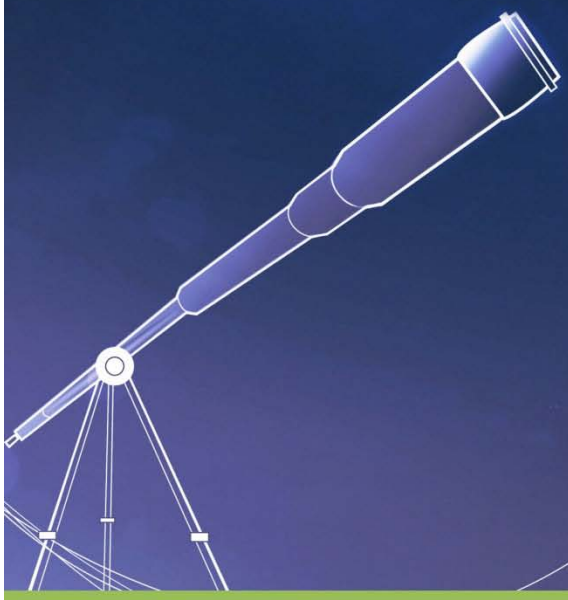
The NIH Common Fund
Office of Strategic Coordination

Summary of Workshops

Forward Focus Workshops: Strategic Planning for the NIH Common Fund



May 2012 Workshops in
Chicago, Illinois; San Francisco, California; and Potomac, Maryland

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
NATIONAL INSTITUTES OF HEALTH

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1.0 Executive Summary

The National Institutes of Health (NIH) hosted two regional meetings in Chicago, Illinois and San Francisco, California, and one local meeting in Potomac, Maryland to commence the strategic planning process for NIH Common Fund programs that will launch in Fiscal Year (FY) 2014. The goal of these meetings, collectively called *The Forward Focus Workshops*, was to gather input from the broad community on emerging scientific opportunities in biomedical, behavioral, and/or social science research that could be accelerated through strategic investment by the NIH Common Fund. The gathering of ideas that resulted from these meetings represents the first step in an 18-month strategic planning process to develop potential new programs for the Common Fund. The Common Fund is managed by the Office of Strategic Coordination (OSC), one of the six offices of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within the Office of the Director.

Participants at the regional meetings were identified by self-selection via an online website hosted by the NIH Common Fund (http://commonfund.nih.gov). Local meeting participants were selected from nominations by the NIH Institute and Center (IC) Directors and Leadership within the NIH Office of the Director (OD) as experts and thought leaders in various biomedical fields. The more than 125 participants who attended the three workshops were asked to identify broad concepts that framed the initial discussions at the meetings. Participant discussions during smaller breakout sessions resulted in merging and refining of the many initial ideas into a finite list of concepts for which the participants developed "rough draft" implementation plans. The concepts that emerged represent challenges and opportunities in four broad categories:

- Cellular and Molecular Biology/Fundamental Biological Principles
- Systems, Technology, and Innovative Approaches
- Human Subjects and Population-Based Research
- Social and Behavioral Determinants of Health and Disease

As part of the initial strategic planning process, concepts that emerge from these external meetings are considered together with potential program areas identified by the NIH ICs and OD through workshops, discussions with their Advisory Councils, or other interactions with their scientific communities. Ideas are reviewed for compatibility with established criteria for Common Fund Programs by the DPCPSI Council of Councils and discussed with the IC and DPCPSI leadership. These discussions inform the selection of a few topics to move to a second phase of planning.

The major concepts that emerged from discussions at the three Forward Focus Workshops are summarized below together with rough draft strategies to pursue them.

1.1 Cellular and Molecular Biology/Fundamental Biological Principles

Concepts developed in the Cellular and Molecular Biology/Fundamental Biological Principles category include:

- **Bridging the Gap between Biomedical Research and Computational Science and Engineering**—Concept involves developing new strategies for principal investigators to provide their students with cross-training in bioinformatics/computational science and engineering, and to provide opportunities for them to contribute on collaborative projects.
- **Cell Typing Program**—Concept focuses on creating the conceptual framework and new tools to create comprehensive profiles of surface markers, post-translational modifications, and primary protein structure in a variety of cells types. A database of "normal" cell types and cell differences would enable new investigator-initiated projects on cellular processes, functions, and states.
- **De-Orphanizing the Druggable Genome**— Concept is to provide functional information about orphan G protein-coupled receptors (GPCRs), nuclear hormone receptors, ion channels, and kinases to aid in the identification of small molecules that target those proteins which have a role in disease-relevant processes.
- **Evolution Informed Analytics (EIA) Using Evolutionary Information to Overcome Barriers in the Development of Diagnostics and Therapeutics**—Concept is to create a new paradigm for the development of therapeutics by leveraging existing knowledge from evolutionary studies of genetic and non-genetic diversity to inform the creation of new diagnostics and therapeutics.
- **Fibrosis**—Concept is to overcome the fragmentation in research field on fibrosis by building the necessary tools and infrastructure to coalesce the field, accelerate the discovery of common mechanisms of disease, and inform the development of new treatments and preventive strategies.
- **Genetic Models of Complex Diseases**—Concept is to yield more human-relevant animal models in which to conduct pre-clinical studies, improve the likelihood of success in translating discoveries from the bench to the clinic, and increase the translational success of basic research programs at NIH.
- **Immunovariability**—Concept is to comprehensively characterize immune capability and status across individuals based on genetic variability to establish a "fingerprint" of immunovariability that can enable hypothesis-testing and comparative studies.
- **Predictive Models**—Concept is to develop a new paradigm of human disease study and prediction based on efficient, "precision construction" of models which reflects observations of human diseases and differences in disease development across species.
- **Regulation and Restoration of Homeostasis: Promotion of Health through Sustained Homeostasis**—Concept is to develop molecular and cellular signatures of homeostasis

for different biological systems and research models, and to use those tools to advance the understanding of homestatic regulation and dysregulation and develop new interventions designed to promote and restore homeostasis.

- **Zip Codes for Drug Delivery**—Concept is to develop fundamental knowledge about cell surface markers that are specifically expressed in target sites which could be used in the design of more efficient drug targeting approaches.

1.2 Systems, Technology, and Innovative Approaches

Concepts developed in the Systems, Technology, and Innovative Approaches category include:

- **Bioengineered Human Tissues and Organs to Replace Experimental Animals**—Concept is to develop new "organ mimics" that can enable studies of disease processes and accelerate the screening of potential new therapeutics for efficacy and safety before testing in humans.
- **Citizen Science**—Concept is to support the development of novel approaches such as games and puzzles that engage and leverage the collective wisdom of all citizens as a means to solve scientifically meaningful biomedical challenges via "crowd sourcing."
- **Expanding the Capabilities of Structural Biology**—Concept is to develop new tools to address the incomplete understanding of the molecular structure and dynamic behavior of cellular membrane protein targets to advance rational drug design and explore new therapeutic targets.
- **Glycomics: Understanding the "Glyco Code" Will Lead to Improvements in Human Health**— Concept is to investigate the role of all glycan structures at the cellular level through development of tools to manipulate the carbohydrate structure.
- **Knowledge Network**—Concept is to create new models for data sharing and access to change the focus of disease investigation from an organ- and system-based approach (e.g., NIH ICs and academic schools of medicine) to a more general approach that would integrate all areas of investigation.
- **Mechanobiology: An Emerging Frontier in Basic and Translational Research**—Concept is to create a coherent field of mechanobiology through a marriage of traditional fields of cell biology, mechanics, and materials science that would enable the development of improved medical devices, biomaterials, and engineered tissues for use in tissue repair and reconstruction.
- **Transdisciplinary Research**—Concept is to promote new approaches to encourage transdisciplinary research in the biomedical health sciences.

1.3 Human Subjects and Population-Based Research

Concepts developed in the Human Subjects and Population-Based Research category include:

- **Allowing Every Individual to Become a Research Subject/BiESTAR**—Concept represents a merging of two similar ideas that were proposed at the regional meetings. Concept is to create a new model for clinical research through inclusion of all patients in biomedical research, potentially changing the culture regarding ownership of clinical data, and leading to the development of pragmatic and sensitive approaches to privacy.
- **Coordinating Data Collection**—Concept is to break down the cultural, technological, and privacy barriers necessary to foster coordination and cooperation amongst investigators in the collection and pooling of data to increase statistical power in research studies.
- **Environmental Contributions to Disease**—Concept is to define the human "exposome" through an integrated approach to data collection and analysis that focuses on periods of developmental susceptibility.
- **Science of Science**—Concept is to use an evidence-based approach to investigate the funding of studies at NIH.

1.4 Social and Behavioral Determinants of Health and Disease

Concepts developed in the Social and Behavioral Determinants of Health and Disease category include:

- **Applying Decision-Science to Serious Illness (ADSI)**—Concept is to create and implement new models and measures of patient-centered decision-making for end of life care that integrate across socio-cultural "patient-family-provider-healthcare setting" axes.
- **Social Determinants of Health and Disease**—Concept is to develop new metrics for measuring social determinants of stress that impact on health (e.g., geography, social status, and economic status) and use these metrics to develop and test new interventions.

2.0 Background to the *Forward Focus Workshops*

The NIH hosted a *Forward Focus Workshop* in Chicago, Illinois on May 1, 2012, another in San Francisco, California on May 3, 2012, and a third in Potomac, Maryland on May 17-18, 2012. This summary report describes the purpose and goals of the three workshops, the process to recruit participants, and a compilation of the major concepts and themes that emerged from these meetings.

2.1 Introduction to the Common Fund

In September 2004, the NIH launched its Roadmap for Medical Research as a way to join together the efforts of the individual ICs to overcome shared obstacles to research and bridge gaps in science. The concept proved so successful that in 2006, Congress established DPCPSI within the Office of the Director, and created the NIH Common Fund as a dedicated resource to support complex research ideas that transcend the missions and boundaries of the individual NIH ICs.

Common Fund programs take advantage of emerging opportunities to fill a strategic niche within a broader field which the NIH ICs are not addressing. They provide support for the development of new tools, technologies, datasets, and models that enable research broadly across IC missions; encourage biological discovery; accelerate research translation; and test new approaches that foster innovation. These programs are required to make a significant contribution to research and complement other current initiatives in biomedical or behavioral science.

Criteria for Common Fund programs include:

- **Transformative**—They need to have exceptionally high and broadly applicable impact. They should be relevant to many diseases and many ICs. They should set new standards for research or clinical practice, create entirely new approaches to research or clinical care, or establish new biological paradigms.
- **Catalytic, Short-Term, and Goal-Driven**—They cannot just work toward a goal; they must achieve it. Programs have deliverables; these deliverables can be data sets, tools, technologies, approaches, or fundamental principles of biology. Programs last between five and 10 years. If the deliverable will require ongoing maintenance costs, the project must have a vision for transition and sustainment.
- **Synergistic and Enabling**—They provide ICs with tools, resources, and knowledge they did not previously have nor could have developed on their own, and the output of a program must facilitate the mission of multiple ICs.

- **Requires a High Level of Trans-NIH Coordination**—They address complex issues that require trans-NIH teams, insights, and perspectives to design and manage. Programs must necessitate strategic coordination.
- **Novel**—They provide new solutions to specific challenges. When similar efforts exist, the Common Fund program requires attention and coordination to prevent the duplication of efforts.

A list of Common Fund programs currently underway is available at http://commonfund.nih.gov/initiativeslist.aspx.

