Advancing NAMs in Regulatory Science

An Academic Perspective on Organoids & New Approach Methodologies

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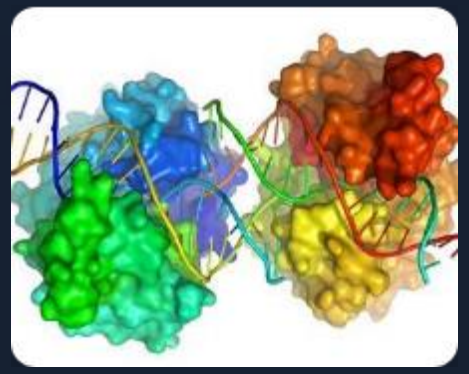
The NAMs Spectrum

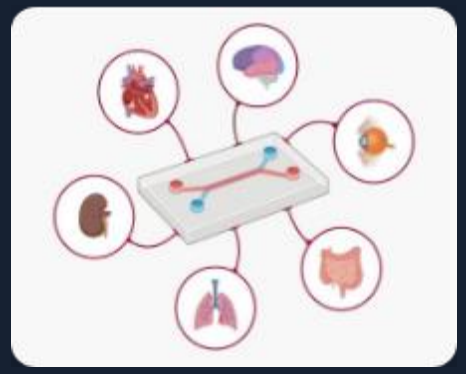


Computational

In silico models utilizing advanced algorithms and AI to predict compound toxicity without physical biology.

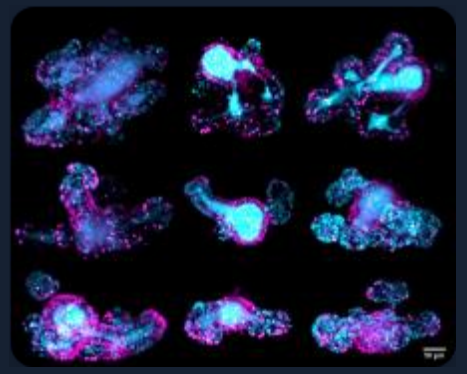
Simple In Vitro

Traditional 2D flat cell cultures and assays used for early-stage hazard and risk assessment.



Complex NAMs

Bioengineered microphysiological systems, like organ-on-a-chip, Multiple cell types combined, non necessarily mimicking 3D architecture.

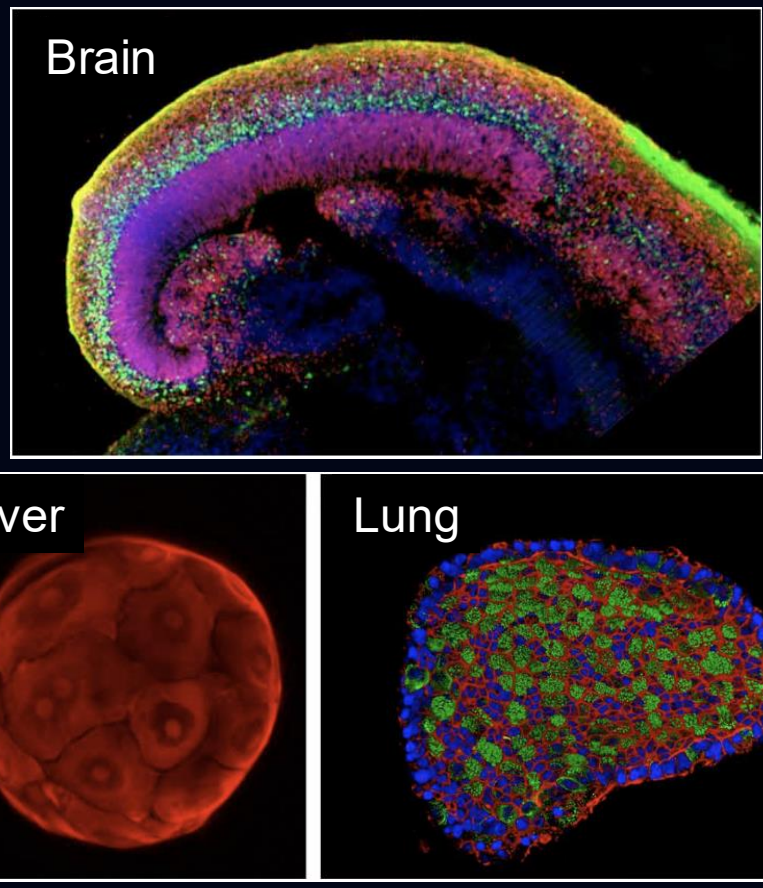


Organoids

3D miniaturized, stem-cell derived versions of human organs with highly realistic micro-anatomy.

