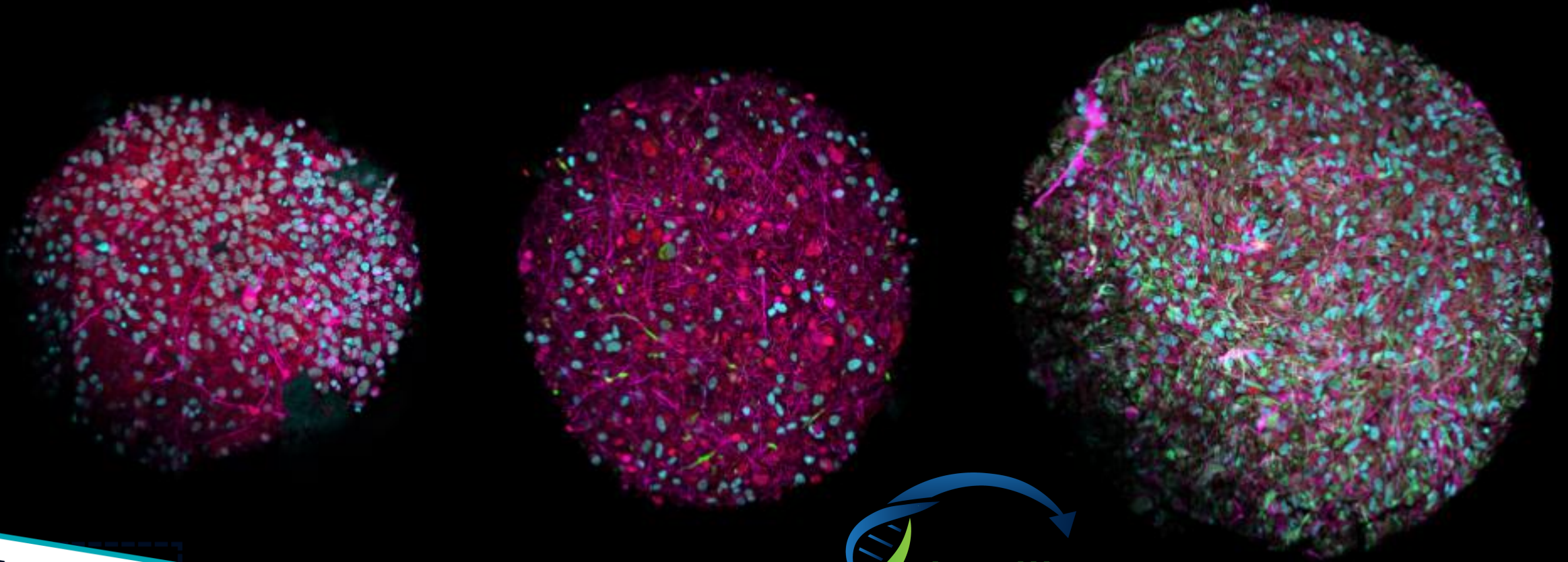




# The Alliance Exchange

Talking Human Relevant Science

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



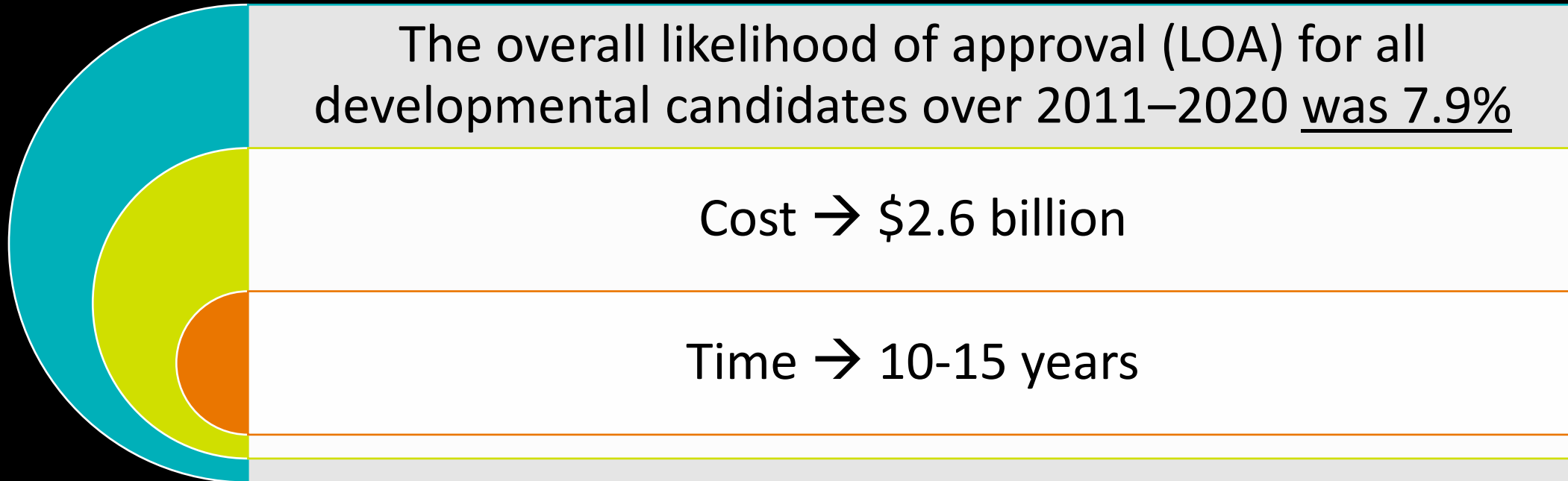
Dr Lilas Courtot  
Science Manager



May 22<sup>nd</sup> 2023

# Drug Development: a 'Business' in Crisis

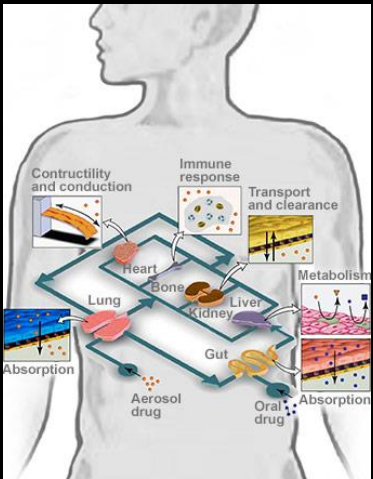
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**With over 90% failure rate, NO other sector has such figures and continues to exist with the bravado of business as usual...**

# Presentation Outline

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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



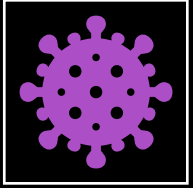
In silico: Big data, AI and computer modelling



Current and Future Challenges and Opportunities

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

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Several thousand human diseases, only ~500 have treatments available



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

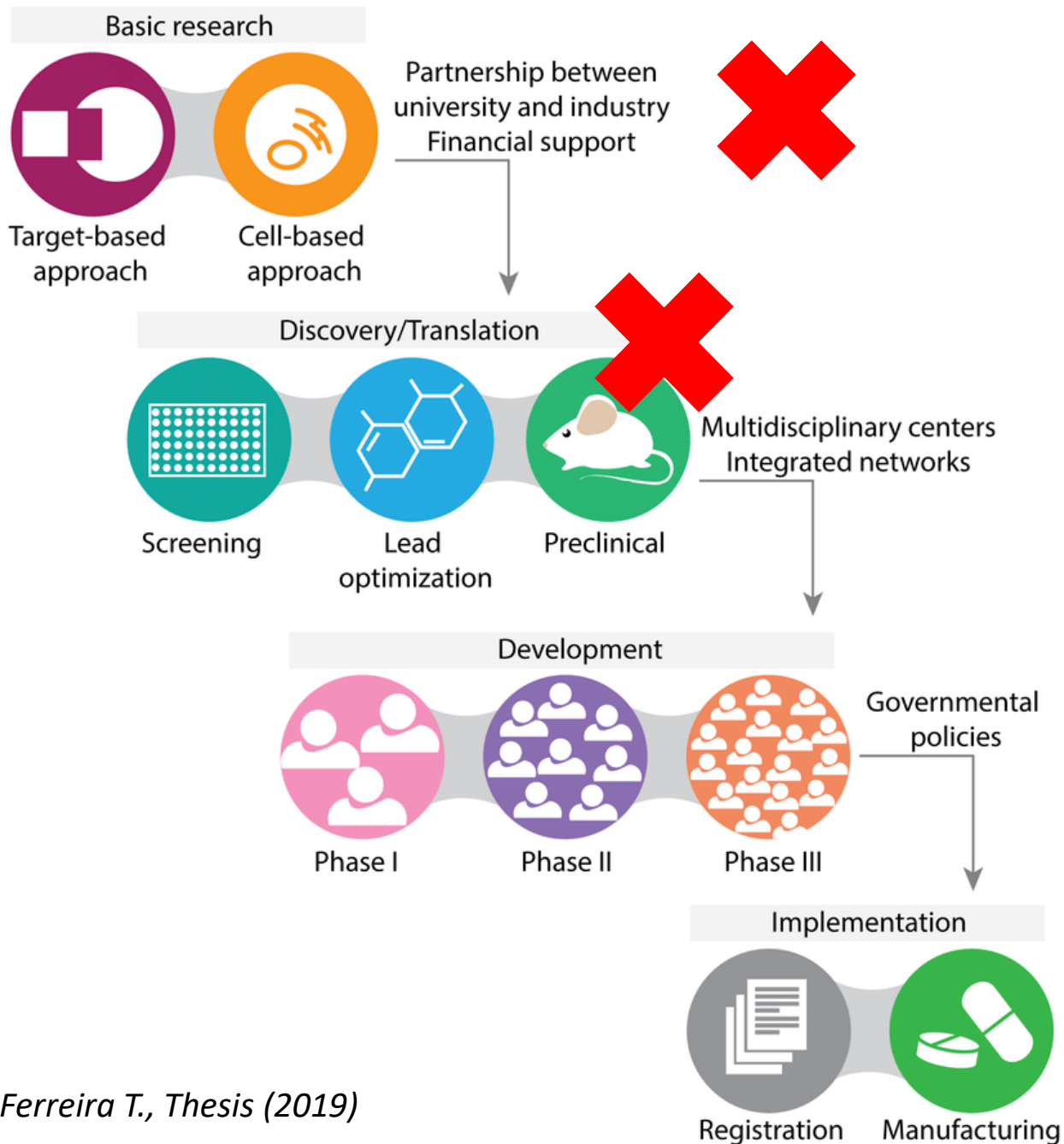


Translation failure due to inadequate preclinical models



Too much reliance on animals

# Drug Discovery Pipeline



## 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

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## 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

