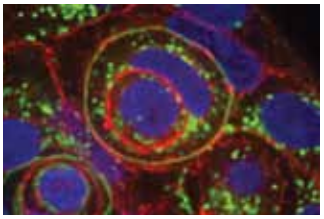
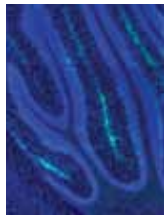









THE GEOFFREY BEENE CANCER RESEARCH CENTER

2010 PROGRESS REPORT

Memorial Sloan-Kettering Cancer Center

TABLE OF CONTENTS

MESSAGE FROM THE CHIEF EXECUTIVE OFFICER, GEOFFREY BEENE FOUNDATION

I could not be prouder of the significant progress that has been made at the Geoffrey Beene Cancer Research Center (GBCRC) over the past five years. In 2005, I approached past Memorial Sloan-Kettering president Dr. Harold Varmus to create a joint venture with MSKCC to focus on accelerated funding for initial-stage research across all cancers. Our shared vision resulted in the establishment in 2006 of the GBCRC, the principal philanthropic endeavor of both the Geoffrey Beene Estate and the Geoffrey Beene Foundation.

I am honored to welcome Dr. Craig Thompson as the new Chair of the GBCRC. I am also pleased to report that combined funding from Geoffrey Beene to the GBCRC through 2010 is $114 million in value. The GBCRC serves as the focal point for revolutionary new research aimed at translating discoveries at the cellular level into preventing, diagnosing, and treating the disease. It brings together researchers and physicians from two complementary areas: 1) the Cancer Biology and Genetics Program, based in the Sloan-Kettering Institute (SKI), and 2) the Memorial Hospital–based Human Oncology and Pathogenesis Program.

Since 2006, forty-two research grants have been awarded, and six proposals for shared resources have been funded. Each grant funds initial-stage research and is renewed for a second year. Last year alone, ten new grants were issued. In addition, each year Geoffrey Beene Graduate Fellowships are awarded to deserving graduate students. These awards provide full stipends for students conducting cancer research in MSKCC labs. Three MSKCC faculty members have also been appointed Geoffrey Beene Junior Faculty Chairs.

The GBCRC has provided substantial funding both for the creation and continued support of the Geoffrey Beene Translational Oncology Core Facility and for existing facilities like the Genomics Core, the High-Throughput Core, and the Microchemistry and Proteomics Core. The Center also supports two annual events: 1) the GBCRC Retreat, designed to stimulate discussion and collaboration among researchers, and 2) the GBCRC Symposium, which invites world-renowned guest speakers.

On a lighter note, Drs. Thompson, Sawyers, and Massagué, all members of the GBCRC Executive Committee, were celebrated as “2010 Rock Stars of Science” for their scientific leadership, lifesaving therapies, and generosity in helping to excite the next generation about careers in science. This nationally recognized campaign, created by the Geoffrey Beene Foundation, also draws attention to the problem of scientific illiteracy in the United States and urges increases in funding for medical research. I am pleased to learn that the MSKCC human resource department will be using our campaign materials in their recruitment programs.

The dedication of the doctors, scientists, and lab members is truly heartwarming, and we are making progress toward our shared goal to make cancer a more manageable and perhaps, one day, curable disease. I thank you all for your dedication and for your lifesaving work!

Very truly yours,

G. Thompson Hutton
CEO & Trustee, Geoffrey Beene Foundation
Executor, Estate of Geoffrey Beene
President and CEO, Geoffrey Beene, LLC

GEOFFREY BEENE CANCER RESEARCH CENTER EXECUTIVE COMMITTEE

Oversight of the GBCRC is provided by an Executive Committee. Members include senior leaders from Memorial Hospital and Sloan-Kettering Institute.

James Allison, PhD, is Director of the Ludwig Center for Cancer Immunotherapy, Chair of the Immunology Program, an Attending in the Department of Medicine, and the David H. Koch Chair in Immunologic Studies at MSKCC. Dr. Allison received his PhD from the University of Texas, Austin, and after postdoctoral training at Scripps Clinic in La Jolla, California, he joined the faculty of the University of Texas System Cancer Center Science Park. He then moved to the University of California, Berkeley, where he remained for 20 years, holding the positions of Director of the Cancer Research Laboratory, Director of the Immunology Program, and Co-Chair of the Department of Immunology. In 2006, he moved to MSKCC. Dr. Allison is a member of the National Academy of Sciences and the Institute of Medicine, a Fellow of the American Academy of Microbiology and the American Association for the Advancement of Science, and an investigator of the Howard Hughes Medical Institute. He has received numerous awards, including the Centeon Award for Innovative Breakthroughs in Immunology, the William B. Coley Award for Distinguished Research in Basic and Tumor Immunology, the AAI-Dana Award in Human Immunology Research, the C. Chester Stock Award for Distinguished Achievement in Biomedical Research, and the iSBTC Smalley Award.

Boris Bastian, MD, is Chair of the Department of Pathology at MSKCC and a member of the Center's Human Oncology and Pathogenesis Program. He is also the incumbent of the James Ewing Alumni Chair of Pathology. Dr. Bastian obtained his MD from the Ludwig-Maximilian University of Munich and completed his residency at the University of Wurzberg, Germany. He conducted fellowships at Ludwig-Maximilian University and the University of California, San Francisco (UCSF), Cancer Center. Prior to his appointment at MSKCC, Dr. Bastian was a professor at UCSF, where he led the Cutaneous Oncology Program at the Helen Diller Family Comprehensive Cancer Center.

Thomas J. Kelly, MD, PhD, is Director of SKI and the Benno C. Schmidt Chair of Cancer Research at MSKCC. Dr. Kelly received his PhD in biophysics from The Johns Hopkins University and his MD from The Johns Hopkins University School of Medicine. He joined MSKCC in 2002 after a thirty-year career at The Johns Hopkins University School of Medicine, where he served as the Director of the Department of Molecular Biology and Genetics and as the Director of the Institute for Basic Biomedical Sciences. Dr. Kelly is a member of the National Academy of Sciences, the Institute of Medicine, and the American Philosophical Society, as well as a Fellow of the American Academy of Arts and Sciences.

Joan Massagué, PhD, is Chairman of the Cancer Biology and Genetics (CBG) program at MSKCC. He is also an investigator of the Howard Hughes Medical Institute, a professor of the Weill-Cornell Graduate School of Medical Sciences, and an Adjunct Director of the Barcelona Institute for Research in Biomedicine. Dr. Massagué received his PhD in biochemistry from the University of Barcelona in 1978 and was a postdoctoral fellow at Brown University starting in 1979. He became a faculty member at the University of Massachusetts Medical School in 1982, prior to joining MSKCC in 1989. Dr. Massagué is an elected member of the National Academy of Sciences, the American Academy of Arts and Sciences, the Institute of Medicine, the Spanish Royal Academies of Medicine and of Pharmacy, and the European Molecular Biology Organization. His honors include the Prince of Asturias Prize, the Vilcek Prize, the Passano Prize, the AACR Clowes Award, and the BBVA Frontiers Prize.

Larry Norton, MD, is Deputy Physician-in-Chief for Breast Cancer Programs, and Medical Director of MSKCC's Evelyn H. Lauder Breast Center. He is the Norna S. Sarofim Chair of Clinical Oncology at MSKCC and a Professor of Medicine at Weill-Cornell Medical College. Dr. Norton received his medical education at the College of Physicians and Surgeons of Columbia University, the Albert Einstein College of Medicine, and the National Cancer Institute. Dr. Norton was a presidential appointee to the National Cancer Advisory Board and served as President of the American Society of Clinical Oncology. He has been Vice-Chair of the Lymphoma Committee and a long-serving Chair of the Breast Committee of the Cancer and Leukemia Group B. Dr. Norton is a founder of the Breast Cancer Research Foundation and is currently its Scientific Director. He has received ASCO's highest honor, the David A. Karnofsky Award, and he was McGuire Lecturer at the San Antonio Breast Cancer Symposium.

Charles L. Sawyers, MD, is an investigator of the Howard Hughes Medical Institute and the inaugural Chair of the Human Oncology and Pathogenesis Program (HOPP) at MSKCC, where he is building a program of lab-based translational researchers across various clinical disciplines and institutional infrastructure to enhance the application of global genomics tools to clinical trials. Dr. Sawyers received his MD from The Johns Hopkins University School of Medicine. He is past President of the American Society of Clinical Investigation and served on the National Cancer Institute's Board of Scientific Counselors. He is a member of the Institute of Medicine, and in 2010, Dr. Sawyers was elected to the National Academy of Sciences. Dr. Sawyers has won numerous honors and awards, including the Richard and Hinda Rosenthal Foundation Award, the Dorothy Landon Prize from the American Association of Cancer Research, the David A. Karnofsky Award from the American Society of Clinical Oncology, and the 2009 Lasker-DeBakey Clinical Medical Research Award.

David A. Scheinberg, MD, PhD, holds the Vincent Astor Chair and is Chair of the Molecular Pharmacology and Chemistry Program. He is a founder and Chair of the Experimental Therapeutics Center and the Nanotechnology Center at MSKCC. Dr. Scheinberg received his PhD from The Johns Hopkins University, Department of Pharmacology and Experimental Therapeutics, and his MD from The Johns Hopkins University School of Medicine. He completed his residency at Cornell University Medical Center and his fellowships at MSKCC and Cornell University Medical College.

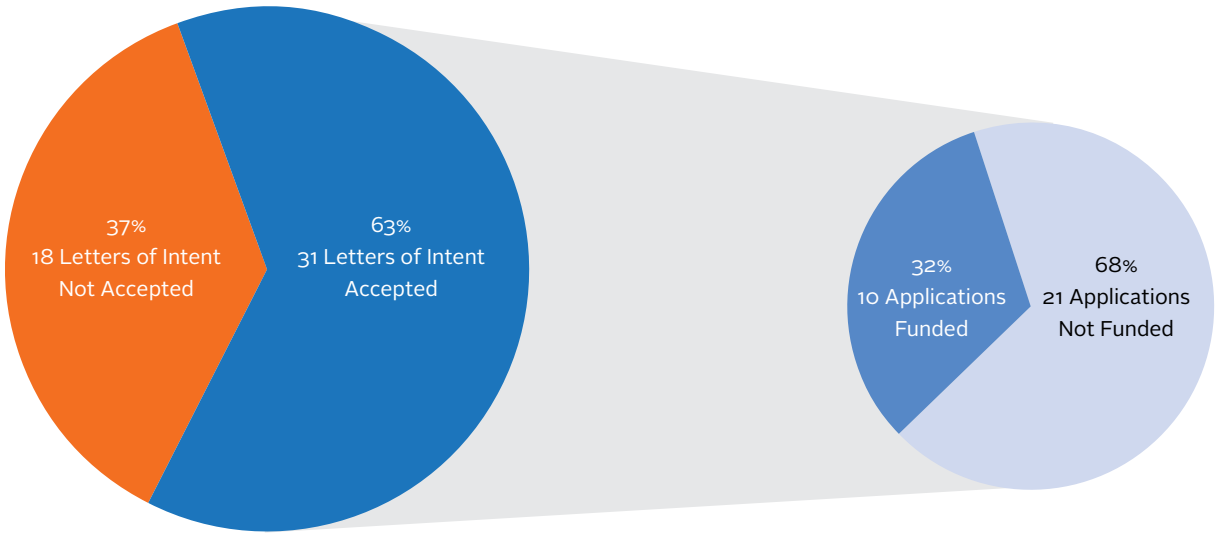
Craig B. Thompson, MD (Chair of the GBCRC), became President and CEO of MSKCC on November 2, 2010. He is a board-certified internist and medical oncologist with extensive research experience in cancer, immunology, and translational medicine. Dr. Thompson attended Dartmouth College and completed his studies at Dartmouth Medical School. He received his MD from the University of Pennsylvania in 1977 and completed his residency at Harvard's Peter Bent Brigham Hospital in 1979. Following his residency, he spent two years as a senior resident at Boston University while serving as a medical officer in the United States Navy assigned to the Naval Blood Research Laboratory. He spent eight years as a Navy medical officer. He came to MSKCC from the University of Pennsylvania, where he had served since 2006 as Director of the Abramson Cancer Center and Associate Vice President for Cancer Services of the University of Pennsylvania Health System. Dr. Thompson is a member of the Institute of Medicine, the National Academy of Sciences, the American Academy of Arts and Sciences, and the Medical Advisory Board of the Howard Hughes Medical Institute.

