

# Complement-ARIE (Complement Animal Research in Experimentation)

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National Institutes of Health

*Office of Strategic Coordination – The Common Fund*

# OSC (Common Fund)

**Concept Clearance:** New Common Fund Program

**TITLE: Complement-ARIE (Complement Animal Research in Experimentation)**

**Objective:** 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.

**Initiatives:**

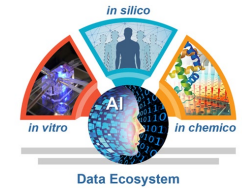
1. Technology development projects/centers
2. Data & NAM resource coordinating center
3. Validation network for regulatory implementation
4. Community engagement and training
5. Strategic engagement

**Funds Available:** \$35-40M per year

**Program Duration:** 10 years

**Council Action:** Vote for approval of the concept for Complement-ARIE

# Acknowledgements



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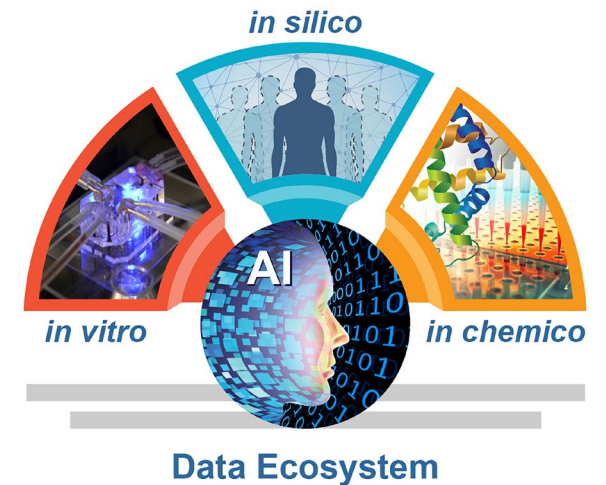
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# Statement of Purpose and Goals of Complement-ARIE

**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

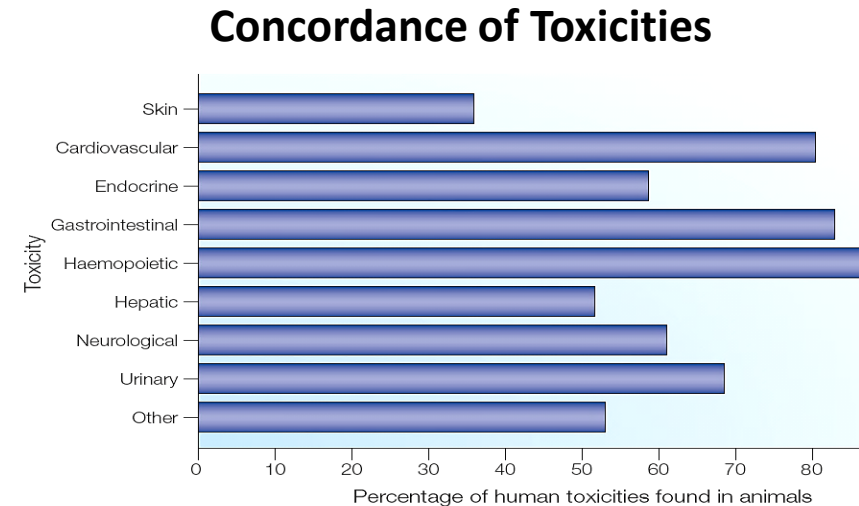
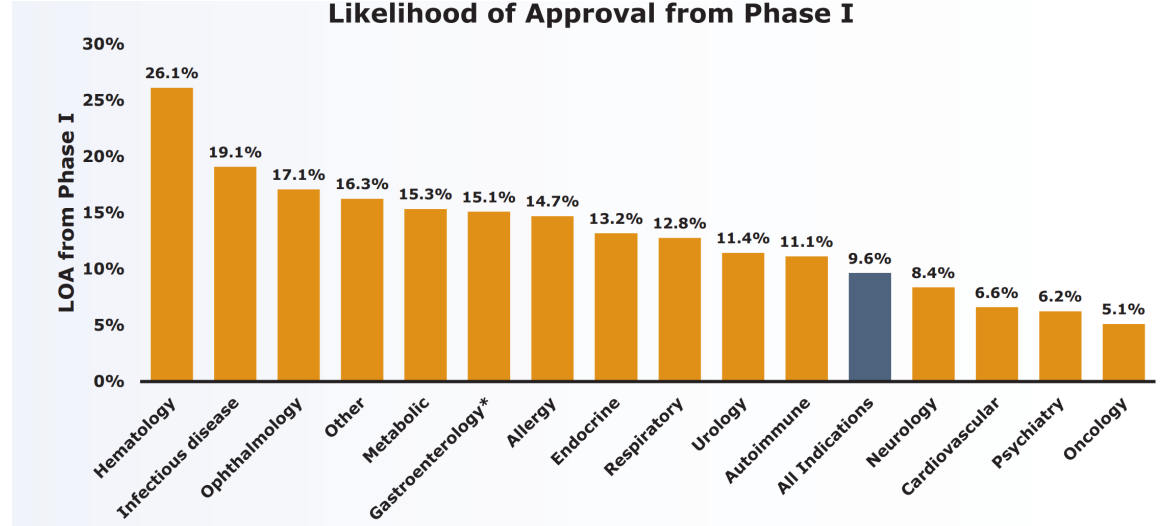
## Goals:

1. Better model and **understand human health and disease outcomes across diverse 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.**



# Complement-ARIE: Background

- Animal testing has led to critical insights and medical advancements for humans.
- However, traditional models do not always predict human responses.
- Less than 10% of drugs entering clinical trials result in an approved medicine, largely due to species-specific differences
  - 55% fail due to lack of efficacy in humans
  - 28% fail due to toxic effects in humans
  - Average time to develop a drug: 10-15 years
  - Average cost to develop a drug to market, including cost of failures: \$2.6 billion
- High priority of the Advisory Committee to the NIH Director to develop novel alternative methods for advancing biomedical research and recommendations were unanimously accepted at the ACD Meeting on Dec 14, 2023.

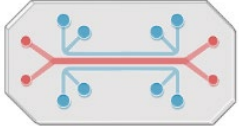


*Arrowsmith and Miller, Nature Reviews Drug Discovery, 2013,, 12: 569*

*Cook et al., Nature Reviews Drug Discovery, 2014, 13: 19*

*Wong et al. Biostatistics, 2019, 20: 273-286*

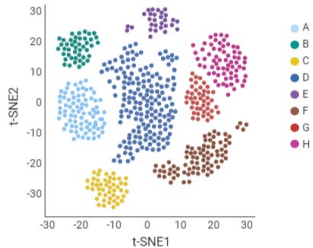
# Complement-ARIE: Why Now?



- The past decade has seen dramatic advances in areas such as complex *in vitro* systems, bioengineering technologies, human data, and computational methods.



- Existing programs in the Common Fund Data Ecosystem and others (e.g. MPS-DB, EHR, Bridge2AI, All of Us) represent a wealth of data to support and enable complementary NAMs.



- We are at a watershed moment in the history of drug discovery and development where the FDA Modernization Act 2.0 is a game-changer in legislating that drugs may be registered without animal studies.



