NIH IRP Long Term Planning

Bob Wiltrout, Director, SD for Basic Science, CCR

Stephen Chanock, Director, SD for Epidemiology and Genetics, DCEG

Lee Helman, SD for Clinical Research, CCR

NCAB September 2014

Outline

- Long term planning charge
- Reflection of the current NCI IRP
  - CCR
  - DCEG
  - Clinical Program (NCI and NIH)
- Proposals for trans-NIH initiatives
- Factors influencing future success

NIH IRP Long Term Planning

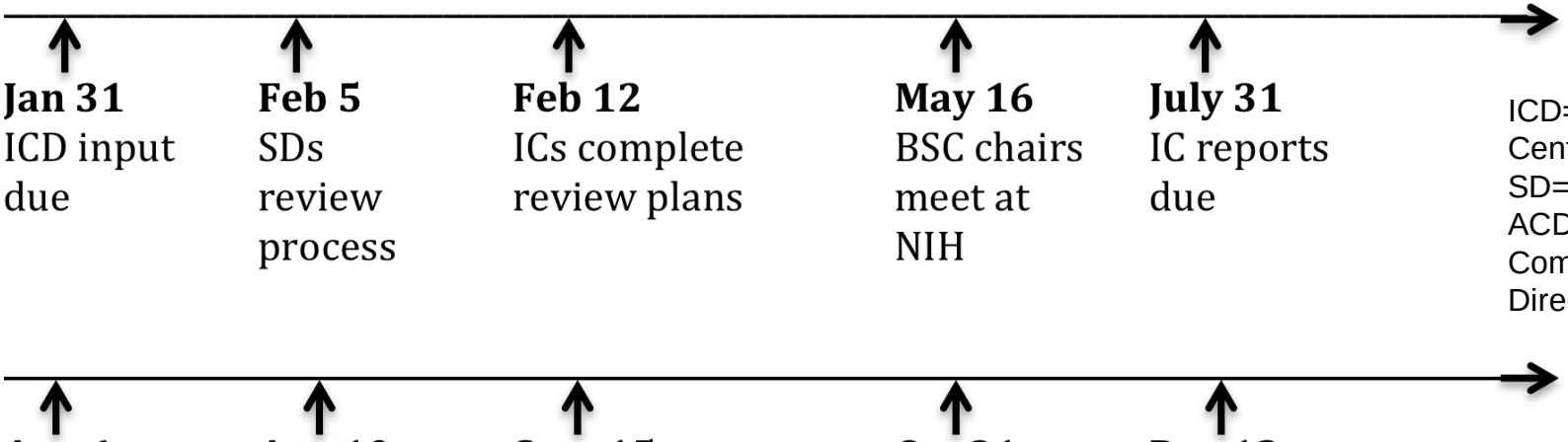
- Early in 2014, Dr. Collins charged all ICs with developing a long-term plan with the broad goal of developing a ‘10 year vision’ for the NIH IRP

- Two major goals:
  1. Develop large-scale initiatives that capitalize on the distinctive features of the NIH IRP
  2. Develop a blue-print for maintaining scientifically distinctive and outstanding science within the NIH IRP- including a sustainable Clinical Research Center

NCI's Perspective on Long-term Planning

- Support NCI's mission by identifying timely projects for broad collaborations across NCI's IRP with potential for trans-NIH collaboration
- Expand opportunities for collaboration with extramural investigators and/or industry
- Develop new ways to improve the use and fiscal health of the Clinical Center
- Identify new organizational elements and cultural features that further enhance the distinctiveness and success of the NIH IRP
- Identify barriers to achieving these goals

Timeline for NIH IRP Planning Process



ICD= Institute & Center Director
SD= Scientific Director
ACD= Advisory Committee to the Director

NIH IRP Long Term Planning Committee

Joan Conaway	Co-Chair	current BSC Chair
Louis Weiner	Co-Chair	current BSC Chair
Doug Lowy	Co-Chair	NCI
Ted Lawrence	Member	past BSC Chair
Liz Jaffee	Member	past BSC member/ current NCAB member
Ken Offit	Member	current BSC member
Margaret Spitz	Member	past BSA member
Jim Wells	Member	current BSC member
Bob Wiltrout	Member	NCI
Lee Helman	Member	NCI
Stephen Chanock	Member	NCI
Bob Hoover	Member	NCI
Crystal Mackall	Member	NCI
Tom Misteli	Member	NCI

- Each IC formed a review and planning committee composed of ~50% IC senior staff + ~50% BSC/extramural members

Important Considerations During the Process of Crafting the NCI IRP Vision

1. How do we balance our commitment to the NCI mission with the NIH Director's vision of trans-NIH big science?
2. How to develop an NCI strategic vision that:
   - Takes optimal advantage of the distinct expertise and resources of the IRP?
   - Focuses on our primary cancer mission while also creating opportunities for broad NIH collaborations across many disease or technology settings?
   - Creates new opportunities for intra/extramural collaboration?
3. How should we balance our commitments to basic, clinical, and population science at a time of declining resources and funding difficulty with the Clinical Center?
4. Are there ways in which the IRP can better utilize the Clinical Center?