Robert E. Wittes, MD, is Physician-in-Chief of Memorial Hospital. He graduated from Harvard College in 1964 and from Harvard Medical School in 1968. He was Director of the Division of Cancer Treatment and Deputy Director for Extramural Science at the National Cancer Institute (NCI) from 1995 to 2002. Prior to 1995, he served as Associate Director, Division of Cancer Treatment, NCI, 1983 to 1988; Senior Vice President for Cancer Research, Bristol Myers, 1988 to 1990; and Chief of the Medicine Branch, Division of Cancer Treatment, NCI, 1990 to 1995. He is currently an Associate Editor of *Clinical Cancer Research*. He was awarded the United States Public Health Service Distinguished Service Medal in June 2000.

G. Thompson Hutton, Esq., is an Ex-Officio Member of the Executive Committee for the GBCRC and is President and CEO of Geoffrey Beene, LLC, and Trustee and CEO of the Geoffrey Beene Foundation. As Executor of the Estate of Geoffrey Beene, Mr. Hutton made the decision to create and support the GBCRC at MSKCC. Mr. Hutton was determined to transform the Geoffrey Beene brand into a unique model of corporate giving — 100 percent of net profits from Geoffrey Beene, LLC, fund philanthropic causes. Mr. Hutton also created the Geoffrey Beene Foundation Alzheimer's Initiative and the Rock Stars of Science™ campaign to bring greater public awareness to our nation's top research scientists and the need for greater funding. In 2010, Mr. Hutton was awarded the Research!America Isadore Rosenfeld Award for Impact on Public Opinion. Prior to becoming CEO of Geoffrey Beene, LLC, in 2004, Mr. Hutton was a practicing attorney in his own law firm. From 1971 until 1989, he was an attorney and partner of Shea & Gould, specializing in corporate law, securities, and mergers and acquisitions. Mr. Hutton received his JD from Columbia University in 1971, is a member of the New York City, New York State, and American Bar Associations, and is admitted to practice before the Federal District Court in the Southern District of New York and in the United States Circuit Court of Appeals for the Second Circuit.

Since 2007, the GBCRC has held an annual grant competition with the goal of supporting innovative research projects that may not initially qualify for other sources of funding. An average of 33 percent of proposals submitted each year are funded. A total of 42 research grants have been awarded from 2007 to 2010, with total support exceeding $16 million. In 2010, ten new awards were issued, and a second year of funding was distributed for 13 projects from 2009.

% APPLICATIONS FUNDED IN 2010



RESULTS FROM GRANT FUNDING

A series of publications has resulted from projects funded by the GBCRC. For a detailed list, please refer to the end of this report.

Beene awards serve as seed funding to enable investigators to produce sufficient preliminary data for proposals to other funding agencies. Of the 32 awardees from 2007 to 2009, 21 investigators (66 percent) have applied for subsequent funding. The GBCRC's investment of $6.3 million in direct support for these projects has resulted in $10.7 million in direct support to investigators from subsequent grants. There were 19 new awards — nine federal and ten non-federal, including a combination of foundation, philanthropic, and industry awards. In addition to the awarded grants, there are 13 pending proposals for projects originating from the Beene awards.

FOLLOWUP FUNDING RECEIVED FROM GBCRC GRANT RECIPIENTS

	Total Number of New Awards	Total Direct Support of New Awards
2007 grantees	10	$5,208,248
2008 grantees	2	$1,432,623
2009 grantees	7	$4,065,889
Total	19	$10,706,760

Sources of subsequent funding from federal awards:

- Department of Energy
- National Cancer Institute
- National Institutes of Health

Sources of subsequent funding from non-federal awards:

- Brain Tumor Center at MSKCC
- Cancer and Leukemia Group B Foundation
- Clinical and Translational Science Center
- Emerald Foundation
- Experimental Therapeutics Center at MSKCC
- Genentech
- Leukemia and Lymphoma Society
- Starr Cancer Consortium
- Susan G. Komen Breast Cancer Foundation

INTERVIEW

Tari King, MD, FACS

Tari King, MD, FACS, is an Associate Attending Surgeon on the Breast Service in the Department of Surgery. She is the incumbent of the Jeanne A. Petrek Junior Faculty Chair and was awarded a Beene grant in 2008 for her project "A Genetic Analysis of the Invasive Breast Cancer Risk Associated with Lobular Carcinoma in Situ."

You're a physician-scientist, so you have both clinical and laboratory responsibilities. How did you become interested in pursuing both avenues?

I am a breast cancer surgeon who diagnoses and treats women with breast cancer, and I have always enjoyed clinical research. Combining my clinical practice with my interest in research is what motivated me to pursue translational research. There is a real need for physician-scientists who can identify clinical problems, figure out how to address them in the laboratory, and then take them back to the clinic.

What is your research focus?

In my clinical practice, we are frequently faced with this lesion called lobular carcinoma in situ (LCIS), which is very poorly understood. Very little is known about this lesion other than the fact that about 20 percent of women with it will develop breast cancer, and the risk of developing breast cancer is a steady risk over time. These women have about a 1-to-2-percent-per-year risk of developing breast cancer, making it the second-highest-known risk factor for breast cancer aside from carrying a mutation in BRC1 or BRC2.

We see women in the office who have a biopsy that shows LCIS and they ask what they should do. We present all women with three options: 1) you can do nothing but continue to have normal breast cancer screening, 2) you can take Tamoxifen for chemo prevention, or 3) you can remove both breasts. Each of those three options are presented fairly equally for women with this very poorly understood lesion so it provides a very good opportunity to try to understand it in order to better tailor our therapies.

What have you been able to do with the Beene funding that you might not otherwise have been able to complete?

We have been very fortunate — the Beene Center funding has played a major role in our success to date. Everything we do with high-throughput genomic analysis is very expensive. The funding has allowed us to collect specimens from over 140 women and compile gene expressions arrays (examine which genes are turned on and off in these lesions) and a small number of SNP arrays (these examine copy number changes in the DNA). The Beene grant has also provided enough preliminary data to apply for other grants, such as the award we received from the Susan G. Komen Foundation, to continue and broaden our research.

We were also able to develop and maintain a clinical database, which we call our historical cohort. At the same time we've been conducting research in the laboratory, collecting specimens from women who are newly diagnosed with LCIS; we also follow almost 900 women here at the institution who have LCIS and participate in our special surveillance breast program. We have created a detailed database that we prospectively maintain, so we know which women of these 900 have developed cancer, how long it took them to get cancer, what kind of cancer they have, and which of the 900 have not developed cancer. We have done some clinical research on cancer development in this cohort, have presented the data at national meetings, and have several papers in progress from the purely clinical aspect of LCIS as well.

Why do you think LCIS is not popularly studied?

There are several reasons. One is that it takes a clinician to recognize that it's a problem. It is also a very lengthy and expensive project. Collecting tissue from 140 women has taken seven years and has been quite costly and time-consuming for the Tissue Procurement Core Facility at MSKCC. The average cost my lab has incurred for processing each breast is around $2,000.

What are some opportunities or challenges you face as a physician-scientist?

I think that being a physician-scientist puts you at an advantage in understanding real life clinical problems that need to be answered by research that is directly translatable. But it also puts you at a disadvantage because it's not your full-time job. Time constraints and other demands can be challenging. I only get to focus on my research approximately 40–50 percent of the work week time, two full days a week on a good week but often in the midst of other patient activities, phone calls, etc. The limited time I have can make it difficult to amass the publications, preliminary data, and the track of success to be competitive for funding against people who are full-time researchers, especially for some of the awards that require a certain amount of protected time to be eligible for the award.

I continue to accept the challenge of balancing clinical and research responsibilities because I get a lot of personal satisfaction out of it. I find the problems and the solutions captivating and I am really enjoying analyzing a problem and trying to understanding it. The ultimate goal is to be able to take your research back to the clinic and see your work actually helping patients.

How has funding from the GBCRC impacted your research?

I am very thankful to have had the support from the Beene Center and I hope they will be able to continue funding grants/projects such as mine. For a lot of investigators, including myself, the Beene award serves as the first major springboard, and this is very important for our future successes.

Boris C. Bastian, MD, PhD

CHAIR, DEPARTMENT OF PATHOLOGY
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM

"A Comprehensive Genomic Approach to Identify Cancer Genes in Uveal Melanoma"
Project Abstract: Uveal melanoma is an aggressive form of melanoma with unique genetic characteristics, which involve frequent mutations in GNAQ or GNA11 and deletions of chromosome 3. In this project, we are performing a systematic genetic and functional analysis to identify the tumor suppressor(s) on chromosome 3, with the goal to improve the understanding of the pathogenesis of this dreadful disease and to find better methods for diagnosis, prognosis, and treatment.

Filippo G. Giancotti, MD, PhD

CELL BIOLOGY PROGRAM

"Early Development of Small Molecule Inhibitors of the E3 Ubiquitin Ligase CRL4^{DCAF1}"
Project Abstract: We have recently provided evidence that the FERM domain protein Merlin, encoded by the neurofibromatosis type II gene (NF2), suppresses tumorigenesis by translocating to the nucleus to inhibit the E3 ubiquitin ligase CRL4^{DCAF1} (Li et al. *Cell* 140:477-490, 2010b, PMID: 20178741). These results indicate that inhibitors targeting CRL4^{DCAF1} will display therapeutic efficacy in NF2 and mesothelioma cases driven by NF2 mutations. We propose to identify and to begin to optimize compounds able to inhibit CRL4^{DCAF1}.

Jason T. Huse, MD, PhD

DEPARTMENT OF PATHOLOGY
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM

"A Comprehensive Genomic and Epigenomic Analysis of the Impact of First-Line Therapy in the Molecular Evolution of Malignant Glioma"
Project Abstract: Malignant gliomas are routinely treated with radiation and chemotherapy, but invariably recur in a state refractory to conventional treatment regimens. The biological mechanisms underlying this resistance, especially with regard to the impact of cytotoxic therapy at the molecular level, remain largely unknown. We intend to comprehensively characterize the effects of first-line glioma treatment on the development of therapeutic resistance in malignant glioma using an integrated, global genomics/epigenomics approach.

Ingo K. Mellinghoff, MD

DEPARTMENT OF NEUROLOGY
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM

"Identification of aberrant signal transduction pathways in Primary CNS Lymphoma"
Project Abstract: Primary CNS Lymphoma (PCNSL) is an aggressive primary human brain tumor. There remains a paucity of knowledge regarding the molecular events driving this disease. Our project will molecularly characterize a clinically well-annotated set of PCNSL samples with the goal to derive new insights into its pathogenesis and to identify new treatment opportunities for its most aggressive subtype(s).

Vincent A. Miller, MD

THORACIC ONCOLOGY SERVICE, DEPARTMENT OF MEDICINE

"Characterization of the Molecular Heterogeneity of EGFR Mutant Lung Adenocarcinoma: Baseline and Post-Treatment Tumor Analysis"
Project Abstract: Lung cancers with mutations in the epidermal growth factor receptor (EGFR) are a unique subset of adenocarcinomas of the lung that are unusually vulnerable to targeted therapy with tyrosine kinase inhibitors (TKIs), such as erlotinib. Despite an unparalleled 14-month median progression-free survival, patients treated with erlotinib exhibit significant differences in benefit, with some gaining years of disease control and others progressing after several months. Response rate is similarly variable. These observations suggest that there are underlying differences among EGFR mutant lung adenocarcinomas. The goal of this study is to more uniformly characterize the biologic heterogeneity of this disease through assessment of intra- and intertumoral changes in key genes linked prospectively to outcome from patient samples taken before and immediately after treatment with erlotinib. This understanding is fundamental to the improvement of current therapies and the generation of new ones.