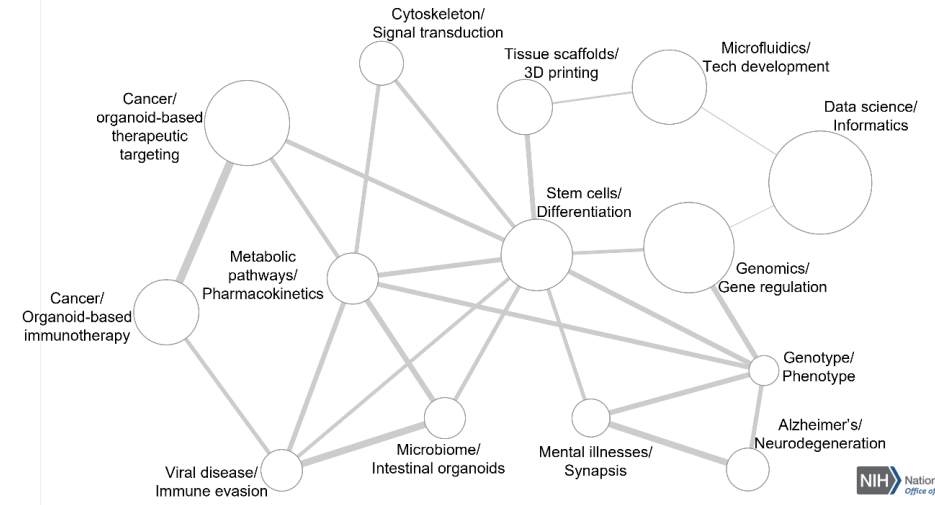
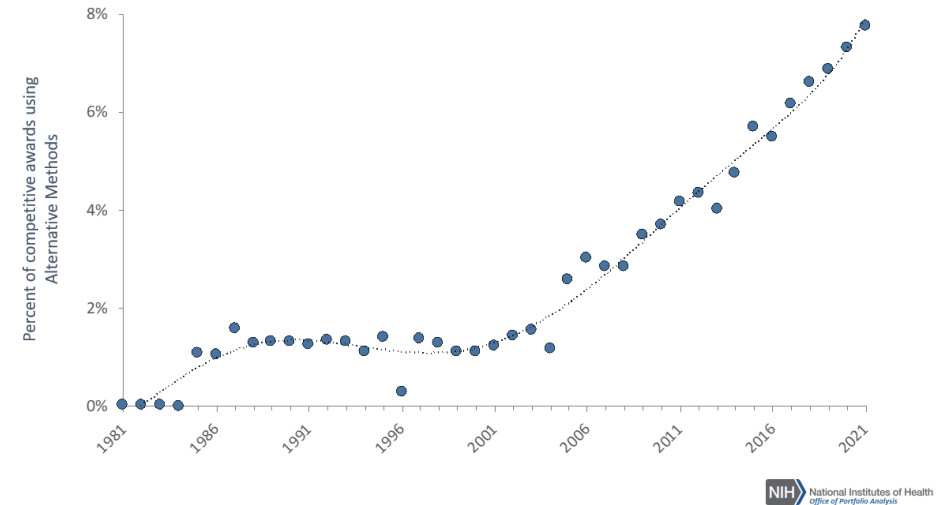


# Complement-ARIE: Why NIH/Common Fund?

- **COORDINATION:** Complement-ARIE is truly a trans-NIH effort that cannot exclusively be accomplished by any one IC and will require coordination of efforts with multiple ICs and potentially other federal partners.
- **IMPACT:** Complement-ARIE will significantly advance understanding of human health, population diversity, and human disease etiology, and have near-term application in:
  - mechanism elucidation
  - personalized medicine
  - safety pharmacology
  - predictive toxicology
  - efficacy evaluation of candidate therapeutics
  - biomaterials as therapeutics
- **OUTCOME:** Complement-ARIE will provide a wide range of validated and standardized NAMs for health and disease biology, ensuring optimal use of valuable animal resources.
- **The outcomes of COMPLEMENT will synergistically promote and advance the individual missions of NIH ICs to improve health.**

# NIH Investment in New Approach Methodologies

- NIH investment in alternative methods has increased over the past 15 years alongside technological advances
- NIH-funded researchers have used alternative methods in a wide variety of scientific disciplines, e.g.
  - cancer, diabetes, cardiovascular disease, Alzheimer's disease, mental illness, infectious disease, rare diseases, and other basic and clinical research



\*Results presented were developed from the ACD Working Group on Human Research Alternatives and Alternatives to Animals in Research and Testing



