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Advancing Research Infrastructure to Study Human Diseases Workshop

June 8 and 12, 2026
Virtual Meeting

Final Report

Table of Contents

Executive Summary 3

Workshop Overview 3

Next Steps 4

Workshop Report 5

Day One 5

Welcome and Workshop Overview 5

Keynote: Complementary Roles for Human Organ Chips, AI, and Animal Models 5

Session 1: The Need for Complex Integration of New Technologies to Study Biological Mechanisms of Human Disease Progression; Complementary Use of Animal Models and NAMs for Preclinical Studies and Therapeutic Development 6

Session 2: Shared Resources to Validate and Promote NAMs; Research Frameworks; Tracking Activities 9

Session 3: Building Comparative Databases and Tools to Support Benchmarking and Model Selection; Promoting Predictivity and Reproducibility Through Interoperable Data Standards and Platforms 12

Session 4: Multidisciplinary Collaboration, Training, and Future Directions 15

Closing Remarks 18

Day Two 18

Welcome and Workshop Overview 18

Session 1: Development and Validation of *In Vitro* NAMs and Integrated Model Systems 19

Session 2: *In Chemico* NAMs and NAMs Supporting Systems 24

Session 3: *In Silico* NAMs—Leveraging Real-World Data for Model Validation 28

Session 4: Future Trends Toward Integration of Model Systems and Clinical Applications 33

Closing Remarks 34

Appendix A: Meeting Agenda 35

Appendix B: Organizing Committee, Presenters, and Panelists 41

Executive Summary

Workshop Overview

The Advancing Research Infrastructure to Study Human Diseases workshop was held on June 8 and June 12, 2026, and was organized by the National Institutes of Health (NIH) Office of Research Infrastructure Programs (ORIP). The workshop offered a platform to discuss complementary approaches addressing complex biological mechanistic questions related to expanding NIH-funded model resources and physical infrastructure, validating new approach methodologies (NAMs), and improving the predictability and scalability of models for human diseases. Attendees included individuals from NIH, other federal agencies, state governments, the military, academia, industry, and other sectors.

Day 1 of the workshop addressed the strategic and translational integration of NAMs and animal models in biomedical research. The keynote talk focused on the complementary roles of human organ chips, artificial intelligence (AI), and animal models. Session 1 outlined the need for complex integration of new technologies to study biological mechanisms of human disease progression and the complementary use of animal models and NAMs for preclinical studies and therapeutic development. Session 2 focused on shared resources to validate and promote NAMs, research frameworks, and tracking activities. Session 3 outlined ways to build comparative databases and tools to support benchmarking and model selection, as well as methods for promoting predictivity and reproducibility through interoperable data standards and platforms. Session 4 discussed multidisciplinary collaboration, training, and future directions.

Day 2 of the workshop focused on presenting emerging NAMs technologies that will advance human disease research, with an emphasis on strategies to integrate and validate combinatorial NAMs. Session 1 outlined the development and validation of *in vitro* NAMs and integrated model systems. Session 2 highlighted *in chemico* NAMs and supporting systems. Session 3 discussed *in silico* NAMs and how to leverage real-world data for model validation. Session 4 featured a keynote presentation that highlighted the use of NAMs to accelerate drug discovery, hit-to-lead identifications and validations, and clinical trials in a dish.

On each day of the workshop, presenters and panelists were asked to discuss key infrastructure limitations that must be addressed to maximize the impact of NAMs in biomedical research.

Several key themes emerged from the workshop:

- Research infrastructure is a vital enabler of scientific progress. Technological advances alone are not sufficient to translate innovation into broad benefits for human health; they must be supported by robust infrastructure development. This includes access to high-quality biological resources and physical infrastructure and facilities, shared platforms, interoperable data systems, benchmarking tools, validation frameworks, and community standards that enable discoveries to be reproduced, compared, trusted, and scaled.
- Each model system has unique strengths, and the research community must bring these approaches together to generate deeper biological insight and more rigorous science. The future lies in the integration of models, not the replacement of one model type with another.

- Researchers should carefully select NAMs based on the research question, using the most realistic model or set of complementary models that remain fit for purpose. Oversimplification can miss key biological complexity and may require multiple simple models to address system-level dynamics.
- Human diseases are complex, and population heterogeneity and variability in patient phenotypes add an additional layer of complexity for studying disease. Human variability is difficult to model accurately but critical to understanding disease.
- Rigorous validation, reproducibility, transparency, and evidence-based benchmarking are needed to establish confidence in NAM performance and applicability as these technologies mature.
- Universities could develop cores or centers that include NAMs as a service to researchers to help promote NAM use. Centralized national systems or repositories also could be developed to support data accessibility, harmonize standards, and provide researchers with access to models or samples.
- Computational modeling and AI are critical for studying complex diseases and analyzing large datasets.
- Automated platforms and systems will increase the use of NAMs and foster their scalability, as well as enhance reproducibility.
- The challenges addressed by NAMs span biology, engineering, computational science, data science, medicine, and technology development, reflecting the growing need for collaborative partnerships across academia, industry, government, nonprofit organizations, and resource providers.
- Developing the next generation of interdisciplinary researchers and ensuring broad access to tools, data, and expertise will be critical to sustaining progress and fostering innovation in this rapidly evolving field.
- Funding opportunities to integrate NAMs into research efforts are available, but support for physical infrastructure hardware and maintenance of resources is needed.

Next Steps

Additional investment and coordination are needed to ensure NAMs can be successfully implemented into the biomedical research community as reliable and sustainable tools. ORIP will analyze the input received from the workshop to identify ways to address current infrastructure gaps.

Workshop Report

Day One

Welcome and Workshop Overview

Nicole Kleinstreuer, Ph.D., Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), Office of the Director (OD), NIH

Dr. Nicole Kleinstreuer commented that this workshop reflects NIH's growing commitment to adopting NAMs and other human-based technologies as efficient, effective, and predictive research tools. She noted that the new NIH Office of Research Innovation, Validation, and Application (ORIVA) and other significant NIH investments are intended to optimize NAMs and ensure their relevance to human biology and fit for each scientific question. Dr. Kleinstreuer emphasized that this effort requires strong links among experimental systems, biology, and human outcomes and provides an opportunity to improve rigor and reproducibility, as well as translation.

Keynote: Complementary Roles for Human Organ Chips, AI, and Animal Models

Donald Ingber, M.D., Ph.D., Wyss Institute, Boston Children's Hospital, and Harvard Medical School

Dr. Donald Ingber outlined the work he and his team have conducted to develop human organs-on-chips, which reconstitute organ-level functions with living human cells. These models have successfully predicted drug effects that do not present in animal models, modeled regimen-specific toxicity, and mimicked drug exposure and pharmacokinetics precisely using the chips' flow capabilities. Organ chips provide a window into molecular-scale activities inside living human cells within a relevant tissue and organ context. These studies could reveal new disease mechanisms and enable drug discovery, and they provide a way to experimentally test predictions. Organs-on-chips also can model host–microbiome interactions. Dr. Ingber commented that when compared with animal models, NAMs' predictive results are often significantly better, more human relevant, and delivered in a fraction of the cost and time.

Chips for various organs can be connected to mimic an integrated human body—Dr. Ingber's team has successfully connected up to 10 organs for 4 weeks to translate *in vitro* to *in vivo* pharmacokinetic parameters, which would reduce the time required to design clinical trials by identifying dosages in advance. Implications for drug development include the ability to conduct small trials in specific patient groups faster, cheaper, and more successfully. AI also can be integrated with human tissue chips by identifying patterns of disease in patient transcriptomics data and predicting drugs that could be effective. Using AI to conduct network analysis, followed by tests in organ chips, can speed translation to more advanced models. Dr. Ingber emphasized that organ chips are more than potential animal replacements—they are also mechanistic drug discovery tools and testbeds for validating newly discovered therapeutics. Human organ chips, animal models, and AI represent synergistic approaches to major challenges in drug development.

In response to attendee questions, Dr. Ingber emphasized that organs-on-chips should be designed to recapitulate the clinical phenotype of interest as simply as possible. They are not intended to reflect the full complexity of the biological system. The specific design will depend

on the question studied; Dr. Ingber recommended using clinical response as a benchmark. He emphasized that increasing cross-validation between animal models, organ chips, humans, and AI analysis will increase the ability to identify useful models.

Session 1: The Need for Complex Integration of New Technologies to Study Biological Mechanisms of Human Disease Progression; Complementary Use of Animal Models and NAMs for Preclinical Studies and Therapeutic Development

Tissue-Engineered NAMs for Drug Discovery and Evaluation

Wolfram-Hubertus Zimmermann, M.D., Institute of Pharmacology and Toxicology, University Medical Center Göttingen

Dr. Wolfram-Hubertus Zimmermann explained that organoids are developed from an undifferentiated or pluripotent cell directed to form organotypic tissue, making them more useful for modeling development than mature tissue. Tissue-engineered models can be used to model specific functions of mature tissues. Tissue-engineered heart muscle has defined cellular composition and maturation states, and models can be designed on demand with the cell type that will best test the question of interest. This type of muscle can be used to identify small molecules helpful in gene-therapeutic approaches and their mechanisms of action. Dr. Zimmermann described several clinical applications of NAMs, including the evaluation of genome-editing approaches for Duchenne muscular dystrophy therapy. Findings in human induced pluripotent stem cells (iPSCs) were supported by safety and biodistribution data from nonhuman primate studies. The team is now advancing toward clinical applications of newly engineered heart muscle tissues. Overall, Dr. Zimmermann suggested that tissue-engineered and organoid models are valuable tools for supplementing nonclinical *in vivo* data and supporting the development of potency assays for clinical trials.

Organoid NAM-Guided Precision Hepatology

Takanori Takebe, M.D., Ph.D., Cincinnati Children's Hospital Medical Center

Dr. Takanori Takebe explained that his laboratory creates liver tissues from embryonic stem cells but often must contend with the complexity required to study the biologies of interest. Complexity typically compromises scalability, so each model must use only the minimal components. In a simple model of drug efflux in drug-induced liver injury (DILI), the team could control the path of a drug and its elimination and was able to identify common genetic factors driving DILI from genomics and toxicity datasets. A polygenic risk score was developed to stratify a number of models across 12 drugs. To conduct more accelerated studies that incorporate heterogenous progression, Dr. Takebe's team mixed organoids from different individuals in the same culture plate.

Dr. Takebe noted that organoids are an immature technology with limited complexity. Their functional ceiling limits broad toxicology and chronic disease modeling, and they do not include systemic cues. Some next-generation organoid systems now address these considerations with multidisciplinary collaborative processes, and transplantation can be used to mature organoids and permeate them into living tissue. Infrastructure is needed to scale organoid NAMs and could include the pooling of donors or conditions, the use of genotyped biobanks with harmonized data, the coupling of organ modules and systemic readouts, and the linking of computational and pharmacological models. Dr. Takebe noted that current iPSC-based organoid models face several

key challenges, including limited cellular and structural complexity, restricted developmental progression, immature cell types, functional constraints, and a lack of systematic biological cues. Several strategies are being explored to address these limitations, including the assembly of multiple organoid types, organ-on-a-chip platforms, and direct integration of organoids in animal models.

Modeling the Regenerative Endometrium Using 3D Organoids and Assembloids
Diana Monsivais, Ph.D., Baylor College of Medicine

Dr. Diana Monsivais explained that animal models have been and continue to be essential in modeling human reproduction and have paved the way for the development of human 3D models that allow the study of endometrial receptivity and early pregnancy under normal and disease conditions. Mouse models are essential for studying the interorgan communication systems that control reproductive function and dysfunction, but endometrial organoid and assembloid models are useful tools to discover mechanistic drivers of disease and model early pregnancy in humans. Mouse models have helped identify cell populations and growth factors that drive endometrial regeneration in humans. In humans, cells with high aldehyde dehydrogenase (ALDH) activity ($ALDH^{HI}$) form more and larger organoids than cells with low ALDH activity. Ectopic organoids from endometriosis lesions exhibit a higher rate of $ALDH^{HI}$ cells and display different gene expression patterns. Dr. Monsivais commented that 3D organ culture systems, particularly endometrial organoids and assembloids, have transformed reproductive research by enabling long-term study of uterine biology, disease, implantation, and cellular interactions outside the body. As more laboratories adapt these model systems, the quality, complexity, and impact of these technologies will continue to improve.

There and Back Again: A Multi-Platform Journey from Cell Lines to Human Tissue Reveals Direct Interactions Between *Helicobacter pylori* and Epithelial Stem Cells
Manuel Amieva, M.D., Ph.D., Stanford University

Dr. Manuel Amieva explained that microbes interact with human cells much more intimately than many people realize. *Helicobacter pylori* is a microbe that lives in the human stomach and colonizes about 50% of the world's population, with 1% of those developing gastric cancer, making it the fifth-most-common cancer and fifth-leading cause of cancer death. *H. pylori* infects children but causes disease much later in life, making early identification difficult. Dr. Amieva's team found that the bacteria form microcolonies on the epithelium, acquiring nutrients and modifying the epithelial polarity to support these colonies. Because the lumen is inaccessible in many human organoids, the team developed a method to alter the polarity of the gastroid, which placed the microvilli and junctions on the outside. Reconstructions of gastric resections showed that *H. pylori* were present on the surface of the stomach, as well as deep in the glands; organoids were used to understand infectious microniches, and gastroids mimic different gland regions.

