Center for Hematology and Oncology Molecular Therapeutics

Research at the Taussig Cancer Center
Cleveland Clinic is at the forefront of the cancer drug discovery and development revolution. We have identified new molecules with anti-tumor effects, developed collaborative ties with biotechnology companies, begun training more young scientists, and expanded our base of financial support. These bold steps will result in discovery and application of new therapies to help us eliminate cancer as a significant cause of mortality.
As a result of our improved understanding of the human genome and its significance for cancer biology, we have found abnormalities within the malignant cell that present more targets for which new drugs and diagnostics can be developed.

Investigators within the Center for Hematology Oncology Molecular Therapeutics (CHOMT) and the Taussig Cancer Center will continue to translate these findings into bedside applications. The ultimate result will be a higher cure rate for cancer and, it is hoped, fewer treatment side effects.

The unique feature of CHOMT is its intimate relationship with the physicians and support staff of the Taussig Cancer Center, which facilitates the delivery of “first in man” studies and the translation of ideas from the laboratory to the clinic.

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Taussig Joins Case Comprehensive Cancer Center

In 2004, the Taussig Cancer Center finalized a partnership with Ireland Cancer Center and Case Western Reserve University to form a third part of the NCI-designated Case Comprehensive Cancer Center. This partnership strengthened the technologies for basic research, increased collaborative research opportunities, facilitated an enlarged clinical trials program, and enhanced external funding opportunities. Another important partner in drug discovery and development initiatives is the Cleveland Clinic Lerner Research Institute whose scientists work on many common and complementary projects with the investigators at Taussig.
The Center for Hematology and Oncology Molecular Therapeutics (CHOMT) was formed in 2005, spurred by a surge in both human and financial resources for therapeutic and diagnostic bench research on new therapeutics and their targets. The Center comprises six research laboratories focusing on drug discovery and development, clinical pharmacology and experimental therapeutics, and experimental hematology and hematopoiesis.

Designed as a premier translational molecular research unit, CHOMT will enhance the scientific and academic stature of the Cleveland Clinic Taussig Cancer Center, produce a new generation of physician scientists and augment availability of new diagnostic and therapeutic modalities for our patients.

Within their individual laboratories, CHOMT investigators are focused on building upon the remarkable advances in molecular biological techniques of the last 30 years. These advances are being applied to new pharmacological, immunological, biological and cellular approaches to therapeutics and diagnostics. Together with their colleagues at Lerner Research Institute, particularly in the departments of Cancer Biology, Cell Biology, Immunology and Molecular Biology and Genetics, new therapeutic and diagnostic approaches based on targeting specific genes and gene products are emerging into preclinical and clinical development.

From inception, the strategic approach of research programs within the Taussig Cancer Center laboratories is the translation of research findings from bench to clinic and the pursuit of clinical observations at the bench. Research on new drugs and diagnostics targeted at defined molecular structures will continue to increase both quality of life and length of life for patients. Our vision is to create an environment of scholarship for advancing knowledge toward curative treatment for our patients. The following are examples of our research activities and advancements as we work to discover and translate laboratory findings into clinical trials and, ultimately, reduce cancer morbidity and mortality. We are positioning CHOMT to become one of the major centers in the world for research on biologically targeted therapeutics.

In addition, Cleveland Clinic participates in the Southwest Oncology Group, Radiation Therapy Oncology Group, Children's Oncology Group, Blood-Brain Barrier Consortium, New Approaches to Brain Tumor Therapy and the Gynecologic Oncology Group. Through physician participation, cancer patients have access to a variety of clinical trials investigating novel therapeutics.
Collaboration
Drug Discovery and Development

**CHOMT** was a natural outgrowth of the Center for Cancer Drug Discovery and Development, founded in 1998 at the Taussig Cancer Center. It enlarged our scope of activities to build for the future but remains focused on a simple mission: to bring cancer patients new, novel and effective drugs for cancer treatment. The intent is to discover and develop therapeutics with a particular focus on biological agents targeted at genes or gene products that determine the course of cancer development. We aim to translate innovative approaches into rigorous clinical trials, thus offering physicians new methods of combating cancer. The center provides a focus for investigation of new molecules in preclinical screening systems and to translate the information about novel cancer-related molecules to clinical trials. By using the principles of pharmacology and the knowledge of cancer biology, we design and develop new compounds or combinations of new biologically targeted compounds that will reduce morbidity from older treatments and reduce both the complications and mortality from cancer. Some of these molecules have already progressed into clinical trials in our ambulatory clinics and at the NIH-funded General Clinical Research Center at Cleveland Clinic.

