

■ FROM THE DIRECTOR

Cancer and Chromosomes: The 2007 NCI Symposium on Chromosome Biology

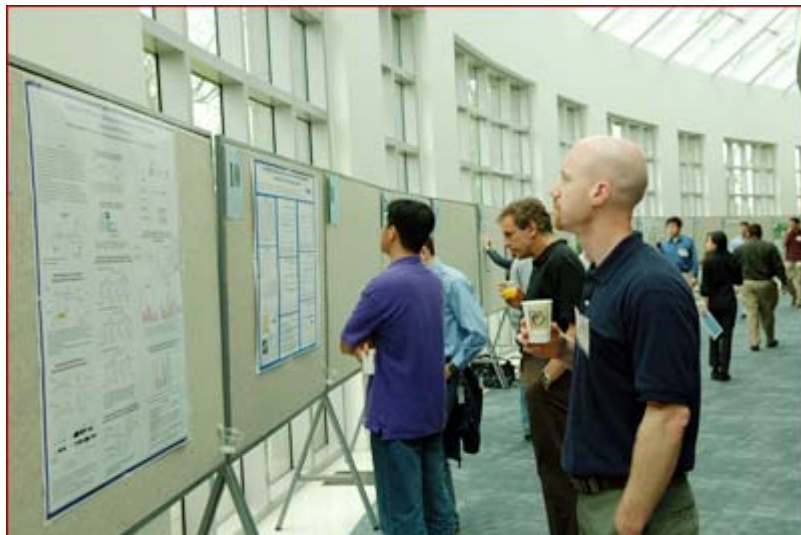
Chromosomes have historically been at the center of cancer biology. Chromosomal mutations, such as translocations, deletions, duplications, and aneuploidy, have long been implicated in certain cancers. The NCI has a strong and proud tradition of cutting-edge, innovative research in this field, and NCI scientists have made



key contributions to the elucidation of basic mechanisms in chromosome biology and in the application of these findings to diagnosis and therapy. In recognition of its strength in this area, the CCR has recently established the Center of Excellence in Chromosome Biology (CECB, <http://ccr.cancer.gov/initiatives/CECB>). Its goals are to integrate the CCR's intellectual and physical resources to promote and lead new initiatives, projects, and collaborations with intramural and extramural scientists from various disciplines to achieve a comprehensive understanding of the mechanisms involved in chromosome biology and to accelerate the translation of laboratory findings into diagnostic and therapeutic applications for patients. As part of these efforts, the CECB organized the NCI Symposium on Chromosome Biology, held on April 26 and 27 in the Natcher Conference Center on the Bethesda campus. This meeting, chaired by Tom Misteli, PhD, of CCR's Laboratory of Receptor Biology and Gene Expression, was highly attended by researchers from around the country and featured outstanding presentations from CCR investigators and leaders in chromosome research from the extramural community.

NCI Director John E. Niederhuber, MD, opened the symposium, expressing his enthusiasm for the meeting, the importance of the work being done, and his thanks to the presenters and organizers. I followed with a brief description of the CCR, including the CECB, explaining how the CCR overall is an integral part of the NCI and elucidating our mission of informing

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



The symposium spanned a wide range of topics, from basic gene control to diagnostic applications of chromosome analysis relevant to cancer. In the first session, the importance of understanding basic genome regulation via biochemical, cell biological, and structural studies was emphasized. Robert Roeder, PhD, of Rockefeller

University, described his ongoing pioneering biochemical studies of transcription factors, and Robert Tjian, PhD, of the Howard Hughes Medical Institute at the University of California, Berkeley, emphasized the need for extending these studies into physiological systems, such as differentiation and development. Mikhail Kashlev, PhD, of CCR's Gene Regulation and Chromosome Biology Laboratory, discussed his advances in understanding the mechanisms controlling the fidelity of transcription by RNA polymerase II. Carl Wu, PhD, and Yawen Bai, PhD, both of CCR's Laboratory of Biochemistry and Molecular Biology, highlighted the power of combined biochemical and high-resolution structural studies, which they used to elucidate the molecular mechanism of histone incorporation into the nucleosome. David L. Levens, MD, PhD, of the CCR Laboratory of Pathology, summarized his efforts to uncover the interplay between conventional transcription factors, dynamic supercoils, and DNA topology-sensing proteins in the control of *c-Myc* expression levels. Gordon Hager, PhD, of the CCR Laboratory of Receptor Biology and Gene Expression, discussed the tremendous contribution cellular imaging methods have made recently to the field, making it possible for the first time to probe the dynamic properties of chromatin proteins in living cells.