Because disease progression and gastric cancer development take decades, Dr. Amieva's team created a biobank of biopsies from different regions and stages of disease. They found that adjacent tissues in the same patient already contained abnormal stem cells, and disease state was preserved epigenetically. He emphasized that organotypic systems can operate beyond yes-or-no questions to help researchers find outcomes that are difficult to see or predict.

Putting the Pieces Together: Inception of Human Neural Circuits in Assembloids to Study Disease

Sergiu Paşca, M.D., Stanford University

Dr. Sergiu Paşca explained that his team studies neurodevelopmental disorders, but human tissue related to these disorders often is inaccessible, and understanding of human brain development remains poor. Models now can generate cell diversity and replicate the states of corticogenesis, and this process can be highly reproducible if the quality of iPSCs and genome integrity is ascertained. The team created an assembloid to identify genes interfering with interneurons migrating toward the dorsal forebrain. Assembloids made with the correct cell types are able to assemble early neural circuits, and the team also has been able to model enterovirus infections that cause encephalitis, including polio. They showed that the viruses infect different types of cells—some infect neurons and some infect astrocytes, which they believe causes the most damage. In moving from three-part to four-part assembloids, the team was able to model the ascending sensory pathway, in which sensory neurons connect with dorsal spinal cord neurons, thalamic neurons, and cortical cells to create a sensory organoid with pain receptors, a dorsal spinal cord, a thalamus, and a cortex. If placed in the correct order, this system replicates the activity of the *in vivo* system absent any stimulus.

Although these preparations are increasing in complexity, they retain a number of puzzling limitations. Even when grown for a long time, the neurons remain many times smaller than developing neurons in the human cortex. If transplanted into the developing rat cortex, they can grow larger, and responses can be triggered, indicating integration into the circuitry, but whether the size is important for disease modeling remains unknown. When patient-derived cells used to generate a cerebral hemisphere in the rat were treated with an antisense oligonucleotide previously shown to rescue the phenotype of interest, the genetic defect was corrected within 1 week. The team is now conducting the preclinical and clinical work necessary for a clinical trial by characterizing this disease in most of the patients in the English-speaking world and conducting systematic testing of potential immune responses in both rodents and macaques, aiming for a potential clinical trial in fall 2026.

Discussion

Dr. Paşca suggested that NAMs are not yet able to capture complex organism-level phenotypes and that researchers are just learning how to connect different organ types. Although some engineered organ systems can communicate with each other, *in vivo* models remain necessary for complex systems. Studying many diseases requires complex readouts, such as behavioral or sensory measurements. Dr. Zimmermann noted that if organoid systems are simplified and precisely defined, they can complement and support many investigations that are not possible *in vivo*.

Dr. Paşca commented that animal models likely will remain necessary for aging studies and pharmacokinetics. Given the time required to develop many cell types, growing cultures for long periods of time is not always practical, and other models, such as transplantation, may be necessary. The timing of aging is conserved in organoids, so third- or fourth-decade aging cannot be captured. However, some circumvention is possible by modeling early-onset neurodegeneration or using direct reprogramming. Early neurodevelopmental phenotypes can be used for some disorders, although whether the early defects relate to later pathophysiology often is unknown. The discussions further framed aging, pharmacokinetics and pharmacodynamics,

immune responses, organism-level physiology, and long-range interorgan communication as areas in which *in vivo* systems remain important comparators or complements. The practical question was not presented as "animal model or NAM," but as which combination of models best fits the biological endpoint and decision context.

Dr. Amieva pointed out that many groups now are integrating other technologies, such as 3D printing, but such integration often requires bioengineering expertise.

Dr. Paşca emphasized that animal models also require continuous improvement. At the same time, they provide valuable insights that support the development of NAMs. For example, Dr. Takebe pointed out that *in vivo* transplantation studies have led to the discovery of new factors that may enhance the maturation of tissue cultures and organoids, as well as improve communication between cells within these systems.

Dr. Amieva noted that until recently, no experimental systems could reproduce species-specific parasites. Some new strategies allow organoids to reproduce human environments sufficiently for parasitic colonization.

Dr. Paşca commented that regulatory implications related to organoids include how well the models predict therapeutic success and country-specific preferences for models. There may be ethical questions about building human systems in a dish, but such systems do not include the emotional components of sensations, and consent protocols still must be followed when collecting patient cells. Dr. Zimmermann added that for a number of investigational new drug studies, allograft experiments in large animal models are more appropriate.

Session 2: Shared Resources to Validate and Promote NAMs; Research Frameworks; Tracking Activities

CuSTOMizing Induced Pluripotent Stem Cells for Modeling Human Disease
Michael Helmrath, M.D., Ph.D., University of Cincinnati, Cincinnati Children's Hospital Medical Center

Dr. Michael Helmrath explained that the Center for Stem Cell & Organoid Medicine (CuSTOM) Accelerator was designed to create a dedicated approach for translating work from research laboratories into humans. The team aimed to build infrastructure with gold-standard benchmarks, including standard demographics and conditions for all iPSC lines established, as well as associated tissues. Dr. Helmrath emphasized that standardization and validation are necessary to ensure that projects that are successful in the laboratory are scalable. The infrastructure requirements, including reporting and administrative support, needed for milestone-driven collaborations with real-time reporting to industry are not typical of NIH-funded laboratories. CuSTOM consists of an academic research team and an accelerator team that work to understand what is required to de-risk and connect NAMs to milestones. CuSTOM's research is conducted in ways that allow the team to assess the stages of the process and demonstrate that the cells are patterned appropriately.

Such consistency is essential to biobanking and sharing resources. Standardization requires the ability to characterize the cell source; the CuSTOM team developed an automated system for liquid handling and imaging, creating a foundation to enable reproducibility, scalability, and impact. In one study, the team was able to predict specific risk of DILI in some populations from

a sample of 30 groups with differing drug responses. Today, CuSTOM conducts essential tasks to support basic science researchers. Dr. Helmrath emphasized that better understanding of rare diseases, generated by organoid medicine, will lead to discoveries that can be generalized to broader populations.

NAMs for Interrogating Cancer
Scott Lowe, Ph.D., Memorial Sloan Kettering Center

Dr. Scott Lowe provided examples of several animal- and human-based approaches in development at the Memorial Sloan Kettering Cancer Center (MSK). He explained that cancer has a complicated pathology—it is highly heterogenous, it involves disruption or alteration of a wide range of basic cellular processes, and it evolves progressively in a complex tissue microenvironment, with heterogeneity that can lead to resistance and recurrence. Historic cell line and mouse models are not strongly predictive because of this complexity. One major resource used at MSK is a patient-derived xenograft system in which tumors isolated from patients are grafted into immune-deficient mice, a method that retains features of human cancers better than cell lines and can capture tumor heterogeneity. The facility is currently housing thousands of unique validated patient-derived xenograft models. However, these models are not human and therefore cannot fully recapitulate human biology. In addition, they can be cost-prohibitive to generate and maintain. Organoid models complement patient-derived xenograft technologies by providing an *in vitro* system that preserves many of the structural and molecular characteristics of the original tumor while enabling more rapid and scalable experimentation. One emerging approach involves generating organoids from multiple tumor lesions obtained from the same patient and studying them in parallel. This strategy enables investigators to characterize intrapatient tumor heterogeneity, compare the biological properties and drug sensitivities of distinct lesions, and identify therapeutic vulnerabilities that may not be apparent from analysis of a single tumor sample.

MSK also has developed new immune-competent mouse models to capture the full tissue context of cancer from early initiation to progression to metastasis to therapy response more quickly than standard mouse models. One approach uses a mouse tumor–derived organoid model engrafted on an orthotopic site; another approach involves engineering alleles in one embryonic stem cell. MSK also integrates models from iPSCs, which can generate cell states that mirror the major gene-driver combinations in human pancreatic cancer; organ-on-a-chip methods are in development that mix human cells (e.g., primary cells, stem-cell derivatives, organoids) and stroma to produce a dynamic microenvironment that mimics the physiology of tumors. Another method in use is preserving native tissue architecture and natural immune composition by using precision-cut slices of tumors that can be cultured and studied with various models. Multimodal datasets are integrated across human patients and experimental models in the cBioPortal for Cancer Genomics, a resource supporting the exploration of multidimensional cancer genomics datasets, for dissemination to the community. Dr. Lowe emphasized that no single model is better than another and encouraged attendees to use the appropriate model to answer the question of interest.

Coordinated Infrastructure for NAMs Benchmarking and Community Access
Brenda Ogle, Ph.D., University of Minnesota

Dr. Brenda Ogle explained that her laboratory is interested in how the extracellular matrix (ECM) affects stem cell behavior and drives differentiation of cell types. Her team has

developed three ECM protein formulations to drive cell specification; Dr. Ogle explained the development of the formulation for cardiomyocyte specification. Researchers first printed ECM proteins using bioink into a geometry that mimics the chamber of the heart. This experiment produced some success, but the cardiomyocytes do not move well or proliferate after specification, so obtaining contiguous muscle function from print to print is challenging. In later experiments, when stem cells were allowed to differentiate in the construct, contiguous muscle function was achieved, and the team was able to mimic cardiac waveforms and model pressure-volume dynamics using mechanical valves outside a bioreactor, creating a model for diseases with altered fluid dynamics.

In addition to studying drugs, NAMs can be used to study and test medical devices. Dr. Ogle's team has faced challenges in providing model systems to other laboratories and has created partnerships to improve the process. Preservation is a particular issue, especially for cardiac tissue larger than cells or organoids, given the short timeframes for using donor hearts and intracellular and electromechanical structures that are particularly susceptible to cryopreservation damage. Dr. Ogle's team recently had a breakthrough in recovering macro-scale electromechanical function in engineered heart tissue in collaboration with a National Science Foundation engineering research center focused on slowing biologic time, suggesting the need for coordinated national infrastructure. The Manufacturing Organoids for Researchers Everywhere concept would support a facility in which mature organoids or model systems could be scaled up for production, quality control, preservation, storage, and distribution via national infrastructure. Dr. Ogle emphasized the need for coordination of the significant work happening in this field.

From Standardized Biological Materials to Validated NAMs: The Role of Resource Stewardship, Quality Frameworks, and Scalable Validation
Carolina Lucchesi, Ph.D., American Type Culture Collection

Dr. Carolina Lucchesi outlined how standardized biological materials combined with quality frameworks and scalable validation are essential for turning promising research tools into reliable, decision-grade platforms. Many organoids and NAMs lack defined performance criteria or consensus guidelines, making interpretation across laboratories and tissue types difficult. Regardless of technology, high quality, well-characterized biological inputs are essential. To make results meaningfully comparable, cells must be authenticated, consistent, and reproducible; protocols must be harmonized; and consensus on qualification criteria must be gathered. Shared resource organizations are uniquely positioned to maintain standards at scale and serve as quality-assured hubs for the research community.

Although animal models and NAMs are useful for different questions, the most usable signal is integration. Dr. Lucchesi stated data that converse raise confidence, and discordance can be informative in driving hypotheses. A centralized infrastructure would enable these sorts of integrations. The Human Cancer Models Initiative is an example of a successful consortium that integrated collaborators' strengths to develop models, deploy the collection, make it visible, and provide end-user training and support. Before NAMs can be used as benchmarks, the biology must be confirmed to represent the disease being modeled, and connecting NAMs with *in vivo* evidence requires reducing noise and benchmarking against reference datasets. Dr. Lucchesi emphasized that the future is a portfolio of models, not one type.

Discussion

Dr. Ogle noted that one critical infrastructure gap currently limiting the broader adoption and validation of NAMs is the need for a neutral, centralized location to provide resources. AI can be used to attempt to identify key features missing from the animal model that can be recapitulated in the NAM. NAMs provide a clear bridge between human and animal models, but animal models are still relevant and needed in many cases.

Dr. Helmrath commented that standardization of human-derived NAMs requires confirmation that tissues representing specific patients or iPSCs can be scaled in real time for appropriate studies. Because models vary in usefulness, the ability to transplant NAMs into positive controls, such as animal models, and back into human systems is important. Some NAMs may be specific to certain questions, and translation requirements for these specific NAMs may not be as stringent as those for NAMs designed to support studies intended for publication. NAMs designed to answer distinct questions may not meet traditional notions of reproducibility; the next generation of researchers may need to be trained to consider standardization in broader ways. Dr. Ogle suggested that funding to evaluate multiple iPSC lines would help improve standardization. Dr. Lucchesi emphasized that multidisciplinary collaboration throughout the community is essential to improve understanding of the multiple factors, such as population-level variation, that challenge standardization.

Dr. Lowe noted that characterization of human models in cancer is relatively straightforward, but variation makes quality control challenging. In cancer, knowing the genetic alteration that drives the cancer can indicate whether a pattern of response in a specific genotype is present, which provides a defined measure of success. Creating reproducible human-based systems that address less specific questions becomes more challenging. Dr. Helmrath added that as reagents evolve, readouts change, and new toolboxes must be developed.

Dr. Ogle explained that challenges in validating NAMs will vary depending on the context of use—for example, a NAM used for discovery might only need to show biological relevance or reproducibility, whereas a NAM for translational or regulatory use will have more defined performance criteria and documentation. Sequencing individual cells is becoming more affordable, and AI will help advance these efforts. Dr. Helmrath pointed out that highly automated systems, although expensive, improve standardization, reliability, and validation of outcomes by removing variability associated with individual users. Dr. Lucchesi added that data generation, storage, quality control, and dissemination to the community are important factors.

