WORKING GROUP STATUS UPDATE

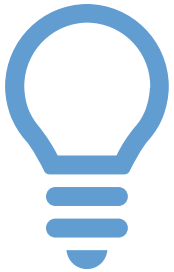
CATALYZING THE DEVELOPMENT & USE OF NOVEL ALTERNATIVE METHODS (NAMS)

Howard Chang
Virginia and D.K. Ludwig Professor of Cancer Research and
Professor of Dermatology and Genetics, Stanford University

Lyric Jorgenson
Acting NIH Associate Director for Science Policy & Acting
Director of the Office of Science Policy
National Institutes of Health

June ACD Meeting
June 9, 2023

GOALS FOR DISCUSSION



Reminder of the impetus for forming the group

Update on status and preliminary findings

Review proposed next steps for engaging communities

WHY WE'RE HERE

IMPETUS FOR EXPLORING NAMS

WHY NAMS ARE VALUABLE

DIVERSIFYING THE TOOLKIT

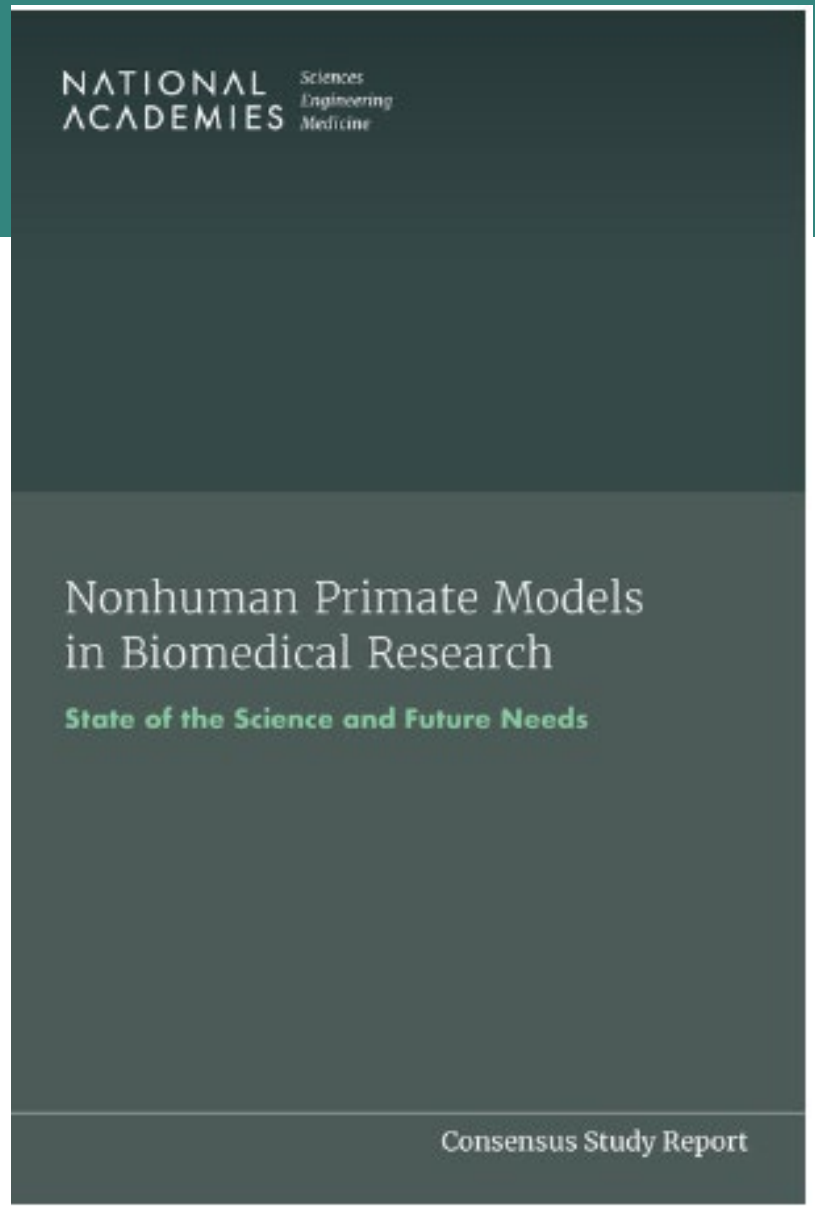
THE USE OF ANY GIVEN APPROACH IS PREDICATED ON NEED, IN TERMS OF SCIENTIFIC APPROPRIATENESS & RELEVANCE FOR THE RESEARCH INQUIRY

