NIH Tissue Chip Program: Metrology & Standards for New Approach Methodologies: Building an Infrastructure for Tissue Chips and Human-Relevant Drug Testing

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National Center for Advancing Translational Sciences

NIST/NIBIB Symposium on Medical Metrology and Standards
for American Healthcare and Commerce
September 24, 2026

No financial conflicts of interest to disclose

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Talk Outline

Introduction

- **NCATS Mission and Vision**
- **The Public Health Challenge: The Drug Development Pipeline**
- **Evolution of in vitro Cell Models – Tissue Chips**

Area I: The NIH/NCATS Tissue Chip Testing Centers

- Independent validation, not self-reported performance alone, builds the confidence needed for broader adoption

Area II: Translational Centers for Microphysiological Systems Resource Cores

- Centralization of specialized fabrication technologies, biological and technical materials, and coordinated SOPs helps transition MPS platforms toward regulatory context-of-use -- a model for shared infrastructure that reduces duplication and harmonizes practice across labs.

Area III: Complement-ARIE NAMs Data Hub and Coordinating Centers

- Showing that NAMs standardization is a data metrology challenge as much as a physical one.



NCATS' MISSION

Turn research observations into health solutions through translational science

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NCATS' VISION

More treatments for all people more quickly

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The Public Health Challenge: The Drug Development Pipeline

10,000

Diseases



and only

5%

Have Treatments or Cures



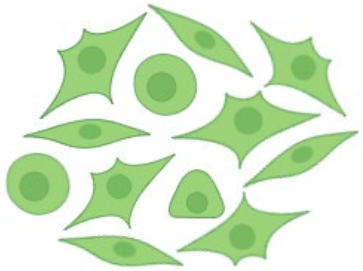
Time from early development to the medicine cabinet takes 10-15 years.

9 out of 10

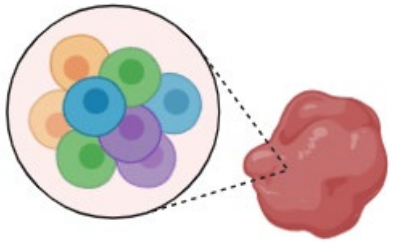
Promising therapeutic candidates that enter clinical trials fail.

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Evolution of in vitro Cell Models



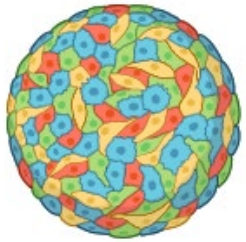
First Generation
Immortalized/ continuous cell lines



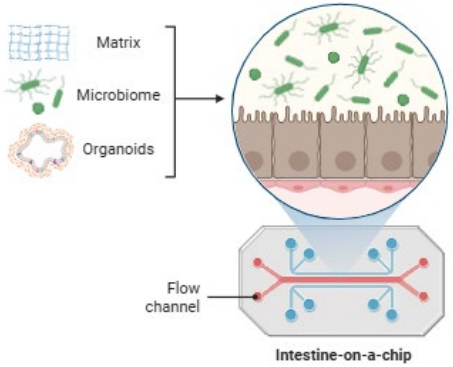
Second Generation
Primary cells
Reporter cell lines
Transfected cell lines



Third Generation
Gene-edited cell lines
Immortalized primary cells



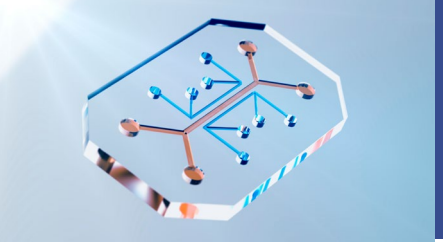
Fourth Generation
Organoids/Spheroids
3D Models



Fifth Generation
Tissue Chip
Organ-on-Chip
Microphysiological Systems

Created with BioRender ; Adapted from C. Lucchessi, ATCC

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The Evolution of NIH Tissue Chips for Drug Screening Program

2012-Current

Disease Modeling and Efficacy Testing / TC2.0

Capture the pathophysiology, mutation spectrum and phenotypic diversity of human diseases and conditions

Clinical Trials on a Chip – Precision Medicine

Inform clinical trial design, planning and execution

Regulatory Acceptance

Translational Centers for MPS

Botulinum Toxin Potency Assay

Total Investment: 500 million and counting!

2012-2017

2017-2021

2016-2022

2021-2025

2022-2024

2024-2028

2026-2031

Safety Pharmacology/ TC1.0

Assessing toxicity where no physiologically and pharmacologically relevant models are available

Building Confidence

Tissue Chip Testing Centers

MPS Database

Building Community

MPS World Summit

International MPS Society

Most Recent Programs

Tissue Chips in Space 2.0

COMPLEMENT-ARIE Common Fund Program

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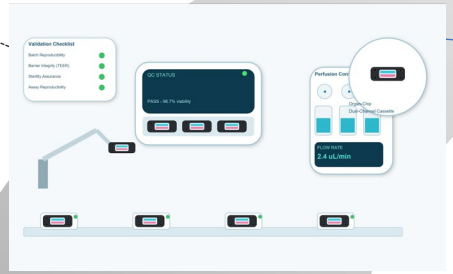
Increasing Confidence and Adoption of Tissue Chip Technology through the NIH Tissue Chip Testing Centers

YOU ARE HERE

Path to Adoption and Commercialization

3) Industrial Validation - 2019

- Use by industry and regulatory agencies
- Proprietary set of compounds
- CRO-type environment



- **Javelin Biotech** (spin off from MIT)
  - CRO business model
- **Texas A&M Tissue Chip Testing Consortium**
  - Play for pay model with academia, government and industry
- **BioSystics Analytics Platform:** https://www.biosystics.com/