Session 3: Building Comparative Databases and Tools to Support Benchmarking and Model Selection; Promoting Predictivity and Reproducibility Through Interoperable Data Standards and Platforms

Bridging the Gap: A Mechanistic Platform to Enhance Translatability of Human-Specific Pharmacology Across Diverse Modalities

Murat Cirit, Ph.D., Javelin Biotech

Dr. Murat Cirit discussed how to improve the reproducibility and predictability of organ-on-a-chip technologies and how to assess biological function to compare application and context of uses *in vitro* to *in vivo.* The team first created a more robust thermoplastic than in standard chips, improving many manufacturing challenges. They then were able to build a physiologically

relevant technology incorporating onboard pumping for robust operations, oxygenation to extend the culture period, and drug addition and sample collection in the same design to improve reproducibility. The team is developing a high-content information system, rather than just another high-throughput approach, by generating thousands of data points from a single tissue over a monthlong study and enabling physiological relevance without any membrane or scaffolding technologies.

The most important step in validating this technology is evaluating the biology and characterizing it for receptor expression relevant to drug delivery systems. The team created a bioinformatics workflow in which they used transcriptomic profiles from 200 human liver biopsies to evaluate inter-donor variability and compare it with samples from nonhuman animal models. Human liver microphysiological systems (MPS) show the highest relevance to human references and were comparable with a profile from the mouse, rat, and nonhuman primate *in vivo* samples. By expanding disease models and human relevance, the team can compare disease pathway similarities between human liver tissues, and these studies can be expanded to multi-organ systems by connecting liver NAMs to kidney and muscle NAMs. Dr. Cirit's team also has studied toxicities that arose only in a larger human population, showing dose-dependent steatosis after 3-week exposures in their complex liver model. Special emphasis is given to procedures in place to assess variability and reproducibility of the data.

Standardizing NAM Data for Mechanistic Discovery and Translational Confidence
Melissa Haendel, Ph.D., The University of North Carolina at Chapel Hill

Dr. Melissa Haendel outlined the Monarch Initiative, which develops data standards and semantic tools for data harmonization. Mechanistic biology and NAMs require modeling a deep, rich collection of associations, and standards must be set to allow researchers to inventory and compare many types of relationships. Currently, information about NAMs is scattered, and holistic data harmonization standards are lacking. NAMs also are advancing more rapidly than the standards used to inventory and compute them, creating a fragmented data landscape and inconsistent methods that limit the confidence in, comparability of, and progress toward using NAMs for regulatory advancements. New Approach Methodologies Ontologies is a schema that characterizes aspects of various types of NAMs, such as listing the specific characteristics of an organoid and how those can be collected. Monarch has been working to determine how to algorithmically compute the degree of concordance across NAMs to demonstrate the evidence needed for translational implications or regulatory approval.

A standard for documenting NAMs should include a defined context of use, the specific biological context, and the specific endpoints. Dr. Haendel emphasized that combining NAMs helps form a complete picture, and multiple NAMs and models improve on single models. For example, an organoid can be used to discover changes, a chip can be used to test behavior under real forces, and physiological models can be used to determine which human exposures make that happen. The same signal must be assessed across layers. Reporting and standards are worth the investment because interoperability, comparability, the ability to conduct meta-analyses, and AI-ready data are critical. Dr. Haendel emphasized that this information has to be investigator-provided because no existing committees or databases support it. The resources mentioned combined with AI can enable evidence-based model selection that will match biology, throughput, and cost while reducing animal use and creating a validation framework with structured importance results or metrics.

From Atlas to Benchmark: The Infrastructure Required to Compare an Organoid to Human Tissue
Jason Spence, Ph.D., University of Michigan Medical School

Dr. Jason Spence outlined the workflow used to develop new organoid or NAMs models, how the cellular complexity is described, and how they can recapitulate some aspects of human biology, with an approach to validation and benchmarking. His work focuses on lung organoids, and his laboratory has developed methods from iPSCs and primary tissue to isolate or differentiate progenitor cells that can be subsequently differentiated into alveolar type 2 cells, which then can be used to give rise to alveolar type 1 cells. The team used single-cell RNA sequencing, multiomics sequencing, and spatial transcriptomics to create a pediatric reference atlas as a queryable benchmark that can be used as a comparator to score NAMs. One challenge in this process is that the team identified two distinct states in the cell samples that were previously undefined; however, other recent papers have defined alveolar cells in different ways, and consistency in linking those models to Dr. Spence's or to models used *in vitro* is lacking. The only existing ontology does not have heterogeneity that encompasses all categories. Dr. Spence's team developed signature scores for their cell types and surveyed other data to find them, but the feature depth in other datasets was too low to find the genes contained in the signature score.

To recapitulate states in the native human lung in alveolar type 2 organoids, Dr. Spence's team screened cytokines and growth factors and assessed genes that were enriched for these two signatures. Patients treated with a specific drug prior to surgery had a higher abundance of a certain type of cell, indicating that features in the tissue culture dish could be reflected in the patient population and the treatments received prior to surgery. Organoids that received different treatments drove transcriptional signatures toward a certain type of cell in the reference dataset. Dr. Spence summarized that benchmarking NAMs and organoids requires certain infrastructure considerations, including clinical context for patient data, which depends on both available data and collaborator relationships. From there, researchers must build a human reference atlas or use existing atlases processed with annotated data to compare across datasets. Data quality matters, and ontologies must keep up with the evolving landscape; they also should be shareable and searchable. The community could benefit from a standardized approach to benchmarking.

Building Confidence Through Curated Data and Open Access Interoperable Computational Tools to Support NAM-Based Chemical Assessment
Bridgett Hill, M.S., General Dynamics Information Technology

Ms. Bridgett Hill provided an overview of the NIH Integrated Chemical Environment (NICE) and discussed general data curation workflows and ways the data can be explored through open access computational tools. NICE was first developed to support the development, evaluation, and application of NAMs. It houses a diverse set of toxicological data, chemical information, and exposure predictions, in addition to a suite of computational tools. This can be used to identify data gaps where a NAM can complement a traditional test method.

Inclusion, curation, and processing of NICE data are guided by the Interagency Coordinating Committee on the Validation of Alternative Methods. Data are retrieved from a number of sources, then reviewed by subject matter experts. The data then are put through a minor processing pipeline to align the information with FAIR principles (i.e., findable, accessible, interoperable, and reusable), remove duplicates, and harmonize information. The data are then uploaded to NICE. Computational tools are available for data exploration, chemical similarity,

biological responses, and understanding potential exposure scenarios. Some tools can generate human-relevant predictions, such as the physiologically based pharmacokinetic (or PBPK) tool, which integrates existing animal and human physicochemical and physiological data and uses mathematical models to predict a drug's absorption, distribution, metabolism, and excretion in humans. Another tool is *in vitro–in vivo* extrapolation, which uses *in vitro* assay information to make human-relevant plasma estimates. These mathematical models allow researchers to explore the question of what equivalent dose in a human will cause the same effect.

Discussion

Dr. Haendel commented that standardizing nomenclature is very difficult for anatomy and diseases, and different communities use different vocabulary and labels. Harmonizing data is also about harmonizing the people who create it, through governance, decision-making, community inclusion, and documenting policies and processes. Provenance and clinical context are critical, and users need to spend time and resources to understand the requirements for using each label. Because of these complexities, what is useful and feasible must be balanced with the appropriate level of standards engineering.

Dr. Spence pointed out that organoids and human tissues can be comparable without vascularization, but many caveats must be considered, and the system must be appropriate for the question at hand. Dr. Haendel added that not all aspects of a human can be included in every model, so researchers must understand what makes a modeling component valid in a particular context and how to combine that information with other models.

Ms. Hill noted that ORIVA will have a broad focus on disease modeling, extending beyond the field's traditional emphasis on toxicology. This broader scope may include advanced *in vitro* systems, organoids, computational models, and other emerging approaches that can improve understanding of disease mechanisms, treatment responses, and human health outcomes.

Dr. Haendel commented that improving model selection and translational relevance is not a problem unique to disease modeling or NAMs—biology as a whole must do better at understanding the evidence generated in any given experiment and how a combination of approaches can create a more comprehensive understanding of how corroborative the evidence generated is. Because disease models built from human tissues often do not include clinical context, the field will need to determine how to capture relevant information in privacy-compliant ways. Each human is unique, and models can only be generalizable if they account for the heterogeneity of the human population. Post-generation data harmonization is more difficult than working together while experiments are being designed and data are being generated.

Session 4: Multidisciplinary Collaboration, Training, and Future Directions

Organs-on-Chips and Organoids: What Can You Ask of Your Microphysiological Systems, How Far Can You Extrapolate Beyond What They Tell You, and What's Needed?
John Wikswo, Ph.D., Vanderbilt University

Dr. John Wikswo commented on the complexity of biology and the magnitude of attempts to capture data for better models. Although biology has classically been reductionist, the demands of MPS require integrative physiology understanding. Few diseases have a single gene of origin, and models must be simple but also able to address some complex aspects of disease. Modeling at scale requires vascularization of tissues, analytical chemistry, and pharmacokinetics and

pharmacodynamics at small volumes; control of systems is critical and understudied. Successful MPS adoption requires a clear understanding of negative predictive value, the meaning of a no-toxicity result, and the sensitivity-specificity trade-offs that arise when fewer tests may increase false negatives. It also depends on making interconnected systems reliable and rigorously qualifying and benchmarking MPS performance against decades of animal data and established no-effect levels. MPS have increasing value for testing drug efficacy and mechanism of action, and interconnected vascularization of organoids and assembloids may replace organs-on-chips. AI will play an increasing role in experimental design, but it requires automated sensors and actuators, and hardware to increase experimental throughput must be developed. Dr. Wikswo suggested that in the current discussion of NAMs, dismissing animal and human experimental evidence entirely in favor of these emerging approaches is unrealistic. He emphasized that at this stage, NAMs should complement and be benchmarked against established animal and human data until their reliability, predictive value, and regulatory relevance are sufficiently demonstrated.

Stem Cells, Genomics, and AI for Drug Discovery
Joseph Wu, M.D., Ph.D., Stanford University School of Medicine

Dr. Joseph Wu emphasized that drug discovery is both time consuming and expensive, but many drugs in the market today do not work as well as perceived. A drug that is effective for only one person and ineffective for many does not meet the goals of precision medicine, and this effect results from a lack of genetic diversity and pharmacogenomic differences in traditional models. The following key research platforms are expected to become transformative upon integration for the purpose of drug development: iPSCs, CRISPR genome editing, genome sequencing, and single-cell multiomics, as well as AI and computational design. To recapitulate the genetic diversity of human populations, Dr. Wu's team has generated cell lines for more than 2,500 patients with different medical histories, ethnicities, and sex and linked these lines to medical information and multiomic sequencing results, and these cells are available to the scientific community. Cells from diverse patients are used to build 3D human cardiac organoids and 3D human-engineered heart tissues, which then can be screened to identify a differentiation cocktail that can give rise to vascularized cardiac and liver organoids. Predictive and generative AI can both be used to find optimal candidates in drug discovery, but those tests should be followed by *in vitro* and *in vivo* studies, and subsequent clinical trials in models can improve the safety and efficacy of a lead compound prior to clinical trials in humans.

Chips for Organoids
Ashutosh Agarwal, Ph.D., University of Miami

Dr. Ashutosh Agarwal focused on external factors driving NAM adoption, including the shortage of nonhuman primates for research in recent years. Chips made without polydimethylsiloxane (PDMS) can be designed with physical constraints and geometric features built into the fluid path, and researchers can solve for the computational flow dynamics within those constraints to enforce a predictable flow. These timelines then can be coupled to biological timescales. For example, insulin dynamics often should include a very quick initial response followed by a slow and sustained plateau response, a response seen in rodents but difficult to recapture in human islets over an extended period. To extend the functional shelf life of pancreatic islets, Dr. Agarwal's team supplemented oxygen through the floor of the device, controlling the concentration in high glucose situations.

Human pancreatic slices with exocrine and endocrine tissues are affected by the speed at which exocrine enzymes degrade endocrine tissue, requiring a fluid device that can continually perfuse oxygen at appropriate levels. Dr. Agarwal's team designed a fluid-handling robot to address this challenge and attached the chip permanently to a microscope, allowing observation of both rare events and pancreatic beta cell cluster action, opening the door to more precise study of immunosuppressants for patients. Partnerships with manufacturers have been crucial in spreading these technologies to other research centers.

Organoids and Mouse Models for Studying and Defeating Human Cancers
David Tuveson, M.D., Ph.D., Cold Spring Harbor Laboratory

Dr. David Tuveson explained that his team has used organoids as a disease model for pancreatic cancer by stratifying pancreatic cancer patients and conducting dynamic assessments on the organoids. Pancreatic organoids were developed from both mice and human tissues and were subsequently shown, in orthotopic models, to recapitulate key stages of pancreatic ductal adenocarcinoma tumorigenesis. Cancers have different transcriptional subtypes, and multiple types can be present within one patient, so identifying drug toxicity is a moving target.
Dr. Tuveson's team has had about a 50% success rate in generating organoids that are predictive of toxicity. Despite many attempts at improvement, the organoids required a median 70 days from sample acquisition to pharmacologic feedback appropriate for clinical colleagues, which is too long for clinical usefulness. To develop predictive approaches, the team created hypersensitive and hyper-resistant organoids, and patients with responder signatures in their organoids could be treated with therapies they were most responsive to. Eventually, a pill was developed that blocks RAS oncoprotein by reactivating the GTPase function of RAS, and 90 to 95% of pancreatic cancer patients can be treated with this pill. Organoids that do not respond well to RAS drugs tend to have wild-type RAS.

