

GEOFFREY BEENE CANCER RESEARCH CENTER

10 Year Report, 2007–2017



Memorial Sloan Kettering
Cancer Center

COVER IMAGES, CLOCKWISE FROM TOP LEFT:

Tumor- and stromal cell-derived cathepsin S expression in primary breast cancer. Shown here is an immunofluorescence image of a human breast cancer specimen stained for the cysteine protease cathepsin S in red, and tumor cells in green. Cathepsin S expression, which is typically associated with immune cells such as macrophages, is expressed in a subset of breast carcinoma cells, and may endow them with the ability to metastasize to the brain

The Iacobuzio lab and Kellan Lutz, an ambassador for the Geoffrey Beene Foundation

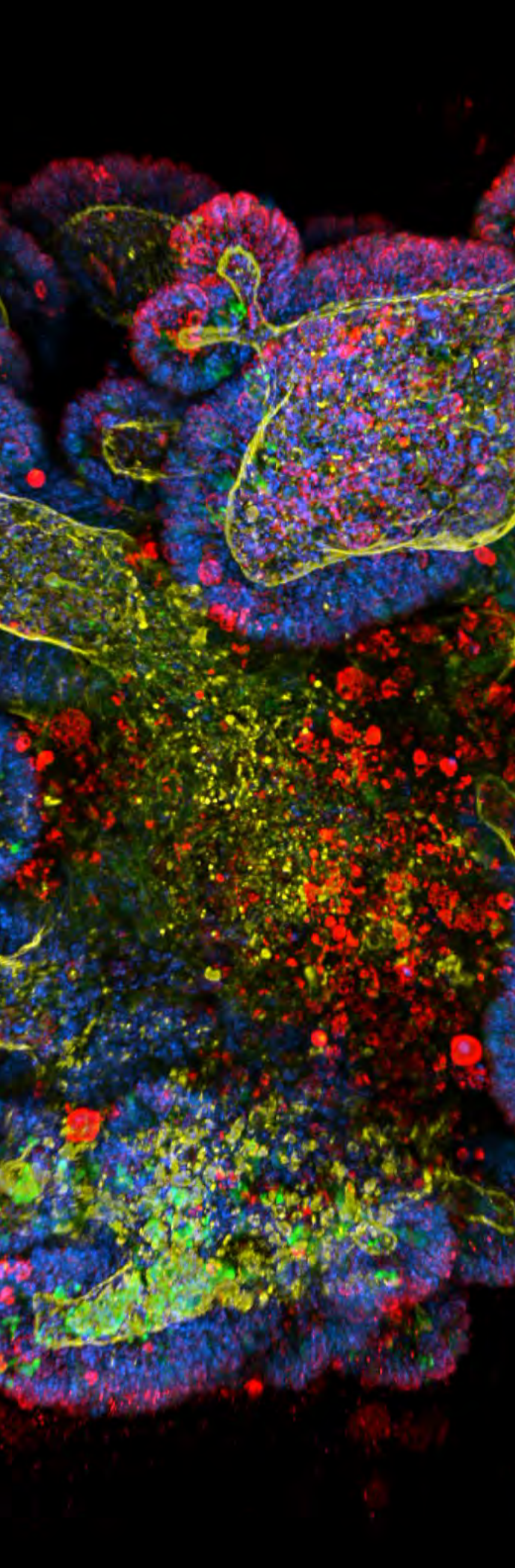
Epifluorescent imaging of transparent casper zebrafish transplanted with the human-derived PC3 prostate cancer cell line exhibits dissemination solely to the spinal column

Epifluorescent imaging of transparent casper zebrafish transplanted with the zebrafish-derived ZMEL1 melanoma cell line exhibits widely disseminated tumors to the skin, eyes, muscles, and brain. Image by Isabella Kim of the White lab

Ping Chi and lab members

Confocal microscopy shows that the nucleolar structure of hematopoietic stem cells is altered with Stag2 loss of function. Image by Aaron Viny of the Levine lab

Scott Lowe and lab member



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Shown are intestinal organoids derived from transgenic shRen mice in which renilla luciferase is suppressed by doxycycline. GFP expression (shRen) and immunofluorescence staining with DAPI (blue), phalloidin (yellow), and anti-Ki67 (red) demonstrates that inducible and reversible gene silencing can be tested in long term ex vivo culture where intestinal stem cells form fully differentiated crypt-villus organoid structures. Image by Kevin O'Rourke and Lukas Dow of Scott Lowe's Lab.

WELCOME



As the founder of the Geoffrey Beene Foundation, my primary goal has been to fund new research to discover revolutionary treatment options and diagnostics across all types of cancer. In 2006, my collaboration with Memorial Sloan Kettering President Harold Varmus led to the creation of the Geoffrey Beene Cancer Research Center at MSK, giving us the opportunity to focus on accelerated funding for initial-stage research. The remarkable progress that has been made at the Geoffrey Beene Cancer Research Center since then has been a great accomplishment for everyone involved. You are all to be congratulated on your shared research vision, made possible by your expertise, passion, and dedication to end suffering from all cancers.

Since its creation, the Geoffrey Beene Cancer Research Center has aimed to translate works at the cellular level into revolutionary research approaches to preventing, diagnosing, and treating the disease. It brings together researchers and doctors, primarily from two complementary areas: the Sloan Kettering Institute's Cancer Biology and Genetics Program and the Memorial Hospital-based Human Oncology and Pathogenesis Program (HOPP). Cancer Biology and Genetics studies what transforms normal cells into cancerous ones, whereas HOPP pursues insights into the molecular causes of cancer from a clinical oncology perspective.

From 2006 through 2017, the Geoffrey Beene Cancer Research Center has awarded 112 research grants and funded 15 proposals for shared resources. Each grant funds initial-stage research and is renewed for a second year. The executive committee reviews submissions of innovative research proposals every year. This highly competitive review process awards grants to the most compelling and profound ideas proposed by researchers from the MSK community. After completion of the funded project, grant recipients have gone on to develop their novel ideas and apply for further grants from external sources. Since 2006, for every dollar of direct support from the Geoffrey Beene Cancer Research Center, grant awardees have received an additional \$1.55 in follow-up funding from external sources based on the early-stage ideas supported by the center.

In addition to the critical funding of initial-stage research, I directed that Geoffrey Beene fund the establishment of multiple junior and senior faculty chairs at MSK, fund fellowships for graduate students, conduct symposiums and conferences (which have evolved into the joint Geoffrey Beene-Nature conferences, most recently held this March), and hold annual retreats, which have increased collegiality across the MSK campus and led to critical collaborations among its members. The Center supported the Geoffrey Beene Translational Oncology Core, as well as the Microchemistry and Proteomics Core Facility and Genomics Core Facility, both of which aim to significantly augment MSK's capacity for translational cancer research in genomics.

It has been my honor and privilege to support MSK and its dedicated mission to save lives. I look forward to leading the Geoffrey Beene Foundation's continued support for new research initiatives and supporting the amazing scientists, doctors, and investigators at MSK.

I am grateful to each of you for your continued dedication and lifesaving work.

Very truly yours,

G. Thompson Hutton

CEO and Trustee, Geoffrey Beene Foundation



In the past ten years, the Geoffrey Beene Cancer Research Center (GBCRC) at Memorial Sloan Kettering has become a bedrock of the MSK community. The center has allowed translational research to proceed within an accelerated time frame. The important science done through many collaborative projects has progressed our journey to fight cancer. It has been my privilege to be Chair of the Geoffrey Beene Cancer Research Center since 2011.

In 2006, the Geoffrey Beene Cancer Research Center was founded by Geoffrey Beene CEO G. Thompson (“Tom”) Hutton through the philanthropy of the Geoffrey Beene Foundation. The mission of the Geoffrey Beene Cancer Research Center is to achieve major advances in controlling cancer and producing better outcomes for people with cancer. The center’s ultimate goal is making cancer a more manageable disease. Tom and the Geoffrey Beene Executive Committee have been wonderful partners in helping us pursue our mission.

I am proud to say that, since its inception, the Geoffrey Beene Cancer Research Center has funded 112 research proposals and 15 shared resource projects, encompassing innovative topics in basic, translational, and clinical cancer research. That is more than \$50 million in direct research support! Furthermore, for every \$1 in grant funding provided by the Geoffrey Beene Cancer Research Center, MSK has received \$1.55 in subsequent grant awards.

During this same period, more than 31 graduate students have been supported by funds from the Geoffrey Beene Center, and as you will read in this report, many of them have gone on to prestigious positions. The center has also supported junior and senior faculty chairs. Positions like these help Memorial Sloan Kettering attract and retain scientists working on the cutting edge of cancer research.

In addition, the Geoffrey Beene Center provides crucial support to several core facilities, enabling MSK to quickly implement new technologies and capabilities. The first of these efforts, the Geoffrey Beene Core, helped investigators obtain and characterize molecularly annotated human tumor material. This core provided key infrastructure that ultimately helped establish what is now the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, which is the main vehicle for establishing personalized cancer therapy at MSK. We hope to continue supporting such important and necessary efforts at MSK.

Finally, the Geoffrey Beene Center has played a critical role in fostering interactions between doctors and basic scientists both within and outside the institution through the annual Geoffrey Beene Cancer Research Center retreat, meetings, and most recently, the Nature-Geoffrey Beene conferences.

On behalf of the GBCRC Executive Committee and all of MSK, we thank the Geoffrey Beene Foundation for its support. We hope that the next ten years continue to bring major contributions to cancer research, a new generation of research scientists and graduate students, and discoveries that lead us closer to a cure for cancer!

Scott Lowe

Chair, Geoffrey Beene Cancer Research Center

MISSION

The goal of the Geoffrey Beene Cancer Research Center is to provide direct support for revolutionary new cancer research, with the ultimate goal of making cancer a more manageable, and potentially curable, disease.

EXECUTIVE COUNCIL



Scott Lowe
Chair, Geoffrey Beene Cancer
Research Center



David Scheinberg
Chair, Molecular Pharmacology
and Chemistry Program



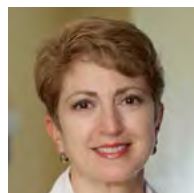
Craig Thompson
President and CEO, Memorial
Sloan Kettering Cancer Center



Alexander Rudensky
Chair, Immunology Program



David Solit
Member, Human Oncology and
Pathogenesis Program



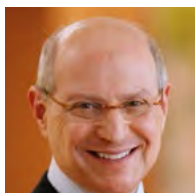
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Acting Physician in Chief



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Institute



Nikola Pavletich
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Larry Norton
Senior Vice President,
Office of the President



