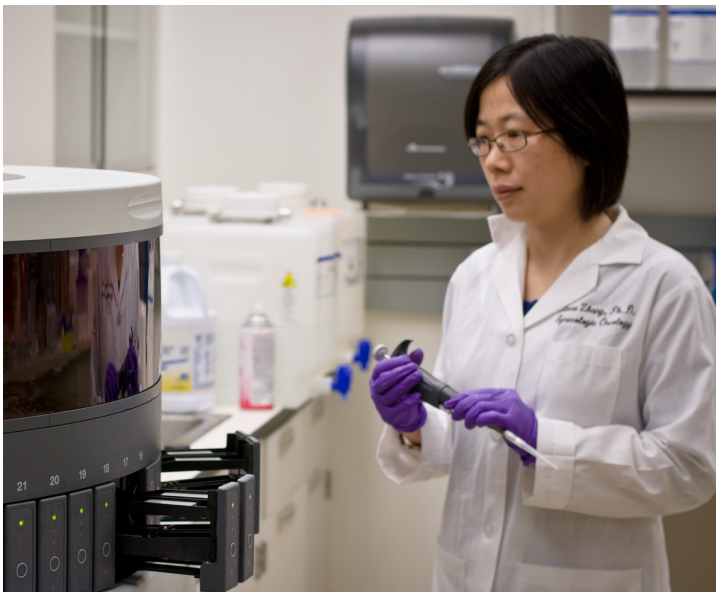




# Red and Charline McCombs Institute for the Early Detection and Treatment of Cancer 2010 Annual Report



THE UNIVERSITY OF TEXAS  
**MD Anderson**  
~~Cancer~~ Center

Making Cancer History®

# Metastasis Research Center

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**Director: Lee M. Ellis, M.D.**



Metastasis is the number one cause of cancer death, and research in the biology of metastasis is essential if we are to make progress in caring for patients with advanced stage disease. The Metastasis Research Center (MRC) at The University of Texas MD Anderson Cancer Center brings together, physically and intellectually, basic scientists and clinical oncologists from different disciplines and departments into a cohesive unit for the purpose of developing new research strategies to better understand the biology of metastasis and to translate this knowledge into improving treatment of patients with metastatic disease.

The accomplishments of the MRC in 2010 include 232 publications, 36 peer-reviewed active grants, 38 non-peer reviewed contracts or support from foundations, 27 collaborations with other McCombs Centers, and 29 extra-institutional collaborations.

In 2010, the leadership of the MRC transitioned from Isaiah Fidler, Ph.D., to Lee Ellis, M.D., as Dr. Fidler wanted to devote more time to his research on therapy for brain metastasis. This transition has also allowed for others within the institute, from different departments, to play leadership roles. Thus, the appointments of Menashe Bar-Eli, Ph.D. (Cancer Biology), Elsa Flores, Ph.D. (Molecular and Cellular Oncology), and Sendurai Mani, Ph.D. (Molecular Pathology), as co-directors allow for different perspectives and insights on metastasis research.

The MRC consists of more than 30 members from diverse departments contributing their knowledge to the field of metastasis biology. All major tumor sites are included in the MRC and members of the MRC are also members of other centers and programs throughout the institute; this leads to extensive sharing of ideas and resources.

The main objectives of the MRC are to provide 1) support for innovative research in the biology of metastasis; 2) educational opportunities in the field of metastasis; and 3) forums for the exchange of ideas and resources. The MRC sponsors an annual retreat that is held in early December of each year. The retreat includes presentations from members of the MRC. The day culminates with the annual Fidler Lectureship in Metastasis Biology, with the speaker selected by members of the MRC. This year's Fidler Lecturer is Joan Massague, Ph.D, from Memorial Sloan-Kettering Cancer Center.

The MRC supports two grant-funding opportunities per year (April and October). Each request for applications is thematic, addressing a distinct area of metastasis research. These grants are provided for one-two years of support with the provision that the recipients of the grant use these funds to generate preliminary data to support the subsequent submission of an R01 (or equivalent) grant.

The MRC consists of sub-themes including 1) the tumor microenvironment (led by Dr. Bar-Eli), 2) genomics and genetics of metastasis (led by Dr. Flores), and 3) cancer stem cells and epithelial-to-mesenchymal transition (EMT) (lead by Dr. Mani, Department of Molecular Pathology). Small working groups meet to discuss strategies to advance the field in these particular areas. In addition, each section of the MRC alternates in leading institutional grand rounds every six months. Lastly, the MRC co-sponsors the Tuesday noon seminar series in conjunction with the Department of Cancer Biology; designated speakers sponsored by the MRC lecture on the topic of metastasis biology and therapy. All individuals from MD Anderson are encouraged to attend these lectures and have the opportunity to meet with the guest lecturer.

## **Background**

The major cause of death from cancer is due to metastases that are resistant to conventional therapy. The pathogenesis of metastasis depends on multiple interactions of metastatic cells with favorable host homeostatic mechanisms. Interruption of one or more of these interactions can lead to the inhibition or eradication of cancer metastasis. For many years, all of our efforts to treat cancer have concentrated on the inhibition or destruction of tumor cells. Strategies both to treat tumor cells (such as chemotherapy, biologic therapy and immunotherapy) and to modulate the host microenvironment (including the tumor vasculature and stroma) offer additional approaches for cancer treatment. Recent advances in our understanding of the biologic basis of cancer metastasis present unprecedented possibilities for translating basic research to the clinical reality of cancer.

## **The Tumor Microenvironment**

The development of tumor metastasis is a complex cascade of events. However, according to the “seed and soil” concept, cells from the primary tumors will preferentially grow in distant organs with supportive tumor microenvironment. An expanding amount of data reveal the importance of an inflammatory microenvironment and stroma in cancer initiation and progression, which brings new directions and approaches to cancer treatment. Genetics and functional experiments indicate that inflammatory cells such as tumor-infiltrating monocytes/macrophages, neutrophils, mast cells eosinophils and activated T and B lymphocytes, as well as stromal fibroblasts, contribute to malignancies by releasing growth and survival factors, extracellular proteases, and proangiogenic factors. It is now clear that any treatment of primary and metastatic tumors should also target the tumor microenvironment. Several of our MRC members focus their work on this emerging field and published seminal studies contributing to our understanding of how the tumor microenvironment supports tumor growth and metastasis with the emphasis on developing new treatment modalities.

## **Genomics and Genetics of Metastasis**

The development of cancer is a multi-step process. Accumulating genetic changes within a tumor lead to the formation of an aggressive tumor and ultimately metastasis of that tumor to distant sites. Understanding the complex genetic events that lead to metastatic cancer is critical to designing targeted therapy for patients with metastatic disease.

Many members of the MRC are focused on understanding the complex genetic changes that lead to metastatic disease using model organisms, such as mice, that can be engineered to express genetic changes that occur in human cancer. Additionally, our investigators are using the latest high throughput technology to understand the genetic changes that have occurred throughout the whole human genome in the metastases of different cancer types. Data from these studies will lead to a more complete understanding of metastatic cancer and can lead to the design of more targeted therapy.

### **Cancer Stem Cells, EMT and Metastasis**

Carcinoma, which originates in epithelial tissues, accounts for more than 80% of all cancers. During carcinoma progression, tumor cells break apart from one another and acquire mesenchymal traits, including invasiveness and the ability to migrate, by activating a latent embryonic program, EMT. However, in order to spawn fully-formed secondary tumors, disseminated tumor cells also seem to require the ability to self-renew, similar to normal stem cells. This recent speculation raised the possibility that the EMT process, which enables cancer cell dissemination, also endows cancer cells with self-renewal capabilities. Indeed, cells induced to undergo EMT were found to exhibit properties associated with normal and transformed stem cells, including increased tumor forming efficiency. This evidence suggests that the EMT process is a potential target for combating metastatic cells at both the primary tumor and the site of dissemination. Several of our MRC members are focused on understanding the biology of EMT and the generation of cancer stem cells with the aim of identifying new therapeutic agents, which could help prevent and treat metastatic tumors.

### **Planned Research**

We are actively pursuing research in three distinct fields: 1) the tumor microenvironment of metastasis and resistance to therapy; 2) genetics and genomics of metastasis; and 3) cancer stem cells and epithelial to mesenchymal transition. The clinical trials of tomorrow are based on today's basic and translational research. For more than 25 years, the nation's leading metastasis research has been conducted at MD Anderson. Our studies are on the cutting edge, using state of the art technology, always keeping in mind that our ultimate goal is to improve the lives of our patients who suffer from metastatic disease.