2) Analytical Validation - 2017

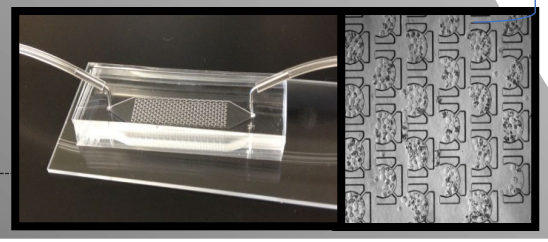
- Independent: testing for **robustness, reproducibility, reliability, relevance**
- Validation set of compounds, biomarkers, assays
- TC Testing Centers



- **Tissue Chip Testing Centers:**
  - Massachusetts Institute of Technology
  - Texas A&M University
- **UPITT MPS Database:** https://mps.csb.pitt.edu/

1) Physiological Validation - 2012

- Organ function and structure
- Training set of reference compounds
- TC developers



Publications: (as of Oct 2017)
A total of 506 original and review articles (cited over 5600 times) published in top tier journals, including *Nature Medicine, Nature Communications, Nature Materials, PNAS, Science, Science Translational Medicine, etc.*

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TEX-VAL: Tissue Chip TESTING Center (funded by NIH-NCATS)

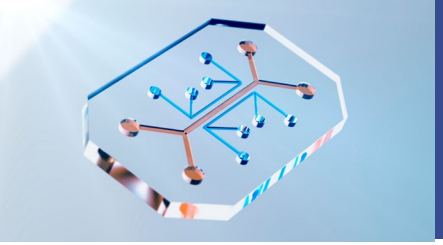
Oct. 2016 – Sept. 2018 (TEX-VAL 1.0) **Oct. 2018 – Sept. 2020 (TEX-VAL 2.0)**

- Did we get these academic lab-made devices to work outside of the developer lab?

  Mostly yes
- Can we replicate the results from the developers? **Mostly yes**
- What was the biggest challenge to technology transfer? **Availability of the functional primary cells**
- Were the devices "ready" for testing drug safety in the "real world"? **Most were not**
- What was the most important "learning" from these studies? **Developers learning about the limits of their technologies and how to make them useful to the end-users**

Lessons Learned: TCTCs

1. Staged validation builds confidence incrementally. Physiological → independent analytical → industrial validation (2012–2019) matured the technology in step with the evidence needed at each stage.
2. Separating developer from validator was the key structural innovation. Independent TCTCs tested platforms against industry-standard assays/biomarkers — not self-validation by developers.
3. Legal/IP infrastructure (template agreements) had to precede scientific collaboration. Standardized CDAs/CRAs let developers and testing centers share proprietary platforms and data at scale.
4. Validation and open data-sharing were coupled by design, not added later — public database integration was required from the outset.
5. One funding cycle wasn't enough. A second generation (NextGen TCTC + dedicated Data Center) was needed to move from analytical to industrial-scale validation.
6. Validated technology diffused into multiple adoption models — CRO spinout, pay-for-play consortium, analytics platform, open database — not a single path.
7. ~7-year arc (2012–2019) from independent validation to industrial adoption — a useful benchmark for newer NAMs.



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Translational Centers for Microphysiological Systems

TraCe MPS ; 2024-2029

National Center for Advancing Translational Sciences

National Institute on Aging

NIH National Institutes of Health
Office of Research on Women's Health

NIH ORIVA

U.S. FOOD & DRUG ADMINISTRATION

CRITICAL PATH INSTITUTE



Translational Centers of Excellence

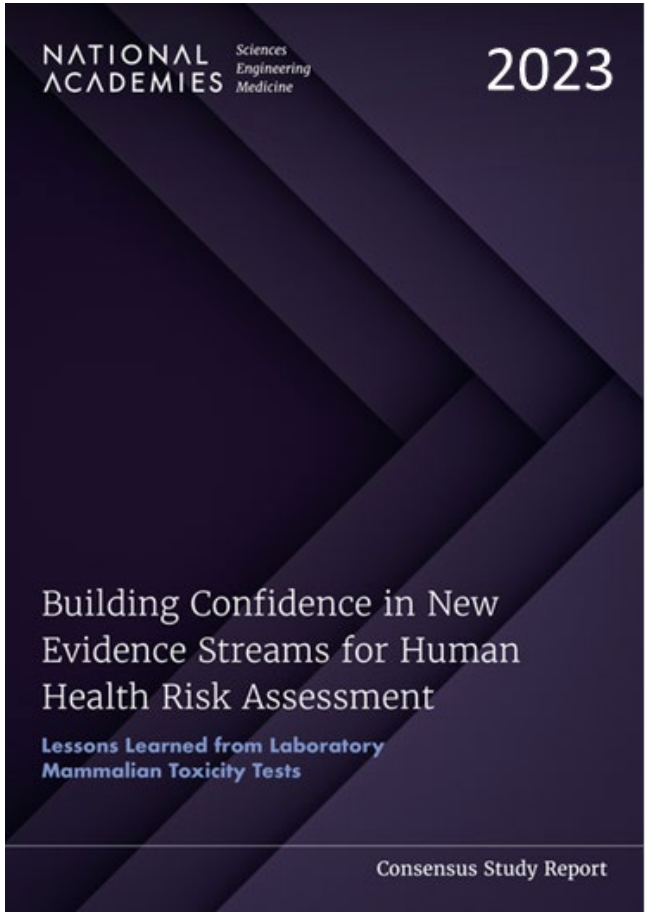
1. Mt. Sinai University and University of Washington – Kidney Diseases
2. The University of Texas Medical Branch at Galveston, Texas Engineering Experiment Station, and Texas A&M – Preterm Birth/Pregnancy
3. University of Pittsburgh - Drug induced liver injury and MASLD
4. University of Rochester and Duke University – Barrier Function