THE PROMISE OF "ALTERNATIVES"

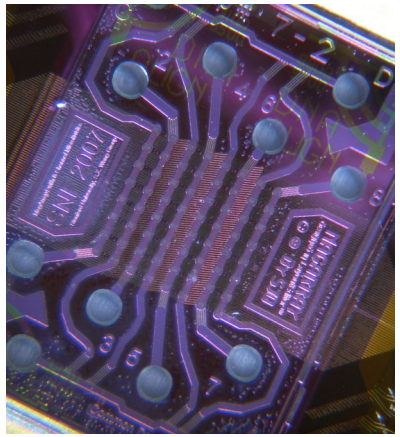
- Alternatives hold promise for some but not all areas
- Important to invest wisely
- External pressures driving the demand for increasingly sophisticated methods to study complex biological phenomena
- NIH aims for a strategic approach to advance use and development of these potentially revolutionary technologies

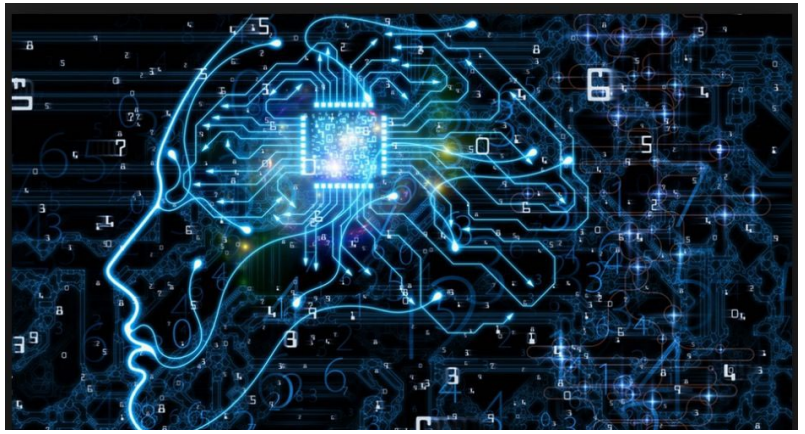
TIMELY

Conclusion 4-2: Select new approach methodologies (in vitro and in silico models) can replicate certain complex cellular interactions and functions. As such, these new approach methodologies may be used to answer specific research questions that contribute to understanding human biology to prevent and treat human disease. Although there currently exist no alternatives that can fully replace nonhuman primates, ***it is reasonable to be optimistic that this may change in the years ahead as new approach methodologies continue to advance.***



PRELIMINARY SCOPING





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

WORKING GROUP CHARGE

- Identify the types of alternative methods being developed for use in biomedical research 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 alternative methods are most applicable or beneficial
- Articulate high-priority areas for NIH investment in the use and development of novel alternative methods 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

WORKING GROUP ROSTER

Howard Chang, MD, PhD *(co-chair)*
Stanford University

Lyric Jorgenson, PhD *(co-chair)*
National Institutes of Health

Antonio Baines, PhD
NC Central University/University of North Carolina

Szczepan Baran, DVM
Verisym Life

Wendy Chapman, PhD
University of Melbourne

Myrtle Davis, DVM, PhD
Bristol-Myers Squibb

Linda Griffith, PhD
Massachusetts Institute of Technology

Ranu Jung, PhD
University of Arkansas

Arnold Kriegstein, MD, PhD
University of California, San Francisco

Nancy Lane, MD
University of California, Davis

Kelly Metcalf Pate, DVM, PhD
Massachusetts Institute of Technology

Sergiu Pasca, MD
Stanford University

Gordana Vunjak-Novakovic, PhD
Columbia University

EX OFFICIO

Namandjé Bumpus, PhD
Food & Drug Administration

Maureen Gwinn, PhD
Environmental Protection Agency

Danilo Tagle, PhD
National Institutes of Health

EXECUTIVE SECRETARIES

Brittany Chao, DPhil
National Institutes of Health

Jessica Creery, PhD
National Institutes of Health

STATUS UPDATE

ACTIVITIES TO DATE

Five Working Group meetings:
- Landscape assessment
- Review of federal programs
- Discussions with experts