2.2 *Forward Focus Workshops*: Purpose and Goals

The Common Fund's strategic planning process is by design both flexible and iterative. By statute, the Director of the NIH must submit a strategic plan to Congress every two years which outlines the strategic planning process and goals for Common Fund programs. A new round of strategic planning is initiated each year in two phases. Phase 1 gathers broad input from the scientific community and stakeholders inside and outside of the NIH to identify critical scientific needs and emerging opportunities. Phase 2 applies a combination of portfolio analysis and expert input from targeted meetings to refine the broad topics into specific research programs and initiatives.

The *Forward Focus Workshops* held in Chicago, Illinois; San Francisco, California; and Potomac, Maryland from early to mid-May 2012 commenced the FY 2012 Phase 1 planning activities to inform potential new programs beginning in FY 2014. Concepts that emerge from these meetings are considered together with ideas generated by the NIH ICs and OD. Portfolio analyses and targeted meetings to gather input from internal and external experts is used to help refine these concepts further and inform decision making by NIH senior leadership.

2.3 *Forward Focus Workshop* Participants

NIH hosted two regional *Forward Focus Workshops*, held in Chicago and San Francisco, to provide an opportunity for members of the community to provide input on significant challenges and opportunities in biomedical research that could potentially be pursued through the NIH Common Fund. Interested persons applied through a meeting website hosted by the NIH and advertised through a number of different listervs for the NIH Common Fund, scientific societies and private companies, deans and chairs of academic departments, and NIH-supported researchers in California, Illinois, Indiana, and Michigan (states closest to the NIH meetings).

The meeting announcements were featured prominently on the Common Fund website (http://commonfund.nih.gov/) and in the Common Fund Connection newsletter. Both the

Common Fund Facebook page and Twitter account announced the upcoming meetings. Advertisements for the meetings commenced in early March 2012, and NIH accepted applications from March 16 to April 13, 2012.

At the time of application, the regional meeting participants indicated why they were interested in attending the workshop. The information was used to assemble the participants into breakout groups for discussion during the meeting. More than 100 external participants registered for and attended the regional strategic planning meetings.

Participants of the local *Forward Focus Workshop* in Potomac were nominated by the NIH ICs and OD to represent expertise in a wide range of scientific disciplines and career levels. A group of 26 participants participated in the local workshop.

2.4 Overview of the Forward Focus Process

Each of the three *Forward Focus Workshops* commenced with presentations by senior NIH leadership in plenary sessions. Dr. Lawrence Tabak, Principal Deputy Director of the NIH, presented the overview at the Potomac meeting, and Dr. James Anderson, Director of DPCPSI, presented the overview at the regional meetings and gave the "charge to participants" at all three meetings. The overview included information about the Common Fund, the process used to establish new programs, a description of current programs, and an outline of the activities that would transpire during the course of the workshop.

At the beginning of each meeting, participants were asked to articulate broad challenges in biomedical research that could potentially be pursued through the Common Fund. These ideas provided the initial framework for the meeting discussions. Following the introductory session, participants assembled into smaller breakout groups where they discussed, merged, and refined their broad challenges into a finite list of 3 to 5 specific topics and developed rough draft implementation plans to address them. During the course of each meeting, NIH staff was on hand to help facilitate the generation of novel ideas by highlighting areas where the NIH already had considerable investment.

This meeting summary represents a compilation of the major concepts and draft implementation plans developed during the three Common Fund strategic planning workshops.

3.0 Results and Recommendations

Participants in the three meetings suggested more than a hundred ideas. Appendix A, "Summary of Participants' Phase 1 Topics," presents a complete list of the ideas that participants proposed during the three planning meetings. Through the process described in the prior section, a finite list of concepts emerged from the three workshops. These concepts fall within one of the following four categories:

- Cellular and Molecular Biology/Fundamental Biological Principles
- Systems, Technology, and Innovative Approaches
- Human Subjects and Population-Based Research
- Social and Behavioral Determinants of Health and Disease

The next four sections of the report present a summary of the discussions about these concepts at the three *Forward Focus Workshops*. For each concept, participants articulated a rough draft implementation plan that addressed the following questions:

- What is the major obstacle/challenge/opportunity that the Common Fund should address?
- What would the goals of the program be?
- Why is a trans-NIH strategy needed to achieve these goals?
- What initiatives might form the strategic plan for this topic?
- If a Common Fund program on this topic achieved its objectives, what would be the impact?

3.1 Cellular and Molecular Biology/Fundamental Biological Principles

During the course of the regional and local workshops, participants proposed a large number of ideas related to cellular and molecular biology and fundamental biological principles.
The process resulted in the following ideas in this category, each of which is summarized below:

- Bridging the Gap between Biomedical Research and Computational Science and Engineering
- Cell Typing Program
- De-Orphanizing the Druggable Genome
- Evolution Informed Analytics (EIA) Using Evolutionary Information to Overcome Barriers in the Development of Diagnostics and Therapeutics
- Fibrosis
- Genetic Models of Complex Diseases
- Immunovariability

- Predictive Models
- Regulation and Restoration of Homeostasis: Promotion of Health Through Sustained Homeostasis
- Zip Codes for Drug Delivery

3.1.1 Bridging the Gap between Biomedical Research and Computational Science and Engineering

Bioinformatics and computer science approaches are necessary to investigate "traditional" questions in cell and molecular biology. However, most principal investigators, and thus their students, do not receive cross-training in both disciplines, largely because the academic infrastructure does not recognize the efforts of bioinformaticists on research studies and because there are no award incentives to receive cross-training. Engaging trained bioinformaticists in research projects is often done piecemeal, resulting in added time to complete projects and frustration on the part of both basic researchers and bioinformaticists. New strategies are necessary to provide an opportunity for students to receive training in research, computational science, and engineering, and allow basic researchers and bioinformaticists who work jointly on projects to receive equal credit.

This goal of this program would be to provide incentives for students to be cross-trained in both research and computer science/bioinformatics and to work collaboratively with basic researchers as equals on joint projects.

Participants identified the need to surmount the obstacles of Big Data as a problem that stymies progress throughout the NIH. New strategies are necessary to train a workforce capable of understanding biomedical research while at the same time skilled in computational science.

Participants proposed the following strategies:

- Have the trainee bring money with them to support their training and research (new type of K-award).
- Provide supplements to the Principal Investigator for needed bioinformatics expertise.
- Provide institutional support for the infrastructure necessary to facilitate these areas.
- Sponsor accelerated courses and online training in bioinformatics for students in other biological disciplines.
- Provide a co-PI or linked awards to enable both basic researchers and bioinformaticists working jointly on a project to receive principal investigator "credit" at their academic institution.

Creating a cohort of investigators proficient in both biomedical research and computational science would help accelerate new advances in biological discovery and speed the pace of biomedical research.

3.1.2 Cell Typing Program

Molecular characteristics of cells such as protein post-translational modifications, surface markers, and primary protein structure are known to differ across cell types and play a role in health and disease, but they have never been catalogued comprehensively. New methods to define post-translational modifications and the complete primary structure of proteins in different cells, studies of the functional consequences of these differences among cell types, and development of public datasets characterizing normal cell types are needed to accelerate discoveries of new biological principles and biomarkers of health and disease.

This program would have 4 goals:

- Develop comprehensive profiles of different cell types in the human body.
- Create new methods to define post-translational modifications, surface markers, and complete primary structure of proteins in different cells.
- Understand the functional consequences of cell-to-cell differences across cell types.
- Develop a database to characterize normal cell types and cell differences.

The development of comprehensive profiles of protein modifications, markers, and primary structures across different cell types in the human body would benefit all IC-supported research and represent a trans-NIH concept.

The initiatives which participants proposed as a possible strategic plan for this topic included the following:

- Conduct a workshop to define different approaches and techniques being used in the community to characterize post-translational modifications, cell surface markers, cell shape, and cell state across different cell types.
- Support production centers to develop comprehensive profiles of protein modifications, surface markers, and primary structure for different cell types in the human body that could enable disease-specific studies.
- Develop new methods to measure these aspects of cells across different cell types.
- Conduct studies using tools developed through the program to determine the functional consequences of differences across cell types.
- Develop a database to characterize “normal” cell types and differences across cells (essentially, the “ENCODE” program without nucleic acids):
    - Include procedures to reference cell types.
    - Determine variability across cells at protein level.

A successful program would result in a variety of important contributions to science with implications for all ICs, including the conceptual frameworks and tools needed to develop a comprehensive profile of cells types. As a result of the project, a public database that

characterizes “normal” cell types and cell differences would fuel future basic and translational studies.

3.1.3 De-Orphanizing the Druggable Genome

Over 90% of drugs target proteins in one of 4 protein classes: G-protein coupled receptors (GPCRs), nuclear hormone receptors, ion channels, or kinases. Although these proteins offer huge potential for new drugs, half of the human proteins in these groups are completely uncharacterized. They are therefore referred to as “orphan” proteins. The challenge for a Common Fund program would be to provide functional information about these proteins. This would lead to the identification of small molecules that target those proteins which have a role in disease-relevant processes.

The overall goal of this program would be to provide functional information about orphan GPCRs, nuclear hormone receptors, ion channels, and kinases.

The wide-ranging functions of orphan proteins across many organ systems give the program its trans-NIH significance. A systematic approach would enable the ICs to explore the function of these proteins.

This program would take advantage of animal models and relevant human cell types through 4 initiatives:

- Human Expression Atlas of Orphan Proteins would begin with RNA expression data for the orphan genes, but could be later verified with protein capture reagents.
- Reagent libraries for functional analyses, including siRNA libraries, morpholinos, or other types of validated reagents, would be needed to provide functional information. In addition, this program would need to coordinate with two ongoing Common Fund programs. Mouse strains which have already been generated should receive top priority in the phenotyping phase of the KOMP project. The Protein Capture program should target these orphan proteins if feasibility is established in the current pilot phase of that program.
- Database of Cellular Functions would be a public database that includes data from the Common Fund projects and from investigator-initiated awards that use Common Fund data and reagents.

This program would provide the foundation for drug discovery. New targets would be identified in many new tissues, and reagents to explore function would be provided. Functional analyses would be stimulated, and data from these studies would be publicly available for the community at large to use so that screens for compounds to interact with these proteins could be conducted.

3.1.4 Evolution Informed Analytics (EIA), Using Evolutionary Information to Overcome Barriers in the Development of Diagnostics and Therapeutics

This idea reflects a synthesis of ideas proposed in the two regional meetings. A new paradigm for therapeutics development – called "evolution-informed analytics (EIA)" – is envisioned which capitalizes on existing knowledge of the evolution of gene variants in human and non-human species to inform a new approach to data reduction, integration, and analysis. This new approach could hasten the identification of promising new therapeutic targets and drugs. Creation of new high-volume centers to develop and apply new approaches to analyzing genetic and genomic data sets across evolutionary lines and a public database and visualization tools could enable new studies of biological discovery and drug development in the research community. A specific application could be development of novel therapies that overcome adherence problems by co-evolving with pathogens such that therapeutic delivery occurs with transmission of pathogens between infections, individuals, or within tissues such as tumors.

Participants articulated 5 goals:

- Define the specific barriers to drug development that can be addressed using EIA.
- Develop new knowledge on variants in non-human species and model systems to apply EIA approaches.
- Assemble collections of biological samples for multiple species to apply EIA approaches.
- Develop new data reduction and analytical approaches to advance EIA.
- Use the resources developed through the program to conduct proof of concept studies.

A new program based on EIA could advance biological discovery and therapeutics development across a wide range of diseases of interest to the NIH. The concept merits a trans-NIH strategy.

