

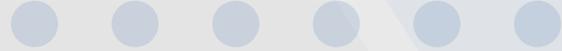
Common Fund Concept Clearance FY 2015 Programs

Council of Councils Meeting
May 14, 2013



Process for FY15 CF programs

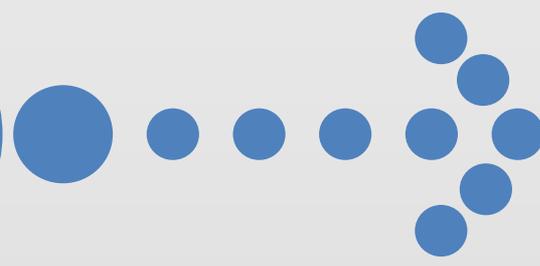
Strategic Planning Meeting



IC Director Ideas



Ideas
filtered
by CoC
Pre-vote



CoC
Meeting:
Discuss
and Vote

Criteria for Common Fund Programs

- **Transformative:** Must have high potential to dramatically affect biomedical and/or behavioral research over the next decade
- **Catalytic:** Must achieve a defined set of high impact goals within 5-10 years
- **Synergistic:** Outcomes must synergistically promote and advance individual missions of NIH Institutes and Centers to benefit health
- **Cross-cutting:** Program areas must cut across missions of multiple NIH Institutes and Centers, be relevant to multiple diseases or conditions, and be sufficiently complex to require a coordinated, trans-NIH approach
- **Unique:** Must be something no other entity is likely or able to do

Concept Review

For each concept, please consider the following:

- Does this concept meet the criteria for a Common Fund program?
- If not, could the concept be expanded or re-focused to produce a Common Fund'able program? How?
- What is the most Common Fund'able component of the concept? Where could strategic Common Fund investment have the biggest impact?

Voting

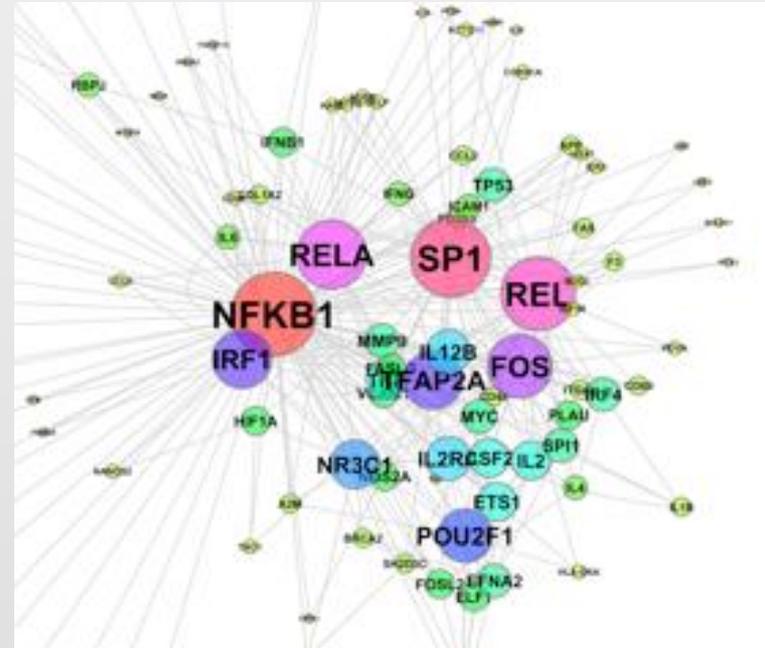
The Council will vote either “Yes” or “No” on each concept

- Those concepts that are cleared will be considered further by Drs. Anderson and Collins, with potential further development by a trans-NIH group of staff and OSC (Phase 2 planning).
 - Workshops, RFIs, or other outreach to the community
 - Portfolio Analyses
 - Development of strategies to achieve specific goals
- Those concepts that are not cleared will receive no further organized development by OSC. IC staff who are interested in the topic may, or may not, continue to flesh out the concept and suggest it for re-consideration next year.