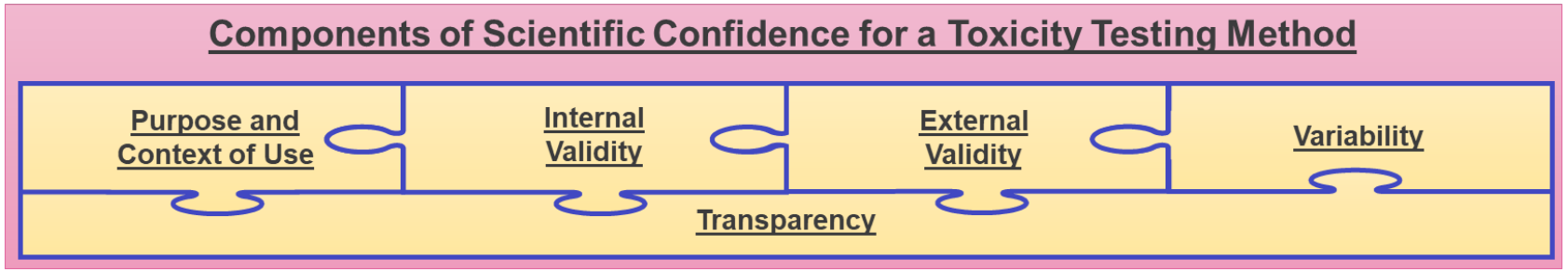
- Program Goals:
  - To accelerate the translational use of MPS in drug development through regulatory acceptance and adoption for industrial use.
  - Qualification of validated MPS for highly specific contexts of use (CoU) through FDA ISTAND Program

- Letter of Agreement between NCATS/NIH and US FDA Innovative Science and Technology Approaches for New Drugs (ISTAND) and Critical Path Institute

Building Confidence via a Scientific Framework for NAMs

1. **Intended purpose and context of use** - the specific question being addressed, commonly framed as a population, exposure, comparator, and outcome (PECO) statement
2. **Internal validity** - the extent to which systematic error/bias can influence the extent to which a study answers its research question 'correctly'
3. **External validity** - whether the study is addressing the relevant research question and is generalizable to other contexts
4. **Biological and experimental variability** - conducting repeatability, transferability, and reproducibility studies
5. **Transparency** - adequate information should be available in order to fully evaluate the above items



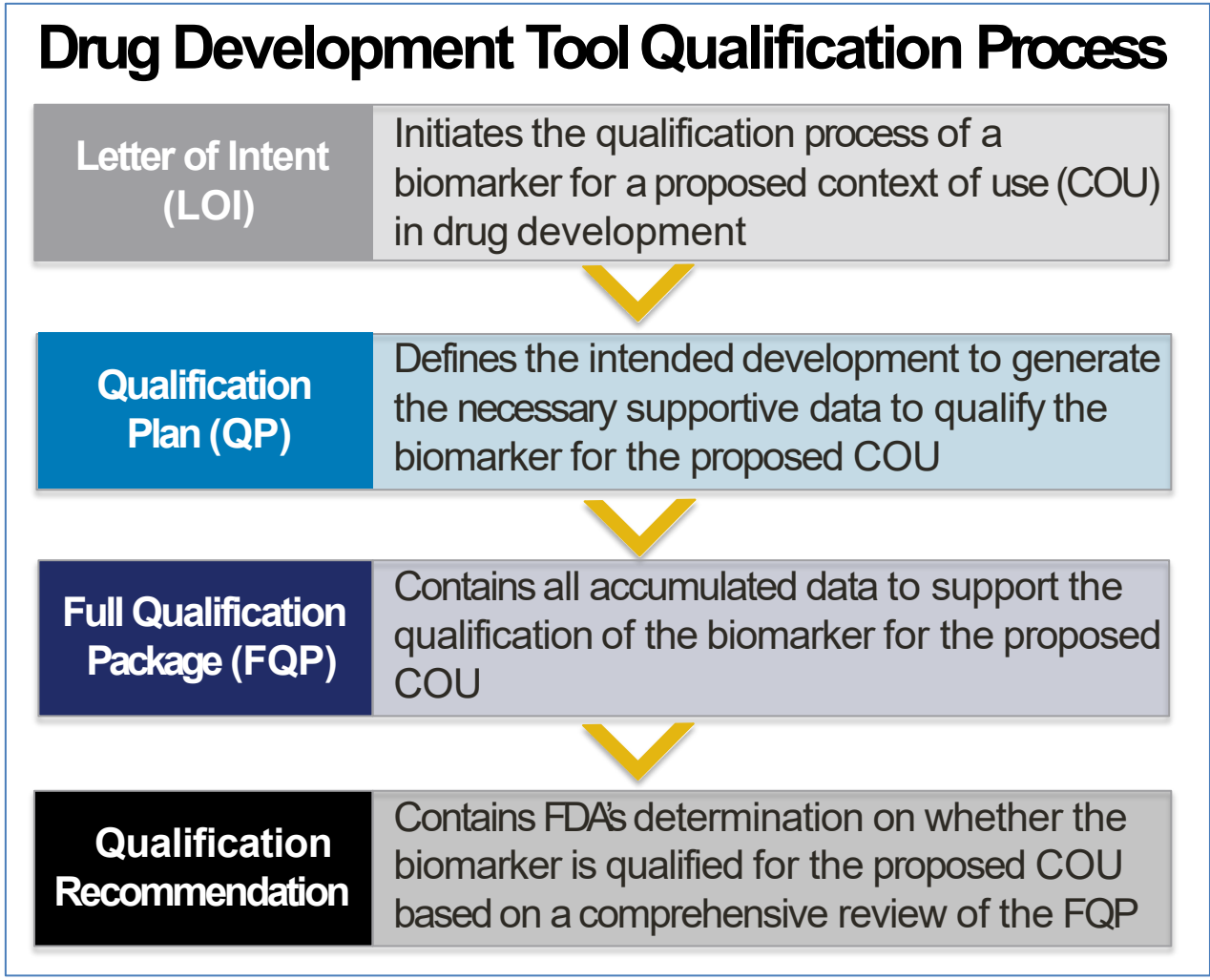


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FDA Qualification Process

- **Qualification:** FDA endorsement of a method/biomarker for a defined context of use
- NAM data can be submitted in investigational or marketing applications