Context for NCI IRP Deliberations

- Current staffing and changes over past decade
  - Reduction by 18% with support of BSC
- Affirmation of the NCI Mission and its scientific culture
- NCI accomplishments
- Current challenges and possible solutions

Organization Membership

Organization	No. CCR Members/Fellows	No. DCEG Members/Fellows
National Academy of Sciences	8	1
Institute of Medicine	9	2
American Academy of Arts and Sciences	8	1
American Association for the Advancement of Science Fellows	20	1
American Academy of Microbiology	21	
Association of American Physicians	15	2
American Society of Clinical Investigation	23	2
NIH Distinguished Investigators	7	
American Epidemiological Society		15

Distinctive Features of NCI's IRP

- Size- nearly 30% of PIs in the NIH IRP program are part of the NCI IRP
- The breadth and depth of its interdisciplinary science, which includes basic biology across multiple disciplines, clinical trials and the largest population science effort within the NIH IRP
- The close geographic proximity of basic and clinical researchers in a "culture of the corridors" environment which facilitates bench to bedside to bench outcomes
- Disproportionate commitment to patient-based science that culminates in 35-40% of all clinical activity performed in the NIH Clinical Center, a unique venue that allows uncommon ability to perform intensive mechanistic studies
- Partnership with the Frederick National Laboratory for Cancer Research

Distinctive Features of NCI's IRP

- Supports a substantial number of commitments to long-term projects that would be difficult to sustain by standard extramural funding mechanisms

- Strong commitment to the study of rare diseases, or diseases disproportionately afflicting underserved patient populations

- Commitment to address challenging epidemiological questions, which are often pursued as a governmental function in most countries
  - Ability to respond to important mandates by access to large populations and the ability to move quickly to exploit opportunities provided by natural experiments wherever they occur throughout the nation or the world

- Charge to address questions in public health within the federal government, free from the constraint of revenue and profit

Interdisciplinary Strengths of CCR's Research Portfolio

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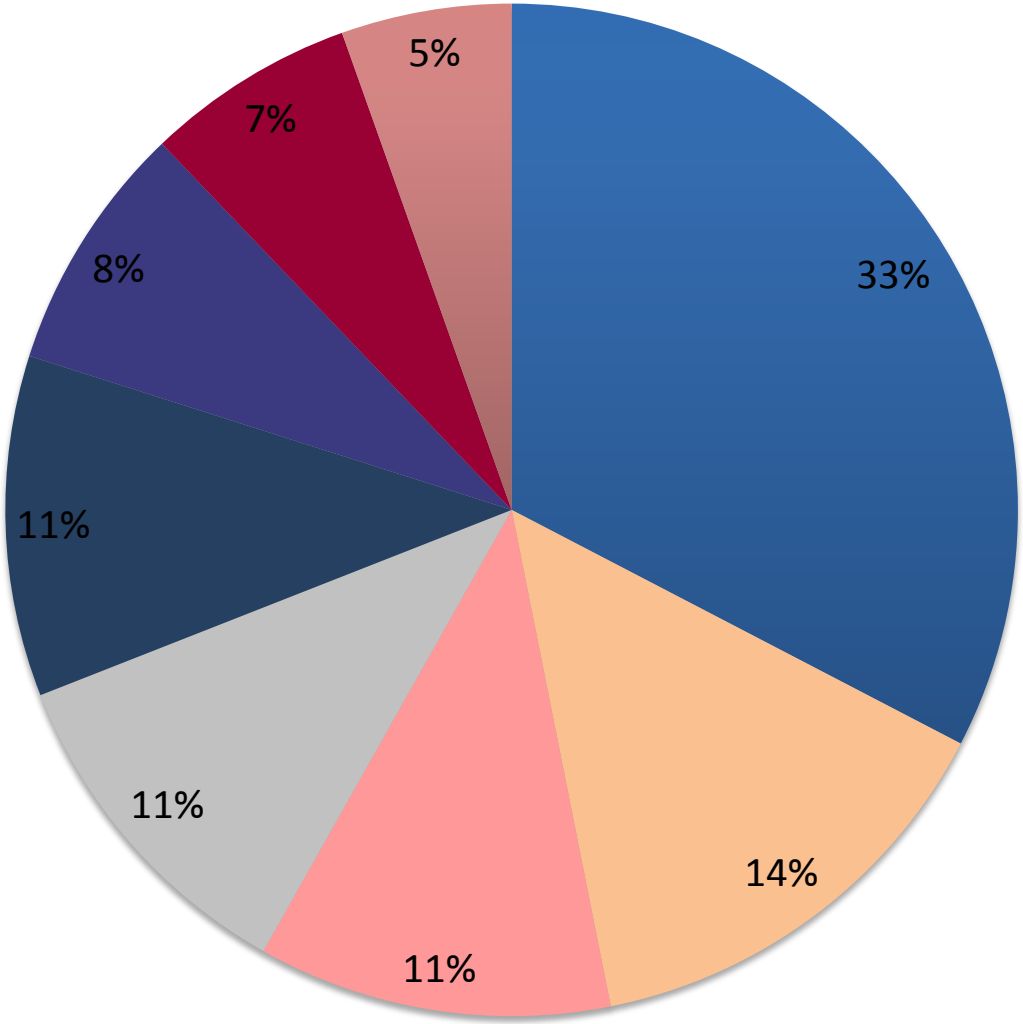

- Cancer Biology
- Immunology
- Chromosome Biology/Epigenetics
- Chemistry/Structural Biology/Biophysics
- Cell and Developmental Biology
- HIV/ Cancer Virology

Some of Our Past and Ongoing Basic and Clinical Achievements

Enabled through collaboration and long-term commitment of resources and retrospective review

- Development of multiple FDA approved drugs for cancer and HIV
- Development of technology to enable HPV vaccine
- Contributions to understanding and treatment of rare cancers
- Key studies demonstrating success of adoptive immunotherapy of cancer
- Development of new, commercialized technology for imaging of prostate cancer
- Notable contributions:
  - Genetic susceptibility to kidney cancer leading to novel interventions
  - New insights leading to targeted interventions for lymphoma
  - Understanding of the role of chromatin structure and genome organization to cancer
  - Organization and regulation of the immune system, including the discovery of multiple key regulatory proteins