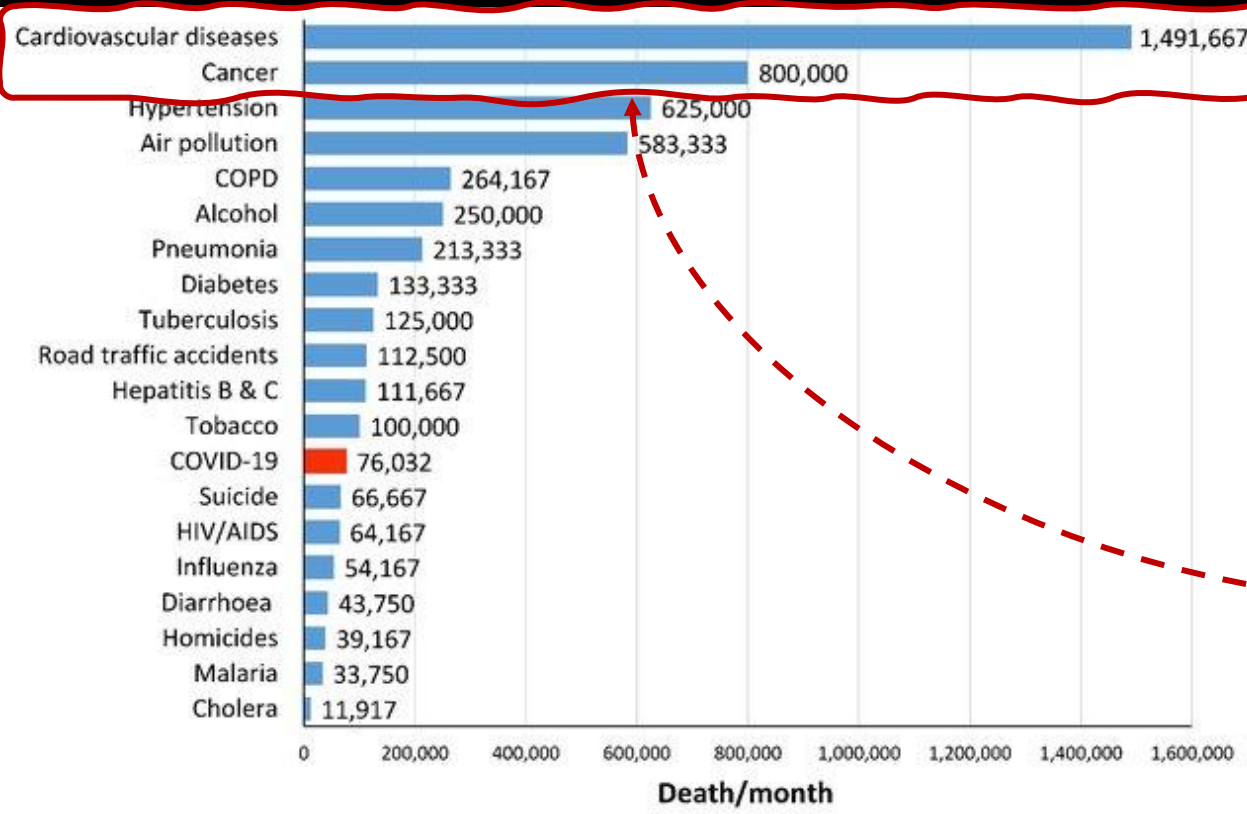
Unpublished negative results

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

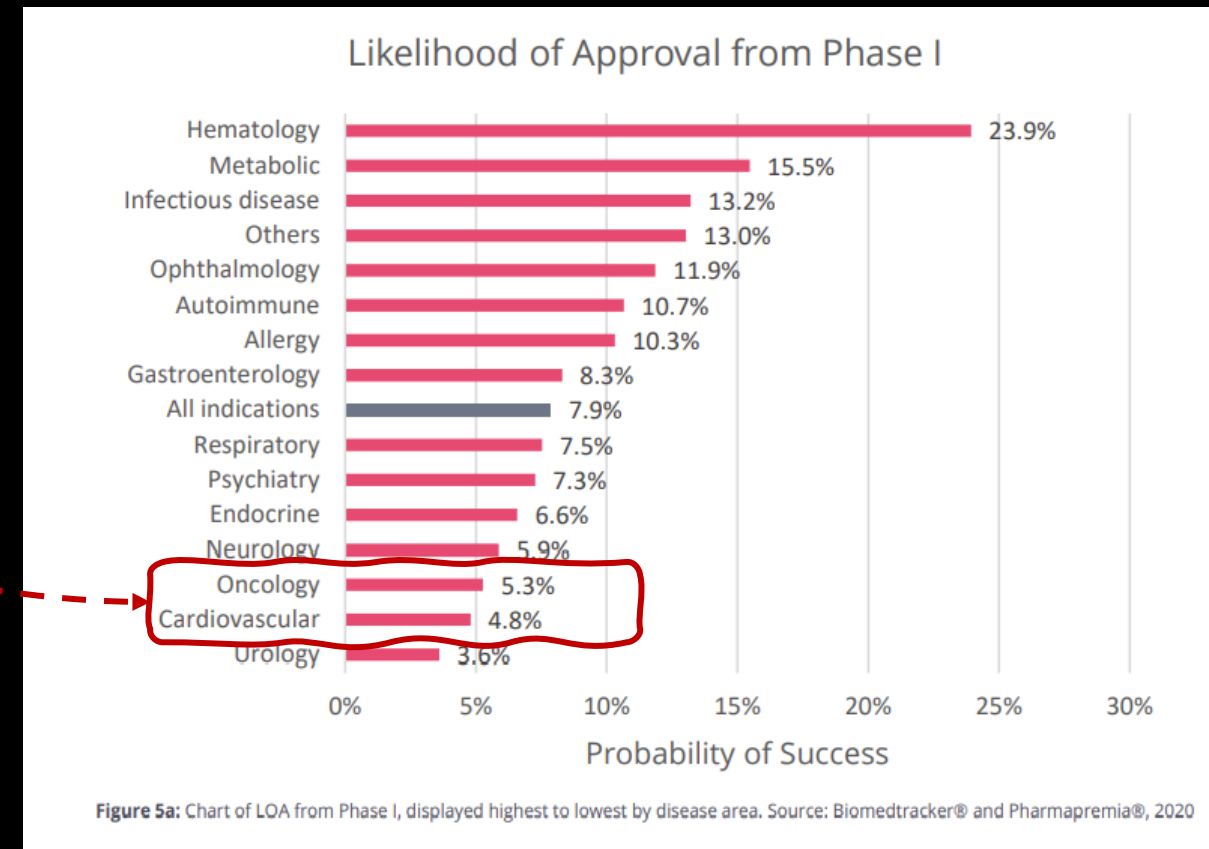


Figure 5a: Chart of LOA from Phase I, displayed highest to lowest by disease area. Source: Biomedtracker® and Pharmapremia®, 2020

Based on the World Health Organization (WHO) report 2018



# The Case of Rheumatoid Arthritis

Over the last 10 years...