- **Superiority of NAMs** must be demonstrated vs. existing methods
- **Context of use** sets boundaries where data support NAM use



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Translational Centers for MPS (TraCe-MPS):
Submissions to FDA ISTAND Program

FDA Innovative Science and Technology Approaches for New Drugs (ISTAND) Program

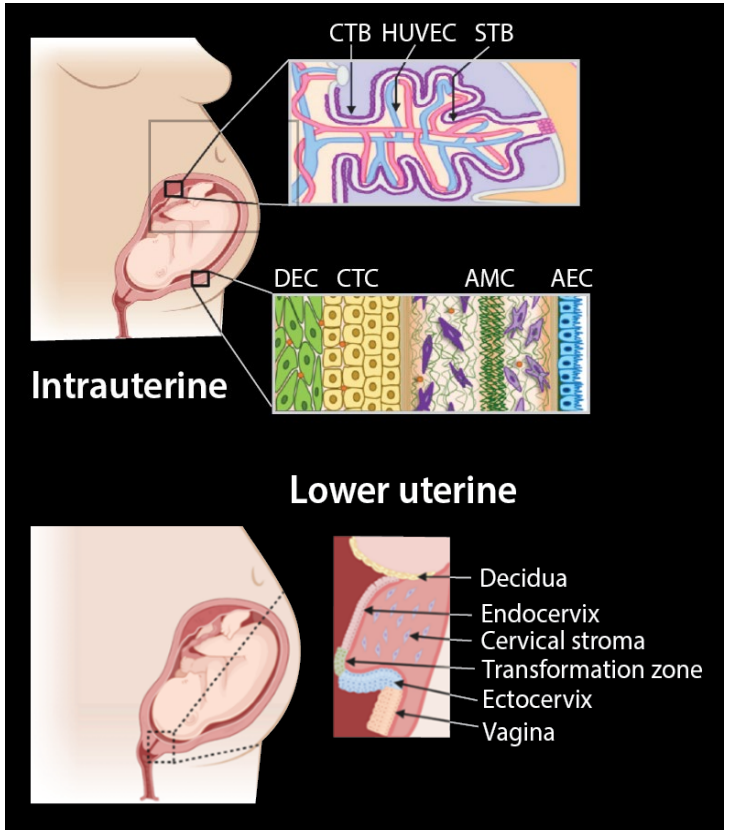
- Accepts submissions for qualification of drug development tools (DDTs) that fall outside existing qualification pathways for biomarkers, clinical outcome assessments, and animal models.
- Piloted by FDA in 2020; made a permanent program on 7/31/2025.
- **25% of accepted LOIs** came from TraCe-MPS Centers — underscoring the program's substantial contribution to regulatory acceptance and adoption of MPS technologies.

Project Institute & #	Project Name	Submission Stage / Status
Organ Pathobiology and Therapeutics Institute DDT-IST-000034	Liver acinus MPS (LAMPS) for determining drug candidate dosing in clinical trials of liver disease	**2026-02-26 - Qualification Plan submitted [RE-SUBMIT]** 2025-06-23 - LOI accepted & QP invited 2025-02-20 - LOI reviewable 2025-01-09 - LOI submission
Texas A&M University — UTMB at Galveston DDT-IST-000047	Human chorio-decidual interface organ-on-chip for derisking positive rodent DART studies for new-modality IND candidates	**2026-06-02 - Qualification Plan submitted [RE-SUBMIT]** 2025-11-13 - LOI accepted & QP invited 2025-07-15 - LOI reviewable 2025-07-07 - LOI submission
Mount Sinai — University of Washington DDT-IST-000045	Human Kidney Chip for assessment of relative nephrotoxicity	**2025-11-13 - LOI accepted & QP invited** 2025-07-03 - LOI reviewable 2025-06-24 - LOI submission
Organ Pathobiology and Therapeutics Institute DDT-IST-000044	Quantifying hepatotoxicity using the liver acinus microphysiological system (LAMPS) for determining drug candidate dosing in clinical trials of liver disease	**2025-11-25 - LOI accepted & QP invited** 2025-07-03 - LOI reviewable 2025-06-19 - LOI submission
Univ. of Rochester Medical Center — Clinical & Translational Science Institute DDT-IST-000065	Microphysiological system for preclinical assessment of CRS and ICANS induced by T-cell-engaging monoclonal antibodies	**2026-06-24 - LOI accepted & QP invited** 2026-03-18 - LOI reviewable 2026-02-20 - LOI submission

A Translational Center for Microphysiological Systems-Based Drug Development Tools for Pregnancy and Women's Health (TraCeR)