Stephen D. Nimer, MD

LEUKEMIA SERVICE, DEPARTMENT OF MEDICINE
MOLECULAR PHARMACOLOGY AND CHEMISTRY PROGRAM

"Establishment of a Unique Mouse Model for Plasma Cell Malignancies"

Project Abstract: We have generated a novel mouse model that allows us to study the development and progression of human plasma cell disorders, including multiple myeloma and plasma cell leukemia. We will use these mice to better understand these diseases, gaining insights into the mechanisms by which these diseases arise, the genetic abnormalities and changes in gene expression that drive their growth, and the precise defects in their growth regulation. This information will be incorporated into new therapeutic approaches, which we will evaluate using these mice. The results of these studies will be used to procure future NCI or NIH funding.

Kenneth Offit, MD

CHIEF, CLINICAL GENETICS SERVICE, LYMPHOMA SERVICE, DEPARTMENT OF MEDICINE
CANCER BIOLOGY AND GENETICS PROGRAM

"Exome Sequencing of Familial Lymphoproliferative Syndrome"

Project Abstract: This project will seek to uncover mechanisms of genetic susceptibility in families affected by multiple cases of lymphoid malignancies. The approach taken will be to utilize next-generation massively parallel sequencing to discover within coding segments of the genome rare events that can explain increased risk for developing lymphoid cancers. We will sequence the exome from one affected individual in each series of families affected by lymphoproliferative malignancies and identify rare events not seen in reference genomes.

John H. J. Petrini, PhD

MOLECULAR BIOLOGY PROGRAM

"DNA Replication Stress and the Sumoylation of RPA"

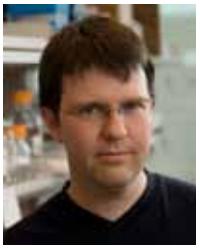
Project Abstract: DNA replication stress, which is caused by DNA lesions or metabolic states that impair the process of DNA replication, causes chromosome alterations. Defects in pathways that respond to DNA replication stress have been definitively linked to the development of cancer. Using human, mouse, and yeast cells, we are analyzing the response to replication stress. Ultimately, the information obtained will illuminate molecular mechanisms of tumor suppression.

Howard I. Scher, MD

CHIEF, GENITOURINARY ONCOLOGY SERVICE, DEPARTMENT OF MEDICINE

"Molecular Profiling in Circulating Tumor Cells (CTC) in Patients with Metastatic Prostate Cancer: Development of Predictive Biomarkers for Targeted Treatment"

Project Abstract: The experience to date with androgen receptor signaling–directed approaches for castration-resistant prostate cancer shows dramatic and durable responses in some patients, an intermediate response in others, and a distinct cohort that is intrinsically resistant to therapy. Our program seeks to establish robust assays for genes associated with intrinsic and acquired resistance in circulating tumor cells isolated from patients enrolled on trials of AR signaling–targeted agents in clinical development at MSKCC. Our long-term objective is to generate data to qualify predictive biomarkers of sensitivity in CTC to guide treatment selection.



Hans-Guido Wendel, MD

CANCER BIOLOGY AND GENETICS PROGRAM

"Oncogenic MicroRNAs in Acute Lymphatic Leukemia"

Project Abstract: Cytogenetic and recent genomic studies from the Downing lab and others have produced great insight into the genetics of acute lymphatic leukemia (ALL). However, the contribution of microRNAs (miRNAs) to the molecular pathogenesis of ALL has not been explored systematically. This proposal focuses on oncogenic miRNAs in ALL, and we expect to gain insight into the contribution of miRNAs to the pathogenesis and clinical course of ALL.

Nai-Kong Cheung, MD, PhD

DEPARTMENT OF PEDIATRICS

"Humanized Antibody 8H9 to Target Immunoinhibitory Molecule B7H3 on Solid Tumors"
Project Abstract: Few curative treatments exist for cancers metastatic to the brain. Liquid radiation delivered by mouse monoclonal antibody 8H9 has prolonged survival measured in years. The humanized form of 8H9 should make the treatment safer and more effective.

Ronald DeMatteo, MD

VICE CHAIR, DEPARTMENT OF SURGERY
HEAD, DIVISION OF GENERAL SURGICAL ONCOLOGY
IMMUNOLOGY PROGRAM

"Combined Molecular Therapy and Immunotherapy for Gastrointestinal Stromal Tumor"
Project Abstract: Tyrosine kinase inhibitors are a new class of drugs that have already proved to be highly effective in certain types of human cancers. We are using a mouse tumor model to investigate the effects of using tyrosine kinase inhibitors with agents that activate the immune system. The hypothesis is that this combination therapy will be more effective than either treatment alone. The work may ultimately provide the basis for human clinical trials.

Filippo G. Giancotti, MD, PhD

CELL BIOLOGY PROGRAM

"Suppression of Mammary Tumorigenesis and EMT by the Atypical Rho Protein Rnd1"
Project Abstract: We are studying the function of the potential tumor suppressor gene RND1, which appears to be altered in about 20 percent of human breast cancers. We have found that RND1 directs the production of a signaling protein that restrains the cell division cycle and prevents the changes in cell architecture and motility that accompany tumor invasion and metastasis. Inactivation of RND1 leads to the conversion of normal mammary epithelial cells to breast cancer cells and renders already transformed breast cancer cells more invasive and metastatic. We are currently studying the mechanism through which RND1 suppresses cellular signaling, examining whether genetic inactivation of RND1 is sufficient to initiate tumorigenesis in the mammary gland of mice, and exploring the genetic mechanisms through which RND1 is inactivated in human breast cancer.

Michael Glickman, MD

INFECTIOUS DISEASE SERVICE, DEPARTMENT OF MEDICINE
IMMUNOLOGY PROGRAM

"BCG Susceptibility of Bladder Cancer Cells: Role of PTEN-AKT Signaling in Pathogen Infection"
Project Abstract: Early-stage bladder cancer is often treated with BCG, a live bacterium, but its mechanism of action is unknown. This project will investigate the possibility that deficiencies in tumor suppressor pathways within bladder cancer tumor cells render them sensitive to BCG therapy. If successful, this project will identify the mechanism of action of BCG therapy and allow targeting of this therapy to specific patients based on their tumor characteristics.

Alexandra L. Joyner, PhD

DEVELOPMENTAL BIOLOGY PROGRAM

"Development of a Novel Technique for Modeling and Characterizing Sporadic Tumors in Mice"
Project Abstract: Most cancer arises sporadically due to genetic mutations that occur in one or a few cells within a tissue. Current animal models of cancer, however, do not accurately model sporadic tumor formation. Using sophisticated mouse genetics, we are developing a novel approach to study the natural progression of sporadic tumors and test cancer treatments.

Andrew Lassman, MD

DEPARTMENT OF NEUROLOGY

"Pulsatile Kinase Inhibitor Therapy for Malignant Glioma: Proof of Concept Clinical Trial"
Project Abstract: Malignant gliomas are the most common brain cancer in adults, and the average survival for patients with the most aggressive type (glioblastoma) is about one year. In many of these tumors, a molecule called epidermal growth factor receptor (EGFR) signals tumor cells to grow. Thus far, drugs that inhibit EGFR have not been effective for most patients, at least partly because drugs do not adequately reach the tumor when given in the standard manner — a low dose every day. To improve results, we are planning a clinical trial that differs from previous studies in two important ways: 1) a different dosing schedule called "pulsatile" dosing with a high dose once per week that blocks EGFR

less frequently, but more completely, than standard dosing; 2) selection of patients likeliest to benefit because EGFR in their tumors is abnormally active (previous trials treated all patients regardless of whether EGFR was "on" or "off"). We will treat 20 patients in this manner, ten of whom will also undergo surgery after receiving the EGFR inhibiting drug so that we can determine whether the treatment effectively turns "off" EGFR. Through this design, we hope to change the current paradigm of drug development for gliomas.

Ross Levine, MD

LEUKEMIA SERVICE, DEPARTMENT OF MEDICINE
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM

"Identification and Characterization of Inherited Predisposition and Modifier Alleles That Contribute to the Pathogenesis of Myeloproliferative Neoplasms"

Project Abstract: The goal of our project is to identify novel inherited DNA changes that predispose individuals to develop chronic leukemias. The long-term goal of our efforts is to improve our understanding of the genetic basis of leukemias to better use existing treatments and develop new therapies.

Jason S. Lewis, PhD

CHIEF, RADIOCHEMISTRY SERVICE,
DEPARTMENT OF RADIOLOGY
MOLECULAR PHARMACOLOGY AND CHEMISTRY PROGRAM

"Zirconium-89 Labeled Antibodies for ImmunoPET Guided Radioimmunotherapy"

Project Abstract: This proposal will focus on the use of trastuzumab (Herceptin), a monoclonal antibody (mAb) that targets the HER2/neu growth factor receptor, a member of the epithelial growth factor receptor (EGFR) family. The central hypothesis is that 89Zr-radiolabeled Herceptin can be used for quantitative PET imaging of breast tumors, improved early detection, staging, monitoring of immunotherapy with Herceptin, and the development of new radioimmunoPET-guided radioimmunotherapeutic agents specific for breast cancer. By the end of this project, we anticipate that we will have translated 89Zr-DFO-Herceptin to the clinic for quantitative PET imaging of HER2/neu-positive breast cancers in patients.

Yueming Li, PhD

MOLECULAR PHARMACOLOGY AND CHEMISTRY PROGRAM

"Role of Notch/γ-Secretase Pathway in the Proliferation and Survival of Breast Cancer Cells"

Project Abstract: Notch signaling may play a causative role in breast cancer. Overall objectives of this proposal are to investigate the function of Notch/gamma-secretase signaling in breast cancer cells and to develop a target-based therapy that is not currently available.

Dimitar B. Nikolov, PhD

STRUCTURAL BIOLOGY PROGRAM

"Novel Anti-Cancer Compounds Targeting the Tie2/Angiopoietin Interactions and Signaling"

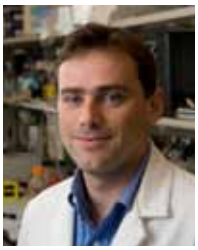
Project Abstract: The Tie2 receptor and its angiopoietin ligands regulate developmental and tumor-induced blood vessel formation. The potential to inhibit tumor formation and growth by blocking tumor-induced blood vessel formation has shown great promise in many cancer types. Our preliminary results indicate that small molecules could disrupt the Tie2/angiopoietin interactions, and we propose to identify such compounds and start developing them into effective anti-tumor therapies.

Michael Overholtzer, PhD

CELL BIOLOGY PROGRAM

"Examining the Role of Entosis in Human Cancers"

Project Abstract: Cancers arise when individual cells evade homeostatic mechanisms that control their growth. By investigating how tumors arise from normal cells in the lab, we discovered a new cellular mechanism called entosis, which eliminates cells by causing cell death. Evidence of entosis has been seen for decades by pathologists in human cancers because it results in the formation of "cell-in-cell" structures, where whole cells are engulfed by others. Characterization of this process will shed light on a novel aspect of how some cancers arise and also on a new cell death program than can kill tumor cells.



David B. Solit, MD

GENITOURINARY ONCOLOGY SERVICE,
DEPARTMENT OF MEDICINE
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM

"The Memorial Sloan-Kettering Cancer Center Colorectal Cancer Oncogenome Project: Somatic and Germline Predictors of Recurrence and Response to Therapy"

Project Abstract: The goal of this project is to identify genetic mutation "signatures" that could be used by physicians and patients to determine whether or not a patient is at high risk of recurrence after surgery (prognostic markers), and whether or not a patient is likely or unlikely to benefit from treatment with a particular chemotherapy agent (predictive markers). We will use these genetic signatures both to guide selection of standard, currently available therapies, and to guide selection of patients for treatment with experimental agents that are specifically designed to target specific driver mutations when present in the tumor.

