS

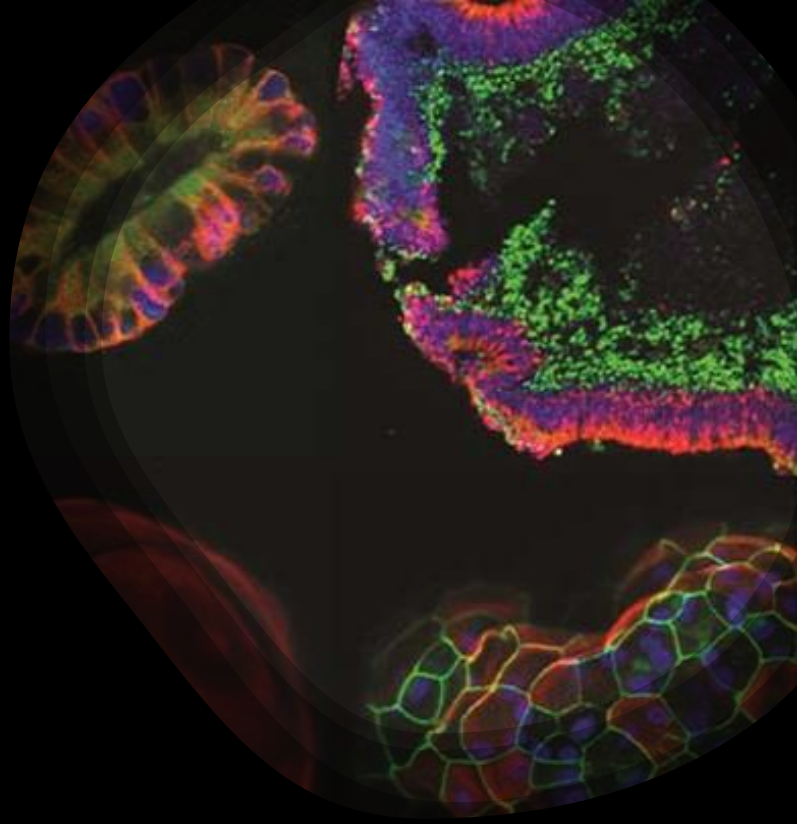
Animal models in biological and biomedical research – experimental and ethical concerns

To accelerate breakthroughs in research and drug development there is an urgent need to use the potential of human model systems offered by New Approach Methodologies (NAMs)





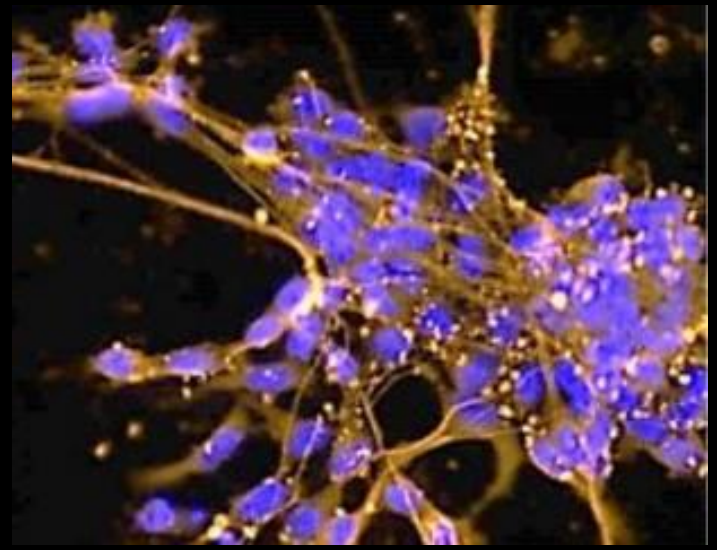




In vitro human-based models

Human-derived 2D *in vitro* models

iPSC, mono-layers, spheroids, co-culture

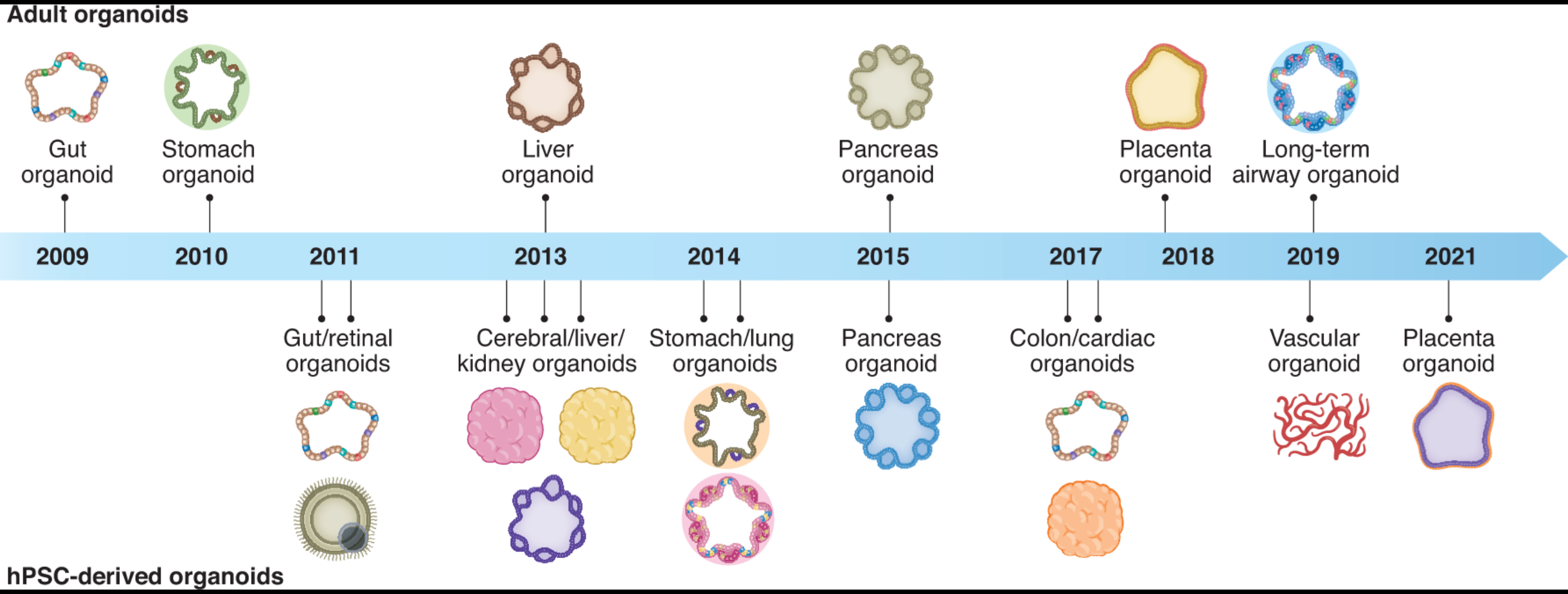


Cassotta et al., ALTEX (2022)