# Build on NAMs activities across NIH

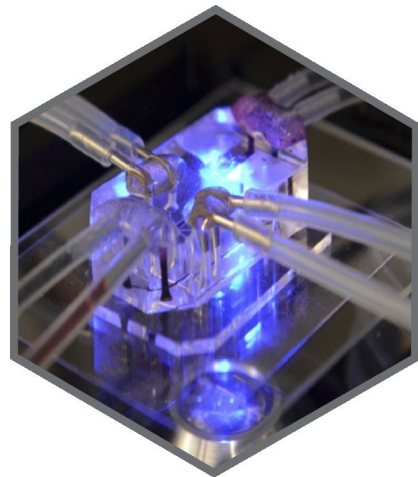
## Digital Twin Models

Digital Twins for treatment of cancers and neuropsychiatric diseases, host-gut microbiome studies



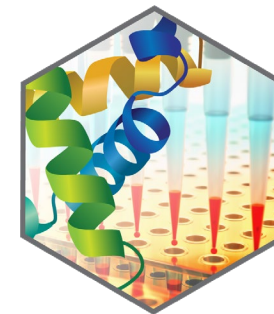
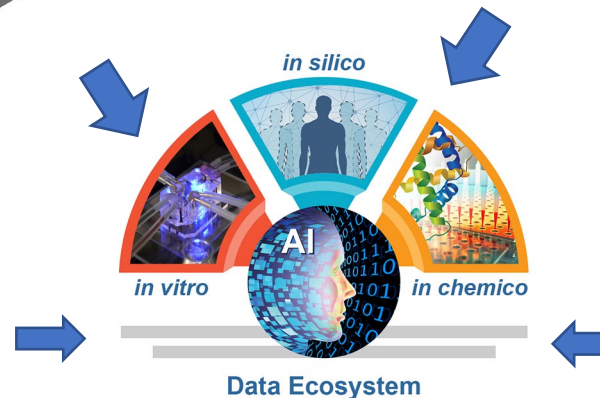
## In Silico Models

In silico and ML/AI models for neurodegenerative disease, wound healing, learning/behavior, SARS-CoV-2 propagation, many other diseases



## Complex In Vitro Systems

MPS and 3D organoid models for multiple tissues, organs and disease conditions



## In Chemico Screening

Tox21 high-throughput studies, biochemical assays for skin irritation, ocular toxicity