# Center for Advanced Biomedical Imaging

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**Interim Director: Marshall Hicks, M.D.**



The Center for Biomedical Imaging Research (CABIR) is housed within the South Campus Research Building 3 (SCRB-3) and is a collaboration between The University of Texas MD Anderson Cancer Center, The University of Texas Health Science Center at Houston (UTHSC-H) and GE Healthcare.

Currently, the CABIR is comprised of staff from a number of departments in the Division of Diagnostic Imaging. These include Imaging Physics (IP), Experimental Diagnostic Imaging (EDI), Nuclear Medicine and Diagnostic Radiology. Additionally, scientists and physicians from UTHSC-H and GE Healthcare are part of the CABIR and occupy offices and laboratories within SCRБ-3. Faculty and scientists pursue the development of innovative diagnostic medicines and devices, useful in current and new imaging technologies, and in the early detection of cancer. Their aims are to 1) develop new diagnostic methods that will be more sensitive and accurate in assessing the extent of disease; 2) develop and evaluate new PET and MR molecular imaging agents; 3) design and test new imaging devices and methods; 4) determine maintenance pathways of cancer; 5) identify targets for anticancer therapy; and 6) monitor anticancer and cellular therapies. These novel imaging approaches will allow physicians to select individualized therapeutic regimens and help predict whether or not a particular therapeutic approach is effective early in the treatment process.

The initial occupation of space in the new facility began in March of 2010 when some faculty and staff from IP and EDI were relocated to occupant-ready office and laboratory space located on levels 1 and 2. Additional moves by faculty and staff continued throughout the year as office and laboratory space became available. By the end of 2010, some IP faculty and staff had occupied offices and established their laboratories on levels 1 and 2.

Level 1 contains a spacious Clinical Imaging Facility for imaging studies involving patients enrolled in clinical imaging protocols. Additionally, large animals will be used to conduct research studies on the biodistribution, pharmacokinetic and pharmacodynamic properties of imaging agents in preclinical development. The major pieces of imaging equipment include PET/CT, MR and CT systems provided by GE Healthcare. Also on level 1, we have constructed a facility that will allow us to produce PET radioisotopes and then formulate these with molecular agents to generate radiopharmaceuticals for research and testing. This facility contains a GE Cyclotron capable of producing a number of PET radioisotopes, a Good Manufacturing Production (GMP) area for production of new radiopharmaceuticals and a series of laboratories dedicated to developing and testing new radiotracers for testing in animals and cancer patients.

The new laboratory spaces on level 2 include the Magnetic Resonance Systems Laboratory and Imaging Processing and Visualization Laboratory of the Department of IP. Plans are currently underway to design and build out additional research space for the Department of IP. These will include the following laboratories:

- Expansion of Imaging Processing and Visualization Space
- Image-Guided Therapy and Navigation
- Optical Imaging
- Digital Imaging
- Photo-Acoustics Imaging Research
- Computational Core Facility
- Nuclear Imaging

Level 2 also houses offices and space for the Advanced Instrument Development Laboratory of EDI.

### **New Hardware Technologies Development**

In order to develop personalized, targeted therapy, the clinician must be able to see the cancer; to pinpoint its location, visualize its molecular and functional abnormalities, guide treatment, and monitor the effects of therapy. New imaging technologies are being invented and continually optimized by faculty working in the CABIR to make this a reality.

Wai Hoi “Gary” Wong, Ph.D., professor in Department of EDI and director of PET instrumentation development, and renowned expert on PET imaging devices, has built a new micro-PET/CT instrument that will allow imaging of small animals with greater resolution compared to existing commercial micro-PET/CT units. In addition, he continues his work on a human clinical PET imaging system that will have greater sensitivity and resolution of detection than comparable systems in the marketplace.

The imaging tools and technologies being developed will ultimately be used to select the best treatment for each patient and to monitor the efficacy of treatment, reduce the need for surgical intervention and confirm that potential targeting technologies discovered by the CABIR and other McCombs Institute centers do, indeed, have a role in our understanding and controlling cancer development and growth.

### **New Imaging Agents Development**

During 2010, research faculty and scientists continued in their pursuit of evaluating the chemical, molecular and biological properties of existing radiopharmaceutical targeting agents and the development of new ones. There were a number of key developments in several research programs during this period.

Histone Deacetylases (HDACs) are a family of enzymes that regulate many biological processes. These enzymes exert their effects directly on specific sites of proteins associated with DNA in the nucleus of cells.

They have been shown to play pivotal roles in regulating processes in a variety of cell regulatory, developmental and disease processes. Cancer is one such disease state where HDAC expression plays a pivotal role in its progression.

A number of commercially available HDAC inhibitors have been developed and tested for their anticancer properties. However, the pharmacodynamics, mechanism of action and optimal dosing parameters for these agents are poorly understood. Furthermore, despite instances of dramatic tumor regressions in some patients treated with HDAC inhibitors, there are no predictive biomarkers for selection of patients who are most likely to respond to treatment with this class of inhibitors.

Our faculty and staff have focused on development of PET imaging agents for visualization and measurement of HDAC activity in various organs and tumor types. We have developed cell and animal models of cancer to facilitate development of pharmaceutical agents that target HDACs and developed methods for molecular imaging of the pharmacodynamic effects of HDAC inhibitors using PET. Specifically, we have developed a novel radiolabeled HDAC substrate, 18F-FAHA, for non-invasive molecular imaging of HDAC activity in tumors and normal organs. To date, our data are very encouraging and indicate that 18F-FAHA is a reliable imaging agent for imaging HDAC and the response of tumors after treatment with HDAC inhibitors. Our scientists have also synthesized novel HDAC substrates that are more specific for certain discrete forms of the enzyme. We are currently developing substrates for particular molecular forms of the HDAC family of enzymes. These research efforts will allow us to develop optimal targeting agents that will be useful for a better understanding of the relationship between HDAC enzymes and tumor progression.

Currently, 18F-FDG is the gold standard for clinical imaging of tumors using PET. While 18F-FDG has been shown to be an excellent imaging agent for a number of cancer types, it has not fared well in some (prostate, ovarian and pancreatic cancers). Patients with adenocarcinoma of the pancreas have one of the poorest five-year survival rates of any form of cancer with median survival around three to six months. Pancreatic cancer is often referred to as a “silent killer” because it not always symptomatic. When symptoms do occur, they are non-specific and varied. It is for this reason that pancreatic cancer often is not diagnosed until the disease is too advanced for current treatment options to be effective.

Therefore, in light of the poor patient prognosis, the need for novel and improved pancreatic cancer diagnosis at an early stage in its development is urgently needed. Our faculty has developed an 18F-derivative of a lactose molecule for imaging of pancreatic tumors and cells surrounding these tumors. This class of molecules is comprised of two sugars and can be chemically labeled with 18F in a way that does not hinder specific binding to HIP/PAP protein, a critical biomarker for hepatic, intestinal and pancreatic tissues. Because this biomarker is over-expressed in these tumor types, we have been able to visualize the localization of 18F-lactose derivatives to pancreatic and liver tumors in mouse and pig models. These important results have led to the filing of two patent applications with the intent to develop this radiopharmaceutical as a diagnostic PET imaging agent in partnership with the appropriate commercial partner.

In the meantime, work continues to understand the biology of this molecule and develop efficient methods for its production under Good Manufacturing Practice so that it can be evaluated in a clinical trial setting.

Human epidermal growth factor receptor type 2, Her2, is a member of the epidermal growth factor receptor family whose over-expression in several types of tumors (breast, ovarian, colon) has been correlated with tumor aggressiveness and poor prognosis for patients. Identification of Her2-expressing tumors and quantitative assessment of levels of Her2 expression by the tumors by imaging would be essential in monitoring disease development and response to therapy and could be used in the development of individualized, patient specific therapeutic regimens.