One of the most fascinating and important areas in chromosome biology has been the emergence of epigenetics, the theme of the second session. Yi Zhang, PhD, of the University of North Carolina at Chapel Hill, highlighted his work in understanding the activity of demethylases and their biological significance. Shiv Grewal, PhD, of CCR's Laboratory of Biochemistry and Molecular Biology, described the recent progress he has made in elucidating the role of RNAi- and heterochromatin-mediated epigenetic control of the genome. Susan Gottesman, PhD, who works in the Laboratory of Molecular Biology at the CCR, discussed the mechanism of action and several regulatory outcomes of small RNAs in bacteria, and Carlo Croce, MD, of Ohio State University, emphasized the benefits of the microRNA expression profiling of human tumors.

The third session focused on cellular organization of gene expression. David Spector, PhD, from Cold Spring Harbor Laboratory, discussed his work in understanding the dynamics of a certain class of proteins essential in epigenetic silencing mechanisms—called polycomb group proteins—and how they contribute to the inherited epigenetic state of a gene. Steven Kosak, PhD, of Fred Hutchinson Cancer Research Center, described the progress he has made in determining whether gene regulation is related to a general pattern of chromosome organization, and Jeannie Lee, MD, PhD, of the Howard Hughes Medical Institute at Harvard Medical School, spoke about the studies she is performing to better understand the process of X-chromosome inactivation.

DNA damage is a leading cause of tumor formation. The fourth session examined factors leading to such damage and several mechanisms of repair. Frederick Alt, PhD, of the Howard Hughes Medical Institute at Children's Hospital in Boston, described his study comparing classical nonhomologous end-joining and an alternative nonclassical pathway in the repair of DNA double-strand breaks. André Nussenzweig, PhD, of CCR's Experimental Immunology Branch, discussed his work in understanding the maintenance of genomic stability in lymphocytes. Dr. Misteli examined the role of genome spatial organization in the formation of chromosomal translocations, and Geneviève Almouzni, PhD, from Institut Curie, discussed the efforts she is making to better understand the function of chromatin assembly factors *in vivo* and also in connection with replication, repair, and control of histone pools. Michael Bustin, PhD, of CCR's Laboratory of Metabolism, described recent findings regarding the cellular response to DNA damage.

In the last session, which focused on genomic instability, Titia de Lange, PhD, of Rockefeller University, highlighted some of her recent findings on the molecular mechanisms by which human and mouse telomeres hide chromosome ends from the DNA-damage response. Thea Tlsty, PhD, of the University of California, San Francisco, discussed the importance of understanding the earliest molecular changes in cancer formation. David Pellman, MD, of Dana-Farber Cancer Institute, described mechanisms by which polyploidy might compromise genetic instability, and Thomas Ried, MD, of CCR's Genetics Branch, discussed his investigations of the relationship between chromosomal aneuploidy, nuclear structure, and gene expression in cancer.



The symposium, which also included a poster session and reception sponsored by the Foundation for the National Institutes of Health, was a tremendous success. As was clear

during the event, the teamwork that the CECB makes possible and the leadership it provides are helping many intramural and extramural scientists make great strides in identifying the role of chromosome biology in cancer and other diseases. The symposium was one of a series of meetings and workshops currently planned by the CECB, including a technical workshop on chromatin immunoprecipitation cosponsored by the Systems Biology Faculty that will be held on July 9, 2007, in the Masur Auditorium on the NIH campus in Bethesda, and a CCR postdoc retreat on chromatin biology on January 28, 2008. For more information on these events, visit the CECB Web site (<http://ccr.cancer.gov/initiatives/CECB>). Chromosome biology is alive and well at the NCI and will be a core component of our basic discovery portfolio and a promising new direction in our efforts to develop novel therapeutic strategies for many years to come.

Robert H. Wiltout, PhD

Director