Organoids: Defining Features

- **Self-Organization:**
  Cells autonomously communicate and dynamically assemble themselves into complex 3D structures without external rigid scaffolding.
- **Stem Cell Derived:**
  Grown in vitro, originating from pluripotent or tissue-resident adult stem cells rather than excised primary tissue.
- **Tissue Organization:**
  Authentically recapitulate the intricate spatial architecture, specific cell lineages, and microanatomy of the target organ.
- **Organ Function:**
  Exhibit localized physiological behaviors, such as secretion, filtration, or synchronous contraction, mirroring in vivo functionality.

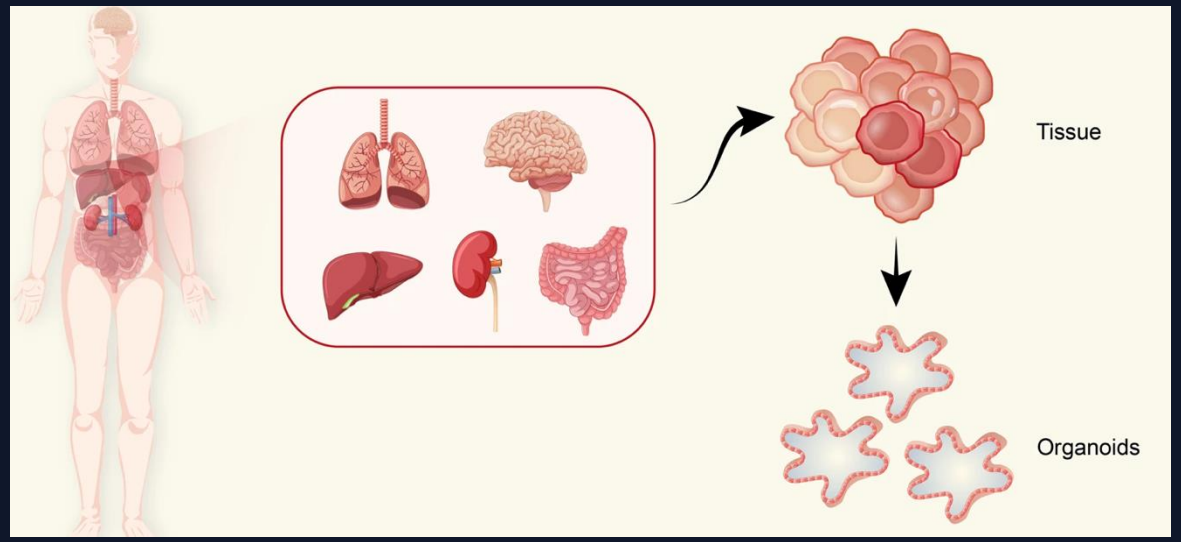


Source: Bredenoord, Clevers, Knoblich, Science 355, eaaf9414 (2017)

I am sure this is a misunderstanding but just so you know.