The participants suggested the following initiatives to implement the strategic plan of the EIA concept:

- Sponsor a workshop to identify existing barriers.
- Support high-volume production centers and coordinate with other ongoing efforts in evolutionary biology.
- Create a public sample repository and set of standardized sampling and analysis approaches for the community.
- Develop new novel methods, databases, and visualization tools.
- Support high risk projects using the tools and data developed through the program.

If successful, the program would create a new paradigm for therapeutics development at relatively low cost by leveraging existing knowledge from evolutionary studies to inform the development of new diagnostics and therapeutics based on EIA.

3.1.5 Fibrosis

Fibrosis is a relatively common illness for which there are currently no effective treatments. Investigators silo current research efforts in small-scale, organ-specific studies and programs. Integration of the field through development of common language; approaches to study normal and diseased tissues; and new and relevant models of disease would accelerate the discovery of new biological principles, identify possible common disease mechanisms, and develop new ways to prevent, diagnose, and treat this disease.

This program would have 5 goals:

- Find common mechanisms, approaches, data sets (e.g., diagnosis, prevention, treatments) across different loci of research to coalesce the field.
- Establish a shared data network and language for the field.
- Develop a repository for normal and disease tissues.
- Develop a non-invasive approach to collect and analyze these tissues.
- Develop new relevant animal models for multiple tissues and systems.

Fibrosis research is supported by several ICs within the NIH, although there is relatively little coordination and collaboration across IC-supported projects and programs. Building the necessary tools and infrastructure to coalesce the field and accelerate the discovery of common mechanisms of disease and ways to treat and prevent this disease is therefore a trans-NIH concept.

Participants proposed the following initiatives:

- Convene a workshop to bring together researchers in the field to identify the state of the science.
- Focus on development of new imaging technology.
- Support studies of proof-of-concept in animal/human models, including validation.
- Make new models created through the program available to multiple investigators.

A successful program would overcome the cultural barriers between disciplines that work on the shared problem of fibrosis. The project would assess and describe the state of the science, establish a shared data network and language for the field, and mine data to identify mechanisms that may be common across different tissues, organs, and disease manifestations. Gaining a deeper understanding of the causes of fibrosis could lead to development of potential new treatments.

3.1.6 Genetic Models of Complex Diseases

The use of animal models was a recurrent theme in all three regional and local meetings. Developing preventative therapies aimed at reducing or delaying chronic diseases is an important priority for biomedical research. Traditional models of drug discovery have frequently failed,

particularly as applied to the complex chronic diseases of the elderly (e.g., cancer, neurodegeneration, diabetes, and cardiovascular disease). A better rate of success in translating studies from model organisms into clinical practice is necessary. At the foundation of this issue is the importance of identifying suitable preclinical models of disease that can effectively represent genetic complexity. Mice (predominantly C57BL/6 young male mice) have become central to biomedical research, and often elaborate manipulations are used in order to approximate the human condition in this model. When used to test drug or treatment efficacy, these inbred murine strains often fall short. No species, much less a single inbred strain, should be expected to be broadly applicable to model all diseases. Nature offers a wide range of phenotypes of interest, and these phenotypes may be more comparable to what is observed in human diseases. Indeed, many models that better resemble human disease have been described, but are not currently exploited to their maximal potential. To maximize the use of animal models, genetic technologies for more species need to be developed, technologies for mice need to be enhanced to allow simultaneous mutation of multiple genes so that complex diseases are more effectively modeled, outbred strains need to be increasingly utilized, and zebrafish mutants should be more systematically phenotyped.

The overarching goal of the program would be to develop new animal models for the analysis of complex traits.

Better translational models would benefit programs at several NIH ICs as well as trans-NIH endeavors. The program would leverage investments made in sequencing the genomes of a number of species and would provide a "proof of principle" with a clear deliverable at the end of the incubator period.

The following activities could form the components of a strategic plan to implement the program:

- Convene a meeting of experts in major chronic diseases (CVD, cancer, inflammation, neurodegeneration) and evolutionary biologists/animal researchers to stimulate discussion of those models which are most worthy of further development and of the opportunities for enhancing mutagenesis methods in mice.
- A series of funding opportunity announcements (FOAs) could then foster the transfer of technologies needed to study causal relationships and to test candidate therapies in new models.
- Systematic phenotyping of zebrafish mutants could be undertaken.
- Technologies for the generation of multiple mutations in mice could be developed.
- In parallel, existing mouse models could be improved to better account for aging (where most chronic diseases develop), as well as genetic heterogeneity (as observed in human populations), by using newly developed tools such as the Collaborative Cross and the Diversity Outcross.

- A source or repository of such animals for easy use by the research community would need to be developed and maintained if outcomes so warranted. Support for these would be expected to emerge based on their research value and would transition beyond Common Fund support.

Investment in this area would yield more relevant models in which to test pre-clinical hypotheses, improve the likelihood of success in translating from the bench to the clinic to increase the translational success rate of a number of NIH programs. The potential impact would be to help increase the number of successful interventions available to provide relief for a variety of diseases and conditions and improve health in the U.S. and around the globe.

3.1.7 Immunovariability

Differences in individual immune capacity, which are likely to have a genetic basis, underlie differences in susceptibility to health and disease. To date, there have been no efforts to comprehensively characterize an individual's immune "fingerprint" or to compare immune capacity across individuals, and consensus is lacking about how best to derive these measures. New metrics, assays, reagents, and/or analytical approaches could be developed and used to create "fingerprints" of individual immune capability that are predictive of health, disease, and response to treatment. These measures could inform the development of new therapies and interventions for at-risk populations based on immunovariablilty.

This program would have 3 goals:

- Devise new approaches to comprehensively characterize human immunovariability based on genetic and physiological/molecular/clinical parameters.
- Develop standardized metrics, assays, reagents, and analytical approaches to predict and determine immunologic phenotype.
- Develop immunovariability fingerprints that predict health and disease outcomes and response to therapy, and define at-risk populations.

Immune function underlies many different health and disease processes such that improving our understanding of human immunovariability, particularly as it relates to genetic variability, would benefit all ICs. Developing the tools and datasets needed to comprehensively characterize individual immunovariability requires a trans-NIH strategy.

Participants proposed a number of strategies to implement the program. These initiatives included:

- Conduct a workshop to catalogue what measures are currently being used in the community, and what measures are needed but not yet developed to define immune function and capacity.

- Develop a set of standards to facilitate development, exchange, and dissemination of approaches and data.
- Conduct studies to determine immunovariability fingerprints that are predictive of health and different disease outcomes, response to therapy, and to define at-risk populations.

Participants suggested a successful project would result in the development of metrics, approaches, and datasets to define individual fingerprints of immune capacity that are predictive of disease outcomes and response to treatments.

3.1.8 Predictive Models

This concept represents the combination of ideas which originated at the two regional meetings. Existing preclinical cellular and animal models of human diseases inadequately represent disease processes and states. A new paradigm based on "precision construction" of disease models based on observations of actual human diseases is needed to improve our ability to predict disease etiology and outcome, and accelerate development of new treatments. Following prototype development, proof-of-concept demonstrations and validation studies would be required to test utility and predictability of the human experience. New biocomputational tools would be needed to analyze cross-species differences.

The program would have 4 goals:

- Identify preclinical models which best replicate human diseases.
- Identify a new paradigm based on efficient "precision construction" of new models inspired by observations in human disease.
- Develop biocomputational tools to analyze cross-species differences.
- Make new tools available to the broad basic and clinical research community.

Participants suggested that the development of better predictive models of human disease that enable cross-species comparisons is a shared interest across all the ICs, and would represent a trans-NIH concept.

Initiatives which participants proposed to guide the program's implementation included:

- Conduct a series of workshops to identify currently available models/approaches for specific diseases.
- Understand where predictive models are inadequate and could be improved or newly developed.
- Develop new preclinical cellular and animal models of human disease and tools and data to understand points of divergence across systems.
- Develop a "systems" biology approach/understanding to model development.

If successful, this program would open the door to development of a new paradigm of human disease study and prediction based on efficient, "precision construction" of models that reflect observations of human diseases and can inform differences in disease development across different species.

3.1.9 Regulation and Restoration of Homeostasis: Promotion of Health through Sustained Homeostasis

Cells, tissues, and organisms sustain health through promotion and restoration of homeostasis. However, the definition of homeostasis varies across biological systems and states. No minimal set of molecular and cellular parameters (signatures) exists that defines homeostasis across these different systems. Development of appropriate models systems, unifying criteria and data sets, and a supply of banked samples that have been "phenotyped" for homeostatic signatures could greatly advance our understanding of homeostatic regulation and dysregulation (i.e., disease), including the possible phenomenon of a "threshold effect" for dysregulation.

This program would have 4 goals:

- Develop criteria and associated approaches to measure and define homeostasis under normal conditions and in response to diverse environmental stressors and altered states in different systems.
- Develop appropriate models systems (*in vivo*, *in vitro*, in life) to study homeostatic regulation and dysregulation.
- Coordinate and data/research across systems.
- Define mechanisms of homeostatic dysregulation, including a possible threshold effect.
- Use model systems and datasets to develop new interventions.

Enhancing our understanding of how homeostasis is promoted and maintained in health and dysregulated in different diseases and conditions could enhance the mission of many ICs, and therefore merits trans-NIH support.

Initiatives which could form the strategic plan to implement this program include:

- Sponsor a workshop to define homeostasis across different biological systems and states.
- Establish new standards/criteria for characterizing homeostasis for these systems.
- Support research to develop these models, including development of new regenerative tissue systems.
- Support appropriate data and research coordinating functions.
- Conduct studies to define mechanisms of homeostatic dysregulation (threshold effect).
- Conduct studies that use the new model systems to develop interventions.

A successful project would leave in its wake an understanding of the molecular and cellular signatures that define homeostasis for different systems. It would create and characterize model systems to enable new studies of homeostatic regulation and dysregulation. The knowledge generated through this program could contribute to the development of novel interventions to promote homeostasis and preserve health. It could also create a culture of cooperation among data and research programs specific to the study of homeostasis.

3.1.10 Zip Codes for Drug Delivery

This concept represents the combination of ideas from participants in the three strategic planning meetings. A major obstacle for drug development is unwanted side effects which are frequently caused by drug action on off-target tissues or cell types. This contributes to the high failure rate of developing preclinically effective compounds into medications, as well as the withdrawal of medications from clinical use due to adverse effects. Recently, advances have been made in drug delivery systems that allow such medications to reach their designated targets and avoid targets that are not involved with the disease, alleviating undesirable side-effects. However, a major obstacle that prevents more targeted therapies is a lack of fundamental knowledge about cell surface markers that are specifically expressed in target sites that may be used in targeting approaches. These markers could serve as "Zip Codes" for delivery, if they can be identified. Such molecules have been described in the vasculature, and vascular Zip Codes offer potential for targeted delivery to the vasculature of specific organs. However, a catalog of Zip Codes of the vasculature and elsewhere needs to be established, and a library of compounds that specifically bind these Zip Codes needs to be established.

The 3 goals of this program are to promote and implement:

- Targeted drug delivery technologies through the identification and cataloging of Zip Code proteins.
- The development of binding reagents which specifically recognize these proteins and have the capacity to deliver therapeutic molecules.
- The development a tracking system which would enable *in vivo* tracking of the binding reagents.