9,665  
papers



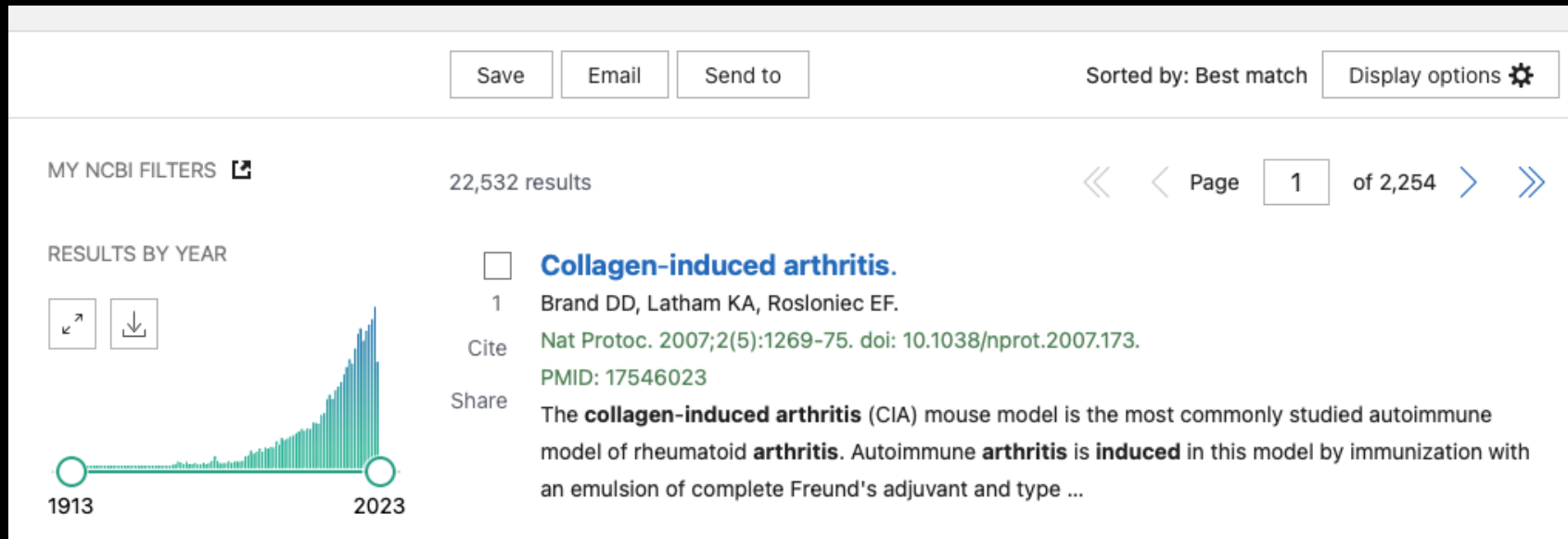
Almost  
1M mice



Zero  
available  
drug



Time to switch to  
new and more  
human-focused  
models



# Inertia towards New Approach Methodologies (NAMs)

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

Journal of  
Translational  
Medicine

## Limitations of Animal Studies for

The **F**  *animals*



Commentary

## Modernizing Medical Research to Benefit People and Animals

Review Article

## Lost in translation: a cancer treatment

Special Section: Moving Forward

*The Flaws and Human Experimentation*



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>

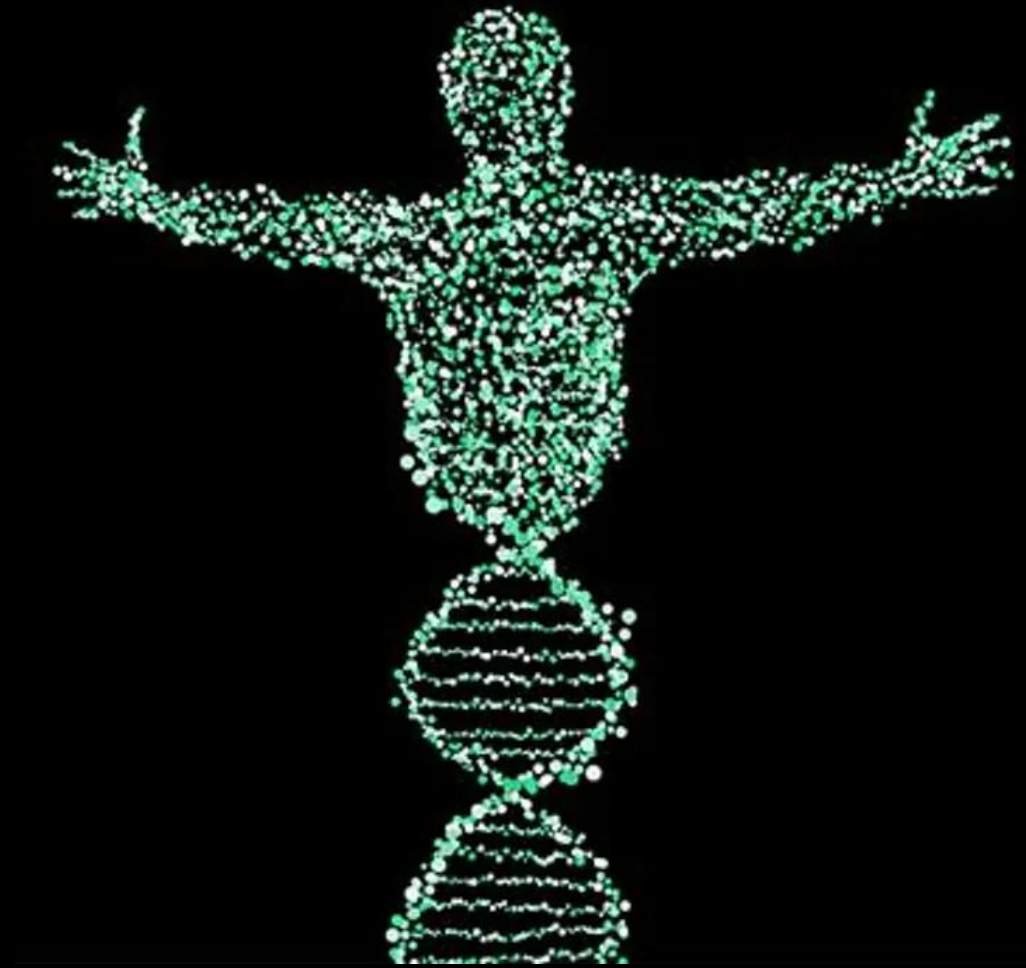
[www.scielo.br/aabc](http://www.scielo.br/aabc) | [www.fb.com/aabcjournal](http://www.fb.com/aabcjournal)

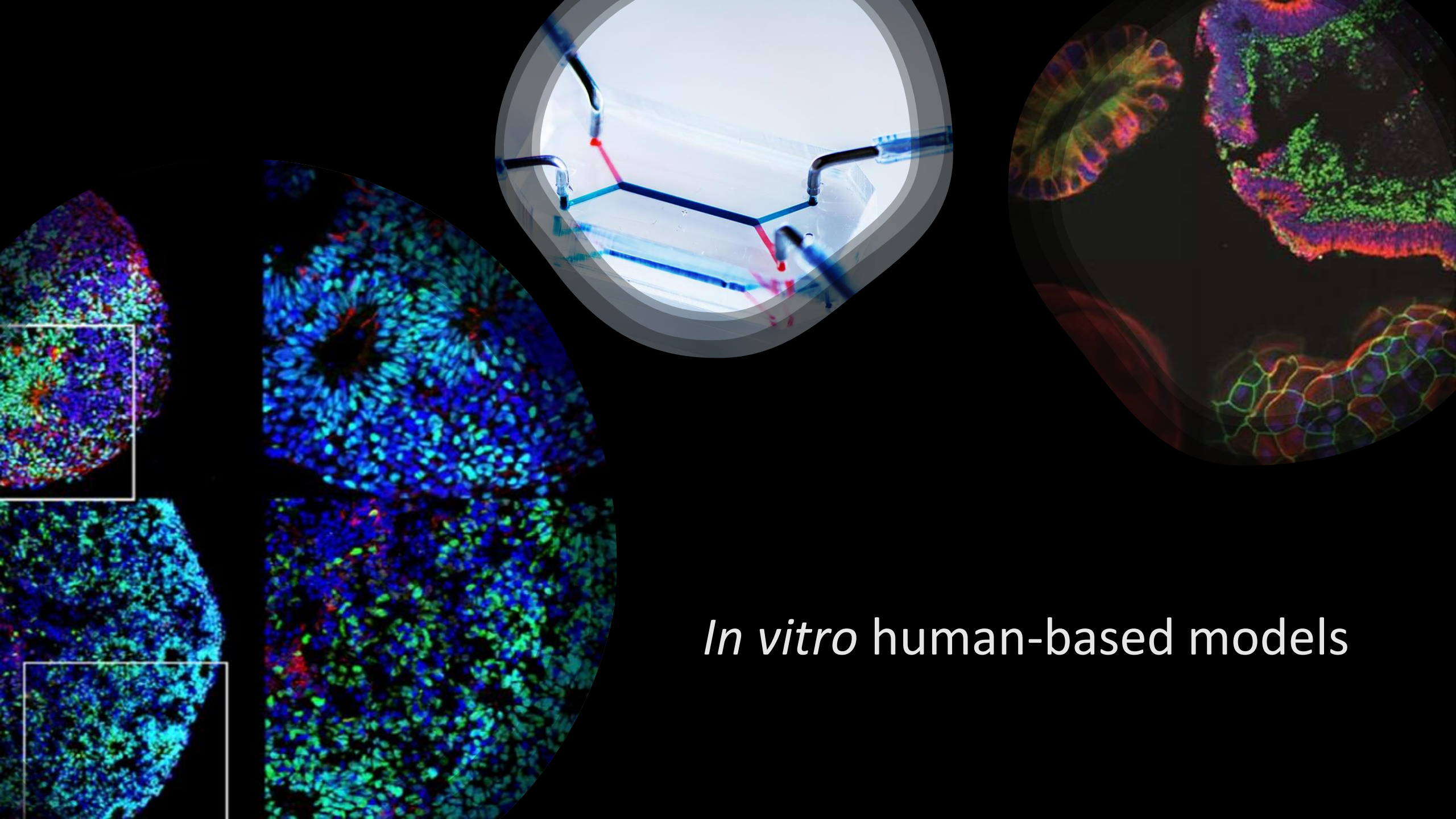
4th Animal Models



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)**



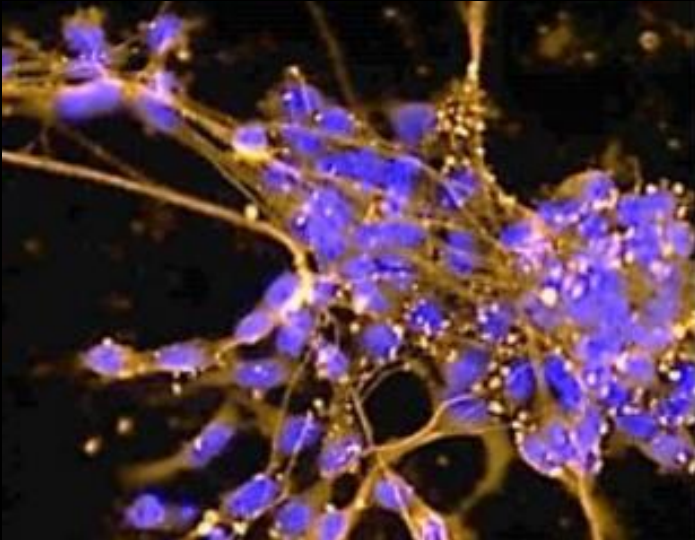


*In vitro* human-based models



# 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

## Adult organoids



Gut organoid



Stomach organoid



Liver organoid



Pancreas organoid



Placenta organoid



Long-term airway organoid

2009

2010

2011

2013

2014

2015

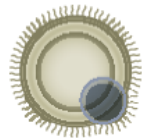
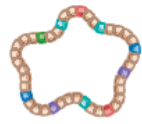
2017