Ramkumar Menon, Arum Han, Ivan Rusyn, Lauren Richardson, Ananth Kumar Kammala

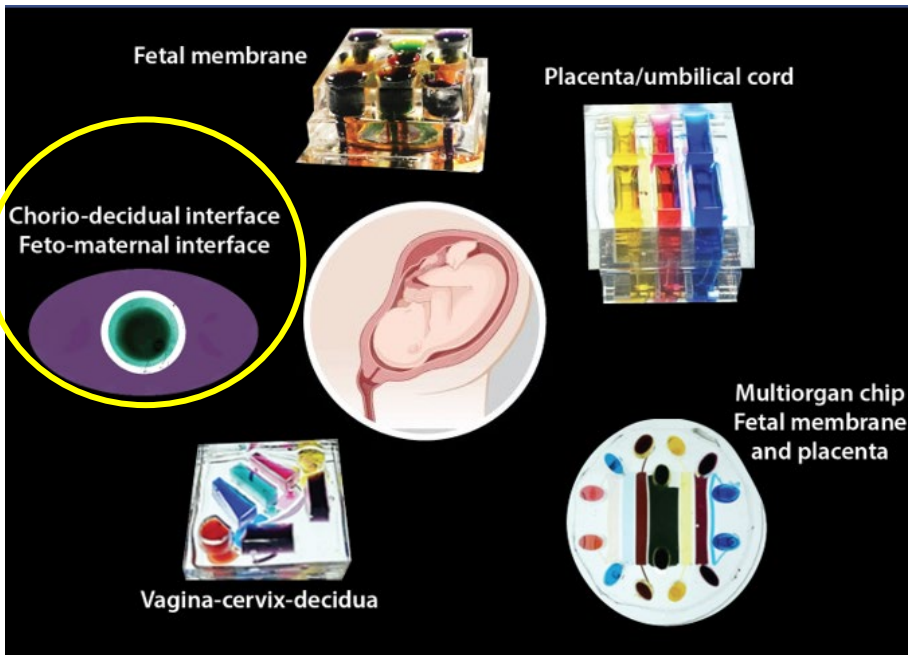
TraCe-R
It's About Saving Babies



Images courtesy: Ramkumar Menon, University of Texas Medical Branch

Public Health Problem: Pregnant women and their fetuses are "Therapeutic Orphans"

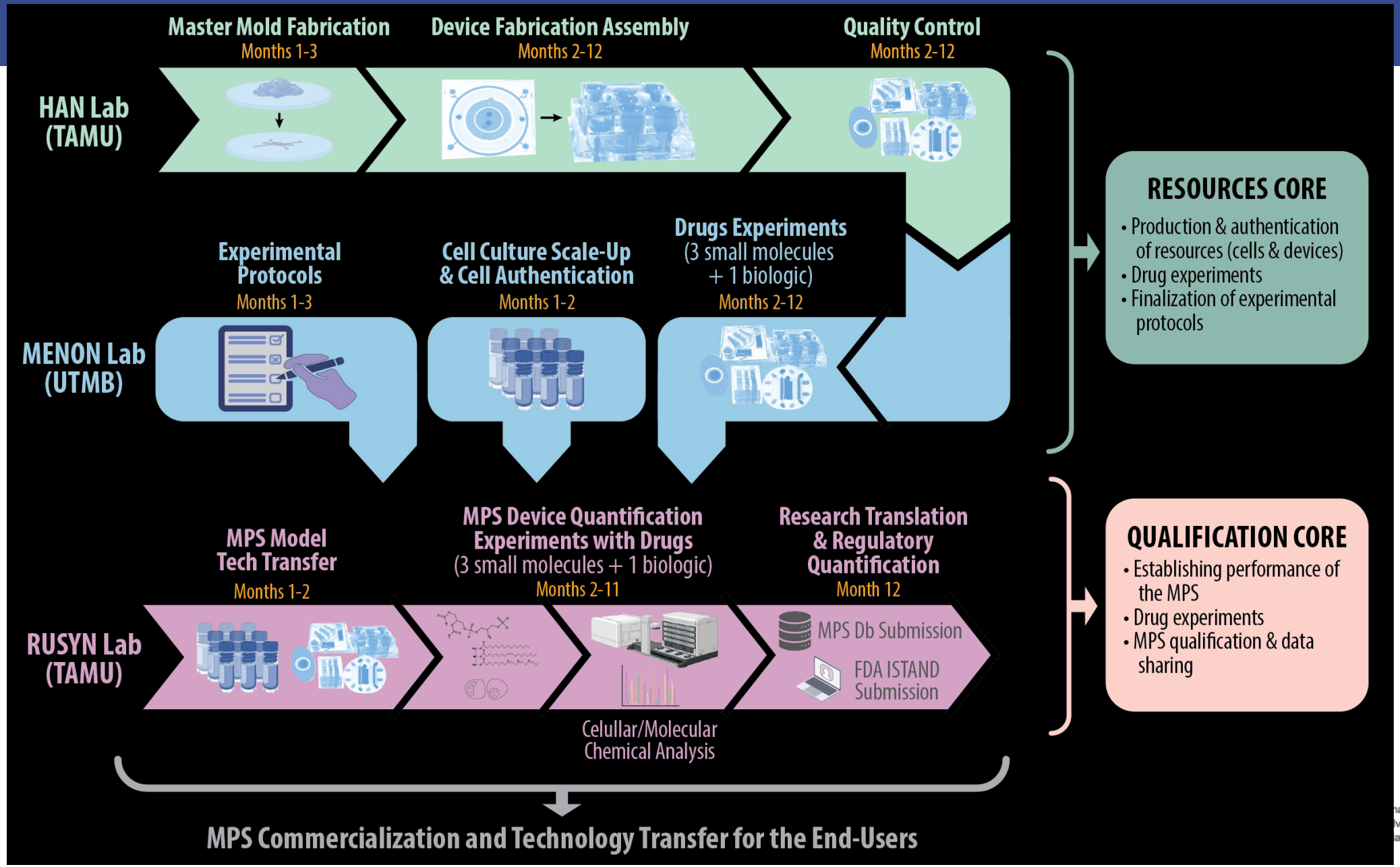
- **Trial gap:** Pregnant subjects excluded from clinical trials
- **Therapy gap:** No new treatments for adverse pregnancy in 40+ years
- **Rising risk:** Increasing maternal and neonatal mortality
- **Current Model limitations:** Lack of predictive preclinical models and biomarkers



Goal: Make pharmaceuticals safer during pregnancy

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TraCe MPS-Based Drug DDTs for Pregnancy and Women's Health



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Lessons Learned: TraCe-MPS Resource Cores

1. Centralized shared infrastructure accelerates regulatory readiness. Centralization of specialized fabrication technologies, biological/technical materials, and coordinated SOPs helps transition MPS platforms toward regulatory context-of-use — reducing duplication and harmonizing practice across labs.