Initiatives to implement the Zip Code program include:

- Zip Code identification–A catalog of cell type- or tissue-specific markers would be identified as Zip Codes for that cell or tissue. This catalog would be fully annotated and available to the public.
- "Packing Material" development–Therapeutic molecules would need to be "packed" for delivery through binding to molecules which would in turn bind to the Zip Code molecules. These packing molecules may be developed via the Common Fund Protein Capture program, or it may require a separate activity.

- Development of Tracking Methodologies–Just as packages can be tracked via UPS, targeted drugs would need to be tracked *in vivo*. Imaging methods which track the packing molecules would need to be developed.
- Demonstration Projects–Proof of concept projects would need to test the utility of the suite of compounds, including the ability of packing molecules to bind a therapeutic compound, its ability to deliver the compound specifically to the target Zip Code, and the ability of the tracking methods to follow delivery and clearance of the packing compound.

The goal of a trans-NIH strategy would be to facilitate integration of knowledge across ICs on different organs, tissues, and cells. If the objectives of targeted drug delivery are achieved, it would increase the success rate of medication development and reduce off-target toxicity. This in turn could significantly impact the efficiency of translating basic research discoveries to treatment of patients.

3.2 Systems, Technology, and Innovative Approaches

Participants in the regional and local meetings proposed a variety of ideas related to biological and mechanical systems, technology, and innovative approaches. They include:

- Bioengineered Human Tissues and Organs to Replace Experimental Animals
- Citizen Science
- Expanding the Capabilities of Structural Biology
- Glycomics: Understanding the "Glyco Code" will Lead to Improvements in Human Health
- Knowledge Network
- Mechanobiology: An Emerging Frontier in Basic and Translational Research
- Transdisciplinary Research

3.2.1 Bioengineered Human Tissues and Organs to Replace Experimental Animals

The use of animal models to replicate and predict human disease is becoming increasingly untenable. Breeding and housing animals for research purposes consumes financial resources, time, and space. Many investigators are resigned to using whole animals to study problems that are specific to isolated organs (e.g., tumor growth and wound healing) simply because equivalent organ models are not available. This practice is under intense scrutiny with the enhanced federal commitment to step down from use of animals for research purposes. Development of new "organ mimics" would greatly enable studies of disease processes and accelerate the screening of new therapeutics for efficacy and safety before testing in humans.

This program would have 2 goals:

- Create high throughput "organ mimics."
- Decrease time to human testing of potential new drugs and therapies.

Participants proposed that reducing use of animals in experimental research is a trans-NIH concern that cuts across the ICs.

Initiatives which could be pursued include:

- Development of vascularized, 3D, anatomically correct scaffolds incorporating basement membrane, stromal, and parenchymal cells to represent specific organs (e.g., skin, liver) that could be perfused/oxygenated in standard chambers in parallel.
- Using the experimental models developed above, mouse-sized (or smaller) organs seeded with human cells could be interrogated/visualized during experiments, decreasing the time to human testing of potential new drug therapies.

Through this program, experimental animal use in drug development and safety assessment would decline, time to human testing would decrease, and human conditions such as trauma and hypoxia could be mimicked for research purposes. One potential application is to characterize the performance of these new cell/organ mimics when infected with viruses or wounded and then infused with experimental drugs. This differs from DARPA-supported initiatives because the basement membrane is incorporated into the model, whereas DARPA-supported models are more static.

3.2.2 Citizen Science

A recent phenomenon has demonstrated an extraordinary opportunity to engage the average citizen in science. A project known as "FoldIt" has involved thousands of non-scientists in structural biology challenges through creation of "rules" and a game structure which rewards players when they identify stable structures (http://fold.it/portal/). Developed by University of Washington scientists, FoldIt enabled gamers to determine the structure of HIV Retroviral Protease in 10 days, after the research community had struggled with it for a decade. The time spent on nonproductive gaming is astronomical. The challenge is to divert attention toward scientifically productive challenges. The goal of this program would be to support the development of games such as FoldIt which connect the average citizen to scientifically meaningful challenges.

Crowd sourcing for scientific challenges is a new phenomenon. Although many types of challenges may be amenable to this approach, the scientific community is not familiar with game development technologies that would allow the community to participate. This program will require a concerted effort to bring game developers and scientists together to consider the possibilities and to create a field of Citizen Science.

Participants envisioned three initiatives to implement this program:

- Brainstorming Workshop with gamers and scientists to define the types of challenges that would be most amenable to a Citizen Science approach.
- Citizen Science Challenge Development would include a set of projects to develop high impact games engaging the public to solve significant scientific challenges.
- An Outreach Initiative would spread the word about the opportunities for citizens to become involved in significant research questions.

This program would be transformative in two respects. First, significant scientific challenges would have an entirely new population from which to gain insights. Second, the population at large would become more familiar with research objectives and outcomes. This approach has the potential to bring the NIH mission to the average citizen and thereby raise awareness of and appreciation for research. Participants proposed that Citizen Science would become the face of the NIH to the average U.S. citizen.

3.2.3 Expanding the Capabilities of Structural Biology

An incomplete understanding of the molecular structure of membrane protein targets and their dynamic behavior limits our ability to advance rational drug design and explore new therapeutic targets. Currently, structural data represent a sampling of the time-and-space-averaged picture of the target that masks the dynamic information potentially important for mechanisms. Additionally, these techniques allow only a limited number of proteins in a cell to be visualized. This approach does not allow us to observe the global motion of molecules (i.e., view "molecular movies"). Crystallizing a membrane complex is difficult; each technique is limited, and data cannot be extracted. Additionally, current techniques allow only a limited number of protein structures within a cell to be visualized. The availability of high resolution models using 10 femtoseconds of radiation which would not damage the cell would greatly increase our ability to visualize almost half of all of crystal structures, representing a vast improvement over current models where only 10% to 15% of the crystal structures can be visualized.

This program would have 3 goals:

- Grow crystals.
- Extract dynamic information.
- Observe global motion of molecules.

Existing tools (e.g., crystallography, NMR, SAXS, molecular dynamics, spectroscopy) need to be combined and physical and biological tools need to be developed that bridge the gaps in these technologies. This requires a concerted trans-NIH effort to delineate existing tools and establish a collaborative agreement with the Department of Energy project managed at Stanford

University to participate in ongoing research using the Linac Coherent Light Source (LCLS) (https://slacportal.slac.stanford.edu/sites/lcls_public/Pages/Default.aspx).

Participants recommended several initiatives to form a strategic plan to implement the program:

- Support initiatives to create nanocrystals (<1 μm) that grow easily and represent approximately 50% of proteins.
- Develop methods/tools (both structure/time)
- Use X-ray laser developed at Stanford to view molecules.
- Advance laser studies.

Participants proposed that visualizing "biology in action" of a single molecule at the atomic level would transform structural biology. Motions in solutions, in addition to crystal studies, would greatly improve understanding of these dynamics. Technology would be made available to the entire community of structural biologists. NIH could partner with DOD/NSF in the development of "beam biology."

3.2.4 Glycomics: Understanding the "Glyco Code" Will Lead to Improvements in Human Health

Investigators have discussed the importance of glycomes for the last 20 years; however, new tools are necessary to profile not only glycoproteins but the entire "glyco code," incorporating an "'omics" approach. The field of glycomics includes questions about genetics, physiology, pathology, and other fields which touch on the glycome. Currently, quantification is extremely difficult. Challenges, compared with other "'omics," are the complexity of sugars (including highly branched vs. linear structures), modifiability, a complex biosynthetic pathway, and high dynamicity. Several web sites exist which focus on glycomics or provide access to glycomics databases (e.g., http://www.functionalglycomics.org/, http://www.glycosciences.de/, http://www.glycome-db.org, and http://www.ebi.ac.uk/eurocarb/gwb/home.action). These resources detail progress to date in the field, but researchers need validated tools to advance the science to a level that leads to the treatment of diseases.

The proposed program would have 3 goals:

- Develop tools to determine structural analysis of oligosaccharides.
- Create chemical/biological tools.
- Expand capacity for researchers to use these tools.

Glycomics encompasses a complexity that transcends the study of a single disease. By understanding the role of all glycan structures at the cellular level through development of tools to manipulate carbohydrate structure, all ICs would benefit from the knowledge gained.

Participants suggested several initiatives which might serve as components of a strategic plan to implement the program. These include:

- Support development of new methods to systematize specific targets.
- Create chemical/genetic/biological tools.
- Create a database, and computational and modeling tools to share discoveries.

The ability to profile and quantitate the role of glycomes could lead to improved health through an improved understanding of cell signaling pathways, leading to development of targets for novel agents and vaccines.

3.2.5 Knowledge Network

There is currently no single database or collection of linked databases that provide basic information about mechanisms of disease. In addition, existing databases are "fossilized" with no means of inserting new information. Ready access to vast quantities of scientific data would make it possible for researchers to keep abreast of new discoveries and progress being made in their field, and enable the design of new studies that build on that knowledge. Accessing data in a coherent form across disparate datasets is currently not possible, since databases lack self-consistency, and data visualization is often a difficult computational task. Additionally, most useful databases are often the domain of a single dedicated individual or research entity. Proprietary databases may hide data from NIH-funded research, and raw data are not always accessible to investigators who wish to conduct meta-analyses or comparative studies. Access to clinical data is especially problematic due to protections under HIPAA and other regulations. New models for data sharing and access are clearly needed.

The program would have 3 goals:

- Create, collect, and aggregate biomedical research data and information from among multiple, heterogeneous databases that can be queried.
- Develop connection points between nodes and between areas of information.
- Create self-consistency within and across datasets.

Having a repository of information that ranges from discovery to patient care would provide transparency about research results, including negative data that may not have been published. This would alleviate redundancy of research efforts; help focus new research ideas; and support meta-analyses, topic evaluation, and data synthesis, while providing mechanisms for knowledge and evaluation.

Participants suggested the following initiatives could form a strategic plan for this program:

- Appoint expert curators to crowd source development of a pilot project.
- Build a data network/information commons with a common access point for all types of health information and data, including behavioral and racial data.

- Form cross-institutional teams based on a common research goal.

The overall goal of creating a knowledge network is to change the focus of disease investigation from an organ- and system-based approach (e.g., NIH ICs and schools of medicine) to a more general approach that would integrate all areas. This approach would enable precision medicine by building an information commons and knowledge network that facilitates integration of data and information, extending from untargeted discovery to patients at the point of care. In some cases, the point of care may be the cell phone.

3.2.6 Mechanobiology: An Emerging Frontier in Basic and Translational Research

Mechanobiology is an emerging frontier in research at the interface of biology and engineering that involves the study of physical forces and changes in cell or tissue mechanics. Cells are exquisitely sensitive to mechanical stimuli, and their ability to detect mechanical cues is critical to stem cell biology, developmental biology, and a wide variety of diseases. A major challenge in the field is the lack of understanding about the principles of mechanotransduction: the molecular mechanisms by which cells and tissues self-organize, sense, and respond to mechanical signals. At present, research in mechanobiology is rather piecemeal, with different communities working on select diseases, cell types, and model organisms. Unifying approaches and datasets that could add much-needed coherence to the field are simply not available. With support from the NIH Common Fund, new research caapcity and insights into the mechanical basis of tissue regulation could lead to development of improved medical devices, biomaterials, and engineered tissues for tissue repair and reconstruction.

This program would have 4 goals:

- Develop new techniques to measure mechanical forces in living organisms, on varying scales, both spatial (nanometers to meters) and temporal (milliseconds to years).
- Integrate understanding of mechanical signal transduction across log scales ranging from the cellular to the tissue to the organism level.
- Apply knowledge to the creation of complex engineered biomaterials (tissues and whole organs).
- Make engineered biomaterials available to the research community to advance development of new medical devices and tissues for reconstruction.

