NIH ADVISORY COMMITTEE TO THE DIRECTOR WORKING GROUP

Catalyzing the Development and Use of Novel Alternative Methods (NAMs) to Advance Biomedical Research

Howard Chang, MD, PhD & Lyric Jorgenson, PhD
NAMs Working Group Co-Chairs

ACD Meeting
December 14, 2023
TODAY’S ROADMAP

Scientific Opportunity

Charge & Process

What Could be Possible

Recommendations
Research using brains-in-a-dish forces a radical rethinking of Huntington’s disease

SARS-CoV-2 Can Infect Human Brain Organoids
The results are a proof-of-concept that the novel coronavirus can replicate in neurons, but it’s too soon to say whether this occurs in people with COVID-19.

NIH to Invest $130M in Biomedical, Behavioral AI Projects

NASA-SpaceX launches will boost science research on the space station
IMPETUS FOR EFFORT
GROWING NIH INVESTMENT IN ALTERNATIVES

% of Competitive Awards using Alternative Methods

*Does not include clinical research
NAMS WORKING GROUP CHARGE

CATALYZE THE DEVELOPMENT AND USE OF NAMs

• Identify the types of alternative methods and assess their general strengths and weaknesses for studying human biology, circuits, systems, and disease states

• Characterize the types of research, condition, or disease for which NAMs are most applicable or beneficial

• Articulate high-priority areas for NIH investment in the use and development with human applicability to:
  • Advance progress into understanding specific biological processes or states
  • Augment the tools and capabilities for biomedical research to complement and/or potentially replace traditional models
APPROACHING OUR TASK
TIMELINE OF ACTIVITIES

GATHERING DATA AND SEEKING INPUT

NAMs ACD WG announced

WG meetings and identification of opportunities and challenges

Seek Public Input through RFI

WG meets to determine recommendations and write report

Winter 2022-2023

Spring 2023

Summer 2023

Fall 2023

Winter 2023

NAMs ACD WG charged

Update to the ACD

Public Workshop

Present recommendations to ACD
HUMAN RELEVANCE IN MIND
DEFINING NAMS AND IDENTIFYING OUR SCOPE

**in Chemico**
- Cell-free methods
- Epigenetics
- Biochemical pathways
- Chemical genetics

**in Vitro**
- Cultured cell methods
- Induced Pluripotent Stem Cells (iPSC)
- Microphysiological Systems (MPS)

**in Silico**
- Computational methods
- Artificial intelligence, deep learning, machine learning
- Mathematical modeling and simulations

Extremely Valuable For:
- Conducting basic research
- Uncovering human patho/physiological mechanisms
- Translating knowledge into products or practice
Current Challenges

- Difficult to study metastasis and how cancer cells move to distant organs
- Current models are poor predictors of stages and progression of cancer in humans

The Vision

Patient-specific NAMs and integrated approaches
WHAT WE HEARD
IMPORTANCE OF INTEGRATION

HIGH PRIORITY NEEDS

- Interoperable, Reliable Datasets
- Effective Technology Dissemination
- Combinatorial NAMs
- Multidisciplinary Teams
- Comprehensive Training
- Coordinated Infrastructure
- Socially Responsible Technologies
**RECOMMENDATIONS TO CATALYZE THE DEVELOPMENT AND USE OF NAMs**

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

COMBINATORIAL NAMs

- Technology combinatorial effect, a phenomenon where the integration or combination of different technologies or their components results in a more significant impact than the sum of their individual effects

- Strategic combination of NAMs can lead to breakthroughs not possible with any single NAM
RECOMMENDATION 1

PRIORITIZE THE DEVELOPMENT AND USE OF COMBINATORIAL NAMs

1.1. Establish benchmarks and standards for individual NAMs and combinatorial NAMs to foster technology integration efforts and demonstrate impact of combinatorial effect

1.2. Support research comparing and benchmarking relevant animal, NAMs and human models to validate translational potential, reduce reliance on singular methods, reduce costs, and identify integration frameworks and strengths and weaknesses in model approach

1.3. Initiate a combinatorial technology pilot for developing process/feasibility of complementing or reducing reliance on a current animal model for an experimental area/condition

1.4. Track NIH’s investment in NAMs including combinatorial NAMs to identify gaps, support new initiatives, identify promising areas for continued investment, and bolster scientific/proposal review for tools and resources
HIGH PRIORITY NEED 2
INTEROPERABLE, RELIABLE DATASETS

- Reliable and interoperable high-quality datasets are needed for appropriate validation or qualification of NAMs
- Data and associated metadata should be generated both from NAMs and traditional approaches
- High-quality data increases overall efficiency, reproducibility, and validity of comparisons
2.1. Define and address barriers to creating shared, reliable, and interoperable datasets, including heterogeneous data/metadata terminology, formats, and standards; inconsistent governance practices and quality curation; and qualified personnel for effective communication, translation, and adoption.