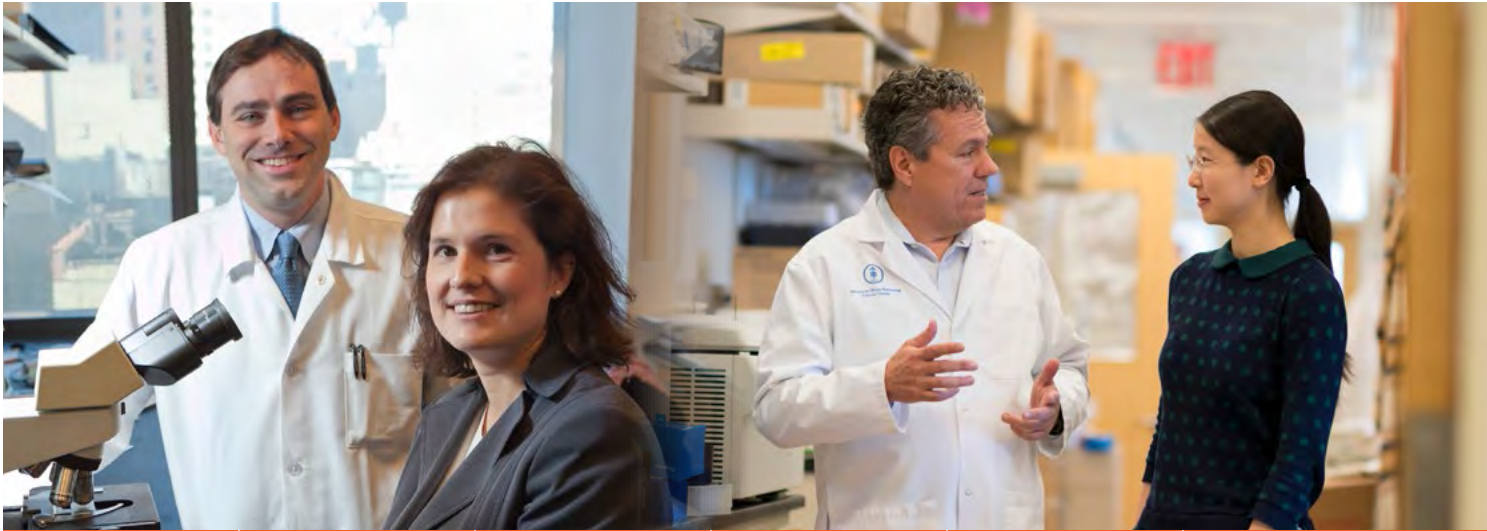
G. Thompson Hutton
Ex Officio
Trustee of the Geoffrey Beene
Foundation
President of Geoffrey Beene



Charles Sawyers
Chair, Human Oncology and
Pathogenesis Program

**SUPPORTING INNOVATION
THROUGH THE YEARS**

MILESTONES



2007

2008

2009

2010

2011

2012



The Geoffrey Beene Translational Oncology Core Facility opens.

Ross Levine and Johanna Joyce are named the inaugural Geoffrey Beene Jr. Chairs.

The first Geoffrey Beene Cancer Research Center retreat takes place in Skytop, Pennsylvania.

The first nine Geoffrey Beene research grants are funded.

An Illumina microarray platform is purchased for the Genomics Core.

A high-throughput screening robotics platform is purchased for the High-Throughput Core.

Scott Lowe joins MSK and becomes Chair of the Geoffrey Beene Cancer Research Center.

Michael Berger is given funding to develop a rapid, high-throughput clinical sequencing test. It is known today as the MSK-IMPACT™ assay.

The Rock Stars of Science campaign launches.



2013

2014

2015

2016

2017

Funding of the Viable Tumor Cell pilot projects leads to the development and funding of the National Institutes of Health-funded Precision Disease Modeling Program, led by Scott Lowe and David Solit.

The Center for Precision Disease Modeling launches with support from the National Institutes of Health and the Geoffrey Beene Cancer Research Center

Funds from the Geoffrey Beene Cancer Research Center allow Andrea Ventura to develop a procedure for generating virtually any chromosomal rearrangement in the cells of adult mice, and potentially other model organisms, using a technique called genome editing.



Nature and Geoffrey Beene present “Cancer as an Evolving and Systemic Disease” at MSK.



HIGHLIGHTS OF **BREAKTHROUGH PROJECTS**

A CRISPR-Based Approach to Generate Chromosomal Rearrangements In Vivo

Structural changes to chromosomes are common in human cancers. They often result in unique gene fusion products that might be targeted with treatments. Unfortunately, although it is possible in some cancer-causing mutations, chromosomal changes are difficult to engineer in model organisms. This limits investigations of their biology as well as their potential uses in treatment.

Thanks to generous funding from the Geoffrey Beene Cancer Research Center, the Andrea Ventura lab at the Sloan Kettering Institute has developed a novel CRISPR-based strategy. Other ongoing investigations in the Ventura lab that are supported by the Geoffrey Beene Cancer Research Center include studies of two forms of pediatric brain cancer. Both are driven by gene fusions involving BRAF to engineer chromosomal rearrangement directly in the somatic cells of adult mice. As proof of concept, the lab generated a mouse model of lung cancer driven by the EML4-ALK gene fusion. (Maddalo L, Nature, 2014). It also demonstrated that a different chromosomal deletion, resulting in a gene fusion between BCAN and NTRK1, is a potent driver of glioma. This particular fusion makes cancer more sensitive to the experimental drug entrectinib.

So that more investigators can use this method to study other cancer-associated mutations more easily, the Ventura lab developed improved experimental and computational tools to design and construct the CRISPR-expressing oncogene. These efforts have greatly expanded scientists' ability to model human cancers in vivo. Tools such as these are leading to the discovery and validation of new targeted therapies. ■

Cancer biologist Andrea Ventura, MD, PhD, Associate Member, Cancer Biology and Genetics Program

**The team can now create
virtually any chromosomal
rearrangement directly in the
somatic cells of adult mice.**

High-Throughput Profiling of Genomic Alterations in Clinical Tumor Specimens

Before joining Memorial Sloan Kettering, Michael Berger was a staff scientist at the Broad Institute in Cambridge, Massachusetts. There, he led some of the first research projects to use next-generation sequencing (NGS) to map cancer genomes, including melanoma and prostate cancer. Dr. Berger was particularly drawn to the idea that this technology could be used to assist in the diagnosis and treatment of disease. He worked with other scientists and doctors at the nearby Dana-Farber Cancer Institute and Foundation Medicine to develop NGS tests that would identify targetable mutations in tumors.

In 2010, Dr. Berger accompanied his wife to MSK when she joined the hematology-oncology fellowship program. He was recruited as an Assistant Member of the Department of Pathology and saw coming to MSK, one of the world's foremost cancer research centers, as an exciting opportunity for him to further the technologies that he had started at the Broad. One of his goals was to create a comprehensive NGS-based tumor-sequencing test for clinical use.

Dr. Berger and his colleagues believed that such a test would enable researchers to identify new biomarkers. These genetic mutations could be used to predict disease outcome or response to targeted therapies. The team envisioned that this test would become a routine part of cancer care. For the test to be useful, however, it would need to be robust yet sensitive enough to work on available patient samples, which were often pathological specimens in limited quantities. Dr. Berger and his team of two research technicians and a computational postdoctoral fellow began to develop an NGS test that included hundreds of genes. They worked closely with collaborating physician-scientists to collect suitable tumor samples from people with cancer.

At a critical time in his research program, Dr. Berger received a grant from the Geoffrey Beene Cancer Research Center to develop new technology that would improve cancer diagnosis and inform cancer treatment. This funding allowed the Berger lab to continue its work and, ultimately, to secure additional support for what has become the MSK-IMPACT™ test.



Geneticist Michael Berger, PhD, Associate Director, Marie-Josée and Henry R. Kravis Center for Molecular Oncology

Dr. Berger's initial research grant was used to:

- design a sequencing test for all known genomic changes related to the diagnosis, prognosis, and treatment of cancer
- optimize the test so that it could handle the challenging low-abundance specimens that are routinely encountered in patient care
- automate and validate the test

Today's cancer research and treatment landscapes are dramatically different because of this and other genomic advances. The MSK-IMPACT assay has enabled MSK doctors to practice precision medicine. In precision medicine, doctors use an individual's mutational profile to inform the therapeutic approach, often a targeted therapy. By including hundreds of cancer-related mutations (currently 468) in a single test, doctors have a high-resolution view of what's happening in a single tumor. What's more, each tumor is unique, and two tumors from the same tissue, or even the same patient, may respond differently to a given therapy. Doctors and scientists have now acquired enough knowledge to make clear distinctions among certain tumor subtypes and to treat them accordingly. Doctors can make informed choices about whether to offer MSK patients available targeted therapies; thousands of patients have been matched to related clinical trials. Doctors can also match patients to basket trials. These specialized clinical trials use agents that target a cancer based on a tumor's mutations rather than the location in

Altogether, more than 35,000 patients have been tested using MSK-IMPACT since 2014

the body. Improved therapies, even for rare cancers, will increase as the data set grows and its resolution increases.

Many MSK patients are now offered MSK-IMPACT sequencing as part of their care, contributing important data to researchers about the particular genetic changes that drive whether a cancer grows, spreads, or is killed, and how individual cancers respond to treatment. For instance, the MSK-IMPACT data revealed insights that led to the Exceptional Responders Initiative, a unique project that seeks to identify the molecular features that make some people responsive to a therapy when most are not. These differences reveal vulnerable spots in biological pathways that support cancer.



Hematologic oncologist Omar Abdel-Wahab, MD, Assistant Member in the Human Oncology and Pathogenesis Program (HOPP) and an Attending Physician on the Leukemia Service in the Department of Medicine

***BRAF* Inhibitors in the Treatment of Hairy Cell Leukemia**

Hairy cell leukemia (HCL) is a rare form of leukemia. It is named for its characteristic hairlike projections on cancer cells. When HCL develops, the bone marrow doesn't produce normal white and red blood cells. This causes people with HCL to be fatigued, and it increases the likelihood of infection. People with HCL usually develop an enlarged spleen as the HCL cells spread to other organs. This decreases their ability to eat and usually results in weight loss.

Scientists have known about HCL for decades. Recently, it was discovered that nearly every person with HCL carries a genetic mutation in the *BRAF* gene, called the *BRAF*V600E mutation. The mutation is also common in other cancers, including melanoma and thyroid cancer. For melanoma, doctors can now prescribe the *BRAF* inhibitor vemurafenib (Zelboraf®). The US Food and Drug Administration approved vemurafenib in 2011 to treat people with *BRAF*-mutant melanoma.

With support from the Geoffrey Beene Cancer Research Center, Omar Abdel-Wahab found that the *BRAF*V600E mutation drives the development of HCL. Through clinical trials, he and his team also determined that vemurafenib was a very effective treatment for people with HCL who are not responsive to conventional treatments for the disease. The results of this study were published in the *New England Journal of Medicine* in 2017. On the basis of these

The Marie-Josée and Henry R. Kravis Center for Molecular Oncology mediates access to MSK-IMPACT data, making it available to the entire research community through their custom web interface cBioPortal. More than 70 papers by MSK investigators using MSK-IMPACT data have been published in Science, Cell, Nature Medicine, the Journal of the American Medical Association, and Cancer Discovery, among others. MSK is highly committed to sharing MSK-IMPACT results with the broader scientific community. We are the leading contributor to the American Association for Cancer Research Project GENIE (Genomics Evidence Neoplasia Information Exchange), an open-access, multi-institutional, international effort to share linked clinical genomics

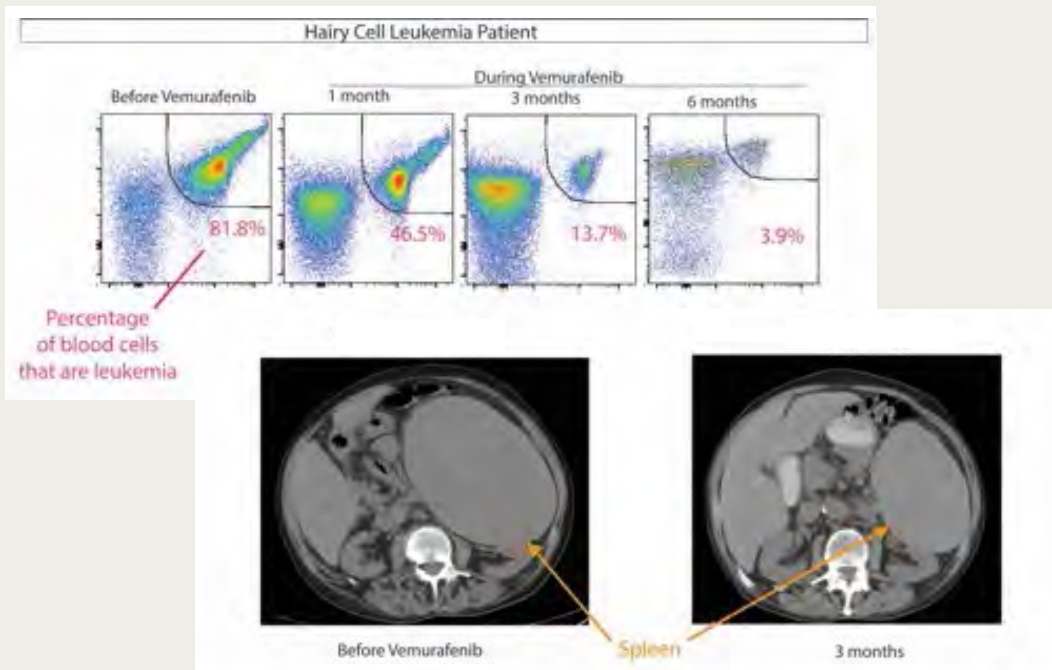
and clinical outcome data for research. GENIE was spearheaded by Charles Sawyers, Chair of the Human Oncology and Pathogenesis Program at MSK.