Andrea Ventura, MD, PhD

CANCER BIOLOGY AND GENETICS PROGRAM

"Investigating the Functions of Oncogenic MicroRNAs in Mammals"

Project Abstract: Using a combination of mouse genetics, bioinformatics and biochemistry, we are investigating the role of Oncomir-1 (also known as miR-17~92) in the pathogenesis of human cancers. Our preliminary results indicate that this cluster of miRNAs is essential for the survival of lymphoma cells, and we are currently identifying the molecular mechanisms underlying its oncogenic properties. These studies extend our basic knowledge of the role of miRNAs in tumorigenesis and may pave the way for an entirely novel approach for the targeted treatment of human cancers.

SHARED RESOURCE AWARDS

In addition to research grants the GBCRC offers a competitive application process for shared resource proposals to make available expensive resources for meritorious projects that can be justified only on a shared-use basis. The Shared Resource Program provides a mechanism for Memorial Sloan-Kettering lab investigators to obtain commercially available, technologically sophisticated resources costing more than $200,000. A total of $1.46 million has been awarded for six shared resource proposals in the past three years.

2010 Funded Shared Resource

Jason T. Huse, MD, PhD

DEPARTMENT OF PATHOLOGY
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM

"High-Throughput Immunohistochemistry"

Project Abstract: We have recently acquired a state-of-the-art immunostainer that will considerably improve our ability to detect proteins of interest directly on tissue slides obtained from patient tumors. The device can hold 30 slides at any one time, is fully automated, and can complete staining runs in six hours. Our lab, along with Ingo Mellinghoff's and Timothy Chan's labs, is already using it extensively.

INTERVIEW

Milind Rajadhyaksha, PhD

Milind Rajadhyaksha is an optical/mechanical engineer on the Dermatology Service in the Department of Medicine. He was awarded a Beene grant in 2008 for his project titled "Line-scanning confocal endoscope for screening oral precancers in vivo."

Tell us about your Beene project.

Our Beene project is to design, research, and build simpler, smaller, and lower-cost microscopes — especially an endoscope for intra-oral imaging.

What progress has been made and what future opportunities do you envision?

We have built a prototype confocal endoscope over the past two years and we are currently evaluating the performance in our laboratory. The current prototype is second generation — an improved design, based upon the learning experience of the first generation. For the last part of the project, we will perform preliminary testing on patients.

We are also exploring the feasibility of shrinking down the size of the instrument for the next version which will be more rigorously tested and on a larger scale in the clinic.

In the long term, I envision that this confocal endoscope will be in the hands of dentists, who would use it for screening purposes during annual dental exams to detect any signs of early disease in the oral cavity. The goal is to screen for oral pre-cancers while reducing or eliminating the need for biopsies.

Do you collaborate with other investigators for this project?

This project is an exciting collaboration between my group; Dr. Snehal Patel, a surgeon in our Head and Neck Service in Memorial Hospital; and Dr. Ricardo Toledo-Crow, who directs the Research Engineer Laboratory Core Facility in SKI. So this project has really been a very productive partnership between our technology developers, researchers, and the clinicians across the hospital and SKI. Together with Dr. Toledo-Crow's group, we developed the optics, mechanics, and electronics. It has been a good combination of personnel and expertise across the hospital and SKI.

Gary Peterson, Engineering Specialist, and Milind Rajadhyaksha

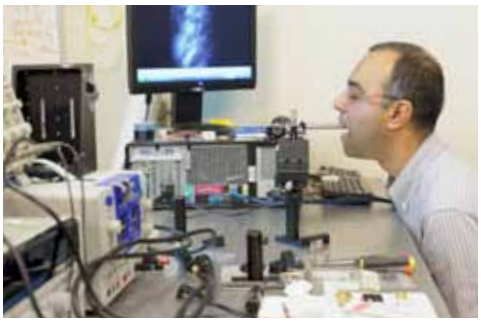
How has the funding you received from the Beene Center affected the progress you've made?

The Beene funding has allowed us to develop our ideas for a small, simple, and low-cost confocal endoscope through two generations, which is pretty rapid because it can otherwise take five to seven years to make the progress we have made. This has allowed me to submit an R01 grant to the National Cancer Institute, which was favorably reviewed, although it was not funded.

How did you become interested in becoming a researcher and how did you end up in Dermatology?

Purely out of curiosity! I am a mechanical engineer by training and I studied traditional mechanical engineering during my undergraduate years and combined it with optical engineering during graduate school. I did a postdoctoral fellowship at Massachusetts General Hospital (MGH) in Boston. That's where I started designing and building confocal microscopes.

After I made my first public presentation at a conference, I learned that the company Lucid had also been interested in trying to create confocal microscopes for imaging skin. I left MGH to work for Lucid and spent five years working with a group building the first commercial product for detecting skin cancer. During the time when I was marketing this product and building clinical partnerships, I met Dr. Allan Halpern at MSKCC.



The toothbrush-shaped probe consists of a lens that is placed on the inside of the lip or cheek or on the tongue. The working distance of the lens determines the depth in the tissue at which the imaging is performed. Images vary from cells and nuclei to capillary vessels and blood flow.

When I decided to leave industry after five years and return to academia, Dr. Halpern's research and the dermatology group at MSKCC was a natural fit to my interests in translating confocal microscopy into the clinic.

What do you think the benefits of collaboration are?

A lot of opportunities today lie at the boundaries within disciplines, not within one single discipline. There is a phrase that one hears often these days — a "valley of death" — which is the chasm that exists between the laboratory and the clinic and between academia and industry. A lot of exciting ideas that show promise in a laboratory end up being published but not subsequently translated into the clinic or commercialized by industry. Good teams and collaborations can be very productive and effective in bridging this chasm. I think the opportunities are increasing in translational research, so working in teams will be increasingly necessary to move ideas forward into clinics and markets.

GEOFFREY BEENE GRADUATE FELLOWSHIPS

Each year the Beene Center awards fellowships to graduate students; a total of ten Geoffrey Beene Graduate Fellowships have been awarded since 2007. These awards provide full stipends for students who work in the labs of MSKCC faculty and are conducting research with direct cancer relevance. In recent years recipients were students enrolled in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences (GSK) program. This year, three students exemplifying academic excellence were recognized at the annual Beene Symposium — Daniel Marks, Oakley Olson, and Piero Sanfilippo.

Daniel Marks grew up in New York City. He attended Yale University, graduating with a BS in biology in 2009. He is currently a PhD student at GSK, working in Robert Benezra's lab. Daniel will be looking for ways to target cells with a hyperactivated mitotic checkpoint as a possible direction for cancer therapeutics. In his free time he enjoys film and music.

Oakley Olson is from Vermont. He graduated from Brown University in 2006 with a BS in biochemistry and molecular biology. He then took a position as a research assistant at the Stanford School of Medicine. He remained there until matriculating to GSK in the summer of 2009. Now in his second year of the program, he has joined the lab of Johanna Joyce. Oakley is interested in using proteomics approaches to identify cathepsin substrates that are functionally relevant to tumorigenesis and therapeutic response.

Piero Sanfilippo is originally from Italy. In 2005, he moved to Ohio where he received his BS in molecular biology at Kenyon College. He is now a PhD student at GSK, working in Christine Mayr's lab. Piero will specifically be investigating the role of the promoter in the choice of polyadenylation signal. He enjoys photography and discussing politics.

GEOFFREY BEENE JUNIOR FACULTY CHAIRS

The Geoffrey Beene Junior Faculty Chairs provide funding to outstanding young researchers from across the institution at a crucial early stage in their careers. In 2010, there were three active Beene Junior Faculty Chair appointments — Johanna Joyce, PhD; Ross Levine, MD; and Andrea Ventura, MD, PhD.

The first Junior Faculty Chair was appointed in 2006 to **Johanna Joyce,** currently an Associate Member in the Cancer Biology and Genetics Program. Dr. Joyce holds a BA in genetics from Trinity College in Dublin, Ireland, and a PhD in biology from the University of Cambridge in England. Prior to joining MSKCC in 2004, Dr. Joyce was a postdoctoral fellow in the Department of Biochemistry at the University of California, San Francisco, where her research centered on the mechanisms by which matrix-degrading enzymes promote tumor malignancy.

In 2007, **Ross Levine** joined MSKCC from Harvard Medical School/Dana-Farber Cancer Institute and became the second Beene Junior Faculty Chair incumbent. Dr. Levine is a physician-scientist with appointments in the Human Oncology and Pathogenesis Program as an Assistant Member and the Leukemia Service as an Assistant Attending Physician. The focus of Dr. Levine's work is to improve our understanding of the genetic basis of myeloid malignancies, with a specific focus on the role of oncogenic disease alleles in the pathogenesis of myeloproliferative neoplasms (MPN) and acute myeloid leukemia (AML) and the development of molecularly targeted therapies for MPN and AML patients. Dr. Levine received his MD from The Johns Hopkins University School of Medicine and completed his residency in the Department of Medicine at Massachusetts General Hospital. His fellowship training was conducted at Dana-Farber/ Partners and Brigham and Women's Hospital.

Andrea Ventura is an Assistant Member in the Cancer Biology and Genetics Program. He joined MSKCC from the Massachusetts Institute of Technology in August 2008 and was appointed the holder of the third Beene Junior Faculty Chair. He was also awarded a Beene grant in 2009 for his project titled "Investigating the Functions of Oncogenic MicroRNAs in Mammals."

INTERVIEW

John Halliday, 2009 Geoffrey Beene Graduate Student

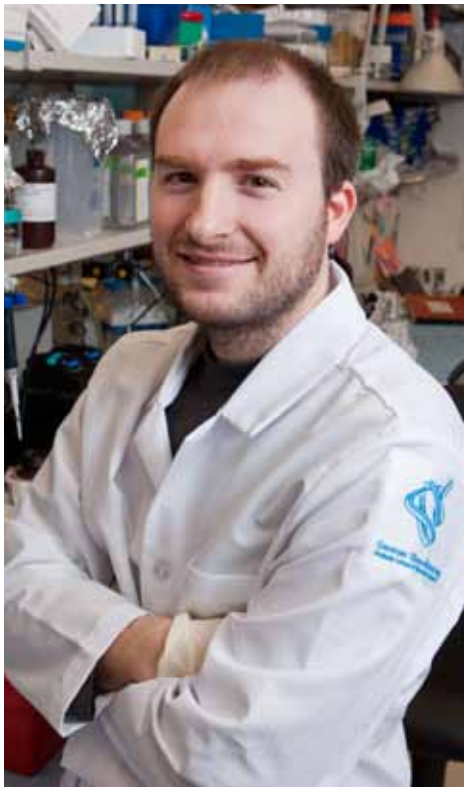
John Halliday is a third-year Gerstner Sloan-Kettering graduate student. As one of the top members of his class after his first year, he was awarded a Beene Graduate Student Fellowship in 2009. He is currently working in the lab of Eric Holland, a neurosurgeon and scientist at Memorial Sloan-Kettering.

Why did you pick GSK's program and what made it unique in comparison to other schools you applied to?

I was interested in doing research that had a clear relationship or relevance to disease. I felt that the structure of GSK's program and the nature of the science at SKI would allow that type of experience. Many of the labs here are specifically focused on the biology of a disease, many are actively involved in translating laboratory findings into clinical treatments, and even the more basic science labs here seemed to be more focused on the clinical relevance of their work than other places I considered. The GSK curriculum is also unique in that it covers most major topics in modern biology, but does so with a view to how each topic is relevant to cancer. That was attractive since cancer biology was one of my top interests heading into graduate school. I also liked the setup of the school — the smaller size (ten people in my cohort), the fact that each specialized topic is taught individually by an expert in the field, and that after your first year of class you are free to do research full-time.

How did you end up in the Holland lab after your first year of graduate school?

I returned to the Holland lab because I ultimately decided that I wanted to work on cancer biology and therapy, and I thought that the lab was working on very interesting questions. I liked that the lab deals with a wide spectrum of questions related to brain tumors, ranging from the basic biology of tumors to clinical questions of drug effectiveness and resistance. Similarly, there is a good mix of people to learn from with varying skill sets, from post-docs with backgrounds in biochemistry, to physician-scientists who run their own phase I trials in patients, to Dr. Holland himself, who is a practicing neurosurgeon as well as lab head.



Tell us about your current research projects.