2018

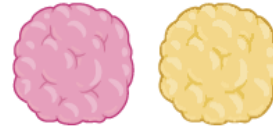
2019

2021

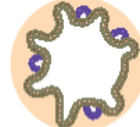
Gut/retinal organoids



Cerebral/liver/kidney organoids



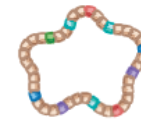
Stomach/lung organoids



Pancreas organoid



Colon/cardiac organoids



Vascular organoid



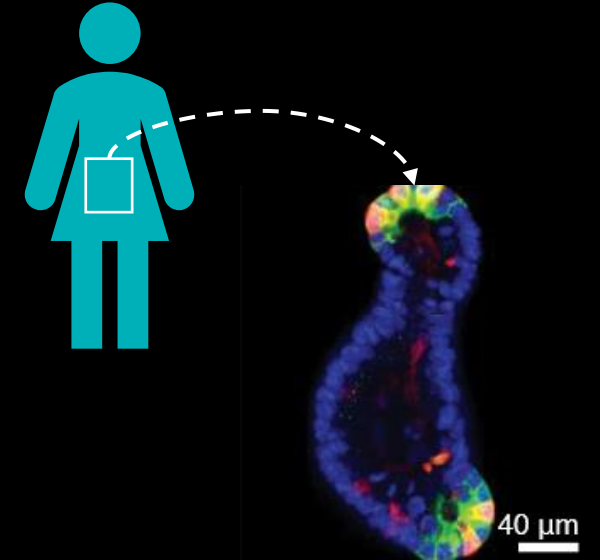
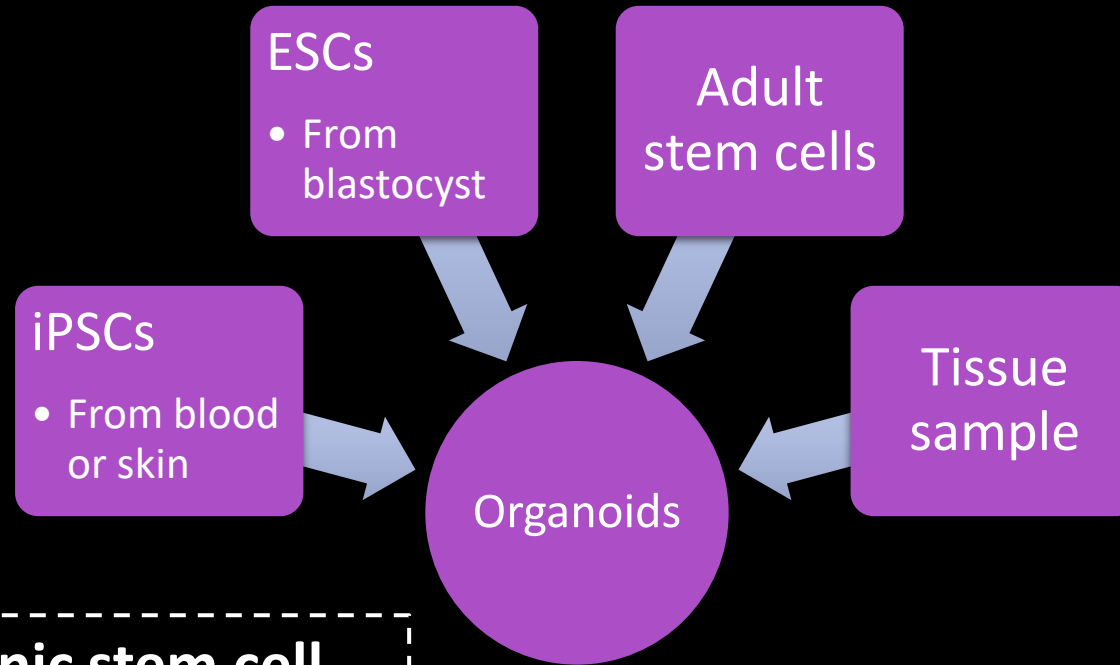
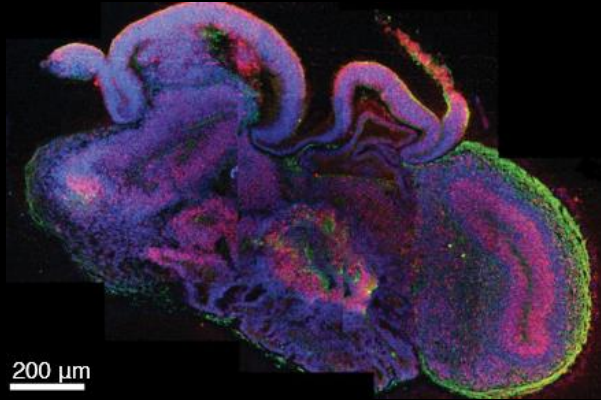
Placenta organoid



## hPSC-derived organoids



# Human-derived 3D Organoids



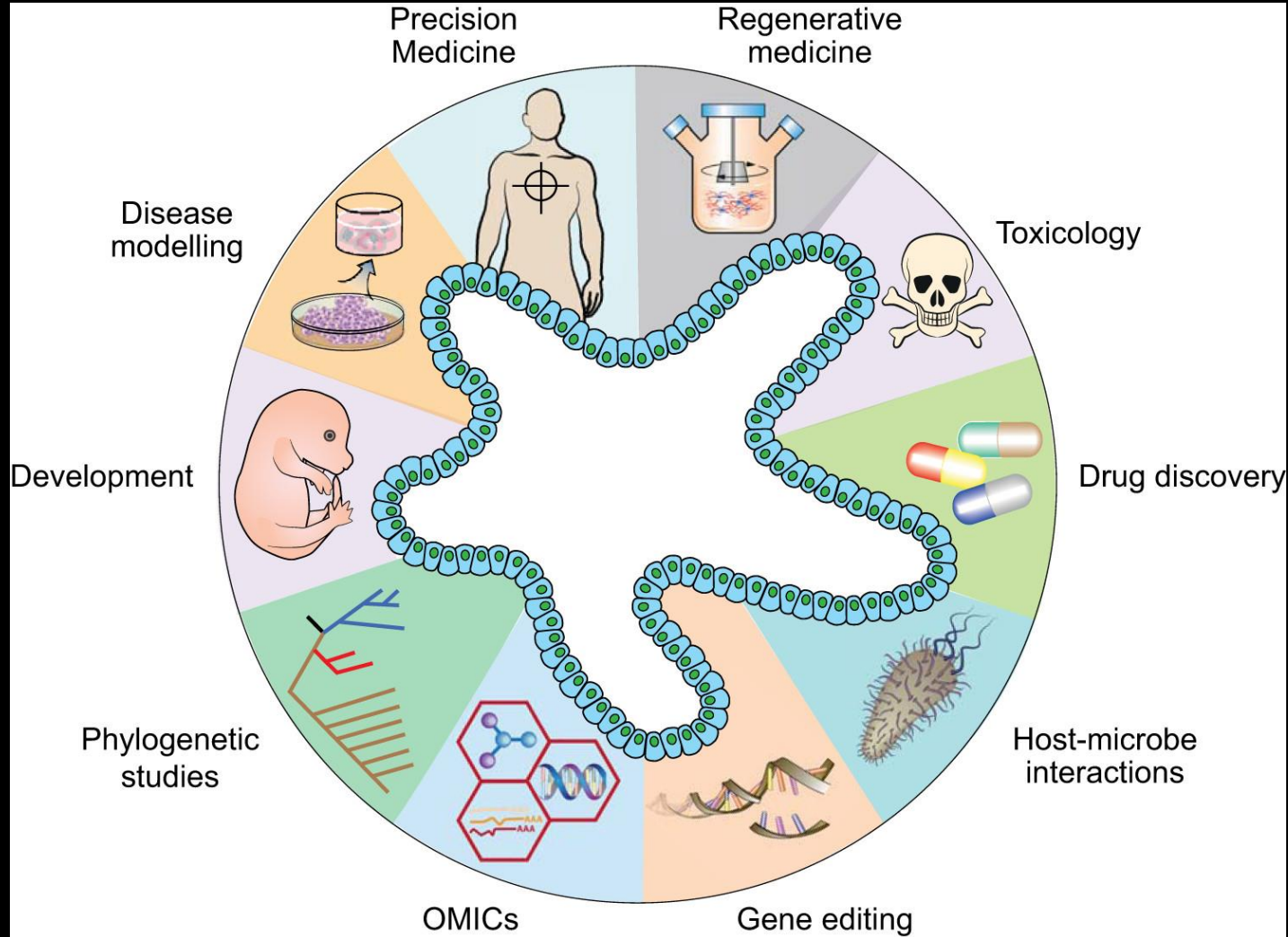
## Pluripotent or embryonic stem cell organoids

- Complex multi-steps protocol
- Versatile
- Technically challenging
- Allow large scale studies (easy scale up)