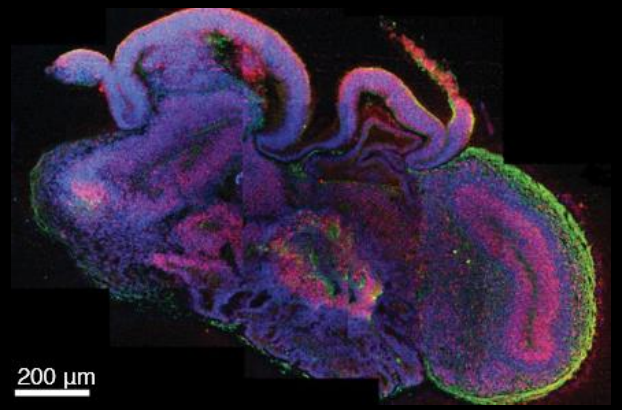
Advantages
Easy to generate and maintain
Low cost
Highly reproducible
Good for high-throughput screening of drug

Limitations
Non natural morphology (flat dishes, monolayers)
Lack of micro-environment
No cellular heterogeneity
Unnatural adhesion forces
Non-predictive/ poor relevance

Human-derived 3D Organoids – More than 10 Years of History



Human-derived 3D Organoids



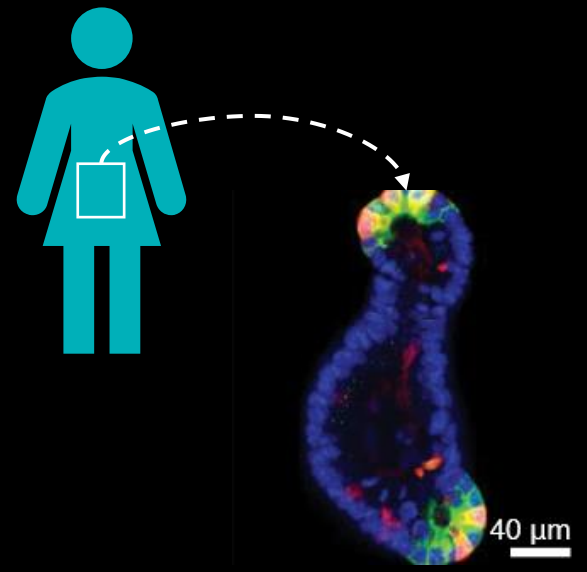
ESCs
- From blastocyst

Adult stem cells

iPSCs
- From blood or skin

Tissue sample

Organoids

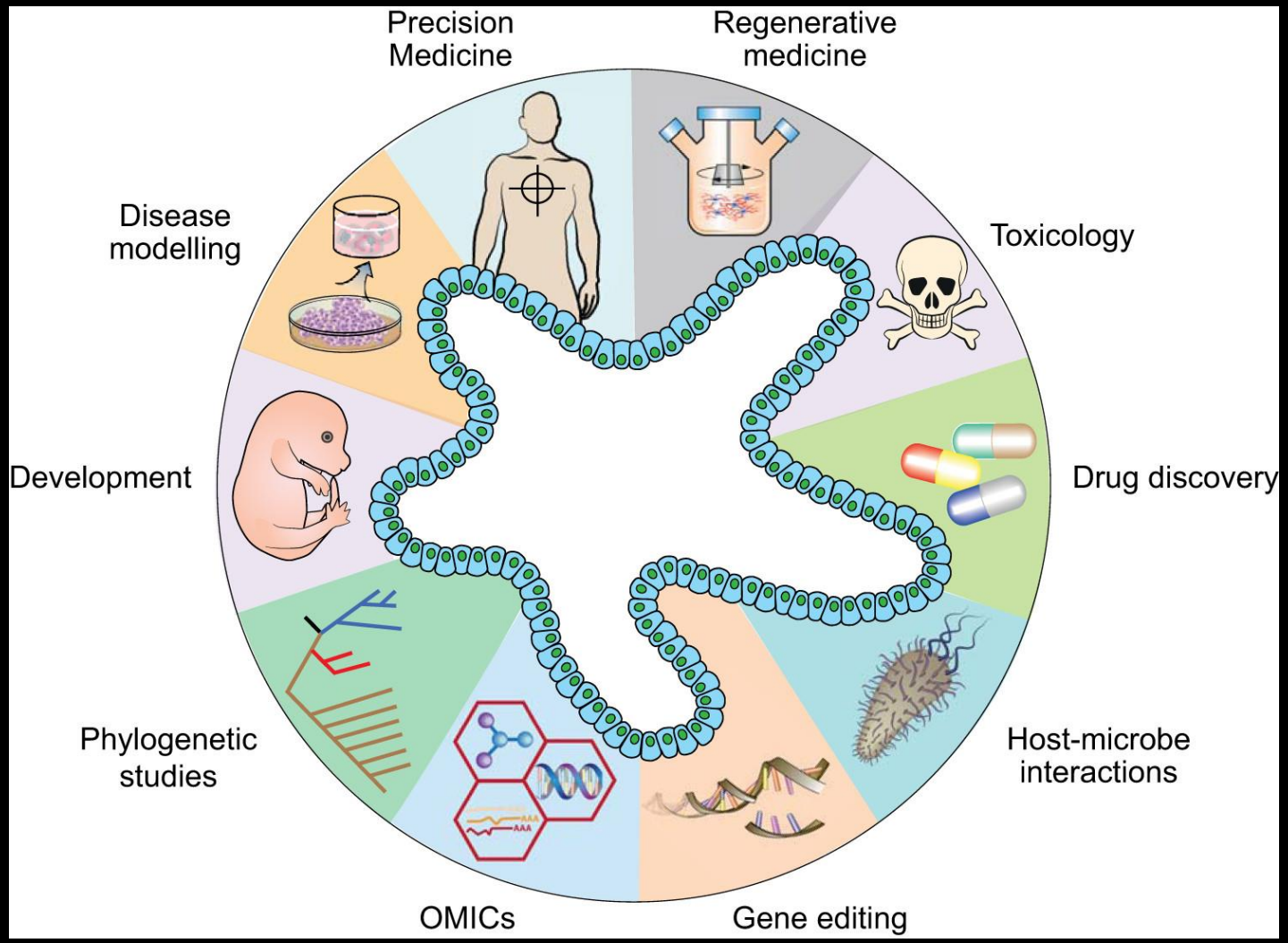


Pluripotent or embryonic stem cell organoids
- Complex multi-steps protocol
- Versatile
- Technically challenging
- Allow large scale studies (easy scale up)