Discussion

Advanced cell and organoid models could play an important role in basic scientific discovery. The speakers noted that patient-derived iPSCs and isogenic cell lines can help researchers understand germline genetic diseases, including conditions that affect the heart and potentially other tissues.

Dr. Agarwal clarified that the lifespan of organoids and their chips is driven by biology and usually unaffected by the chip itself.

A key collaboration model would involve bringing these systems directly into drug-development and clinical-trial workflows. Researchers could use them before or alongside trials to screen new treatments for acute toxicity and to gather early evidence about whether a therapy is likely to be effective.

The discussion identified nerve integration and tissue innervation as an important technical challenge. Peripheral nerves influence blood vessels, epithelial tissues, and normal organ function, but it remains difficult to incorporate biologically meaningful nerves into laboratory-grown tissue models.

Dr. Wu noted that one significant infrastructure gap for many investigators is the difficulty of accessing healthy and disease cell lines, but after they access the lines, researchers also need to learn how to use them. Many trainees are hesitant to ask experts for education in these

techniques, but most researchers are excited to share their knowledge, and NIH could help provide structure to disseminate concepts. NIH also could invest in hardware support.

Dr. Wu emphasized that complementary model integration requires large biobanks, clinical trials *in vitro* to validate results, and consideration of human variability. Industry partnerships also must be enabled to provide safe spaces for failure and incorporate input from across the field. Dr. Wikswo pointed out that academia often is limited in its ability to purchase expensive hardware and automated systems, which delays work and reduces reproducibility.

Dr. Tuveson commented that the field could progress by using existing models for basic discovery and trials of novel agents, as well as identifying how to integrate innervation of normal tissue into NAMs. Overall, the discussion emphasized collaboration among organoid researchers, cancer scientists, neurologists, toxicologists, gene-therapy developers, and trainees. Combining expertise across these fields could produce more realistic models and improve both the safety and effectiveness of future treatments.

Closing Remarks

Stephanie Murphy, V.M.D., Ph.D., Office of Research Infrastructure Programs (ORIP), DPCPSI, OD, NIH

Dr. Stephanie Murphy outlined the overarching themes of Day 1. First, the future lies in integration rather than replacement. Each model system or computational approach has unique strengths, so the community must bring these approaches together in a way that generates deeper biological insight and more predictive science. This workshop also reinforced the importance of research infrastructure as a scientific enabler. Advances in technology alone are not enough; progress depends on access to high-quality biological resources, shared platforms, interoperable data systems, benchmarking tools, validation frameworks, and community standards that allow discoveries to be reproduced, compared, and scaled. Many speakers focused on the rigorous validation, reproducibility, transparency, and evidence-based benchmarking needed to establish confidence in NAM performance and applicability as these technologies mature. Discussions also emphasized that challenges span biology, engineering, computational science, data science, medicine, and technology development, reflecting the growing need for collaborative partnerships across academia, industry, the government, nonprofit organizations, and resource providers. Finally, the discussions noted that developing the next generation of researchers and ensuring broad access to tools, data, and expertise will be critical to sustaining progress and fostering innovation in this rapidly evolving field. Across the workshop, a recurring theme was that model selection should be organized around context of use rather than a universal hierarchy of methods. The workshop therefore emphasized integrated model portfolios—*in vivo* models, human-derived NAMs, computational models, clinical data, and shared reference datasets—designed to answer specific mechanistic, translational, or safety questions.

Day Two

Welcome and Workshop Overview

Monika Aggarwal, Ph.D., ORIP, DPCPSI, OD, NIH
Benjamin Freedman, Ph.D., University of Washington

Dr. Monika Aggarwal welcomed attendees and introduced her colleagues, Drs. Yong Chen and Jeffrey Spector. She provided an overview of ORIP's mission, divisions, and small business

programs. Dr. Aggarwal noted that this workshop provides a platform for discussing complementary approaches that will advance human health. She emphasized that technological frontiers of NAMs, emerging technologies, model validation and adoption, and infrastructure gaps would be a focus for this portion of the workshop. Dr. Aggarwal introduced Dr. Benjamin Freedman, Associate Professor of Medicine at the University of Washington, who served as the chair for Day 2 of the workshop. She highlighted Dr. Freedman's achievements and accolades before inviting him to present.

Dr. Freedman briefly outlined the utility of human kidney organoids to recapitulate polycystic kidney disease (PKD). Cyst formation, a fundamental characteristic of PKD, can be recreated with this *in vitro* model. Dr. Freedman uses a form of automation—a liquid handling robot—to grow PKD organoids in 384-well plates. Each well can be treated with a unique drug, a screening method that is more efficient than studying many potential therapies *in vivo*. Because many NAMs are still in the proof-of-concept stage, it is difficult to comprehend the full scope of infrastructure needs. NAMs must be fast, affordable, and reliable for end users to adopt the technology. Infrastructure is needed for a wide range of applications, including minimizing variability and accelerating NAMs development.

Session 1: Development and Validation of *In Vitro* NAMs and Integrated Model Systems

Linda Griffith, Ph.D., Massachusetts Institute of Technology

Dr. Linda Griffith introduced the session by emphasizing the importance of integrating *in silico* and *in vitro* NAMs from the outset of a study. She noted that the session's speakers will provide practical insights based on their experience building and advancing these technologies in academia, industry, and government. She highlighted both the promise and current challenges of NAMs for drug development and disease modeling, stressing the need for interoperable platforms; multidisciplinary expertise; and iterative integration of patient data, computational models, and MPS to create systems that can better predict clinical outcomes.

Designing and Interpreting NAMs Using System Biology

Douglas Lauffenburger, Ph.D., Massachusetts Institute of Technology

Dr. Douglas Lauffenburger highlighted how NAMs align with the capacity priorities of the *ORIP Strategic Plan Fiscal Years 2026–2030*. He emphasized that NAMs infrastructure centers around three fundamental aspects: (1) integrated technology, (2) a systems biology–centric approach, and (3) training and career development. Computational systems biology models connect molecular data to phenotypic data, and this technology allows researchers to understand the heterogeneity of phenotypes. Direct predictions from mouse gene expression signatures are not accurate, and conserved pathways are not always comparable across species. Instead, mouse-predicted associations can be used to construct computational models, and then patient cohort data are projected onto the model before completing regressions and classifications. This modeling approach allows researchers to elucidate human-relevant pathways, processes, and biomarkers from animal studies and predict human phenotypic outcomes based on animal studies. Numerous MPS do not readily facilitate quantitative molecular-level measurements for mechanistic predictions, so MPS technologies that do should be prioritized. MPS are missing key pathways and processes because of the lack of specific cell types needed for interactions. Forward and reverse translation modeling allows for this limitation to be overcome.

Dr. Lauffenburger presented a collaborative study with Novo Nordisk that used these modeling techniques for metabolic dysfunction–associated fatty liver disease.

The Massachusetts Institute of Technology (MIT), in collaboration with partnering institutions, is establishing a Complement Animal Research in Experimentation (or Complement-ARIE) Center to advance the clinical translation of therapies for systemic gynecological diseases. The center integrates clinical, molecular, and cellular phenotype data from endometriosis patients; mathematical and computational models; living patient avatars; and a system biology approach to predict clinical outcomes for candidate drugs. MIT also is developing a NAMs Core, which is integrated with its Division of Comparative Medicine, to reduce barriers for researchers to use humanized models. The NAMs Core will include an immune core and a 3D model and MPS core. Researchers will have access to imaging, microfabrication, and computational technologies.

How Biological Insights Drive Development of Clinically Relevant NAMs Tools
Christopher Hughes, Ph.D., University of California, Irvine

Dr. Christopher Hughes discussed vascularized micro-organs (VMOs), which are more complex than 2D monolayer and 3D spheroid cultures. VMOs highlight gravity-driven arterial and venous flow—which is important to mimic the vascularization of organs—and model diseases (e.g., hereditary hemorrhagic telangiectasia) and clinical manifestations (e.g., port-wine birthmark [PWB]). Dr. Hughes outlined how VMOs help researchers identify drugs that block PWB lesion growth, and he highlighted several bottlenecks. MPS development is not hypothesis driven, which limits funding opportunities, and rapid adaptation requires specific infrastructure. Publication-quality research from MPS may not be ready for commercialization, and existing validation is not clearly defined or standardized. Collaborative projects also are limited.
Dr. Hughes recommended that NIH provide funding for rapid turnaround infrastructure, promote regional hubs and core facilities, establish clear validation guidelines, allow easier access to failed drugs, and support the transition of models into commercial-ready products.

Parsing Systemic Immunity with NAMs
Martin Trapecar, Ph.D., Johns Hopkins University

Dr. Martin Trapecar presented on the use of NAMs to parse systemic immunity and metabolism. He highlighted how different NAM categories (e.g., context of use, biology native, context of exploration) enter biological science, noting that their infrastructure needs vary significantly. NAMs may differ in routes into the research community, core questions, and support systems. Dr. Trapecar emphasized that most drugs fail because the underlying biology was wrong or misunderstood, not because of differences in species. MPS are a complement to animal models; they can provide access to scalable complexity for causal studies of human biology and should preserve biological interactions to support reliable inferences.

In Dr. Trapecar's research, combinations of human tissues are assembled within modular multiorgan tissue interaction vessels in a platform that allows researchers to control and modulate complexity, exchange, perturbations, and readouts. Dr. Trapecar presented active projects using this platform to culture tissue-resident immune (TRI) cells, which are donor and tissue specific. Co-culturing TRI cells with specific cell types results in significant changes in immune responses, and these multiorgan models highlight that the immune system balances immunity with tolerance. TRI cells play a fundamental role in MPS, especially for such studies as safety and toxicity. Other cells (i.e., peripheral blood mononuclear cells and iPSC-derived

immune surrogates) do not preserve key characteristics (e.g., antigen history). Interorgan crosstalk shapes TRI cells, directs metabolic states, impacts nutrient stress, and resolves drug responses. Dr. Trapecar highlighted that advanced MPS have specific infrastructure needs (e.g., interaction controls, perturbation standards, computational translation to clinical cohorts). Donor-matched, immune-preserved tissue should be made accessible for immune NAMs because standard cell banks do not have the necessary cells available. This work highlights that interactions transform tissue behavior into system behavior, revealing biological functions that cannot be understood in isolation.

Scaling and Automation to Support NAMs in Routine Screening: A Pharma Perspective
Anna Bremser, Ph.D., Genentech Inc.
Kimberly Homan, Ph.D., Genentech Inc.

Drs. Anna Bremser and Kimberly Homan provided a pharmaceutical perspective for implementing complex NAM technologies throughout the drug discovery and development pipeline. At Genentech, the Complex *in vitro* Systems group, in coordination with other internal teams, is incorporating NAMs, including organoids and MPS, to enhance translational outcomes. While NAMs can provide important insights during drug development, the field still struggles with NAM selection and validity for the specific drug modality and mechanistic question of interest. Thus, demonstrating NAM predictivity in a specific context of use should be prioritized and validated before significant deployment and scaling of the technology is undertaken. In general, automation of NAMs is important to overcome challenges in user variability, capacity limitations, skillset gaps, and human availability. Dr. Bremser outlined a phased approach for incorporating automation to meet user needs. Academic researchers can work with smaller automated walk-up systems instead of fully automated systems to achieve the benefits of advancing scale without the full overhead of maintaining integrated workcells. These technologies also train early-stage investigators (ESIs) in automation techniques that will help them transition to pharmaceutical companies, if desired.

Scaling, Validating, and Translating NAMs for Detecting Risks to Human Neurodevelopment
Randolph Ashton, Ph.D., University of Wisconsin–Madison

Dr. Randolph Ashton presented on scaling, validating, and translating NAMs for detecting risks to neurodevelopment. Neural organoids are too variable because these *in vitro* models form spontaneously and do not have predictable tissue and circuit formation. The RosetteArray® and OrganoidArray™ technology platforms, which are standardizable and scalable, have been developed to address this limitation. Dr. Ashton briefly outlined the RosetteArray workflow, which allows for quantitative high-throughput screening for neurodevelopmental risk. Human pluripotent stem cells are isolated from control patients and patients with neurological disorders. These cells are seeded into the RosetteArray plate, which uses micropatterned substrate, and can be cultured in the presence of different chemicals and drugs before automated microscope imaging is completed. The RosetteDetect™ software allows researchers to study neurotoxicity and test precision medicine drugs for neurological diseases. Dr. Ashton presented the applicability, reproducibility, scalability, and standardizability of the RosetteArray platform and data acquired from this technology. The OrganoidArray technology platform allows researchers to model additional developmental stages of the prenatal neural system.