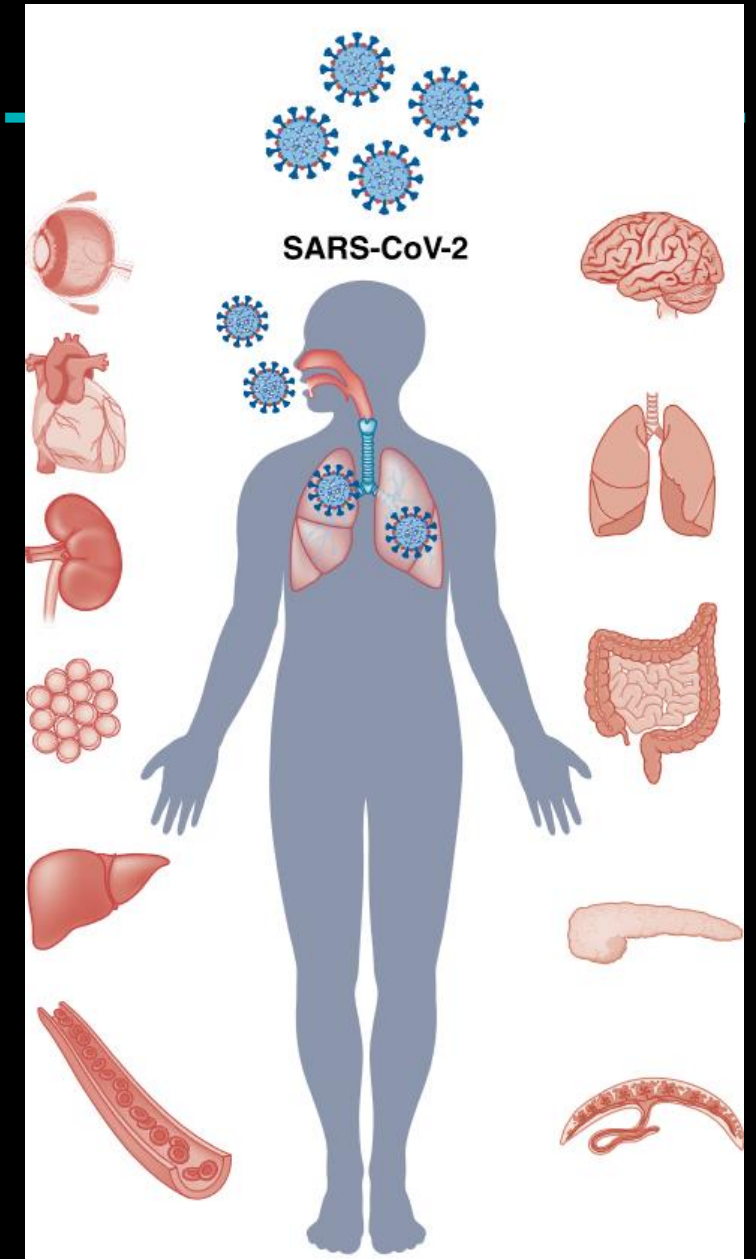
## Adult stem cell or tissue organoids

- Straightforward protocols
- Highly reproducible
- Limited self-renewal capacity
- Technically challenging

# Human-derived 3D Organoids – Applications

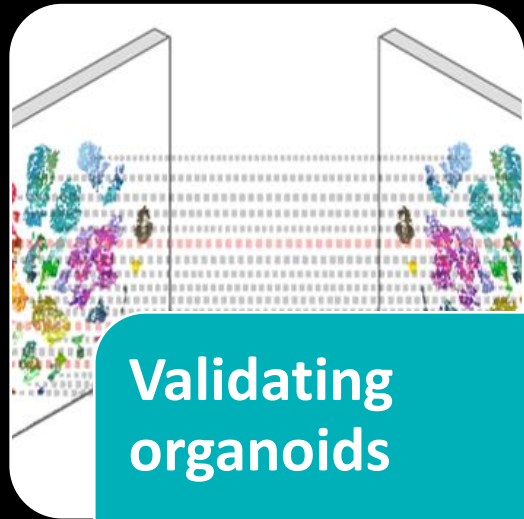


Wang, Q., Guo, F., Jin, Y. et al. *Sig Transduct Target Ther* (2022)



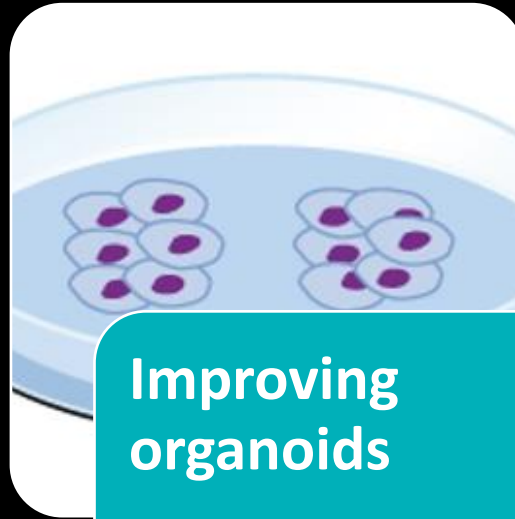
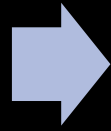
Han, Y., et al. *Nat Methods* **19**, 418–428 (2022)

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



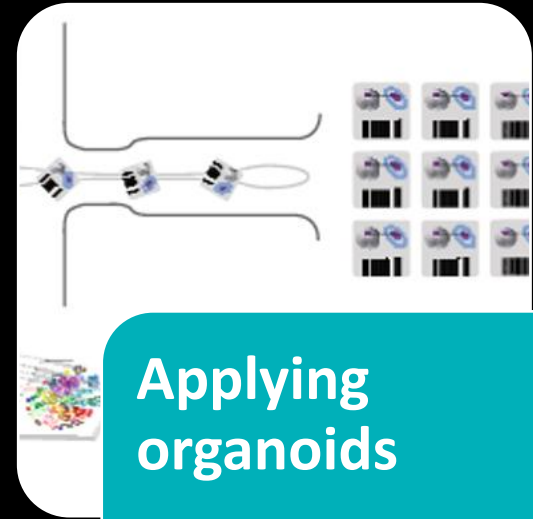
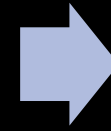
## Validating organoids

- 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



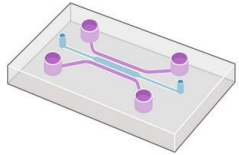
## Applying organoids

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

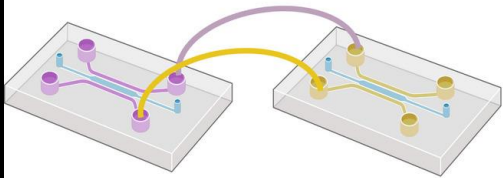
# Human Organ-On-Chip

## Microphysiological systems

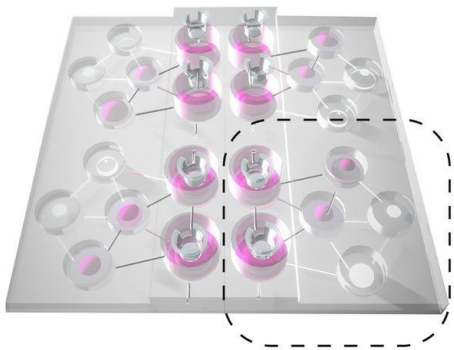
Single-organ MPS



Coupled individual single-organ MPSs

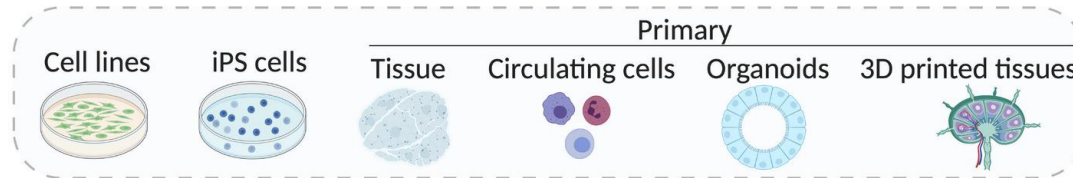


Multi-organ MPS platform with 4 individual units

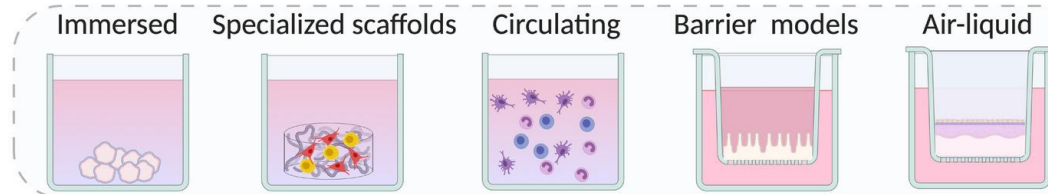


Integrated multi-organ MPS unit composed of fluidically connected MPSs

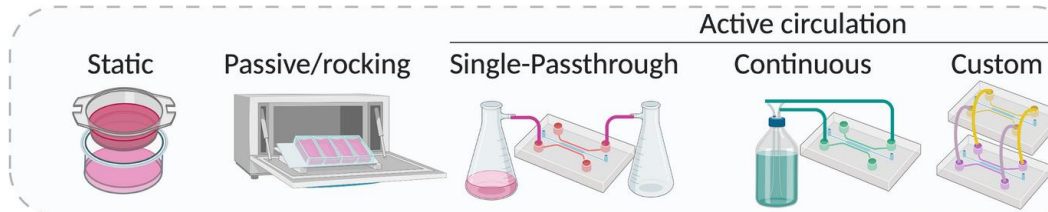
## Biological material



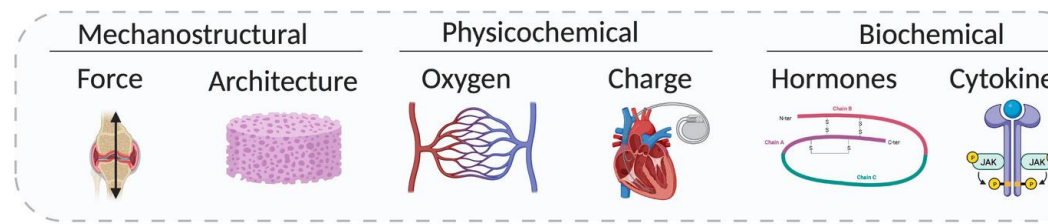
## Cellular integration



## Circulation



## Integration of physiological cues



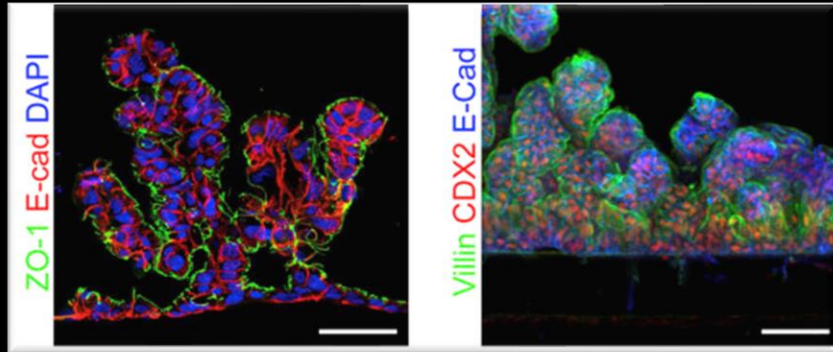
## Organ-On-Chip = Microscale Models of Human Physiology