Dec 2022

Working Group Launched

January-May 2023

Identification of needs, challenges, and opportunities

June 2023

Update to the ACD

June-Dec 2023

WHO WE'VE HEARD FROM *(SO FAR…)*

Heard from experts across:

- Academia/Industry/Federal Partners
- Sampling of types of disease/research programs (neuroscience, tox, etc.)
- Sample of types of models (organoids, computational, etc.)

Topics discussed:

- Federal priorities and complementary efforts across the government
- Innovations in NAMs in academia
- Use of NAMs in private sector
- Fostering integration of NAMs

EMERGING THEMES *(PRELIMINARY)*

NAMs currently showing high scientific value for:

- Elucidating fundamental functions of cells and basic biological mechanisms
- Providing information on how cell types interact in a localized environment
- Complementing assessments for predicting drug safety and efficacy in humans
- Enhancing selection of potential targets for maximizing drug discovery

NAMs less successful for:

- Reconstructing complex biological systems
- Predicting whole-body responses under pathophysiological conditions

EMERGING THEMES *(PRELIMINARY)*

Unique challenges for NAMs are a lack of (varying dependent on type):

- thorough characterization of the biological materials used in the models
- authentication of cell lines, stem cells, and tissues
- accepted biological and analytical performance standards
- approaches to biological qualification of relevance to humans
- consistency in the analytical platform and endpoints measured
- available relevant decision frameworks to support regulatory decision-making
- approaches to analytical validation/biological qualification of *in silico* methods

WORKING GROUP APPROACH

PHASE 1. Assess the needs, challenges, and opportunities.

- **The use of NAMS to study human biology, circuits, systems, and disease states**
  - Features of NAMs that maximize scientific utility
  - Limitations of NAMs in understanding specific biological processes, including addressing human variability
  - Areas where NAMS could improve human health, including currently underserved areas
- **Catalyzing the development and validation of NAMs**
  - Challenges for building in robustness, replicability, and reproducibility
  - Strategies for bolstering technology readiness and reliability
  - Factors limiting successful integration of NAMs across research approaches
- **Maximizing the research value of novel alternative method technologies**
  - Coordinating approaches across research disciplines/sectors to advance development/use
  - Deploying NAMs equitably across labs, including incentives for reliable/reproducible methods integration
  - Factors for maximizing translatability and minimizing bias regarding human variability

WORKING GROUP APPROACH *(CONT.)*

PHASE 2. Identify high-priority areas for NIH investment.

- Where can we **expand use of NAMs** to provide scientific value and spur new discoveries?
- Where would **creation of new or more reliable NAMs** open new doors for inquiry?
- Are there big ideas that could be achieved by a coordinated, interdisciplinary approach?