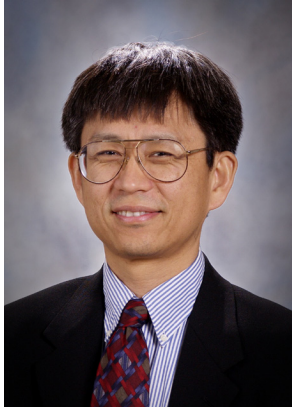
To this end, we are developing a new class of imaging agents for PET of Her2-expressing tumors, which are derived from a unique class of rationally designed protein carriers called Designed Ankyrin Repeat Proteins (DARPin). DARPins are uniquely suited for this role due to their high affinity and specificity for Her2, high systemic stability, ease with which they can be modified genetically and chemically, and produced at large scale and with high purity. To develop DARPin-based radiotracers for PET, we have designed and produced a thiol-containing derivative of a high-affinity Her2-specific DRAPin and conjugated it with DOTA chelator. This protein conjugate is now ready for labeling with such established PET-enabling radiotracers as Gallium-68 (Ga-68) and Copper-64. We have conducted pilot labeling of this protein carrier with Ga-68 and demonstrated the feasibility of such labeling at small scale. In parallel we have developed a highly metastatic model of Her2-expressing breast cancer in mice, which will be used to test the tracer. Importantly, once the feasibility of Her2 imaging with DARPin-based tracers is established, other tumor-associated tumor markers could be imaged using similarly designed DARPins specific for those markers, which are available.

To date, we have more than 25 molecular imaging agents in the research and development pipeline at various phases of exploration and development. Two of these are awaiting regulatory approvals and finalization of production capabilities in the CABIR before proceeding to early phase clinical trials. It is anticipated that these studies will commence sometime this year.

# Center for Cancer Immunology Research

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**Director: Yong-Jun Liu, M.D., Ph.D.**



Created in 2003 and led by Yong-Jun Liu, M.D., Ph.D., the Center for Cancer Immunology Research (CCIR) is the primary program for consolidating, integrating and supporting basic, translational and clinical immunology research conducted at The University of Texas MD Anderson Cancer Center. It is the first research center in the nation where laboratory and clinical immunologists work side by side to facilitate the “bench-to-bedside” transition of cancer immunotherapy that activates and instructs our immune system to eliminate cancer and prevent its recurrence. In Fiscal Year 2010, 292 people worked at the CCIR as faculty (55, tenure and non-tenure track), research staff (106), postdoctoral/clinical fellows (74), graduate students (26) and administrative staff (31). The MD Anderson SCRB-I houses all CCIR laboratories, core facilities and administrative offices.

During the past year, CCIR research output has remained very strong, as indicated by the number of publications, grant awards and investigator-initiated pre-clinical studies and clinical trials. CCIR investigators continue to make groundbreaking discoveries on the role of T-cells in regulating inflammation and immune responses, the role of dendritic cells (DCs) in sensing microbes and in programming different T-cell immune responses, and the discovery of the signaling mechanisms that control immune responses versus tolerance. In Fiscal Year 2010, CCIR investigators published 101 manuscripts with many appearing in prestigious medical or scientific journals, such as *Nature*, *Nature Immunology*, *Immunity*, *Journal of Experimental Medicine*, and *Proceedings of the National Academy of Sciences*.

A total of 113 grant awards (106 active grants and seven multi-investigator grants) from various types of agencies support CCIR research. The total number of active grants includes large center grant awards (i.e., U19, SCOR, P01, P50, and RC2), which support multidisciplinary research projects that are specifically designed to accelerate the translation of scientific discoveries in basic immunology into the development of cancer immunotherapy that can be readily tested in a clinical setting. Listed below is a brief description of each center grant.

## **1. U19: Asthma and Allergic Diseases Cooperative Research Center**

National Institute of Allergy and Infectious Diseases, Award Period: July 1, 2006 – June 30, 2011  
Principal Investigator: Yong-Jun Liu, M.D., Ph.D.

Scope of Research Project: The major goal of this research project is to investigate the role of human thymic stromal lymphopoietin (TSLP) in the development and maintenance of the T-helper type 2 (TH2) immune responses that dominate the allergic phenotype. The proposed studies are anticipated to significantly enhance our understanding of the molecular and cellular mechanisms that are clinically relevant for treating allergies and asthma.

Project 1 – Mechanisms Regulating TSLP Expression, led by David Huston, M.D., Texas A & M Institute of Biotechnology

Project 2 – Function of TSLP and Dendritic Cells in Maintaining CD4+CRTH2+ TH2 Memory T-cells in Human Allergic Inflammation, led by Yong-Jun Liu, M.D., Ph.D.

Project 3 – Association Between TSLP and IL17 in Human Asthma Diseases, led by Chen Dong, Ph.D.

## **2. SCOR: Translational Development of Novel Vaccine Therapies**

Leukemia and Lymphoma Society, Award Period: October 1, 2007 – September 30, 2012

Principal Investigator: Larry W. Kwak, M.D., Ph.D.

Scope of Research Project: Our central hypothesis is that promoting proinflammatory T-cell responses and suppressing regulatory T-cells (Tregs) will improve the therapeutic potential of tumor-specific T-cells induced by immunotherapy. This highly synergistic program combines mechanistic insights acquired from studies using well-defined murine tumor biology models and human tumor immunology with proof-of-concept clinical trials focusing on acute lymphocytic leukemia, lymphoma and multiple myeloma.

Project 1 – Modulate Costimulatory Pathways to Boost Antitumor Immune Responses, led by Chen Dong, Ph.D.

Project 2 – Enhance Antitumor T-Cell Immunity by Targeting Human Plasmacytoid Dendritic Cells (pDCs) and Myeloid Dendritic Cells (mDCs), led by Yong-Jun Liu, M.D., Ph.D.

Project 3 – Targeted Immune Therapy for Acute Lymphocytic Leukemia (ALL), led by Jeffrey Molldrem, M.D.

Project 4 – Adoptive Immunotherapy with Donor-derived, Tumor Idiotype-specific T-Cells, led by Larry W. Kwak, M.D., Ph.D.

## **3. Research Center for Cancer Vaccines**

W. M. Keck Foundation, Award Period: January 1, 2008 – December 31, 2010

Principle Investigator: Yong-Jun Liu, M.D., Ph.D.

Scope of Research Project: Most tumor vaccines only induce a transient tumor-specific T-cell response, possibly due to the presence of Tregs that are normally generated in the thymus and prevent other immune cells from causing autoimmune diseases.

Recent studies showed that Tregs are actively recruited into or generated within tumors and function as “bodyguards” to protect the tumors from anti-tumor immune responses. Our central hypothesis is that by understanding the molecular mechanisms by which dendritic cells regulate the generation and function of immunosuppressive Tregs, we will be able to develop more effective tumor therapies that eliminate Tregs or block their function.

Project 1 – Understand the Mechanisms Behind the Generation of Tregs in the Human Thymus, led by Yong-Jun Liu, M.D., Ph.D.

Project 2 – Understand the Mechanisms Behind the Generation and Function of Tregs in the Human Tumor Environment and Develop Methods to Block Treg Function to Boost Antitumor Immune Responses, led by Larry W. Kwak, M.D., Ph.D., and Patrick Hwu, M.D.

#### **4. P01: Activation of Plasmacytoid Dendritic Cells (pDCs) to Induce Antitumor Activity**

National Cancer Institute, Award Period: September 10, 2008 – August 31, 2013

Principal Investigators: Patrick Hwu, M.D.; Yong-Jun Liu, M.D., Ph.D.

Scope of Research Project: Our central hypothesis is that activation of plasmacytoid dendritic cells (pDCs) by Toll-like receptor (TLR) agonists will not only trigger potent T-cell priming, but it will also lead to enhanced migration and function of the primed T-cells to the tumor site. We have four integrated research projects that will systematically evaluate our hypothesis through laboratory investigations involving molecular studies and murine tumor models and ultimately a clinical vaccine trial utilizing TLR agonists to activate pDCs in patients.

Project 1 – Molecular Mechanisms of pDC Interactions, led by Yong-Jun Liu, M.D., Ph.D.

Project 2 – Activation of pDCs in Murine Tumor Models, led by Willem Overwijk, Ph.D.

Project 3 – Activation of Intratumoral pDCs by Self-DNA Coupled with Antimicrobial Peptide, led by Michel Gilliet, M.D.

Project 4 – Clinical Trial Utilizing the Melanoma gp100 Vaccine with TLR Agonists to Activate pDCs, led by Patrick Hwu, M.D.

#### **5. P50: MD Anderson Lymphoma SPORE**

National Cancer Institute, Award Period: September 1, 2009 – August 31, 2012

Principal Investigator: Anas Younes, M.D.