NIH Inventions Translate Into Drugs and Biologics With High Public Impact

- Of the 153 drugs brought to market before 2008:
  - 22 (14.4%) are from the NIH IRP
    - 13 from NCI (7.2% total) --most of all institutes (NIH or extramural)
- In 2010, the total global net sale of the NIH IRP drugs was $6.9B with $5.7B of that deriving from NCI inventions
- 35-45% of all NIH IP activity (MTAs, patents, licenses, etc) in 2013

NCI

Videxa	Zenapex*
Taxol	Vitravene*
NeuTrexin	LYMErix*
Zevalin	Hivid*
Kepivance	Velcade**
Gardasil	Fludara**
Prezista	Cervarix***

NICHD
Certiva*

NIDCR
Acu Tect
NeoTect

NIAID
Havrix
Synagis
Twinrix
RotaShield*

NIA
Sporanox

NIDDK
Thyrogen

* No longer on market
** Not from CCR
*** approved in 2009

Chatterjee and Rohrbaugh. Nat Biotechnol. 2014 Jan;32(1):52-8

Creating New Opportunities

New competitive, time-limited funding options to support novel, high-risk and/or distinctive science

- **Major Opportunities Program**
  - 3 ongoing projects (matrix drug screening; metabolic features of cancer; chromatin profiling)
  - Projects aimed at accelerating development of innovative cancer treatment strategies by exploiting technological strengths within the CCR
- **Rare Tumor Initiative**
  - Apply existing NCI expertise in basic and clinical studies of patients with rare tumors in the CC to identify and translate new therapies
  - Pilot: Focused effort on desmoid tumors and plexiform neurofibromas (Widemann/Kummar)
- **New FLEX Programs**
  - Series of new, competitive programs to support methods development, new intra-CCR collaborations
    - Methods and Technology Development Program
    - Creation of “Interdisciplinary Team awards”
    - “New Directions” Program
  - To be launched fall/winter 2014

Global Impact on Science

Distinctive alumni with ties to NCI are contributing across the globe

- Three Nobel laureates
- Department chairs for over 100 U.S. medical centers and universities
- Leaders of many biotechnology companies
- Leaders at NCI-cancer centers (21% of current directors)

NCI Director Harold E. Varmus, M.D.

NCI IRP National and International Collaborations

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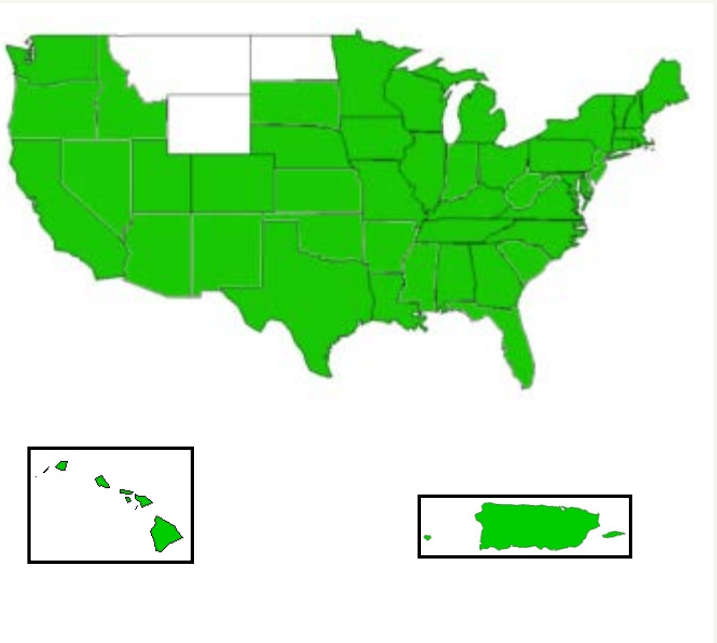
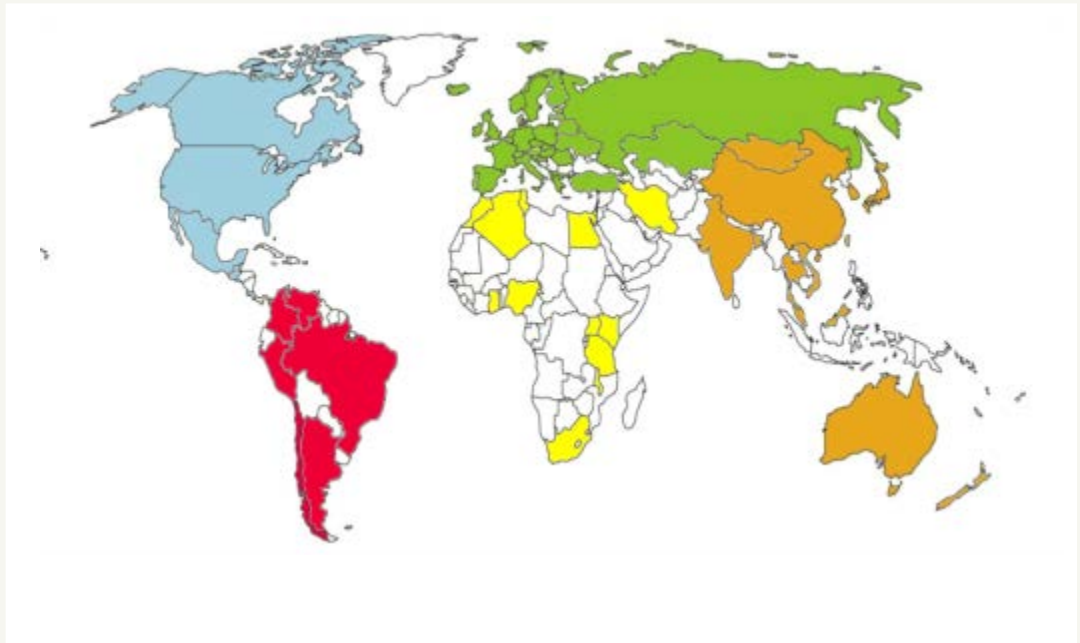
More than 2,000 formal collaborations with extramural academic investigators at over 800 academic institutions in 46 states and the District of Columbia and globally in 68 foreign countries

