

■ FROM THE DIRECTOR

High Risk, High Rewards: The 2007 NCI Director's Innovation Awards

The 2007 NCI Director's Innovation Awards, presented at the recent Intramural Scientific Retreat, demonstrate once again the breadth and depth of CCR's research program.

These awards recognize and support those scientists who are exploring novel, high-risk research projects that, if successful, could have a substantial impact on their respective fields. First awarded in 2006, these awards provide additional funding for a scientist to pursue a new idea or technique that he/she has developed into a thoughtful, well-designed research proposal. This highly competitive process involves conceptualizing, justifying, and planning a study that is focused on 1) the development of a new approach or technique, or 2) the novel application of an existing approach/technique to a highly significant and/or difficult problem in cancer research. Each proposal is evaluated by a review panel of experts. This year's Principal Investigator (PI) award recipients included five CCR investigators: Steven K. Libutti, MD; Jacek Capala, PhD; Tom Misteli, PhD; Christoph Rader, PhD; and Di Xia, PhD. In addition, 25 other CCR scientists received the Career Development Award. This article highlights the proposals of CCR's PI award recipients.



Robert H. Wiltrott, PhD

Tumor-Targeting Nanoparticles and Radiotherapy: A Promising Combination

Drs. Libutti (Surgery Branch) and Capala (Radiation Oncology Branch) are a great example of combining complementary strengths. They submitted a winning joint proposal for a study that will explore the use of tumor-targeting nanoparticles to increase the efficacy of radiation therapy for cancer patients.

Colloidal gold is a neutral gold particle synthesized through the combination of gold chloride and sodium citrate. It has been used safely for decades as a therapeutic for patients with arthritis. The particle measures 20–30 nm in diameter and can be linked irreversibly to proteins, peptides, synthetic drugs, and nucleotides. In addition to its properties as a nano-carrier, colloidal gold, being a high-Z element, may also increase the radiation dose delivered specifically to the target cells. TNF α -PEG-colloidal gold (CYT-6091), a recently developed nanoparticle, has been shown to selectively travel to tumor tissue, based on the nanoparticle properties of colloidal gold. Currently, this agent is being evaluated for its ability to selectively deliver TNF α to tumors in a phase 1 clinical trial that is being

conducted by the Surgery Branch's Tumor Angiogenesis Section.

Given the high mass of gold, Drs. Libutti and Capala believe that tumor tissue containing CYT-6091 will receive higher doses of radiation because of the secondary photoelectrons induced in the gold nanoparticles by conventional radiotherapy. The possible synergistic effect of such a combination will be studied *in vitro* using clonogenic survival assays, and *in vivo* using both mouse xenograft and syngeneic tumor models. If successful, this combined approach may result in the ability to lower the external radiation doses necessary to control cancer and, thereby, minimize the side effects while enhancing the benefits of radiation therapy. The potential benefits of this research are significant, both with respect to its therapeutic promise as well as the potential to develop new technologies based on the properties of colloidal gold. In addition, this collaboration between the Surgery Branch, the Radiation Oncology Branch, and an industry partner utilizes the unique environment of the CCR, which fosters innovation and high-risk, yet potentially high-impact translational science.

Aging and Tumor Formation: Investigating the Molecular Link

Aging is a major cancer risk factor. The innovative proposal by Dr. Misteli (Laboratory of Receptor Biology and Gene Expression) explores basic cell biological discovery to address one of the most pressing issues in cancer research—the mechanisms of age-related tumor formation. It is estimated that by the year 2030, more than 70% of new tumors will occur in individuals 65 years and older. Elucidation of the molecular mechanism involved in physiological aging is critical for advancing our understanding of tumor formation. The naturally occurring premature aging disorders are powerful tools for studying human aging. Dr. Misteli's laboratory has used the premature aging disease Hutchinson-Gilford progeria syndrome (HGPS) as a model for understanding how genome organization contributes to physiological processes, disease, and aging. ([Click here to see his article](#) on this topic in this issue.) HGPS is caused by a single point mutation in the lamin A/C gene, which encodes for one of the key structural proteins of the cell nucleus, and is characterized by numerous nuclear defects, including increased DNA damage and aberrant chromatin organization. The same molecular mechanism responsible for HGPS is also at work during normal aging. Dr. Misteli's award-winning proposal builds on his previous research in this area.

Dr. Misteli and his team will now undertake the first comprehensive investigation of the molecular link between aging and tumor susceptibility. They will systematically compare the gene expression profiles in a collection of tumor-prone and tumor-resistant premature aging disorders. The major premature aging diseases are ideally suited to address this question because they can be sharply classified according to their tumor susceptibility: Bloom syndrome and Werner syndrome's are characterized by dramatically increased tumor susceptibility, whereas Cockayne's syndrome, trichothiodystrophy, and HGPS patients do not develop tumors.