Altogether, more than 35,000 patients have been tested using MSK-IMPACT since 2014. The test now incorporates an option to counsel patients and family members who share inherited mutations. In 2017, the US Food and Drug Administration authorized the New York State Department of Health to report MSK-IMPACT results to patients and their doctors, the first test of this kind to receive this designation. Support from the Geoffrey Beene Cancer Research Center has been instrumental to the success of MSK-IMPACT and the growth of precision oncology. ■

results, the FDA is considering approving vemurafenib for people with HCL that has come back or become resistant to conventional firstline therapies.

Dr. Abdel-Wahab and colleagues continue to study vemurafenib as treatment for HCL. They have

identified genetic changes that drive the development of HCL and can cause resistance to vemurafenib in people with HCL. They have designed another clinical trial for people with HCL who no longer respond. ■

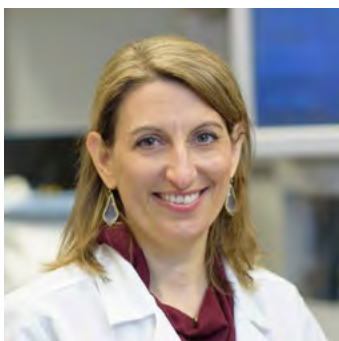


This analysis of the blood of a person with hairy cell leukemia who is undergoing treatment with vemurafenib (Zelboraf®) as part of a clinical trial shows that the percentage of leukemia cells in the bloodstream greatly diminished during therapy. This patient had relapsed following three prior treatments using conventional chemotherapy. CT scans of the abdomen of a person with hairy cell leukemia show an enlarged spleen before treatment (below left), with shrinkage to normal size after treatment with vemurafenib (below right).

Antitumor Assessment Core

As part of its commitment to supporting innovative approaches to cancer research, the Geoffrey Beene Cancer Research Center funds the Shared Resource Awards. These awards go toward purchasing shared scientific instruments and developing or improving Core facilities.

MSK investigators routinely use cancer models — ranging from cultured cell lines to patient-derived tumor models to genetic mouse models — to test new drugs or therapeutic approaches. Many MSK investigators also develop new drugs for patient care. The Antitumor Assessment Core helps these researchers conduct early-stage drug investigation assessments, including pharmacokinetic, toxicity and efficacy studies.



Elisa de Stanchina, PhD,
Facility Head, Antitumor
Assessment Core

Since 2014, the Geoffrey Beene Cancer Research Center has funded two initiatives to enhance the Antitumor Assessment Core, led by Facility Head Elisa de Stanchina. The first has focused on establishing an in-house toxicology laboratory that is compliant with federal good laboratory practices (GLP), offering investigators a cost- and

time-efficient way to conduct animal safety studies. The second initiative has been to develop a centralized resource for the creation of patient-derived xenograft (PDX) models, thereby coordinating expertise and resources, and standardizing the workflow for MSK investigators interested in using these valuable tools.

Good Laboratory Practices-Compliant Laboratory for Safety Toxicology Studies

Before beginning first-in-human clinical trials, the US Food and Drug Administration requires that animal safety studies be conducted in accordance with federal regulations for GLP. Previously, MSK investigators would contract with outside vendors to do these GLP studies, which is extremely costly. Frequently, there are delays or problems in method development, technology transfer, or the initial characterization of novel agents.

So MSK investigators can stay competitive, the Antitumor Assessment Core set out to conduct GLP

studies efficiently on-site. Grants from the Geoffrey Beene Cancer Research Center were used to build a state-of-the-art GLP-compliant laboratory and purchase:

- histopathology equipment (a tissue processor, an embedder, a microtome, slide-staining and cover-slipping instruments, and a digital microscope)
- clinical pathology equipment (hematology and clinical chemistry analyzers)
- a preclinical laboratory information system that can capture, analyze, and assemble drug-testing data while meeting the FDA's requirements for data integrity

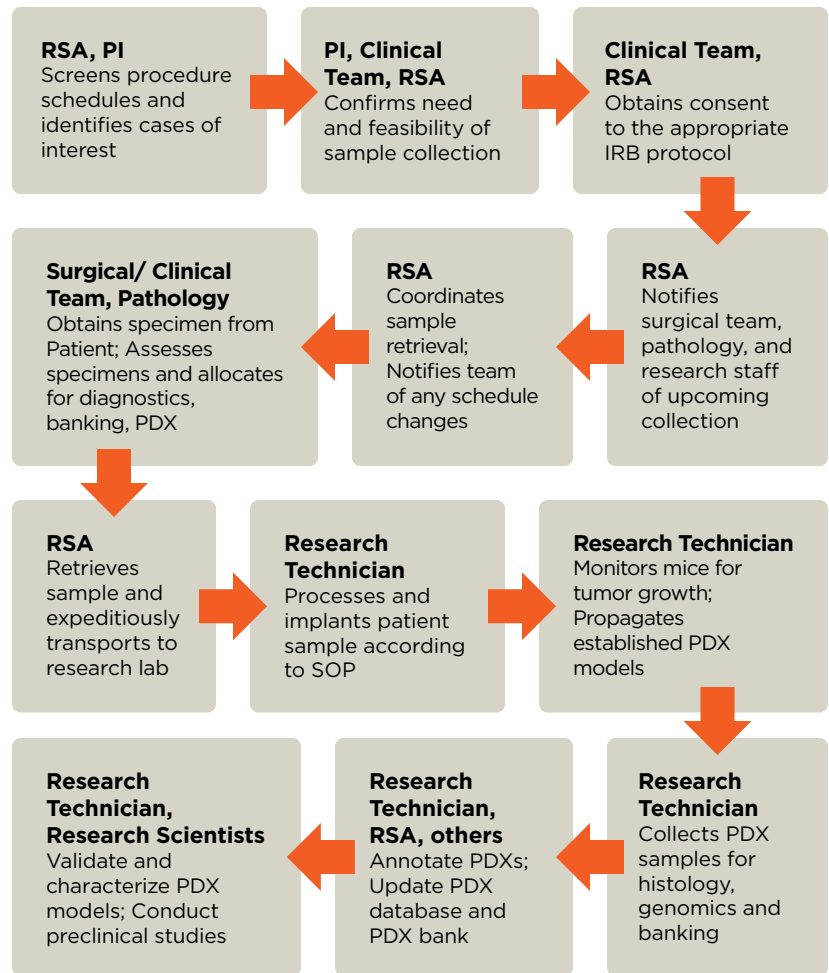
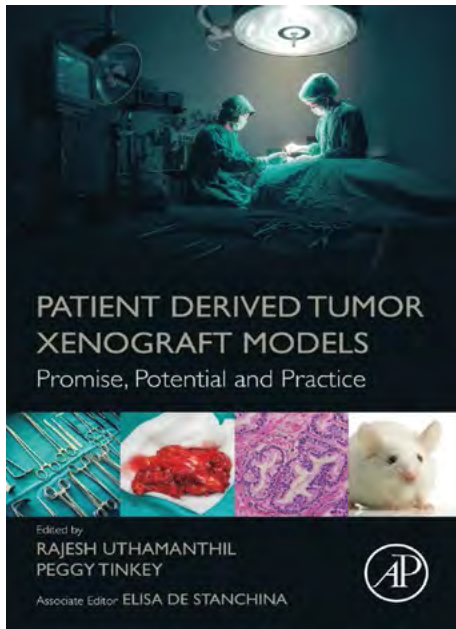
In 2016, the lab transitioned into a fully GLP-compliant facility capable of conducting up to ten large safety toxicology studies per year. The GLP lab has overseen the development of 15 products, including new imaging agents, antibodies, and chimeric antigen receptor T cells. Several of the GLP lab's products are currently being tested in phase I trials. In fact, MSK is one of very few academic institutions in the United States with this capability. The GLP facility allows for the entire development process to occur in-house — a major benefit to the MSK translational research community.

Patient-Derived Xenograft Centralized Core

During the past decade, PDX models have become an invaluable tool for cancer research. Investigators can conduct myriad human cancer studies relating to tumor genetics, new biomarker identification, cancer spread (metastasis), personalized therapy, and the development of novel therapies for early, advanced, and drug-resistant tumors, for example, facilitated by specialized animal models.

Obtaining the patient samples to develop PDX models, however, is a complex and challenging process. It requires a high degree of coordination among multiple clinical and research teams. With funding from the Geoffrey Beene Cancer Research Center, the Antitumor Assessment Core streamlined the workflow for developing PDX models, insight that they recently published in the textbook *Patient-Derived Xenograft Models: Promise, Potential, and Practice*. Their workflow template can be used for a variety of difficult to treat cancers and cancers with no applicable laboratory model.

At MSK, umbrella Institutional Review Board and Animal Care and Use Committee protocols permit the



The workflow (right) was provided as a template in a recently published book on PDX models (left).

collection of samples for both xenograft and organoid models from a spectrum of patients who have cancer. Four dedicated research study assistants identify appropriate study participants, gain patients’ consent, and collect their samples. Core research technicians then graft the samples into immunocompromised mice and grow them via serial transplantation. As a quality-control measure, newly established models are characterized histologically and genomically to ensure that they resemble the original patient sample.

Through this system, the core has created a very extensive, meticulously annotated PDX library. It has overseen the generation of more than 1,000 PDX models, including breast, lung, gastric, pancreatic, colon, liver, bladder, ovarian, prostate, brain, and head and neck cancer, along with sarcoma, neuroblastoma, melanoma, myeloma, leukemia, and lymphoma. In all, these PDX models represent more than 150 cancers. Of particular note, the core has generated PDX

models from the same patient at different stages of the disease, allowing doctors to study how tumors change over time, specifically, the events related to cancer spreading or its resistance to specific therapies

To accompany the library, the Antitumor Assessment Core has built a sophisticated PDX database, supported in part by the Geoffrey Beene Cancer Research Center. This tool allows investigators to directly compare the genomic profiles of primary tumors and matched PDX samples, as well as review data over time, such as genomic changes in a certain period or assessing the reasons for drug resistance. The database also gives investigators a place to make meticulous notes about each PDX model, such as a timeline of a patient’s clinical history (such as surgeries or treatments) along with the PDX model’s establishment. This data is stored in a HIPAA-compliant manner in MSK’s cBioPortal for Cancer Genomics. ■

RETREATS AND SPECIAL CONFERENCES

Each year, the Geoffrey Beene Cancer Research Center hosts a retreat for researchers in the Cancer Biology and Genetics Program and the Human Oncology and Pathogenesis Program. The center has also hosted the following special conferences and workshops on current topics in cancer.

