

## **CENTER FOR CANCER RESEARCH: OUR MISSION**

To inform and empower the cancer research community by making breakthrough discoveries in basic and clinical cancer research by developing them into novel therapeutic interventions for adults and children afflicted with cancer or infected with HIV.

## The National Cancer Institute

The National Cancer Institute (NCI) is the Federal Government's principal agency for cancer research and training.

As the leader of the National Cancer Program, the NCI provides vision and leadership to the nationwide community of researchers, public health workers, healthcare providers, patients, advocates, and

policy makers working to defeat cancer. The investigators at NCI work in broad research areas and use existing and novel approaches to develop and apply evidence-based interventions for preventing and controlling cancer with a focus on basic, clinical, and translational research.



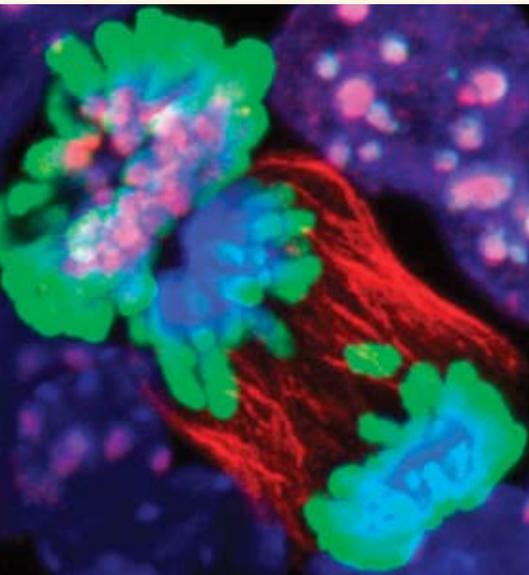
## The NCI Center for Cancer Research

The Center for Cancer Research (CCR) is the largest component of the NCI intramural research program. Our vision is to better understand and more effectively detect, treat and prevent cancer.

To achieve our mission, we:

- Perform rigorous basic scientific research to discover fundamental mechanisms of biology and to understand the molecular changes that occur in cancer
- Translate these advances rapidly from the laboratory to the clinic to develop lifesaving interventions
- Develop innovative technologies that enable more accurate detection, diagnosis, and treatments
- Pioneer novel interventions for underserved patient populations worldwide
- Share expertise, scientific data and technologies to broaden the impact of our work and enhance the overall productivity of the nation's cancer research community in the US and abroad
- Provide an unparalleled scientific environment to cultivate and train the physician-scientists and the biomedical researchers of the 21st century





## Center of Excellence in Chromosome Biology

The Center of Excellence in Chromosome Biology (CECB) is one of several Centers of Excellence in the NCI intramural research program. The Centers of Excellence build upon existing structures and areas of expertise. They promote new initiatives, projects, collaborations, as well as the intramural research program's role in interdisciplinary and multidisciplinary translational research.

The CECB integrates CCR's intellectual and physical resources to support outstanding research in chromosome biology.

### Objectives:

- Facilitate interaction and collaboration among researchers within the NCI, NIH, and beyond
- Promote advances and opportunities for research in chromosome biology
- Leverage cutting-edge tools, approaches, and resources to advance chromosome biology as it applies to cancer research
- Train young investigators to address complex scientific questions through collaboration and multidisciplinary approaches



### Steering Committee Members:

*Front row (left to right):* Michael Bustin, Michael Lichten, Tom Misteli

*Back Row (left to right):* Gordon Hager, Thomas Ried, Susan Gottesman, Andre Nussenzweig, Carl Wu

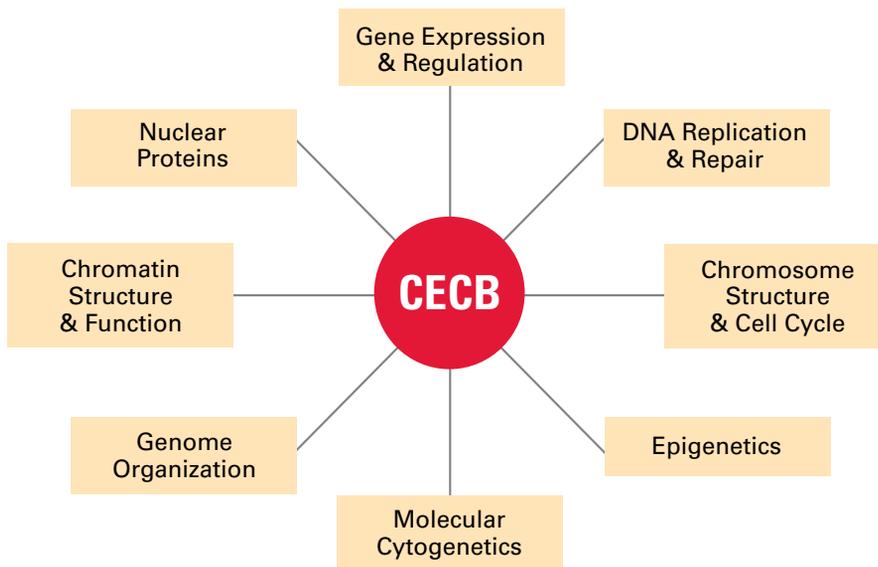
*Not pictured:* Shiv Grewal and Jeffrey Strathern

