

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Advances at the Center for Cancer Research at the National Cancer Institute's Medical Oncology Branch

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H&O What is the role of the Center for Cancer Research within the National Cancer Institute?

GG The Center for Cancer Research (CCR) is the basic and clinical research arm of the Intramural Research Program (IRP) of the National Cancer Institute (NCI; see <http://ccr.nci.nih.gov/>). It is a community of scientists who integrate basic research discovery with the development of novel interventions against cancer and AIDS. CCR is home to a unique mix of basic, translational, and clinical scientists who work in multidisciplinary teams to pursue new approaches for the prevention and treatment of cancer and AIDS. Our strengths span several key areas, including immunotherapy, molecularly targeted therapies for cancers and viruses, and vaccines against cancer and HIV/AIDS. We are developing strategies to detect cancer earlier, diagnose it more precisely, and prevent or treat it more effectively. As a National Institutes of Health (NIH) program, the IRP can commit resources for longer-term and relatively high-risk studies that, despite their potentially high impact, would be difficult for other research institutions to undertake. Our researchers collaborate not only with their CCR colleagues, but with many external researchers in both the private and public arenas. We draw on their expertise and they on ours to make the fastest progress possible, and to ensure that innovative findings and technologies are rapidly dispersed throughout the cancer research community.

H&O What are the recent changes at the National Cancer Institute's Medical Oncology Branch?

GG In the preceding decade, the Medical Oncology Branch (MOB) of the NCI had undergone a certain amount of fragmentation into discrete branches. We are currently in the process of rebuilding the MOB, which will optimize the clinical scientific productivity of all CCR investigators who are involved in medical oncology clinical research. There is a set of clinicians and clinician-scientists who form the core of the MOB. This structure is further buttressed by the expertise and excellence of a number of affiliated programs. My vision is to increase the affiliation between the core and affiliated branches and to carry out clinical studies under the aegis of the MOB. Additionally, the Fellowship Program, which has been one of the largest fellowship programs in the United States, will be revitalized in order to maintain a high level of excellence. The goal of the Program is to foster the development of physician-scientists with excellent clinical and research skills. Finally, within the MOB, a focus of our effort will be to hire new leaders and reconstitute programs in the four major tumor types—lung, breast, gastrointestinal, and prostate—so that each is functioning at an equally high level.

H&O Could you discuss the changes to be made to the programs in these four major tumor types?

GG It is important that both clinical research and translational studies take place in these four tumor types. My own expertise is in lung cancer, and I will organize the investigators who are already at work researching new therapies for lung cancer. The breast cancer program is currently recruiting a new leader. The gastrointestinal cancer program has been less active in recent years than the others, and we are in the process of rebuilding it now. Finally, the prostate cancer program has been running well under the leadership of Dr. William Dahut for several years; this program has developed many innovative studies. In addition to the NCI's focus on these common tumor types, there is a strong interest in rare malignancies. We have research currently under way in renal cell cancer as well as in rare hematologic malignancies such

as cutaneous T-cell lymphoma, a setting in which there are four studies currently running. The NCI's research into hematologic malignancies is quite well-established. In addition to lymphoma research, there is a good deal of research on transplantation, both in hematologic and solid-tumor malignancies. It is important to emphasize that affiliated, but independent, branches share resources, technology, nursing staff, and facilities, so the focus is on what we are able to achieve working cooperatively.

H&O How does the CCR make use of high throughput technology?

GG Facilities have been set up on the Bethesda and Frederick, Md., campuses to provide NCI scientists with access to sophisticated and high throughput genomic and proteomic technologies. For example, DNA microarrays are being used across CCR laboratories to obtain a detailed characterization of genetic alterations of cancer cells and genome-wide expression changes that lead to cancer development. Microarray platforms are now being used to interrogate the entire human chromosome to look for DNA aberrations that can be fine-mapped to specific cancer genes. Through its new Molecular Profiling Core, headed by Dr. Paul Meltzer in the Genetics Branch, CCR is embarking on a new effort to bring next-generation, ultrahigh throughput DNA sequencing technology to bear on specimens from cancer studies. With the adoption of this cutting-edge sequencing technology, the CCR will be in a position to ask important clinical genomic questions related to very low-level mutations in patients undergoing therapy. CCR scientists also have access to a broad spectrum of highly integrated, advanced proteomic capabilities through the Advanced Technology Program (ATP). For example, the ATP provides quantitative, high throughput mass spectrometry to comprehensively identify and characterize proteins in complex biological samples. All of these resources make the NCI a highly enriched environment to conduct basic, translational, and clinical research.