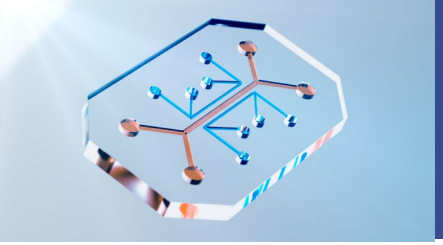
2. A narrow, well-specified context of use (CoU) — not generic platform validation — makes qualification tractable. Requiring Centers to target specific CoUs (per FDA/ISTAND) early gave Resource Cores a concrete target for building SOPs and materials, rather than validating a platform in the abstract.

3. Early, built-in FDA input surfaces regulatory expectations before they become late-stage obstacles. Embedding regulatory engagement at the design stage — not after platform development — helped anticipate requirements like multi-site reproducibility before ISTAND submission.

4. Harmonized SOPs and terminology must work across, not just within, platform types. Centers spanning different organ systems and chip architectures (barrier, kidney, reproductive/women's health MPS, etc.) still converged on shared protocol standards — showing reproducibility frameworks need to be modular across technologies.

5. Centralized training reduces the "tacit knowledge" bottleneck. Hands-on technology transfer through Resource Cores lowered a major adoption barrier: expertise previously confined to originating labs, distinct from technical validation itself.

6. Common Resource Cores de-risk the multi-site reproducibility requirement central to ISTAND qualification. Independent sites trained and supplied through a shared Core can replicate results more reliably than sites working from a publication alone.



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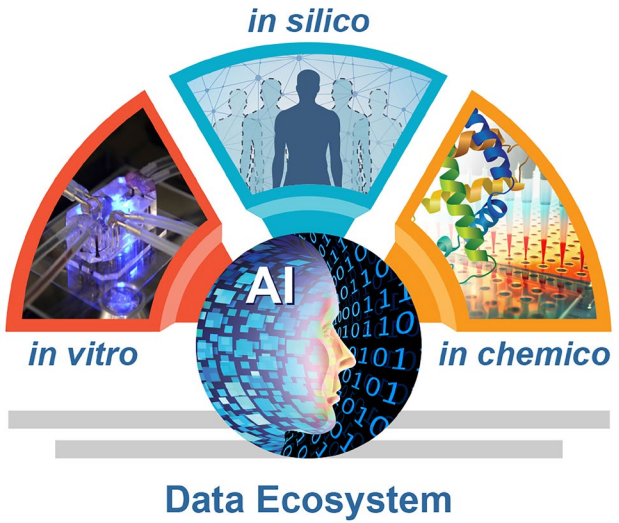
Complement-ARIE

Complement Animal Research In Experimentation

A New NIH Common Fund Program

Statement of Purpose and Goals of Complement-ARIE

Purpose: To catalyze the development, standardization, validation and use of **human-based new approach methodologies (NAMs)** that will transform the way we do basic, translational, and clinical sciences



Goals:

1. Better model and **understand human health and disease** outcomes **representative of the patient populations**.
2. Develop NAMs that **provide insight into specific biological processes** or disease states.
3. Validate mature NAMs to **support regulatory use** and standardization.
4. Complement traditional models and **make biomedical research more efficient and effective**.

Link to Complement-ARIE website

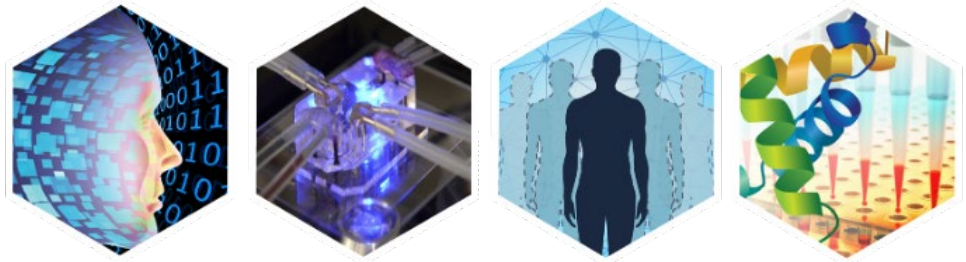
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NIEHS-Administered NYU-Sage NAMs Data Hub & Coordinating Center (NAM Hub)

The NAM Hub, administered by NIEHS, will provide overarching support for the Complement-ARIE Consortium. It is responsible for coordinating consortium engagement with the scientific community and data integration and standards for NAMs.

Objectives

1. Develop an adaptive **FUSION framework (FAIR, Unified Schema for Interoperability of Ontologies in NAMs)**
2. Implement **FAIR-compliant repository**
3. Deploy a battery of **analytical and visualization methods** across the network.
4. Cultivate a **collaborative research community** which ensures sustainability of the NAMs ecosystem.