The NCI IRP partners with more than 180 biotechnology and pharmaceutical organizations





NCI IRP Vision Statement Timeline

- February-March: Request input from community
  - All Staff
  - Lab/Branch Chiefs
  - Centers of Excellence
  - CCR Science Board
  - BSC
- March: Brief BSC and solicit initial input
- April: All proposals vetted by CCR Science Board (with DCEG rep)
- May 2: Compile input into draft for review, discussion and comment by NCI committee
- May 16: Committee meeting in association with NIH BSC Chairs meeting
- June 13: NCI Committee meeting -firm up conclusions and recommendations
- June: Solicit input from PIs on proposals
- July 14-15: Solicit input by BSC
- July 31: Submitted NCI's report to NIH

Scientific Opportunities for Consideration

- 30 proposals received
- CSB reviewed all proposals
- 5 emerged for further consideration:
  - Precision Medicine and Prevention
  - Cell-based Therapies
  - The Human Microbiome
  - National Program for Natural Products Discovery
  - Human RNA Project

Current Status of Process

- Subcommittee of Advisory Committee to the Director (S-ACD), NIH
- Draft "synthesized" trans-NIH planning document written, shared with SDs and IC Directors, and with the S-ACD – All major focal points of NCI's report included!
- S-ACD currently conducting onsite interviews with various ICs
- NCI leadership met with S-ACD on September 2

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Population-based Science in the NCI and Distinctive Contributions to the NIH IRP

Stephen Chanock, Director, Division of Cancer Epidemiology and Genetics

Value of Population-based Studies for the NIH

- **Distinctive niche within the NCI IRP**
  - **Largest population science effort in IRP**
- **Contributions to trans-NIH activities**
- **Value of the NIH Clinical Research Center for population-based studies**

Public Health Advances: DCEG

- Risk for cancer following Chernobyl
- Long-term cohort analysis of DES exposure across multiple generations
- Risk for lung cancer for miners exposed to diesel fuel
- Family studies - identification of high penetrance mutations
- Discovery and characterization of nearly three-quarters of published common susceptibility alleles (GWAS)
- Lack of risk for cell phone use and brain cancer
- Electromagnetic fields and childhood leukemia risk
- Cancer risk and pediatric CT scans
- Cancer risk assessment tools and software
- Risk of testosterone replacement therapies
- NCI Cohort Consortium Pooled Studies
  - Vitamin D
  - BMI

Commitment to the Collaborative Network of DCEG

- Balance of PI-driven science with team science
- Support excellence in collaborative science involving epidemiologists, biostatisticians and laboratory science
- Support current structures of DCEG
  - Encourage PI-driven science reviewed prospectively
  - Pursuit of long-range goals
  - Respond to emerging opportunities with rapid assembly of expertise from different disciplines

DCEG Research

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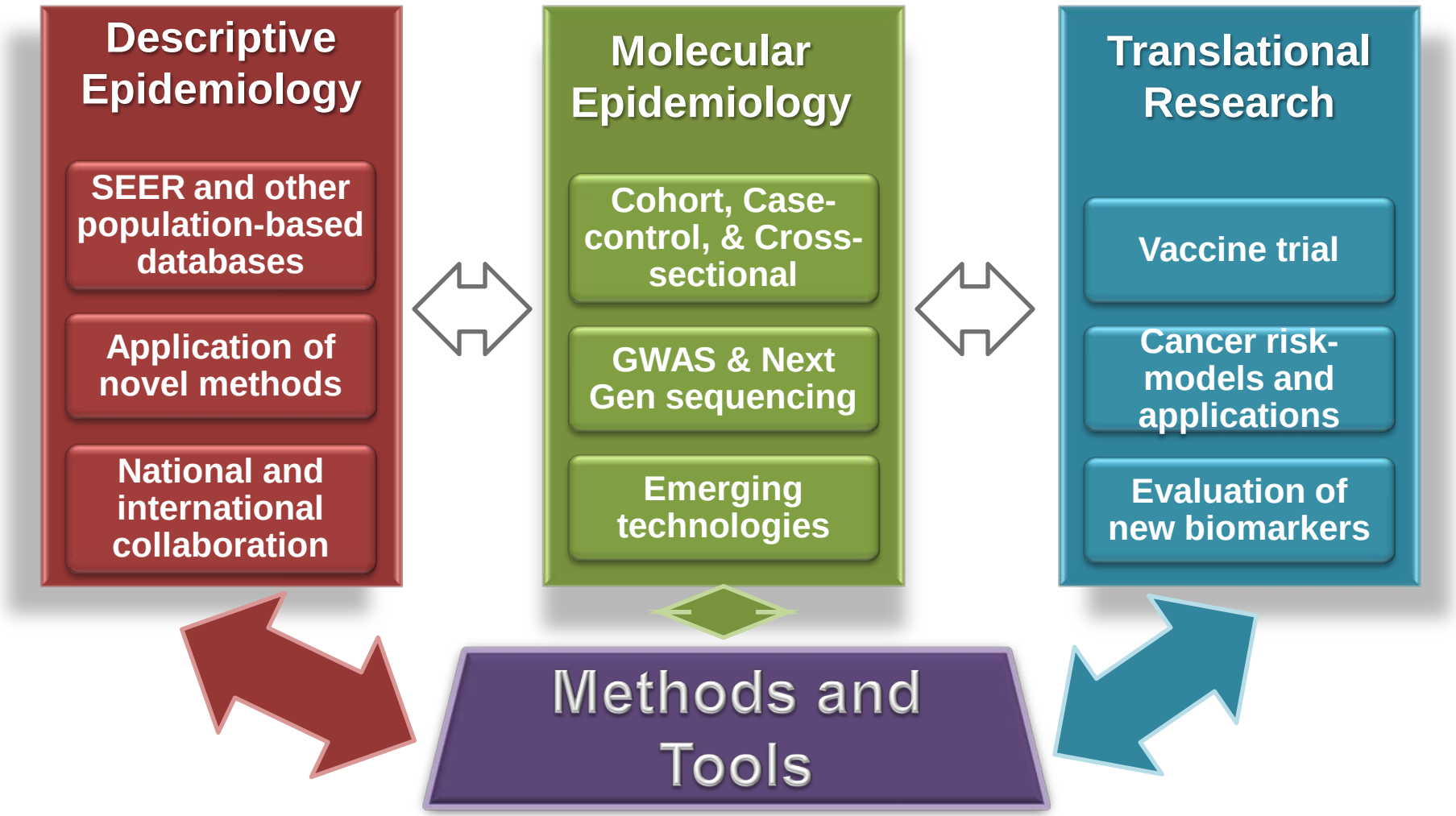