Joint Conference on Cancer as an Evolving and Systemic Disease

This special conference was held at MSK and sponsored by the Geoffrey Beene Cancer Research Center, *Nature*, *Nature Cell Biology*, and *Nature Reviews Cancer*. It brought together 200 researchers with diverse perspectives on cancer's dual qualities as both an evolving and systemic disease. To develop and grow, cancer negotiates a relationship between the tumor and the body as a whole. Certain genetic changes in a cell may set its course to becoming cancerous, but tumor cells continually change in order to survive and spread. This involves complex interactions between tumors and the local stroma, such as extracellular matrix molecules and nontumor cells, as well as tumor-derived factors at distant locations.

This conference highlighted recent progress in the field. Researchers discussed how such interactions influence immune responses, mobilize cell types that foster tumor growth, and establish environments that are hospitable for cancer growth. Tumor burden has additional adverse effects at an organismal level, including such conditions as cachexia and paraneoplastic syndrome. They discussed the challenges in understanding how these features of tumor development influence one another and how current knowledge may be used to improve patient care.

Think Tank Conference

Splicing Factors Meeting

Hosted by Omar Abdel-Wahab

Great progress has been made in identifying genetic changes in people with cancer. One of the most surprising findings has been the relatively high frequency at which the RNA splicing mutations occur in cancer cells. These so-called "spliceosomal mutations" are among the most common mutations

in several blood cancers and are also mutated in many other cancers, including lung cancer and breast cancer. These mutations can actually drive cancer progression. Understanding these changes could lead to new treatments that are effective for cancers caused by the mutations.

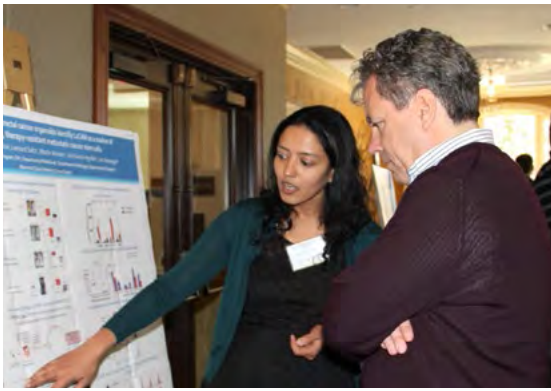
Learning more about the role of altered spliceosomes in cancer requires the involvement of RNA biochemists, bioinformaticians, cancer biologists, and translational clinical researchers. Recognizing this need, Harold Varmus of the National Cancer Institute and Weill Cornell Medicine, Siddhartha Mukkherjee of Columbia University, and Omar Abdel-Wahab of Memorial Sloan Kettering hosted this one-day meeting at MSK. Investigators from a variety of fields came together for deeper collaboration in this new avenue of cancer research.

Workshop on the Microbiome and the Immune System

Hosted by Miguel-Angel Perales

For this full-day event, more than 40 doctors, data managers, and translational scientists from 20 institutions convened at MSK to discuss the PREDICT trial. This first-in-class multi-institutional trial combines microbiome and immune system monitoring. PREDICT aims to create the first clinically annotated hematocrit biospecimen repository that includes samples for immune monitoring, transcriptomics (such as peripheral blood mononuclear cells and plasma), and microbiome analysis (like stool samples). Investigators will study about 300 people who are undergoing allogeneic stem cell transplants to look for molecular predictors of outcome, including the rebuilding of the microbiome and immune system.

The trial's state-of-the-art analyses will be run in centers in the Blood and Marrow Transplantation Clinical Trials Network (BMT CTN). The BMT CTN, which is funded by the National Heart, Lung, and Blood Institute and the National Cancer Institute, has approved the PREDICT trial.



Dr. Lowe, Chair of the Geoffrey Beene Cancer Research Center (top right), and Dr. Massague, Director of Sloan Kettering Institute (bottom right), are among the Beene-affiliated researchers who have attended our Annual Geoffrey Beene Cancer Research Retreats.

Geoffrey Beene Retreat

This two-day retreat, sponsored by the Geoffrey Beene Cancer Research Center, focuses on a wide range of translational research topics. The retreat is a highly anticipated annual event that has fostered collaborative

interactions between clinicians and basic science researchers across the institution. In addition to several short talks by program members, a world-renowned guest speaker is invited to the retreat each year.

Past retreat speakers:

2008

Charles Sherr
St. Jude's Children's
Research Hospital

2009

David Livingston
Dana-Farber Cancer
Institute and Harvard
Medical School

2010

Louis Staudt
Center for Cancer
Research, National
Cancer Institute

2011

Jacqueline Lees
Koch Institute for
Integrative Cancer
Research

2012

William Sellers
Novartis Institutes for
BioMedical Research

2013

Stephen Elledge
Harvard Medical School,
Brigham and Women's
Hospital

2014

Frank McCormick
University of California,
San Francisco,
Helen Diller Family
Comprehensive Cancer
Center

2015

Lewis C. Cantley
Sandra and Edward
Meyer Cancer Center
at Weill Cornell Medical
College

2016

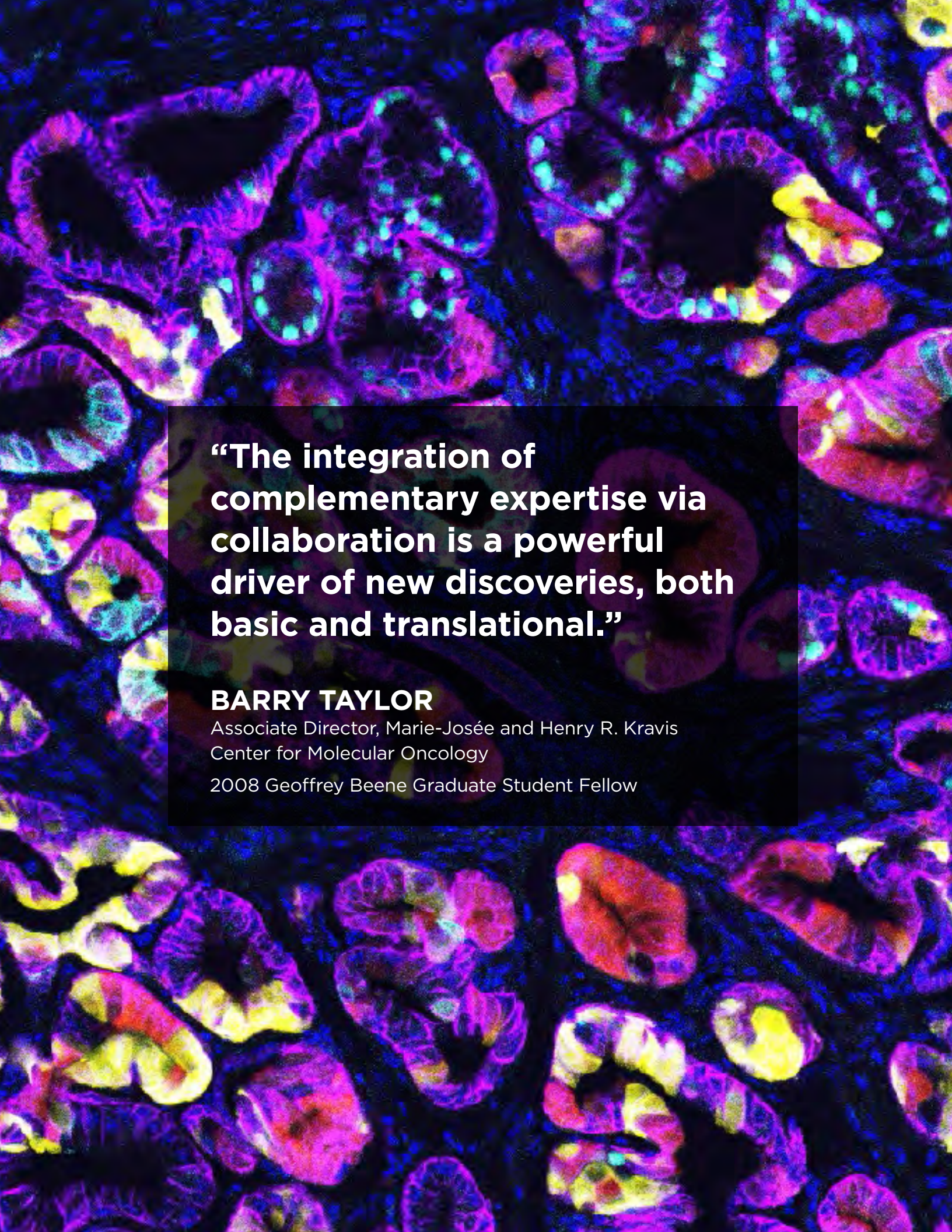
Ton Schumacher
Netherlands Cancer
Institute

2017

Titia de Lange
Rockefeller University

SUPPORTING NOVEL RESEARCH

IF exhibiting clonal complexity of PanIN
formation in murine model of pancreas cancer.
Image by Kelly Lafaro in the Leach Lab



**“The integration of
complementary expertise via
collaboration is a powerful
driver of new discoveries, both
basic and translational.”**

BARRY TAYLOR

Associate Director, Marie-Josée and Henry R. Kravis
Center for Molecular Oncology

2008 Geoffrey Beene Graduate Student Fellow

FACULTY

Senior Chairs



Scott Lowe

Dr. Lowe is Chair of the Cancer Biology and Genetics Program at the Sloan Kettering Institute. He is interested in tumor-suppressor gene networks that control apoptosis and senescence. His laboratory studies how disrupting these networks influences varied features of cancer, such as tumor growth, survival, and metastasis.



David Solit

Dr. Solit is a physician-scientist, a member of the Human Oncology and Pathogenesis Program, and director of the Marie-Josée and Henry R. Kravis Center for Molecular Oncology. His laboratory uses genomics and chemical biology approaches to understand functional characteristics of human tumors. This approach can reveal “druggable” alterations that drive cancer development and progression, and informs rational therapeutic strategies focused on molecularly defined subclasses of people with cancer.

Junior Chairs



Johanna Joyce, 2007-2011

Dr. Joyce led a lab investigating the molecular mechanisms of tumor-host interactions. She joined the Ludwig Institute for Cancer Research in Switzerland in 2016.



Kitai Kim, 2012-2016

Dr. Kim is a stem cell biologist who studies the epigenetic regulation of DNA methylation in stem and cancer cells and the role it plays in pluripotency and cancer.



Ross Levine, 2007-2011

Dr. Levine was an inaugural Junior Chair. He is a physician-scientist who focuses on the genetic basis of hematopoietic cancers.



Joseph Sun, 2014-2018

Dr. Sun is an immunologist who investigates the natural killer cell response to infection and cancer.



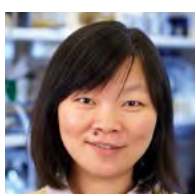
Andrea Ventura, 2008-2012

Dr. Ventura is a cancer biologist who studies noncoding RNAs and their contribution to the pathogenesis of human cancer.



Alan Ho, 2015-2019

Dr. Ho is a medical oncologist who specializes in the treatment of head and neck cancers, specifically cancer of the salivary glands and thyroid.



