National Cancer Institute

The Cancer Systems Biology Consortium (CSBC)

A new RFA/PAR concept to support Cancer Systems Biology

BSA Presentation
March 11, 2015

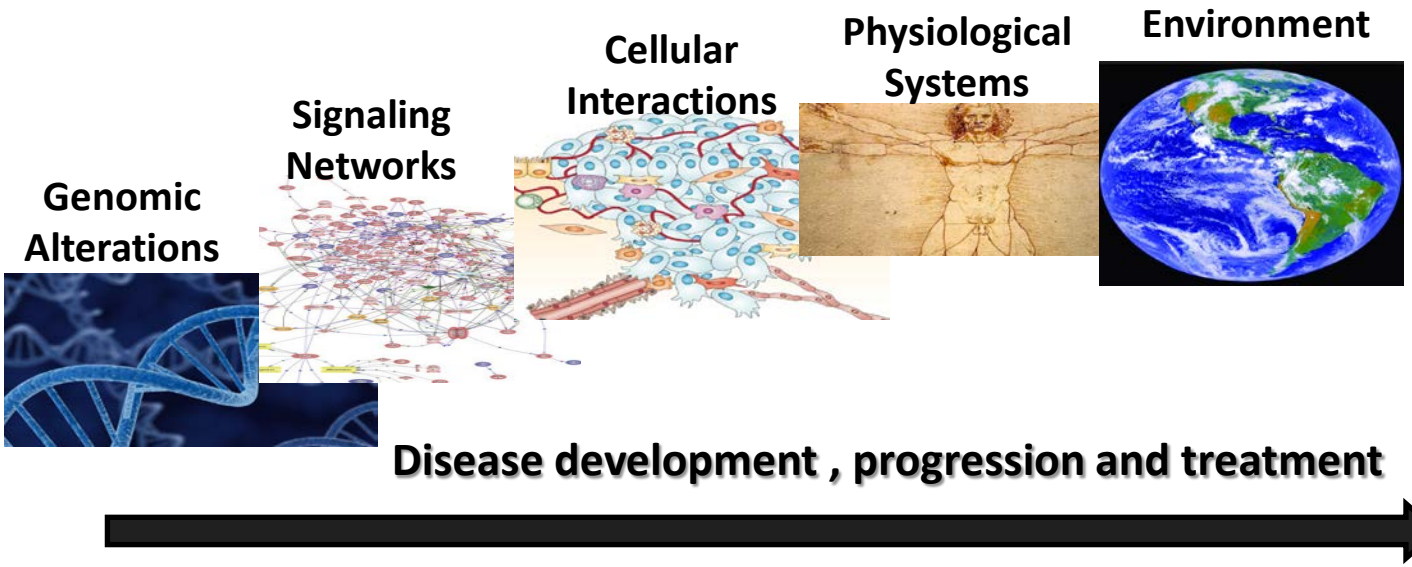
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

The Cancer Systems Biology Consortium (CSBC) Initiative

Goals:

- Continued development of predictive computational models that integrate across multiple molecular, cellular, organ and temporal scales
- Building a community of researchers focused on applying systems approaches to problems in cancer biology



Recent Advances of Cancer Systems Biology

- Uncovering new regulatory networks
  - Newly discovered transcription process involving competitive endogenous RNA or ceRNA. Models to predict these interactions in cancer.
- Integration of multiple data sets
  - Use of a multiscale statistical mechanical framework to integrate biophysical and genomic data from SH2 domain-phosphoproteins to predict the functional effects of mutations in cancer.
- Large scale functional genomics
  - Use of large scale functional studies and computational models to predict genetic changes essential in cancer.
- Predictive intervention
  - Determination of how sequential therapeutic application of anticancer drugs can enhance cell death by purposely “rewiring” molecular networks within TN breast cancer cells.
  - Application of evolution algorithms to identify early events in glioblastoma that represent fundamental driver lesions.

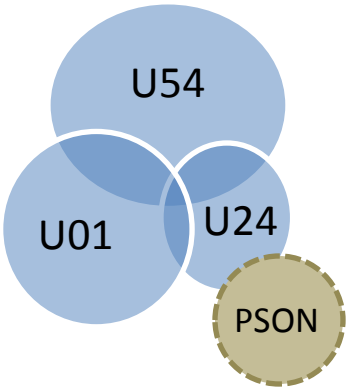
Examples of Questions Approachable by Systems Analyses

- What are the critical players and processes in tumor heterogeneity and can they be modeled?
- Can inter-cellular and stromal interactions and their functional consequences within the tumor microenvironment be modeled and predicted?
- Can various states of cancer (pre-malignancy, metastasis, and dormancy) be modeled and progression predicted?
- Can the effects of specific environmental factors on tumor initiation and progression be modeled and predicted?
- Can epigenetic interactions be identified and their phenotypes predicted?
- Can "–omic" features and regulatory networks of cancer cells be modeled to predict cancer behavior and therapeutic responses?

Scientific Goals of CSBC

- Develop predictive mathematical models that generate or test new biological hypotheses in cancer biology
  - Scope includes all cancer phenotypes and dynamics
  - Emphasize the use of multi-dimensional information to address complex cancer biology questions
  - Validation of models through experimental biology
- Develop a consortium of multi-disciplined investigators and resources to promote collaborations across and outside of the CSBC
- Support training and outreach program to ensure the dissemination of approaches and to ensure the next generation of systems biologists.