Participants suggested the Common Fund is uniquely positioned to drive progress across the NIH to coordinate the emerging field of mechanobiology into a coherent whole.

Initiatives which attendees suggested to implement the program included:

- Facilitate the development of new techniques for studying mechanotransduction in natural and bioengineered materials.
- Emphasize mechanical principles underlying cellular unity.

- Create nature-inspired biomaterials using molecular self-assembly.

A successful program would create a coherent field of mechanobiology. Since mechanobiology requires interdisciplinary knowledge, the program would integrate concepts from the traditional fields of cell biology, mechanics, and material science.

3.2.7 Transdisciplinary Research

Transdisciplinary teams are better positioned than single research investigators to address certain complex research questions. The ability to sustain such teams, including partnerships with universities and industry, is lacking.

The Transdisciplinary Research program, as proposed by participants in the strategic planning meetings, would encompass 3 goals:

- Create a pilot for developing a conceptual framework of vertical integration of research in a seeding/incubating environment.
- Influence NIH culture regarding support of transdisciplinary research projects.
- Set aside funding for transdisciplinary projects.

Attendees indicated that a new culture within NIH would influence policy to create transdisciplinary research teams, change funding mechanisms, and add facilitators.

Initiatives which participants suggested for the Transdisciplinary Research program included:

- Assemble a diverse group to work on a complex research question efficiently.
- Establish a rapid turnaround funding mechanism that is sustainable.
- Issue new funding opportunity announcements (FOAs).

Participants indicated that transdisciplinary ideas could be developed and tested within 6 months to a year, as opposed to the current timelines for grant mechanisms which are considerably longer; in addition, there would be no penalties for research "failures." Study sections devoted entirely to supporting transdisciplinary research would help bridge the physical and life sciences.

3.3 Human Subjects and Population-Based Research

Participants in the three external strategic planning meetings proposed the following concepts related to human subjects and population-based research:

- Allowing Every Individual to Become a Research Subject/BiESTAR
- Coordinating Data Collection
- Environmental Contributions to Disease

- The Science of Science

3.3.1 Allowing Every Individual to Become a Research Subject/BiESTAR

An idea proposed at the local meeting called BiESTAR (Body Information + EHR System Transformation Augmented Research Translation and Discovery) was combined with a similar idea proposed during the San Francisco regional meeting called Allowing Every Individual to Become a Research Subject to create this concept.

Participants suggested that identifying, enrolling, and maintaining human subjects in health research studies presents unique challenges. Despite the vast number of patients currently served by healthcare systems in the U.S., health data collected by these systems are rarely accessible to outside investigators. Participants suggested that no widely accepted policies and approaches currently exist to allow individual healthcare patients to enroll freely in research studies. Yet the contribution of these data to the research enterprise could have an enormous impact on advancing clinical discoveries and improving patient care by establishing a positive feedback loop to provide patients with timely health information. Barriers to allowing every patient to become a research subject include ethical, legal, and social impediments, uncertainty about which types of data to capture, difficulty in linking disparate patient data sources, and lack of approaches to measure impact on patient health.

This program would have 4 goals:

- Address ethical, legal, and social implications of enabling every patient to become a research subject.
- Define ideal data sources and sets for capture, including from mobile sensors and devices.
- Integrate datasets via visually intuitive formats.
- Measure impact of program on improving human health and well being.

Participants suggested that incorporation of all patients into a collective pool of research subjects is too massive an enterprise for any one IC, although creation of such a program would likely benefit all ICs.

Initiatives which participants indicated might form the components of a strategic plan included:

- Address privacy/policy/ethical issues/anthropology.
- Develop procedures for every patient to give informed consent.
- Develop procedures to share results with subjects.
- Develop educational tools for the public.
- Incentivize patient participation.
- Develop standards for consistent data collection.
- Expand and systematize patient outcomes in a way that increases benefits.

- Create links to Knowledge Network.
- Develop storage and sharing methods.
- Provide training to ensure input of quality data.
- Develop ontologies.
- Systemize outcomes.
- Develop tools, methods, and analytical procedures to measure impact.

A successful program would create a new model for clinical research, potentially change the culture regarding ownership of clinical data, and lead to development of pragmatic and sensitive approaches to privacy, ultimately improving human health.

3.3.2 Coordinating Data Collection

Large sample sizes increase statistical power and can lead to greater reliability of research results, whereas comparable studies which rely on small samples often yield contradictory findings. Greater coordination and cooperation among investigators in collecting and pooling the data from studies has the potential to significantly increase knowledge in all fields. The development of a culture of collegiality among investigators coupled with technological advances in the storage and access to pooled data could break down barriers between labs and allow investigators greater flexibility to publish more reliable findings. For this model to be successful, however, issues of privacy with regard to data on individual human subjects and the use of these data in research would need to be addressed.

The program would have 6 goals:

- Establish procedures to collect standardized data from diverse sets of investigators
- Standardize phenotypes.
- Remove barriers to capturing and sharing data as a consortium when groups did not initially develop as consortia.
- Expand the data pool to include school districts, state healthcare systems, and similar entities.
- Establish interoperability standards and a data warehouse for data mining and sharing data.
- Address the issues and ethics surrounding privacy.

The cultural, technological, and privacy issues that form barriers to data coordination transcend the boundaries that separate the missions of the various ICs. These issues are relevant to data collection across disciplines and require the attention all parts of NIH.

Initiatives which attendees in the workshops indicated might form a plan to implement this program included:

- Develop a list of different issues that require an integrated approach.
- Collect data from each human subject for use in studies across a variety of different domains.
- Incentivize participation by investigators.
- Build an NIH-housed data repository, analogous to PubMed, which is accessible to investigators both to input and access data.
- Create a stipulation in consent forms about the sharing of data in the data repository.

A successful program to coordinate data collection could lead to more robust findings based on larger sample sizes, an outcome which would contribute to more rapid advancement across the fields of health. It could potentially standardize both the definitions and measures of variables of interest and create an infrastructure to capture findings from multiple studies in a manner that makes data accessible while it incentivizes collegiality among investigators and fosters collaboration between disciplines.

3.3.3 Environmental Contributions to Disease

The accumulation of exposures (e.g., radiation, stress, diet, environmental pollution) which individuals experience over their lifetime -- the human “exposome” -- may account for the variability in human disease that genetic markers fail to explain. The difficulty of measuring accurately the myriad of day-to-day exposures and their combined effect on processes and substances present in human body have frustrated efforts to link environmental exposures to disease. Currently, investigators can measure only three to eight thousand chemicals in serum; a major effort to study the "dark matter" and "get into the noise" ultimately might yield a chemical library of banked samples from large cohorts that would expand the metabolome through measurements of a million chemicals in serum, saliva, and urine. Research is also needed to understand the sources of exposure. Moreover, investigators have not characterized the developmental windows of susceptibility to different exposures over the life spectrum. A team science approach could define these windows, measure relevant human exposures at these points of time, and describe the consequences over the life course by developing existing human studies to avoid waiting time and serve as proof of concept.

This program on Environmental Contributions to Disease would have 4 goals:

- Develop technologies to measure the internal human exposome.
- Define external exposures and measure them.
- Apply exposome technologies to established cohorts to assess the relationship between the exposome and disease across the life spectrum.
- Develop tools and approaches to data analysis and informatics.

The effort to define the human exposome, including understanding the sources of exposure and the effects of that exposure at different points across the life span, would require a multi-

disciplinary approach that transcends the ICs. Since the findings which could emerge from this effort are relevant to the NIH as a whole, the project is appropriate for Common Fund consideration.

Initiatives which participants proposed to implement the program included:

- Develop technologies to measure exposures.
- Develop a virtual repository.
- Develop procedures to collect standardized data from diverse sets of investigators.
- Develop measurement tools.
- Enlist interdisciplinary teams to characterize developmental windows of susceptibility.
- Involve healthcare systems which do not typically conduct research.
- Incentivize investigators' contributions to a database.
- Provide training to ensure the quality of data.
- Address "Big Data" problems and develop the tools necessary to look for patterns in large data sets.

Participants noted that research efforts and approaches used to investigate the relationship between environmental risk factors and categorical diseases are fractured. The integrated exploration of the exposome, employing an approach sensitive to issues of developmental susceptibility, could lead to the discovery of the key exposures responsible for chronic diseases. With a clear definition of the exposome, including understanding of the sources of exposure and measurements during windows of susceptibility, health science would be positioned to develop strategies to mitigate the deleterious effects of these exposures and complement the advances in understanding the human genome.

3.3.4 Science of Science

Participants felt that many of the policies and processes related to the funding of science that are developed by the NIH and research institutions are not evidence-based. These policies and processes include peer review, predictors of investigator success, and predictors of program success. Although scientists collect data to make rational decisions, participants argued the NIH does not employ evidence-based policies and processes to make funding decisions. According to the participants, the concept of “evidence for the validity of decisions to fund science” remains a lacuna in knowledge.

The Science of Science program would have 3 goals:

- Define the desired outcomes for developing an evidence-based approach to decision making about science funding.
- Establish research teams to address these issues related to science funding.

- Review the ecosystem for doing research and how this interfaces with healthcare and academic systems.

Participants argued that because of its implications for how the NIH funds research, the Science of Science program cuts across all the ICs and requires support from the NIH as a whole. Initiatives which participants proposed to implement the Science of Science program included:

- Issue new funding announcements to define outcomes for developing an evidence-based approach to science funding.
- Hire contractors, issue new funding announcements, and/or establish workgroups to address the need for new approaches and policies.
- Establish an independent assessment of peer review processes and funding decisions.

Participants believed that the results of a successful program would include an entirely new and evidence-based approach to fund research at the NIH. The program would provide NIH with evidence for the validity of decisions to fund science and provide a basis for rational decisions in the funding process.

3.4 Social and Behavioral Determinants of Health and Disease

The need to define the social and behavioral determinants of health and health care delivery was an idea that emerged in all three strategic planning meetings. Because of the similarity in ideas across the three meetings, two unique concepts emerged for this category:

- Applying Decision-Science to Serious Illness (ADSI)
- Social Determinants of Health and Disease

3.4.1 Applying Decision-Science to Serious Illness (ADSI)

Approximately one-third of healthcare costs in the U.S. occur in the last 6 months of life. Patients are resigned to die in pain in health care settings they would not normally choose if provided the "right" information to make informed decisions. Advance care planning and hospice care are shown to improve a patient's quality of life and reduce the costs of care, but these options are often not implemented effectively because of poor decision-making by patients, families, and clinicians. Emergent research at the cross-roads of neuroscience, bioinformatics, communication, health literacy, and behavioral economics provides novel insights into basic mechanisms and optimal strategies for informed decision-making. However, to date, much of what we know about decision-making is derived from laboratory scenarios which are largely hypothetical, decontextualized from reality, affect-poor, and rarely map to actual clinical choices which are highly emotional and socially and culturally embedded. New approaches to real-world decision-making that integrate across socio-cultural axes of "patient-family-provider-health care setting" are clearly needed.

Goals of the program would be:

- Develop and implement comprehensive, robust, and valid theoretical models of decision-making.
- Develop measures of effective and patient-centered decision-making (akin to the NIH PROMIS program).
- Implement effective strategies in practice:
    - Increase the implementation of decision-making tools.
    - Document improved patient quality of life.
    - Reduce healthcare costs at the end of life.

Serious illness spans many diseases and all ages, and therefore requires a coordinated, trans-NIH approach.