Scope of Research Project: The primary goal of the MD Anderson Lymphoma Specialized Program of Research Excellence (SPORE) is to improve the cure rate of lymphoma through innovative therapeutic strategies based on effective and focused translation of recent discoveries in lymphoma biology, immunology, and molecular genetics. The MD Anderson Lymphoma SPORE is a multidisciplinary collaborative effort between basic and translational scientists, clinical investigators, hematopathologists, and biostatisticians that is organized into four research projects and four core resources, as well as programs for developmental research and career development.

Project 1 – Epigenetic-based Therapy of Hodgkin Lymphoma, led by Anas Younes, M.D. and Yong-Jun Liu, M.D., Ph.D.

Project 2 – Development of 8-Chloro-adenosine Therapy, led by Varsha Gandhi, Ph.D. and Sattva Neelapu, M.D.

Project 3 – Non-genotoxic p53 Activation as a Novel Therapeutic Concept for Lymphomas, led by Michael Andreeff, M.D., Ph.D., and Susan O'Brien, M.D.

Project 4 – Gene Profiling and Identification of Therapeutically Relevant Targets for Peripheral T-cell non-Hodgkin Lymphoma, led by John Chan, M.D., and Julie Voge, M.D.

#### **6. RC2: Transcriptome and Epigenome Analyses of Helper T-Cell Specification and Plasticity**

National Institute of Arthritis and Musculoskeletal and Skin Diseases, Award Period: September 29, 2009 – August 31, 2011

Principal Investigator: Chen Dong, Ph.D.

Scope of Research Project: The central goal of this project is to perform large-scale, genome-wide transcriptome and epigenome analyses of regulatory Treg, Th17 and Tfh cells to determine the direct functions of key transcription factors and their likely synergistic and antagonistic interactions.

Projects affiliated with the grant are led by Chen Dong, Ph.D., Roza Nurieva, Ph.D., Stephanie Watowich, Ph.D., Xin-Hua Feng, Ph.D., and Qiang Tian, Ph.D.

#### **7. P50: MD Anderson Multiple Myeloma SPORE**

National Cancer Institute, Award Period: July 1, 2010 – June 30, 2015

Principal Investigator: Robert Orlowski, M.D., Ph.D.

Scope of Research Project: Multiple myeloma is a clonal plasma cell malignancy, which remains incurable in the vast majority of the over 59,000 patients in the United States afflicted with this disease. Therefore, MD Anderson, in collaboration with The University of Pennsylvania and the Virginia Commonwealth University, has established this SPORE in Multiple Myeloma.

The primary goal of this program is to translate promising new strategies from the bench to the bedside to reduce the morbidity and mortality, and improve the quality of life of multiple myeloma patients. To do so, a multidisciplinary, collaborative group of experienced investigators are pursuing four highly innovative projects.

Project 1 – Combination of Activated T-Cell and Vaccine Therapy in Myeloma, led by Larry Kwak, M.D., Ph.D.

Project 2 – Anti- $\beta$ 2-microglobulin Antibodies as Therapeutic Agents for Multiple Myeloma, led by Qing Yi, M.D., Ph.D.

Project 3 – Targeting the HDM-2 E3 Ligase in Multiple Myeloma, led by Robert Orlowski, M.D., Ph.D.

Project 4 – Targeting Multiple Myeloma by Combining CDK Inhibitors and Bcl-2 Antagonists, led by Steven Grant, M.D.

Numerous CCIR investigators are conducting pre-clinical studies and clinical trials in order to test the therapeutic efficacy of a vaccine, T-cell therapy or antibody in combating cervical cancer, lymphoma, neuroblastoma, leukemia and melanoma. The chart on the following page depicts the current status of the immunotherapy as it advances from a pre-clinical study into each phase of a clinical trial.

### **Future Plans**

Dr. Liu is currently seeking seed funding for pre-clinical programs and Phase I clinical trials in order to accelerate this translational aspect of the center, which is critical to its success. The CCIR plans to develop—at the minimum—three such programs in the next five years. Private support will also help to defray costs associated with early stage clinical trials, costs that are not often covered through existing federal and other peer-reviewed mechanisms.

	Pre-clinical	Phase of Clinical Trial		
		I	II	III
<b>Drs. Y-J. Liu, L. Bover and K. Voo</b> Humanized anti-OX40 mAbs for cancer therapy	→			
<b>Dr. J. Sastry</b> HPV -peptide Vaccine Cervical Cancer	→			
<b>Drs. L. W. Kwak and S. Neelapu</b> Liposomal formulation Lymphoma Vaccine	→			
<b>Dr. L.J. Cooper</b> CD19-specific CAR T Cell Therapy B-lymphoid Malignancies	→	→		
<b>Dr. L.J. Cooper</b> Haploidentical NK Cells Relapsed Neuroblastoma	→	→		
<b>Dr. L.J. Cooper</b> Haploidentical NK Cells + epratuzumab Relapsed ALL	→	→		
<b>Dr. L.J. Cooper</b> Haploidentical NK Cells + p53TCR-IL-2 Relapsed AML	→	→		
<b>Drs. M. Gilliet, P. Hwu, and Y-J. Liu</b> TLR7/9 agonist + gp100 and MAGE Melanoma Vaccine	→	→	→	
<b>Dr. P. Hwu</b> T Cell Therapy + Dendritic Cells Melanoma	→	→	→	
<b>Dr. P. Hwu</b> gp100 Melanoma Vaccine	→	→	→	→
<b>Dr. L.W. Kwak</b> Idiotypic Lymphoma Vaccine	→	→	→	
<b>Drs. J. Molldrem and M. Qazilbash</b> PR1 Leukemia Vaccine AML, CML and MDS	→	→	→	
<b>Dr. S Neelapu</b> Idiotypic + GM-CSF Lymphoma Vaccine	→	→	→	→

# Center for RNA Interference and Non-Coding RNAs

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**Director: Anil K. Sood, M.D.**



The Center for RNA Interference and Non-Coding RNAs (RNA Center), hosted in the Department of Gynecologic Oncology, is the latest of Centers in the Red and Charline McCombs Institute for the Early Detection and Treatment of Cancer. The RNA Center is co-directed by Anil K. Sood, M.D., professor, gynecologic oncology and cancer biology, and George Calin, associate professor of experimental therapeutics and cancer genetics. Drs. Sood and Calin are internationally recognized experts in the biology and translational applications of RNAi, miRNAs and other ncRNAs. Gabriel Lopez-Berestein, M.D., professor, experimental therapeutics, is the associate director of the center, bringing his expertise in cancer biology and drug development. Current members of the RNA Center include a

multidisciplinary group of basic and clinical scientists from within The University of Texas MD Anderson Cancer Center and other institutions including Baylor College of Medicine, The UT Health Science Center at Houston, Rice University and University of Houston. The RNA Center's mission is to gain insights into the role of newly discovered non-coding RNAs in cancer initiation, progression and dissemination, focusing on early detection, biomarker identification and development, and new treatments based on siRNA, miRNA, and other ncRNAs.

**Director: George Calin, M.D., Ph.D.**

The focus of the RNA Center has been to develop collaborations and work towards developing specific projects to fulfill the mission of developing ncRNAs and RNAi based therapeutic applications.

The RNA Center is leveraging three critical advantages in pursuit of its mission:

1. Extensive expertise in the subcellular regulation of cancer cell growth and death
2. Demonstrated ability to use neutral nanoliposomes, polysaccharide based nanoparticles, and other biocompatible nano-platforms to deliver siRNAs directly to tumor cells
3. World renowned expertise in dissecting the role of miRNA in cancers from discovery to identification of novel molecular markers, validating and developing diagnostics, prognostics and therapeutics.



## Resource Development and Access

In the last year, the RNA Center has been working toward setting up the following services that would serve as major resources for researchers at MD Anderson:

1. **In-situ Hybridization:** The RNA Center is in final stages of establishing the first in-situ hybridization service for non-coding RNA applications. This resource would benefit researchers across MD Anderson, including the Cancer Center Support Grant (CCSG). To date, the RNA Center has hired an expert for in-situ hybridization, established the technological infrastructure, trained personnel, and conducted key tests to set up standard operating procedure to open the in-situ hybridization service to all. As a part of the development, the RNA Center is currently testing specific miRNAs to be offered as a part of the in-situ hybridization service.
2. **Bioinformatics, Biostatistics and Data Analysis:** In the next generation genomics era, one of the major concerns is the bottleneck in data analysis. Specifically in next generation sequencing and in-situ hybridization, wealth of data is generated that require specific expertise in handling and analysis. We also have an expert in biomathematics to provide bioinformatics services for the analysis of in-situ hybridization, non-codingRNA arrays and next generation sequencing projects. This service can be accessed by all researchers at MD Anderson.
3. **RNAi Expertise:** The RNA Center has been lending expertise on the RNAi research by helping several researchers with RNAi planning, and delivery of RNA, based on years of pioneering work done by the RNA Center team. The center researchers have now shown, via multiple tumor models in mice, that specific cancer molecular signals can be regulated by using siRNAs incorporated into these biocompatible nanoparticles. The next phase of development will be to translate these findings into clinical trials. The technologies available at the RNA Center will ultimately lead to a better understanding of the events regulating tumor cell growth, invasion and metastasis. This knowledge will be applied to improve diagnostic and treatment capabilities using siRNAs and other ncRNAs.