Discussion

Dr. Georgette Jones presented the NIH Standardized Organoid Modeling (SOM) Center, which will serve as a first-of-its-kind NIH-wide integrated platform dedicated to developing standardized organoid-based NAMs. The NIH SOM Center will initially focus on specific tissues. The central nervous system is complex, with many components that require unique neural organoids to model diseases. The NIH SOM Center should collaborate with biotechnology companies and university cores to ensure that researchers have access to more models. In addition, organoid models need to mimic the variability observed in patient populations, and the center should support the development of platforms that expand data analysis capabilities. Dr. Jones emphasized that advancing NAMs will require addressing scientific limitations alongside investments in physical infrastructure, workforce training, and administrative support systems that enable multidisciplinary collaboration and technology adoption.

Infrastructure gaps can limit the ability to adapt to evolving NAMs and technologies. Dr. Lauffenburger commented that existing data from preclinical models and clinical multiomics studies can be a foundation for human studies, but the data often are siloed or difficult to access.

Dr. Lauffenburger emphasized that to reduce barriers, universities should consider developing NAMs cores that integrate MPS with multiomics and computational platforms. The cores should emphasize education, access, and consultation to broaden the use of NAMs. Not all research laboratories have access to or experience with systems biology approaches, and cores could provide systems biology researchers to support principal investigators.

Identifying and implementing relevant validation steps are critical for NAMs and *in vivo* models. Dr. Hughes explained that perfusion is a vital validation step for an MPS that includes vessels. To mimic *in vivo* conditions, 100% of media flow should be through the vasculature, so vascularized MPS should be examined for leaking ports before use in a research study.

Dr. Hughes highlighted that the MPS substrate is important to consider when designing a drug study. Water-soluble drugs do not stick to plastic or PDMS, but hydrophobic drugs do, which can skew results and impact the translation of findings.

Dr. Ashton noted that the loss of expert personnel in response to funding challenges limits the development of MPS; bridge funding for staff to continue MPS-related research and pilot funding for collaborations between MPS and non-MPS researchers are needed. Because the MPS field is advancing quickly, fast-turnaround funding is vital.

Dr. Trapecar emphasized that study sections are needed that focus on reviewing NAMs. MPS proposals have been examined in study sections in which reviewers lack the relevant experience to accurately assess the material.

Dr. Homan stated that automated platforms and systems will broaden the implementation of MPS in research and increase reproducibility. In addition, automation will expand the number of research projects that a laboratory can work on simultaneously and ensure that the heterogeneity of the patient population is accurately represented. Standard operating procedures for automated platforms should be developed.

Dr. Lauffenburger explained that education and training opportunities are crucial and should be implemented at the undergraduate, predoctoral, postdoctoral, and ESI stages. Dr. Homan

continued that trainees should gain experience with automated systems and cross-disciplinary research; this will give them a competitive advantage when applying for internships or entering the workforce.

Training the next generation of NAMs researchers will require integrating biological expertise with engineering, computation, data science, and MPS technologies. ORIP's existing D.V.M. training programs provide a strong foundation for this interdisciplinary approach by bridging biological sciences with bioengineering and quantitative methods. Expanding these cross-disciplinary training models could help build the workforce needed to develop, validate, and translate increasingly complex NAMs.

Collaborations are vital. Biological engineers and systems biology researchers should be incorporated into research teams to help the teams effectively understand and operate NAMs.

Dr. Anthony Atala commented that the variability of MPS can make comparing systems difficult, and standards are needed for reproducibility.

Dr. Trapecar commented that tissue-resident immunity is important to include in MPS to understand the full extent of bidirectional crosstalk between organs. Cells act differently in the presence of specific cell types, which may release soluble factors.

Immune-competent MPS are not available. NAMs can model specific immune processes that support research areas, including vaccine development and regenerative medicine, but these do not mimic complex immune dynamics. Dr. Trapecar explained that MPS that lack immune cells can provide insights about cellular crosstalk through such mechanisms as parenchymal, metabolic, endocrine, barrier, and drug response. Immune cells are necessary when the research questions involve key areas, including immune sensing, amplification, and inflammatory remodeling.

Dr. Ashton noted that datasets derived from organoid platforms (e.g., RosetteArray) can be used to develop and train systems biology– and pharmacology-based AI models. Using these data would improve the predictive power of these models.

Dr. Ashton commented that for the RosetteArray platform, tissues are exposed to compounds through the morphogenesis process. This method may be altered for the OrganoidArray, and compound exposure depends on the research question of interest.

Dr. Ashton highlighted that micropatterned plate systems and automation will promote reproducibility and scalability of neurodevelopment models.

Dr. Ashton clarified that the RosetteArray platform captures the first 6 weeks of central nervous system (CNS) development. A key limitation is that neuronal, glial, vascular, and immune components are not incorporated, but this will be captured with the OrganoidArray platform. The OrganoidArray platform may be useful for modeling neurodevelopment in infection-mediated preterm birth.

Dr. Homan explained that predictive readouts are different for disease and toxicity models. Depending on the objective, toxicity readouts (e.g., viability) normalized by exposure can be useful and preferred over multiomics data.

Session 2: *In Chemico* NAMs and NAMs Supporting Systems

Robert Damoiseaux, Ph.D., University of California, Los Angeles

Dr. Robert Damoiseaux introduced the session by highlighting the evolution of *in chemico* approaches—from traditional chemistry-based methods to modern technologies that embed drug discovery within complex cellular, tissue, and disease models. He provided a brief overview of the session's talks, noting that the session was organized around the themes of scale, reproducibility, fidelity, and integration.

High-Throughput Phenotyping in Autism

Daniel Geschwind, M.D., Ph.D., University of California, Los Angeles

Dr. Daniel Geschwind presented a multimodal systems biology approach for translating the autism genome toward precision medicine strategies. Autism spectrum disorder (ASD) is a heterogeneous neuropsychiatric syndrome with numerous genetic variations and modes of inheritance; more than 200 high-confidence ASD risk genes have been identified, but each variation accounts for less than 1% of clinical cases. Convergent pathways may help researchers better understand ASD. CRISPR activation (CRISPRa)–targeting gene enhancers can restore gene expression to normal levels when haploinsufficiency causes ASD. Dr. Geschwind's research demonstrates that in 2D cell cultures and 3D organoids, CRISPRa rescues the ASD risk genes—*CHD8* and *SCN2A*—in iPSC and neural progenitor cells. Dr. Geschwind noted that CRISPRa is a viable treatment with advancements made in nucleic acid therapeutic strategies, but this treatment targets one gene at a time and requires a large engineering effort. Transcriptomics and networks analyses have elucidated a convergence point for rare and common ASD gene variants at early fetal cortical development in progenitor cells and developing glutamatergic neuron populations. Molecular profiling of post-mortem cortex tissue shows shared patterns of dysregulation—specifically in glutamatergic neurons, somatostatin interneurons, and regulons—driven by ASD risk genes. Dr. Geschwind highlighted that modern genomic tools allow researchers to validate *in vitro* models to ensure these tools mimic *in vivo* patterns. Two-dimensional neural stem cell cultures and human cortical organoids recapitulate key aspects of development and ASD. Brain organoids modeling 50 patients and eight major ASD mutations demonstrated that early time points harbor the largest mutation-specific changes and a shared RNA and protein interaction network drives convergent downstream changes in biological pathways.

The University of California, Los Angeles established the High-Throughput Neuropsychiatric Disorder (NPD) Phenotyping Center, which aims to investigate multiscale phenotypic results of NPD gene knockouts to understand gene function in the nervous system. The center will be able to study hundreds of mutations in parallel culture systems. Dr. Geschwind briefly reviewed the aims, experimental design, and outputs for this research. To date, 924 samples have been profiled that span 71 genes of interest. Knockout cell lines for 39 ASD genes of interest have shown variable impact on gene expression; overlapping patterns have been identified. Human *in vitro* models with postmortem tissues provide a foundation for understanding how genetic risk propagates across development and creating therapeutics. *In vitro* NAMs also provide an opportunity to scale research studies to create reliable pathophysiological models for ASD.

Building a Hub for Human-Based and AI-Partnered Drug Discovery
Angela Koehler, Ph.D., Massachusetts Institute of Technology

Dr. Angela Koehler discussed building a hub for human-based and AI-partnered drug discovery. MIT has launched the Health and Life Sciences Collaborative, which is a multidisciplinary initiative to overcome health challenges and improve health outcomes through cutting-edge research, life-centered innovation, data and resource sharing, and education. Three pillars—talent, discovery, and impact—are fundamental for the initiative, and Dr. Koehler outlined key research topics that the collaborative is trying to address. The Next-Generation Chemistry Center focuses on developing new chemical biology strategies to accelerate drug discovery and advancing agents for oncofusion-driven pediatric cancer to address the unmet therapeutic needs of patients. The center is a collaborative effort across several universities and institutes that focuses on structural biology, protein and nanobody science, automation and screening, cell pharmacology and high-content imaging, biochemistry and biophysics, medicinal and computational chemistry, chemoproteomics, and *in vivo* pharmacology. Dr. Koehler highlighted that early-stage drug discovery processes have been successful.

Dr. Koehler's laboratory focuses on drug discovery by exploring chemical–biology tools—particularly screening platforms and small molecules—that help identify or serve as probes to target disease-causing proteins. Dr. Koehler emphasized that limited treatment options are available to address pediatric cancers. Dependency map data highlights oncofusion transcription factors as a driver of pediatric cancers. Drug discovery processes, specifically computational modeling, are hindered when proteins are purified alone without binding partners. Dr. Koehler discussed developing screening strategies that use proteins bound to binding partners, which is physiologically relevant. When the research team identifies small molecules that successfully bind to interacting proteins, it partners with the High Throughput Sciences laboratory at MIT and the Swanson Biomedical Center to explore the function of these small molecules in cell models using automated processes. The laboratory also works with clinicians to develop morphology-based predictive modeling that accelerates drug response profiling for patients. Dr. Koehler discussed lessons learned from this effort—including automated pipelines to reduce the notification to sample receipt time, the necessity of pre-printed drug plates for assay success, rigorous plate designs to collect high-quality data, and optimization of pipeline features. Efforts are focused on incorporating machine learning (ML) models to automate and shorten the workflows. Dr. Koehler emphasized that they are collaborating with several groups to maximize efficiency, expand capabilities, and share data.

It Takes a Village (of Robots): Scaling Human Gene-by-Environment Studies in a Dish via AI-Enabled Cell Culture Automation
Robert Damoiseaux, Ph.D., University of California, Los Angeles
Michael Wells, Ph.D., University of California, Los Angeles

Drs. Damoiseaux and Michael Wells presented on scaling human gene-by-environment (GxE) studies through AI-enabled cell culture automation. Conventional tools for GxE studies include genome-wide association studies and human stem cell models, but each has limitations. To overcome these limitations, the cell village system was developed. The system is an *in vitro* platform that enables population genetics research at the cell culture level. Stem cells are isolated from many individuals, and each person's cells are converted into a specific cell type of interest before pooling the cells into the same culture. These cell villages can be presented with different

exposures (e.g., pathogens, toxins) to capture genetic, molecular, and cellular phenotypic heterogeneity in a shared *in vitro* environment. Dr. Wells provided an example of a cell village study that demonstrated differential susceptibility to Zika virus infection across human donor neural progenitor cell lines. This *in vitro* system identified a specific *IFITM3* gene variant that enhances risk to Zika virus infection. Dr. Wells highlighted that this gene variant also serves as a risk factor for infection by the viruses that cause influenza and COVID-19. The cell village system also identified *ARNT2* gene variants as a risk factor for lead sensitivity. The cell village system is being improved in several areas—including additional cell types, larger donor sample sizes, and faster genomic readouts—to accelerate scalability of the platform.

Dr. Damoiseaux discussed scaling the cell village system to incorporate high-throughput methodologies in GxE studies. Approximately 700,000 data points were generated by testing about 4,700 compounds on 150 donor cell lines. Testing compound concentrations is necessary to maximize cell recovery for downstream analysis and minimize cell death–driven clumping. Dr. Damoiseaux highlighted that the experimental workflow can be automated using equipment and software to reduce workload and ensure the reproducibility and scalability of NAMs. CellXpress.ai® is a vital piece of equipment for automating the cell village system; it allows for autonomous cell culture, imaging, and analysis in a single location. Data from a proof-of-concept study of a four-donor cell village system were provided.

Models for Fibrotic Disease: A Fibroid Case Study
Jennifer Elisseeff, Ph.D., Johns Hopkins University

Dr. Jennifer Elisseeff presented models for fibrotic diseases. Fibrosis—dysregulated ECM production—is associated with abnormal vasculature and is a hallmark of many diseases. Biomaterials, including breast implants, can cause deposition of dense ECM by fibroblasts. *In vitro* NAMs can help provide a multiscale view of fibrosis. Dr. Elisseeff provided a uterine fibroids case study that utilized NAMs. She highlighted that fibroids are a heterogeneous disease with a complex environment, rely on surgery because efficient therapies do not exist, and have no available accurate preclinical animal models. A challenge of studying fibroids is digesting the dense ECM to isolate cell types associated with this microenvironment; the digestion enzyme impacts cell composition results, which can affect building an accurate cell atlas dataset for fibroids. Biological and computational models can be combined to identify and enrich target cells (e.g., senescent cells) within fibroid samples. Senescent cells have diverse morphological features and tissue niches in fibroids, and the secretory phenotype of senescent cells can be predicted using senescence signature transfer learning. Dr. Elisseeff's laboratory is focused on understanding cellular communication, networks, and spatial niches in repair versus fibrosis. She provided data on cell identity and gene co-expression patterns.