I am currently looking at the biology of the vasculature and perivascular regions in brain tumors. My project is to tease apart what the different cells present in the perivascular regions are doing to enhance tumorigenesis and how they are promoting resistance to different therapies. We're trying to figure out partly why that is and how that helps the tumor grow back after radiation. I am also interested in the effects of anti-angiogenic therapy. One focus of my research is to determine what happens to the vasculature and perivascular cells when these antiangiogenic drugs are given, cell type by cell type.

As a student, what, if any, exposure do you get to the clinical side at Memorial?

In our first year of graduate school, we had what they called "clinical rotations." The school made arrangements for us to shadow a doctor in the hospital or clinic once every couple months, seeing patients (with their permission) and discussing the cases with the physicians. GSK offers an optional clinical mentor program after your first year; you pick a clinician and they expose you to the clinical side. There are two other students in my class who are doing brain tumor-related research, so Dr. Holland set up a program that allows the three of us to meet with seven different clinicians associated with the Brain Tumor Center, including neuro-oncologists, neurosurgeons, and neuro-pathologists. It is a unique program and a great opportunity because there are basic concepts about the human disease you learn from the clinic that you don't necessarily pick up in the lab or from reading papers.

2009 GBCRC Graduate Student Awards presented by Harold Varmus, then MSKCC President, and faculty mentors.

What were some of the memorable experiences you had at Beene Retreat?

I thought the speakers were very good; there was a good breadth of topics and I liked the way they were organized. I enjoyed getting away from the laboratory for a few days and being able to focus on big picture scientific questions with other researchers and clinicians. That was actually my first scientific retreat so it was interesting and enjoyable to see the faculty members mingling with the students.

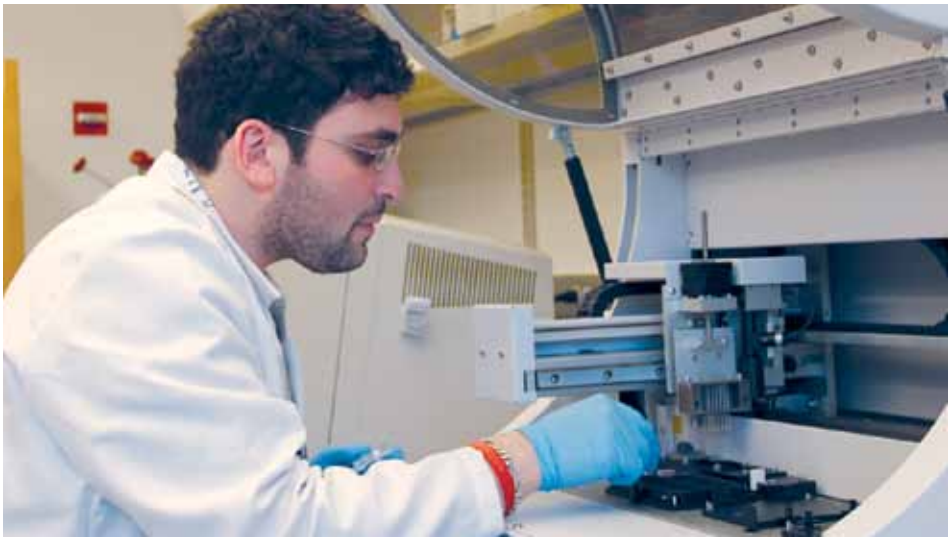
Is there anything else you'd like to add about being a Beene student?

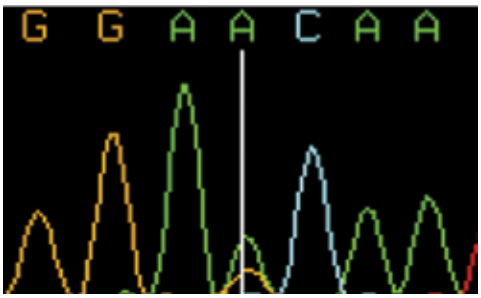
Being recognized as a Beene student and formally receiving the Beene Fellowship from Dr. Harold Varmus was one of the best moments I've had so far in science.

SUPPORT FOR CORE FACILITIES

Since its inception, the GBCRC has provided $2.8 million in support to existing core facilities, including the Genomics Core, the High-Throughput Core, and the Microchemistry and Proteomics Core. It has also committed $3 million to date for the creation and support of the Geoffrey Beene Translational Oncology Core Facility. The Beene Core performs genomic analyses of clinical material by applying state-of-the-art genome-scale molecular profiling technologies. The lab makes it possible to characterize the genomic features of tumors by looking for variations that might be linked to certain clinical responses.

Adriana Heguy was hired in 2007 to start up the Geoffrey Beene Translational Oncology Core Facility and take on the role as its Core Manager. She is also an Associate Lab Member of the Human Oncology and Pathogenesis Program. The Beene Core is located in the Zuckerman Research Building and provides services to the MSKCC community.





This image shows the detection of a mutation in a brain tumor by DNA sequencing. The double trace indicated by the vertical line shows the position of the mutation in the DNA sequence.

INTERVIEW

Adriana Heguy, PhD

What are some of the services the Beene Core offers to the MSKCC community?

The Beene Core was created for the processing of MSKCC clinical and pre-clinical samples, mostly human samples, to allow for mutation detection, gene expression, and other kinds of technology specific to translational medicine. The goal is to have a clinical translation with the results of these genetic types of studies.

We provide genotyping, or detection of mutations, using two major techniques: 1) sequencing and 2) Sequenom. Sequencing reads all the bases of the DNA and aligns it to a template of what the sequence is supposed to look like in normal DNA, enabling us to detect discrepancies and identify mutations. Sequenom is based on mass spectrometry, measuring the specific mutated allele.

The Beene Core recently added DNA methylation to its list of services. This popular procedure allows us to look at marks on the DNA that indicate whether the DNA is going to be transcribed or not, meaning it will either be silenced or function. DNA methylation plays a huge role in tumor processes and is being very highly studied. We do DNA methylation using the same Sequenom system we use for genotyping; it uses different methodology but is based on the same technology and uses the same machine. The service we provide looks at specific areas and specific genes to determine if they are methylated or non-methylated. For example, we can compare tumor samples to normal samples or tumor samples versus metastasis. DNA methylation is a service we started at the end of 2009 and has really picked up during 2010.

The Beene Core is often mentioned in conjunction with the Genomics Core — tell us about the relationship.

The Genomics Core has some overlap with our services and technologies, but our processes are more robotic, enabling a high-throughput screening mode for investigators who have a large number of samples. What differentiates our Core from the Genomics Core is that we selectively amplify regions of interest for next-generation sequencing using new technologies that allow many more reads per section of the DNA.

Tell us about your user group — is it a diverse group, or does it mainly consist of repeat users?

Our users are people from everywhere across the institution. Logically, because the HOPP department is very genetically oriented, we naturally did and still do a lot of projects for HOPP researchers, but we've done projects for a spectrum of people and disease management teams all over the hospital including the Departments of Surgery, Medicine, and Pathology, the Lung disease management team and numerous other areas.

You've been with the core since its inception. How have you seen the core develop and expand throughout the past four years?

The core started off with just two other people in the lab. We realized very quickly with the amount of data we were generating that we needed a bioinformatics expert to help with the data analysis. He was hired almost immediately after we identified the need. Now we've grown to five people and me due to the increasing demand for our services and purchases of new equipment.

Our Core has also developed with the addition of advanced technologies. One of our recent purchases last year was an instrument called the Nanostring. This allows you to look at gene-expression signatures, a collection of genes that get expressed in a particular way and in a particular tumor, enabling you to identify the behavior of the tumor according to the type of signature it has.

FOSTERING A TRANSLATIONAL RESEARCH ENVIRONMENT

During discussions at the 2009 Beene Retreat, attendees expressed interest and need for more interaction among the clinical and basic researchers at MSKCC. Postdoctoral research fellows, in particular, identified their desire 1) to know more about how their research contributes to the creation of clinical trials; 2) to know the relevance of their science in the clinical realm; 3) to learn about clinical trial terminology, disease progression, pathology, treatment options, etc.; and 4) to obtain input from clinicians on shaping their scientific questions and vice versa. The chief fellows of the four largest clinical fellows programs at Memorial Hospital provided positive feedback, supporting participation in events that would encourage interactions with basic science fellows. To address these needs, the GBCRC piloted two new initiatives in 2010, a Translational Research Journal Club and a speed networking event.

TRANSLATIONAL RESEARCH JOURNAL CLUB

There were three Translational Research Journal Club meetings held in 2010. Each meeting featured two speakers — a basic science postdoctoral fellow and a clinical fellow — who were chosen because of their similar interests on a particular disease. They gave presentations on two articles with overlapping themes. More than 30 individuals attended the first journal club, including three Attendings from the Breast Cancer Service. The presence of Attendings who had specialized knowledge of the disease was very useful in explaining complex concepts and answering questions that may not have been easily explained by the trainees. The Attendings also had useful questions for the basic scientists about methodology. During the Q&A session, participants offered opinions about potential research directions for the future. A follow-up questionnaire provided positive feedback from attendees, encouraging future opportunities for the groups to engage in collaborative discussions.

May 6, 2010 — "Breast Cancer"

Debyani Chakravarty
Research Fellow, Human Oncology and Pathogenesis Program
"Out of Context Activation of Developmental Pathways Results in Breast Cancer: Role of Six1 in Mammary Tumorigenesis"

Mustafa Khasraw
Clinical Fellow, Department of Neuro-Oncology
"Brain Metastases in Breast Cancer"

June 29, 2010 — "Personalized Medicine for Lung Cancer: Importance of Finding the Correct Targets and the Correct Patients"

Aime Franco
Research Fellow, Human Oncology and Pathogenesis Program
"Targeting the Microenvironment: Genotype Effects Response"

Paul Paik
Clinical Fellow, Thoracic Oncology Service, Department of Medicine
"Inhibition of Fibroblast Activation Protein (FAP) in the Treatment of Non-Small Cell Lung Cancer"

November 4, 2010 — "Targeting DNA Methylation: Manipulating DNA Methyltransferases in Normal and Malignant Hematopoiesis"

Brian Betts
Clinical Fellow, Hematologic Oncology Service, Department of Medicine
"Pre- and Post-Transplant Epigenetic Therapy for Hematologic Disorders"

Alan Shih
Clinical Fellow, Human Oncology and Pathogenesis Program
"Role of DNA Methyltransferases in Normal Hematopoiesis Stem and Progenitor Cells"

SPEED NETWORKING EVENT FOR CLINICAL AND RESEARCH FELLOWS

In an effort to bridge the gap between basic science and clinical research trainees, a speed networking event was held on February 18, 2010. All MSKCC basic science trainees and clinical fellows were invited, and a social hour was held immediately following the session. Online registration was required, and the following information was collected from each participant: headshot photo, contact information, degree, title, department/program, research focus, research goals, what they can offer to potential collaborators, and their needs. Packets with each participant's bio were distributed to the group one week prior to the event. This program utilized innovative social networking techniques that have become increasingly popular in recent years. The goals of the event were to 1) encourage interactions between basic scientists and clinicians, 2) create opportunities for collaboration, 3) create a forum for networking, and 4) foster a community of translational researchers.

Physician-scientist Timothy Chan gives a keynote address.

Basic scientists and clinical trainees engage in conversations with members of the opposite group.

The speed networking event had 18 participants — nine basic science fellows and nine clinical research fellows. The participants reported that they had met potential research partners or gained new resources from the event. The event also fostered innovativeness by stimulating new ideas on both the clinical and research sides. Due to the success of the initiatives the Beene Center has implemented, translational research programs continue to be a future focus for the Beene Center.

On April 8 and 9, 2010, the GBCRC held its third annual retreat at Skytop Lodge in Pennsylvania. The agenda focused on a wide range of topics related to translational research in oncology, a field that is at the core of the Beene Center's mission. Attendees included lab members in the Cancer Biology and Genetics program, members of HOPP, and senior faculty from other areas of MSKCC.