Current Analytical Challenges in the DCEG Portfolio

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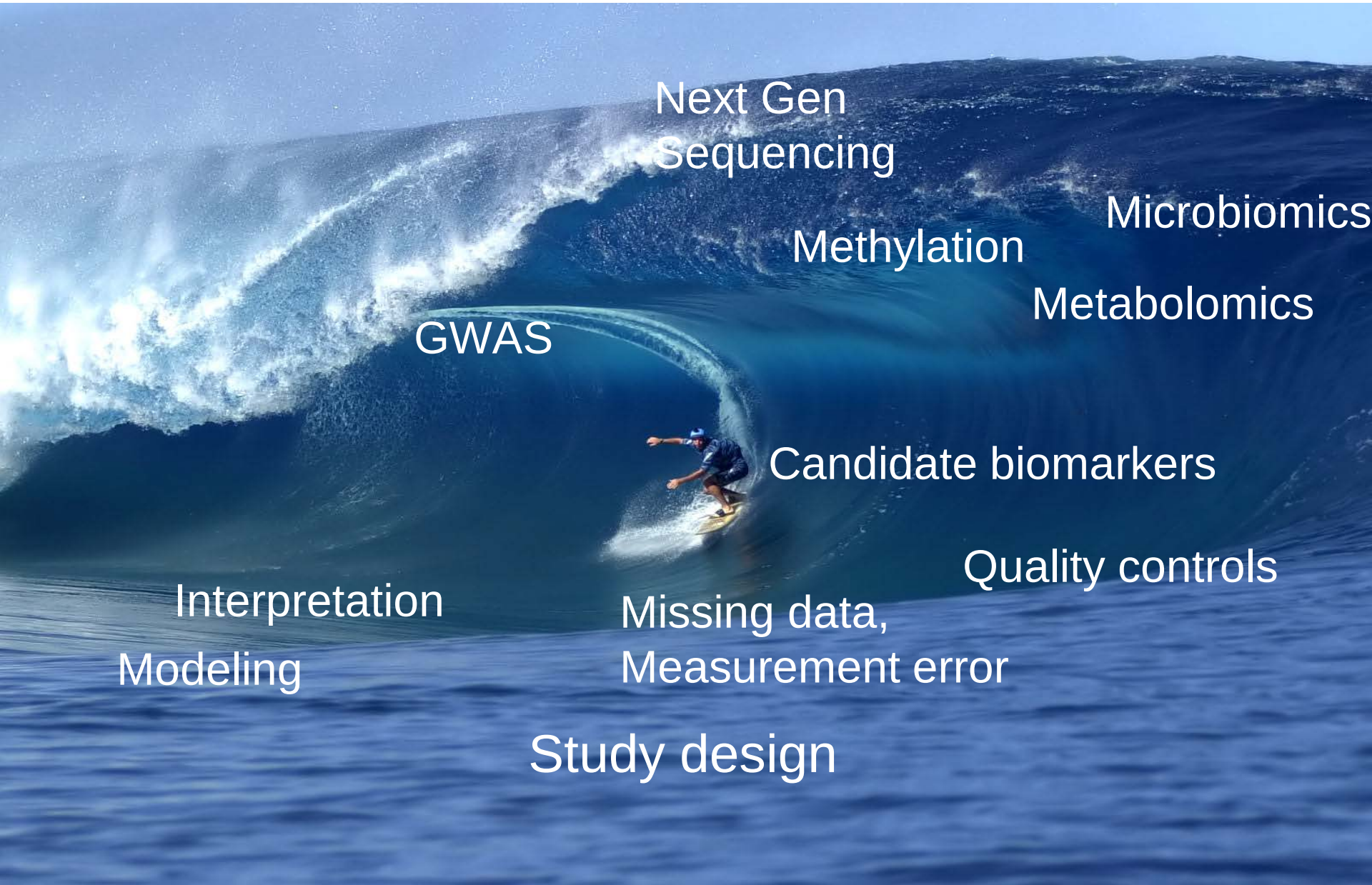

DCEG Research

- **Balance of team science and PI-driven research**
- **High-risk, high-reward research**
- **Longitudinal resource commitment**
- **Program-based budget and review**
- **New cross Branch research programs**
    - **Tobacco**
    - **Translational Epidemiology**
    - **Genetic Mosaicism**
    - **Breast Cancer**
    - **Microbiomics**

Leverage Areas of Special Expertise

Radiation Exposure

- **Environmental**
  - Risk assessment in Chernobyl and atomic bomb survivors
  - Genomic characterization of radiation-induced thyroid cancer
- **Medical and Occupational**
  - CT scans
  - Healthcare workers
    - Nuclear medicine
    - Angiography