### CECB Steering Committee

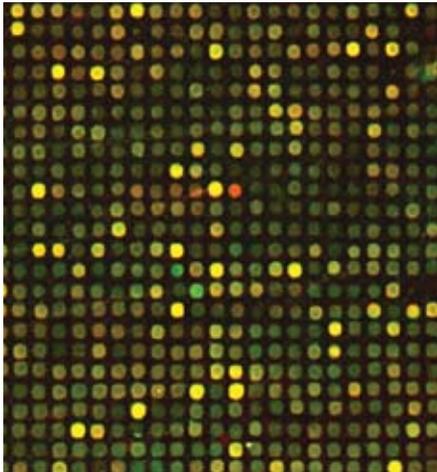
The current CECB steering committee consists of ten CCR investigators, including two members of the National Academy of Sciences. The steering committee meets monthly to plan initiatives and to catalyze advances in basic and translational research related to chromosome biology in order to develop successful therapies for cancer and move them to the clinic.

## Mission

The mission of the CECB is to achieve a comprehensive understanding of the mechanisms involved in chromosome function, how aberrations in chromosomes and chromatin lead to disease, and how these defects can be corrected. The CECB brings together internationally renowned experts in the fields of gene expression and regulation, chromatin/chromosome structure and function, DNA replication and repair, epigenetics and molecular cytogenetics to achieve this mission.



Deoxyribonucleic acid (DNA) contains the instructions a cell uses to build proteins essential to life. The complete supply of DNA is packaged inside the cell as macromolecules called *chromosomes*; the complete set of chromosomes is called a *genome*. Each chromosome houses many working units called *genes*, and each gene sits within tightly coiled DNA strands that are wrapped around eight histones proteins in a package called a *nucleosome*. *Chromatin* is the full collection of these nucleosomes. The genome is stored in the cell nucleus.



## Gene Expression and Regulation

Understanding of the fundamental mechanisms of gene expression and regulation will provide opportunities to develop novel diagnostic and therapeutic strategies for cancer.

CECB research on gene expression and regulation includes:

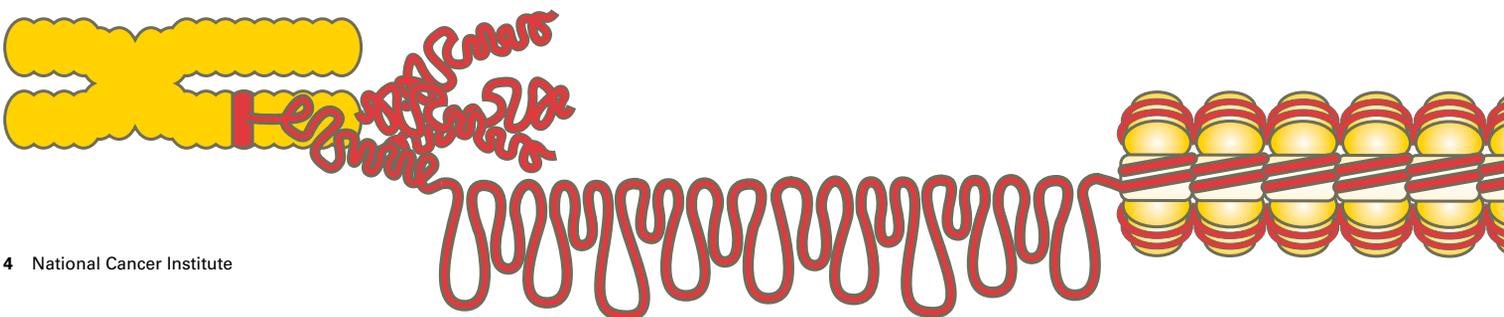
- Understanding the mechanisms of genetic recombination and gene regulation
- Examining chromatin regulation of eukaryotic gene expression in humans and a number of model systems
- Employing molecular techniques in combination with live-cell microscopy to study gene expression in the intact nucleus of living cells
- Exploring the role of genomic instability and associated gene expression changes during cancer development
- Investigating novel mechanisms for gene regulation and how these mechanisms contribute to global control circuits
- Identifying gene expression signatures that assist in disease prognosis and therapy
- Advancing research in transcriptional regulation to the preclinical and clinical levels

## DNA Replication and Repair

DNA damage is a leading cause of tumor formation. When DNA is damaged, the cells attempt to repair it. Failure to repair can lead to cell death. This life-or-death process involves a complex interplay between DNA damage sensing and repair pathways, pathways controlling the cell cycle, and cell death mechanisms.