When considering *in vitro* NAMs to understand fibroids, researchers should consider which cells and niches to incorporate, the correlation between *in vivo* phenotype and organization, and the predictive capacity for therapeutic efficacy. Dr. Elisseeff has optimized patient-derived fibroid organospheres to retain the complexity of tissue networks and performed screening of senolytic compounds. She highlighted that fibroid organospheres mimic a disease and provide data. Navitoclax and fisetin combinatorial therapy provides the most robust response for senescence markers, increases vasculature, reduces immune cells, and decreases NOTCH signaling. Additional drugs and compounds will be screened in future studies using these fibroid organospheres. Dr. Elisseeff emphasized that localized networks are impacted by global tissue-

organ communication (e.g., microbiome, co-morbidities, sex-based stimuli) within the body and provided data showing the effects of a distal tissue injury on tumor features. In summary, integrated scales of knowledge are needed to develop new therapeutic strategies.

DNA-Encoded Chemical Library Screening in Living Tissues
Brian Paegel, Ph.D., University of California, Irvine

Dr. Brian Paegel discussed a DNA-encoded chemical library screening technique completed in living tissue. DNA-encoded chemical synthesis is a target-based approach that requires prior knowledge about what molecules are driving the molecular pathology. Synthesis of these libraries requires several repetitive coupling and enzymatic ligation steps to bind oligonucleotide sequences. Dr. Paegel's laboratory expanded on this technology to develop solid-phase DNA-encoded synthesis using microscopic resin beads; the loading capacity of resin beads depends on the bead's size. Custom designing numerous molecules simultaneously requires split-and-pull synthesis, which exponentially increases the broad collection of molecules with oligonucleotide tags. Dr. Paegel uses a photocleavable linker to sever the small molecule from the resin bead. He provided an example of a library design that included 192 amino acids capped with 288 carboxylic acids. Dr. Paegel has collaborated with pharmaceutical companies to create a microfluidic activity–based screening approach.

Dr. Paegel presented a new strategy that grows cells directly on the DNA-encoded resin bead surface to establish a cell–bead communication technique. The cells are engineered to secrete a fluorescently labeled protein reporter for a particular molecular pathway of interest. If the reporter is secreted, it binds to an affinity ligand on the resin bead surface. A fluorescence-activated cell sorter identifies hits based on the presence of fluorescent proteins on the resin bead. A polyacrylamide shell, along with cell adhesion promoters, is used to encourage cells to bind and grow on the resin beads. Dr. Paegel provided data to demonstrate that affinity-tagged protein capture is concentration dependent. *In vitro* testing shows that HEK293T cells develop spheroids around the resin beads. Dr. Paegel emphasized that a promoter and a secretion tag are required to capture the secreted protein reporter on the resin bead. The different optical properties of the HEK293T cells and beads are used to differentiate and dissociate the spheroid–bead pairings. He provided data from experiments, including a collaborative study that engineered a commercially available cGAS-STING (stimulator of interferon genes) cell line to express the Cherry-HaloTag. In addition, Dr. Paegel's laboratory has developed and screened a STING agonist library. In summary, spheroids can form around resin beads. Photocleavage induces signaling and proximity-driven reporter protein capture that can be sorted and sequenced to obtain hits in these cellular DNA-encoded library screens.

Discussion

Target-based discoveries should not be prioritized. Dr. Paegel noted that pharmacophore models are useful for identifying potential drugs. *In vitro* degradation assays still need to gain momentum.

NAMs vary in complexity. Dr. Wells stated that prioritizing more complex models will provide insights into traits and disease risk. The relevance of individual NAMs to human disease should be clearly defined. In addition, different techniques and modalities should be incorporated into data collection to ensure findings are comprehensive.

Dr. Damoiseaux questioned whether AI should be incorporated into data analysis methodologies because it can be difficult to manually analyze large amounts of data. Dr. Lauffenburger stated that information derived from AI should still be verified for accuracy.

Dr. Lauffenburger highlighted that industry partnerships would be helpful to bridge the gap between NAMs and regulatory agencies.

Drs. Damoiseaux and Geschwind explained that rigor and validation are key. Researchers should ensure that models are accurate for the research questions being studied. For example, cells may interact differently depending on which cell types are present in the NAMs. Signaling pathways may be missing if a certain cell type is not present.

Dr. Lauffenburger noted that computational models provide a critical mathematical framework for studying complex systems.

Dr. Geschwind explained that developmental targets are unique compared with standard overexpression and underexpression of genes and proteins observed in other disease settings (e.g., cancer). Preclinical models demonstrate that postnatal treatment and restoration of gene expression is beneficial for developmental diseases. Organoids and MPS are useful for identifying effective periods for treatment while *in utero* gene therapy undergoes testing and modifications to be a useful treatment strategy.

Dr. Koehler noted that challenges may arise with imaging and analyzing specific cell types. High-content microscopy and cell painting assays should be optimized for each research project depending on complexity and samples.

Dr. Wells highlighted assays, including phase contrast microscopy and cell painting, that could be incorporated into research projects that utilize cell village systems.

Dr. Elisseeff commented that models for fibrotic remodeling are vital for elucidating the underlying signals and mechanisms of disease progression and chronicity.

Session 3: *In Silico* NAMs—Leveraging Real-World Data for Model Validation

Reinhard Laubenbacher, Ph.D., University of Florida

Virtual human twins are individual-specific digital representations using real-time data to predict, monitor, diagnose, and treat diseases. These digital twins (DTs) also can be used to review and select personalized intervention strategies. DTs are composed of hardware, middleware, and software. DTs can be developed at multiple biological scales—including cells, tissues, organs, and whole-person systems—and can be used to support disease prevention, prediction, diagnosis, and treatment, as well as the evaluation of interventions.

The Virtual Human Twin Initiative: From an Engaged Ecosystem to an Incipient Infrastructure

Lisbet Geris, Ph.D., University of Liege, Belgium

Dr. Lisbet Geris presented examples of how these personalized models are already being used in the clinic across health care settings, including the intensive care unit. A collaboration among In Silico World, Sano, and Università di Catania is using DTs to design and augment a clinical trial. Dr. Geris provided examples of DTs and *in silico* NAMs for skeletal muscle regeneration research in her laboratory. The modeling framework was calibrated with genetic algorithms and

validated by comparing the model with *in vivo* experiments. Dr. Geris also is using a cartilage-on-chip to model osteoarthritis. For both research studies, screening experiments are conducted *in silico,* and mechanostimulation devices are important for validation data.

The European Virtual Human Twin (VHT) initiative is a framework that supports the emergence and implementation of DTs for patients. The EDITH (Ecosystem for Digital Twins in Healthcare) Coordination and Support Action was launched to bring together the ecosystem and develop the roadmap that outlines the necessary infrastructure to support the multisectoral VHT initiative. Discussions with different stakeholders identified the unique needs of each group, including access to resources, integration of clinical workflow, and improvement of patient outcomes. Infrastructure requirements include a catalogue and repository, the simulation platform, and advanced computing technologies. More than 150 ethical, legal, social, and regulatory standards for DTs are available, but gaps are still present. Dr. Geris highlighted that good simulation practices and recommendations for successful VHTs have been published. She noted that successful uptake of VHTs requires incentives, including delivering clear benefits, addressing practical challenges, aligning with workflows, and increasing patient engagement. In summary, the European VHT initiative will provide researchers, clinicians, and innovators with access to resources, assets, and data that can develop and combine VHTs to improve patient outcomes.

A Roadmap to Integrated *In Silico* Resources: Biology, Data, Model
Reinhard Laubenbacher, Ph.D., University of Florida

Dr. Reinhard Laubenbacher emphasized that DTs are an innovative category of NAMs for personalized medicine. Scalability of DT construction and deployment is hindered by a lack of data, standardized technological infrastructure, and an integrated network of resources. Dr. Laubenbacher explained that *in silico* models are not constructed on enough data to be reliable, emphasizing that models need to integrate more data and the underlying biological mechanisms. ImmPort Shared Data is a database with more than 1,400 studies, 189,000 subjects, 180 diseases, and 7 million total results. BioModels is the largest repository of curated biological models, with more than 1,000 manually curated models that combined have about 900,000 model parameters. Reactome is a database that includes more than 2,700 human pathways, 15,500 reactions, and 11,500 proteins. Comprehensive FAIR infrastructure that includes resources, tools, and experimental data sources is needed. Dr. Laubenbacher highlighted that DTs are constructed for a specific purpose, and the data collected to build the model must fit that purpose. In addition, calibration and validation data must be dynamic for DTs. He provided examples of previous research focused on developing and applying DT technology. Guidelines, similar to FAIR standards, should be established for computational models of biological systems. Dr. Laubenbacher commented on a collaborative effort to define computational model standards known as credible, understandable, reproducible, and extensible (or CURE). Gaps in infrastructure and *in silico* NAMs for personalized medicine include an integrated network of data, biological mechanisms, and mathematical models; data collection that fits the purpose of the DTs; standardized technological infrastructure; automation of workflows; and stable funding opportunities.

Beyond Static Protein Models: *In Silico* Infrastructure for the Disordered and Flexible Proteome

María Rodríguez Martínez, Ph.D., Yale University

Dr. María Rodríguez Martínez emphasized that predicting protein structure is important for understanding protein function, which helps researchers manipulate pathological forms of proteins and target proteins for therapeutic strategies. Proteins are not static, so models must accurately mimic conformational dynamics of proteins. Current AI tools to study proteins are insufficient for modeling intrinsically disordered and flexible proteins—approximately 30–40% of human proteins are intrinsically disordered. T-cell receptor (TCR) and antibody development requires animal models, including mice, rabbits, and nonhuman primates, but these animal models have several limitations. AI and deep learning models, including AlphaFold2, have transformed the research landscape for predicting protein structure and function. AI-driven models are available for protein language, structure prediction, and protein design. However, these models cannot reliably infer antibody binding interfaces and predict cross-reactive receptors. Dr. Martínez provided data showing that models could not accurately predict TCR binding affinity, in part, because of protein flexibility. In collaboration with the University of Notre Dame, Dr. Martínez is characterizing TCR flexibility using molecular dynamics simulations. New technology must integrate molecular dynamics, coarse-grained simulations, and generative AI to accurately model the flexible and disordered proteome. She highlighted that disordered proteins are understudied and play a vital role in diseases.

In collaboration with the Yale School of Medicine, Dr. Martínez is developing a vaccine for the protein ATXN1. A mutation that causes a polyglutamine expansion disrupts ATXN1 binding with CIC, and—depending on the number of repetitions in the expansion—a different neurodegenerative disease manifests. This highlights the need for ensemble-level modeling approaches to understand disease mechanisms caused by disordered proteins. Dr. Martínez summarized a framework for modeling flexible and disordered proteins, which incorporates computational and experimental systems, to connect molecular sequences with clinical actions. In conclusion, infrastructure is needed to develop next-generation AI models that predict flexible and disordered protein systems, and computational predictions must be validated with biophysical and functional data.

Cheminformatics and Data Infrastructure for *In Silico* NAMs

Alexander Tropsha, Ph.D., The University of North Carolina at Chapel Hill

Dr. Alexander Tropsha provided a cheminformatics perspective for incorporating chemical information with biological data for *in vitro* extrapolation and modeling. NAMs are developed to screen chemical compounds and examine chemical effects on biological systems. Hybrid models that incorporate both cheminformatics and bioinformatics will improve chemical bioactivity and toxicity predictions. Dr. Tropsha highlighted that data transparency, comprehensive data curation, thorough internal development and validation workflows, rigorous external validation, applicability to domain, prediction confidence, and mechanistic interpretation are key principles for using quantitative structure-activity relationship (or QSAR) models as *in silico* NAMs. Systemic and Topical chemical Toxicity (STopTox) is a web-based tool to enable accurate predictions for acute toxicity (e.g., skin irritation, ocular irritation) of chemicals as an alternative to animal testing. The tool was externally validated in compliance with Organisation for Economic Co-operation and Development (or OECD) guidelines. STopTox is a reliable *in silico*

NAM that has an accuracy rate of 70–75%, emphasizing the importance of further developing NAMs to increase accuracy. Dr. Tropsha presented an example of a hybrid QSAR model that predicts subchronic hepatotoxicity from 24-hour toxicogenomic profiles. Another hybrid model is chemical-biological read-across (CBRA), which integrates inferences from both chemical and biological similarities to predict toxicity. CBRA is more accurate than models created from only chemical or biological data. In addition, hybrid models are currently being used to enhance the prediction of DILI.

Dr. Tropsha emphasized that robust, high-quality data and data processing infrastructure are critical for successful NAMs. He provided examples of algorithms and high-quality data that enabled critical breakthroughs in drug discovery. To continue to accelerate drug discovery, new high-quality data, new protocols (e.g., data liberation), and new success metrics are needed. Rigorous, reproducible, and replicable NIH-funded research that utilizes *in silico* NAMs must incorporate "accurate" and "factual" into the FAIR standards. Dr. Tropsha emphasized that these criteria should be included to ensure that unreliable and irreproducible data do not promote additional poor data. Standardized processing protocols and structured primary data will accelerate AI-guided experimental research. Dr. Tropsha highlighted that digital disruption can accelerate the drug discovery pipeline through data expansion, AI, automation, public–private partnerships, and open science.