Harold Varmus, then MSKCC President and CEO, recognizes Praveen Raju for his award-winning poster

Attendees enjoy a walk along the scenic grounds of Skytop Lodge

Joan Massagué

Filippo Giancotti

Neal Rosen, David Solit, and Andrew Lassman taking a break on the patio

Faculty members provided entertainment during the evening festivities

Then-President Harold Varmus kicked off the retreat on Thursday with opening remarks. He recognized G. Thompson Hutton, Trustee of the Geoffrey Beene Foundation, for his vital role in the creation and continued support of the Beene Center at MSKCC. His introduction was followed by presentations from Beene grant recipients Cameron Brennan, James Fagin, Filippo Giancotti, Michael Glickman, Tari King, Robert Klein, and Michael Overholtzer. For the first time, this year's retreat also featured lectures by two Beene graduate-student fellowship awardees, Sindy Escobar-Alvarez and Vasilena Gocheva.

HOPP and CBG faculty members Robert Benezra, Jason Huse, Joan Massagué, Christine Mayr, Christopher Park, Charles Sawyers, and Hans-Guido Wendel also presented on the topics of tumor invasion and metastasis, tumor initiation by microRNAs, and approaches to targeting aberrant signal transduction.

Louis Staudt gave a feature talk titled "RNAi Screening and Cancer Gene Resequencing for the Achilles Heel of Cancer." Dr. Staudt is Deputy Chief of the Metabolism Branch at the National Cancer Institute, and he also co-directs the Lymphoma/Leukemia Molecular Profiling Project (LLMPP), a multi-institutional consortium that aims to develop a new molecular framework for the diagnosis of all lymphoid malignancies.

The cocktail hour/poster session included 41 poster presentations by trainees. This year, research fellows/scholars and faculty members judged the posters and presented awards to the top five posters. Awardees included Nikki Charles from Eric Holland's lab, Semanti Mukherjee and Jason Willis from Robert Klein's lab, Praveen Raju from Beene grant recipient Alexandra Joyner's lab, and Tanya Shree from Johanna Joyce's lab.

Guest speaker Louis Staudt from the National Cancer Institute.

The annual retreat continues to be the Beene Center's most successful event due to the enthusiastic participation of the various departments throughout MSKCC, emphasizing the importance of translational research in both the clinical and lab environments. The Beene Center has implemented new initiatives to encourage interactions among clinicians and basic scientists and plans to continue its endeavors to strengthen the translational programs at MSKCC.

Members of HOPP gather for a song

Ingo Mellinghoff and David Solit put on their game faces

Cameron Brennan, James Fagin, and Charles Sawyers were featured speakers

GBCRC grant recipient Michael Glickman

Trainees prepare for a group shot

Juan Manuel Schvartzman presents his poster to Mustafa Sozen

Robert Klein gives a talk on prostate and gastric cancers

CBG members

Chris Sander

Joan Massagué and Robert Benezra enjoy karaoke

"Perivascular Nitric Oxide Activates Notch Signaling and Promotes Stem-Like Character in PDGF-Induced Glioma Cells"

Nikki Charles, Tatsuya Ozawa, Massimo Squatrito, Anne-Marie Bleau, Cameron W. Brennan, Dolores Hambardzumyan, and Eric C. Holland

Project Abstract: eNOS expression is elevated in human glioblastomas and correlated with increased tumor growth and aggressive character. We have identified a novel role for nitric oxide (NO), which is produced from eNOS in the tumor vasculature and promotes stem-cell-like characteristics in glioblastomas. By activating the Notch signaling pathway in a population of stem-like cells residing in the microvascular environment of a subset of gliomas, we demonstrate that nitric oxide accelerates glioma progression and shortens the survival of mice.

"Evaluating Statistical Power of Shared Controls in Genome-Wide-Association Studies"

Semanti Mukherjee and Robert J. Klein

Project Abstract: Genome-wide-association (GWA) studies have become the method of choice for identifying genetic variants associated with specific diseases. In shared control study design, a common group of healthy individuals are used as controls for multiple diseases. We evaluated the idea of using genotype data of controls from publicly available sources as shared controls in our GWA study. We observed that the analytical power of a GWA study increases with increasing number of cases, genotype relative risk, disease allele frequency, and case:control ratio. The maximum power reaches at 1:10 ratio of cases and controls. We analyzed pancreatic cancer cases genotyped in-house with shared controls from publicly available sources. To correct for population stratification resulting from combining data, we used principal component analysis (PCA). Our simulated studies demonstrate that the PCA-corrected method significantly lowers the false-positive rate. We found that in real datasets, PCA can reduce the inflation of test statistics effectively. The performance of four known disease loci associated with pancreatic cancer improved in our dataset as we increased case:control ratio by adding shared controls. Thus, we reported a systematic method for using shared controls that will substantially lower time and cost of GWA studies.

"Genetic Inducible Mosaic Analysis (GIMA): A Novel Genetic Method for Modeling and Characterizing Sporadic Tumorigenesis in the Mouse"

Praveen Raju, Zhimin Lao, Luis Barraza, Brian Bai, and Alexandra L. Joyner

Project Abstract: Cancer arises sporadically from one or a few cells within a tissue that acquires a number of critical genetic changes. However, current animal models of cancer do not accurately model sporadic tumor formation. Using sophisticated mouse genetics, we are developing a novel approach to study the natural progression of sporadic tumors and test cancer treatments.

"Inhibition of Cysteine Cathepsin Proteases Enhances Effects of Chemotherapy in Reducing Primary and Metastatic Breast Cancer Progression"

Tanaya Shree, Benelita T. Elie, Alfred Garfall, Katherine Bell-McGuinn, Kenishana Simpson, Violetta Barbashina, and Johanna A. Joyce

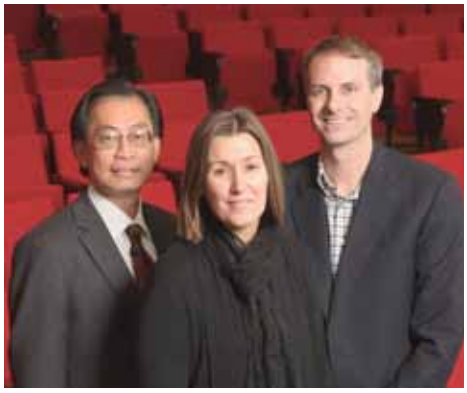
Project Abstract: The tissue environment in which tumors arise and grow can profoundly influence the trajectory of those tumors; namely, how aggressive they can become and even whether or not they metastasize. Recent studies suggest that a tumor's environment can also influence how it responds to treatment. In our studies of breast cancer, we have found that enzymes called cathepsins are increased when tumors are treated with chemotherapy, and that inhibiting these enzymes while giving chemotherapy greatly enhances antitumor effects of the chemotherapy. Thus, these enzymes may be involved in helping tumors recover from chemotherapy and regrow, and inhibiting them allows us to impair this process. Taking this strategy further, a triple-drug therapy we designed — targeting tumor blood vessels in addition to cathepsins while administering standard chemotherapy — was highly effective at reducing tumor growth in an animal model, and also significantly reduced lung metastases. Thus, we believe that targeting "normal" cells in the microenvironment of tumors in addition to our standard treatments targeting tumor cells will help us achieve maximum therapeutic benefit.

"Excess Germline Copy Number Variation Is Associated with Pancreatic Cancer Risk"

Jason A. Willis, Sarah H. Olson, Robert C. Kurtz, and Robert J. Klein

Project Abstract: The goal of our project is to locate inherited mutations in DNA that predispose some individuals to pancreatic cancer and influence their overall prognosis. The research is a collaborative effort between geneticists, statisticians, and physicians at MSKCC. We hope that this project will lead to a better understanding of how pancreatic cancer arises and to the development of new therapies. The poster describes some of our preliminary findings. First, a certain type of inherited mutation (called copy number variation) is more common in patients who have multiple family members affected by pancreatic cancer. We are currently investigating how and why this type of mutation may lead to increased risk of cancer. Second, at least one previously undiscovered mutation seems to correlate with very poor survival from pancreatic cancer. We are confirming this result in a much larger study.

The Geoffrey Beene Cancer Research Symposium is held annually at MSKCC. The symposium features renowned scientists with remarkable work to report. Each speaker gives a 35-minute talk, with additional time for Q&A. Following the presentations a reception is held, enabling the speakers to engage in discussions with the research community. This year's Symposium was held on November 2, 2010. The featured topic was "Cancer Metabolism," fitting for the first day of MSKCC's new President, Craig Thompson, whose research focuses on cancer metabolism. Three speakers in the field included Chi Dang, MD, PhD; Valeria Fantin, PhD; and Matthew Vander Heiden, MD, PhD.



Speakers Chi Dang, Valeria Fantin, and Matthew Vander Heiden

Chi Dang with David Scheinberg talk prior to the symposium

Ronald Blasberg asks a question

Neal Rosen, Charles Sawyers, and Craig Thompson pose at the reception

Mara Hutton and G. Thompson Hutton

Chi Dang, MD, PhD, is The Johns Hopkins Family Professor of Oncology Research and Vice Dean for Research at The Johns Hopkins University School of Medicine, and he oversees the Hopkins Institute for Cell Engineering. He received his BS in chemistry from the University of Michigan, his PhD in chemistry from Georgetown University, and his MD from The Johns Hopkins University School of Medicine. He was an Osler medical resident at Johns Hopkins and a hematology-oncology fellow at the UCSF.

Presentation abstract: Cancer cells are addicted to making copies of themselves without restraint, owing to defective cancer genes that result in stuck cellular accelerators and broken brakes. Cancer genes, such as MYC, also regulate the fuel lines that bring in energy and building blocks from food substances like glucose and the amino acid glutamine for the cancer cells to make copies of themselves. Through molecular targeting and disrupting the fueling line, we have been able to demonstrate that a new strategy for cancer therapy is feasible.

Valeria Fantin, PhD, is Senior Director of Biology at Agios Pharmaceuticals. She is interested in studying the metabolic adaptations in cancer. After receiving her PhD in molecular and cellular biology at Dartmouth Medical School, Dr. Fantin completed her postdoctoral training in the Department of Genetics at Harvard Medical School. Prior to joining Agios, Dr. Fantin held scientific positions at Merck Research Laboratories and Ariad Pharmaceuticals.

Presentation abstract: Mutations in the isocitrate dehydrogenase (IDH) enzymes are frequently found in gliomas, as well as in acute myeloid leukemia. The nature of the heterozygous point mutations inspired the Agios team to investigate their impact on the biochemical activity of these enzymes. Soon, it became clear that the mutations identified impaired the ability of IDH1 and IDH2 to catalyze the conversion of isocitrate to alpha ketoglutarate (αKG), while conferring a gain of a novel enzymatic activity leading to the reduction of αKG to the metabolite 2-hydroxyglutarte (2HG). Several hypotheses implicating the elevated levels of 2HG and tumorigenesis, and the therapeutic potential of targetingmutant IDH enzymes, were discussed.

Matthew Vander Heiden, MD, PhD, is an Assistant Professor in the Koch Institute for Integrative Cancer Research and the Department of Biology at MIT. He is also an Instructor of Medicine at the Dana-Farber Cancer Institute and Harvard Medical School. Dr. Vander Heiden received his MD and PhD from the University of Chicago. He also completed clinical training in internal medicine and medical oncology at the Brigham and Women's Hospital/Dana-Farber Cancer Institute prior to completing a postdoctoral fellowship at Harvard Medical School.

Presentation abstract: Cancer cells metabolize glucose differently from normal tissues; however, this metabolic difference has never been exploited for therapy. Cancer cell metabolism depends on a specific form of the enzyme pyruvate kinase. What makes this enzyme unique is its ability to be turned off. Turning off pyruvate kinase allows cells to use glucose in a way that enables construction of building blocks for cells to grow and divide. This suggests activation of pyruvate kinase may be a novel strategy to target cell metabolism for therapy.

INTERVIEW

Andrea Ventura, MD, PhD

How did you become interested in becoming a researcher?