NAMHub
NAMs Open Ecosystem

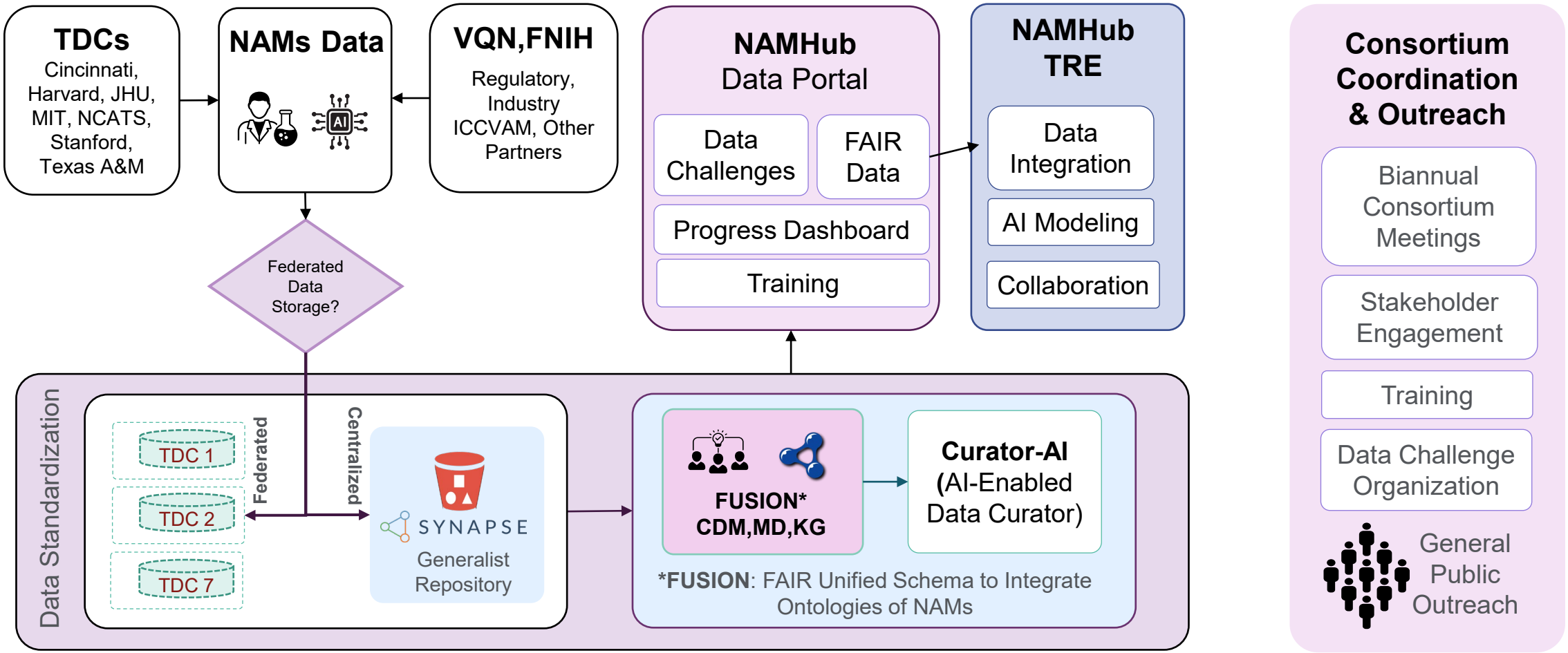
Seminar Series

NAMs IN FOCUS

Register here:

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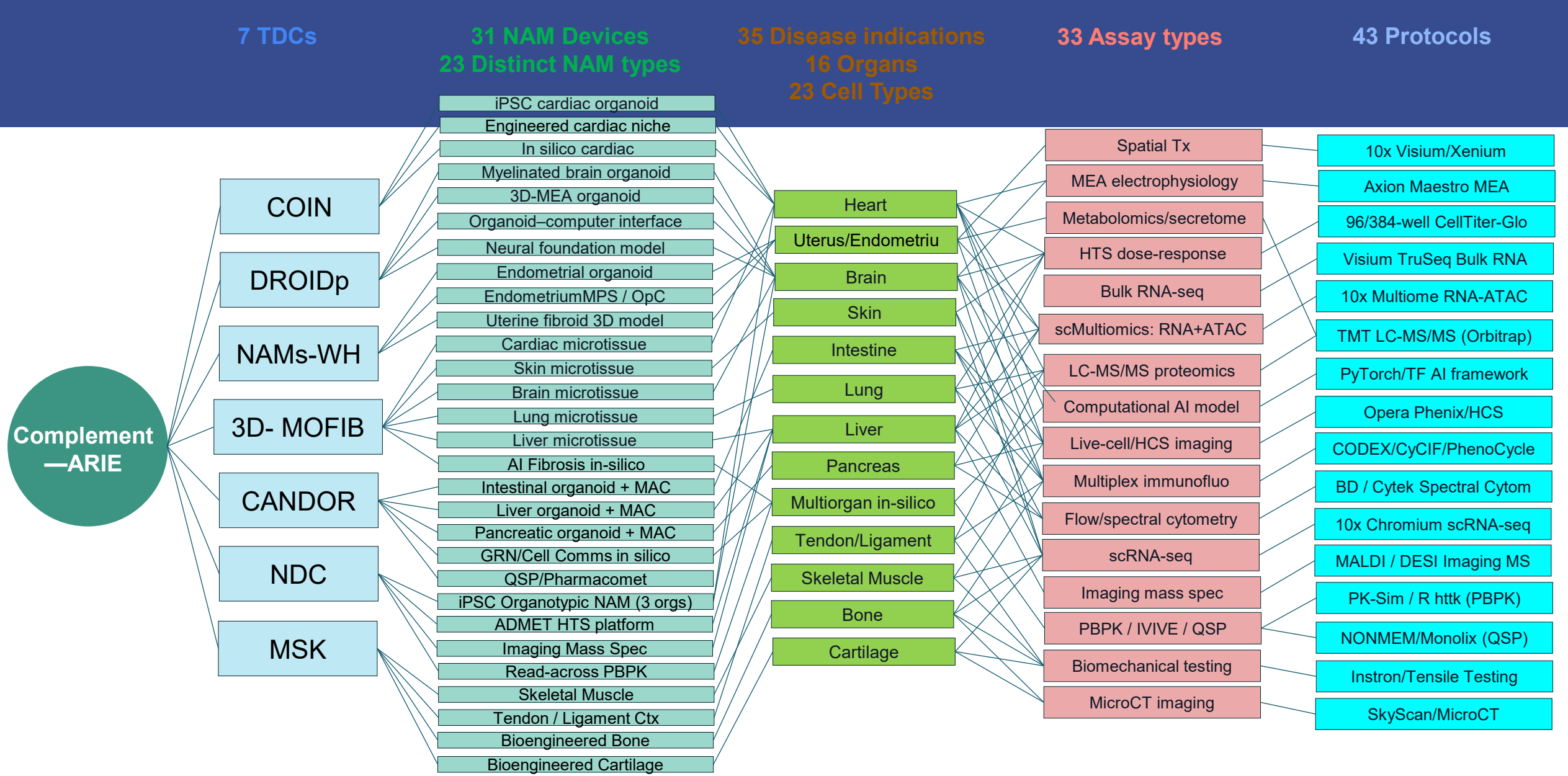
The NAMHub Architecture