CECB research focuses on:

- Understanding the molecular mechanisms of genetic recombination and DNA damage repair
- Examining mechanisms by which cells monitor and repair DNA double-strand breaks
- Deciphering the complex interplay between DNA damage detection, signaling, and repair
- Identification of novel DNA repair mechanisms



## Chromatin Research

Chromatin plays a central role in the orderly progression of DNA-related activities such as transcription, replication, and repair, as well as a key role in epigenetic regulation of gene expression. Understanding chromatin is key to the development of novel intervention strategies and approaches to the treatment of cancer and other diseases.

CECB research on chromatin includes:

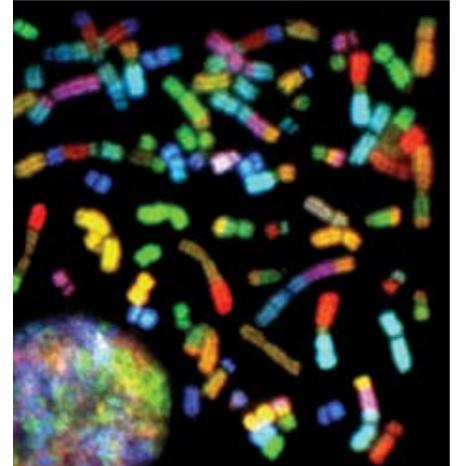
- Exploring the role of chromosomal proteins in chromatin function and cancer
- Determining the influence of chromatin structure on the maintenance of genomic stability
- Investigating the role of small regulatory RNAs
- Using novel molecular imaging techniques to explore gene and protein function in living cells and applying these methods to understand the contribution of genome organization to differentiation and disease
- Analyzing the link between RNAi and heterochromatin assembly and its implications for human biology and cancer
- Elucidating the mechanisms by which oncogenic translocations are formed
- Developing chromatin based diagnostic methods
- Discovering and testing of chromatin drug targets

## Epigenetics

The dramatic changes in gene expression that characterize tumor cells come about through both genetic and epigenetic mechanisms. Epigenetics is the study of heritable changes in gene function that occur without a change in DNA sequence. Epigenetics plays a critical role in the development of cancer through DNA methylation, histone modification and changes in higher order chromatin structure.

Research highlights in CECB include:

- Examining epigenetic control of higher-order chromatin assembly
- Exploring mechanisms regulating the establishment of epigenetic markers
- Development of interventions that target systemic and local epigenetic changes that occur during cancer initiation and progression

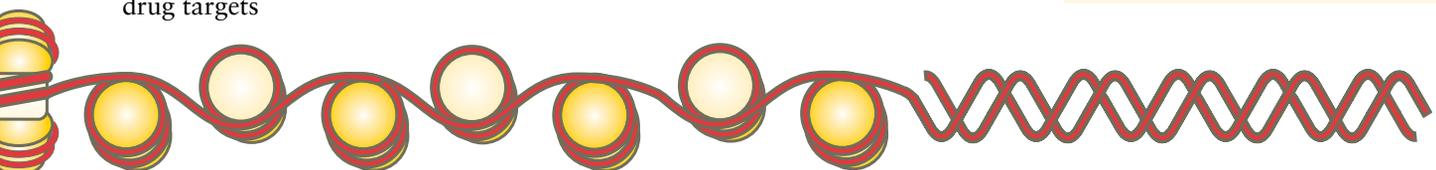


### CHROMOSOMES, AGING AND CANCER

**Cancer is a disease of aging. The majority of cancers are diagnosed in individuals over the age of 65 and cancer incidence increases dramatically with age. One of the most likely reasons for this dramatic increase is the accumulation of chromosomal and genome defects in aging cells.**

**CECB scientists are working towards:**

- **Elucidating how the structural and epigenetic properties of genomes change during the natural aging process**
- **Discovering how DNA repair mechanisms are altered during aging**
- **Identifying age-associated tumor risk factors**
- **Using naturally occurring premature-aging diseases to uncover the molecular mechanisms of aging**
- **Probing the role of age-related chromatin changes in the process of tumor formation**