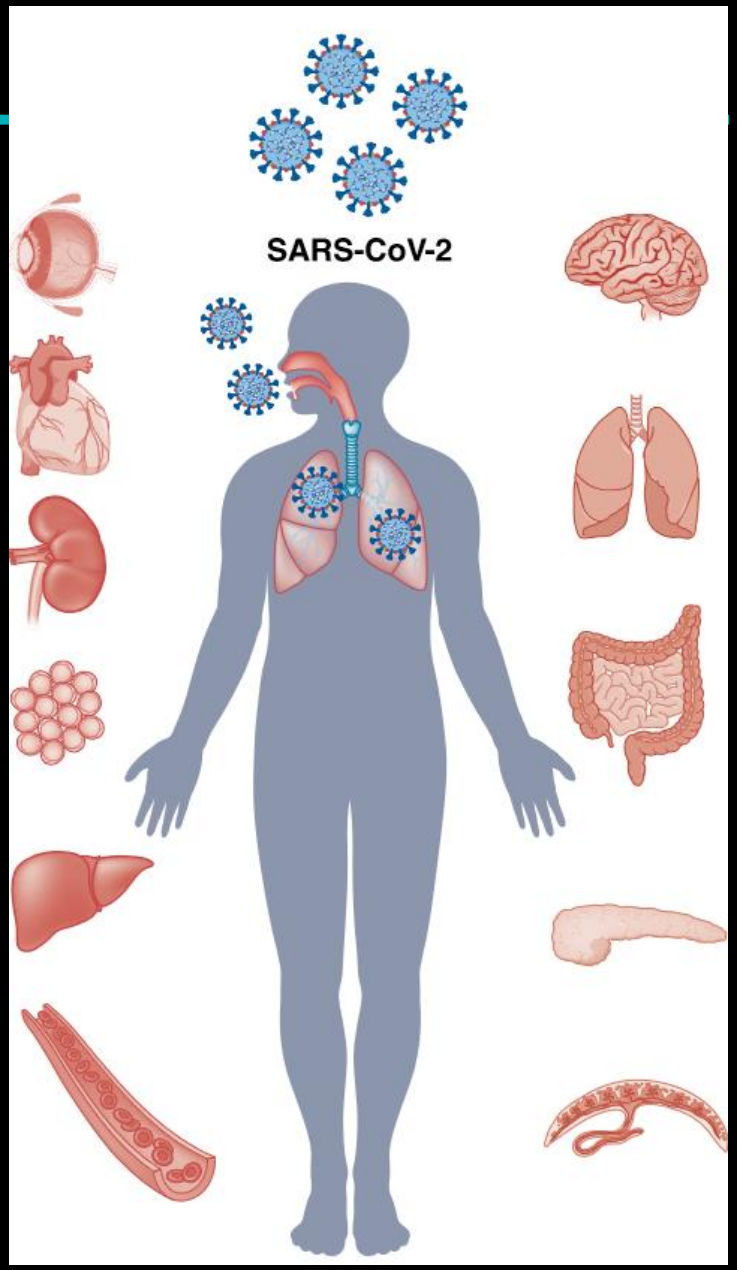
Adult stem cell or tissue organoids
- Straightforward protocols
- Highly reproducible
- Limited self-renewal capacity
- Technically challenging

Adapted from Wang, Q., *et al. Sig Transduct Target Ther* (2022)

Human-derived 3D Organoids – Applications

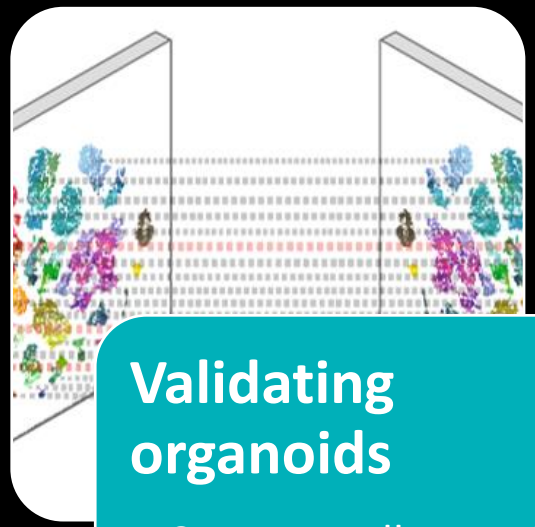


Wang, Q., Guo, F., Jin, Y. et al. Sig Transduct Target Ther (2022)



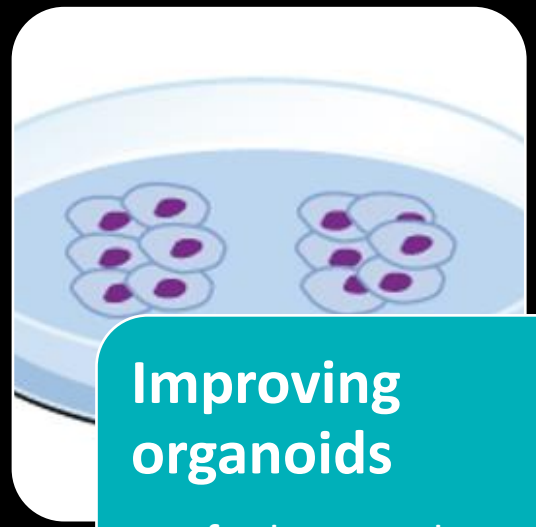
*Han, Y., et al. Nat Methods **19**, 418–428 (2022)*

The Organoid Cell Atlas – Openly Available in a “living biobank”



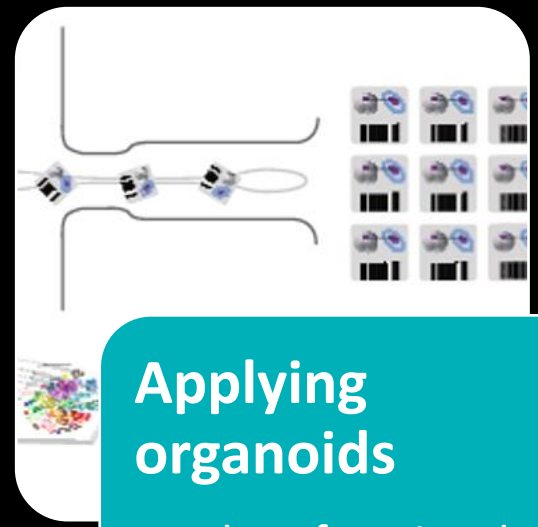
Validating organoids

- Connect cell types in organoids vs in tissue
- Identify and flag outliers



Improving organoids

- Infer key regulators from single-cell profiling data
- Refine and validate protocols