Digital Twins for the Win: Infrastructure from Molecules to Medicine
Colleen Clancy, Ph.D., University of California, Davis

Dr. Colleen Clancy commented that NAMs using integrated approaches are needed to investigate complex diseases that have not been resolved with conventional solutions. She reiterated that DTs can be used as a unifying framework to accelerate biomedical research and health care. Ethics, security, verification, validation, and uncertainty quantification should be considered when using DTs. Integrated computing and data infrastructure are needed to enable DTs that span scales—from molecules to populations—for precision health and to improve patient outcomes. Dr. Clancy provided examples of DT applications in the biomedical landscape. DTs are available for lead compound discovery, medicinal chemistry, *in vitro* studies, *in vivo* studies, and clinical trials; DTs can be combined to develop workflows that accelerate current processes.

The AlphaFold Protein Structure Database can be used as a DT of cryo-electron microscopy. DTs for drug discovery and drug safety are limited by static protein structures. Dr. Clancy provided an example in which hERG channel conformational states were predicted by AlphaFold and then refined and validated using custom codes and experimental data. Drugs have unique binding affinities for different conformational states of a protein. DTs hold promise for predicting optimal patient therapy for diseases and for programming physical devices. Dr. Clancy's research team successfully developed an autonomic nervous system DT that could interact with the sinoatrial node and ventricular myocardium to eliminate disease-associated arrhythmias. Identification of the optimal therapy for chemical-induced atrial fibrillation—flecainide and ibutilide—used a DT. DT-based clinical trials can predict clinical risks and generate new insights—including the risk of anthracycline-mediated cardiac injury during treatment for metastatic cancer. Convergence of platforms and pipelines will promote scalability and productivity for identifying new therapies for complex diseases. CATVariant is an open-access web-based tool that allows researchers to visualize structural changes caused by gene and protein variations. Dr. Clancy emphasized that DTs allow researchers to develop more robust experiments that can be conducted on an

accelerated timeline, and she explained that strategic investment by NIH in shared research infrastructure will drive innovative biomedical discoveries using DTs.

Discussion

Dr. Gary An noted that assumptions of mathematical models should be clearly documented. Criteria for selecting a mathematical model should be implemented to deter researchers from choosing those that they are familiar with rather than the most relevant model for the research question. Dr. Tropsha continued that potential data inaccuracies should be documented as uncertainties when systems biology data are combined with mathematical models.

Dr. An highlighted that developers of mathematical models should distribute information regarding the design and construction of the models. Researchers who use a specific mathematical model should be able to clearly justify why that model was selected, and any associated metadata should be made available to the research community.

Dr. Martínez stated that flexible regions of a protein are considered a sequence of 50 amino acids or less, and proteins can have specific portions (e.g., receptor) that are flexible. Disordered regions are flexible but have longer amino acid sequences. Approximately 40% of human proteins cannot be modeled properly because of binding interactions caused by flexible or disordered regions.

Drs. Laubenbacher and Wikswo emphasized that funding agencies need to support hardware and maintenance of resources. Additional investments in resources, including Reactome pathway databases, are needed.

A repository should be established to minimize fragmentation and prevent investments into repetitive development efforts of tools and technologies. Dr. Geris noted that this was a major reason behind the establishment of the VHT—limiting funds to reinvent old tools that had lost funding support and been siloed. In addition, a repository would provide an opportunity to connect tools, models, and resources to maximize collection and analyses of data and metadata.

Dr. Tropsha stated that primary data registration, data organization, and a centralized national data operational system are key pillars for the success of modern science. Dr. Clancy emphasized that when such a system is established, staff should be hired who would focus on modifying the data into a format that can be incorporated into the database. She continued that requiring individual researchers to alter their data into a compatible format would create a bottleneck and has caused issues in the past when similar regional initiatives were implemented. Noninvasive molecular imaging would advance computational models and DTs. Dr. An commented that funding opportunities that incorporate NAMs are available for researchers to pursue (e.g., the Advanced Research Projects Agency for Health Intelligent Generator of Research program).

A national data infrastructure is needed to connect existing databases, models, and repositories and maintain linkages among them, reducing fragmentation and improving interoperability. Data curation, standardization, and preparation for data-sharing systems can create substantial burdens for investigators and may require centralized infrastructure and dedicated support personnel to avoid bottlenecks.

Dr. Geris explained that the underlying computational models of DTs use differential equations and data. Certain computational models are data-driven while others use both properties; researchers select and apply the appropriate technology based on the research question.

Dr. Laubenbacher commented that assumptions in mathematical models should be based on the applicable biology when data are not available, and researchers should minimize and control the assumptions incorporated into mathematical models.

Dr. Tropsha noted that implementation of the data lifecycle is a concern and that the culture and infrastructure are limiting factors for data reporting.

Session 4: Future Trends Toward Integration of Model Systems and Clinical Applications

New Approach Methodologies to Accelerate Clinical Trials In-a-Dish
Joseph Wu, M.D., Ph.D., Stanford University School of Medicine

Dr. Joseph Wu delivered a keynote presentation that highlighted the use of NAMs to accelerate drug discovery, hit-to-lead validations, and clinical trials in a dish (CTiD). Integrated human-centric biology requires four key platforms: iPSCs, next-generation sequencing and single-cell multiomics, CRISPR genome editing, and AI and computational designs. In collaboration with Greenstone Biosciences, Inc., the Stanford Cardiovascular Institute has developed the largest biorepository of patient-derived iPSC lines, with more than 2,500 stocks available. Dr. Wu provided demographics and disease classification data for the iPSC biorepository. He reiterated that this biorepository is available to the research community, emphasizing that more than 600 rare disease patient samples have been collected. More than 4,000 iPSC cell line samples have been shared with at least 400 researchers. Dr. Wu briefly outlined how his team generates NAMs from patient-derived samples by using a cocktail of growth factors identified from a screen of 35 combinations to enable the vascularization of cardiac and hepatic organoids. Dr. Wu's laboratory tests drug metabolism with the vascularized hepatic organoids and examines drug metabolites with the vascularized cardiac organoids.

The standard drug discovery pipeline for the Stanford Cardiovascular Institute incorporates human genomics, *in silico*, *in chemico*, and *in vivo* target validation. Collaborations with computational scientists at Greenstone Biosciences allow AI-enabled drug screening and molecular docking. Dr. Wu explained that a multidimensional analysis of drug-like properties (e.g., on-target effects, off-target effects, toxicity) is conducted and provided examples of hit-to-lead validation studies, including the suppression of cardiac fibrosis through the selective inhibition of stromal mechanosensing. Genetic heterogeneity across patients results in different clinical outcomes for the same disease and variability with drug responses. Cell villages recapitulate patient population heterogeneity in response to a drug and are important for finding effective targets during preclinical drug discovery processes.

Dr. Wu emphasized that cell models are expanding drug approvals for rare diseases, which is important for overcoming challenges associated with rare disease drug development. *In vitro* efficacy data are useful to reduce the number of clinical trials, inform regulatory decisions, streamline drug development, and expand indications. Dr. Wu highlighted three examples of CTiDs to identify therapeutic targets that allow patients to receive treatment beyond the standard of care. One study used patient-specific models to identify pathways driving cardiac and vascular

dysfunction and to test repurposed drugs that improved disease-associated cellular phenotypes. A second study combined human cell models with AI-guided screening to identify a potential strategy for reducing marijuana-associated cardiovascular injury by blocking cannabinoid receptor signaling. A third study used *in chemico* and *in silico* approaches to identify an inhibitor of fibrosis-promoting signaling, supporting its advancement into clinical testing for idiopathic pulmonary fibrosis.

Dr. Wu explained that biological twins allow researchers to elucidate the unique molecular mechanisms of disease for different patients. Drug compounds selected by AI may not work, which requires retraining the AI on results from biological twin and DT tests. NAMs and CTiDs will help refine selection to identify compounds that are potent, effective, and safe.

Discussion

Dr. Wu highlighted that Greenstone Biosciences provides iPSC cell lines to nonprofit organizations and academic institutions free of charge to increase use of NAMs in research.

Dr. Douglas Lauffenburger noted that sex-related effects can be observed with iPSC cells.

A participant commented that methods to ensure a fair peer-review process and reduce animal methods bias should be considered to improve NAM-related publication rates.

Closing Remarks

Robin Kawazoe, ORIP, DPCPSI, OD, NIH

Ms. Robin Kawazoe, Acting Director of ORIP, thanked the organizing committee, speakers, panelists, and attendees and outlined key takeaways from the workshop. Computational modeling, ML, and 3D systems provide unique opportunities to study complex physiological and disease states to accelerate the identification of disease mechanisms and therapeutic targets. NAMs will serve as complementary tools in biomedical research, and the strategic integration of human-based NAMs with other preclinical models will improve rigorous validation efforts, reliable study endpoints, drug development, and translational success.

Appendix A: Meeting Agenda

Virtual Meeting
Day 1 – June 8, 2026

9:00–9:15 a.m. **Welcome and Workshop Overview**
Oleg Mirochnitchenko, Ph.D., ORIP, Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), Office of the Director (OD), NIH
Nicole Kleinstreuer, Ph.D., DPCPSI, OD, NIH

9:15–10:10 a.m. **Keynote: Complementary Roles for Human Organ Chips, Artificial Intelligence (AI), and Animal Models**
Donald Ingber, M.D., Ph.D., Wyss Institute, Boston Children's Hospital, and Harvard Medical School

10:10–10:20 a.m. **Break**

10:20 a.m.–12:35 p.m. **Session 1: The Need for Complex Integration of New Technologies to Study Biological Mechanisms of Human Disease Progression; Complementary Use of Animal Models and New Approach Methodologies (NAMs) for Preclinical Studies and Therapeutic Development**

Session Chairs: *Rebecca Roof, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS), NIH; Jason Shepherd, Ph.D., The University of Utah*

Presentations

Tissue-Engineered NAMs for Drug Discovery and Evaluation
Wolfram-Hubertus Zimmermann, M.D., Institute of Pharmacology and Toxicology, University Medical Center Göttingen

Organoid NAM-Guided Precision Hepatology
Takanori Takebe, M.D., Ph.D., Cincinnati Children's Hospital Medical Center

Modeling the Regenerative Endometrium Using 3D Organoids and Assembloids
Diana Monsivais, Ph.D., Baylor College of Medicine

There and Back Again: A Multi-Platform Journey from Cell Lines to Human Tissue Reveals Direct Interactions Between *Helicobacter pylori* and Epithelial Stem Cells
Manuel Amieva, M.D., Ph.D., Stanford University

Putting the Pieces Together: Inception of Human Neural Circuits in Assembloids to Study Disease
Sergiu Paşca, M.D., Stanford University

Panelists
Manuel Amieva, M.D., Ph.D.
Diana Monsivais, Ph.D.
Sergiu Paşca, M.D.
Rebecca Roof, Ph.D.
Jason Shepherd, Ph.D.
Takanori Takebe, M.D., Ph.D.

Wolfram-Hubertus Zimmermann, M.D.

12:35–1:15 p.m. **Lunch**

1:15–2:45 p.m. **Session 2: Shared Resources to Validate and Promote NAMs; Research Frameworks; Tracking Activities**

Session Chairs: *Christine Nadeau, Ph.D., National Cancer Institute (NCI), NIH; Thomas Bell, Ph.D., M.S., National Disease Research Interchange*

Presentations

CuSTOMizing Induced Pluripotent Stem Cells for Modeling Human Disease
Michael Helmrath, M.D., Ph.D., University of Cincinnati, Cincinnati Children's Hospital Medical Center

NAMs for Interrogating Cancer
Scott Lowe, Ph.D., Memorial Sloan Kettering Center

Coordinated Infrastructure for NAMs Benchmarking and Community Access
Brenda Ogle, Ph.D., University of Minnesota

From Standardized Biological Materials to Validated NAMs: The Role of Resource Stewardship, Quality Frameworks, and Scalable Validation
Carolina Lucchesi, Ph.D., American Type Culture Collection

Panelists
Thomas Bell, Ph.D., M.S.
Michael Helmrath, M.D., Ph.D.
Scott Lowe, Ph.D.
Carolina Lucchesi, Ph.D.
Christine Nadeau, Ph.D.
Brenda Ogle, Ph.D.

2:45–2:55 p.m. **Break**

2:55–4:25 p.m. **Session 3: Building Comparative Databases and Tools to Support Benchmarking and Model Selection; Promoting Predictivity and Reproducibility Through Interoperable Data Standards and Platforms**

Session Chairs: *Christine Happel, Ph.D., National Center for Advancing Translational Sciences (NCATS), NIH; Alice Tarantal, Ph.D., University of California, Davis*

Presentations
Bridging the Gap: A Mechanistic Platform to Enhance Translatability of Human-Specific Pharmacology Across Diverse Modalities
Murat Cirit, Ph.D., Javelin Biotech

Standardizing NAM Data for Mechanistic Discovery and Translational Confidence
Melissa Haendel, Ph.D., The University of North Carolina at Chapel Hill

From Atlas to Benchmark: The Infrastructure Required to Compare an Organoid to Human Tissue
Jason Spence, Ph.D., University of Michigan Medical School

Building Confidence Through Curated Data and Open Access Interoperable Computational Tools to Support NAM-Based Chemical Assessment
Bridgett Hill, M.S., General Dynamics Information Technology

Panelists
Murat Cirit, Ph.D.
Melissa Haendel, Ph.D.
Christine Happel, Ph.D.
Bridgett Hill, M.S.
Jason Spence, Ph.D.
Alice Tarantal, Ph.D.