Gene Regulatory Networks: A Foundation for Therapeutic Discovery

Challenge/Opportunity: Computational models of gene regulatory networks (GRNs) could provide a predictive understanding of the genetic control of all cellular functions in normal and abnormal conditions. Advances in genomic sequencing, analysis of gene regulatory elements, quantification of gene expression, bioinformatics, and computational modeling make it now feasible to chart the GRNs of complex vertebrate organisms.

Goals: To attain Boolean-level global GRN models for the regulation of embryonic development of four key vertebrate developmental model systems (zebrafish, *Xenopus*, chick, and mouse).



*A GRN in cancer;
Auckland Bioengineering Institute*

Gene Regulatory Networks: A Foundation for Therapeutic Discovery

Initiatives:

- U19 cooperative agreements to assemble coalitions of investigators to produce GRN models
- Establishment of shared data repository/computational modeling coalition
- Each coalition will provide access to facilities, data, and expertise to independent collaborators whose work would contribute to the models

Potential impact:

- Provide in-depth understanding of endogenous genetic control mechanisms regulating biological processes
- Facilitate identification of targets for therapeutic interventions
- Provide framework for understanding the implications of genetic variants in human disease
- Identify sensitive and specific markers of disease and clinical progress

Sustained Release Pharmacologic Formulations to Prevent and/or Treat Chronic Diseases



Challenge/Opportunity: The development of effective sustained release (SR) pharmacologic formulations has the potential to revolutionize the care for a wide variety of chronic diseases. However, there are several challenges to development of SR formulations, including physical/mechanical properties that might prohibit use of certain formulation technologies, bioavailability/tissue penetration characteristics, unknown consumer preferences, the need to re-conduct basic PK/PD studies, patent/IP issues, and others.

Goals: To stimulate the coordinated development and clinical evaluation of SR formulations of pharmacologic agents to prevent and/or treat a variety of chronic diseases (e.g., HIV, TB, diabetes, seizure disorders, mental illness)

Sustained Release Pharmacologic Formulations to Prevent and/or Treat Chronic Diseases

Initiatives:

- Identification of behavioral factors that affect patient adherence
- Identification of attributes of SR formulations that might contribute to acceptability by patients
- Milestone driven preclinical/clinical evaluation of products
- Development of new formulations technologies/platforms that can be applied to a variety of different medications
- Development of new SR formulations utilizing currently available treatments and/or new drug compounds
- Identification/development of novel drug compounds more amenable to SR formulations

Potential impact:

- SR formulations that drastically improve patient adherence might substantially improve the outcomes of many chronic diseases, especially for vulnerable patient populations
- Improved treatment outcomes will result in better health, lessening the impact of the disease on both the individual and the health care system

Cachexia- defining measures, triggers, and metabolic reprogramming to develop early interventions

Cachexia (“wasting syndrome”): *condition characterized by loss of muscle with or without loss of fat mass, usually diagnosed by unintentional weight loss.*

Challenge/Opportunity: The lack of mechanistic understanding of cachexia and associated metabolic reprogramming has thwarted efforts for evidence-based approaches to develop interventions. However, the prospect of a major advance in treating this condition appears real with increased understanding of biological processes such as protein degradation, lipolysis, nutrient metabolism, inflammation, insulin resistance, and appetite/energy balance dysregulation.

Goals: To provide in-depth understanding of cachexia mechanisms, origin, and progression in different diseases, with the ultimate goal of informing the development of effective treatments.