H&O Could you highlight agents currently under research within the IRP?

GG The NCI clinical program routinely makes long-range commitments of resources to support high-risk, long-term basic and translational research. The close collaboration among scientists with diverse backgrounds enables the NCI clinical program to fuse new technologies with biology, to perform clinical studies that emphasize science-driven trials. Clinical studies are aimed at answering critical questions in a particular disease or disease process, and at identifying promising new therapeutic interventions that can then be confirmed in larger studies carried out across the country at centers that are part of the NCI-supported extramural program.

The CCR has many examples of collaboration between institutions or between intramural investigators, extramural investigators (including collaborative arrangements with general clinical research centers), and/or investigators in the private sector. Specifically, CCR's clinical program is actively participating in a several trans-NIH initiatives and in partnerships with researchers outside CCR that focus on establishing interdisciplinary and multidisciplinary research teams. Here are some examples of our collaborative research efforts.

Topoisomerase I Inhibitors: Indenoisoquinolines

Investigators, led by Dr. Yves Pommier, Chief of the Laboratory of Molecular Pharmacology (LMP), from the CCR, the Developmental Therapeutics Program (DTP), and the Division of Cancer Treatment and Diagnosis have been collaborating with Dr. Mark Cushman of Purdue University in synthesizing derivatives that would show greater activity as topoisomerase I (TOP1) inhibitors and anticancer agents. As a result of that collaboration, a class of derivatives called indenoisoquinolines was discovered. In comparison with the camptothecins, the indenoisoquinolines are more potent inhibitors of TOP1 and target the genome at different sites. The indenoisoquinolines are also more stable chemically. Three lead compounds have been selected for joint development by DTP and CCR from approximately 400 derivatives. Dr. William Bonner of the LMP discovered and holds the patent for the histone gamma-H2AX as a pharmacodynamic biomarker for the indenoisoquinolines. This biomarker is being developed in collaboration with Dr. James Doroshow of the LMP and will be available when the drugs are tested in early-phase clinical trials.

Molecular Diagnosis of Lymphoid Malignancies

Dr. Louis Staudt, Deputy Chief of the Metabolism Branch at the CCR, focuses on the molecular diagnosis of lymphoid malignancies. His group has developed an accurate and reproducible single DNA microarray that can provide diagnostic and prognostic information for patients with cancer. Dr. Staudt and colleagues have also developed molecular predictors of outcome—length of survival or response to therapy—in diffuse lymphoma, mantle-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia, based on gene expression profiling of diagnostic biopsies. This technology was also used to determine that diffuse large B-cell lymphomas (DLBCL) can be subclassified into three molecularly and clinically distinct diseases: germinal center B-cell-like DLBCL, activated B-cell-like DLBCL, and primary mediastinal B-cell lymphoma. These subtypes arise from B cells at different stages of differentiation, use different oncogenic pathways, and exhibit distinct survival rates following treatment. The discovery of the lymphoma subtypes has

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also led to the identification of new molecular targets. Dr. Staudt's group is currently attempting to identify additional molecular targets in lymphomas. Recently, it was demonstrated that gene expression profiling is an accurate, quantitative method to distinguish Burkitt lymphoma from DLBCL, which is a critical diagnostic decision that alters treatment choice. A diagnostic test based on gene expression profiling was 100% accurate in identifying cases of classic Burkitt lymphoma.