FOR DISCUSSION: PROPOSED NEXT STEPS

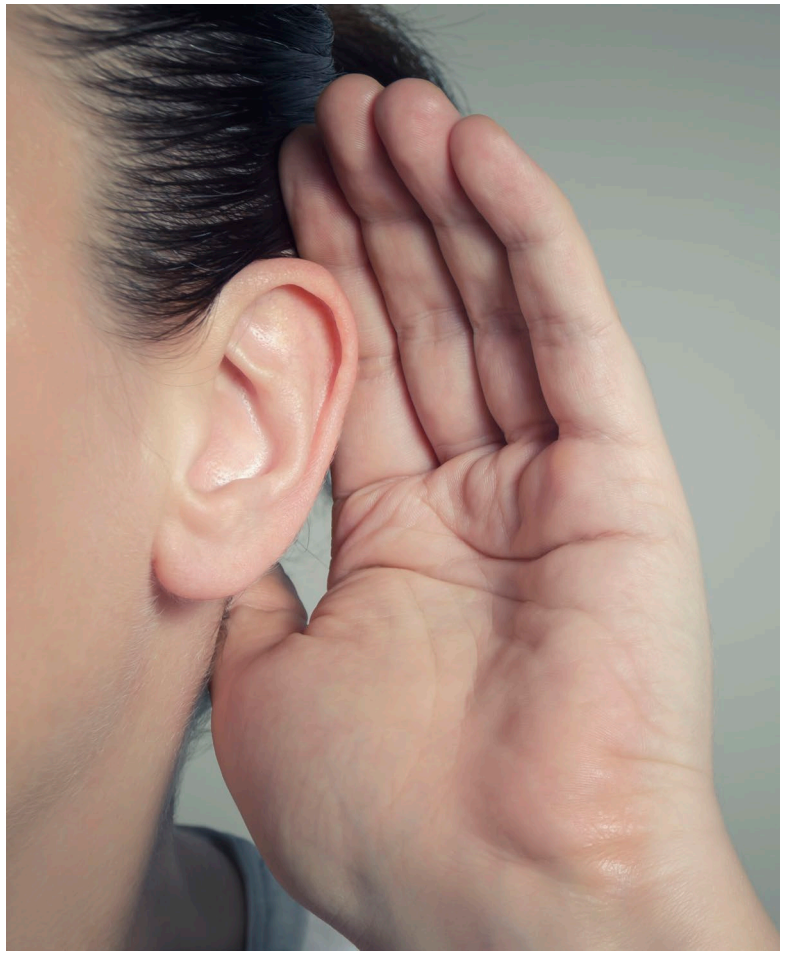
BROADER ENGAGEMENT – SIGNIFICANT ACTIVITIES

Engaging the Public - Request for Public Input *(next week)*

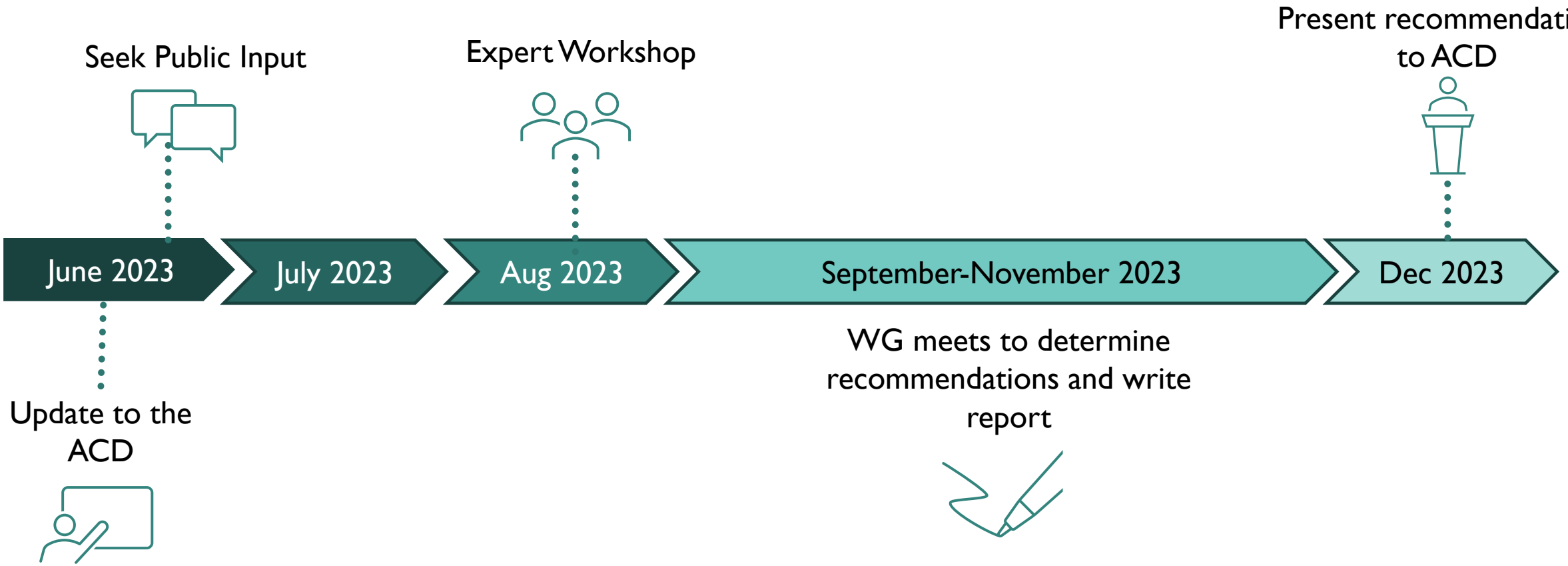
- NIH seeking input from interested individuals and communities to inform working group discussions and recommendations
- NIH specifically interested in information on challenges and opportunities for the development and use of NAMs in biomedical research