Applying organoids

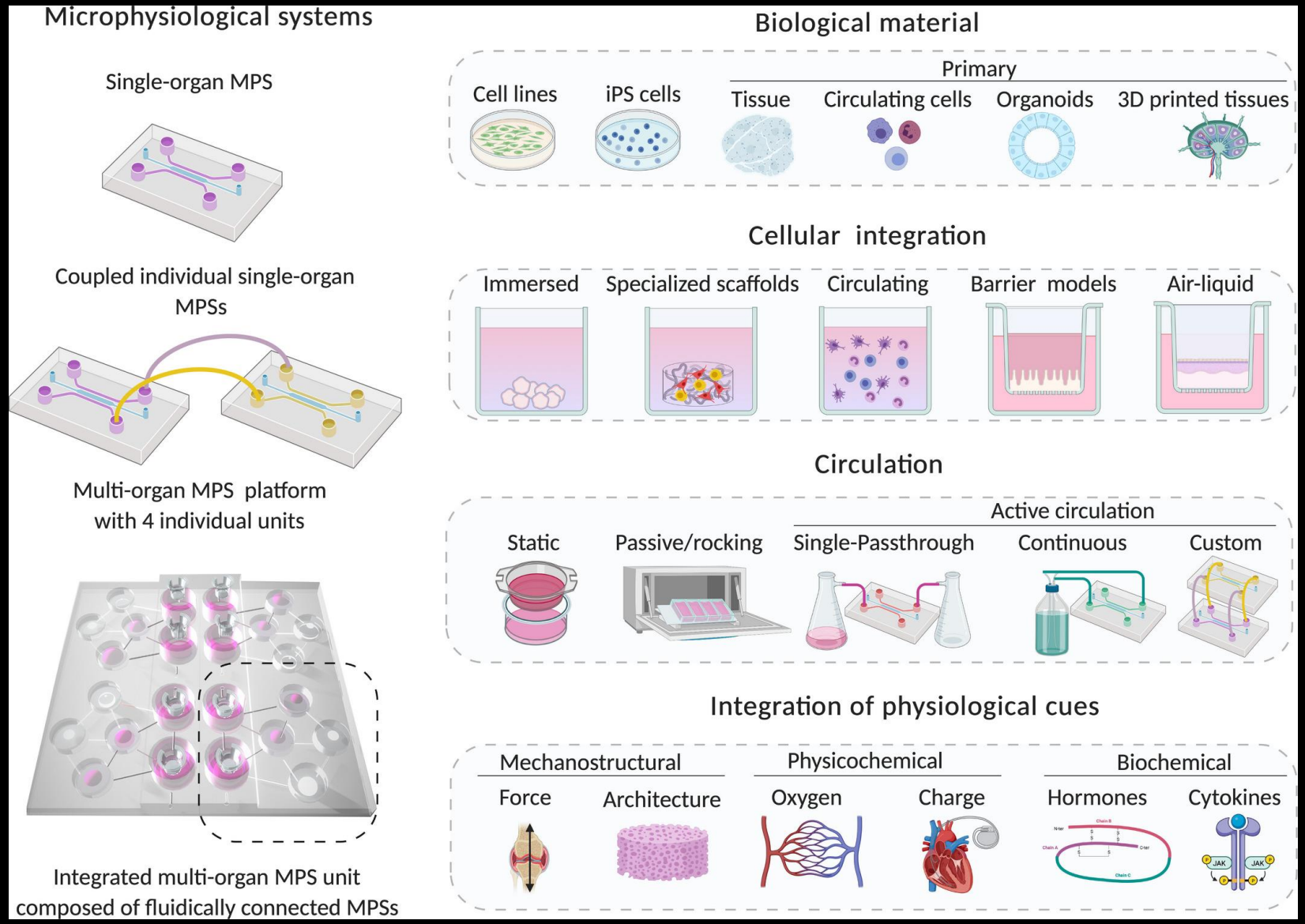
- Induce functional perturbations
- Asses effects by single-cell sequencing

https://hca-organoid.eu/

HCA Organoid has received funding from the European Union’s Horizon 2020 research and innovation programme

Bock, C. et al. Nat Biotechnol (2021)

Human Organ-On-Chip



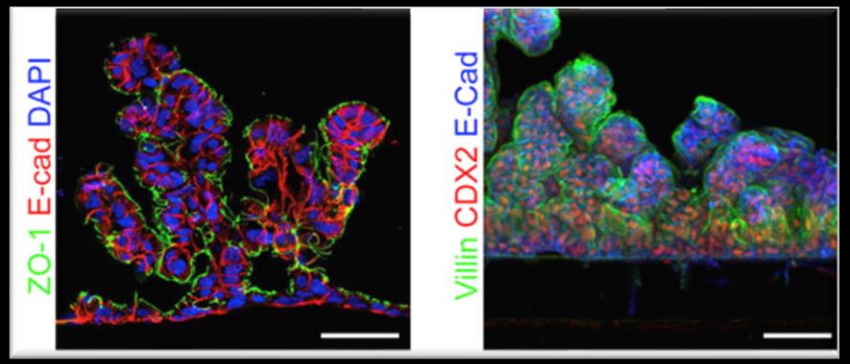
Organ-On-Chip = Microscale Models of Human Physiology

- ✓ Natural cell morphology
- ✓ Tissue-tissue interfaces
- ✓ Immune system
- ✓ Real time monitoring
- ✓ Patient specific
- ✓ Experimental versatility
- ✓ Physiological relevance
- ✓ Mechanical forces
- ✓ Versatile
- ✓ Can be combined and connected (body-on-chip)

Trapecar, M. FEBS Lett, (2022)

Human Organ-On-Chip – Last Breakthroughs

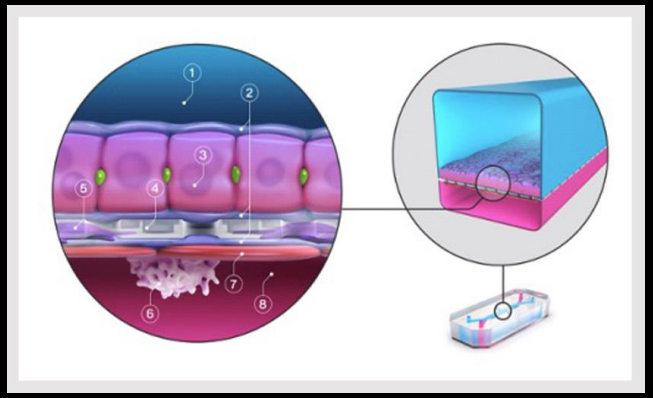
Advancing precision medicine with patient-on-a-chip



- Human intestinal organoids cells incorporated into the Chip
- Intestine-Chip polarised, contains all the intestinal epithelial subtypes
- Biologically responsive to exogenous stimuli

Workman MJ. et al., Cell Mol Gastroenterol Hepatol (2017)