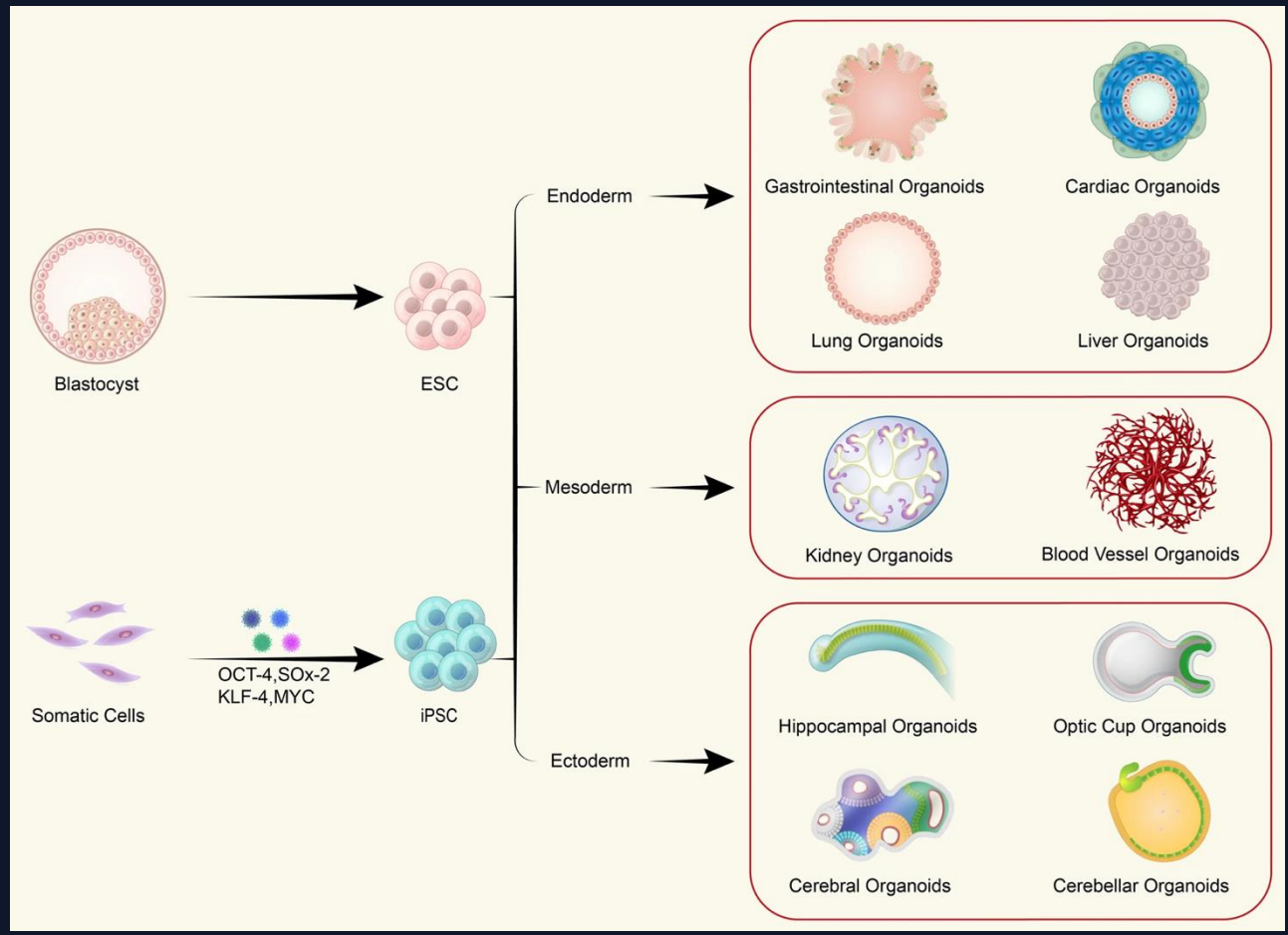
Two kinds of organoids

From adult stem cells



Sato…Clevers, 2009, Nature, 459, 262-5

From embryonic stem cells



Eiraku…Sasai, 2008, Cell Stem Cell, 3, 519-32

Eiraku…Sasai, 2011, Nature, 472, 51-6

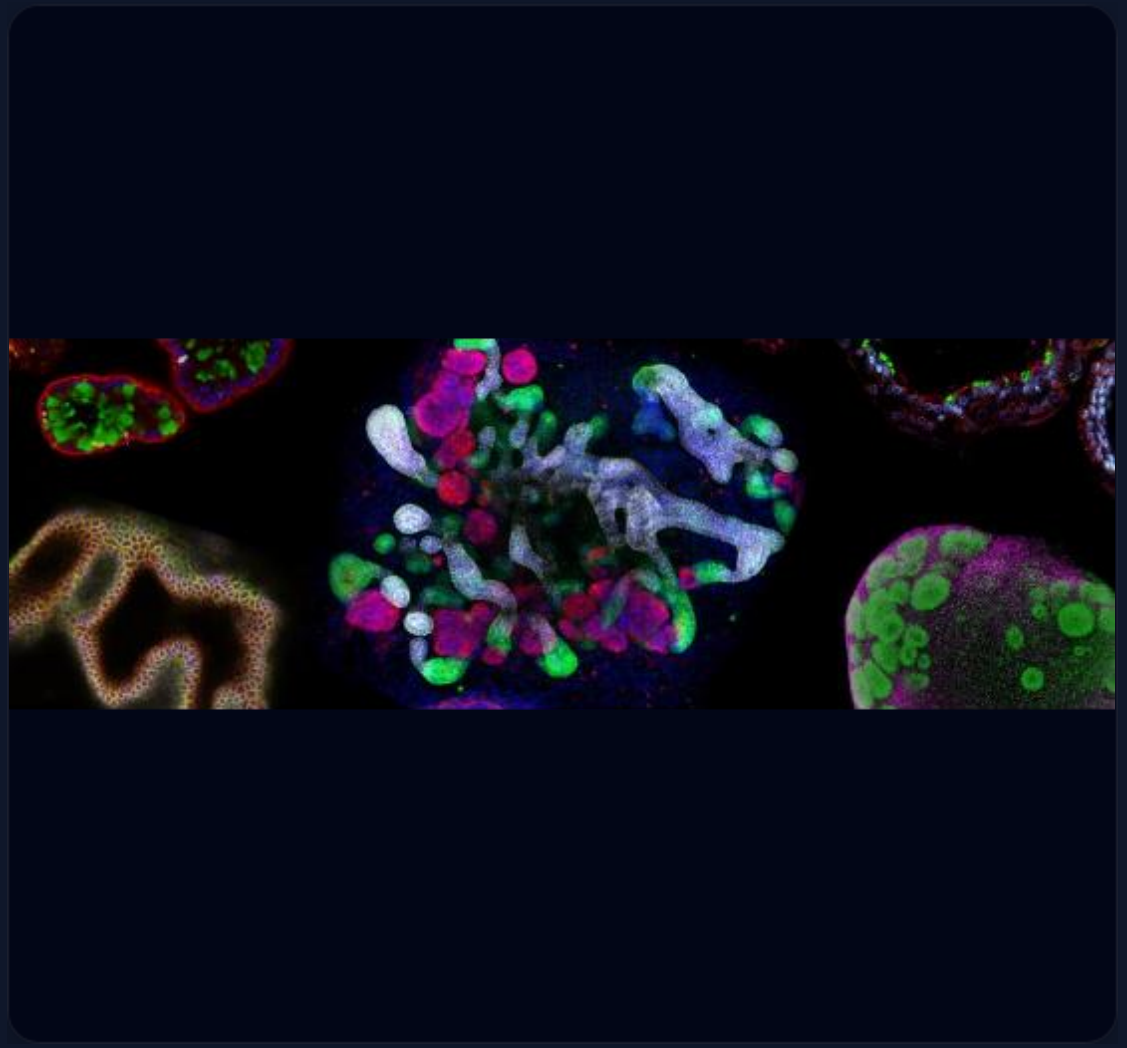
Lancaster…Knoblich, 2013, Nature, 501, 373-9

Comparing the Methodologies

Model System	Key Advantages	Major Limitations
Computational (In Silico)	High throughput, highly scalable, cost-effective, avoids biological variability entirely.	Relies heavily on existing data quality; cannot predict entirely novel biological pathways.
2D In Vitro (2D)	Well-established, standardized protocols, highly reproducible, inexpensive, easy to scale.	Lacks 3D architecture, poorly represents in vivo physiology, cells rapidly lose phenotype.
Complex NAMs (MPS)	Incorporates physical forces (e.g., shear stress), fluid flow, allows linked organ-crosstalk.	High engineering complexity, low throughput, expensive, standardisation remains difficult.
Organoids (3D)	High genetic fidelity, realistic micro-anatomy, enables personalized/patient-specific medicine.	Low throughput, high biological batch-to-batch variability, Often lacks endogenous vasculature & immune cells,