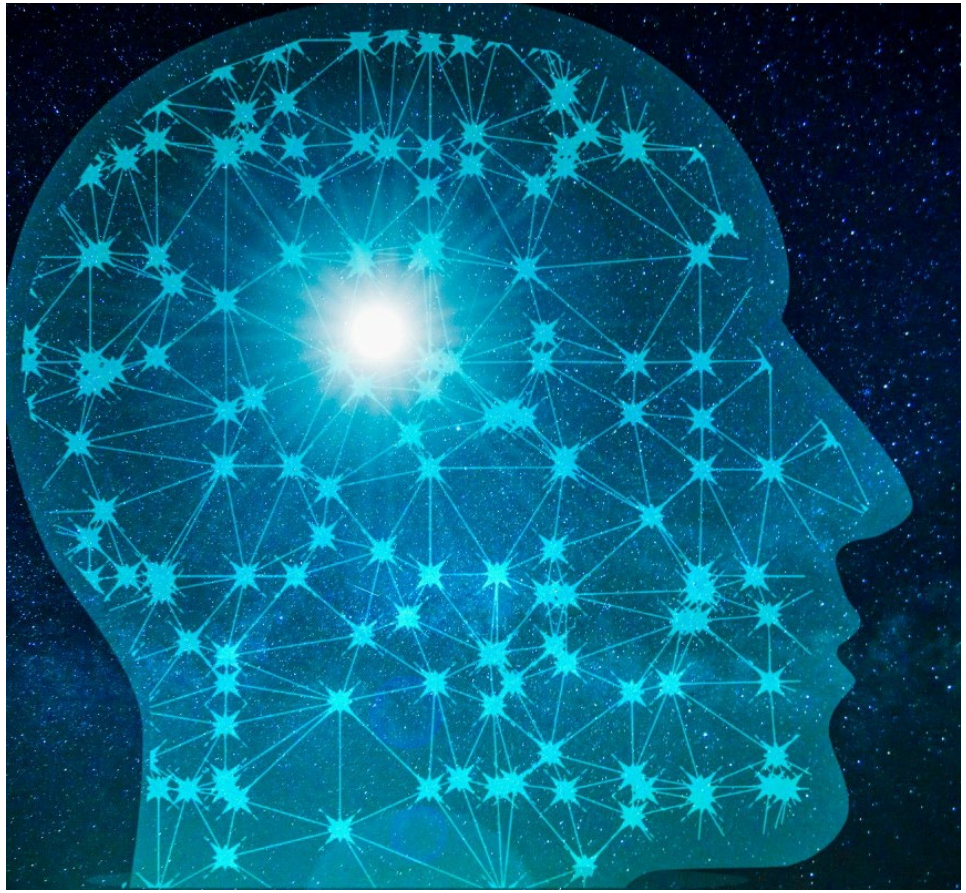
Expert Workshop *(August)*

- NIH hosting a workshop to review progress and discuss potential high priority areas
- Will be webcast – more to come!



TIMELINE OF PROPOSED NEXT STEPS





ACD DISCUSSION