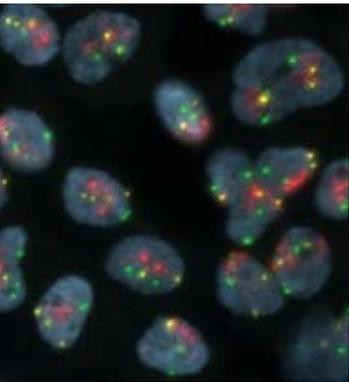


### Molecular Cytogenetics

Molecular cytogenetic approaches have led to the identification of chromosomal aberrations and genomic imbalances in cancer cells linking specific chromosomal abnormalities to specific human cancers. Molecular cytogenetics data are clinically useful for the diagnosis, classification, prognostication, and treatment planning for patients. They play an important role in the discovery of new clinical-pathological associations, cancer gene identification, monitoring patient response, and for our understanding of the structure/function relationship between alterations of the cancer genome and associated gene expression changes.

CECB investigators are exploring:

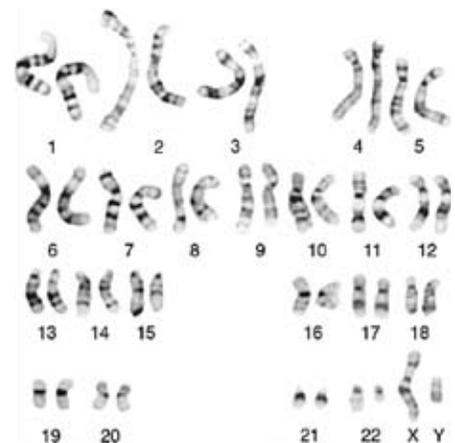
- Dynamic changes of the genome and transcriptome during tumorigenesis
- Utilization of models of human tumorigenesis, including mouse models, with a variety of genomic technologies, including comparative genomic hybridization (CGH), spectral karyotyping (SKY), fluorescent in situ hybridization (FISH), gene expression profiling, and proteomic methodologies
- Aneuploidy as a molecular marker for cancer diagnostics
- Translational research for early cancer diagnosis, prognosis, and rational therapy planning



## Clinical Implications

CECB research programs have direct implications for translational medicine. Examples include:

- Examining the chromatin fiber as a promising molecular target for a variety of therapeutic drugs, such as the histone deacetylase inhibitors or modifiers of DNA methylation
- Developing ligands for steroid/nuclear receptor superfamily members that are critically involved in the development and progression of many human neoplasias, including ovarian, breast, and prostate cancer
- Exploring interphase genome organization in the early diagnosis of tumor cells and cancer stem cells
- Utilizing high-throughput imaging approaches to provide useful methodologies for drug discovery
- Employing high-resolution mapping of genomic imbalance and associated gene expression changes as an entry point for the molecular cloning of novel cancer genes, and novel targets for improved detection, diagnosis, and prognosis
- Applying these approaches and results towards the realization of an individualized medicine in patients with cancer

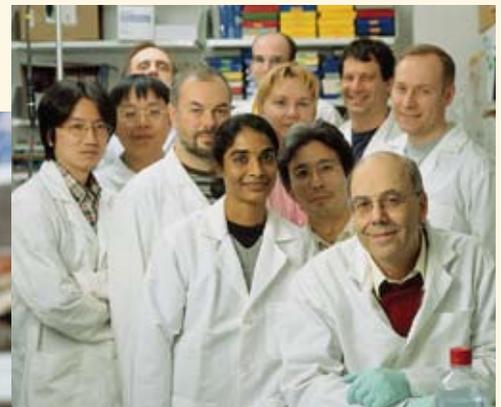




## Training Opportunities at the CECB

The CECB is committed to supporting and training the next generation of cancer researchers, helping launch careers in science, and enabling established investigators to pursue investigator-initiated research. The CECB works to create a research environment for scientists and clinicians with a high quality of science. Training of young investigators to address complex scientific questions through collaboration and

multi-disciplinary approaches is a major goal of the CECB. Trainees at the CECB have the unique opportunity to learn from experts in the field of chromosome biology in one of the world's leading scientific institutions. Current openings for postdoctoral fellows, staff scientists and research fellows in any CECB laboratory in the CCR can be found at <http://ccr.cancer.gov/careers/positions.asp>.



**FOR MORE INFORMATION**

For more information on the CECB  
or the CCR please visit

<http://ccr.cancer.gov/initiatives/CECB/>

and <http://ccr.nci.nih.gov/>

respectively.





NATIONAL<sup>®</sup>  
CANCER  
INSTITUTE

---

NIH Publication No. 07-6133  
Printed April 2007