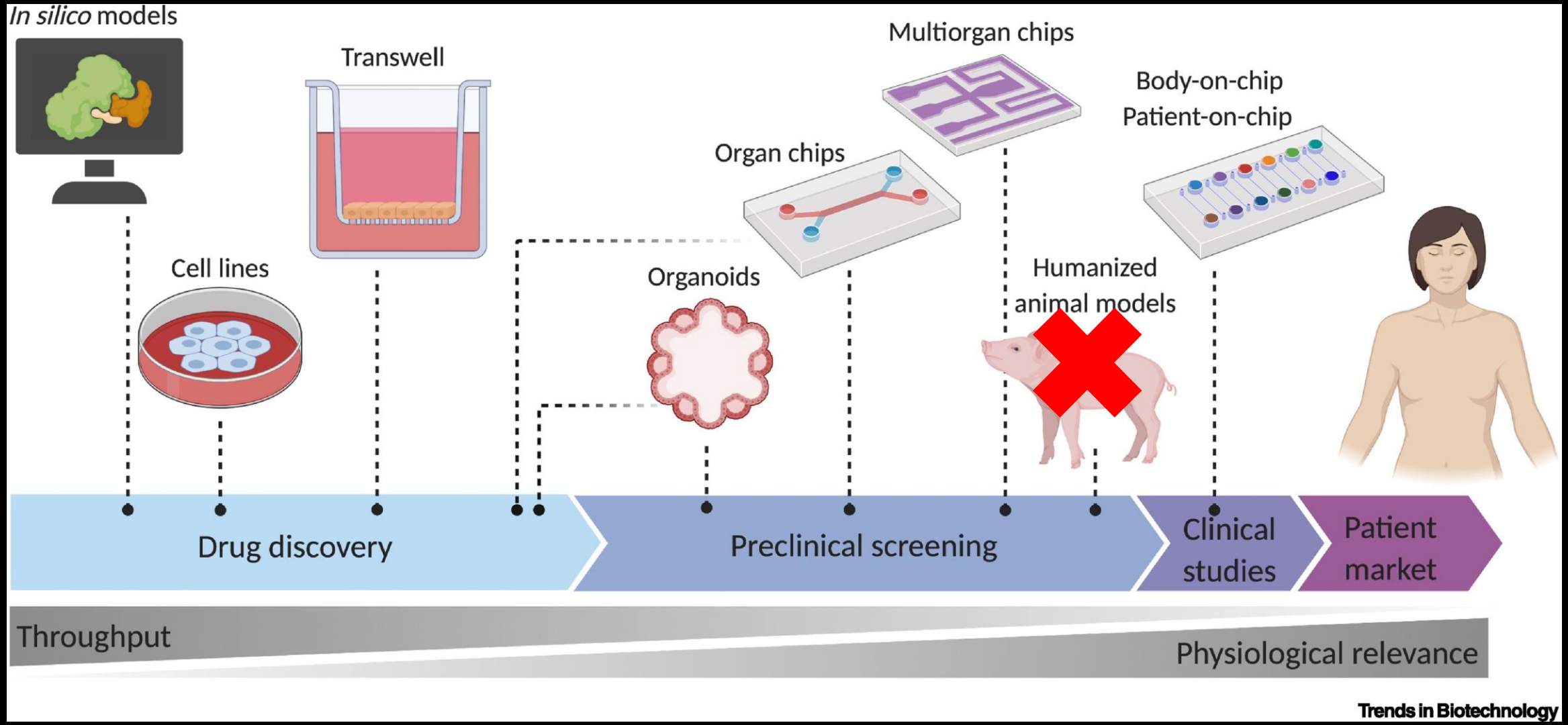
Systematic and quantitative evaluations of Liver-Chips' predictive value



- A blinded set of **27 known hepatotoxic and non-toxic drugs**
- **870** Liver-Chips
- Sensitivity of 87% and a specificity of 100%.
- $3 billion annual benefit for Pharm companies

Ewart L. et al., Comm Med (2022)

Body-On-Chip to Replace Animals for a Fully Human-based Pipeline



Jalili-Firoozinezhad S, et al., Trends Biotechnol. (2021)

Defining the right *in Vitro* model for drug discovery

Static 3D models

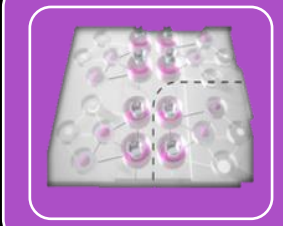
- Reproducible
- High-throughput

➢ **Suitable for target identification**

Organ-on-chip (OOC)

- Mimic tissue complexity
- Multi-cellular interaction

➢ **Suitable for drug toxicity and efficacy testing**



Multi-OOC

- Possibility to study PK/PD
- Interorgan crosstalk

➢ **Suitable for drug toxicity and efficacy testing**

Body-on-chip

- Mimicking living organism
- Potential to replace animals

➢ **Potentially suitable for conducing clinical trials**

Throughput

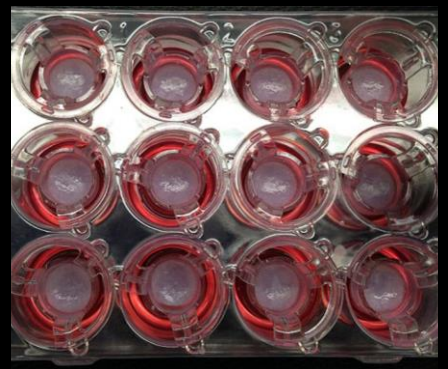
Complexity
Human Relevance

OOC Limitations

No yet suitable for high-throughput screening
Lack of validated protocols
Variability
Cost of instruments and reagents
Limited ability of long-term growth of tissue/organs

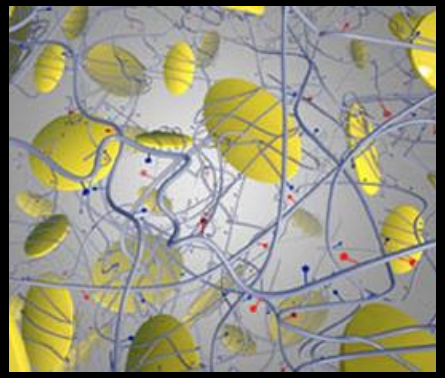
3D Bioprinting

Organoids



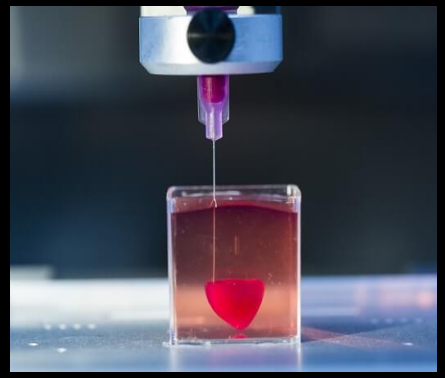
- Patient-Specific Disease Modelling
- Drug testing

Biomaterials



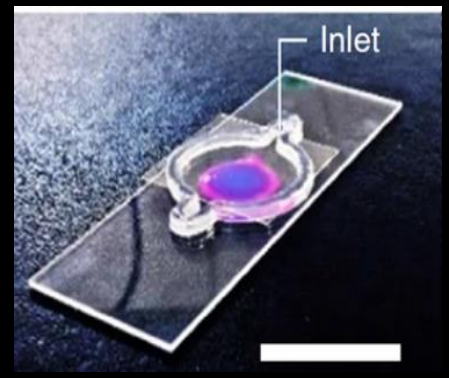
- Hydrogels
- Scaffolds

Organs



- Drug testing
- Regenerative medicine
- Organ transplant

OOC/MPS



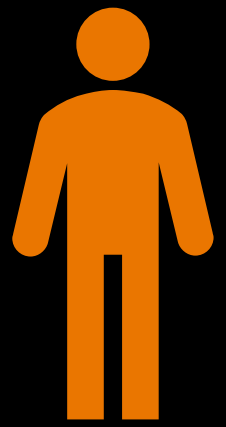
- Patient-Specific Disease Modelling
- Drug discovery

- Can use patient cells
- Recapitulate the human tumour tissues and microenvironment for high-throughput drug screening.
- Must be optimised such that cell viability and multi-omics profiles are preserved during the printing process.