Ping Chi, 2011-2015

Dr. Chi is a physician-scientist who studies the genetic and epigenetic mechanisms of transcriptional regulation by oncogenic factors in solid tumors.

GRADUATE STUDENTS

The Geoffrey Beene Graduate Student Fellowship program provides full stipends for up to two years for exemplary graduate students at the Gerstner Sloan Kettering Graduate School of Biomedical Sciences (GSK) who are conducting research at Memorial Sloan Kettering research labs. Recipients are selected at the end of their first year of study based on academic excellence. By providing support for outstanding GSK students, the Beene Fellowships are designed to expand the pool of investigators trained to pursue research in the highly complex, multidisciplinary field of cancer biology.

2007

Hyung Song Nam

Sindy Escobar-Alvarez

Currently: Senior Program Officer at the Doris Duke Foundation

2008

Vaseilena Gocheva

Barry Taylor

Currently: Faculty at MSK

2009

Neha Bagwat

Currently: Research Scientist at Prelude Therapeutics

John Halliday

Ellen Hukkelhoven

Currently: Biotech Analyst at Perceptive Advisors

2010

Daniel Marks, Oakley Olson, Piero Sanfillipo

2011

Robert Bowman, Jenny Karo, Gregory Mazo

2012

Emily Casey

Currently: Medical Writer at Health Interactions

Edward Kastenhuber, Neel Shah

2013

Kelsey Temprine, Mary Klein, Kinisha Gala

2015

Kinisha Gala, Ryan Smith, Hannah Johnsen

2016

Jacob Boyer, Nicolas Kuhn, Xiayo Li

2017

Anton Dobrin, Hsuan-An Chen, Caroline Gleason

Q&A WITH BARRY TAYLOR



Barry Taylor, Associate Director, Marie-Josée and Henry R. Kravis Center for Molecular Oncology; 2008 Geoffrey Beene Graduate Student Fellow

How did the Geoffrey Beene fellowship help your graduate studies?

The Geoffrey Beene fellowship made me part of a community of GBCRC-supported and GBCRC-affiliated scientists who were doing like-minded basic and translational genome-driven research. My graduate studies benefited greatly from the collaboration and mentorship of so many young and senior investigators affiliated with GBCRC. These collaborations proved pivotal for accelerating my graduate studies and broadening their scientific horizons.

How would you describe our research to nonscientists?

Our research centers on understanding how genetic changes of all sorts, from inherited to somatic and from individual mutations to broader molecular alterations, drive the genesis and progression of human cancers

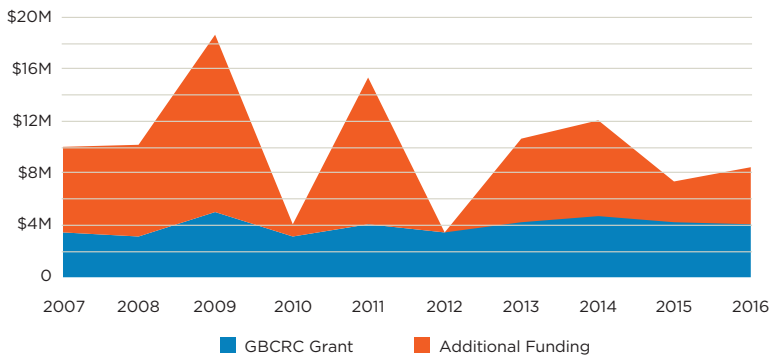
and, in particular, may determine sensitivity to anticancer therapy.

How did the Geoffrey Beene fellowship lead to your current success?

The Geoffrey Beene fellowship was instrumental. It gave me the freedom to foster long-lasting and productive collaborations with so many MSK investigators that continue to this day. These collaborations have pushed my science in new directions. They showed me, at the earliest stage of my scientific training and career, that the integration of complementary expertise via collaboration is a powerful driver of new discoveries, both basic and translational. They showed me that team science is possible, it is productive, it is fun, and that has carried through to my work today and will typify our approach far into the future.

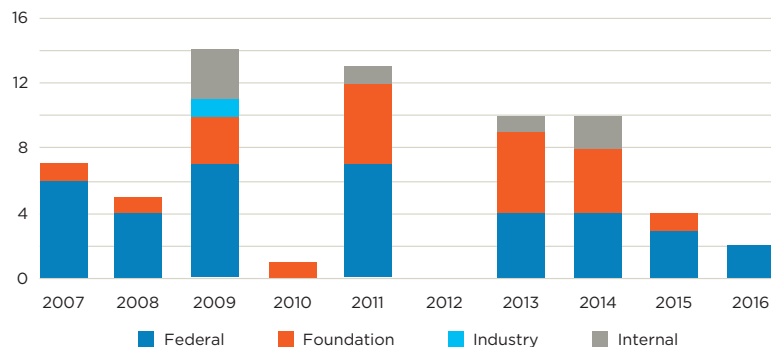
FINANCIAL STATISTICS

2007-2016 Followup Funding Summary



Follow-up Funding: The Geoffrey Beene Cancer Research Center carefully follows the progress of grant recipients in the years after their support from the center ends. Since the center issues seed funding, many of the proposals it funds generate enough good data to continue research with other sources of external funding. For most years, the external income exceeds the amount of seed funding initially provided

Sources of Additional Funding

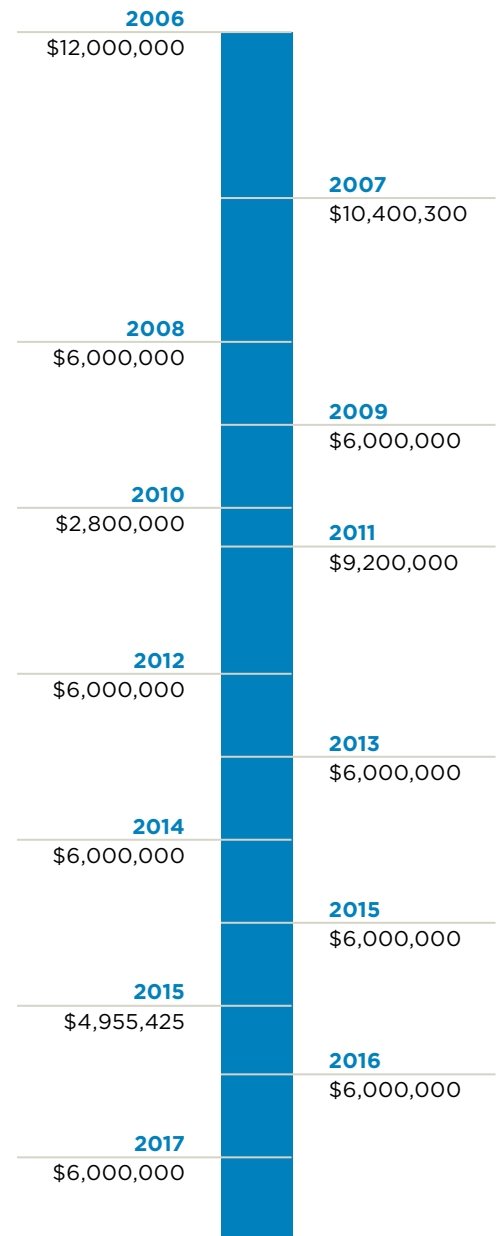


Return on Investment

\$1.55 for every \$1 awarded

For every \$1 the Geoffrey Beene Cancer Research Center invested in an innovative research project, MSK investigators received \$1.55 in other grant funding.

Geoffrey Beene Foundation Directed Donations



Total:

\$87,355,725

RESEARCH GRANTS

Since 2007, the Geoffrey Beene Cancer Research Center has issued an annual Request for Applications within the Memorial Sloan Kettering community, with the goal of supporting innovative research projects that may not qualify for other sources of funding. In addition, the center began offering funding for shared resource proposals starting in 2008, in an effort to make expensive resources that can only be justified on a shared-use basis available to MSK research labs for meritorious projects. Letters of Intent are submitted to

the Geoffrey Beene Cancer Research Center Executive Committee. The invitation to submit a full application is extended to 50 percent of the applicants. Applications are peer-reviewed by members of the Geoffrey Beene Executive Committee, and investigators throughout MSK. The Geoffrey Beene Cancer Research Center has provided more than \$40 million in grant funding and more than \$3 million for shared instrumentation.

2007

Applying the Glioblastoma Genome Atlas to Glioma-Relevant Signaling

Cameron Brennan, MD

The genome of glioblastoma, the most common brain tumor in adults, has recently been analyzed in unprecedented detail through a national collaborative project: the Cancer Genome Atlas. Early results point to three distinct subclasses of glioblastoma, which differ in gene expression and mutations. We are investigating the activation state of signal transduction pathways among these genomically defined subclasses of glioma to identify which might be good candidates for therapeutic inhibition.

Genetic Modifications to Enhance the In Vivo Survival and Antitumor Activity of Gene-Modified CD19-Targeted T Cells

Renier Brentjens, MD, PhD

T cells are immune cells that may be genetically altered to recognize a patient's own tumor cells. The goal of this project is to better design these genetic modifications such that these T cells are more likely to fully eradicate all of the tumor cells when injected back into the patients. Data generated from these studies will be used to design better clinical trials for cancer therapy using genetically targeted T cells.

Chemical and Proteomic Mapping of Cancer-Specific Molecular Therapeutic Targets

Gabriela Chiosis, MA, PhD

Cancer is complex, and no two patients present an identical disease. Because of the diversity of molecular alterations, it is difficult in clinical settings to determine the exact combination of drugs that will result in the best outcome. Our technology offers the promise of identifying, patient by patient, the subset of proteins that become aberrant in every cancer cell type/patient tumor tissue. The information gained may be compiled in creating a molecular map of cell- and cancer-specific transformation pathways. This will ultimately allow physicians to design a personalized therapy for patients. Such proteomic map has obvious advantages over the more common genetic signature maps because most anticancer agents are small molecules that target proteins, not genes, and many small molecules targeting specific molecular alterations are currently in development. Thus, our efforts aim to set the basis for designing combination therapies with better efficacy and less toxicity in the treatment of patients with cancers and, moreover, to define the specific molecular alterations in a particular tumor, facilitating the development of novel molecularly targeted therapies.

A Gain-of-Function Genetic Screen for Human Breast Cancer Metastasis Genes

Filippo Giancotti, MD, PhD

We are studying the genetic instructions that induce cancer cells to become metastatic. We have constructed a library of genes from metastatic breast cancer cells, added a molecular tag, and introduced them into nonmetastatic cells. The recipient

cells have been injected into mice, and those that have acquired the ability to metastasize to the lung have been recovered from this organ. Sequencing of the tagged genes has led to the identification of two novel genes that play a key role in metastasis. One of the two genes directs cells to make a secreted protein, called Coco, which blocks a signaling receptor, called the BMP receptor. We are isolating new metastasis genes and studying their mechanism of action. We hope that a better understanding of the molecular processes that drive metastasis will lead to the design of drugs that specifically block this process.

PTEN Signaling in Cancer: Novel Regulation and Potential Therapy

Xuejun Jiang, PhD

PTEN is a potent tumor suppressor and a master regulator for multiple cell-signaling processes. Mounting evidence indicates that PTEN itself is also under precise regulation, and such regulation dictates its signaling and tumor suppressive function. This project aims to understand regulation of PTEN by its ubiquitin ligase NEDD4-1, the potential of NEDD4-1 as a cancer therapeutic target, and potential novel functions of PTEN in other tumor-related signaling events.