4:25–4:35 p.m. **Break**

4:35–6:05 p.m. **Session 4: Multidisciplinary Collaboration, Training, and Future Directions**

Session Chairs: *Malgorzata Ochocinska, Ph.D., Office of Strategic Coordination (OSC), DPCPSI, OD, NIH; Yongjun Sui, Ph.D., ORIP, DPCPSI, OD, NIH*

Presentations

Organs-on-Chips and Organoids: What Can You Ask of Your Microphysiological Systems, How Far Can You Extrapolate Beyond What They Tell You, and What's Needed?
John Wikswo, Ph.D., Vanderbilt University

Stem Cells, Genomics, and AI for Drug Discovery
Joseph Wu, M.D., Ph.D., Stanford University School of Medicine

Chips for Organoids
Ashutosh Agarwal, Ph.D., University of Miami

Organoids and Mouse Models for Studying and Defeating Human Cancers
David Tuveson, M.D., Ph.D., Cold Spring Harbor Laboratory

Panelists
Ashutosh Agarwal, Ph.D.
Malgorzata Ochocinska, Ph.D.
Yongjun Sui, Ph.D.
David Tuveson, M.D., Ph.D.
John Wikswo, Ph.D.
Joseph Wu, M.D., Ph.D.

6:05–6:10 p.m. **Closing Remarks**
Stephanie Murphy, V.M.D., Ph.D., ORIP, DPCPSI, OD, NIH

Day 2 – June 12, 2026

10:00–10:15 a.m. **Welcome and Workshop Overview**
Monika Aggarwal, Ph.D., ORIP, DPCPSI, OD, NIH
Yong Chen, Ph.D., ORIP, DPCPSI, OD, NIH
Benjamin Freedman, Ph.D., University of Washington
Jeffrey Spector, Ph.D., ORIP, DPCPSI, OD, NIH

10:15 a.m.–12:30 p.m. **Session 1: Development and Validation of *In Vitro* NAMs and Integrated Model Systems**

Session Chair: *Linda Griffith, Ph.D., Massachusetts Institute of Technology*

Session Moderators: *Linda Griffith, Ph.D., Massachusetts Institute of Technology; Georgette Jones, Ph.D., NCI, NIH*

Presentations
Designing and Interpreting NAMs Using System Biology
Douglas Lauffenburger, Ph.D., Massachusetts Institute of Technology

How Biological Insights Drive Development of Clinically Relevant NAMs Tools
Christopher Hughes, Ph.D., University of California, Irvine

Parsing Systemic Immunity with NAMs
Martin Trapecar, Ph.D., Johns Hopkins University

Scaling and Automation to Support NAMs in Routine Screening: A Pharma Perspective
Anna Bremser, Ph.D., Genentech Inc.
Kimberly Homan, Ph.D., Genentech Inc.

Scaling, Validating, and Translating NAMs for Detecting Risks to Human Neurodevelopment
Randolph Ashton, Ph.D., University of Wisconsin–Madison

Panelists
Randolph Ashton, Ph.D.
Anthony Atala, M.D.
Anna Bremser, Ph.D.
Linda Griffith, Ph.D.
Kimberly Homan, Ph.D.
Christopher Hughes, Ph.D.
Georgette Jones, Ph.D.
Douglas Lauffenburger, Ph.D.
D. Lansing Taylor, Ph.D.
Martin Trapecar, Ph.D.

12:30–12:40 p.m. **Break**

12:40–2:55 p.m. **Session 2: *In Chemico* NAMs and NAMs Supporting Systems**

Session Chair: *Robert Damoiseaux, Ph.D., University of California, Los Angeles*

Session Moderators: *Douglas Lauffenburger, Ph.D.; Albert Hwa, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH*

Presentations
High-Throughput Phenotyping in Autism
Daniel Geschwind, M.D., Ph.D., University of California, Los Angeles

Building a Hub for Human-Based and AI-Partnered Drug Discovery
Angela Koehler, Ph.D., Massachusetts Institute of Technology

It Takes a Village (of Robots): Scaling Human Gene-by-Environment Studies in a Dish via AI-Enabled Cell Culture Automation
Robert Damoiseaux, Ph.D., University of California, Los Angeles
Michael Wells, Ph.D., University of California, Los Angeles

Models for Fibrotic Disease: A Fibroid Case Study
Jennifer Elisseeff, Ph.D., Johns Hopkins University

DNA-Encoded Chemical Library Screening in Living Tissues
Brian Paegel, Ph.D., University of California, Irvine

Panelists
Robert Damoiseaux, Ph.D.
Jennifer Elisseeff, Ph.D.
Daniel Geschwind, M.D., Ph.D.
Albert Hwa, Ph.D.
Angela Koehler, Ph.D.
Douglas Lauffenburger, Ph.D.
Brian Paegel, Ph.D.
Michael Wells, Ph.D.

2:55–3:15 p.m. **Lunch**

3:15–5:30 p.m. **Session 3: *In Silico* NAMs—Leveraging Real-World Data for Model Validation**

Session Chair: *Reinhard Laubenbacher, Ph.D., University of Florida*

Session Moderators: *Gary An, M.D., The University of Vermont; Raphael Isokpehi, Ph.D., Office of Data Science Strategy (ODSS), DPCPSI, OD, NIH*

Presentations
The Virtual Human Twin Initiative: From an Engaged Ecosystem to an Incipient Infrastructure
Lisbet Geris, Ph.D., University of Liege, Belgium

A Roadmap to Integrated *In Silico* Resources: Biology, Data, Model
Reinhard Laubenbacher, Ph.D., University of Florida

Beyond Static Protein Models: *In Silico* Infrastructure for the Disordered and Flexible Proteome
María Rodríguez Martínez, Ph.D., Yale University

Cheminformatics and Data Infrastructure for *In Silico* NAMs
Alexander Tropsha, Ph.D., The University of North Carolina at Chapel Hill

Digital Twins for the Win: Infrastructure from Molecules to Medicine
Colleen Clancy, Ph.D., University of California, Davis

Panelists
Gary An, M.D.
Colleen Clancy, Ph.D.
Lisbet Geris, Ph.D.
Raphael Isokpehi, Ph.D.
Reinhard Laubenbacher, Ph.D.
María Rodríguez Martínez, Ph.D.
Alexander Tropsha, Ph.D.

5:30–5:50 p.m. **Session 4: Future Trends Toward Integration of Model Systems and Clinical Applications**

Presentation
New Approach Methodologies to Accelerate Clinical Trials In-a-Dish
Joseph Wu, M.D., Ph.D., Stanford University School of Medicine

5:50–6:00 p.m. **Closing Remarks**

Robin Kawazoe, ORIP, DPCPSI, OD, NIH

Appendix B: Organizing Committee, Presenters, and Panelists

Organizing Committee, Day 1
Thomas Bell, Ph.D., M.S., National Disease Research Interchange
Kelly Chandler, Ph.D., Office of Research on Women's Health (ORWH), DPCPSI, OD, NIH
Christine Happel, Ph.D., NCATS, NIH
Helena Hoegberg-Durdock, Ph.D., National Institute of Environmental Health Sciences (NIEHS), NIH
Qing Lin, Ph.D., National Heart, Lung, and Blood Institute, NIH
Scott Lowe, Ph.D., Memorial Sloan Kettering Cancer Center
Oleg Mirochnitchenko, Ph.D., ORIP, DPCPSI, OD, NIH
Christine Nadeau, Ph.D., NCI, NIH
Malgorzata Ochocinska, Ph.D., OSC, DPCPSI, OD, NIH
Rebecca Roof, Ph.D., NINDS, NIH
Jason Shepherd, Ph.D., The University of Utah
Yongjun Sui, Ph.D., ORIP, DPCPSI, OD, NIH
Alice Tarantal, Ph.D., University of California, Davis
Elizabeth Worthey, Ph.D., The University of Alabama at Birmingham

Presenters and Panelists, Day 1
Ashutosh Agarwal, Ph.D., University of Miami
Manuel Amieva, M.D., Ph.D., Stanford University
Murat Cirit, Ph.D., Javelin Biotech
Melissa Haendel, Ph.D., The University of North Carolina at Chapel Hill
Michael Helmrath, M.D., Ph.D., University of Cincinnati, Cincinnati Children's Hospital Medical Center
Bridgett Hill, M.S., General Dynamics Information Technology
Donald Ingber, M.D., Ph.D., Wyss Institute, Boston Children's Hospital, Harvard Medical School
Nicole Kleinstreuer, Ph.D., DPCPSI, OD, NIH
Scott Lowe, Ph.D., Memorial Sloan Kettering Cancer Center
Carolina Lucchesi, Ph.D., American Type Culture Collection
Oleg Mirochnitchenko, Ph.D., ORIP, DPCPSI, OD, NIH
Diana Monsivais, Ph.D., Baylor College of Medicine
Stephanie Murphy, V.M.D., Ph.D., ORIP, DPCPSI, OD, NIH
Brenda Ogle, Ph.D., University of Minnesota
Sergiu Paşca, M.D., Stanford University
Jason Spence, Ph.D., University of Michigan Medical School
Takanori Takebe, M.D., Ph.D., Cincinnati Children's Hospital Medical Center
David Tuveson, M.D., Ph.D., Cold Spring Harbor Laboratory
John Wikswo, Ph.D., Vanderbilt University
Joseph Wu, M.D., Ph.D., Stanford University School of Medicine
Wolfram-Hubertus Zimmermann, M.D., Institute of Pharmacology and Toxicology, University Medical Center Göttingen

Organizing Committee, Day 2
Monika Aggarwal, Ph.D., ORIP, DPCPSI, OD, NIH
Anthony Atala, M.D., Wake Forest University School of Medicine
Julia Bachman, Ph.D., NINDS, NIH
Kelly Chandler, Ph.D., ORWH, DPCPSI, OD, NIH
Yong Chen, Ph.D., ORIP, DPCPSI, OD, NIH
James Cherry, Ph.D., National Institute of Allergy and Infectious Diseases, NIH
Colleen Clancy, Ph.D., University of California, Davis
Tiziana Cogliati, Ph.D., National Institute on Aging, NIH
Robert Damoiseaux, Ph.D., University of California, Los Angeles
Benjamin Freedman, Ph.D., University of Washington
Linda Griffith, Ph.D., Massachusetts Institute of Technology
Helena Hoegberg-Durdock, Ph.D., NIEHS, NIH
Albert Hwa, Ph.D., NIDDK, NIH
Raphael Isokpehi, Ph.D., ODSS, DPCPSI, OD, NIH
Georgette Jones, Ph.D., NCI, NIH
Jonathan Kulwatno, Ph.D., National Institute of Biomedical Imaging and Bioengineering, NIH
Reinhard Laubenbacher, Ph.D., University of Florida
Douglas Lauffenburger, Ph.D., Massachusetts Institute of Technology
Xiang-Ning Li, M.D., Ph.D., ORIP, DPCPSI, OD, NIH
Ananda Roy, Ph.D., OD, NIH
Jeffrey Savas, Ph.D., Northwestern University Feinberg School of Medicine
Jeffrey Spector, Ph.D., ORIP, DPCPSI, OD, NIH
Alexander Tropsha, Ph.D., The University of North Carolina at Chapel Hill
Joseph Wu, M.D., Ph.D., Stanford University School of Medicine

Presenters and Panelists, Day 2
Gary An, M.D., The University of Vermont
Randolph Ashton, Ph.D., University of Wisconsin–Madison
Anthony Atala, M.D., Wake Forest University School of Medicine
Anna Bremser, Ph.D., Genentech Inc.
Colleen Clancy, Ph.D., University of California, Davis
Robert Damoiseaux, Ph.D., University of California, Los Angeles
Jennifer Elisseeff, Ph.D., Johns Hopkins University
Benjamin Freedman, Ph.D., University of Washington (Day 2 Workshop Chair)
Lisbet Geris, Ph.D., University of Liege, Belgium
Daniel Geschwind, M.D., Ph.D., University of California, Los Angeles
Linda Griffith, Ph.D., Massachusetts Institute of Technology
Kimberly Homan, Ph.D., Genentech Inc.
Christopher Hughes, Ph.D., University of California, Irvine
Albert Hwa, Ph.D., NIDDK, NIH
Raphael Isokpehi, Ph.D., ODSS, DPCPSI, OD, NIH
Georgette Jones, Ph.D., NCI, NIH
Robin Kawazoe, ORIP, DPCPSI, OD, NIH
Angela Koehler, Ph.D., Massachusetts Institute of Technology
Reinhard Laubenbacher, Ph.D., University of Florida
Douglas Lauffenburger, Ph.D., Massachusetts Institute of Technology

María Rodríguez Martínez, Ph.D., Yale University
Brian Paegel, Ph.D., University of California, Irvine
D. Lansing Taylor, Ph.D., University of Pittsburgh
Martin Trapecar, Ph.D., Johns Hopkins University
Alexander Tropsha, Ph.D., The University of North Carolina at Chapel Hill
Michael Wells, Ph.D., University of California, Los Angeles
Joseph Wu, M.D., Ph.D., Stanford University School of Medicine