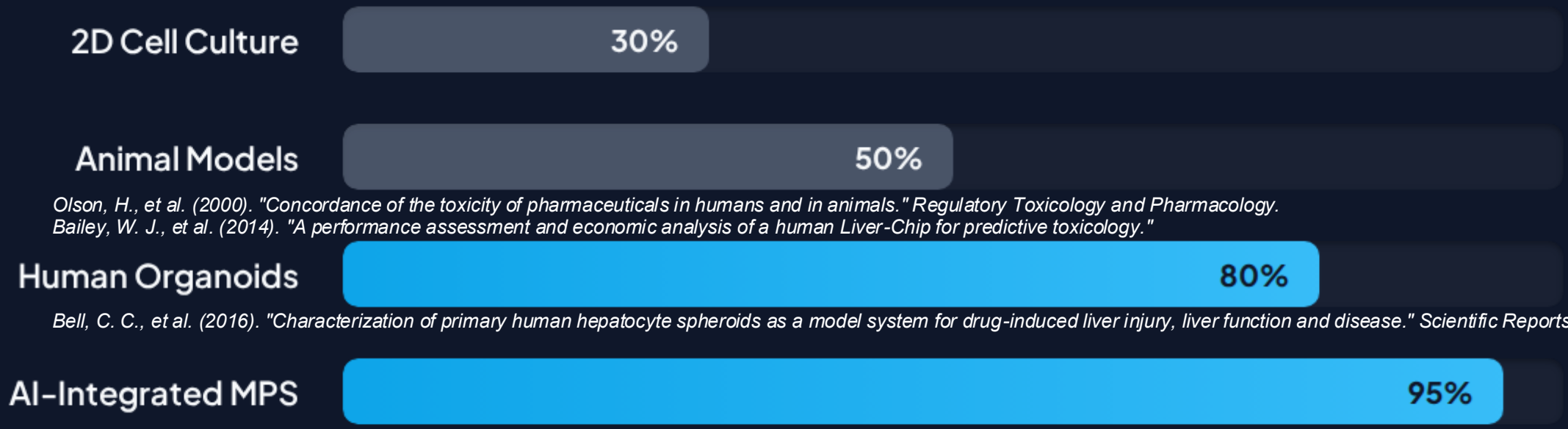
Success Stories in Medicine R&D

- Patient-derived iPSC models of ALS have generated therapeutic candidates that advanced into clinical testing (ropinirole)
- Patient-derived tumor organoids predict responses to chemotherapy, targeted therapy, chemoradiation, and emerging cell therapies.
- AI-integrated NAMs and engineered cardiac systems transform cardiotoxicity prediction
- AI-discovered compounds such as INS018_055 show accelerated transition from discovery to human testing.



See: Liu et al., Cell 2026 New approach methodologies for drug discovery.

Predictive Validity (Human Hepatotoxicity)



Olson, H., et al. (2000). "Concordance of the toxicity of pharmaceuticals in humans and in animals." Regulatory Toxicology and Pharmacology.
Bailey, W. J., et al. (2014). "A performance assessment and economic analysis of a human Liver-Chip for predictive toxicology."

Bell, C. C., et al. (2016). "Characterization of primary human hepatocyte spheroids as a model system for drug-induced liver injury, liver function and disease." Scientific Reports.

("best in class" rather than average: *Ewart, L., et al. (2022). "Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology." Communications Medicine.*

Data conceptually illustrates the predictive accuracy leap provided by advanced NAMs over traditional preclinical models in identifying human drug-induced liver injury.

Key Biological Challenges

Process Isolation

Organoids can mimic isolated cellular mechanisms beautifully but lack whole-organism systemic context. Thus, they are very good in predicting toxicity but can not predict overarching safety.

Organ Crosstalk

The absence of integrated endocrine and immune systems makes studying organ-to-organ communication difficult. An isolated liver model cannot predict an immune cascade.

Vascularization

Many 3D models still lack complex, functional blood vessel networks, limiting the accurate study of drug absorption, distribution, metabolism, and excretion (ADME).