# Strategic planning activities: Stakeholder outreach

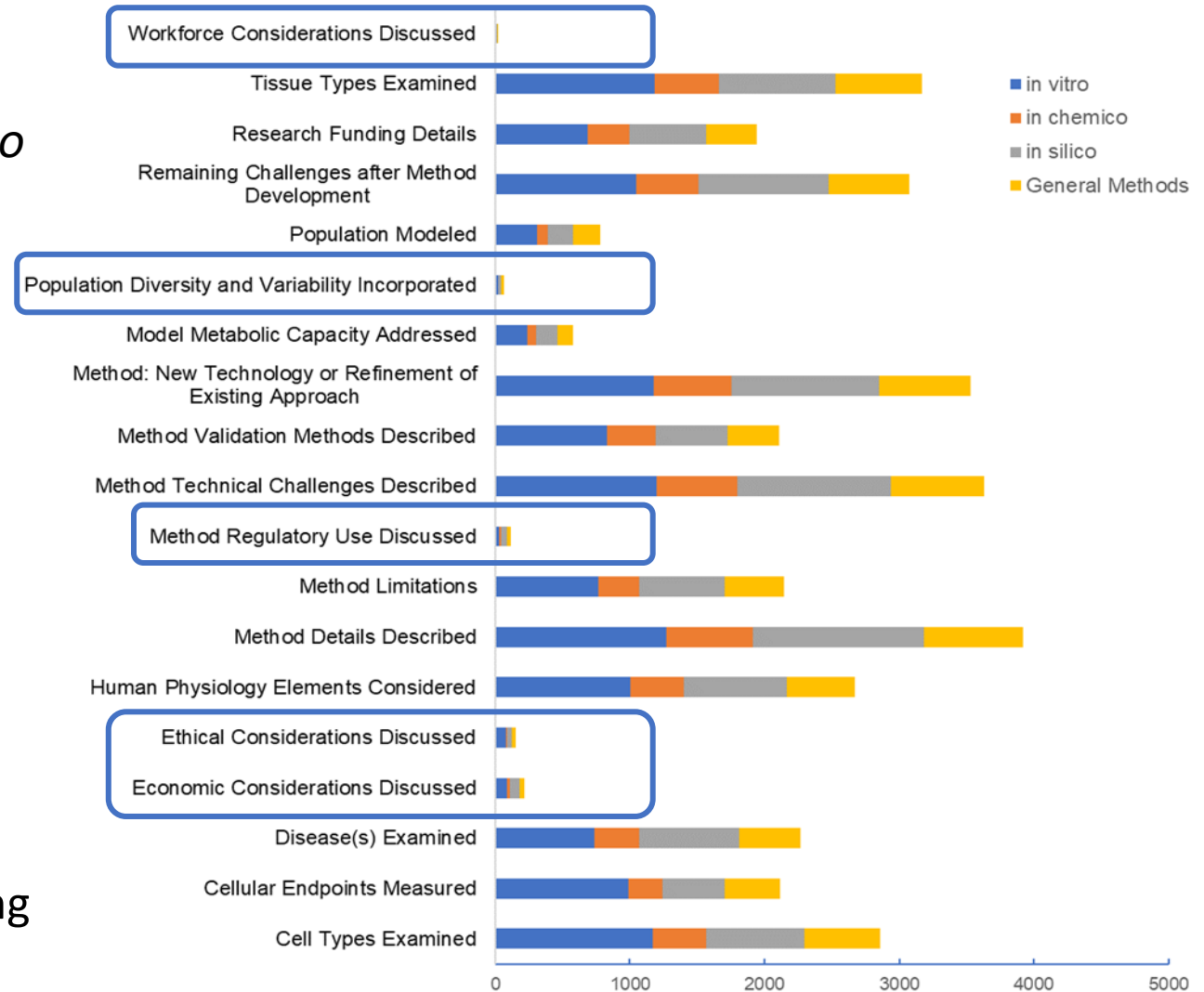
- 3 listening sessions were held with major stakeholders (**Academia, Industry, NGO, Government, International**)
- Federal Inter-agency retreat Oct 19-20, NIH/Natcher
  - **NIH, FDA, EPA, NSF, ARPA-H, BARDA, VA, DARPA, NIST, NASA, ICCVAM**
- Scientific Needs: *Innovate and Transform*
  - **Chronicity**
  - **Neuroscience**
  - **Personalized health**
  - **Cross-disease pathogenesis**
  - **Population diversity**
- Operational Needs: *Integrate, Coordinate, and Collaborate*
  - **Shared data infrastructure**
  - **Standardized frameworks**
  - **Validation**
  - **Training**
- Other strategic planning activities informing concept development: Landscape Analysis, Ideation Prize (both underway)