Participants proposed several initiatives to implement the program, including:

- Develop and implement standardized assessments of clinical decision-making.
- Convene a workshop to bring together stakeholders (e.g., patients, clinicians, basic scientists, clinical researchers).
- Develop new tools to support personalized decision-making in diverse settings.
- Coordinate cross-Institute programs:
    - Increase the external validity and applicability of basic science in decision-making.
    - Promote theoretically driven and methodologically stringent research in clinical decision-making.

A successful program would establish a new paradigm for clinical care decision-making based on real world contexts and utilization of robust, clinically validated approaches.

3.4.2 Social Determinants of Health and Disease

Social determinants such as geography, social status, and economic status have a well recognized impact on health; however, strategies to measure the impact are lacking. Without these metrics, investigators cannot assess the impact of interventions. For example, the Civil Rights Act has influenced the social environment for minorities, with a presumed reduction in racial bias and the stresses which accompany it. However, behavioral science has no metrics for racism or for the stresses which it produces. Therefore, the impact of the Civil Rights Act on health is impossible to measure. The overall goal of this program, as participants conceived of it, would be to develop metrics of social stressors, use these metrics to assess social determinants of health, and develop and test interventions.

Social factors influence many aspects of health which cut across the missions of the various NIH Institutes and Centers. The fundamental problem which faces all social scientists, regardless of the specific disease or condition that they are interested in, is a lack of effective measures of social determinants. This challenge needs a coordinated approach to develop these metrics.

Participants proposed several initiatives to implement the program; these initiatives included:

- A workshop with members of the community to provide an overall scope for the program and to identify disciplines that will need to participate.
- Develop and validate metrics for a series of social factors.
- Develop and test interventions which employ these metrics.

If the goals of this program are achieved, health would be improved for the many people for whom current therapeutic strategies are ineffective due to social factors. New therapies would be developed which factor in the social environment of individual patients, thereby enabling personalized medicine which considers personal social circumstances.

Appendix A: Summary of All Participants' Initial Broad Ideas

Appendix A presents a comprehensive list of the initial broad ideas that all participants of the *Forward Focus Workshops* in Chicago, Illinois; San Francisco, California; and Potomac, Maryland presented at the workshops by breakout group category.

CATEGORY 1: CELLULAR AND MOLECULAR BIOLOGY/FUNDAMENTAL BIOLOGICAL PRINCIPLES: Participants of the three strategic planning workshops who attended this breakout group proposed the following initial broad concepts for discussion at the meetings (in alphabetical order).

Accelerating or Reversing Cell "Age"—Develop tools to accelerate/reverse cell "age."

Animal Models of Human Disease—Develop clinically relevant animal models of disease.

Cell Decision Mechanism—Understand in-cell activity, including movement and modification, to understand the transition from a normal cell to the development of cancer. Determine a pathway and describe it in molecular detail.

Cellular and Molecular Responses to Co-Infection—Understand mechanisms that underlie cellular and molecular responses to co-infections that drive disease development and progression.

Comprehensive Human Disease State Models—Develop new modeling approaches and data storage methods to assimilate knowledge from the molecular, tissue, organ, intact individual, and cohort level into comprehensive disease state models to create spaces where researchers contribute knowledge that improves these models in measurable ways.

Comprehensively De-Orphaning Highly Druggable Classes of Targets—Provide functional information about orphan GPCRs, nuclear hormone receptors, ion channels, and kinases.

Cross-Training in Bioinformatics and in Cell and Molecular Biology—In light of the recognized and growing need to use bioinformatics and computer sciences to investigate traditional questions in cell and molecular biology, cross-train investigators and their students in the computational sciences.

Deploy the Common Fund for Short-Term Investments to Solve Pressing Needs in Biomedicine—One such strategic reposition could focus on the biology and targets of Alzheimer's Disease.

Disease-Associated Targeted Mutagenesis (DATM)—Address disease-associated targeted mutagenesis by improving available technologies and developing new resources and knowledge for the field.

Evidence-Based Disease Diagnosis—Develop the necessary methodology; collect and evaluate data on disease phenotype and its association with genotype; and identify the responsible mechanisms, susceptibility, and predictors of response to therapy to promote evidence-based disease diagnosis.

Evolution-Proof Therapies for Infectious Diseases—Develop therapies that are evolution-proof, can overcome adherence problems, and target highest risk infectious superspreaders. Develop evolvable and transmittable therapies that co-evolve with pathogens and transmit between individuals with new infections.

Experimental Model of Evolution in Medicine—Use evolutionary principles to test the effects of environmental manipulation on the rate and nature of natural selection and to understand the relationship between phenotypic diversity in a population and genetic assimilation within subpopulations.

Genes and Exposures in Chronic Diseases—Explore exposures in samples collected from longitudinal studies prior to chronic disease development to reveal critical insights that can be used for the design of individualized prevention strategies in people.

Fibrosis—Study fibrosis across organs and pathologies in an attempt to identify therapies.

From Genomes to Function—Investigate the mutational landscape, not for disease studies, but instead to determine how mutations ultimately affect phenotypes and to describe the range of possible mutations.

Functional Analyses of Microbes—The Human Microbiome Project will advance the field of microbiology exponentially. To follow up on this project, develop methods to analyze the genetic phenotypes of the microbes.

Human Systems Biology Consortium—Combine clinical facilities, technology assimilation, and a common informatics platform to assemble the spectrum of gene sequencing, gene expression, proteomics, metabolomics, complex molecular and systems imaging, and continuous virtual physiological monitoring.

Increase Basic Science Talent—Recruit and retain talent to basic science and motivate young students to enter science careers.

Inflammation and Chronic Disease—Investigate the underlying causes, molecular signaling pathways, and other opportunities for prevention and therapeutic intervention related to the wide number of molecular and cellular processes of inflammation.

Invest More in the Basic Sciences—Investigate how molecules form networks, how these processes form cells and tissues, and how organisms achieve and maintain robustness.

Long Non-Coding RNAs—Develop tools and investigate the mechanistic role and function of long non-coding RNAs in disease development.

Maintaining Homeostasis—Investigate methods to maintain homeostasis and solve why aging causes chronic disease. Create technologies that target maintenance in the face of chance.

Male and Female Biology, Beyond Reproduction—Perform studies in both males and females to promote fundamental biological advances on the contribution of hormones and genomic factors in biology, disease risk factors, and drug efficacy in both genders and the advance of medicine and treatments adapted to the specific biology and needs of each sex.

Microenvironment—Consider the microenvironment in "'omics," methods for development of drug screening, and comparisons between adult and embryonic microenvironments with implications for drug sensitivity and cellular movement.

Mouse Model Relevant to Human Disease—Identify irrelevant models, assess the key differences in mouse models and human disease pathogenesis, and reconstruct mouse genes and biological pathways to resemble humans.

Non-Coding RNA and Brain Function—Investigate non-coding RNA to understand its function in the healthy and diseased brain.

Pediatric Research—Include pediatric research in Common Fund projects.

Predictive Evolutionary Medicine—Use evolutionary knowledge to analyze and inform performance.

Predictive Preclinical Models of Human Disease for Predicting Pharmaceutical Efficacy—Develop transformative technologies which predict and lower clinical risk for drug candidates.

Programmable, Predictable Immunity—Develop novel therapies and extend new and broad patient groups through a multidisciplinary investigation of immune modulation.

Revise Structure of Research Support—Increase the number, length, and diversity of NIH-funded research and evaluation criteria for funding R01 grants.

Rodent Models of Human Neurological Disorders—Facilitate relevant bottom-up discovery and insight within the controlled environment of rodent models, while simultaneously providing mechanistic insight into the actual neurological human disorder being modeled.

Somatic Variation—Investigate somatic variation in the context of health, aging, and disease.

Systems Open Data Access & Analysis (SODAA)—Facilitate open access, analysis, and interpretation of large complex data by the creation of various tools and resources and harnessing the power of cloud computing.

Transcription Factor Codes to Produce Human Neuronal Subtypes—Study the fundamentals of human cellular and molecular neurobiology as well as capture key aspect of disease phenotype.

Unnatural Amino Acids—Investigate whether unnatural amino acids can support life.

Tissue Mechanotransduction—Describe the nature of mechanotransduction by tissues.

Vascularization and Innervation—Investigate vascularization and innervation and their interaction.

CATEGORY 2: SYSTEMS, TECHNOLOGY, AND INNOVATIVE APPROACHES— Participants of the three strategic planning workshops who attended this breakout group proposed the following initial broad concepts for discussion at the meetings (in alphabetical order).

Bioelectronics—To translate revolutionary developments in electronics and signal processing and nanofabrication to the biomedical field, create platform-type interfaces that enable two-way communication between biological and electronic systems for diagnostic, stimulation, and treatment.

Bioengineered Human Tissues and Organs to Replace Experimental Animals—Engineer tissue with vascularized scaffolds incorporating appropriate basement membrane, and stromal and parenchymal cells to represent specific organs. Mouse-sized (or smaller) organs seeded with human cells could be visualized and interrogated during the experiment, which would decrease the time needed to move to human testing.

Biomaterials—Develop biomaterials with architectures that mimic natural biomaterials (e.g. bone) to apply molecular self-assembly to build nature-inspired biomaterials.

Biomechanics and Mechanobiology—Develop a holistic approach for regeneration purposes and integrate powerful concepts from the traditional fields of cell biology to mechanics to materials science.

Biosystems Engineering—Address biosystems from an engineering control theory approach with innovation in instrumentation and analysis to work out the basic logic in the normal state to readily deduce or even predict disease states.

Bridge Basic/Translational Research—Since many discoveries for protein interactions *in vitro* cannot be confirmed *in vivo,* develop innovative high throughput technology to determine kinetics and dynamics of pathways and networks *in vitro* and *in vivo* in normal physiological and pathological conditions to bridge basic research and translation research.

Centers for the Study of Drug Attrition *in Vivo*—Develop a partnership between industry and academia through research, education, and outreach that focuses on the innovation and development of new technologies, including biomarker-based animal models.

Close the Gap in Knowledge about *E. coli*—Coordinate an effort to close the many known gaps in our knowledge of *E. coli* by determining functions for the ~20% of genes of unknown function and fill the knowledge gaps in the *E. coli* regulatory network. Determine the pathways that produce the many *E. coli* metabolites of unknown origin.

Coalesce Multiple Levels of Science—Investigate how to connect individual and personal genetic variation, including point mutations in rare disease, to systems and structural level mechanisms.

Computational Sciences and Biology—Generate approaches to advance computational sciences to organize computational representations that interest biologists.

Create Bridge from Molecular to Clinical Studies—Bridge the divide between biochemical/cellular potency and *in vivo* efficacy, including organ and cell localization, metabolism, and distribution.

Create "Center for Quality Management" for "'Omics" and Other Centers—Establish centers to coordinate and develop tools and reagents to evaluate performance of "'omics." Develop tools and reagents to test, disseminate, and evaluate results to set standards for quality management.

Create Model Integrating Biological, Chemical, and Physical Data to Explain Complex Diseases, Drug Therapy—Create model to integrate multiple types of information, including DNA, RNA, protein, protein modification, and location, which explains complex diseases and drug therapy.

Create Secure "Dropbox" for Genomics Data—With all ethical issues resolved, create a dropbox to share, store, backup, secure, and make safe genomics data.

Develop an Infrastructure to Treat Environmental Health Problems—Develop approaches to better forecast environmental health problems that can arise through cumulative effects, especially those that may increase in prevalence with global climate change, and develop an infrastructure to provide treatment delivery in circumstances of emergency.