- ✓ 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)



# Human Organ-On-Chip – Last Breakthroughs

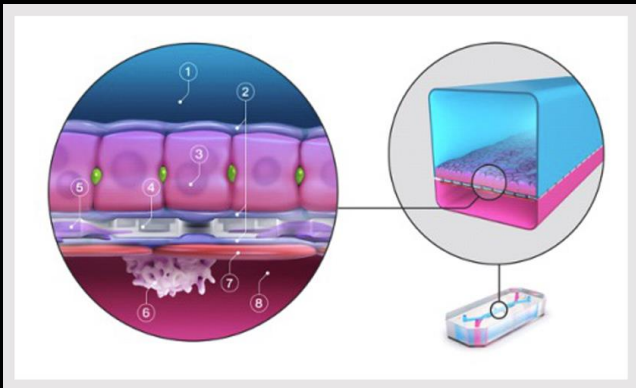
## Advancing precision medicine with patient-on-a-chip



- 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)*

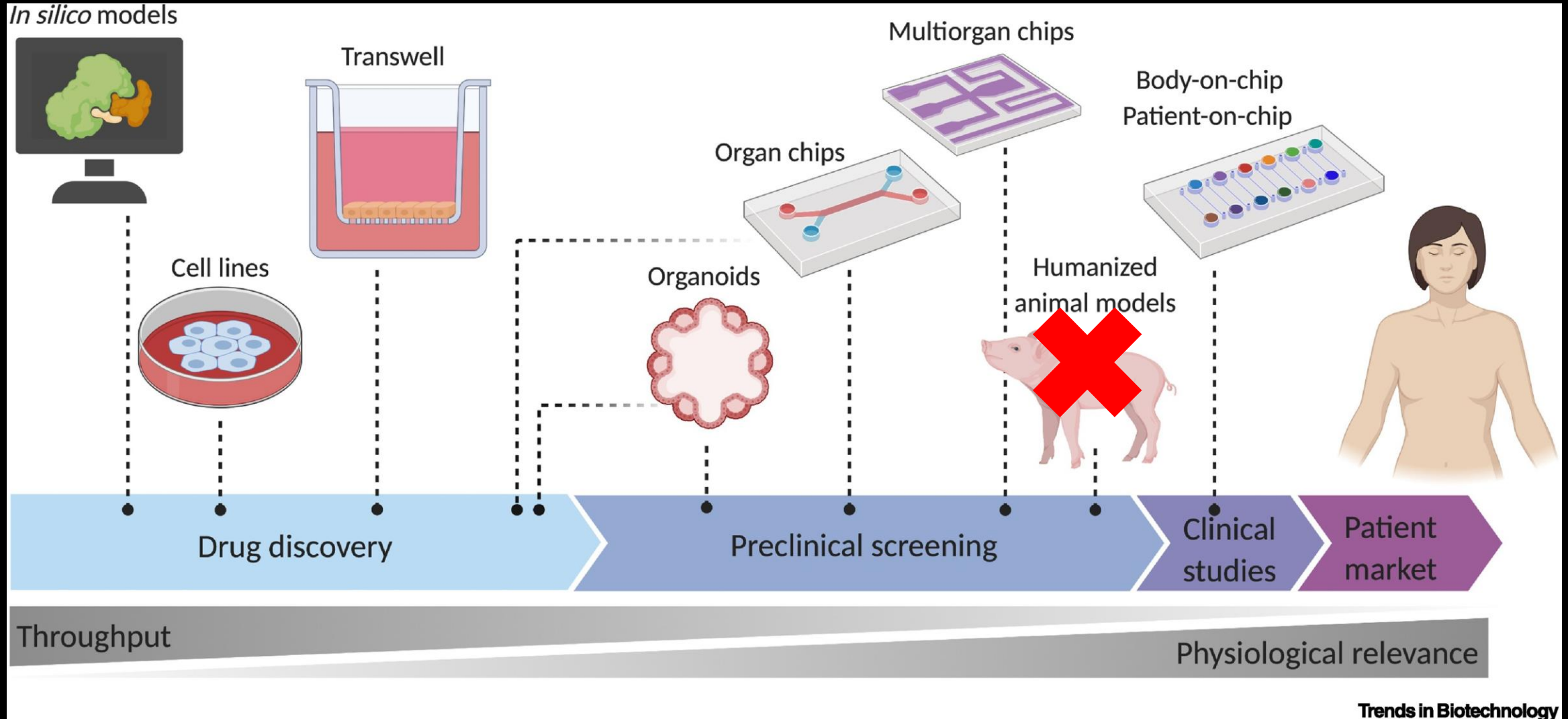
## Systematic and quantitative evaluations of Liver-Chips' predictive value



- 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





# Defining the right *in Vitro* model for drug discovery



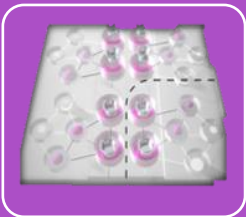
## Static 3D models

- 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

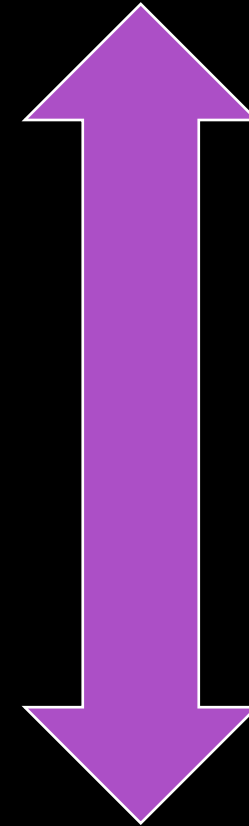
- Possibility to study PK/PD
- Interorgan crosstalk
- Suitable for drug toxicity and efficacy testing



## Body-on-chip

- Mimicking living organism
- Potential to replace animals
- Potentially suitable for conducting clinical trials

Throughput



Complexity  
Human Relevance

## OOC Limitations

No yet suitable for high-throughput screening

Lack of validated protocols

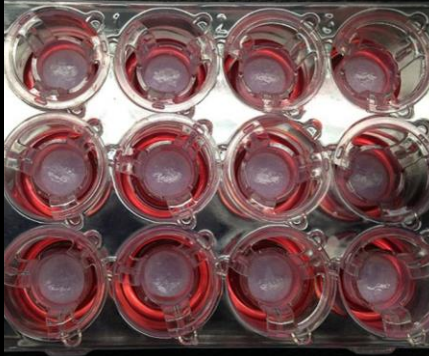
Variability

Cost of instruments and reagents

Limited ability of long-term growth of tissue/organs

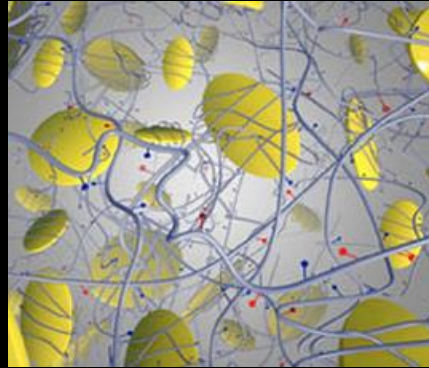
# 3D Bioprinting

## Organoids



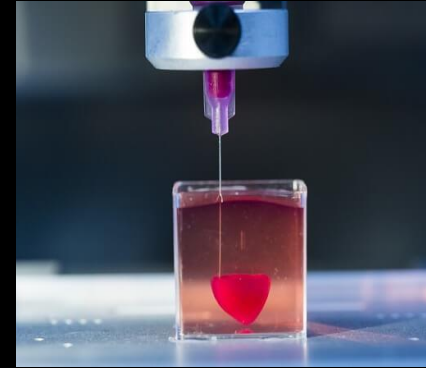
- Patient-Specific Disease Modelling
- Drug testing

## Biomaterials



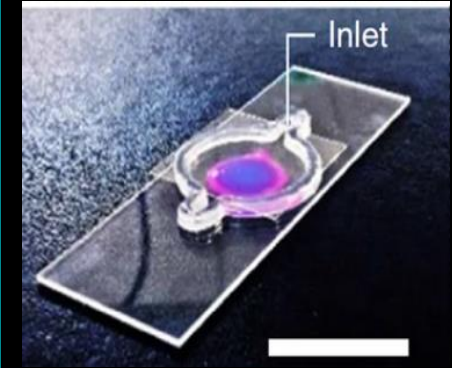
- Hydrogels
- Scaffolds

## 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.

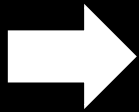
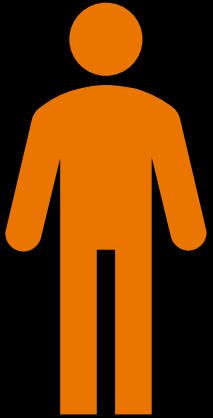