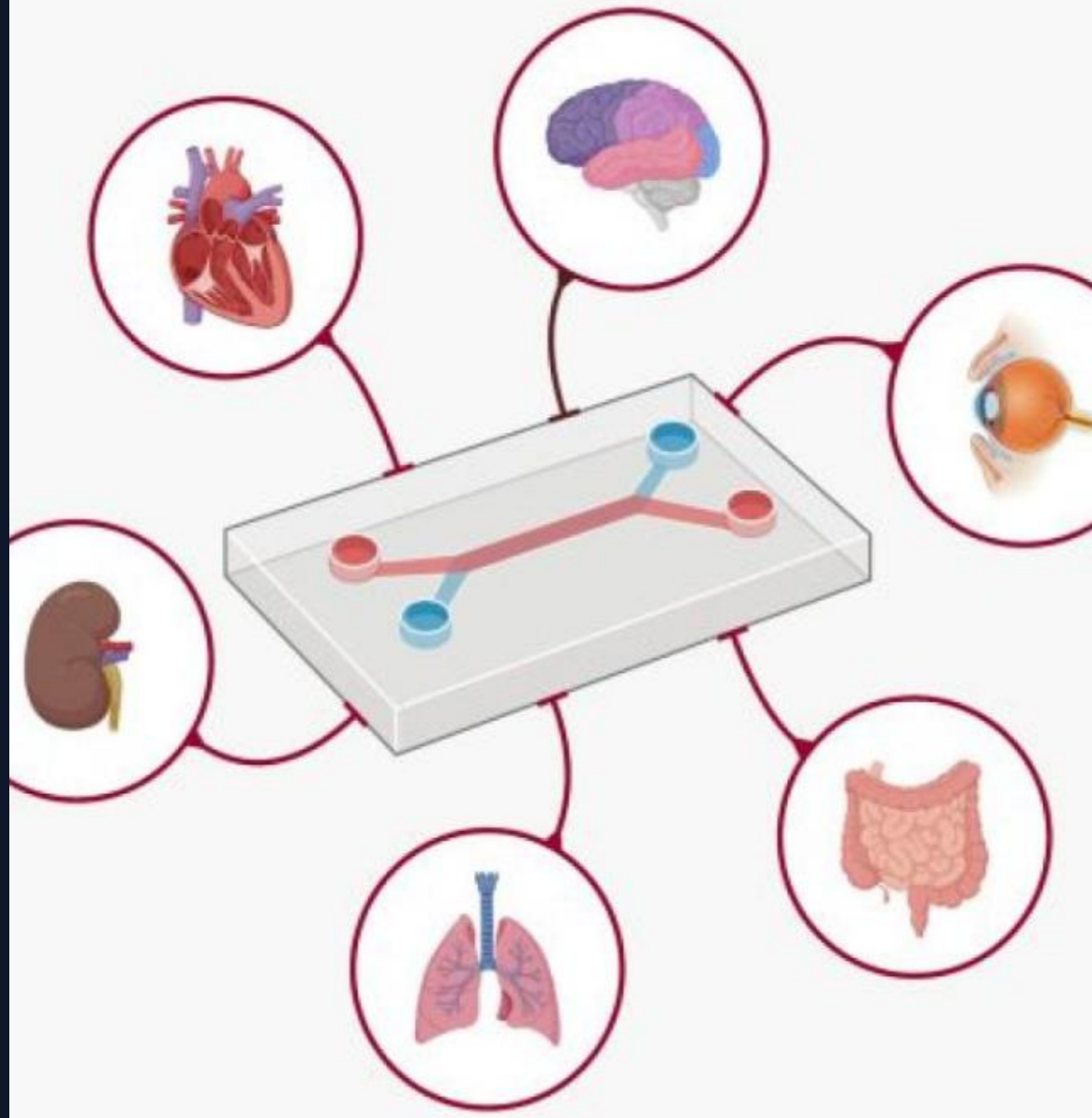
Research progresses dynamically:

Multi-Organ Systems

To overcome biological isolation, researchers are adopting multi-organ-on-a-chip technologies. By fluidically connecting distinct organoids, we simulate dynamic organ crosstalk and immune responses.

In Silico Integration

When coupled with Physiologically Based Pharmacokinetic (PBPK) modeling, these hybrid NAMs bridge the gap from isolated cellular assays to highly predictive whole-organism physiology.



Researchers need to understand regulatory language

Purpose-Driven Model Development

A NAM is rarely universally "qualified" to completely replace an animal model. Instead, regulators and industry evaluate new methodologies strictly within a clearly defined Context of Use.

To successfully translate a model, researchers must define its exact purpose and Domain of Applicability: *"This specific system is utilized to de-risk [X specific toxicity] for [Y specific drug class] during [Z stage of preclinical safety decision-making]."*

Bridging the Gap: Academic vs. Industry

Parameter	Academic Priority	Industry Expectation
Primary Goal	Biological novelty and increasing complexity	Robustness, reproducibility, and predictive validity
System Design	Bespoke, highly specialized, low-throughput	Standardized, scalable, and high-throughput compatible
Data Output	Deep mechanistic insights and novel biomarkers	Clear, reproducible risk metrics for Go/No-Go decisions
Quality Control	Lab-specific, dynamic, flexible protocols	Stringent, internationally standardized GLP alignment

Identifying R&D Applications

Analyzing Translational Failures Academics target biological areas where traditional animal models historically exhibit poor predictive validity, focusing efforts on urgent, unmet needs like neurodegeneration or specific hepatotoxicities.

Mapping to Adverse Outcome Pathways (AOPs) By measuring causally linked key events (like oxidative stress) within established AOP frameworks, researchers ensure the biological model directly informs standardized regulatory risk assessment.

Early Regulatory Dialogue Academics pursue viable applications by engaging early with platforms like the EMA Innovation Task Force, ensuring novel methodologies address genuine regulatory needs prior to full qualification.