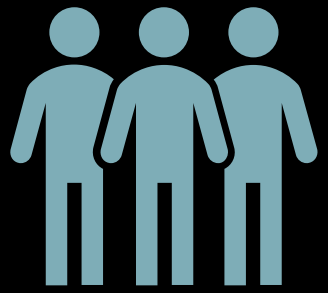
In silico: Big data, AI and computer modelling

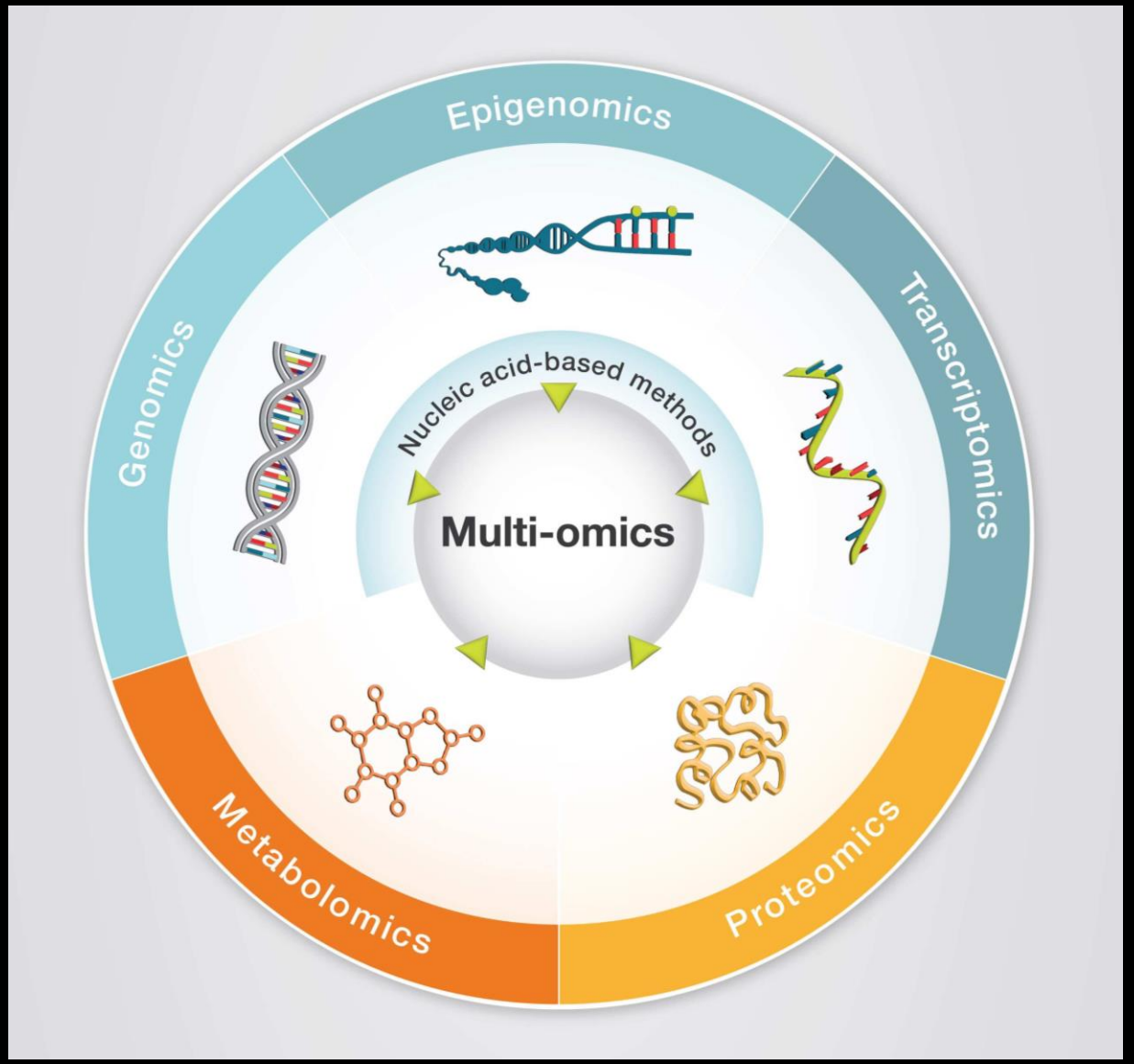
Big data – Single cell Omics/ Multi-omics

Biobank



Cohorts





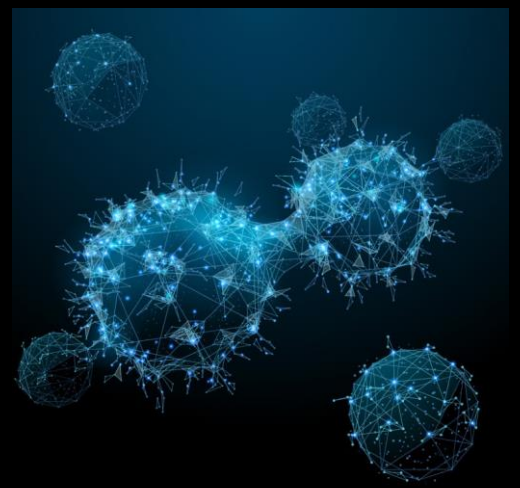
Key applications

- Finding biomarkers
- Defining genetic and environmental risk factors
- Stratifying patients' population
- Define the molecular mechanisms underlying diseases

Artificial Intelligence ‘AI’ and computer modelling

Key applications

- Computational augmentation of existing clinical and imaging data sets
- Combine genomic and clinical data to detect new predictive models
- Predict drug toxicity and long term effect
- Predict pharmaceutical properties of molecular compounds and targets
- Faster and better disease diagnoses and progression monitoring
- **Optimise drug development and patient treatment**