Cachexia- defining measures, triggers, and metabolic reprogramming to develop early interventions

Initiatives:

- Observational studies on the physiologic and molecular course of cachexia
- Basic research on the underlying causes and mechanisms of cachexia
- Collaborative programs between basic and clinical scientists to translate pre-clinical findings into a clinical setting
- Development of model systems to study cachexia
- Application of 'omic technologies to identify altered transcriptional/metabolic programs, biomarkers, and susceptible populations
- Development of functional and physical measures of cachexia

Potential Impact:

- Definitive diagnostic and outcome measures of cachexia could be developed
- Basic research support could identify altered pathways and provide targets for therapeutic development
- Collaborations between basic research and clinicians could translate these findings into clinical practice through early diagnosis and combination therapy

Affordable Technologies for Global Health through Existing Biomedical Networks



Challenge/Opportunity: Diagnostic and therapeutic technologies are critical for quality health care. Yet, there remains a wide disparity between those who have access to modern medical technologies and those who do not.

Goals:

- Stimulate development of new low cost devices for evaluation, diagnosis, and treatment
- Develop and implement technologies that can be easily transported, maintained, and operated
- Encourage formation consortia to develop or adopt affordable technologies, and ensure the placement of these technologies to benefit low resource settings
- Encourage collaboration between developers of new technologies and health practitioners in low resource areas to test, use, and evaluate the benefit of new technologies
- Develop reduced cost technological innovations which can be transferred back to the US in order to minimize healthcare costs

Affordable Technologies for Global Health through Existing Biomedical Networks

Initiatives:

- Cooperative Consortia focused on low cost technologies to address specific health problems
- Technology Coordination Center to centralize technology development and disseminate results
- Ethical, Legal, Cultural, and Social Implications (ELCS) studies
- Data Repository to facilitate data sharing

Potential Impact:

- Development of sustainable collaborations to provide needed technologies and maintenance of health in underserved populations
- Improvement in health care access and quality of care in underserved populations; reduction in health disparities
- Application of technologies developed and lessons learned could benefit patients and health practitioners in the U.S.



Human Cell Identity and Lineage (HCIL) Project



*Genetic Engineering &
Biotechnology News*

Opportunity/Challenge: Our knowledge of human cellular space is not keeping pace with our growing knowledge in other key areas of biology. Although there is agreement on the major human cell types, rigorous definitions, standards, and key assay parameters are still lacking to ascertain the identity and lineage of a cell

Goals:

- Provide a set of verifiable definitions of a human cell type (parameters can be morphological, biochemical, cell biological, and functional); and, in association, a reference samples/stock (primary cells)
- Provide a map of the developmental relationships among the major human cell types (i.e. a cell lineage and fate map)

Human Cell Identity and Lineage (HCIL) Project

Initiatives:

- Defining human cellular space, including cell types and their distribution (tissue composition)
- Developing definitions of each cell type
- Mapping the developmental origin of major cell types
- Developing new technologies for imaging, lineage tracing, function assessment, rapid isolation and identification, quick assessment of cellular function and health
- Establishing human cell standards, reference resources, and repositories
- Developing widely accessible databases, informatics tools, and user interfaces
- Conducting ethical studies on the use of human cellular information

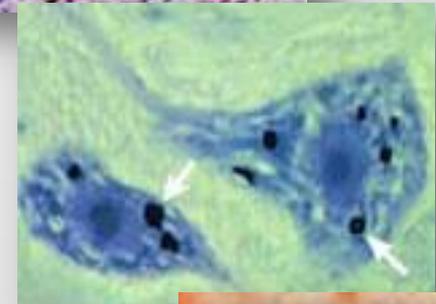
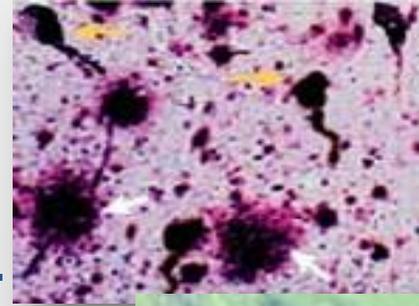
Potential Impact:

- Having an understanding of the infrastructure of human cells and lineage maps could benefit the entire disease fighting enterprise, from bench to bedside
- Important for NIH priorities, such as research on rare diseases, exploration of stem cells, and cell engineering/therapy

Proteostasis (Protein Homeostasis) Project

Challenge/Opportunity: Disruption of protein homeostasis is implicated in many diseases, including **neurodegenerative diseases, diabetes, cancer, cardiomyopathy, metabolic deficiencies, and more.** There has been substantial effort to understand many of the individual components of proteostasis; however, the underlying disease etiology of unbalanced proteostasis remains poorly understood.