Both conceptually and technically innovative, this genome-wide expression analysis is the first systematic approach toward identifying age-related tumor genes and is also the first transcriptome comparison among premature aging disorders. Candidate genes will be

validated by comparing their expression levels in young and old individuals, and in old individuals with and without a history of cancer. Given that splice variants of the lamin A/C gene are found in HGPS (Scaffidi P and Misteli T. *Science* 312: 1059–63, 2006), these analyses will be complemented by a systematic search for alternative splice variants of 600 cancer-associated genes using LISA (layered and integrated system for splicing annotation) high-throughput RT-PCR analysis developed by a collaborator, Dr. Benoit Chabot (University of Sherbrooke, Québec, Canada). In the long-term, identification of age-related tumor-susceptibility genes will provide the basis for novel diagnostic and therapeutic strategies.

Engineering Hybrid Therapeutics

Dr. Rader (Experimental Transplantation and Immunology Branch) won an award for his plan to develop an innovative technology that will impact both translational cancer immunotherapy and antibody engineering. This new technology allows for the development of hybrid therapeutics consisting of a small molecule component and antibody component.

In collaboration with Terrence R. Burke, Jr., PhD (Laboratory of Medicinal Chemistry), Dr. Rader's team will generate and evaluate a hybrid therapeutic that targets a cell surface receptor expressed on acute myelogenous leukemia cells with picomolar affinity. Although the focus of Dr. Rader's research is cancer immunotherapy, the generic design of the technology will have broad applicability beyond oncology, particularly in areas with approved monoclonal antibodies, including infectious and autoimmune diseases.

P-glycoprotein: Solving Its Crystal Structure

Multidrug resistance (MDR) has a profound clinical impact in the treatment of microbial infections, in cancer chemotherapy, and in organ transplantation. Although the mechanisms of MDR appear to be complicated, the expression of P-glycoprotein (P-gp), an integral membrane protein with 12 predicted transmembrane segments, on the surface of a number of cancer cells has been shown to play a role in MDR. Because an understanding of the mechanism of P-gp function requires a detailed three-dimensional (3-D) knowledge of the molecule, a high-resolution crystal structure of P-gp has been sought for many years, yet remains a major challenge. In fact, structures of very few integral membrane proteins have been solved due to two main obstacles: (1) obtaining large amounts of these proteins, and (2) growing crystals suitable for X-ray diffraction experiments. Dr. Xia (Laboratory of Cell Biology) submitted a winning proposal that deals with the second aspect of this problem.

Conformational variability is a unique property essential for the function of biological macromolecules, and visualization of different conformers is critical for understanding the mechanisms by which these proteins function. However, protein mobility is highly undesirable in the process of their structural elucidation by X-ray crystallography, and P-gp appears to be conformationally heterogeneous in solution. Dr. Xia plans to use a number of different conformation-sensitive monoclonal antibodies (mAbs) to select specific conformations of P-gp for crystallization. He believes that the use of mAb fragments will aid crystallization by trapping and stabilizing specific conformers. Monoclonal antibodies have been used before to enhance crystallization, but not to selectively isolate specific

conformers. Dr. Xia and his team plan to use known P-gp mAbs to quantitatively assay their binding to P-gp in the presence or absence of various compounds to select for drugs that specifically enhance the binding of mAb. The resulting P-gp-mAb complex will then be purified and crystallized using methods developed by Dr. Xia's laboratory that have proven successful in obtaining two other membrane protein crystals. Collaborators on this project include Drs. Suresh Ambudkar and Michael Gottesman (Laboratory of Cell Biology) and Dr. Dimiter Dimitrov (CCR Nanobiology Program).

In addition to these four award-winning proposals, 25 other CCR scientists and clinicians received the Career Development Award. Congratulations to Dalit Barkan, PhD; John A. Beutler, PhD; Chi-Ping Day, PhD; Michael G. Espey, PhD; Jeffrey S. Isenberg, MD; Amy Jacobs, PhD; Jonathan L. Jacobs, PhD; Chamelli Jhappan PhD; Andrew Jobson, PhD; Su Young Kim, MD, PhD; Christophe Marchand, PhD; Oyindasola Oyelaran, PhD; Jung-Eun Park, PhD; Jason W. Rausch, PhD; Christophe Redon, PhD; Olga Sedelnikova, PhD; Rosalba Salcedo, PhD; Christina H. Stuelten, PhD; Binwu Tang, PhD; Michael Tangrea, PhD; William Telford, PhD; Masaki Terabe, PhD; Takeshi Tomita, PhD; Tiffany A. Wallace, PhD; and Yili Yang, PhD.

For the complete list of this year's winning proposals, visit http://ccr.cancer.gov/news/ccr_news_innovation_awards.asp.

Robert H. Wiltrott, PhD

Director