We use innovative biostatistical methodologies to expedite evaluation of drug therapies. Our efforts include the development of online networks to acquire clinical data for rapid, comprehensive analysis. Collaboration is key. In addition to those at Lerner Research Institute and Case Comprehensive Cancer Center, preclinical and clinical research on new molecules is underway in association with organizations and companies in China, Switzerland, Israel and across the U.S. These, and collaborations with biotechnology companies in Cleveland and across the U.S. provide new drugs that inhibit tumor cell growth. Thus, as advances from **CHOMT** are ready for the more advanced stages of clinical trials, Phase II and Phase III, a rapid and efficient process can be initiated for the final steps in bringing new drugs to patients. Our objectives are to develop innovative drug screening technologies while continuing our research in the design of small molecules targeted at cellular signal transduction. We aim to use normal programmed cell death (apoptosis) as a means by which to curtail tumor development through induction of identified genes. Over the next few years, new investigators will be recruited for **CHOMT** to add to existing expertise.

Linking research to cure, the center is contributing to the emergence of the Taussig Cancer Center as one of the leading cancer research centers in the country.
Evolution

CT scans of a patient with metastatic renal carcinoma successfully treated at the Taussig Cancer Center with a new type of interferon being investigated in CHOMT laboratories. (A) Chest CT at baseline demonstrating right upper lobe pulmonary metastasis. (B) Repeat CT showing near resolution of metastatic lesion. (C) Abdominal CT at baseline demonstrating tense ascites. (D) Abdominal CT after 12 weeks of therapy showing reduction in ascites. In addition to tumor response, studies demonstrate increased interferon-stimulated genes and better patient tolerance with this type of interferon. The research is a collaborative effort between the Ministry of Health in Shanghai, which produces the interferon by recombinant DNA technology, and CHOMT, conducted as an FDA-approved investigational trial.
Interferons (IFNs) have proven an important paradigm for establishing the role of biologicals as effective therapy in human malignancies. IFNs are possibly the most potent modulators of gene expression used in clinical medicine. Through gene profiling, our laboratory and others have identified over 300 IFN-stimulated genes that influence apoptosis, immune responses and angiogenesis, and are induced in expression by IFNs. These newly identified genes may be particularly critical in mediating the anti-tumor effects of not only IFNs but also other cancer therapeutics. As a result of gene modulation, IFNs are a prototype for therapeutics that work through regulation of cellular signaling pathways. Despite substantial progress, we still do not understand the underlying mechanisms of tumor sensitivity and resistance. How to overcome resistance to IFNs and other cytokines in non-responding patients with melanoma and other malignancies has been little explored.

Our goal is to define defects in expression or activation of signal transduction components and extend our studies of interventions to correct abnormalities. These include studies of reversal of silencing of IFN-stimulated genes by methylation of tumor DNA and to enhance the effectiveness of IFN-stimulated genes by inhibition of signaling phosphatases. To determine effectiveness of these approaches, in addition to studies at the laboratory bench, we are assessing IFN-stimulated genes in patients receiving IFNs and other biologically targeted therapeutics. We anticipate that these studies will translate into more effective therapies with IFNs and other cytokines.

**Publications:**


Imagination

Drs. Joseph Bauer and Daniel Lindner were recently awarded an NIH RAID (Rapid Application to Intervention Development) award to further the preclinical development of nitrosylcobalamin (NO-Cbl).
A better understanding of how interferons (IFNs) induce apoptosis may allow their improved clinical utilization as anti-tumor agents. IFNs induce cytotoxicity in several tumor cell lines in culture and in vivo. The mechanism by which this occurs requires the function of IFN-induced gene products. To identify functionally relevant death-associated gene products, this laboratory has employed an antisense technical knockout strategy. In this approach, specific death-inducing genes, termed Regulators of Interferon-induced Death (RIDs) are inactivated by antisense gene products, thus providing a growth advantage to transfected cells in the presence of IFNs. Currently, we are studying one of these genes, inositol hexakisphosphate kinase 2, to determine how it promotes apoptosis.