The activities of the RNA Center are in accordance with the mission of MD Anderson and CCSG:

1. Developing and facilitating innovative collaborations in ncRNA and RNAi applications that would lead to translational projects
2. Providing unique expertise in ncRNA and RNAi applications
3. Providing in-situ hybridization and bioinformatics services
4. Actively developing unique ncRNA and RNAi resources that could be leveraged to develop grants by any researcher
5. The development of new ncRNA arrays to be used by any of the MD Anderson and UT interested scientists

6. We are playing a major role in promoting the MD Anderson and CCSG mission by offering grants for projects on a competitive basis that are vital for young researchers to generate critical data to leverage and further develop into larger grants
7. Actively developing RNA Center grants by applications to federal agencies

### **Education and Seminar Programs**

The RNA Center has been actively involved in developing educational programs via seminars and institutional grand rounds to increase participation in the RNA Center activities. To date, the RNA Center directors and invited top scientists in the ncRNA field have given seminars and lectures at MD Anderson. This is an ongoing program that utilizes established seminar structures at MD Anderson to encourage and disseminate ncRNA-centric information and developments.

### **Nanotechnology**

The RNA Center has been actively supporting and participating in several research activities in the ncRNA, siRNA, and RNAi fields. In the last year, the RNA Center has been collaborating with the Texas Center for Cancer Nanomedicine (TCCN), one of the few centers of excellence in the country and the first of its kind center in Texas. The main mission of TCCN is to develop novel nanotechnology-based diagnostics, prognostic and therapeutic applications to treat ovarian and pancreatic cancers and extend these treatment methodologies to other cancers. The RNA Center is actively collaborating and supporting this effort. In September 2010, The Texas Center for Cancer Nanomedicine awarded an overall budget of \$13.8 million over five years to multi-principal investigators including Drs. Sood and Lopez-Berestein with Dr. Mauro Ferrari of The Methodist Hospital and Dr. David Gorenstein at The UT Health Science Center at Houston. Portions of this grant directly support the RNA Center.

### **Leveraging Philanthropic Support**

The RNA Center-Laura and John Arnold Foundation Award has been established to fund ncRNA focused research. The intention of this award is that work funded will lead to collaborations and grant proposals for extramural funding in the future. Under this award, research proposals must pertain to basic or translational research focused on RNA interference and/or ncRNAs.

Through this program, the RNA Center has awarded \$25,000 per year for up to two years to Chun-Ju Chang, Ph.D., postdoctoral fellow, molecular & cellular oncology, MD Anderson, for the project, "The role of miR-200c as a biomarker for predicting p53 deficiency and its potential use as a treatment for aggressive breast cancer." \$25,000 per year for up to two years was also awarded to Dean Tang, Ph.D., professor, molecular carcinogenesis, MD Anderson, for the project, "miRNA regulation of prostate cancer stem cells."

In October 2010, RGK Foundation Grant awarded \$1 million to directly support the RNA Center. The RNA Center is planning to leverage this funding by supporting innovative collaborative studies to develop them to extramural funding opportunities.

# Center for Targeted Therapy

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**Director: Garth Powis, D.Phil.**



The Center for Targeted Therapy (CTT) gives researchers and clinicians alike the opportunity and ability to coordinate all stages of the drug discovery and development process and to design new, more effective and specific drugs that are targeted, personalized and less toxic. Currently, 73 faculty members from 14 departments are participating in CTT research. There are now 39 drugs or new agents in the development pipeline.

To accelerate the delivery of new therapies, the CTT mission begins with hypothesis driven research that identifies and validates targets; continues with the discovery, development and design of biological therapies and drug agents; and is followed by pre-clinical and clinical trials—with each step working toward the goal of personalized medicine.

An important aspect of the work of the CTT is a close association with the Center for Advanced Biomedical Imaging Research, which develops non-invasive image tests, and the Robert J. Kleberg, Jr. and Helen C. Kleberg Center for Molecular Markers, which gives investigators the opportunity to maximize the therapeutic benefits of treatment and limit undesirable side effects. Minimally invasive imaging procedures and tissue biomarkers are used to identify those patients who are likely to respond to a drug treatment, and then used after treatment to follow the response of the drug. The CTT also has inter-institutional agreements with the University of California, San Diego and the Burnham Institute, which has a huge screening program.

The anchor academic department for the CTT is the Department of Experimental Therapeutics. With 45 research faculty, this is the largest basic research department at The University of Texas MD Anderson Cancer Center. Investigators are involved in all aspects of cancer drug discovery and development, ranging from the discovery of cancer relevant drug targets, lead compounds and lead optimization to preclinical pharmacology and toxicology.

Drug discovery in academia is faster, less expensive and more innovative than through the pharmaceutical industry. The CTT offers a number of key core services to assist all investigators at MD Anderson in bringing their discoveries from concept to clinic. They include a short interfering RNAs (siRNAs) screening service to help identify new targets; the Translational Chemistry Core Facility that offers custom synthesis and development services; the Pharmaceutical Development Center for preclinical drug development; the Sequencing and Non-coding RNA Program for identifying undiscovered genes through state-of-the-art genomic research and technology development; and, finally, the Molecular Modeling/Structural Biology Service that offers computer-based core services for lead identification. Each CTT core service facilitates the rapid development of new cancer agents for patients at MD Anderson, in Texas and throughout the nation and the world.

## **Translational Chemistry Core Facility**

Fully operational in July 2006, the Translational Chemistry Core Facility (TCCF) is available to all MD Anderson investigators and assists with the design, custom synthesis, development and manufacture of compounds of biological interest. A research laboratory manager, two research chemists, and a molecular modeler are lead by William Bornmann, Ph.D., in manufacturing specific compounds for use in research. For instance, if a small amount of a previously reported compound is needed for antitumor and biological testing, but is difficult to obtain from a pharmaceutical company, the compound can be legally synthesized by the chemistry core facility and used for non-human applications. New compounds can also be designed and synthesized to order with desired chemical properties and biological activity against molecular targets. The chemistry core scientists can develop analogs to known classes of compounds and modify existing drugs to enhance their therapeutic effects.

During the last year, the TCCF completed 37 projects for 15 investigators, including development, custom synthesis, mass spectrometry, molecular modeling, consultation services and x-ray structure analysis.

## **The siRNA Screening Service**

Short interfering RNAs are short strands of RNA that modify the function of genes. Fully operational in August 2007, the siRNA Screening Service helps investigators identify potential new targets for therapeutic drugs. The service's technology—high-throughput screening and a human genome siRNA library that contains siRNAs that target approximately 21,000 known human genes—is available to all MD Anderson investigators at a reasonable cost. A skilled four member research staff, directed by Geoffrey Bartholomeusz, Ph.D., assists with the entire process. The service averages two to three screens each month and has completed a total of 90 screens to date, including ten during the last year, with ten additional screens in the pipeline. The service is expanding its high-throughput capabilities to include 3-dimensional cell culture models. The siRNA Screening Service continues to be an invaluable resource to investigators seeking to identify previously unknown modulators of genes of interest as potential targets for cancer therapy.

## **The Pharmaceutical Development Center**

After more than a decade of operations, the Pharmaceutical Development Center (PDC) continues to assist MD Anderson faculty in rapidly translating novel therapeutic discoveries into new treatment choices for patients. An integrated platform of scientific, laboratory and regulatory expertise, the PDC carries out all aspects of cancer drug development for promising anticancer treatments. The PDC draws upon current strengths within pharmacy, chemistry, pharmacology, veterinary medicine and other components of drug development in place within our institution to facilitate the flow of therapeutic concepts and novel compounds from the early stages of development through clinical trials and U.S. Food and Drug Administration (FDA) approval.