A Genome-Wide Association for Pancreatic Susceptibility Loci

Robert J. Klein, PhD

Although it is known that individuals whose relatives have had pancreatic cancer are at a greater risk of developing this deadly malignancy, it is not known what particular genes are responsible for this increased

susceptibility. Here, we have used individuals from the MSK Familial Pancreatic Cancer Registry to conduct the first stage of a genome-wide association study aimed at identifying common genetic changes responsible for an inherited susceptibility to pancreatic cancer. Our ultimate goal with this research is to identify genes that can be used to predict both who is at risk of developing pancreatic cancer and whose action can be targeted for treatment of this disease.

The Impact of PIK3CA Mutations on the Efficacy of Bevacizumab in Recurrent Hormone Receptor-Positive Breast Cancer

Mary Ellen Moynahan, MD

In our work funded by the Geoffrey Beene Cancer Research Center, we identified PIK3CA mutations in approximately one-third of invasive breast primary tumors. PIK3CA mutations are associated with favorable clinicopathologic features: lower tumor grade, hormone-receptor positive status, HER2 negativity, older age at diagnosis, lower tumor stage, and lymph node negativity. Notably, and in accordance with these favorable pathologic predictors, patients with mutated tumors demonstrate an improvement in overall and breast cancer-specific survival. The protective role imparted by a PIK3CA mutation will significantly affect future clinical trial design for PI3K-targeted therapy.

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

William Pao, MD, PhD

Patients whose lung cancers harbor epidermal growth factor receptor (EGFR) gene mutations have a high likelihood of responding to the tyrosine kinase inhibitors (TKIs) gefitinib (Iressa®) or erlotinib (Tarceva®). However, after about one year, these patients develop progression of disease. In this proposal, we aim to genetically characterize resistant tumors in order to develop new strategies to treat progressive disease and suppress the development of acquired resistance.

RNAi Screen to Identify Suppressors and Modifiers of Treatment Response

Hans Wendel, MD

Using a process called RNA interference (RNAi), we can selectively inactivate genes in living cells. Moreover, we can use libraries of RNAis to target every gene in the human genome. This technology now allows us to investigate genes whose inactivation contributes to various cancers and may affect therapeutic responses.

2008

Synthetic Lethal Screen for Viability Genes in MEK Inhibitor-Treated Thyroid Cancer Cell Lines with BRAF Mutation

James Fagin, MD

BRAF is the most common oncogene in aggressive forms of thyroid cancer and is believed to be important in causing the disease. This proposal aims to identify kinases that may allow thyroid cancer cells to remain viable after the function of BRAF is blocked, as these could potentially be targeted selectively with small molecule inhibitors.

Identifying the Biological Consequences of Cdc7 Kinase Inhibition in Human Cells

Mark Frattini, MD, PhD

Cdc7 is a protein kinase whose activity is required to begin the process of DNA duplication and is essential for normal passage through the cell cycle. Both Cdc7 and its known substrate, the minichromosome maintenance complex, are overexpressed in the majority of leukemias, lymphomas, and solid tumors, making Cdc7 kinase activity a potential therapeutic target. To this end, we have recently identified a novel, naturally occurring small molecule inhibitor of Cdc7. The goal of this project is to more precisely define the result of inhibiting Cdc7 kinase activity in cancer cells and to begin to look at possible mechanisms through which cancer cells might become resistant to Cdc7 kinase inhibition.

Discovery and Evaluation of Novel Adjuvants for Cancer and Infectious Disease Vaccines

David Gin, PhD

The clinical success of vaccines against cancer and infectious diseases critically depends on the identification of novel potent adjuvants, substances that augment a patient's immune response. The aims of this collaborative effort will involve the chemical synthesis and preclinical evaluation of novel molecular adjuvants from botanical sources, with the goal of discovering new vaccine formulations of increased potency.

Identification of Rho GTPase Signaling Pathways Involved in Breast Cancer Cell Proliferation

Alan Hall, PhD

Cell division is most obvious during embryonic development, but although it is much more restricted in adults, cell division is nevertheless crucial — for example, in the maintenance of tissues and organs through the division of stem cells. Whether a cell chooses to enter the cell cycle is mostly determined by signals in the external environment, such as growth factors, growth inhibitors and cell-cell and cell-matrix interactions. Inappropriate cell division is a hallmark of cancer, and the aim of this program of work is to identify new biochemical pathways that drive the growth of human breast cancer cells.

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

Clifford Hudis, MD

Subtypes of breast cancer that responded differently to targeted drugs can be identified by examining their genetic material for certain changes. One example is the identification of HER2 (human epidermal growth factor receptor) positive breast cancer by finding extra copies (amplification) of the gene for HER2. We are using a newer method — comparative genomic hybridization, or CGH — to examine HER2 (and other genes of interest) to allow us to more accurately identify patients with HER2 positive breast cancer for treatment with an anti-HER2 drug.

A Genetic Analysis of the Invasive Breast Cancer Risk Associated with Lobular Carcinoma In Situ

Tari King, MD

Lobular carcinoma in situ (LCIS) is most often an incidental finding in a breast biopsy performed for another reason, yet once a woman is diagnosed with LCIS, she faces a much higher risk for the subsequent development of invasive breast cancer. Historical data suggests that the lifetime risk of breast cancer is 20 to 25 percent and is conferred equally to both breasts. New research, however, suggests that all LCIS may not behave in the same way, and therefore, all LCIS may not confer the same increased risk of breast cancer. The objective of this proposal is to identify different types of LCIS by examining which genes are turned on and off in different LCIS specimens. Our hypothesis is that in some LCIS specimens, we will find that the same genes are turned on as in invasive lobular breast cancer (ILC), and therefore these particular LCIS specimens will be the ones that carry the highest risk for ILC.

Integrated MicroRNA Genomics in Endometrial Cancer

Douglas Levine, MD

Most women with early endometrial cancer will be cured, and only 10 to 15 percent of these women are likely to have a recurrence. Nonetheless radiation therapy is frequently given after surgery to prevent cancer from coming back. This study aims to use microRNA gene expression profiling and DNA copy number analyses to predict which women are most likely to recur so that postsurgical therapy can be better individualized.

Evaluation of Antiangiogenic Therapies by Hypoxia-Imaging Methods

Joseph O'Donoghue, PhD

Some recent drugs for cancer treatment work by preventing the development of new blood vessels. Without these new vessels, the cancer is unable to keep growing. It is important that physicians are able to monitor how well these drugs are working, preferably as early as possible after treatment begins. Our project aims to identify new ways in which the effectiveness of such drugs

can be measured. The methods involve the use of noninvasive tumor imaging, which would make this process more convenient and less traumatic for patients than other methods currently available.

Line-Scanning Confocal Endoscope for Screening Oral Precancers In Vivo

Milind Rajadhyaksha, PhD

Confocal endoscope technology will be created for noninvasive screening and diagnosis of oral and head and neck cancers and to guide surgery of such cancers. The screening, diagnosis, and surgical guidance will be directly on the patient, with minimal need for biopsy, minimal pain, and minimal expense. The technology may also prove useful for noninvasively detecting other cancers, such as in the skin, cervix, breasts, and other tissues.

Inhibitors of Hedgehog Palmitoylation to Block Pancreatic Cancer Cell Growth

Marilyn Resh, PhD

The Sonic Hedgehog (Shh) protein is a key contributor to the growth of pancreatic cancer cells. The goal of the proposed research is to identify and develop drugs that inhibit the attachment of the fatty acid palmitate to Shh. Since palmitoylation is required for Shh function, inhibitors that block Shh palmitoylation could be developed into novel chemotherapeutics that will be efficacious in the treatment of pancreatic cancer.

SHARED RESOURCES AWARDS

Expansion of the Functional Genomics Platform at the High-Throughput Screening Core Facility

Hakim Djaballah, PhD

TRC lentiviral particle-based shRNA libraries for both human and mouse species, covering 15,000 genes, as well as bacterial stocks harboring shRNA plasmids.

System for Research Image Management, Storage, and Processing

Peter Kijewski, PhD

The equipment will be a core facility to be used by MSK investigators who

require images for their research projects. The System for Research Image Management, Storage, and Processing will be referred to as Research PACS (picture archiving and communication system), analogous to the clinical PACS currently in operation at MSK.

Capillary LC-MS/MS System for High-Complexity, High-Sensitivity, Quantitative Proteomics

Paul Tempst, PhD

A THERMO 'LTQ Orbitrap XL' electrospray linear ion trap hybrid FT tandem mass spectrometer, coupled online to an Eksigent 'NanoLC' capillary multidimensional high-performance liquid chromatography separation system with autosampler. The combined system, commonly known as cLC-MS/MS, can identify up to 1,000 proteins per analysis, at accuracies of less than two parts per million, and will be used to characterize very complex protein mixtures, including relative quantitative comparisons of two or three different samples in a single analysis.

2009

Humanized Antibody 8H9 to Target Immunoinhibitory Molecule B7H3 on Solid Tumors

Nai-Kong Cheung, MD, PhD

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.

Combined Molecular Therapy and Immunotherapy for Gastrointestinal Stromal Tumor

Ronald DeMatteo, MD

Tyrosine kinase inhibitors are a new class of drugs that have already proven 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.

Suppression of Mammary Tumorigenesis and EMT by the Atypical Rho Protein *RND1*

Filippo G. Giancotti, MD, PhD

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 if genetic inactivation of *RND1* is sufficient to initiate tumorigenesis in the mammary glands of mice and exploring the genetic mechanisms through which *RND1* is inactivated in human breast cancer.

BCG Susceptibility of Bladder Cancer Cells: Role of PTEN-AKT Signaling in Pathogen Infection

Michael Glickman, MD

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.

Development of a Novel Technique for Modeling and Characterizing Sporadic Tumors in Mice

Alexandra L. Joyner, PhD

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.

Pulsatile Kinase Inhibitor Therapy for Malignant Glioma: Proof of Concept Clinical Trial

Andrew Lassman, MD

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 plan a clinical trial that differs from previous studies in two important ways. First, it has 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. Second, the selection of patients will be made based on those who are most likely to benefit because EGFR is abnormally active in their tumors; previous trials treated all patients regardless of whether EGFR was "on" or "off." We will treat 20 patients in this manner, 10 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.

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

Ross Levine, MD

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.

Zirconium-89 Labeled Antibodies for ImmunoPET-Guided Radioimmunotherapy

Jason S. Lewis, PhD

This proposal will focus on the use of trastuzumab (Herceptin®), a monoclonal antibody 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 trastuzumab can be used for quantitative PET imaging of breast tumors, improved early detection, staging, monitoring of immunotherapy with trastuzumab, 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-trastuzumab to the clinic for quantitative PET imaging of HER2/neu-positive breast cancers in patients.

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

Yueming Li, PhD

Notch signaling may play a causative role in breast cancer. The overall objectives of this proposal are to investigate the function of Notch/ γ -secretase signaling in breast cancer cells and to develop a target-based therapy that is not available today.

Novel Anticancer Compounds Targeting the Tie2/Angiopoietin Interactions and Signaling

Dimitar B. Nikolov, PhD

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 antitumor therapies.

Examining the Role of Entosis in Human Cancers

Michael Overholtzer, PhD

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. For decades, pathologists have seen evidence of entosis in human cancers because it results in the formation of “cell-in-cell” structures, where whole cells are engulfed inside of 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.

The MSK Colorectal Cancer Oncogenome Project: Somatic and Germline Predictors of Recurrence and Response to Therapy

David B. Solit, MD

The goal of this proposal 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 to guide the selection of both standard currently available therapies and patients for treatment with experimental agents that are designed to target specific driver mutations when present in the tumor.