In order to potentiate their clinical efficacy, IFNs are increasingly being utilized in combination therapy. In collaboration with Dr. Ernest Borden’s laboratory, our research has shown that combination of IFNs with anti-estrogens such as tamoxifen or with retinoids such as all-trans retinoic acid results in enhanced anti-tumor effects, both in cell culture and in xenograft models. Part of the increased anti-tumor activity is due to direct anti-cellular effects mediated by the drug combination, and a portion of the anti-tumor effect is secondary to enhanced host effects. One of the most important anti-tumor effects mediated by IFNs is the inhibition of tumor-induced angiogenesis. On a molar basis, IFNs are the most powerful anti-angiogenic agents currently known.

Our laboratory is also active in the area of cancer drug development. Dr. Joseph Bauer has synthesized a novel chemotherapeutic compound, nitrosylcobalamin (NO-Cbl), that consists of nitric oxide bound to vitamin B12. NO-Cbl acts as a “Trojan Horse,” and we believe this approach may target tumors through their high requirement for vitamin B12. The recent RAID award from NIH will move NO-Cbl rapidly toward clinical development.

Publications:


Vaccines have been an attractive and aggressively pursued approach to the management of cancer. A number of vaccines have been shown to generate immune responses in cancer patients. To date, however, there has been little evidence of clinical activity. A major problem is that antigens expressed by tumors are poor immunogens. Whereas viral antigens are “foreign” and highly immunogenic, tumor antigens are “self antigens,” for which a high degree of immunologic tolerance exists. It is also becoming increasingly apparent that tumors can express properties that enable them to escape immune responses. This laboratory’s research, which involves preclinical laboratory studies in animal models and clinical trials in cancer patients, has focused on how to improve the ability to break tolerance and deal with tumor escape phenomena.

An increasing body of evidence indicates that whether or not immune tolerance is broken and anti-tumor T cell responses are effectively generated depends on the function of dendritic cells, widely distributed antigen-presenting cells that are far more efficient than other antigen-presenting cells in stimulating critical cellular immune responses. This laboratory is examining methods of studying dendritic cell subpopulations and methods of targeting and activating dendritic cells in patients with cancer. The laboratory is using a novel assay to identify activated circulating dendritic cells, a cellular target for CSF-GM function that leads to enhanced immune recognition. Clinical trials applying novel methods of assessing dendritic cell function are in progress in patients with prostate cancer.

Cancer vaccines mimicking viruses may prove to be an effective approach to breaking tolerance. This laboratory is studying recombinant viral vectors encoding full-length tumor antigens to exploit the inherent immunogenicity of the virus as well as the endogenous processing and presentation of several tumor antigens. Our researchers also have been evaluating the use of a non-pathogenic virus, adeno-associated virus, as a vaccine vector. Preclinical studies targeting carcinoembryonic antigen in models of colon cancer are in progress.

Publications:


Improvement in platelet count in a patient with aplastic anemia treated with immunosuppressive therapy.

Hematologic recovery (improvement of absolute neutrophil count) in a patient with severe neutropenia due to large granular lymphocyte leukemia.

In this patient presumed to have myelodysplastic syndrome, large granular lymphocyte leukemia was diagnosed in the laboratory and successfully treated with cytoxan.
Researchers in this laboratory conduct translational investigations of the pathophysiology of bone marrow failure syndromes, including aplastic anemia, paroxysmal nocturnal hemoglobinuria, myelodysplastic syndromes and related diseases. Bone marrow failure syndromes, as stem cell disorders, are instructive with regard to the function of the stem cell compartment, factors that regulate blood cell production and causes of malignant clonal diseases of the hematopoietic system. Two pathophysiologic aspects are the focus of our research: defective hematopoietic stem cell function and its consequences and immune pathogenesis of stem cell damage.