# Strategic planning activities: AI-enabled Landscape Analysis

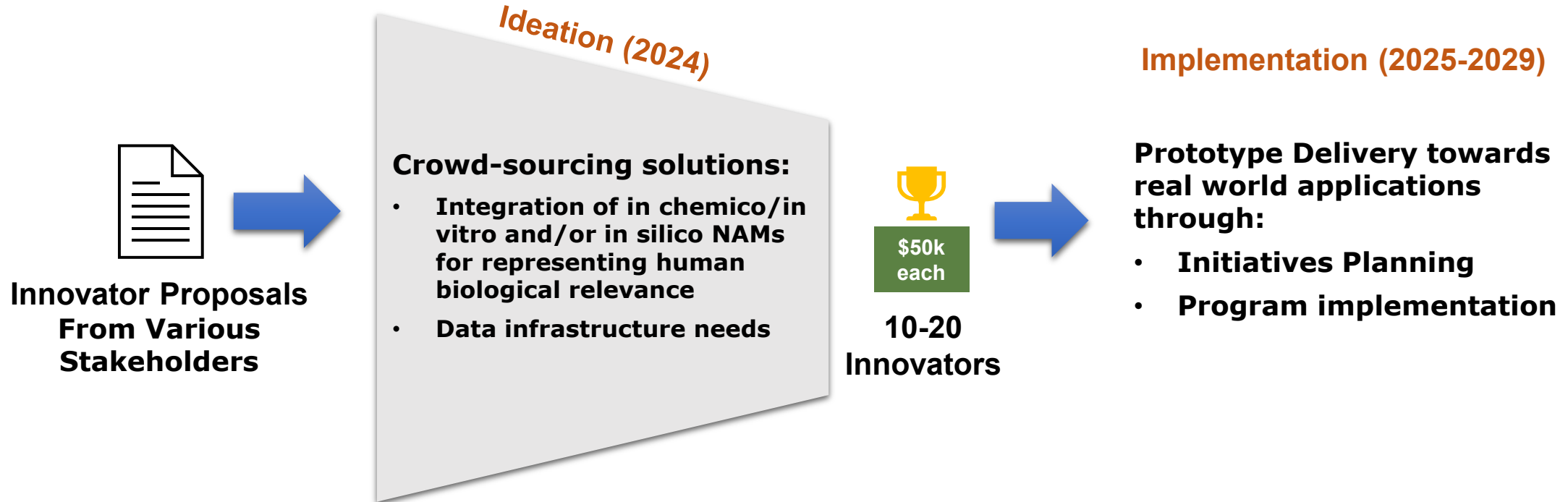
Describe existing efforts, and highlight gaps, challenges, and opportunities in the areas of human-relevant *in vitro*, *in chemico*, and *in silico* NAMs, and FAIRness of data resources

- **Comprehensive Scientific Lit Review**
  - Delivered via interactive Tableau dashboard
- **Current Focal Areas**
  - e.g., cell lines, organoids/MPS, AI/ML, HTS, specific disease types
- **Future Directions**
  - e.g., clinical translation, immune components, digital twins, combinatorial NAMs
- **FAIRness** of data resources
  - Application of FAIR assessment rubric to existing resources (e.g. HuBMAP = 100% FAIR)



# Strategic planning activities: ideation through crowd-sourcing

- The Challenge Prize competition is part of the strategic planning process and will serve to inform topic areas for program implementation.
- \$1,000,000 to make up to 20 awards (\$50K each) across all categories.
- Time frame: Submission period Nov 7, 2023 – Jan 11, 2024, judging in January 2024, winners announced in February of 2024.