The 18 member research staff, including scientific director, Timothy Madden, Pharm.D., and director of operations, Mary Johansen, Pharm.D., assists investigators with formulation, antitumor testing, pharmacologic and pharmacokinetic investigations, analytical assay development, toxicology, investigational new drug preparation and small scale manufacturing of clinical grade testing material. They currently complete 3.5 projects each year, and demand is increasing for their services. During the last six years, 22 drugs have entered clinical trials; eight drugs are awaiting FDA approval; and 39 drugs are in the pipeline.

The PDC also is pursuing the creation and development of a good laboratory practice compliant bioanalytical facility within its operations. To insure a high level of quality for investigational new drug-directed drug development research, the FDA has guidelines for conducting these studies. PDC provides a method of insuring constant quality assurance, quality control, data chain of custody and data security. Analytical projects conducted at the El Rio Street lab will utilize standard operating procedures and computer-based chromatographic and data analysis tools that meet these regulations.

### **Sequencing and Non-Coding RNA Program**

Non-coding RNAs (ncRNAs) are a large group of RNA molecules that are not translated into protein but have been found to play roles in a great number of important cellular processes such as cancer initiation, progression and metastasis. So many ncRNAs have been found that the challenge now is to determine the size of the full complement of ncRNAs and to discover and clarify their functions, particularly as they relate to disease, and more specifically at MD Anderson, to cancer. The work performed by this program represents the most active research areas in cancer genomics and continues to shed light on the human genome. Already, miRNAs have shown promise as diagnostic and prognostic markers in cancer and as targets for the development of new therapeutic approaches.

Fully operational since its launch in December 2008, the Sequencing and Non-Coding RNA Program, directed by Chang-gong Liu, Ph.D., professor in the Department of Experimental Therapeutics, provides expertise and technologies to support cancer genomics research with high quality data, quick turnaround time and affordable costs. During the last year, the program completed 52 projects for 34 investigators, servicing more than 1,957 samples.

The program has grown to meet the demands and needs of investigators with state-of-the-art technology. Our next generation sequencers, Sequencing by Oligonucleotide Ligation Detection (SOLiD) systems, continuously run in the laboratory and the program soon will add four new SOLiD 5500XLs upon moving to its new South Campus location. Next generation sequencing is a powerful platform that focuses on deep sequencing and the discovery and genome wide profiling and indexing of the ncRNA transcriptome. It has superior capabilities and can generate millions of sequences that tell us which region of the human genome, at the DNA level, is transcribed into ncRNA. The results obtained from the program's services are extremely useful to cancer genomics research, biomarkers and future clinical applications.

## **Molecular Modeling/Structural Biology Service (Computational Drug Design)**

The Molecular Modeling/Structural Biology Service at MD Anderson is led by Shuxing Zhang, Ph.D., assistant professor in the Department of Experimental Therapeutics and a computational drug design expert. This service assists molecular biologists and medicinal chemists in target function studies, lead discovery and optimization, and ADME/toxicity predictions. Another important component of this service is the ability to conduct protein expression, protein crystallization and structure determination using x-ray crystallography of newly discovered cancer causing proteins and their complexes with drug inhibitors. These studies are essential for further drug development efforts and provide the structural information needed for the validation and refinement of the computer models.

The service also uses computer aided drug design in collaboration with wet lab investigators to identify and optimize novel compounds for various targets. Modern drug discovery uses novel, computational biology approaches that permit the effective and efficient high throughput virtual screening of millions of compounds and the rapid rational design of new analogs. Computer simulation molecular modeling, data management and informatics, both bio and chemo, are increasingly important, not only in how we generate research data but also in how we manage and interpret the information for further application.

The service is building an online integrated molecular discovery platform for inhibitor identification and function studies and has launched the prototype. We are actively recruiting a postdoctoral fellow to work with Stefan Knapp, Ph.D., and the Structural Genomics Consortium affiliated with Oxford University in the United Kingdom for one year and with John Ladbury, Ph.D., of the Molecular Modeling and Structural Biology Service at MD Anderson for a second year. Closer ties with structural biology are important to our drug discovery efforts because, ultimately, the target-drug structures must be elucidated in order to validate the computer simulation modeling necessary to move the field ahead.

### **CTT Grant Programs**

In 2010, the Center for Targeted Therapy's Translational Chemistry Core Facility (TCCF) launched an "Ignition Project" grant program to award MD Anderson investigators up to \$20,000 to assist in the design and synthesis of new small molecule inhibitors, new peptides and new anticancer chemicals for those who have identified new key molecular targets.

During the course of their research, it is common for investigators to identify new key molecular targets that require the use of new small molecule inhibitors, peptides and anticancer chemicals to block tumor growth. Due to the "newness" of these targets, investigators typically find themselves limited because of lack of expertise or funding to accomplish the design and synthesis necessary to move forward with these promising ideas. We identified a need for this type of grants program based on the number of TCCF requests not funded once an estimate for services is provided.

The TCCF will design and synthesize new small molecule inhibitors, peptides and anticancer chemicals in quantities that will ensure investigators are able to prove antitumor activity in vitro and in vivo. This grant program is open to all MD Anderson investigators and promotes collaborative research efforts between the TCCF and basic and translational investigators at MD Anderson aimed at determining proof-of-principle and obtaining preliminary results to provide a foundation for potential extramural funding.

### **Educational Initiatives**

During the last year, Varsha Gandhi, Ph.D., professor in the Department of Experimental Therapeutics, spearheaded the development of a graduate program in Experimental Therapeutics at The University of Texas Graduate School of Biomedical Sciences at Houston that was approved by the Texas Higher Education Coordinating Board in March 2010. The program trains students who have an understanding of normal biology to apply the scientific method of hypothesis testing to research projects that include testing in preclinical laboratories and mouse models and validating preclinical efforts in the clinic, the classic “bench to bedside” approach.

The program began in the fall 2010 semester and has enrolled 13 students. The program offers its students two degree options, M.S. or Ph.D., and is supported by more than 50 faculty members, with a diversity of research expertise, representing more than 20 different departments, institutes or centers.

# Proton Therapy Center

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**Director: Andrew K. Lee, M.D.**



The Proton Therapy Center (PTC) at The University of Texas MD Anderson Cancer Center is one of only five clinical proton therapy centers in the United States and one of the largest proton centers in the world. The 94,000-square-foot patient treatment facility at 1840 Old Spanish Trail resulted from a unique partnership between MD Anderson and a group of community, business and industry leaders. We are grateful to all parties who helped make this leading-edge patient care facility and radiation treatment available to cancer patients.

Facility construction began in May 2003 and was completed in the fall of 2004. A year later, equipment installation and testing was complete.

In the PTC, a high-energy synchrotron particle accelerator delivers the carefully calibrated proton beams to three of four treatment rooms where huge wheel-like gantries, 35 feet in diameter and weighing approximately 190 tons each, rotate around the patient to direct the proton beam at a tumor with an accuracy of less than a millimeter. The facility also includes a fixed-beam treatment room, 16 exam rooms and a simulation suite with positron emission tomography, computed tomography, and magnetic resonance imaging for accurate treatment planning.

Unlike traditional radiation therapy that affects everything in its path, a proton beam has a low “entrance dose” (the dose delivered from the surface of the skin to the front of the tumor), a high dose designed to cover the entire tumor and no “exit dose” beyond the tumor. The combined effect is greater precision in targeting the tumor with a more potent dose of radiation. The precision of treatment is increased with daily x-ray images taken before every treatment to align the anatomy with the proton beam.

On May 4, 2006, the first patient received treatment at the PTC. As of mid-March 2011, more than 2,500 patients have been treated, including more than 400 pediatric cancer patients. At the PTC, physicians specialize in one disease site, but the PTC applies the multidisciplinary approach, including peer review of all patients treated and protocol-driven patient care. We have more than 20 different physicians treating patients with proton therapy and typically treat 120-130 patients each day. All of the centers in the Red and Charline McCombs Institute for the Early Detection and Treatment of Cancer contribute valuable research to improve patient care. The PTC is unique among them because it actually delivers patient treatment.

## **Spot Scanning Technology (a.k.a. Pencil Beam Scanning)**

The PTC continues to expand its treatment capabilities. For example, it is the first and only center in North America to implement the technique of “spot-scanning” protons—the delivery of a focused proton therapy dose in all three dimensions—as a patient treatment.