Investigating the Functions of Oncogenic MicroRNAs in Mammals

Andrea Ventura, MD, PhD

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 RESOURCES AWARDS

LC/MS/MS Instrument for Use in Translational Research and Drug Discovery and Development Research at MSK

Gabriela Chiosis, MA, PhD

The requested instrument will provide investigators with the new capability of conducting rapid, routine, and comprehensive drug metabolism and pharmacokinetics and absorption, distribution, metabolism, and excretion/tox analyses of hit compounds and lead candidates, with the goal of facilitating and accelerating the translation of novel therapies from bench to bedside.

Human Tissue Procurement Service and Tissue Bank, Clinical Database for Hematologic Oncology Division

Marcel van den Brink, MD, PhD

To develop in collaboration with the Human Tissue Procurement Service and Tissue Bank Core Facility at MSK, a Human Tissue Procurement Service and Tissue Bank for the Division of Hematologic Oncology at MSK (HemTPS/TB). To develop a point-of-entry clinical database for the Hematologic Oncology Division at MSK.

2010

A Comprehensive Genomic Approach to Identify Cancer Genes in Uveal Melanoma

Boris C. Bastian, MD, PhD

Uveal melanoma is an aggressive form of melanoma, with unique genetic characteristics that involve frequent mutations in *GNAQ* or *GNAI1* and deletions of chromosome 3. In this project, we are performing a systematic genetic and functional analysis to identify the tumor suppressors on chromosome 3, with the goal of improving the understanding of the pathogenesis of this dreadful disease and finding better methods for diagnosis, prognosis, and treatment.

Early Development of Small Molecule Inhibitors of the E3 Ubiquitin Ligase CRL4DCAF1

Filippo G. Giancotti, MD, PhD

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 CRL4DCAF1. These results indicate that inhibitors targeting CRL4DCAF1 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 CRL4DCAF1.

A Comprehensive Genomic and Epigenomic Analysis of the Impact of First-Line Therapy in the Molecular Evolution of Malignant Glioma

Jason T. Huse, MD, PhD

Malignant gliomas are routinely treated with radiation and chemotherapy, but they 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.

Identification of Aberrant Signal Transduction Pathways in Primary CNS Lymphoma

Ingo K. Mellinghoff, MD

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 of deriving new insights into its pathogenesis and identifying new treatment opportunities for its most aggressive subtypes.

Characterization of the Molecular Heterogeneity of EGFR Mutant Lung Adenocarcinoma: Baseline and Post-Treatment Tumor Analysis

Vincent A. Miller, MD

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, such as erlotinib (Tarceva®). 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 the 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.

Establishment of a Unique Mouse Model for Plasma Cell Malignancies

Stephen D. Nimer, MD

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 gain 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 the mice. The results of these studies will be used to procure future National Cancer Institute or National Institutes of Health funding.

Exome Sequencing of Familial Lymphoproliferative Syndrome

Kenneth Offit, MD

This project will seek to uncover the 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 an 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.

DNA Replication Stress and the Sumoylation of RPA

John H. J. Petrini, PhD

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 the molecular mechanisms of tumor suppression.

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

Howard I. Scher, MD

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 (CTCs) isolated from patients enrolled in trials of androgen-receptor-signaling-targeted agents in clinical development at MSK. Our long-term objective is to generate data to qualify

predictive biomarkers of sensitivity in CTCs to guide treatment selection.

Oncogenic MicroRNAs in Acute Lymphatic Leukemia

Hans-Guido Wendel, MD

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.

SHARED RESOURCES AWARD

High-Throughput Immunohistochemistry

Jason T. Huse, MD, PhD

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, are already using it extensively.

2011

High-Throughput Profiling of Genomic Alterations in Clinical Tumor Specimens

Michael Berger, PhD

Efforts to understand cancer at the molecular level have revealed genetic biomarkers that reflect the nature and course of disease and, in some cases, predict the likelihood that a patient will benefit from a particular treatment. We plan to develop and apply a robust and cost-effective methodology, empowered by massively parallel next-generation sequencing, by which any clinical tumor specimen may be characterized for DNA mutations and copy number changes in all known cancer genes. By systematically deploying this platform across clinically annotated tumors and, ultimately, every patient at MSK, we hope to

facilitate individual approaches to cancer treatment through improved diagnostics and the identification of novel biomarkers.

Targeting AKT Inhibitor-Induced Feedback Signaling in Breast Cancer

Sarat Chandarlapaty, MD, PhD

The PI3K/AKT/mTOR pathway is mutationally activated in the majority of breast cancers. While this pathway is druggable by a variety of compounds, the pathway is subject to multiple forms of negative feedback regulation, and these feedback pathways become relieved under conditions of drug inhibition of the pathway. We hypothesize that the loss of negative feedback limits the effectiveness of drugs targeting this pathway. We propose to identify the specific mechanisms of the feedback regulation of PI3K/AKT/mTOR-pathway-activated breast cancers, to determine the consequences of the loss of negative feedback on the efficacy of drug therapy, and to clinically evaluate combining an AKT inhibitor with an inhibitor of a known oncogenic pathway that is hyperactivated through AKT-inhibitor-mediated loss of feedback.

Understanding Clonal Evolution and the Heterogeneity of the Therapeutic Response by Lineage Tracing in Mouse Models of Glioma

Eric Holland, MD, PhD

It is increasingly appreciated that cancer cells within any given tumor differ considerably from one another, and such heterogeneity is likely a major hurdle in cancer therapeutics. Still, little is known about the mechanisms underlying the emergence of tumor cell heterogeneity. Traditionally, all cells within a tumor were assumed to originate from a common ancestor. However, in addition to bona fide tumor cells, solid tumors also contain numerous cells derived from the normal host microenvironment, such as blood vessels and immune cells. In brain tumors, a large number of normal brain cells are trapped within the growing tumor. Our research indicates that such normal cells can become corrupted by the tumor environment and actually become bona fide tumor cells

themselves, suggesting that cancer cells within the same tumor may be unrelated to one another and may thus differ considerably in their response to specific therapeutic agents. By developing a new mouse model, we aim to characterize the corruption of such initially normal brain cells within gliomas, a common group of brain tumors, specifically with regard to their contribution to resistance to commonly used anticancer therapeutics and tumor recurrence.

Mechanism and Therapeutic Potential of PTEN Regulation upon Hypoxia

Xuejun Jiang, PhD

The overall goal of this proposal is to understand the molecular basis underlying the context-specific regulation of the PTEN tumor suppressor and the cancer therapeutic implications of such regulation. Specifically, we will study how the ubiquitin ligase NEDD4-1 regulates PTEN function, AKT activation, cell survival/apoptosis, and tumorigenesis in the context of hypoxia. The success of this study will not only elucidate the molecular mechanisms governing the context-specific regulation of PTEN and novel aspects of hypoxia biology but will also provide insights into the therapeutic targeting of the NEDD4-1-PTEN circuitry in treating specific human cancers.

Combined Pre- and Intraoperative Brain Tumor Imaging Using a Novel Dual-Modality Raman-MRI Nanoparticle Probe

Moritz Kircher, MD, PhD

Malignant brain tumors remain a therapeutic challenge, in part because of the difficulty of visualizing the tumor borders during surgical resection. Our project seeks to validate a new molecular approach to brain tumor imaging based on a dual-modality MRI/SERS (surface-enhanced Raman spectroscopy) nanoparticle, allowing combined preoperative staging and intraoperative high-resolution imaging using a single contrast agent. This will include biodistribution and cytotoxicity studies and an assessment of the accuracy of tumor delineation by MRI and Raman imaging in transgenic mouse models.

Transcriptional Regulatory SNPs as a Mechanism for Prostate Cancer Risk Loci

Robert Klein, PhD

While genome-wide-association studies have identified numerous single nucleotide polymorphisms (SNPs) associated with the risk of prostate cancer and other diseases, little is known about the biological mechanism by which these SNPs operate. Here, we will test the hypothesis that the functional alleles at many prostate cancer risk loci alter a functional transcription factor binding site, thereby resulting in the misregulation of nearby genes that influence the carcinogenesis process. This research will give new insights into the biology of prostate cancer by identifying both a general mechanism underlying prostate cancer risk SNPs and specific genes that may mediate this altered risk.

Development of ⁸⁹Zr-5A10 for the Measurement of AR Signaling in Advanced Prostate Cancer with Positron Emission Tomography

Jason Lewis, PhD

We propose to evaluate ⁸⁹Zr-5A10 as a pharmacodynamic and predictive biomarker for two important classes of therapies for castration-resistant prostate cancer (CRPC) — antiandrogens and PI3K inhibitors — and to conduct a phase 0 study with a humanized version of 5A10 in rodents and men with CRPC. This translational project represents one of the first systematic efforts to develop a biomarker for the evaluation of AR signaling in patients with CRPC, and the findings from this proposal have the potential to substantially impact the customization of individual patient care, as well as influence the design and execution of future clinical trials..

Squamous Cell Carcinoma of the Lung Mutation Analysis Program (SQC-MAP)

Paul Paik, MD

Patients with squamous cell carcinomas of the lung (SQCLC) comprise 20 percent of all non-small cell lung cancers diagnosed in the United States annually, amounting to nearly 40,000 patients per year. Unfortunately, no targeted therapies

have been identified for these patients, this despite the success of drugs that target the mutant epidermal growth factor receptor and anaplastic lymphoma kinase in a third of lung adenocarcinoma (ADCL) cases. Exciting new work has identified putative driver oncogenic events in upward of 50 to 60 percent of SQCLC patients. The complex nature of these mutations, which have almost no overlap with those found in ADCL, necessitates the creation of a new molecular profiling infrastructure. SQC-MAP will fulfill this role, prospectively validating these molecular aberrations in a cohort of 100 SQCLC patients at MSK while simultaneously serving as the platform by which patients will be paired to emerging clinical trials of new targeted therapies.

Genomic Determinants of Radiosensitivity

Simon Powell, MD, PhD

The project aims to understand the genetic factors that underlie the individual differences in sensitivity to ionizing radiation. We have developed a high-throughput assay of DNA damage and repair using flow cytometry for lymphoblastoid cell lines. By studying the 1000 Genomes Project cell lines, where whole-genome sequencing data are available, we can study genetic locus association markers for radiation sensitivity as well as candidate mutations and polymorphisms in known radiation response genes. The ultimate goal is to develop a radiogenomics profile for predicting sensitivity or resistance to radiation that will help in planning radiation therapy.

Endothelial Precursor Cells in Allogeneic Bone Marrow Transplantation during Graft-versus-Host Disease and Graft-versus-Tumor Activity

Marcel van den Brink, MD, PhD

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important therapy with curative potential for a variety of malignant and nonmalignant diseases. The major obstacles to a more favorable therapeutic outcome are tumor relapse and acute graft-versus-

host disease (GVHD), which is an inflammatory process primarily involving the intestine, liver, and skin. Neovascularization has been implicated in both tumor growth and inflammation, suggesting that neovascularization could be an attractive therapeutic target in patients with malignancies who are undergoing HSCT. Based upon our promising preclinical studies, we hypothesize that the therapeutic targeting of neovascularization in allo-HSCT recipients can simultaneously ameliorate GVHD and inhibit post-transplant malignant relapse, resulting in improved overall survival in allo-HSCT recipients.

Investigating the miR-34 Family of Tumor Suppressor MicroRNAs

Andrea Ventura, MD, PhD

Over the past decade, microRNAs (miRNAs) have emerged as key modulators of gene expression in metazoan and plants. Deregulated expression of miRNAs is a common feature of human cancers, and a number of miRNAs have been proposed to act as oncogenes or tumor suppressors. We will investigate a recently described family of p53-regulated miRNAs whose members have been proposed to act as tumor suppressors in a variety of human cancers. By combining in vivo studies in the mouse and high-throughput approaches, we will determine the physiologic functions of the various members of this family of miRNAs, their potential activity as tumor suppressors, and their mechanism of action.