Environmental and Occupational Exposures

- Ultrafine particulates and lung cancer
- Pesticides and cancer
- Systematically characterize mechanisms of action of leukemogens and lymphomagens
  - Benzene
  - Formaldehyde
  - Trichloroethylene
  - Perchlorethylene

DCEG Research Protocols at the NIH Clinical Center

- **Rare Familial Syndromes**
  - **Inherited bone marrow failure**
  - **Li-Fraumeni**
  - ***DICER1***
- **Family Studies of Common Cancers**
  - **Melanoma**
  - **Hodgkin disease**

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NCI's Identified Areas of Scientific Opportunity: Dependence on Clinical Program and the NIH Clinical Research Center

Lee Helman, Scientific Director for Clinical Research, CCR

Clinical Research Priorities

- Design and execute novel, science-based clinical trials
- Take discoveries from within the CCR or other NIH laboratories to the point of first-in-human trials
- Focus on molecularly-based, tailored medicine
- Utilize technology and correlative science difficult to support elsewhere
- Foster the education and research of physician-scientists
- Study rare cancers that are not being adequately studied elsewhere

Areas of Clinical Strength

- NCI IRP will continue its active and growing programs in:
  - Lymphoma
  - Genitourinary malignancies (prostate, bladder and renal)
  - Neuro-oncology
  - Pediatric malignancies
  - Thoracic tumors
  - Marrow Transplant
  - Immunotherapy
  - Rare cancers

Reengineering of the NCI's Clinical Research Program

- Major changes over the last few years:
  - Reorganization of Labs and Branches
  - Creation of Medical Oncology Clinical Service
  - Changes to protocol concepts and review
  - Accelerated the timeline for development and execution of clinical trials
  - Created a Protocol Support Office for Staff Training and Administrative Support in Protocol Development

NIH Clinical Center Received Lasker~Bloomberg Award for Public Service

- **"The Clinical Center, the world's largest clinical research hospital, exists to help scientists who are clinicians rapidly translate promising discoveries in the laboratory into new and better ways to treat and prevent disease. The Clinical Center's 58-year research portfolio has resulted in remarkable medical advances." –Francis Collins**

Some NCI/CCR contributions noted:

- **development of chemotherapy for cancer**
- **the first use of an immunotoxin to treat a malignancy (hairy cell leukemia)**
- **identification of the genes that cause kidney cancer leading to the development of six new, targeted treatments for advanced kidney cancer**
- **the first gene therapy**
- **the first treatment of AIDS (with AZT)**
- **the development of tests to detect AIDS/HIV, which led to a safer blood supply**
- **applied new imaging approaches to the diagnosis of prostate cancer**

CCR's current contributions to CRC Infrastructure include surgery, pathology, dermatology, radiation oncology, and urology

The Necessity of Maintaining the Vitality of the NIH Clinical Center

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- A more stable funding strategy must be developed to sustain the infrastructure of the Clinical Center in a time of projected resource constraints

- Ensure that optimal oversight and decision making processes are used to maximize the efficiency of the Clinical Center to continue meeting it's mission as an important intramural and national shared resource

- Clinical research done in the Clinical Center should continue to be of the highest quality

- Continue to pursue mechanisms to allow extramural/intramural collaborations that would allow extramural colleagues access to the Clinical Center for high priority clinical studies

Scientific Opportunities for Consideration

- 30 proposals received
- CSB reviewed all proposals
- 5 emerged for further consideration**
  - Precision Medicine and Prevention
  - Cell-based Therapies
  - The Human Microbiome
  - National Program for Natural Products Discovery
  - Human RNA Project

**All currently included in draft consolidated document for the NIH to the NIH Director's Advisory Committee to the Director

Precision Medicine and Prevention

Approach:

Develop PM strategies tailored to several pediatric and rare cancers, as well as several tumor types already prominently featured in the IRP portfolio

Exploit:

- access to well-characterized patient populations in the Clinical Center
- availability of molecular epidemiological datasets in DCEG
- strong expertise in molecular cancer mechanisms in CCR's basic science labs

Developing Cell-based Therapies at the IRP

Approach:
Drive a new wave of cell-based therapies by combining genome engineering, cell engineering and immunobiology

Goals:
Development of novel cell-based therapy approaches for:

- Cell therapy to common epithelial cancers using antigen identification with personal genomics
- Correction of monogenic disorders using genome engineering methods

Establish infrastructure for dissemination of cell-based therapies

- Focus on approaches and disease types that are not desirable for the current business plans of commercial entities, but which may inform future commercialization.

The Human Metaorganism in Cancer Biology and Medicine

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Approach:

Focus resources and efforts to move the field from descriptive biology to mechanistic insight and metaorganism processes affecting cancer initiation, progression and therapy

Goals:

- Microbiome mapping in health and disease (genomic approaches)
- Mechanistic studies of microbiome function (inflammation, signaling, immune function)
- Microbiome in cancer treatment (susceptibility, progression, drug response, biomarkers)

National Program for Natural Products

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Approach:

Contribute to a National Program for Natural Products Discovery for new molecules that target biological processes central to human disease --a national resource fully accessible to extramural investigators

Goals:

- Develop a comprehensive Natural Products Library (NPL) that includes:
  - pre-fractionated compounds (1 million) for modern high-throughput targeted screening technologies
  - analytical resources for isolation, structure elucidation, medicinal chemistry
  - public database and bioinformatics platform to integrate source organism, activity, structural, and genomic data
- Establish a national resource for Natural Products screening efforts for:
  - assay development
  - execution of natural product drug screens
  - resupply of active molecules
  - bioinformatics support to extramural users

The Human RNA Project

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Approach:
Take leadership role in the development of a comprehensive program for the investigation and therapeutic exploitation of RNA