2.2. Develop and disseminate methods for assessing the quality of NAM data, leveraging existing data quality metrics.

2.3. Establish and maintain NAM data management policies and infrastructure to facilitate heterogeneous NAM data sharing and integration, including:
   - creation of registries, harmonizing nomenclature, development of ontologies, etc.
   - policies to promote timely and accessible publication of studies with concurrent deposition of related datasets, assigned codes, and algorithms.
2.4. Identify or establish a designated repository for NAM data sharing, consistent with FAIR principles, privacy protections, and security practices, with sufficient metadata requirements to promote equitable reuse of high quality NAMs data

2.5. Create alliances and collaborations for collecting, managing, sharing, and publishing high-quality NAMs data, including increasing access to hard-to-access data such as:
   - Industry data, focusing on the pre-competitive space and regulatory approval submissions
   - Unpublished data, particularly from failed studies in an effort to address survival bias

2.6. Crowdssource new methodologies that enable access to quality data to use for qualification or generated by NAM research, to improve characterization of data and increase confidence in NAM-generated data
HIGH PRIORITY NEED 3
EFFECTIVE TECHNOLOGY DISSEMINATION AND INTERCONNECTION

- Effective and rapid technology dissemination requires NAMs developers to consider users through development process.
- Successful deployment requires clarity regarding technology “maturity” for use and dissemination.
- Importance of designing to be “fit for purpose”
3.1. Establish mechanisms to support testing, validation, qualification, and benchmarking of integrated systems to maximize uptake of these systems by the community, including frameworks for describing which stakeholder should advance which component

3.2. Create accessible and reliable sources and repositories for disseminating validated NAMs.
   - Integrate strategies for deploying technologies broadly and equitably
   - Create and expand access to repositories

3.3. For integrated NAMs, incentivize research focused on making the technology simpler, faster, and cheaper (e.g., automation, miniaturization) and promote accessibility through easily navigable licensure procedures to manage intellectual property, commercial applications, and use issues

3.4. Define expectations for NAM studies to follow established reporting guidelines for funders and publishers regarding NAMs development and use
HIGH PRIORITY NEED 4
COMPREHENSIVE TRAINING

• Technology dissemination is necessary but not sufficient – need to support skills/knowledge to use them appropriately

• Particular focus on ensuring equity both in terms of institution, career stage, and role in the process

• Key to success is integrated and interdisciplinary collaboration
RECOMMENDATION 4
INVEST IN COMPREHENSIVE TRAINING TO BOLSTER CONTINUOUS ADVANCES IN NAMs DEVELOPMENT AND USE

4.1. Incentivize cross-training opportunities across scientific disciplines, animal to human approaches, and technologies, including across sectors such as:

- Initiate mechanisms to support multiple aspects of NAMs-based research, especially the frontier of merging abiotic and biotic NAMs and combinatorial expertise across traditional models
- Establish trainings in responsible data management and sharing, unique to NAMs data types to foster integration
- Promote training for grant reviewers to better understand how to evaluate the use of NAMs in fundamental and applied research grants

4.2. Create funding mechanisms for technology developers to both receive and advance training in different methods and strategies for reliable technology deployment
4.3. Invest in training across the research to implementation pipeline, including addressing hurdles in bringing technologies to fruition, such as regulatory and policy requirements, patient care, etc. For example:

- Embed academic researchers in industry, regulatory, national laboratories, and policy not-for-profits
- Create collaborations between researchers and clinicians to incorporate patient perspectives in NAMs development
- Foster entrepreneurship training

4.4. Promote awareness and understanding of NAMs through publicly available educational course modules and workshops covering the lifecycle of NAMs, from conceptualization to dissemination, use, and commercialization
HIGH PRIORITY NEED 5
MULTIDISCIPLINARY TEAMS

• Collaboration is needed across multiple sectors, disciplines, and expertise across lifecycle of development

• Incentives are lacking for integrating cross-disciplinary research with implementation in mind

• Different lexicon and approaches creates barriers to communication across fields and sectors
RECOMMENDATION 5
FACILITATE MULTIDISCIPLINARY TEAMS WITH EXPERTISE ACROSS TECHNOLOGIES AND THE LIFECYCLE OF NAMs DEVELOPMENT AND USE

5.1. Develop funding opportunities to support multi-disciplinary teams, considering potential scientific, technological, and engineering needs; regulatory or policy requirements; ethical considerations; and patient/public adoption