Since protons are charged particles, they can be easily and quickly focused and deflected by the action of magnetic fields under computer control. Moreover, the dose distribution delivered to tissues by a proton pencil beam retains much of the original shape of the undisturbed beam until the protons stop. Therefore, by superpositioning a very large number of individual proton “beamlets” on the targeted tumor, the radiation oncologist can totally conform the dose to the volume of the tumor. For example, using spot scanning, a radiation oncologist can deliver a proton dose to 1,800 scanned spots on a prostate tumor in 24 layers in 68 seconds. Spot scanning offers tighter dose conformity and concave dose distributions. The PTC is one of three clinical centers in the world to have the technology to provide this three-dimensional proton therapy approach.

The PTC has improved spot-scanning technology in 2010 with two new treatment methods: Simultaneous Integrated Boost (SIB), and Multi-Field Optimized-Intensity Modulated Proton Therapy (MFO-MPT). The SIB technique allows us to treat a patient’s tumor with different dose intensities within the target depending upon where the bulk of the disease lies. For example, we may treat the center of the tumor with a very high dose radiation and use a slightly lower dose for the periphery. Since the extra radiation dose is delivered simultaneously (rather than sequentially), the overall treatment course is shortened by days or weeks. This allows higher radiation doses to the tumor but with less inconvenience to the patient.

In 2010, the PTC continued to make cancer history by becoming the first and only center in North America to use scanning proton beam technology to treat a patient with multi-field optimized-intensity modulated proton therapy (MFO-IMPT). This technology allows different proton beams to “partner” with each other in order to provide the most conformal dose coverage of the tumor and minimize the dose to adjacent normal tissue. We have been using MFO-IMPT to treat cancers of the brain, skull base and head and neck in both adults and children for several months and still represent the only North American center to use this technique to treat patients.

All patients at the PTC participate in protocols or studies that allow their doctors to use the results of their treatment to further study the effect of protons. Treatment results are objectively evaluated to answer critical cancer questions and advance the science of proton therapy. One of our largest studies, which examines the impact of proton therapy on normal tissues and the subsequent side effects, has accrued more than 1,200 patients. Other major sites under investigation include:

**Prostate:** More than 1,250 prostate cancer patients have completed treatment and approximately 800 men have received, at minimum, a three-month follow-up evaluation. Also underway is the protocol “Prospective evaluation of quality of life after proton therapy for prostate cancer.” Current enrollment in this study is 900 with an accrual goal of 1,034 men.

**Lung:** Proton therapy reduces radiation dose to the total lung, opposite lung, esophagus, spinal cord and heart. It also allows for a higher radiation dose to the tumor with fewer side effects and helps patients better tolerate chemotherapy.

More than 200 patients are enrolled in the following lung cancer studies at the PTC: “Assessing Motion of Tumors and Normal Tissues Using 4DCT Technology,” “Concurrent Proton and Chemotherapy in Locally Stage III A/B,” “Escalated/Accelerated Proton Radiotherapy for Inoperable Stage I Disease,” and “A Bayesian Randomized Trial of Image-Guided Adaptive Conformal Photon vs. Proton Therapy, with Concurrent Chemotherapy for Locally Advanced Non-small Cell Lung Carcinoma: Treatment Related Pneumonitis and Locoregional Recurrence.”

Pediatric cancers: In only a few years, the PTC has become one of the top three centers in the world in terms of the number of children treated with proton therapy (more than 400 children). Children are very sensitive to radiation and even low doses of regular x-ray therapy can produce long lasting side effects in young children. Therefore, tissue-sparing proton therapy is an important advance for children with cancer. An example is the difference between using x-ray therapy or proton therapy in treating a medulloblastoma, a type of brain tumor that occurs in children in the lower part of the brain and spreads along the spine. As much as 50 percent of the radiation dose of x-ray therapy can exit the tumor target, moving into healthy tissue beyond the tumor volume. With proton therapy, none of the dose exits beyond the target volume. Surrounding tissue is spared and the possibility of side effects is reduced.

The PTC medical team believes that all children who need radiation therapy for their tumors should be treated with proton therapy. Currently, the PTC is conducting several pediatric central nervous system studies: “Normal Tissue Toxicity for Proton Therapy for Pediatrics,” “Collection and Storage of Lymphocytes in Pediatric Patients Receiving Proton Therapy,” “Phase II Evaluation of Proton Beam Therapy for Skull Base Chordoma,” “Phase II Trial of Proton Radiation for Treatment of Pediatric Rhabdomyosarcoma,” and a “Phase II Study of Proton Beam XRT for Medulloblastoma and Pineoblastoma: An Assessment of Acute Toxicity and Long-term Neurocognitive, Neuroendocrine, and Ototoxicity.”

### **Future Clinical Goals**

In the future, the faculty and staff of the PTC want to increase the utilization of proton therapy to a wider array of tumor sites. In the past year, we have expanded the use of proton therapy to several new disease sites. For example, we are now treating patients with gastrointestinal cancers such as recurrent rectal cancer and unresectable liver tumors. With the implementation of MFO-IMPT, we are now treating more patients with cancers of the head and neck and also treating complex cases that were not previously possible. In fact, we are becoming known as the proton center that can handle cases that others cannot.

We are also interested in fractional dose-escalation, giving fewer doses per day and finishing treatment in one to three weeks rather than eight. We have implemented several studies to examine this technique in cancers of the lung, liver, and breast.

The breast cancer study will employ partial breast irradiation with proton therapy in just a few daily fractions with the goals being tumor control and preserving cosmesis. We are also dedicated to increasing clinical availability, especially for children, and to improve combination therapy to produce a more effective clinical result.

Finally, the PTC wants to optimize treatment of disease sites with MFO-IMPT such as skull base tumors and consider proton therapy for cancers such as lymphoma, where there is a valid clinical rationale but not a large historic experience. We also plan on commissioning the eye-line for the treatment of intra-ocular tumors such as ocular melanoma in the upcoming year.

### **Future Technical and Research Goals**

The PTC faculty and staff also are moving ahead with goals for improving the technology and research of proton therapy. We are committed to optimizing the practice of proton therapy for the field of oncology and advancing it to the next level for our patients. For example, the PTC has a goal of increasing the accuracy of radiation delivered to the patient by improving image guidance and using techniques such as respiratory gating or breath-hold. In addition to the technical advancements, studying the impact of proton therapy on patient outcomes will be increasingly important as our own experience grows and our patients have more mature follow-up.

With funding from a National Cancer Institute PO1 Program Project grant, the PTC will optimize proton therapy by continuing basic physics research that will impact proton therapy and by conducting related clinical trials. PTC faculty will also continue development of intensity modulated proton therapy, studies of the biological aspects of proton interactions, and conducting more prospective clinical trials in randomized comparisons between x-rays and protons for lung cancer. Members of our faculty were also recently awarded a grant to collaborate with another proton center in Germany (DFKZ, the German Cancer Research Center) on research and further refinement of intensity-modulated particle therapy.

### **Conclusion**

Proton therapy allows for one the most aggressive cancer therapies possible, while keeping the damage to healthy tissues and the side effects to a minimum. Combined with MD Anderson's almost 70 years of expertise and pioneering research in radiation therapy, the PTC is the premier destination for cancer patients desiring the best treatment by the most experienced radiation oncologists. We are grateful for the support that has made this facility possible.

# Robert J. Kleberg, Jr. and Helen C. Kleberg Center for Molecular Markers

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**Director: Gordon B. Mills, M.D., Ph.D.**

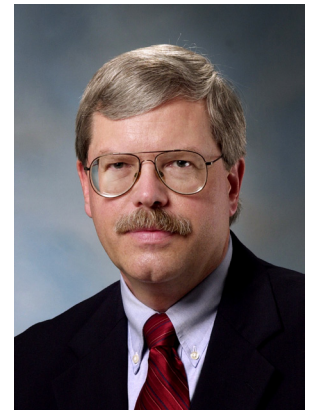


The Robert J. Kleberg, Jr. and Helen C. Kleberg Center for Molecular Markers was established in 2005 with a mission to develop methods to identify patients likely to benefit from specific therapies, expand approaches to identify patients with a high risk of developing malignancy and to widen screening approaches for early diagnosis and detection of minimal residual disease. The overarching goal of the Kleberg Center for Molecular Markers is to implement approaches arising from a greatly extended ability to interrogate patient's tumor and germline DNA, RNA, and protein, to improve patient management. The Kleberg Center has taken on the challenge of identifying and overcoming the challenges to the implementation of personalized cancer therapy.