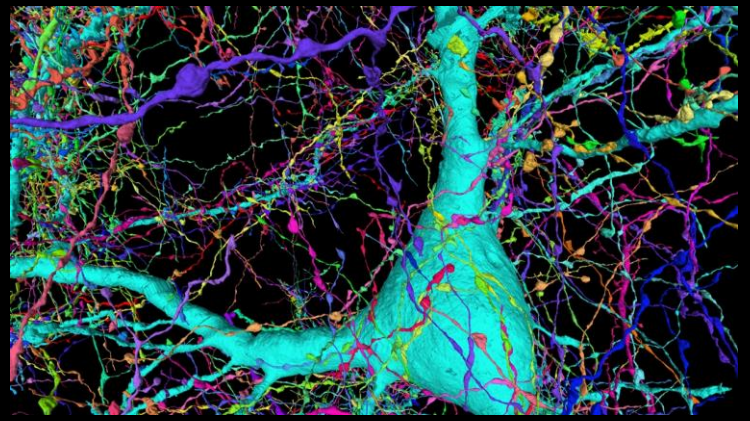
frontiers in Physiology

ORIGINAL RESEARCH
published: 12 September 2017
doi: 10.3389/fphys.2017.00668

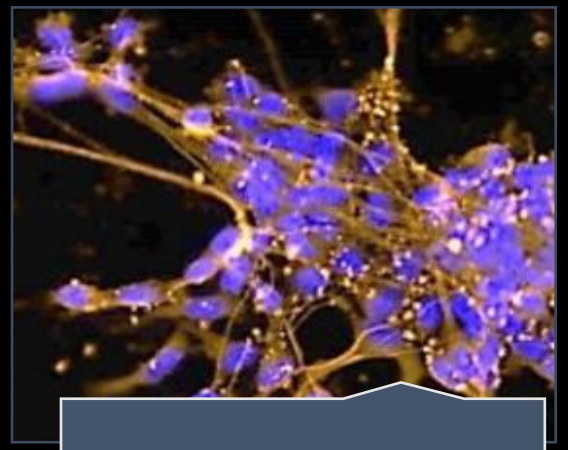
Check for updates

Human *In Silico* Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity

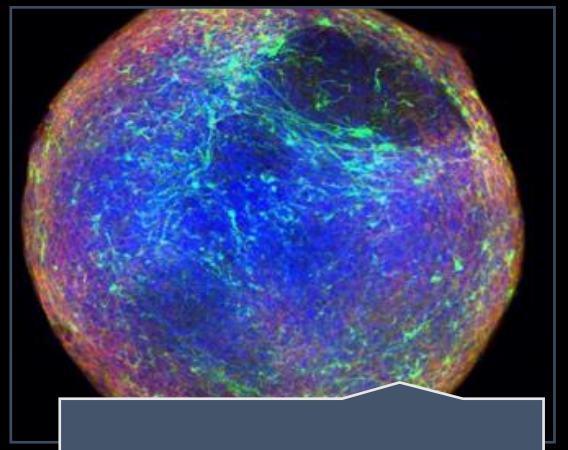
Elisa Passini[1], Oliver J. Britton[1], Hua Rong Lu[2], Jutta Rohrbacher[2], An N. Hermans[2], David J. Gallacher[2], Robert J. H. Greig[3], Alfonso Bueno-Orovio[1] and Blanca Rodriguez[1]*