Goals:
Use a strong foundation in molecular biology and synergy with other ICs for:
- Systematic mapping of the RNAome in health and disease
    - genome-wide sequencing of mRNAs and unconventional RNAs
    - synergy with Precision Medicine data collection
- Elucidation of RNA structure
    - develop and apply methods to determine RNA structure (SHAPE, SAXS)
- Development of RNA-based therapeutic approaches
- Development of new clinical targets and trials

Barriers to Success

Administrative impediments to success:

- **Disproportionately low salaries for recruitment and retention of clinical tenure-track and tenured investigators**
- **Ineffective centralized human relations/employee relations functions, which slow hiring, limit ability to deal with underperforming staff, and limit accountability to "customers"**
- **Increasingly onerous conflict of interest regulations and processes that make partnerships, acceptance of outside honorific awards, participation in scientific committees and organizations difficult and demoralizing**
- **Burdensome and complicated travel and meetings policies, which limit the exchange of scientific ideas and impair training by imposing quotas on attendance at scientific meetings and conferences, and which often lead to higher airfares and registration costs due to last minute approvals**

A New Approach to Enhancing Diversity at NCI: Diversity Task Force

Background

- **Limited success in recruiting underrepresented minority TT/Tenured scientists**

Charge

- **Develop culture of community of minority scientists and trainees**
- **Tap into collections of well-trained minority scientists (i.e., CURE Program, HBCUs, Meyerhoff, Xavier, etc.)**
- **Improve information provided to advisors/mentors/diversity departments at various colleges (i.e., videos, etc.)**
- **Consider career pathways for minority trainees**
  - **Bench Research (TT and non-TT)**
  - **Information Technology**
  - **Clinical Research (include pool of Minority MDs)**

Task Force Members

Jonathan Wiest (Chair)
Sanya Springfield
Bob Wiltrout
Lee Helman
Stephen Chanock
Warren Kibbe
Brian Lewis (UMass/BSC member)
1 – 2 Trainees

Along with Dr. Hannah Valantine, the newly appointed NIH Chief Officer for Scientific Workforce Diversity

Questions and Discussion

- EXTRAS

Areas of Emphasis for CCR

- **Scientific opportunities identified by NCI planning process**
- **Re-engineering of NCI's Intramural Clinical Program**
- **Sustainment of NIH Clinical Research Center**
  - **Support for trans-NIH areas of focus identified through long-term planning process**
  - **Improvements to strategic planning and efficiencies**
  - **New opportunities for accelerating progress through partnerships with extramural collaborators**

Strategic Initiatives in Genomics

- **Somatic Molecular Epidemiology –**

"How does the germline inform the somatic?"

  - Investigate interaction between exposures, germline and somatic profiles in high-quality studies
    - EAGLE - lung cancer
    - Chernobyl radiation-induced thyroid cancer
  - Close partnership with Center for Cancer Genomics and CCR
  - TCGA-related projects
    - PanCan analysis of germline susceptibility

Collaborations Across NCI: DCEG

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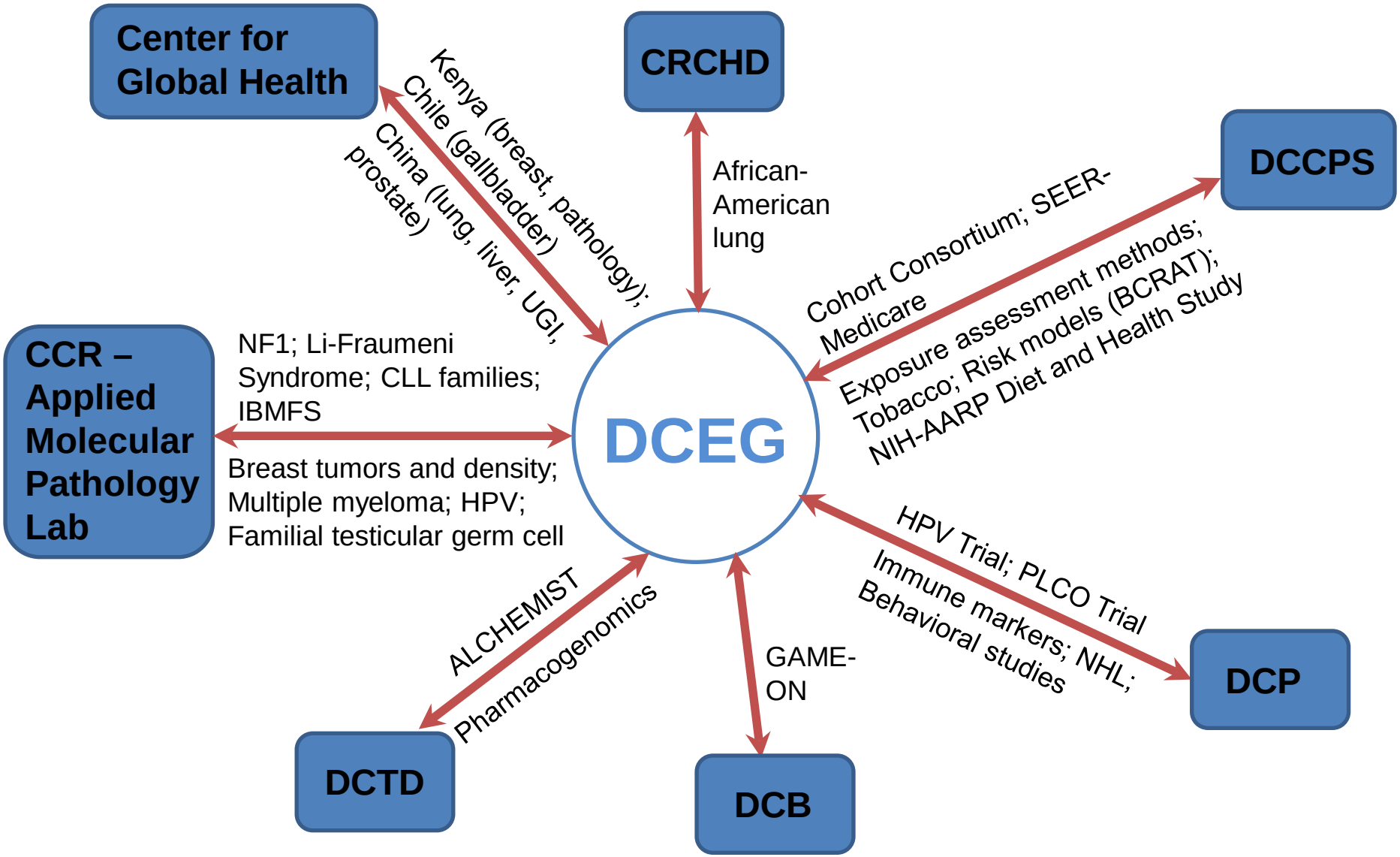