Consortium Coordination & Outreach

- Biannual Consortium Meetings
- Stakeholder Engagement
- Training
- Data Challenge Organization
- General Public Outreach

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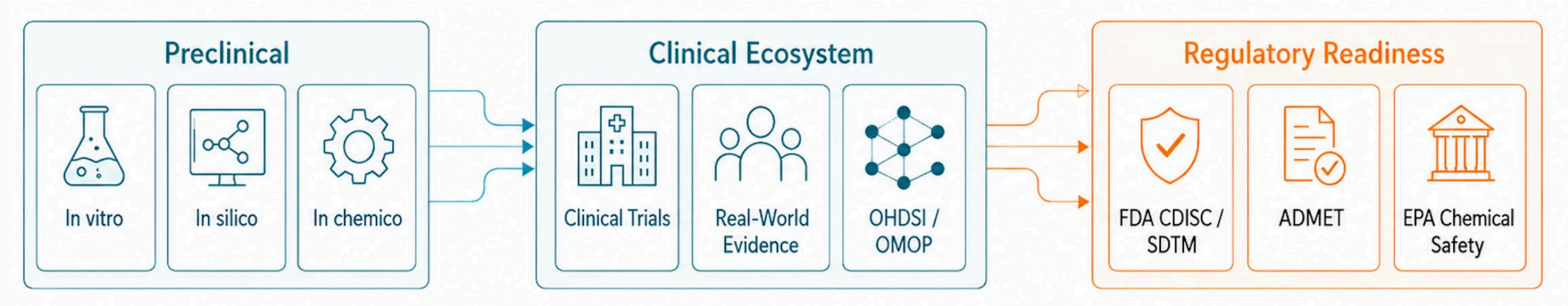
34 data modalities **56 file formats** **19 Frameworks/Standards** **17+ Ontologies**

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Work with the VQN on standards for regulatory approval

The NAMHub will contribute to create a semantic bridge to align early-stage laboratory data with clinical realities and strict regulatory pipelines.

FUSION NAM standards + Model Risk and Credibility + Clinical Ontologies → Regulatory Readiness



Data quality control

Missing data: Is it within bounds?
Metadata: Is metadata complete?
Distributions: Are there outliers?

Model Risk and Credibility

Verification: is the model reproducible
Validation: Is the performance robust
Uncertainty: Are errors within bounds

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We Propose these Additions to the Roadmap:

1. Reference materials & inter-lab standards:
Establish common reference materials and ring-trial protocols for core tissue chip readouts (barrier function, metabolic activity, contractility) → makes platforms comparable across labs and vendors.

2. Harmonized data & metadata standards:
Bridge TraCe MPS SOPs, the NAM Hub's FUSION framework, and FDA data expectations into one crosswalk → data captured once serves research, sharing, *and* regulatory submission.

3. Sustained independent validation capacity:
Make Tissue Chip Testing Center–style third-party validation permanent infrastructure, not a time-limited program → gives developers and regulators a trusted, ongoing benchmark.

4. Clear pathway to regulatory qualification:
Build on ISTAND/FDA Modernization Act 2.0 momentum with published qualification templates and earlier sponsor engagement → cuts the cost/timeline uncertainty currently blocking adoption.

Diverse stakeholder input — from developers, resource core operators, data scientists, regulators, and industry — will be essential to sequencing these priorities.

NIH Tissue Chip Consortium

Partnership + Collaboration = Program Success



Passley Hargrove-Grimes



Dmitry Krepkiy

Office of Special Initiatives, NCATS



Tiziana Cogliati
NIA



Raven Hardy Richard
ORWH



Warren Casey
ORIVA

IQ Consortium MPS Affiliate: AbbVie, Alnylam, Amgen, Astellas, AstraZeneca, Biogen, Bristol-Myers Squibb, Company, Celgene, Eisai, Eli Lilly, Genentech, GlaxoSmithKline, Janssen Pharmaceuticals, Merck & Co., Merck KGaA, Mitsubishi Tanabe, Novartis, Pfizer, Sanofi, Seattle Genetics, Takeda, Theravance, Vertex

Trans-NIH MPS Working Group:

>55 Program Officers from NCATS, NCI, NHLBI, NIA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCR, NIDCD, NIDDK, NEI, NIEHS, NIMH, NINDS, ORWH/OD

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