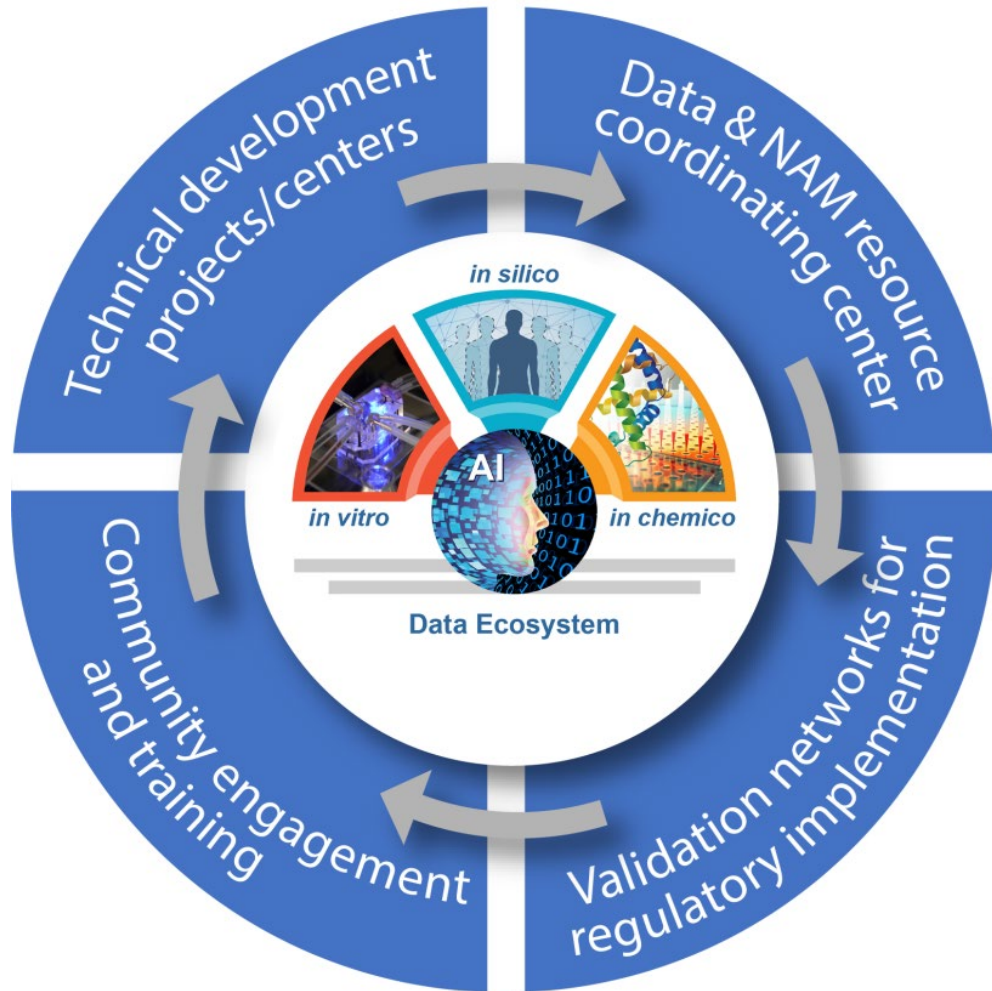


# Complement-ARIE: Proposed Program Structure

- **Technology development projects/centers** – stimulate the development of NAMs to fill in areas of greatest need, with emphasis on increased biological complexity and throughput, innovative combinatorial approaches, and data sharing. Training component required. (*\$23 – 26M per year*)
- **Data & NAM resource coordinating center** – create integrated data structures, including standards for model credibility, improve FAIRness (Findability, Accessibility, Interoperability, and Reusability) of NAM-relevant data, create searchable NAMs repository (*\$5 – 6M per year*)
- **Validation network for regulatory implementation** – establish common data elements and standardized reporting, apply validation/qualification frameworks, accelerate deployment and regulatory implementation of NAMs (*\$3 – 4M per year*)
- **Community engagement and training** – promote the development of an inclusive, diverse biomedical research workforce with the skills to build/use new NAMs, community engagement, societal and ethical considerations (*\$3 – 4M per year; begins in year 3*)
- **Strategic engagement** – set aside ~2-5% of program funds to dynamically engage with emerging opportunities (*\$1 – 2M per year*)



# Complement-ARIE: Comprehensive center model



- Comprehensive centers will require embedded projects on *in vitro*, *in chemico*, and *in silico* approaches plus combinatorial approaches.
- Cores will include admin, validation, resources, and training components.
- Phased milestone-driven projects that pilot some of the truly innovative approaches can also be transitioned for integration with the centers.



# Projected 10-Year Timeline and Budget

2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
\$35M	\$35M	\$40M	\$40M	\$40M	\$40M	\$40M	\$40M	\$40M	\$40M