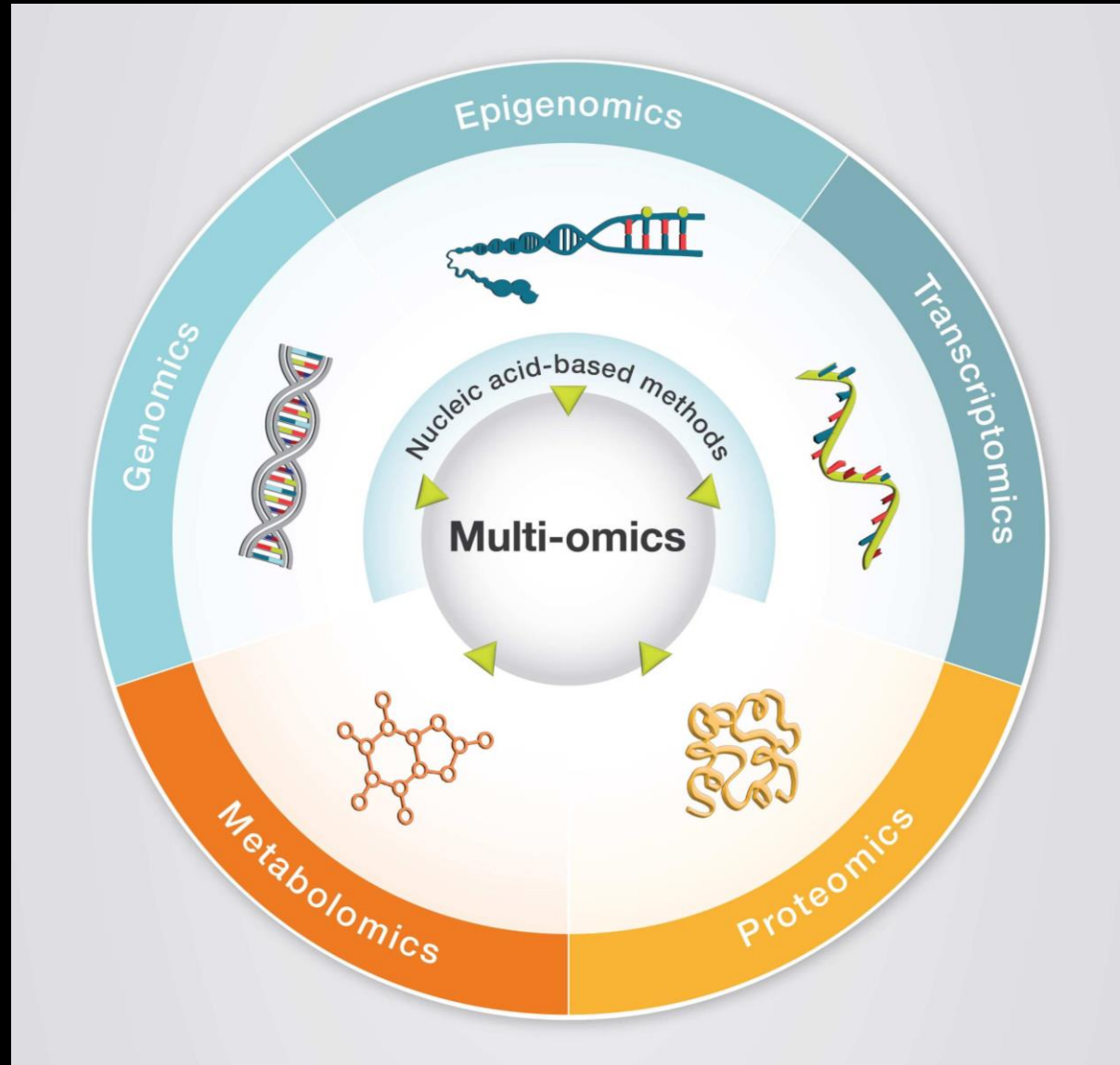
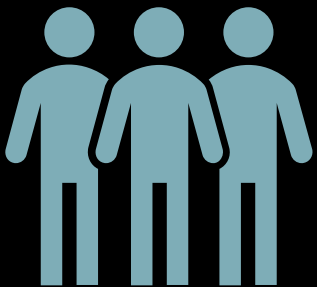
*In silico:* Big data, AI and computer modelling

# Big data – Single cell Omics/ Multi-omics

**Biobank**



**Cohorts**



## Key applications

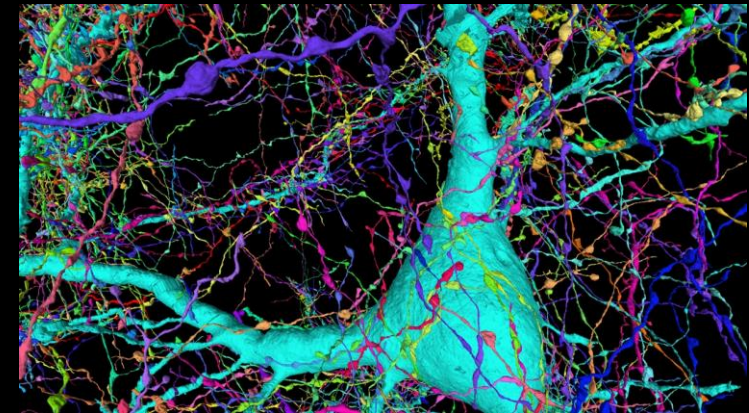
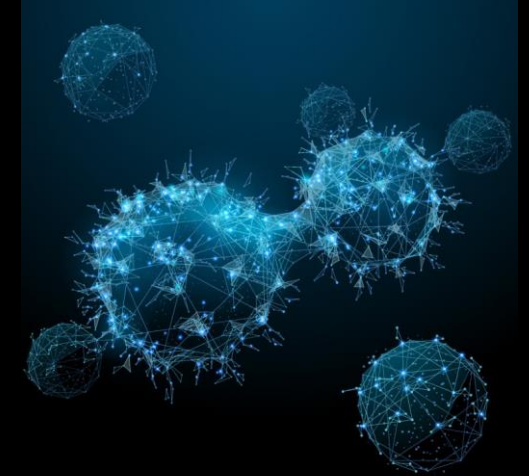
- Finding biomarkers
- Defining genetic and environmental risk factors
- Stratifying patients' population
- Define the molecular mechanisms underlying diseases



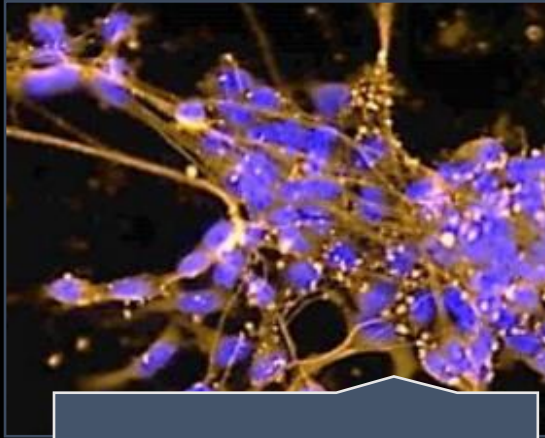
# Artificial Intelligence 'AI' and computer modelling

## Key applications

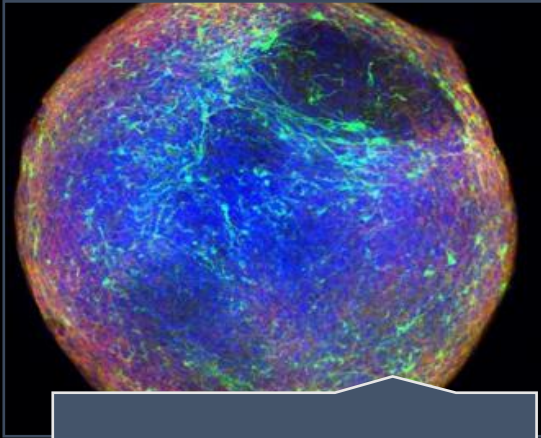
- Computational augmentation of existing clinical and imaging data sets
- Combine genomic and clinical data to detect new predictive models
- Predict drug toxicity and long term effect
- Predict pharmaceutical properties of molecular compounds and targets
- Faster and better disease diagnoses and progression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