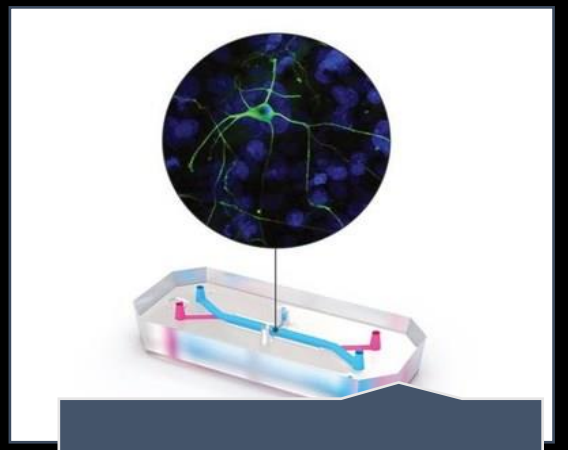
The power of combining NAMs



2D in vitro cells

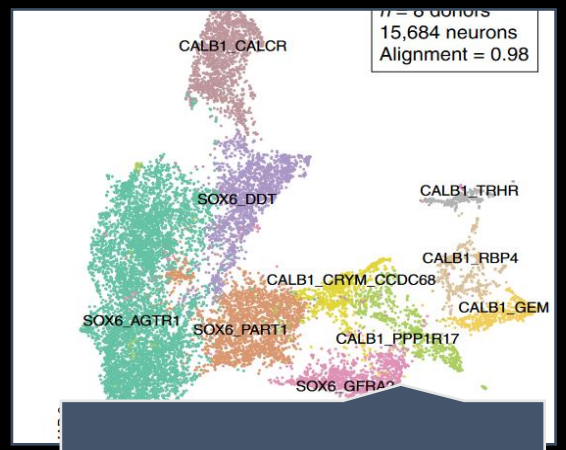


3D organoids

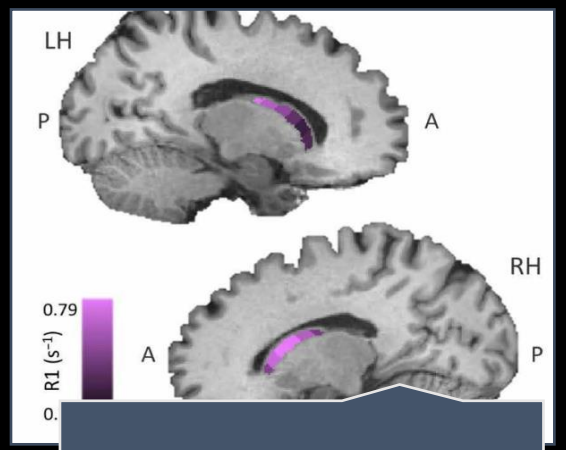


Organ-chips

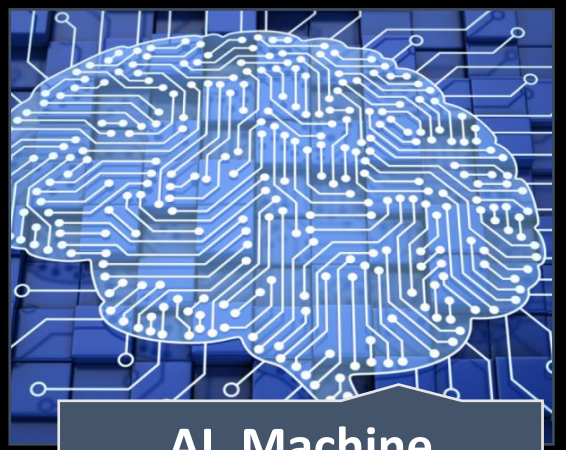
3D Bio-printing



Omics/ Multi-omics

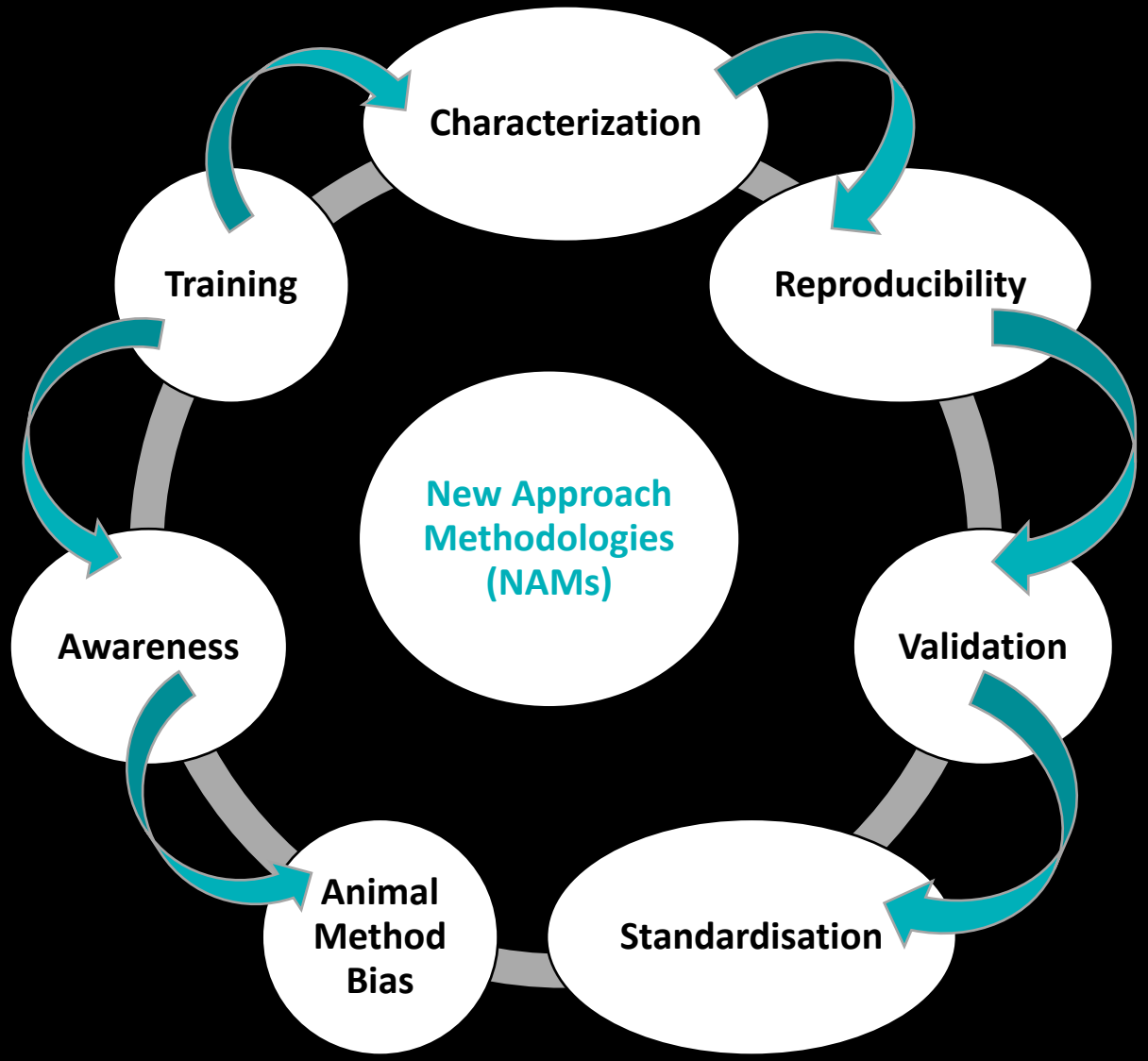


Advanced imaging



AI, Machine Learning

Future challenges and opportunities



Most NAMs do not seek to provide a like-for-like replacement or simulation of an existing animal test, but instead approach the problem from a human data-driven and mechanistic perspective that provides a deeper biological understanding of the mechanisms involved in human conditions, drug efficacy as well as toxicity.

Wind of change?

➢ U.S FDA Modernization Act 2.0

"This bill allows an applicant for market approval for a new drug to use methods other than animal testing to establish the drug's safety and effectiveness. Under this bill, these alternative methods may include cell-based assays, organ chips and microphysiological systems, computer modeling, and other human biology-based test methods."

➢ Roche launches Institute of Human Biology

- Brings together scientists from academia and industry
- To lead the broad adoption of human model systems in pharmaceutical R&D as well as in clinical practice.
- To accelerate breakthroughs in R&D by unlocking the potential of human model systems.
- To better predict which drug candidates are safe and most effective in patients by evolving and increasing the use of human model systems.

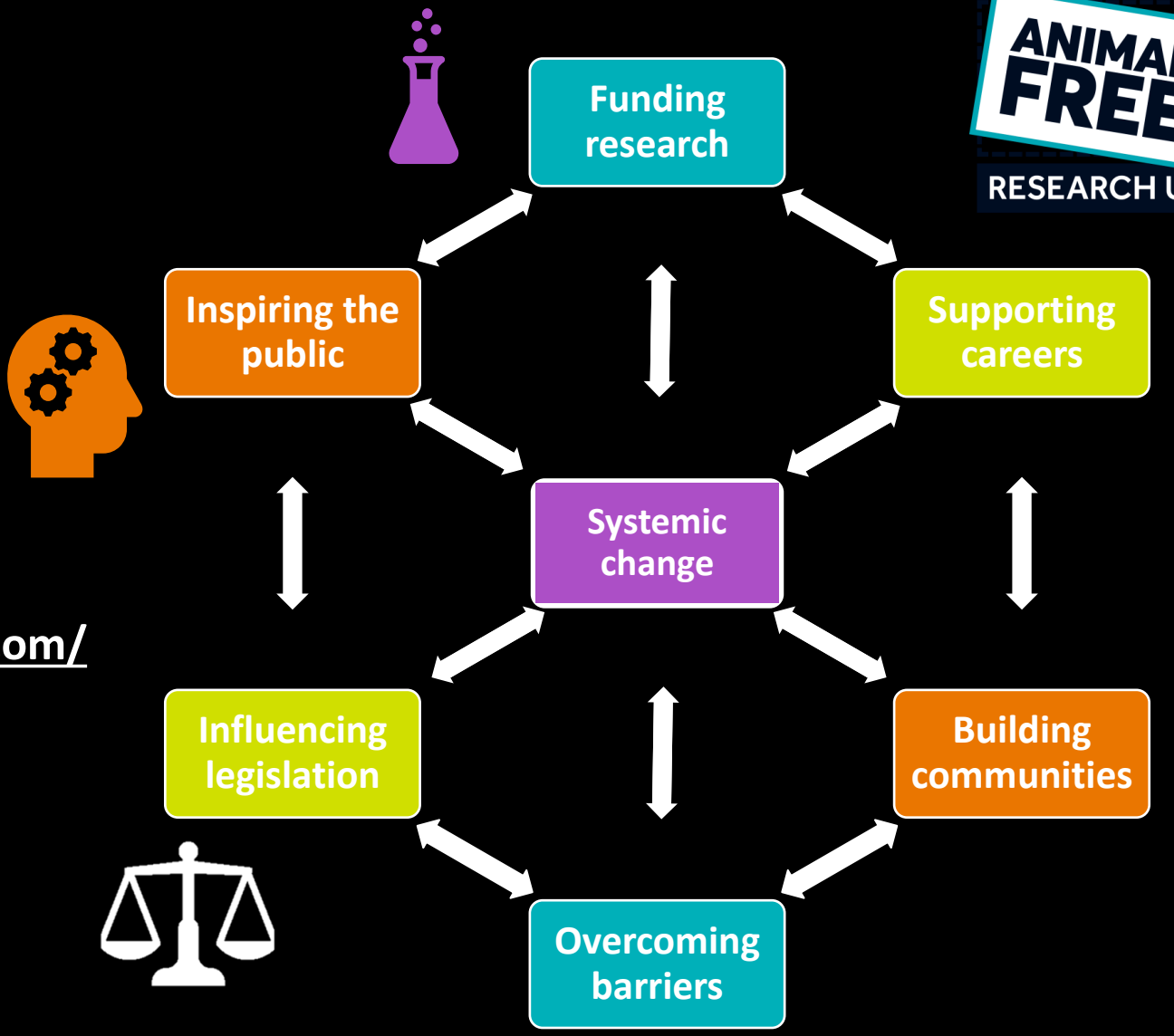
How can we work together?

https://www.animalfreeresearchuk.org/

- Science Conference: 4-5 October 2023 (Cambridge)
  - TED-talk
  - Helpathon
  - Poster
- Community of Practice Platform
  - https://animalfreeresearchcommunity.com/

CONFERENCE

COMMUNITY



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