**Technology development projects/centers - \$23 – 26M per year**

**Data & NAM coordinating center - \$5 – 6M per year**

**Validation network for regulatory implementation - \$3 – 4M per year**

**Community engagement and training - \$3 – 4M per year**

**Strategic engagement- \$1 – 2M per year**

**RMS: NIH staff salary, travel - \$1M per year**

# Complement-ARIE Program Development Timeline

**NIH Common Fund  
Complement-ARIE Working Group**

**NIH ACD Working Group on Catalyzing the Development  
and Use of NAMs to Advance Biomedical Research**

**June:** Convene Complement-ARIE WG

**June–October:**  
Program Planning/ Development

- **Deep landscape analysis**
  - data infrastructure needs
  - current use of NAMs
- **Listening sessions (roundtables)**
  - engage investigators and
  - current challenges in NAM development
- **Inter-agency workshop**
  - Shared interests with other stakeholders in the NAM space (Oct. 19-20)
- **Ideation/Design Prize**
  - engage community
  - identify opportunities in NAM development, validation, and adoption

**Nov - Jan:**  
Concept refinement and approvals for continued development and implementation

- ICD presentation (**Dec 21, 2023**)
- Council of Councils (**January 25, 2024**)



**June 8-9** ACD WG present preliminary findings

**June – November:**  
ACD WG Stakeholder Engagement

Expert Workshop on “Catalyzing Development and Use of Novel Alternative Methods – August 21-22 (videocast)

RFI published:  
<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-23-140.html>  
Closed September 5

**December 14**  
ACD WG present final report w/recs

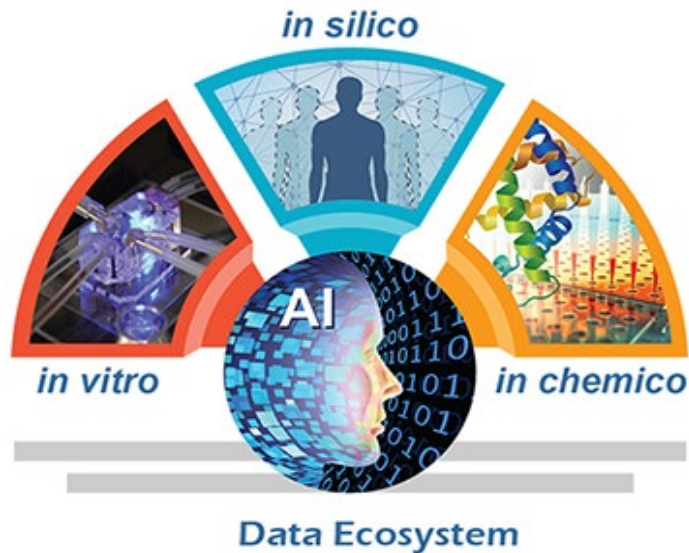
# Complement-ARIE aligns with the ACD WG recommendations

## RECOMMENDATIONS TO CATALYZE THE DEVELOPMENT AND USE OF NAMs

✓	Recommendation 1.	Prioritize the development and use of combinatorial NAMs.
✓	Recommendation 2.	Establish resources, infrastructure, and collaborations to promote the use of interoperable, reliable, and well curated/high quality datasets produced from research using NAMs.
✓	Recommendation 3.	Promote effective dissemination and interconnection of NAMs technologies.
✓	Recommendation 4.	Invest in comprehensive training to bolster continuous advances in NAMs development and use.
✓	Recommendation 5.	Facilitate multidisciplinary teams with expertise across technologies and the lifecycle of NAMs development and use.
✓	Recommendation 6.	Promote social responsibility in both the creation and deployment of NAMs across the research lifecycle.
✓	Recommendation 7.	Support and maintain coordinated infrastructure to catalyze effective and responsible NAM development and use.

\*Results presented were developed from the ACD Working Group on Human Research Alternatives and Alternatives to Animals in Research and Testing

# Complement-ARIE: Innovate, Integrate, Coordinate, and Transform



- **Innovate** understanding of human health and disease pathways across diverse populations
- **Integrate** innovative NAMs (*in vitro*, *in chemico*, and *in silico*) with AI and FAIR data ecosystems
- **Coordinate** with ICs, agencies, and public-private partnerships
- **Transform** the way we do basic, translational, and clinical sciences by leveraging the full scientific toolbox

# Council Action: Vote for approval of the concept for Complement-ARIE



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