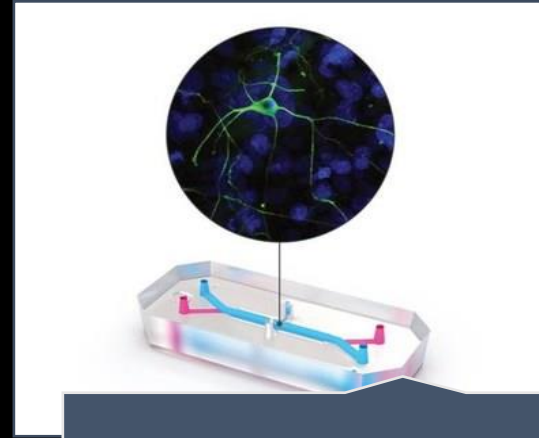
# The power of combining NAMs



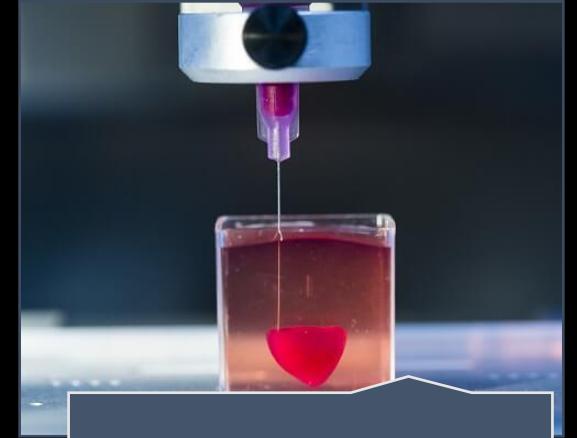
2D in vitro cells



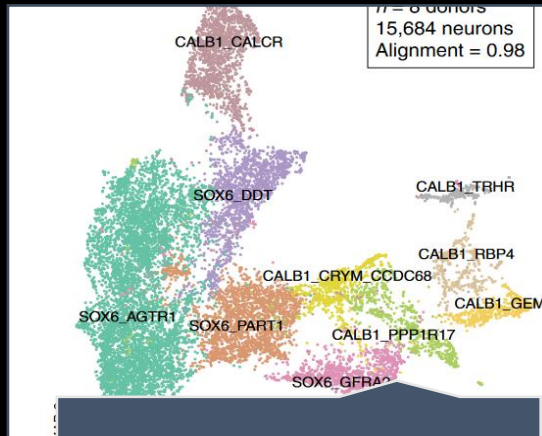
3D organoids



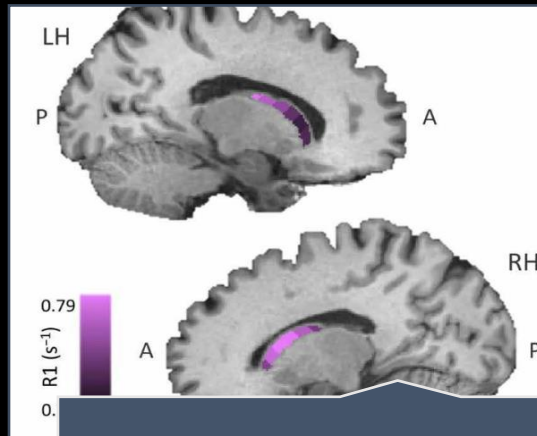
Organ-chips



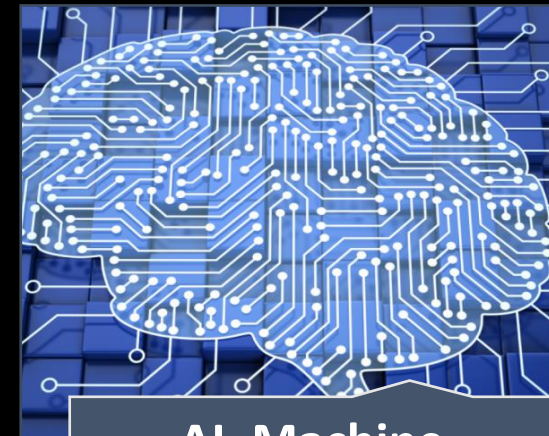
3D Bio-printing



Omics/ Multi-omics



Advanced imaging

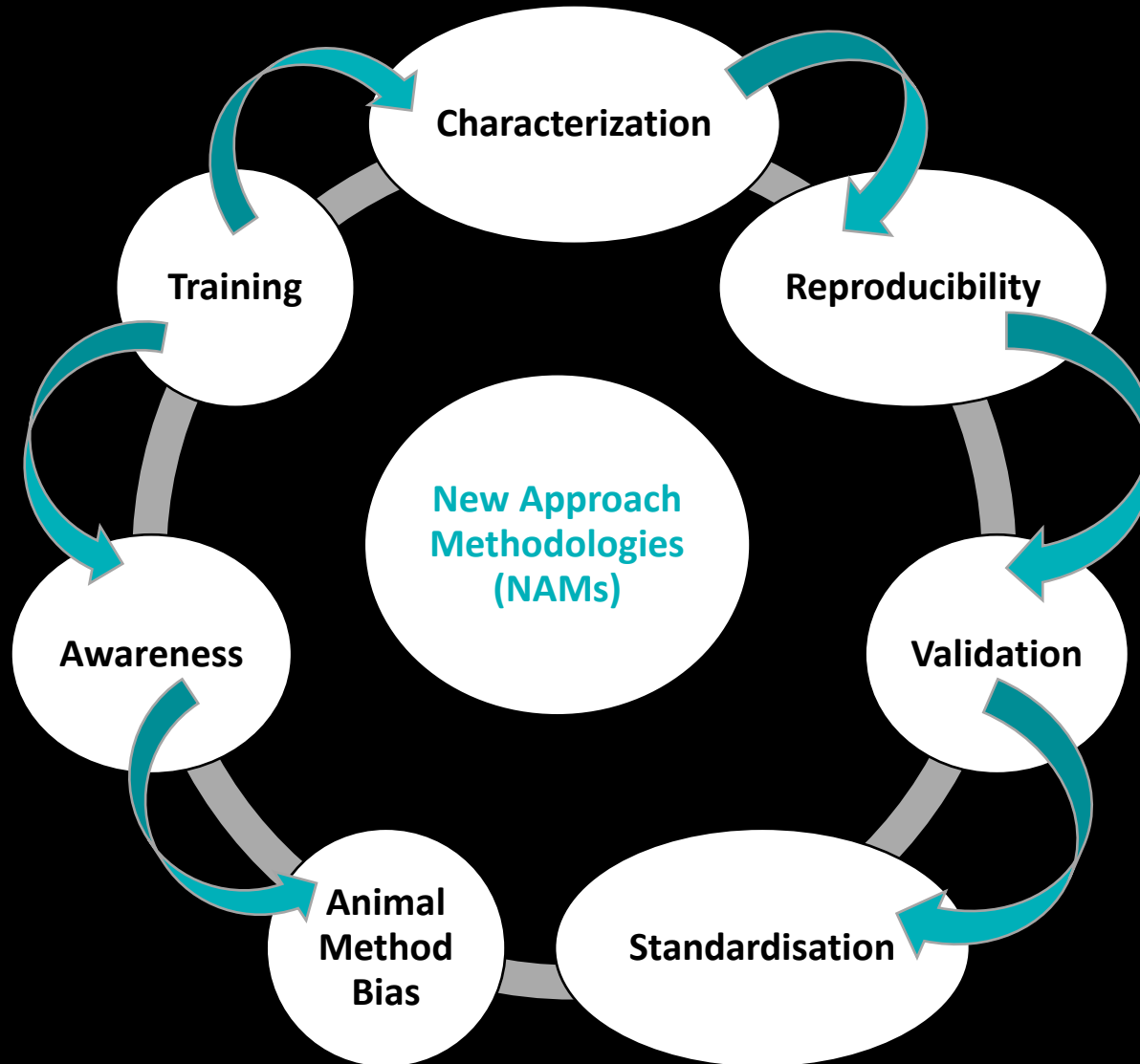


AI, Machine Learning



# Future challenges and opportunities

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*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?

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## ➤ 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?

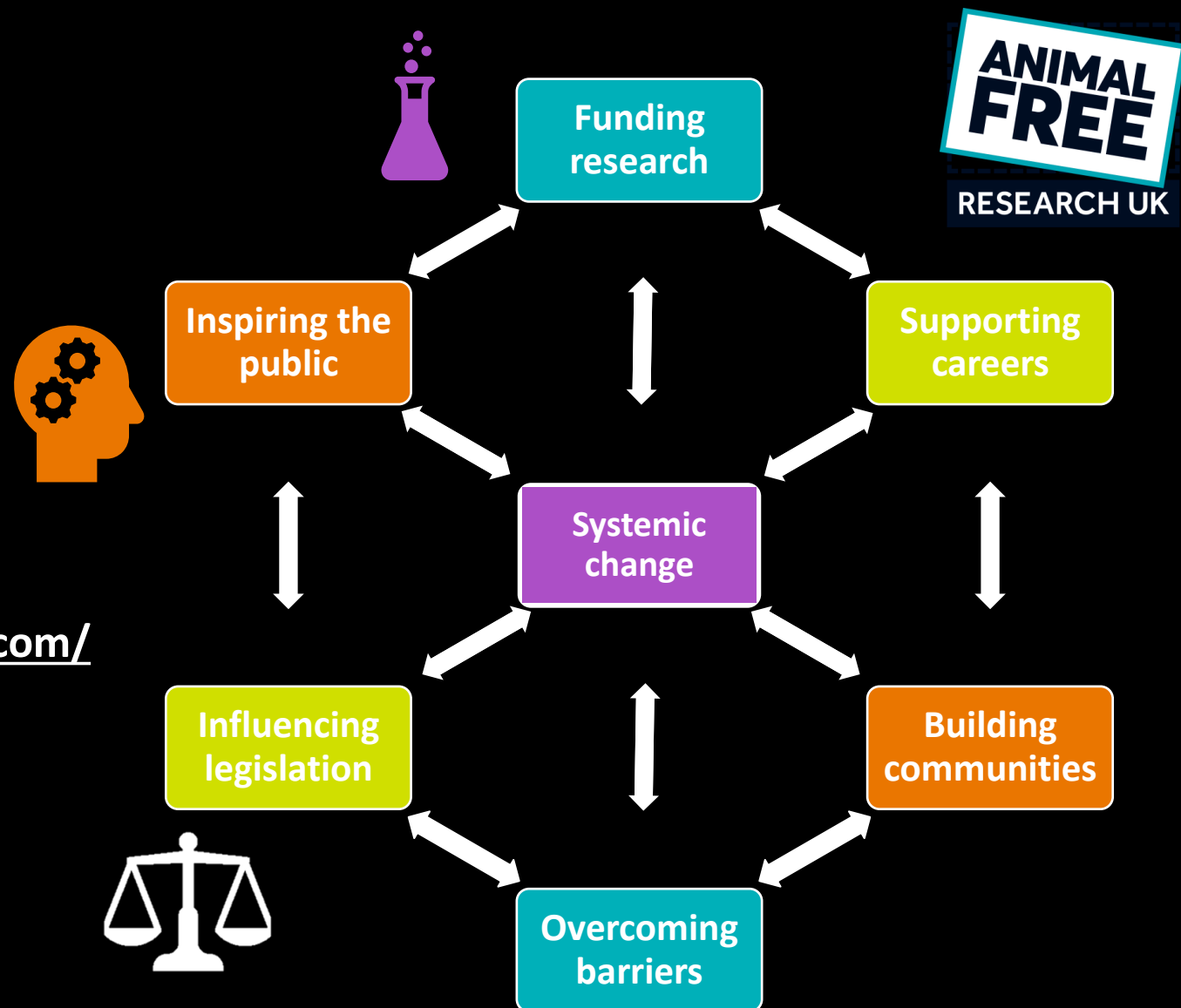
<https://www.animalfreeresearchuk.org/>

➤ Science Conference: 4-5 October 2023  
(Cambridge)

- TED-talk
- Helpathon
- Poster

➤ Community of Practice Platform

- <https://animalfreeresearchcommunity.com/>



[lilas@animalfreeresearchuk.org](mailto:lilas@animalfreeresearchuk.org)

 Lilas Courtot

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