Cancer Systems Biology Consortium Proposed Organization



- Research Centers (U54)
  - A centers program supporting research and providing infrastructure in cancer systems biology including training, outreach activities, and research resources for the community
- Specialized Research Grants (U01)
  - Focused on specific problems in basic and clinical cancer research without incorporating the entire infrastructure required of a full center
- Coordinating Center (U24)
  - This center will be responsible for coordinating, administering, and enhancing interactions across the Consortium, along with the related programs.

Current Portfolio Analysis

- Integrative Cancer Biology Program (ICBP) U01 – 12 active grants
- Currently only 14 NCI R01 grants identified as “systems biology/modeling” research

NCI Programs with a Systems Biology Component

Program	DOC	Purpose
ICBP (CSBC) U01s only	DCB	Facilitate the development of a research community in cancer systems biology focused on predictive computational modeling of cellular networks, intercellular interactions, multiscale modeling across molecular, cellular, organ and temporal scales.
PS-ON	DCB	Facilitate the formation of interdisciplinary research teams focused on understanding of cancer biology from a physical sciences-based approach.
CTD2	OCG	Support research projects focused on identification, characterization, and early development of novel targets for cancer treatment and probes affecting those targets. Perform comprehensive molecular characterizations on various cancers to develop therapeutics and response prediction.

Proposed Mechanisms and Budget

- Research Centers (U54)
  - RFA with 3 receipt dates, spread over 1.5yrs
  - 8-10 Centers at $1.5M (dc)
  - Requested set-asides: $12M in FY16, $6M in FY17
  - Total cost over 6 years: $72M
- Specialized Research Grants (U01)
  - PAR with 2 receipt dates each year for 3 years
  - No set-aside
  - DEA review
- Coordinating Center (U24)
  - RFA with 1 receipt date
  - Set-aside $750K (dc) in FY16

RFA Evaluation Criteria

The consortium will be evaluated in response to the following broad questions:

1. Has the CSBC supported the development and broad application of systems biology and computational modeling in cancer research?
2. Did the program address and advance solutions to complex questions in the cancer research continuum?
3. Did the program expand this field of research through education, training and outreach center and consortium activities?

In addition to these broad goals, the CSBC will also be evaluated as to the extent to which the program functioned as a consortium bringing groups and projects together productively.

Questions?

External ICBP Program Review (2009-2014)

- Chair - Dr. Susan K. Gregurick
  Director, Division of Biomedical Technology, Bioinformatics, and Computational Biology
  NIGMS
  - Dr. Grace Peng - Division Of Discovery Science & Technology, NIBIB
  - Dr. Jamie Zwiebel - Chief, Investigational Drug Branch, NCI
  - Dr. Rocky Feuer - Chief, Statistical Methodology and Applications Branch, NCI
  - Dr. Daniel Janes - Division of Genetics and Developmental Biology, NIGMS
  - Dr. Ken Pienta - Professor of Oncology, Johns Hopkins University

Review Executive Summary

- “contributed significantly to growth and credibility of the systems biology field and there has been extensive interaction among investigators within each of the ICBP centers.”
- “innovative in formulating the scientific questions to be addressed using a framework that best fit their own creative view of how to attack the problem.”
- “U54 mechanisms … provided the proper structure and design to help achieve the three ICBP research objectives”
- “The training and educational components of the ICBP program resulted in new degree programs offered in Cancer Systems Biology and the development of training curriculum across different Centers. This was another strength of this program and resulted in developing the field in cancer systems biology”

Program Review - Recommendations

- Future funding opportunities should develop consortium activities and encourage comparative modeling exercises across the centers. For example, linking of models where one model's output logically becomes another model's input, and encourage sharing of experimental data used to inform model calibration and validation.

- The ICBP program should explore research beyond molecular to cellular understanding of cancer dynamics and treatments to include opportunities for whole organism modeling. The systems biology field in general is moving towards understanding the linkage between genetic, molecular and larger scale processes within model organisms that include modeling genetic variations and physiological responses to environments and understanding drug therapy response within an organism, including tissue and organ response.

- Future activities should place a greater emphasis on representing more of the different types of cancers and disease areas within the ICBP program.

Related NCI Programs

Program	DOC	Purpose
Clinical Proteomic Technologies	CSSI	To discover and verify protein biomarkers for cancer that can be qualified in clinical studies.
Cancer Nanotech Alliance	CSSI	Apply nanotechnology to cancer, by developing reagent, tools, and supporting infrastructure
CISNET	DCCPS	To generate sophisticated, evidence-based decision tools that could inform international/national/regional/local decisions on the most efficient utilization of existing and emerging technologies and strategies for the control of cancer.
EDRN	DCP	To discover, develop, and validate biomarkers for risk assessment, detection, and molecular diagnosis and prognosis of early cancer
Informatics Technology (ITCR)	All DOCs	To support innovative investigator-initiated research-driven informatics technology development to improve the acquisition, management, analysis, and dissemination of data and knowledge in the investigation and management of cancer.
NCI Cancer Genomics Cloud Pilots	CBIIT	To create one or more public "cancer knowledge clouds" in which data repositories would be co-located with advanced computing resources, thereby enabling researchers to bring their analytical tools and methods to the data

NCI FOAs with a Systems Biology Component

Program	DOC	Purpose
ICBP Collaborative Research	DCB	To encourage new research into integrative cancer biology by fostering collaborations between investigators currently supported through the Integrative Cancer Biology Program (ICBP) and those currently unaffiliated with the ICBP.
Bridging the Gap	DCB/ DCCPS	To encourage applications for projects that bridge biological mechanism to population level scales.
NIH Multiscale Modeling	DCB	Supports the development of non-standard modeling methods and experimental approaches to facilitate multiscale modeling, and active participation in community-driven activities through the Multiscale Modeling (MSM) Consortium