5.2. Support incentives for multi-laboratory coordination, especially mechanisms for supporting expertise across the lifecycle of development and use

5.3. Create novel funding opportunities such as cross-disciplinary challenge programs or prize competitions

5.4. Promote annual conferences or symposia that mobilize varying perspectives and expertise and establish resources and mechanisms to assist researchers in connecting with experts across disciplines, sectors, and research stages

5.5. Support pilot studies incorporating multidisciplinary expertise focused on studying the predictivity of certain models before publishing draft policies and risk assessments
• Trust throughout the lifecycle of NAMs development and use is required to promote uptake

• Ethical considerations must be considered upfront to ensure inequities are addressed, both in terms of design and ultimate access and cost

• The opportunity is clear – caution is needed to ensure hyperbolic narrative doesn’t derail efforts
RECOMMENDATION 6
PROMOTE SOCIAL RESPONSIBILITY IN BOTH THE CREATION AND DEPLOYMENT OF NAMs ACROSS THE RESEARCH LIFECYCLE

6.1. Foster equitable development and use of NAMs for research and public benefit:
   - Characterize individual differences, method biases, etc. to understand, minimize, and correct for variability and biases
   - Promulgate guidance for considering sources of tissues, cells, and data/metadata to source ethically and/or represent population diversity
   - Promote open sharing of technology and data when possible

6.2. Strengthen interagency partnerships to develop a coordinated federal approach to NAMs that enables science to advance efficiently, safely, and ethically while minimizing administrative and regulatory burden
6.3. Support cost effective analyses of proposed technologies with existing methods, including animal studies, looking at time, scalability, and resource efficiency

6.4. Support bioethical research on ethical, legal, and social issues unique to NAMs, including research to maximize responsible deployment, promote equity, and provide “return of value” to research participants and communities

6.5. Partner research initiatives with robust public engagement to incorporate social norms and promote awareness of emerging technologies
HIGH PRIORITY NEED 7
COORDINATED INFRASTRUCTURE

• There is a clear need for dedicated resources and venues to support NAMs

• Venues for communication and collaboration:
  • Create organic environments for common language and standards
  • Reduce redundancy to maximize investment
  • Spur new collaborations for integrated approaches
RECOMMENDATION 7
SUPPORT AND MAINTAIN COORDINATED INFRASTRUCTURE TO CATALYZE EFFECTIVE AND RESPONSIBLE NAM DEVELOPMENT AND USE

7.1. Create mechanisms for disseminating NAMs resources, technologies, and expertise efficiently, equitably, and reliably across researchers and institutions. For example:

- Protocols for technology development and use, qualification of reagents and equipment, tracking of materials and experimental details, and standard operating procedures for teams
- Clearing houses and repositories for easy, reliable, and inexpensive access to specialty reagents and custom syntheses
- Knowledge-bases for tracking NAMs, how they are used, for what purposes, and how in combination with what other models

7.2. Promote or establish consortia and venues for sharing established best practices, standards, definitions, frameworks, and harmonized approaches for NAMs
7.3. Invest in infrastructure to support institutions in keeping pace with the rapid pace of NAMs, including:
  - Establishing "recruitment and placement" platforms and collectives so that researchers can identify colleagues with specialized expertise
  - Small to mid-scale physical laboratory infrastructure

7.4. Identify opportunities to build upon existing efforts both nationally and internationally to link resources and identify a clear source of coordination for NAMs resources

7.5. Establish dedicated and centralized core facilities as national or regional resources to develop and run NAM assays to reduce costs, leverage scale, and train
OUR VISION

AN INTEGRATED ECOSYSTEM TO CATALYZE SCIENTIFIC DISCOVERY

- Combinatorial NAMs
- Interoperable, Reliable Datasets
- Effective Technology Dissemination
- Comprehensive Training
- Multidisciplinary Teams
- Technological Social Responsibility
- Coordinated Infrastructure

Integrated NAM Ecosystem
TRANSFORMATIVE PROJECTS

(WHAT WE CAN ACCOMPLISH WITH SUCCESS)
RECOMMENDATIONS POSITION US TO TRANSFORM OUR UNDERSTANDING OF HUMAN HEALTH AND DEVELOP NEW TREATMENTS

- Leveraging *in vitro* and *in silico* techniques for actionable insights in complex biological models
- Uncovering new understanding of neuropsychiatric disorders
- Combining *in vitro*, *in vivo* (clinical and preclinical), and *in silico* approaches to minimize dependent on preclinical *in vivo* models
- Combinatorial approaches to improve treatment of chronic inflammatory conditions
- Data integration across NAMs, traditional models, and the clinic to emulate patient-specific tumor-immune environments