Develop Technologies to Validate Potential Drug Targets at the Biochemical Level—Develop new technologies to enable rapid annotation of protein functions at the biochemical level and their validation as potential drug targets. These technologies would fill a large gap between genetic approaches and chemical probes.

Drug Design—Develop a new approach to the Pharma economic model which emphasizes discovery rather than design. Create a computer simulation of biochemical interactions that is large, fast, and chemically quantitatively accurate. Develop a new approach from other fields such as physics and improve efficiency.

Expanding the Capabilities of Structural Biology—Develop tools and methods to bridge the static snapshots of structural biology into a dynamic picture of the processes of mechanisms. Combine existing tools and develop the physical and biological tools to bridge gaps in these techniques. Visualize biology in action at the atomic level.

Export Surgical Technologies—Develop consortia and individual approach to promote knowledge networks to export surgical technologies to the world populations that do not have access to them.

Facilitate Interaction between Mechanobiology and Molecular Biology—Facilitate the interaction between mechano- and molecular biology across different fields to integrate mechanobiology with more traditional molecular studies.

Glycomics: Understanding the "Glyco Code" Will Lead to Improvements in Human Health—Develop tools to profile and quantitate sugars (and not just glycoproteins).

Graduate Education—Rethink graduate education in the biomedical sciences to prepare students for the full spectrum of careers that will benefit science and society.

Implementation Science—Create mechanisms to efficiently translate research into practice.

Incentivizing Sound Research Practices and Addressing the File Drawer Effect—Create the infrastructure to encourage researchers to publish null results and replications to test the robustness of findings, identify false positives, and evaluate practical implications.

Incorporating Quantitative Environmental and Behavioral Measures into Biomedical/Genetic Research: An Interdisciplinary Approach—Develop technology to promote healthy behavior to maintain and improve quality of life in large populations with a focus on health promotion rather than health monitoring.

Information Gathering from the Brain and Control of Brain Function—Since the brain interacts with all other bodily systems and is critical for most biological functions, develop tools to measure its activity on more than just the smallest scale. Also develop tools to sculpt activity with the necessary resolution.

Intelligence Augmentation: Leveraging Big Data into the Clinic—Develop systems to augment the ability of physicians and other healthcare providers to integrate and utilize available and emerging data.

Interdisciplinary Research Support—Develop new standing study sections that support and value interdisciplinary research between the physical and life sciences.

***In Vivo* Biosensors**—Since *in vivo* biosensors are non-functional in the body due to the biological reaction at the material tissue interface, develop standards to permit sharing and comparison of data among researchers to enhance understanding and control of material-tissue interfaces and allow sensors to exist and function in the body.

Knowledge Network—Enable "precision medicine" by building an information commons and knowledge network that facilitates integration of data and information extending from untargeted discovery to patient at the point of care.

Mechanobiology—Given the fragmentation of mechanobiology by disease, cell type, and model organism, coordinate efforts in the emerging field to make mechanobiology into a coherent whole.

Molecular Model Multiplexed Systems—Investigate common mechanisms across diseases and systems to develop molecularly guided therapeutics.

Multidisciplinary Projects—Encourage cross-institutional multidisciplinary projects with flexible deadlines for completion.

Novel Technology to Generate Fast, Efficient, and Multi-Gene (>3) Targeting and KOs—Develop techniques for fast and multi-gene (i.e., three genes or more) targeting in the mouse or any other genetically amenable experimental system.

Partnership Programs—Develop university-based partnership programs with pharmaceutical companies to facilitate the translation of discovery to therapeutics.

Petascale Connectomics through Machine and Crowd Intelligence—Advance computational science to map every connection between neurons in the volume of newly generated image data from brain tissue through advances in artificial intelligence and crowd sourcing large and heterogeneous populations of people.

Predicative Phenotyping (Multidisciplinary)—Create a multidisciplinary approach to predicative phenotyping through translation of laboratory discovery to elementary and secondary school teachers and scientists. Integrate biomaterials, bioengineering, and regenerative medicine to deliver real-time monitoring of tissue regeneration and individualized treatment.

Provide More Effective, Efficient Management of Science Resources by Training the Next Generation Biomedical Workforce—Develop training programs for the next generation of the biomedical workforce.

Remove Bottlenecks in Biomedical Data Analysis—Develop innovative hardware architectures and low-level software that specifically addresses bottlenecks in biomedical data analysis.

Role of Light Exposure in Development, Health, and Disease—Develop tools to generate comprehensive data on human light exposure.

SPARK Progressing Academic Research Breakthroughs to the Clinic with Industry Experts—Develop university-based partnerships with pharmaceutical companies to facilitate the translation of discovery to therapeutics.

Software Development for "Nanobio Hub"—Develop comprehensive software for complex modeling to incorporate feedback similar to the Nano Hub at Purdue and make them available broadly to expert and lay populations.

Solve Multidisciplinary Questions—Raise productivity in solving multidisciplinary questions given the increased engineering component of research through the development of a complete set of supporting mechanisms and tie academic tenure to team participation and outcomes through incentives.

Sourcing Structural Biology Data Using Femtosecond X-ray Diffraction—Since femtosecond X-ray pulses can potentially be a transformative source of structural biology data, develop new knowledge and tools to overcome barriers.

Speeding up Treatment Development—Convene stakeholders to translate academically-defined therapeutic targets through development to Phase I trials and speed treatment development by more than 10-fold.

Support New Investigators—Provide more vehicles and opportunities to support new investigators.

Synthesizing Knowledge—Investigate what does and does not work for translation in light of what is appropriate for different populations and settings. Support meta-analysis, evaluations of a topic, data synthesis, mechanisms for synthesizing knowledge, and evaluation.

Technology Development Grants—Fund technology development grants that are not tied to specific disease areas.

Translating Basic Decision-Making Research to Applied Settings—Investigate basic mechanisms of decision-making and the translation of such findings into realistic contexts.

Translational Research—Promote translational (interdisciplinary) research to bring an innovation to solution and then make it ready for the market.

Use Functional Image-Based Correlative Biomarkers for Disease Detection, Response to Therapy—Develop capacity for non-invasive image-based biomarkers based on standardized, quantitative imaging.

Visualize Interactions at the Cellular and Subcellular Level—Provide experimental tools to manipulate and model spatially resolved systems to visualize interactions on biological surfaces and signaling.

CATEGORY 3: HUMAN SUBJECTS AND POPULATION-BASED RESEARCH— Participants of the three strategic planning workshops who attended this breakout group proposed the following initial broad concepts for discussion at the meetings (in alphabetical order).

Affording Research that Crosses Boundaries—Investigating the optimal means and mechanisms to tackle diseases and problems requires more than the typical duration of grants. Investigate mechanisms that afford research to go over typical boundaries (e.g., duration, age, fields, and different institutes).

Brain/Mind/Gut Axis—Tie together biological brain function and cognitive psychological function and capability based on nutritional choices and other external factors.

Bedside to Bench to Bedside—Develop the means to culture primary biospecimens of lung cancer to generate biomarkers of aggressive disease for diagnosis to prognosis and define both novel targets to rational combination approaches.

Behavioral Vaccines—Employ a consortium of investigators across fields to develop information and communication technology to package behavioral "vaccines" that change the risk and disease trajectory for children and adolescents.

Build Systems to Integrate Data—With a focus on low-resource settings, investigate the means to integrate multiple "digital health" interventions data that exist in silos.

Centers of Excellence in Clinical Device Development—Create centers of excellence in clinical device development to speed translation through design, clinical trials, and approvals.

Cell-Based Human Proteome Project—Increase global research on mass spectrometry-based proteomics and redress the blurred approaches in the field that are neither isoform- nor gene-specific.

Characterization of Injury Responses—Given the inadequate understanding of disease initiation, progression, and organ specificity or commonality, establish a comparison of injury responses in time and between organs.

Coordinate Data Collection—Coordinate data collection across laboratories and disciplines.

Cross-Institute, Cross-Cultural Support Systems for Clinician Scientists—Create a structure for clinician scientists to systematically access and work with other clinician scientists and

transactional scientists to bring forward ideas, discussion, platforms, and integration with others to develop proposals that ultimately lead to best practices that integrate across disciplines.

Data Analysis for the Individual: Addressing the Long Tail of Biology—Develop tools that target specific, complex analysis needs, and create processes and methods to create these tools in a scalable way to address the challenge of Big Data in biology.

Engaging "Hidden" Populations and Communities—Engage populations that are outside the medical system because of systemic, cultural, logistical, financial, or personal barriers when gathering baseline data, conducting screening, prevention, treatment, and follow-up activities.

Every Patient is a Research Subject—Develop policies, processes, and systems to allow each patient to be a research subject. Develop a feedback loop that allows relevant new information to go back to the patient.

Generalized Approach towards Real-Time *in Vivo* Metabolite Biosensors—Develop new methods for real-time, *in situ* measurement of metabolites.

Human Developmental Windows of Susceptibility to Exposure—Characterize developmental windows of susceptibility to the environment and measure relevant human exposure at those time points and consequences over the life course using team science and by developing existing human studies to avoid waiting time and to serve as proof of concept.

Interdisciplinary Approach to Improving Care for Patients with Serious Illness—Coordinate an interdisciplinary approach to identify best changes in the processes of care for seriously ill patients both to reflect the perspectives of the patient and family and meet scientific evidence for efficacy and effectiveness.

Interdisciplinary Teams—Investigate the obstacles to creating interdisciplinary teams that truly reflect all aspects of a problem.

Million Molecule Exposome—Measure the internal exposome though expansion of the metabolome to the "million molecule exposome" through investigation of a million chemicals in serum and other media to discover causes of disease in banked samples from large cohorts.

Modern Tissue Banking—Conduct a translational study of human tissues (e.g., the central nervous system) using specimens preserved by appropriate methods for analysis to integrate data about human tissues with clinical data and family history.

National Cohort for Health, Genomics, and Environment—Develop a well-phenotyped study population and methods to measure their environment.

Optimizing Existing Data through Incentivized Collaboration—Offer financial incentives for funded studies to contribute data to a common data set with pre-determined variables, and offer a separate incentive for funded studies to conduct analysis using this common data set.

Oral Fluids—Evaluate the potential of saliva as a diagnostic tool for systemic health and the potential of oral health professionals as gatekeepers for early detection of problems.

Personalized Genome Medicine—Translate theory into practice to optimize outcomes and minimize toxicity. Use genome sequencing to predict disease susceptibility with a prevention and screening plan to maximize health.

Pilot Studies for Clinical Trials—Since funding for pilot studies for clinical trials is uneven across Institutes (i.e., not all Institutes support the parent R21 mechanism), the Common Fund might support investigator-initiated research not linked to any specific disease or condition.

Post-Translational Modifications of Proteins—Focus on post-translational modification of proteins as a potential path to identify the basis of cellular defects and selective cell loss in diseases.

Prospective Study of Developmental Processes and Risk in Special Populations—Coordinate prospective study of developmental processes and risk in special populations to gain insight into etiopathology of disease in the larger and typically developing population.

Pseudo-Pragmatic Randomized Clinical Trial—Take advantage of existing data collected as a part of clinical practice to assess prospective effectiveness using retrospective data.

Reference Control Sample—Create an experimentally friendly control sample of more than 100,000 human subjects with phenotypic characterization to be decided by NIH, and multiple tissues with multiple times of collection.

Science of Science—Create a new funding mechanism for research on research that uses evidence-based policies and processes, including peer review, predictors of investigator success, and predictors of program success.