In aplastic anemia, stem cell destruction is mediated by cytotoxic T cells. We are employing molecular methods of T cell receptor (TCR) analysis to identify and characterize autoimmune T cell clones. Their TCR clonotypes have diagnostic utility, and researchers are developing tests for autoimmune conditions based on the measurement of the frequency of the pathogenic clones in blood and tissues affected by the disease. Identification of expanded T cells clones based on their unique TCR structure can also be applied to study anti-tumor immune surveillance such as that seen following allogeneic bone marrow transplantation in the form of the graft versus leukemia effect. Using this technology, various studies are conducted in clonal T cell malignancies such as large granular lymphocyte leukemia, hairy cell leukemia and T cell lymphomas.

Defective stem cell function may result not only in aplastic anemia but also in other hematologic conditions. Myelodysplastic syndrome often evolves from aplastic anemia. Genetic damage is a key aspect in the pathogenesis of myelodysplasia that often progresses into leukemia. Due to the high incidence of this condition in the elderly, our studies also deal with the function of stem cell compartment in age. Stem cell senescence and exhaustion in age or during disease are important targets of this laboratory’s investigations, conducted using high-density expression and SNP-arrays.

**Publications:**


Invention
This laboratory is focused on finding a key in biochemical change in phosphorylation of topoisomerase II, a DNA replication enzyme, for therapeutic activities of the chemotherapies, doxorubicin or etoposide. A classic example of translating research findings into clinical care, this discovery may lead to development of an antibody that might be predictive of therapeutic response to topoisomerase II inhibitors.

In the area of Clinical Pharmacology-Experimental Therapeutics, research currently is being conducted in the regulation of topoisomerases during cell growth and differentiation, the goal of which is to determine the regulatory function of topoisomerase IIα and β as downstream effectors of all-trans retinoic acid in cell growth and differentiation. In the area of molecular pharmacology of topoisomerase inhibitors, researchers are testing the functional role of site-specific phosphorylation of topoisomerase II isozymes in cell proliferation and drug stabilized DNA cleavable complex formation. Finally, novel agents for the treatment of cancer are being evaluated during Phase I and Phase II trials in patients. Promising pre-clinical leads are actively being pursued in translational studies to maximize efficacy and reduce toxicity of cancer chemotherapy.

**Publications:**


**Taussig Cancer Center: One of the Nations Best**

The Cleveland Clinic Taussig Cancer Center is recognized by *U.S. News & World Report* as one of the top 15 cancer centers in the country and the No.1 cancer center in Ohio in its annual hospital survey. The 2006 survey also ranked Cleveland Clinic the 3rd best hospital in the country. For details, visit clevelandclinic.org.

**The Cleveland Clinic Taussig Cancer Center**, which was dedicated in July 2000, is one of the world’s newest and most advanced center for cancer treatment, research and education. Designed by world-renowned architect Cesar Pelli, the $50 million facility occupies 165,000 square feet on Cleveland Clinic’s main campus. Two hundred fifty physicians at Cleveland Clinic in a variety of specialties are involved in the treatment of cancer, and scores of basic and clinical research projects are under way here at any given time.

**The Cleveland Clinic Lerner Research Institute** houses state-of-the-art resources for scientists as they investigate the causes of disease and develop new treatments to prolong and improve the lives of patients. The institute oversees more than 1,000 research projects with a budget of over $124 million. Four-fifths of this budget are received from external grants and contracts — a dramatic endorsement for the quality of Cleveland Clinic research. Residents and fellows are frequently involved in these projects.
From inception, the strategic approach of research programs within the Taussig Cancer Center laboratories have focused on translation of research findings from bench to clinic and the pursuit of clinical observations at the bench. This research on new drugs and diagnostics targeted at defined molecular structures will continue to increase both quality of life and length of life of patients at Cleveland Clinic and worldwide.

For more information on collaboration, training opportunities or clinical trials, please call Dr. Ernest Borden at 216.444.8183 or 800.553.5056, ext. 48183, or any of the other investigators through these numbers.

Our vision is to create a premier translational molecular research unit that will enhance the scientific and academic stature of the Taussig Cancer Center, produce a new generation of physician scientists, and augment availability of new diagnostic and therapeutic modalities for our patients.

For more information, visit the Taussig Cancer Center Web site at clevelandclinic.org/cancer.