Current NCI IRP Staff

	Tenure Track PIs	Senior Investigators
CCR-Basic	29	124
CCR-Clinical	21	62
DCEG	27	44
Total	77	230

The number of PIs in the NCI IRP has been reduced by 18% from a high of 375 in 2002 to the current number of 307

180 departures and 113 new principal investigators

Active engagement with NCI's Basic and Clinical/Epidemiology Boards of Scientific Councilors (BSC)

Precision Medicine and Prevention

- Diseases are molecularly defined rather than by signs-and-symptoms
- Promise of earlier diagnosis, improved assessment of prognosis, and targeted treatment tailored to the identified molecular abnormalities

Approach: *Develop PM strategies tailored to several pediatric and rare cancers, as well as several tumor types already prominently featured in the IRP portfolio.*

Exploit:

- *access to well-characterized patient populations in the Clinical Center*
- *availability of molecular epidemiological datasets in DCEG*
- *strong expertise in molecular cancer mechanisms in CCR's basic science labs*

Goals:

- *Systematically collect multi-parameter molecular data from patient populations (genomic, transcriptomic, epigenetic, proteomic, metabolomics, and microbiomic etc.)*
- *Identify molecular features associated with disease, disease progression, outcome, treatment response or susceptibility*
- *Develop preventative, prognostic and therapeutic tools based on mined data*
- *Exploit cohorts to molecularly define disease and inform mechanisms for treatment and prevention*

Developing Cell-based Therapies at the IRP

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- Medicine has long relied on drug-based therapies to treat disease
- Breakthroughs in stem cell biology and genetic engineering technologies make it increasingly possible to develop cell-based therapies
- The NCI IRP has pioneered cell transfer therapies

Approach: ***Drive a new wave of cell-based therapies by combining genome engineering, cell engineering and immunobiology***

Goals:

Development of novel cell-based therapy approaches for:

- cell therapy to common epithelial cancers using antigen identification with personal genomics
- Correction of monogenic disorders using genome engineering methods

Establish infrastructure for dissemination of cell-based therapies (cell production and vector production laboratories)

- Focus on approaches and disease types that are not desirable for the business plans of commercial entities due to perceived difficulty associated with the biology or limited market potential

THE HUMAN METAORGANISM IN CANCER BIOLOGY AND MEDICINE

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- Humans are metaorganisms (symbionts) composed of host and microbial cells with their own genes (metagenome) and shared metabolic processes and products (metabolome)
- All phases of human cancer are affected by the microbiome

Approach: ***Focus resources and efforts to move the field from descriptive biology to mechanistic insight and metaorganism processes affecting cancer initiation, progression and therapy***

Goals:

- *Microbiome mapping in health and disease* (genomic approaches)
- *Mechanistic studies of microbiome function* (inflammation, signaling, immune function)
- *Microbiome in cancer treatment* (susceptibility, progression, drug response, biomarkers)

- Build on strong, existing and complementary strengths within the NCI (immunology and immunotherapy, microbial and human genomics, cohort studies, access to well-defined patient populations in the Clinical Center, animal model systems)

- Strong synergy with complementary efforts on other disease types in numerous IRPs (NIAID, NHGRI, NIDCR, NIDDK, NHLBI, NIEHS)

National Program for Natural Products

- Natural Products are an excellent source of molecular diversity for drug discovery
- Large pharmaceutical companies have severely reduced NP discovery efforts
- NCI houses unique infrastructure in NP discovery against cancer targets

Approach: *Contribute to a National Program for Natural Products Discovery for new molecules that target biological processes central to human disease*

Goals:

- *Develop a comprehensive Natural Products Library (NPL)* that includes:
  - pre-fractionated compounds(1 million) for modern high-throughput targeted screening technologies
  - analytical resources for isolation, structure elucidation, medicinal chemistry
  - public database and bioinformatics platform to integrate source organism, activity, structural, and genomic data
- *Establish a national resource for Natural Products screening efforts* for:
  - assay development
  - execution of natural product drug screens
  - resupply of active molecules
  - bioinformatics support to extramural users

• Make this a national resource fully accessible to extramural investigators

The Human RNA Project

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- RNA is recognized as one of the most versatile biological molecules and RNAs affect virtually all biological processes
- Functions of RNAs are poorly understood and the therapeutic potential of RNA is highly under-explored

Approach: ***Take leadership role in the development of a comprehensive program for the investigation and therapeutic exploitation of RNA***

Goals: Use a strong foundation in molecular biology and synergy with other ICs for:

- *Systematic mapping of the RNAome in health and disease*
  - genome-wide sequencing of mRNAs and unconventional RNAs
  - synergy with Precision Medicine data collection
- *Elucidation of RNA structure*
  - develop and apply methods to determine RNA structure (SHAPE, SAXS)
- *Development of RNA-based therapeutic approaches*
- *Development of new clinical targets and trials*