The Kleberg Center is directed by Gordon Mills, M.D., Ph.D., and Stanley Hamilton, M.D. Margaret Spitz, M.D., acted as a co-director responsible for epidemiology prior to her retirement in 2010. This position has not been refilled and the epidemiology efforts have now been transitioned to The Duncan Family Institute for Cancer Prevention and Risk Assessment. The Kleberg team includes personnel with industry, academic, clinical and basic science expertise from the fields of cancer to computer science.

**Director: Stanley Hamilton, M.D.**

The Kleberg Center has made great progress towards its goals, including: providing infrastructure support for clinical studies, forging collaborations nationally and internationally, taking the lead in projects such as The Cancer Genome Atlas, Human Proteomics Atlas, Clinical Proteomics Technologies Assessment in Cancer and Integrative Cancer Biology Program, generating data on more than ten cancer clinical studies, developing collaborations with 50 companies, spinning off a company, generating multiple disclosures and patent applications, more than 100 scientific papers, more than 20 grants and sponsored research funds and training ten clinicians and ten post doctoral fellows.



The direction of the Kleberg Center has evolved extensively since its inception. The Kleberg Center now also supports the efforts of The Duncan Institute in identifying patients with a high risk of developing malignancy and developing screening approaches for early diagnosis and detection of minimal residual disease.

As a result, the Kleberg Center has increased its emphasis on identification of patients likely to benefit from targeted therapy and on implementation of personalized cancer therapy. It is providing the infrastructure support for multiple molecular marker driven trials at The University of Texas MD Anderson Cancer Center and is providing discovery, technology evaluation and implementation, and infrastructure for the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy (IPCT) that is co-directed by Dr. Mills and John Mendelsohn, M.D. (co-director designee). Some examples of this focus on personalized therapy through the Kleberg Center as well as some of the supported grants and collaborations are described below.

## **Project T9**

Following the 2010 Cancer Center Support Grant (CCSG) External Advisory (EAB) board meeting, recommendations were made that MD Anderson take the lead in the development and implementation of large scale projects that could deliver on the promise of personalized medicine. Ideally, these projects should be implemented based on competitive advantages offered by MD Anderson with the large number of patients (greater than 10,000 per year) entered on interventional clinical trials. In particular, there is an opportunity to capitalize on the “perfect storm” created by the rapid evolution in the technologies described here to evaluate patient and tumor characteristics combined with the approximately 800 targeted therapies entering or in early clinical trials.

As a first step in this effort, with philanthropic support from the Kleberg Foundation, we implemented project T9, that will perform genetic analysis through ten thousand tests on ten thousand tumors to develop ten thousand treatments for individualized therapy. The 10,000 patient T9 project is considered a pilot project to identify and overcome the challenges for the implementation of personalized medicine.

## **Molecular Evolution**

Data has demonstrated a significant difference between the frequency of mutations in primary tumors compared to metastasis and recurrent tumors. With this observation, we have created a program where we are determining the scale of the problems associated with molecular evolution. This includes an active rebiopsy program and focus on the following goals:

*Determine molecular evolution between primary tumors and metastases.* It is clear that the patterns of mutations and comutations are different between primary tumor and metastasis. We will determine the patterns to improve the efficacy of patient care and clinical trials by treating the aberrations present at the metastatic site.

*Determine molecular evolution with treatment.* It is clear that chemotherapy induces mutations in many tumors. The effect of targeted therapy on the spectrum of mutations in tumors is unknown. We will develop an approach that will determine the consequence of each effective targeted therapy on underlying aberrations in tumors.

## **Unexpected Responders and Non Responders**

While analyzing data that has emerged from the Kleberg Center, we have determined that approximately 5-10% of patients entering clinical trials demonstrate remarkable responses to therapy. We and others have already demonstrated that these patients can be highly informative in terms of the mutations that indicate benefit. Continued study will define the mechanisms underlying major responses in clinical trials and why patients fail to respond. We expect to analyze and determine mechanisms of resistance to multiple targeted therapeutics.

## **Technology Evaluation and Implementation**

The Kleberg Center allowed us the ability to purchase a Sequenom Mass Array. This equipment provides an ideal technology for screening for hot spot mutations in genes that are aberrant in patient tumors. The Sequenom Mass Array was purchased to assess mutations in the circulating DNA. The technology did not demonstrate adequate sensitivity or specificity for this purpose. Through further evaluation, however, we have demonstrated that the equipment is ideal for detecting and characterizing activating mutations in tumor tissue. Given the success with the Sequenom Mass Array and the functional proteomics core, combined with the recommendation of the 2009 CCSG EAB meeting, the Kleberg Center has expanded its program in technology evaluation and implementation. A number of approaches have been implemented with the intention of moving this forward to CCSG cores or Clinical Laboratory Improvement Amendments (CLIA) patient management. In each case, equipment is evaluated through academic industrial collaborations and only purchased when appropriate.

One of the greatest successes has been the Functional Proteomics Reverse Phase Proteomics Core. The mission of this core is to provide reverse phase proteomics array services to MD Anderson researchers. The genomic lesions that cause tumor initiation and progression integrate at the level of protein function to result in the cellular correlates of the hallmarks of cancer. Indeed, the correlation between DNA, RNA and protein changes is only about 40%, requiring an ability to assess the functional proteome in order to understand the underlying processes in patient tumors. Thus, a cell-based functional proteomics approach is required to determine the consequence of genetic aberrations in cancer cells. Targeted therapeutics interferes with the function of cellular proteins, pathways and networks. A functional proteomics approach is needed for the validation of targets, demonstration of an off-target activity of drugs and evaluating pharmacodynamics.

The core was initiated with equipment including an Aushon Arrayer, a robotics platform and multiple autostainers initially implemented and evaluated in the Kleberg Center. Further, a collection of more than 250 validated or partially validated antibodies were transferred. In the 18 months since its inception, the core has assessed close to 30,000 independent samples for between 140 and 300 different signaling events using highly characterized antibodies. These samples include those from the Kleberg Center, the Medical Center and samples from around the world. Indeed, there is a remarkable change in process with MD Anderson analyzing patient samples from multiple different sites.

The Functional Proteomics Reverse Phase Proteomics Core has been awarded an American Recovery and Reinvestment Act (ARRA) supplement to run all TCGA samples as the sole source proteomics facility for the TCGA. The reverse phase protein array (RPPA) platform continues to be a driver of the efforts in the Kleberg Center. The platform has shown utility for prognosis, prediction and pharmacodynamics as well as for the underlying mechanisms of drug activity.

### **The Cancer Genome Atlas Project**

The National Institutes of Health's National Human Genome Research Institute (NHGRI) recently announced a joint project with the National Cancer Institute (NCI) to unravel the genetic makeup of cancer, calling it The Cancer Genome Atlas Project (TCGA). A genetic map of cancer cells will advance the development of targeted drugs for treatment as well as the development and improvement of molecular-imaging tools for cancer prevention efforts.

These studies are being conducted in collaboration with the Human Genome Sequencing Center at Baylor College of Medicine, researchers at Broad Institute, Memorial Sloan-Kettering Cancer Center and Washington University. Separately, Kleberg Center researchers have been working with researchers at Lawrence Berkeley National Laboratory and University of California, San Francisco to prepare a response to the TCA project of the NCI and the NHGRI. Results from the project will be made rapidly available to investigators worldwide, thus creating maximum opportunities for findings to be translated into targeted cancer treatment and prevention solutions. External collaborations also exist with UT Southwestern Medical Center at Dallas, Dana Farber Cancer Institute, University of British Columbia and other institutions worldwide.

Based on the success of the TCGA pilot, the TCGA has now been extended to 22 different tumors. Members of the Kleberg Center and the resources put in place are active participants in these projects.

The Kleberg Center has been funded, through an ARRA grant, as the sole source of functional proteomics analysis for all samples included in the TCGA. This will allow a linkage of DNA, RNA and protein analysis to patient outcomes and eventually management.

### **Industry Interactions**

The Kleberg Center has forged novel modes of interaction with industry to facilitate the clinical and translational research by the state-of-the-art technology solicitation, evaluation and finally collaboration with industry leaders. This role taken up by the Kleberg Center allows the researchers to collaborate and compare technologies in the market without limited costs, and to drastically reduce the time to evaluate a novel technology. The Kleberg Center has developed a technology evaluation program to seek out cutting edge technologies that have a direct impact on the fulfillment of its mission of personalizing cancer treatment, and matching those technologies with the clinical groups that require them.