When I was young, in elementary school, I was fascinated by science. I wanted to be an astronomer — my grandfather had bought me a telescope so I would always look at the stars, wondering about the universe. As I grew older I became interested in the complexity of biology and the beauty of the living world. I went to medical school thinking I would become a doctor. In Italy being a biologist can be difficult; there is not a lot of funding for research. But when I was in medical school I fell in love with doing experiments and decided I wanted to be the one to make the discoveries.

Tell me about your research and the projects your lab focuses on.

My research focuses on a new class of genes called microRNAs. These were discovered almost two decades ago but became popular less than ten years ago, when they were found in humans and mice. They are now known to be present in almost all multicellular organisms. We know very little about what individual microRNAs do, so my lab is studying these genes.

What discoveries have you been able to make through Beene funding?

One of our most recent findings that we published recently, thanks to Beene funding, is that one microRNA called miR-19 is a key oncogene in a subset of B cell lymphoma and is likely present in many other tumors. What we found is that we can induce tumor cell death by making mice that develop B cell lymphoma and removing that particular microRNA from these mice by using a genetic trick. This seems to be specific for the tumor cells; the normal cells are unaffected. So if we can find a pharmacologic way to inactivate miR-19, we can perhaps improve the treatments for this type of tumor.

What made you decide to focus your studies on microRNAs?

I was a postdoctoral fellow at MIT, working on the tumor suppressor gene p53, and I was looking for a research area on which to establish my own lab. I didn't want to work on p53, because it is a very well studied tumor-suppressor gene; I wanted to study something more novel. There are many reasons why studying these microRNAs is not easy, but that makes it even more interesting.

How has being a Beene Junior Chair and a Beene grant recipient affected your experience here?

Foundation money is important because it enables us to take chances by providing funding for riskier projects. Our lab has developed eight knockout mice the last two years and we published a paper that allowed us to apply for an R01. The seed money has enabled us to produce enough preliminary data for federal funding, which has indeed been successful because our first R01 was recently funded. The Beene Junior Chair appointment played a role in my decision to accept the position at MSKCC by providing me with assurance that I would have continuous funding to try new things. Because funding is rare, many people stay with doing safe and obvious experiments, but I wanted to do more challenging and risky ones that build for long-term projects.

What was one important takeaway you had from the Beene Retreat?

It was a good opportunity for faculty members to interact and establish collaborations. It is not always easy to interact with people in other departments, especially when we're spread across several buildings. The retreat allowed us to listen to what other labs are doing, which is an excellent way to start collaborations.

When you're not working in the lab, what are some activities you enjoy?

My hobbies are soccer and chess, and I enjoy the occasional opera at Lincoln Center.

PUBLICATIONS FROM BEENE GRANT RECIPIENTS

The following is a list of publications that have resulted from Beene funded projects.

2007 GRANTS

Renier Brentjens, "Genetic Modifications to Enhance the in Vivo Survival and Antitumor Activity of Gene Modified CD 19-Targeted T Cells"

1. **Brentjens RJ**, Santos E, Nikhamin Y, Yeh R, Matsushita M, La Perle K, Quintás-Cardama A, Larson SM, Sadelain M. Genetically targeted T cells eradicate systemic acute lymphoblastic leukemia xenografts. Clin Can Res. 2007 Sep 15;13(18 Pt 1):5426-35. [PMID: 17855649]
2. Stephan MT, Ponomarev V, **Brentjens RJ**, Chang AH, Dobrenkov KV, Heller G, Sadelain M. T cell-encoded CD80 and 4-1BBL induce auto- and transcostimulation, resulting in potent tumor rejection. Nat Med. 2007 Dec; 13(12):1440-9. [PMID: 18026115]
3. Quintás-Cardama A, Yeh RK, Hollyman D, Stefanski J, Taylor C, Nikhamin Y, Imperato G, Sadelain M, Rivière I, **Brentjens RJ**. Multifactorial optimization of gammaretroviral gene transfer into human T lymphocytes for clinical application. Hum Gen Ther. 2007 Dec;18(12):1253–60. [PMID: 18052719]
4. Zakrzewski JL, Suh D, Markley JC, Smith OM, King C, Goldberg GL, Jenq R, Holland AM, Grubin J, Cabrera-Perez J, **Brentjens RJ**, Lu SX, Rizzuto G, Sant'Angelo DB, Rivière I, Sadelain M, Heller G, Zúñiga-Pflücker JC, Lu C, van den Brink MR. Tumor immunotherapy across MHC barriers using allogeneic T-cell precursors. Nat Biotechnol. 2008 Apr;26(4):453-61. [PMID: 18376399]
5. Santos EB, Yeh R, Lee J, Nikhamin Y, Punzalan B, La Perle K, Larson SM, Sadelain M, **Brentjens RJ**. Sensitive in vivo imaging of T cells utilizing a membrane bound Gaussia princeps luciferase. Nat Med. 2009 Mar;15(3):338-44. [PMID: 19219023]
6. Hollyman D, Stefanski J, Przybylowski M, Bartido S, Borquez-Ojeda O, Taylor C, Yeh R, Capacio V, Olszewska M, Hosey J, Sadelain M, **Brentjens RJ**, Rivière I. Manufacturing validation of biologically functional T cells targeted to CD19 antigen for autologous adoptive cell therapy. J Immunother. 2009 Feb-Mar;32(2):169–80. [PMID: 19238016]
7. Lee J, Sadelain M, **Brentjens RJ**. Retroviral transduction of murine primary T lymphocytes. Methods Mol Biol. 2009;506:83-96. [PMID: 19110621]
8. Sadelain M, **Brentjens RJ**, Rivière I. The promise and potential pitfalls of chimeric antigen receptors. Curr Opin Immunol. 2009 Apr;21(2):215-23.[PMID: 19327974]

Gabriela Chiosis, "Chemical/Proteomic Mapping of Cancer-Specific Molecular Therapeutic Targets"

1. Solit DB, **Chiosis G**. Development and application of Hsp90 inhibitors. Drug Disc Today. 2008 Jan:13(1-2):38-43. [PMID: 18190862]
2. **Chiosis G**, Kang Y, Sun W. Discovery and development of purine-scaffold Hsp90 inhibitors. Expert Opin. Drug Disc. 2008;3(1):99-114. [doi: 10.1515/17460441.3.1.99]
3. Taldone T, Gozman A, Maharaj R, **Chiosis G**. Targeting Hsp90: small-molecule inhibitors and their clinical development. Curr Opin Pharmacol. 2008 Aug;8(4):370-4. [PMID: 188644253]
4. Moulick K, Ahn JH, Beebe K, Ma Y, Zatorska D, Taldone T, Caldas-Lopes EM, Gross SS, Neckers L, **Chiosis G**. Probing cancer-specific activating signaling pathways through a tumor-specific Hsp90inhibitor. Abstract: American Association for Cancer Research (AACR) Annual Meeting, Denver, CO, April 18-22, 2009.
5. Cerchietti LC, Lopes EC, Yang SN, Hatzi K, Shaknovich K, Robles AI, Walling J, Bhalla K, **Chiosis G**, Melnick A. A purine scaffold heat shock protein 90 (Hsp90) inhibitor destabilizes BCL6 and has specific antitumor activity in BCL6 dependent lymphomas in vitro and in vivo. Abstract: AACR Annual Meeting, Denver, CO, April 18–22, 2009.
6. Lopes EC, Cerchietti L, Ahn JH, Robles AI, Varticovski L, Melnick A, **Chiosis G**. Targeting triple-negative breast cancer via PU-H71, a purine-scaffold heat shock protein 90 (Hsp90) inhibitor. Abstract: AACR Annual Meeting, Denver, CO, April 18-22, 2009.
7. Caldas-Lopes ME, Cerchietti LC, Ahn JH, Clement CC, Robles AI, Rodina A, Moulick K, Taldone T, Gozman A, Guo Y, Wu N, de Stanchina R, White J, Gross SG, Ma Y, Varticovski L, Melnick A & **Chiosis G**. Hsp90 inhibitor PU-H71, a multimodal inhibitor of malignancy, induces complete responses in triple-negative breast cancer models. Proc Natl Acad Sci U S A. 2009 May 19;106(20):8368-73. [PMID: 19416831]
8. Cerchietti LC, Caldas EC, Yang SN, Hatzi K, Bunting K, Tsikitas L, Mallik A, Robles AI, Walling J, Vartikovski L, Shaknovich R, Bhalla K, **Chiosis G**, Melnick AM. A purine scaffold Hsp90 inhibitor destabilizes Bcl6 and has specific anti-tumor activity in Bcl6 dependent B-cell lymphomas. Nature Med. 2009 Dec;15(12):1369-1376. [PMID: 19966776]
9. Beebe K, Moulick K, Tokita M, Scroggins B, Xu W, Mollapour M, Agard A, **Chiosis G**, Neckers L. Structurally diverse Hsp90 inhibitors trap unique conformational states of the chaperone. In preparation.

10. Moulick K, Beebe K, Ahn JH, Smith-Jones P, Rodina A, Cerchietti L, Caldas-Lopes E, Zatorska D, Taldone T, Chen C, Gross SS, Larson SM, Erdjument-Bromage H, Melnick A, Nimer S, Neckers L, **Chiosis G**. Probing the malignant phenotype through a tumor Hsp90-directed chemical biologyproteomics method. In preparation.

Filippo Giancotti, "A Gain-of-Function Genetic Screen for Human Breast Cancer Metastasis Genes"

1. We are currently writing up a paper describing the role of Coco in exit from dormancy at metastatic sites. We intend to submit this paper to Nature before the end of July. We plan to submit an NIH grant on the gain-of-function genetic screen as soon as the paper on Coco is accepted for publication.

Xuejun Jiang, "PTEN Signaling in Cancer: Novel Regulation and Potential Therapy"

1. Wang X, **Jiang X**. PTEN: a default gate-keeping tumor suppressor with a versatile tail. Cell Res. 2008 Aug;18(8):807–16. [PMID: 18626510]
2. Wang X, Shi Y, Wang J, Huang G, **Jiang X**. Crucial role of the carboxyl terminus of PTEN in antagonizing NEDD4-1-mediated PTEN ubiquitination and degradation. Biochem. J. 2008 Sep 1;414(2):221-9. [PMID: 18498243]
3. Wang X, **Jiang X**. Post-translational regulation of PTEN. Oncogene. 2008;27:5454-63. [doi:10.1038/onc.2008.242]
4. Kwak YD, Wang B, Pan W, Xu H, **Jiang X**, Liao FF. Functional interaction of PTEN with the E3 ligase NEDD4-1 during neuronal response to zinc. J Biol Chem. 2010 Mar 26;285(13):9847–57. [PMID: 20100827]

Robert Klein, "A Genome-Wide Association for Pancreatic Susceptibility Loci"

1. We have one manuscript in preparation, and expect to have two more completed within the next 12 months.

Mary Ellen Moynahan, "The Impact of PIK3CA Mutations on the Efficacy of Bevacizumab in Recurrent Hormone Receptor Positive Breast Cancer"

1. Kalinsky K, Jacks LM, Heguy A, Patil S, Drobnjak M, Bhanot UK, Hedvat CV, Traina TA, Solit D, Gerald W, **Moynahan ME**. PIK3CA mutation associates with improved outcome in breast cancer. Clin Can Res. 2009 Aug 15;15(16):5049-59. [PMID: 19671852]
2. PIK3CA and AKT1 mutations are independent in invasive breast cancer. Kalinsky K, Jacks LM, Patil S, Heguy A, Drobnjak M, Traina T, Bhanot U, Howard J, Solit D, Gerald W, Hudis C, **Moynahan ME**. Poster presentation: San Antonio Breast Cancer Symposium, December 10-14, 2008.
3. Kalinsky K, Jacks LM, Hedvat C, Bhanot U, Patil S, Heguy A, Asher M, Drobnjak M, Hudis C, **Moynahan ME**. Multiplex mutation genotyping identifies novel and protective mutations in breast cancer. American Society of Clinical Oncology (ASCO) Annual Meeting, Orlando FL, May 29-June 2, 2009. Oral Presentation/ASCO Merit Award to Dr. Kalinsky.
4. Kalinsky K, Bhanot U, Jacks LM, Hedvat C, Patil S, Heguy A, Drobnjak M, Hudis C, **Moynahan ME**. Mutant PIK3CA is detected in both pre-invasive and recurrent breast cancer. Abstract: ASCO, Orlando FL, May 29-June 2, 2009.