Goals: To systematically survey proteostasis function in health and multiple classes of disease to establish how protein imbalance contributes to disease, and provide a foundation for development of novel therapeutics to rebalance proteostasis and restore health.



*Nature Reviews
Neuroscience, 2003*

Proteostasis (Protein Homeostasis) Project

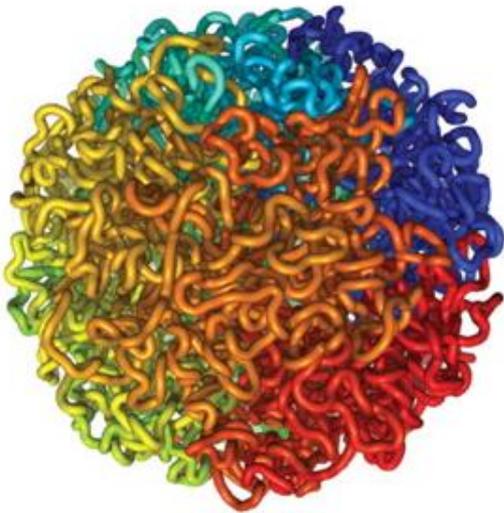
Initiatives:

- Systematic assessment of proteostasis in normal development, aging, and disease
- Development of new technologies to survey proteome changes
- Development of a central bioinformatics resource to integrate information on proteome health
- Address how non cell autonomous stress may induce disease by interrogating connections of neuronal, neurohormonal and cellular stress pathways
- Address how environmentally induced changes in protein conformation cause heritable disease through protein based epigenetics (prions and prion-like proteins)
- Perform high throughput screens to identify novel proteostasis modulators
- Initiation of clinical trials with proteostasis modulators

Potential Impact:

- Gain critical insights about the role of proteostasis network in human health and disease
- Provide plausible treatment options for a diverse array of chronic disorders that currently lack adequate therapy

3D Nucleome



Science, 2009

Challenge/Opportunity: Over the past decade, it has been established that the genome is arranged non-randomly within the nucleus. A central question that remains to be answered is investigate how changes to the genome and epigenome affect the 3D architecture of the nucleus (the 3D Nucleome), and thereby affect the tightly controlled transcriptional equilibrium.

Goals:

- Generate comprehensive 3D maps of the interphase nucleus of cells
- Explore how the cellular transcriptome is affected by changes to the 3D structure of the nucleus
- Explore the functional role of epigenetic modification and chromatin remodeling in nuclear architecture
- Uncover mechanisms governing lineage specific 3D nuclear conformations and their perturbation in disease states
- Develop bioinformatics tools and a reference database

3D Nucleome

Initiatives:

- Form consortia to address both methodological and conceptual aspects of 3D nucleome
- Promote international effort to generate a 3D complementation of the linear landscape of the genome
- Novel experimental, analytical, and bioinformatics tools, as well as a publically accessible reference database will be developed
- Scientific meetings to present findings

Potential impact:

- Launch post-sequence era of genomics and biology, with the goal of integrating structure/function relationships
- Provide framework required for the ultimate understanding of the complexity of multicellular organisms, including human
- Elucidate mechanisms on how changes induced by alterations to the genome/epigenome govern fundamental biological processes
- Determine how disturbances of physiological equilibrium result in pathological disease states, required for identification of potential therapeutic interventions