Stop Wasting Data—Coordinate national and perhaps international data integration/aggregation of genotype, phenotype, diagnosis, and treatment outcome to promote better diagnoses, prognoses (accuracy and outcome) and personalized medicine.

Standardize IRB Processes—Standardize the Institutional Review Board (IRB) process.

Understanding the Association of Vitamin D Deficiency with Various Pathologies—Promote basic research to elucidate the mechanisms by which vitamin D deficiency causes cardiovascular disease, diabetes, and metabolic syndrome.

Using Observational Data to Understand Multi-Component Interventions—Develop methods for input assessment at the population level for multi-component interventions using observational data to understand the impact of interventions using observational data.

CATEGORY 4: SOCIAL AND BEHAVIORAL DETERMINANTS OF HEALTH AND DISEASE— Participants in workshops discussed the social and cultural determinants of health and disease. The following ideas were proposed by participants in the Chicago, San Francisco, or Potomac workshop.

Addressing the Elephant in the Room: Identifying and Overcoming Health Literacy-Related Barriers to Informed Health Decision-Making—Identify medical, scientific, and/or mathematical concepts which represent barriers to understanding and impede informed health decision making.

Health and the American City—Investigate the social determinants of health in U.S. cities to understand multiple levels of factors that increase or protect against health risk and investigate the impact of structural, place-based interventions.

Intergenerational Studies—Conduct intergenerational and community studies following disciplinary traditions that divide geriatrics, adults, adolescents, and children.

Stress and Health: Understanding the Role and Implications of Biological, Social, Cultural, and Behavioral Factors—Coordinate cross-disciplinary research focused on the complex effects of stress on health within individuals.

Technology to Realign Health Care Delivery—Restructure health care delivery through the use of technology, human factors, psychological tools, and space engineering to align with known factors associated with positive health outcomes.

Understand the Social Determinants of Health—Establish the extent to which and the mechanisms by which social determinants influence the health of individuals, and develop interventions to mitigate adverse effects and potentiate beneficial effects.

Understanding and Treating Established Social Risk Factors—Develop biobehavioral models of how social factors influence mental, and physical health and interventions to modify how social factors impact health.

Appendix B: Participant List for Chicago, Illinois

Chicago, May 1, 2012

Community Participants

Marc Atkins	University of Illinois at Chicago
Jeffrey Aubé	University of Kansas
Daniel Barker	University of Southern California
Michael L. Biehl	University of Illinois College of Veterinary Medicine
E-Shien Chang	Rush Institute for Healthy Aging
Seth Corey	Northwestern University
Robert Cormier	TheraMind Research
Silvia Curado	New York University - School of Medicine
Constance Dallas	University of Illinois at Chicago
Karen R. Dobkins	University of California at San Diego
Samuel C. Dudley	University of Illinois at Chicago
Dorothy D. Dunlop	Institute Healthcare Studies
Brian G. Fox	University of Wisconsin
Xiaowu Gai	Loyola University Chicago Stritch School of Medicine
Pablo V. Gejman	
Chad Haney	University of Chicago
William Hendrickson	University of Illinois at Chicago
Philip Hockberger	Northwestern University
Margaret Browne Huntt	University of Illinois (Urbana-Champaign)
Kristen C. Jacobson	University of Chicago
Victor Jongeneel	University of Illinois
Niranjan Karnik	University of Chicago

Leslie Kay	University of Chicago
Neil Kelleher	Northwestern University
Jeffrey Kidd	University of Michigan
Jhumku Kohtz	Children's Memorial Research Center, Chicago
Sooky Koh	Children's Memorial Hospital, Northwestern University Feinberg School of Medicine
Shohei Koide	University of Chicago
Elizabeth Kovacs	Loyola University Chicago
Eaton Lattman	Hauptman-Woodward Institute
Joshua N. Leonard	Northwestern University
Irena Levitan	University of Illinois at Chicago
Lei Li	Indiana University-Purdue University Indianapolis (IUPUI)
Rick Lieber	University of California
Yan Liu	Indiana University School of Medicine
Kent Lloyd	University of California Davis
Craig E. Lunte	University of Kansas
David Meltzer	University of Chicago
William A. Muller	Northwestern University Feinberg School of Medicine
Harikrishna Nakshatri	Indiana University School of Medicine
Dan Nicholson	Neurological Sciences
P. Hande Ozdinler	Northwestern University
Umadevi Sajjan	University of Michigan
Edward Snell	Hauptman-Woodward Medical Research Institute
Julian Solway	University of Chicago
Benjamin W. Van Voorhees	University of Illinois at Chicago
Richard B. Warnecke	University of Illinois at Chicago
Bryan A. White	University of Illinois
Fruma Yehiely	Northwestern University

NIH Participants

James Anderson
Director, Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
NIH

Christine Colvis
Director of Program Integration, National Institute on Drug Abuse (NIDA)
NIH

Greg Germino
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NIH

Brenda Weis
Policy and Communications Leader, Office of Strategic Coordination
DPCPSI/NIH

Elizabeth Wilder
Director, Office of Strategic
Coordination
DPCPSI/NIH

Appendix C: Participant List for San Francisco, California

San Francisco, May 3, 2012

Community Participants

Adrian Aguilera	University of California at Berkeley
David Ardell	University of California at Merced
Raj K. Batra	University of California at Los Angeles/West LA VA
Elliott Beaton	University of California Davis MIND Institute
Lee Bruno	E-Cubed Ventures, LLC
Atul Butte	Stanford University
Susan Carter	University of California at Merced
Songcang Chen	University of California at San Francisco/Diabetes Center
Sukyung Chung	PAMFRI
Misha Ruth Cohen	Quan Yin Healing Arts Center
Barbara Cohn	Public Health Institute
Joel Dedrick	
Kathryn DeRiemer	University of California at Davis
Vidusha Devasthali	University of Oregon
Catherine DeVries	University of Utah
Paul Dodd	University of California at Davis
Daniel Dohan	University of California at San Francisco
Mi-Suk Kang Dufour	UCSF Center for AIDS Prevention Studies
Alex Dunn	Stanford University
Eric Engelhard	University of California at Davis
Loren Frank	University of California at San Francisco
James Fraser	University of California at San Francisco

Peter Hallinan	Blindsight
Michael Helms	Stanford University School of Medicine
Steven W. Hetts	University of California at San Francisco
Susanne Hildebrand-Zanki	University of California at San Francisco
Sunita P. Ho	University of California at San Francisco
Fumiko Hoeft	University of California at San Francisco
Michael Hout	University of California at Berkeley
Tzung Hsiai	University of Southern California
Tri Huynh	University of California at San Francisco School of Dentistry
S. Claiborne Johnston	University of California at San Francisco
Peter Karp	SRI International
Joanna Kelley	Stanford University
David Kleinfeld	University of California at Davis
Bruce Koch	Stanford University School of Medicine
Robert Krencik	University of California at San Francisco
Sanjay Kumar	University of California at Berkeley
Sudhir Kumar	Biodesign Institute, Arizona State University
Jiayu Liao	University of California at Riverside
Daniel Lim	University of California at San Francisco
Gordon J. Lithgow	The Buck Institute
Mignon Loh	University of California at San Francisco
Chuanbin Mao	University of Oklahoma
Jian-Hua Mao	Lawrence Berkeley National Laboratory
Gary W. Mathern	University of California at Los Angeles, Department of Neurosurgery
William Mobley	University of California at San Diego
Nancy Moore	Health Solutions, Arizona State University
Mirka Negroni	Center for Research and Education on Gender and Sexuality
Martina Newell-McGloughlin	University of California at Davis
Lauren Nicholas	University of Michigan
Aleksandr Noy	LLNL and University of California at Merced
Theresa O'Brien	University of California at San Francisco

Jose Otero	University of California at San Francisco
Natalie Rasgon	Stanford University School of Medicine
Elise Riley	University of California at San Francisco
Nicholas K. Sauter	Lawrence Berkeley National Laboratory
Richi Singhal	University of Southern California
Pandurangan Vijayanand	La Jolla Institute for Allergy and Immunology
Leor Weinberger	University of California at San Francisco
Natalie Wisniewski	Medical Device Consultancy
Keith Yamamoto	University of California at San Francisco
Yunzhi Peter Yang	Stanford University
Paul Yu	University of California at San Diego

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Brenda Weis
Policy and Communications Leader, Office of Strategic Coordination
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Elizabeth Wilder
Director, Office of Strategic
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Appendix D: Invited Participants and NIH Participants for Potomac, Maryland

Invited Participants:

Robert Califf	Duke University
J. David Creswell	Carnegie Mellon University
J. Randall Curtis	Harborview Medical Center/University of Washington
Catherine Dulac	Harvard University
Ronald Evens	Washington University School of Medicine
Andrew Feinberg	Johns Hopkins University
Linda Griffith	MIT
John Groopman	Johns Hopkins School of Public Health
Ed Harlow	Harvard University
Adron Harris	University of Texas, Austin
Simon Kasif	Boston University
Brian Kotzin	Amgen
Daniel Kraft	Singularity University
Naa Oyo Kwate	Rutgers University
Richard Lang	University of Cincinnati
Corinna Loeckenhoff	Cornell University
Miriah Meyer	University of Utah
Daria Mochly-Rosen	Stanford University
Richard Morimoto	Northwestern University
Sheila Murphy	USC Annenberg

Kristala Jones Prather	MIT
John Reed	Sanford-Burnham Medical Research Institute
Sebastian Seung	MIT
Shannon Wiltsey Stirman	Womens Health Sciences Division, VA National Center for PTSD and Department of Psychiatry, Boston University
Clifford Woolf	Harvard Medical School
NIH Participants	
James Anderson	Director, DPCPSI
Jim Battey	Director, NIDCD
David Balshaw	NIEHS
Ravi Basavappa	OD
Lisa Begg	ORWH
Ann Cashion	NINR
Janine Clayton	Director, ORWH
Francis Collins	NIH Director
Cindy Davis	ODP/ODS
Richard Fisher	NEI
Isabel Garcia	NIDCR
Patricia Grady	Director, NINR
Judith Greenberg	NIGMS
Story Landis	Director, NINDS
Jane Lockmuller	NIAID
Karin Lohman	NCCAM
Yvonne Maddox	NICHD
Susan Maier	ORWH
Joan McGowan	NIAMS

Pamela McInnes	NIDCR
Aubrey Miller	NIEHS
Deb Olster	OBSSR
Mike Rogers	NIGMS
Jeff Schloss	NHGRI
Belinda Seto	NIBIB
Susan Shurin	Director, NHLBI
David Shurtleff	NIDA
Chris Siemon	NCI
Dinah Singer	NCI
Phil Smith	NIDDK
Michael Steinmetz	NEI
Lawrence Tabak	NIH Principal Deputy Director
Kenneth Warren	Director, NIAAA
Linda Weglicki	NINR
Sam Zakhari	NIAAA

NIH Office of Strategic Coordination (OSC) Participants	
Eddie Byrnes	OSC
Stephanie Courchesne-Schlink	OSC
Leslie Derr	OSC
Tanya Hoodbhoy	OSC
Scott Jackson	OSC
Trish Labosky	OSC
Tiffani Bailey Lash	OSC
Michael Morse	OSC
Ellie Murcia	OSC

Emmanuel Peprah	OSC
Mary Perry	OSC
Rebecca Roth	OSC guest
Brenda Weis	OSC
Elizabeth Wilder	Director, OSC
Caira Woods	OSC guest