William Pao, "Characterizing the Cancer Genome in Lung Adenocarcinomas from Patients with Acquired Resistance to EGFR Tyrosine Kinase Inhibitors"

1. Yang CH, Yu CJ, Shih JY, Chang YC, Hu FC, Tsai MC, Chen KY, Lin ZZ, Huang CJ, Shun CT, Huang CL, Bean J, Cheng AL, **Pao W**, Yang PC. Specific EGFR mutations predict treatment outcome of stage IIIB/IV patients with chemotherapy-naive non-small-cell lung cancer receiving first-line gefitinib monotherapy. J Clin Oncol. 2008 Jun 1;26(16): 2745–53. [PMID: 18509184]
2. Bean J, Brennan C, Shih JY, Riely G, Viale A, Wang L, Chitale D, Motoi N, Szoke J, Broderick S, Balak M, Chang WC, Yu CJ, Gazdar A, Pass H, Rusch V, Gerald W, Huang SF, Yang PC, Miller V, Ladanyi M, Yang CH, **Pao W**. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci U S A. 2007 Dec 26;104(52):20,932–7. [PMID: 18093943]
3. Bean J, Brennan C, Shih JY, Riely G, Viale A, Wang L, Chitale D, Motoi N, Szoke J, Broderick S, Balak M, Chang WC, Yu CJ, Gazdar A, Pass H, Rusch V, Gerald W, Huang SF, Yang PC, Miller V, Ladanyi M, Yang CH, **Pao W**. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Oral presentation: AACR-NCI-EORTC International Conference, Molecular Targets and Cancer Therapeutics, San Francisco, CA, October 22–26, 2007.

Hans Wendel, "RNAi Screen to Identify Suppressors and Modifiers of Treatment Response"

1. Mavrakis KJ, Zhu H, Silva RL, Mills JR, Teruya-Feldstein J, Lowe SW, Tam W, Pelletier J, **Wendel HG**. Tumorigenic activity and therapeutic inhibition of Rheb GTPase. Genes Dev. 2008 Aug 15;22(16): 2178–88. [PMID: 18705878]

2008 GRANTS

Mark Frattini, "Identifying the Biological Consequences of Cdc7 Kinase Inhibition in Human Cells"

1. A manuscript is currently in preparation containing some of this data. In addition, some data was presented at the MSKCC Translational Research seminar series in November 2008 and in an oral presentation at the 2009 GBCRC retreat.

Clifford Hudis, "Use of Array CGH to Improve HER2 Testing and Better Identify Trastuzumab Sensitivity in Breast Cancer"

1. McArthur HL, Brogi E, Patil S, Wigler M, Norton L, Hicks J, **Hudis CA**. High resolution microarray copy number analysis (array CGH) suggests that determination of HER2 amplification by FISH (FISH+) is inaccurate in human breast cancer specimens that are HER2 2+ by immunohistochemistry (IHC2+). Abstract: European CanCer Organisation, European Society for Medical Oncology (ESMO) Multidisciplinary Congress, Berlin, Germany, September 20-24, 2009.
2. McArthur HL, Brogi E, Patil S, Wigler M, Norton L, Hicks J, **Hudis CA**. "High resolution comparative genomic hybridization (CGH) indicates that genomic profiles are very heterogeneous for HER2 and TOP2A in FISH-amplified human breast cancer specimens." Abstract: San Antonio Breast Cancer Symposium, December 10-13, 2009.

Tari King, "A Genetic Analysis of the Invasive Breast Cancer Risk Associated with Lobular Carcinoma in Situ"

1. Morrogh M, Giri DP, Paik W, Arroyo CD, Andrade VP, Sakr R, Hassan M, Brogi E, Morrow M, **King TA**. The Effect of TWIST and SNAIL on dissociation of the E-cadherin-catenin-complex as a late event in lobular neoplasia (LN). Abstract: American Society of Clinical Oncology (ASCO) Breast Cancer Symposium, San Francisco, CA, October 8-10, 2009.
2. Andrade VP, Morrogh M, Dilip G, Li-Xuan Q, Sakr R, Olvera N, Paik W, Shirin M, Brodi E, Morrow M, **King TA**. Gene expression profiling identifies two stable clusters of lobular carcinoma in situ. Abstract.
3. Shirin M, Morrogh M, Andrade VP, Sakr R, Paik W, Morrow M, **King TA**. Risk for subsequent breast cancer after lobular carcinoma in situ: Do clinical factors matter? Abstract: ASCO Annual Meeting, Chicago, IL, June 4-8, 2010.

Joseph O'Donoghue, "Evaluation of Antiangiogenic Therapies by Hypoxia-Imaging Methods"

1. Oehler-Janne C, **O'Donoghue J**, Ling C, Carlin S. Evaluation of tumor response to the antivascular agent DMXAA using 18F-FMISO PET. Presentation: Society of Nuclear Medicine Annual Meeting, Toronto, Canada, June 13-17, 2009.
2. Oehler C, **O'Donoghue J**, Zanzonico P, Russell J, Ling C, Carlin S. Use of 18F-MISO PET imaging to monitor the response of colorectal xenografts to DMXAA. PV Presentation: American Society for Therapeutic Radiology and Oncology Annual Meeting, Chicago, IL, November 1-5, 2009.

2009 GRANTS

Ronald DeMatteo, "Combined Molecular Therapy and Immunotherapy for Gastrointestinal Stromal Tumor"

1. Manuscript in progress. We have made two recent presentations. One was to the Houghton lab meeting, and the other was to the Ludwig Immunology group. The presentations were extremely well received. A portion of our data was included in the Melanoma SPORE grant as rationale to combine molecular and immune therapy. We are currently preparing an R01 using the data we have generated from the Beene grant.

Filippo Giancotti, "Suppression of Mammary Tumorigenesis and EMT by the Atypical Rho Protein Rnd1"

1. Okada T, Lopez-Lago M, Schiavon G, Esposito I, Abele C, Sapino A, Inghirami G, **Giancotti F**. Loss of the Rho-family GTPase-Rnd1 drives mammary tumorigenesis and epithelial-to-mesenchymal transition by activating Ras. Submitted to Cell Press on May 7, 2010.

Alexandra L. Joyner, "Development of a Novel Technique for Modeling and Characterizing Sporadic Tumors in Mice"

1. Raju P, Lao Z, **Joyner AL**. Genetic inducible mosaic analysis (GIMA): improving mouse models of sporadic cancer. Abstract: American Association for Cancer Research, Genetics and Biology of Brain Cancer Meeting, San Diego, December 13-15, 2009.
2. Raju P, Lao Z, **Joyner AL**. Genetic inducible mosaic analysis (GIMA): Improving mouse models of sporadic cancer. Abstract: Brain Tumor Center Retreat, New York, March 5, 2010.
3. Raju P, Lao Z, Barraza L, Bai B, **Joyner AL**. Genetic Inducible Mosaic Analysis (GIMA): A novel genetic method for modeling and characterizing sporadic tumorigenesis in the mouse. GBCRC Annual Retreat, Skytop, PA, April 8-9, 2010.

Andrew Lassman, "Pulsatile Kinase Inhibitor Therapy for Malignant Glioma: Proof of Concept Clinical Trial"

1. Clarke JL, Pao W, Wu N, Miller VA, **Lassman AB**. High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer. J Neurooncol. 2010 Sept;99(1):283-6. [PMID: 20146080]
2. Grommes C, Oxnard GR, Kris MG, Miller VA, Pao W, **Lassman AB**. "Pulsatile" high dose weekly erlotinib for central nervous system (CNS) metastases from EGFR-mutant non-small cell lung cancer. Abstract: Society for Neuro-Oncology Annual Meeting, Montreal, Canada, November 18-21, 2010.

Jason S. Lewis, "Zirconium-89 Labeled Antibodies for ImmunoPET Guided Radioimmunotherapy"

1. Holland JP, Caldos-Lopes E, Divilov V, Longo VA, Taldone T, Zatorska D, Chiosis G, **Lewis JS**. Measuring the pharmacodynamic effects of a novel Hsp90 inhibitor on HER2/neu expression in mice using Zr-DFO-trastuzumab. PLoS One. 2010 Jan 25;5(1)e8859. [PMID:20111600]
2. Ruggiero A, Holland JP, **Lewis JS**, Grimm J. Cerenkov luminescence imaging of medical isotopes. J Nucl Med. 2010 Jul;51(7):1123-30. [PMID: 20554722]
3. Holland JP, Divilov V, Bander NH, Smith-Jones PM, Larson SM, **Lewis JS**. 89Zr-DFO-J591 for immunoPET imaging of prostate-specific membrane antigen (PSMA) expression in vivo. J Nucl Med. 2010 Aug;51(8):1293-300. [PMID: 20660376]

Yueming Li, "Role of Notch/γ-Secretase Pathway in the Proliferation and Survival of Breast Cancer Cells"

1. Chien JW, **Yueming L**. Role of the notch/γ-secretase pathway in breast cancer. Poster Session: American Association for Cancer Research, Advances in Breast Cancer Research Meeting, San Diego, CA, October 13-16, 2009.

Dimitar B. Nikolov, "Novel Anti-Cancer Compounds Targeting the Tie2/Angiopoietin Interactions and Signaling"

1. Seegar TC, Eller B, Tzvetkova-Robev D, Kolev MV, Henderson SC, **Nikolov DB**, Barton WA. Tie1-Tie2 interactions mediate functional differences between angiopoietin ligands. Mol Cell. 2010 Mar;37(5): 643–55. [PMID: 20227369]

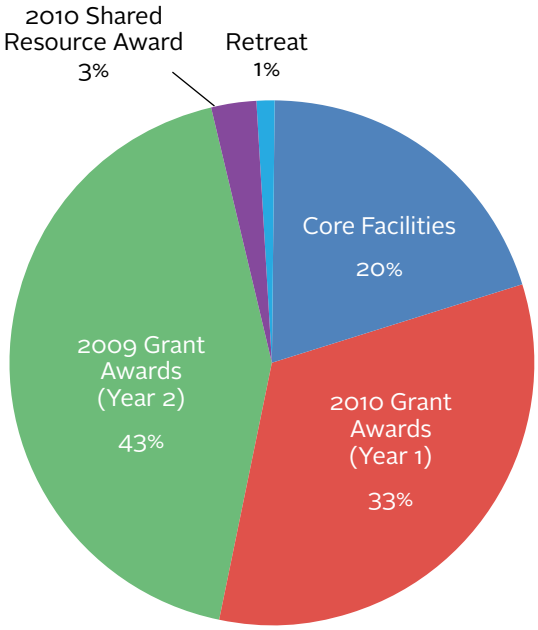
Michael Overholtzer, "Examining the Role of Entosis in Human Cancers"

1. Krajcovic M, Johnson NB, Sun Q, Normand G, Hoover N, Yao E, Richardson AL, King RW, Cibas ES, Schnitt SJ, Brugge JS, **Overholtzer M**. A non-genetic route to aneuploidy in human cancers. Nat Cell Biol. 2010 Mar;13(3)324-30. [PMID: 21336303]

Andrea Ventura, "Investigating the Functions of Oncogenic MicroRNAs in Mammals"

1. Mu P, Han YC, Betel D, Yao E, Squatrito M, Ogrodowski P, de Stanchina E, D'Andrea A, Sander C, **Ventura A**. Genetic dissection of the miR-17~92 cluster of microRNAs in Myc-induced B-cell lymphomas. Genes Dev. 2009 Dec 15; 23(24):2806-11. 15. [PMID: 20008931]

2010 GBCRC OPERATING EXPENSES



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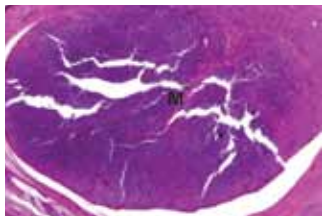



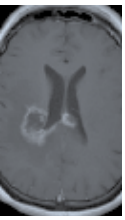




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