Cancer Vaccines

The field of therapeutic cancer vaccines is in an active stage of both preclinical and clinical investigation. Research at the CCR in this setting is led by Dr. Jeff Schlom, Chief of the Laboratory of Tumor Immunology and Biology (LTIB). Though no therapeutic cancer vaccine has yet been approved by the US Food and Drug Administration, recent clinical trials employing a range of vaccines and different cancer types are presenting evidence of enhanced patient survival with minimal toxicity. The LTIB has been extremely active in studies developing and analyzing new recombinant vaccines/strategies. These novel vaccines not only contain genes for tumor antigens, but also for multiple immunostimulatory molecules to enhance the host immune response to the tumor antigen. These vaccines are being employed in clinical trials in patients with melanoma as well as prostate, colorectal, ovarian, and breast cancers. In addition to clinical trials being carried out by the MOB at the NIH Clinical Center and the National Naval Medical Center, collaborative trials employing the new vaccines developed at the CCR are being conducted at numerous cancer centers throughout the United States.

Recent evidence has also emerged from both preclinical and clinical studies that therapeutic cancer vaccines can be employed safely and effectively with conventional therapeutics such as local radiation of tumor, certain chemotherapeutic agents, and hormones. This will potentially enable the use of such vaccines earlier in the disease process.

Therapeutic Immunotoxins

Dr. Ira Pastan, Chief of the Laboratory of Molecular Biology, is leading the effort to develop therapeutic immunotoxins. Here are some examples:

- Immunotoxin HA22 (CAT-8015), a new therapy for B-cell malignancies, now being tested, or soon will be, at centers in the United States, England, and Poland.
- An immunotoxin for mesothelioma and ovarian cancer (SS1P) was also developed, and tested at NIH and University of Oklahoma and University of Chicago.
- An immunotoxin against glioblastoma (TP38) was tested at Duke University by Dr. Bigner.
- A new discovery of the mesothelin gene identified the protein, and monoclonal antibodies were made against it. Monoclonal antibodies have been given to

many investigators in the United States and Japan for research studies.

- New antibodies made against mesothelin have been humanized, licensed, and are in phase I clinical studies for mesothelioma and pancreatic cancer therapy.

Hematopoietic Stem Cell Transplantation

Some of the goals of the Experimental Transplantation and Immunology Branch, led by Dr. Ronald Gress, are to offer the potentially curative therapy of hematopoietic stem cell transplantation to patients with cancer who cannot otherwise receive it by overcoming the four primary barriers of transplant: graft rejection, graft-versus-host disease (GVHD), tumor relapse, and lack of immune reconstitution; and to join with an extramural partner in these efforts to complement strengths of each. The approach to this research is based on an intramural transplant program that integrates efforts across four laboratories, each focused on an aspect of biology relevant to the four barriers, using investigators with research interest and clinical expertise in transplantation. One translational initiative arising from this effort is the characterization of the role of cytokine-defined T-cell subsets in transplant biology, carried out by Dr. Dan Fowler. Certain such subsets were found to inhibit graft rejection, regulate GVHD, and mediate antitumor effects in preclinical work. These cells have been generated as a therapeutic product and have passed through phase I trials. In collaboration with Hackensack University Cancer Center, which has a large transplant patient population but a limited laboratory base, we will jointly assess using these cells to perform hematopoietic stem cell transplant therapy with the intent that the cells will act to replace the conventional use of high- (or intermediate-) dose chemotherapy or irradiation, thus allowing patients who would not otherwise be eligible for transplant therapy to receive it as a cancer treatment.

Ovarian Cancer: Combination Therapy

Dr. Elise Kohn of the Laboratory of Pathology is leading a phase I study of the safety and antitumor effects of a combination of two drugs that impede angiogenesis, bevacizumab (Avastin, Genentech) for the treatment of advanced colorectal cancer and sorafenib (Nexavar, Bayer/Onyx) for the treatment of advanced kidney cancer. Each agent attacks tumor blood vessels through different mechanisms. A preliminary look using dynamic contrast-enhanced magnetic resonance imaging indicates that the combination reduced the blood supply to many patients' tumors. Also, tumor size decreased in 33% of patients (some with rapid shrinkage), and tumors stabilized in almost all other ovarian cancer patients. A greater benefit than expected was seen with the combination.

In summary, a great deal of exciting research is ongoing through the CCR, with more planned in the future.