SHARED RESOURCES AWARD

Raman Microscope for Label-Free Tissue Characterization and High-Sensitivity Detection of Raman Contrast Agents

Moritz Kircher, MD, PhD

The instrument purchased with this grant is a Renishaw InVia Raman microscope with Streamline upgrade. It allows for the rapid acquisition of Raman spectra and Raman imaging maps of materials, cells, and tissue sections, as well as of small animals in vivo.

2012

The Mutational Landscapes Underlying Tumor Aggressiveness in Adenoid Cystic Carcinoma

Timothy Chan, MD, PhD

Adenoid cystic carcinoma (ACC) is a deadly malignancy about which very little is known. Our study will define the mutational landscape underlying this cancer and define the changes that drive tumor aggressiveness. We will make use of several rigorous genome-wide strategies to elucidate the genetic changes in ACC. Our work will identify new biomarkers for disease progression and potential novel targets for therapy.

Genetic Basis of mTOR Treatment Response and Its Implication in Kidney Cancer

James Hsieh, MD, PhD

This translational Beene grant focuses on understanding the molecular underpinnings of treatment response and resistance to mTOR inhibitors (targeted drugs that have approved by the US Food and Drug Administration for treating kidney cancers). To achieve this outstanding goal, we employ a state-of-the-art integrated genomic, structural, biochemical, and mouse genetic approach. Results are expected to help better predict the response and resistance of renal cancers to targeted anticancer agents, with an ultimate goal of personalizing cancer therapies.

Role of Reciprocal Epithelial-Stromal Signaling Elicited by Hedgehog-GLI Signaling in Prostate Cancer

Alexandra Joyner, PhD

Most research on prostate cancer (PCa), the second leading cause of cancer-related deaths in American men, has concentrated on the signaling pathways active in tumor cells; however, there is growing evidence that cancer-associated fibroblasts (CAFs) have profound effects on tumor growth, with normal stroma reducing tumor burden and CAFs augmenting tumor growth. The hypothesis we will test using mouse models is that a hedgehog protein secreted by PCa stimulates expansion of CAFs that, in turn, secrete factors that enhance tumor progression. Since small molecule hedgehog pathway inhibitors

have been effective in the clinic and mouse cancer models, the results of our studies should be applicable to translational studies.

Integrated Genetic Profiling to Predict Response to Therapy in Acute Myeloid Leukemia

Mithat Gönen, PhD

Although induction chemotherapy, consolidation, and allogeneic stem cell transplantation offer the possibility of a cure to patients with acute myeloid leukemia (AML), the variable outcome of patients with AML has limited the optimal use of antileukemic therapies. Most recently, randomized trials have established high-dose daunorubicin (Cerubidine®) as the current standard of care for patients 18 to 60 years of age with newly diagnosed AML; however, it was not clear from these studies whether there were specific patient subsets that derived benefit from more-intensive therapies. Previously, we used data from a trial of younger adults with AML to demonstrate that mutational analysis can identify which patients benefit from dose-intensive daunorubicin induction chemotherapy and which patients do not derive benefit from the more intensive regimen. We now aim to expand our knowledge of the genomic predictors of response or resistance to therapy through a study of elderly patients enrolled in multicenter randomized trials. The results will help us refine our prognostic signature of the overall outcome in AML, identify mutations that predict response to therapy, and based on mutational analysis, determine the patient subsets that benefit from more-intensive therapies, including dose-intensive chemotherapy and allogeneic hematopoietic stem cell transplantation.

Targeting CD99 in Leukemic Stem Cells in Acute Myeloid Leukemia

Christopher Park, MD, PhD

We have shown that leukemic stem cells in acute myeloid leukemia (AML) express the cell surface protein CD99. Because AML stem cells can be selectively targeted by antibodies that recognize CD99, we will investigate whether such an antibody can be utilized clinically as a novel AML therapy. We will also determine the

function of CD99 in AML stem cells, which are the cells that must be eliminated in order to effect cures for this difficult-to-treat disease.

A Phase II Study of the BRAF Inhibitor Vemurafenib in Patients with Relapsed or Refractory Hairy Cell Leukemia

Jae Park, MD

A recent exome sequencing study of hairy cell leukemia (HCL) has identified that the BRAF V600E mutation is present in nearly 100 percent of primary HCL samples while absent in other B cell lymphoid malignancies. The exclusive presence of the BRAF V600E mutation in HCL implicates its role in pathogenesis and provides a rational therapeutic target. Therefore, we propose to study the clinical efficacy of the BRAF inhibitor vemurafenib (Zelboraf®) in patients with relapsed or refractory HCL. Our project will also systematically characterize the mutation profiles of HCL and investigate the potential mechanisms of resistance to BRAF inhibition. The ultimate goal of the project is to provide a better understanding of the implication of the BRAF mutation and develop the first molecularly targeted therapy in patients with HCL.

Oxidative DNA Damage and Oncogenesis: A New Function for the Ku Heterodimer

John Petrini, PhD

This study will examine the interplay between oxidative DNA damage and the process of DNA synthesis. Previously, the protein called Ku has been shown to regulate DNA repair. We have discovered a new function for Ku, which is that during this process, it helps suppress the potential of oxidative DNA damage to cause cancer. We are examining the importance of this process and the role of Ku in preventing breast cancer.

Human ES Cells as Candidates for Modeling Glioma

Viviane Tabar, MD

Human pluripotent stem cells represent highly promising novel tools for modeling human disease. Our lab has expertise in inducing the differentiation of human pluripotent stem cells into neural precursors. Here, we propose

using these cells for the purpose of modeling human glioma. Mutations uncovered in genomic studies of human brain tumors will be introduced into human neural precursors in an effort to uncover the oncogenic pathways required for the initiation of brain tumors from specific cells of origin. We hope to demonstrate that human pluripotent stem cells can serve as a platform for modeling gliomas and potentially other cancers in human cells.

New Therapeutic Opportunities in Follicular Lymphoma

Hans-Guido Wendel, MD

Follicular lymphoma (FL) is the most common form of indolent non-Hodgkin lymphoma (NHL), with 18,300 new cases diagnosed per year in the United States. FL is not curable by chemotherapy and is characterized by continuous relapses and disease progression. Genetically, FLs are characterized by the t(14;18) that deregulates Bcl2, and additional genetic events are required for lymphoma development and progression. The identity of the oncogenic drivers in FL is not established. FL is clearly a significant health concern; however this cancer has been somewhat neglected scientifically. We have developed a new murine model of FL and established reagents and collaborations that put us in a unique position to conduct the proposed studies.

Somatic Genetic Alterations in the Pathogenesis and Therapy of Histiocytic Disorders

Omar Abdel-Wahab, MD

The histiocytic disorders are a collection of diseases characterized by an accumulation of white blood cells called macrophages or dendritic cells in various tissues throughout the body. These diseases present with a wide array of clinical manifestations and have a variety of subtypes based on the microscopic appearance of white blood cells. Because of the rarity of each individual subtype of histiocytic disease and their very heterogeneous clinical presentations, the clinical experience and biologic understanding of many of these diseases has been limited. A major breakthrough in the

biology and therapy of these disorders came with a recent discovery that 40 to 50 percent of patients with the most common histiocytic disorders have mutations in the oncogene BRAF. Based on this finding, we organized a group of physicians and scientists at MSK who are committed to identifying the genetic abnormalities underlying histiocytic disorders and treating these patients as part of monitored clinical trials using approaches targeting these genetic alterations. Thus far we have made great progress in the treatment of BRAF-mutant histiocyte patients with the mutant BRAF inhibitor vemurafenib (Zelboraf®) and found new genetic alterations, which are promising targets for novel therapies for additional histiocytic disorder patients.

SHARED RESOURCES AWARD

Beckman Coulter SPRIworks HT Fragment Library System

Adriana Heguy, PhD

Next-generation deep sequencing of human tumors is revolutionizing the cancer genomics field by facilitating the correlation of genomics data with clinical data, which aims to inform diagnosis and risk stratification, and ultimately result in individualized treatment. Regardless of the platform used, libraries of template genomic DNA, cDNA, or amplicons have to be prepared prior to sequencing. The manual preparation and quality control of libraries is labor intensive and is the main bottleneck in the efficient production of sequence data. The use of automation will reduce the time burden for technicians, eliminate human error, and increase the volume and efficiency of library construction. We have received a Shared Equipment Grant to purchase the Beckman Coulter SPRIworks HT Fragment Library System. This instrument comes with a validated suite of methods for the various library construction steps, and its software is flexible, permitting, for example, the creation of new methods for target enrichment. The purchase of this equipment will benefit many departments and investigators across MSK.

2013

Generation of Personalized Models of Prostate Cancer for Correlates of Disease Response and Progression

Yu Chen, MD, PhD

Cancer cells growing in the laboratory are extensively used to study tumorigenesis and therapy. Prostate cancer cells are uniquely difficult to grow in the laboratory, hampering the ability of researchers to study the mechanisms of disease and drug resistance. Using newly developed methods to grow prostate cancer cells that are directly derived from patient biopsies, we propose establishing a panel of lines from patients entering clinical trials in prostate cancer. We will characterize these lines for genetic mutations and drug sensitivity to study the genetic basis of tumor growth and drug resistance.

Bispecific Antibody to Engage T Cells for Cancer Therapy

Nai-Kong Cheung, MD, PhD

T lymphocytes are ferocious killers. They kill serially, and while killing, they multiply, setting up killer colonies at the sites where they encounter tumor cells. Unfortunately, many tumor cells, including neuroblastoma, are immune to these killer T cells. Bispecific antibodies (BsAb) are engineered to carry the binding sites of two different antibodies — one site is to bind to T cells; the other is to handcuff T cells to the tumors. Now T cells can do what they are trained to do: be killing machines. With BsAb, tumors can no longer escape the immune system. First, the expression of antigens called HLA on tumors is no longer required. Moreover, nearly all T cells can be recruited, and they no longer need to be prior educated, or “primed,” to the tumor. Early studies in leukemia and lymphoma have shown dramatic positive clinical results. In this proposal, a BsAb to retarget T cells to the ganglioside GD2 on human tumors will be developed into a clinical drug and be made ready for first-in-human clinical trial. Since GD2 is present on many pediatric tumors — including neuroblastoma, osteosarcoma, the Ewing family of tumors, and rhabdomyosarcoma — this drug will be

useful for some of these difficult-to-cure childhood cancers. If it is proven safe and effective, this BsAb may have broad application to adult cancers with GD2 present, such as small cell lung cancer, melanoma, and brain tumors.

Clinically Targeting ETV1 in Advanced Gastrointestinal Stromal Tumor (GIST)

Ping Chi, MD, PhD

Gastrointestinal stromal tumor (GIST) is characterized by activating mutations in the KIT or PDGFRA receptor tyrosine kinases. Despite the clinical success of imatinib (Gleevec®), nearly all advanced GIST patients develop imatinib resistance and eventually die of their disease. We have recently discovered that ETV1 — an ETS family transcription factor and a well-established oncogene involved in recurrent genomic alterations in prostate cancer, Ewing sarcoma, and melanoma — plays a critical role and cooperates with mutant KIT/PDGFR in GIST pathogenesis. Here, we propose examining a novel therapeutic strategy that simultaneously targets both the mutant KIT/PDGFR and ETV1 in preclinical murine GIST models and in a phase Ib/II clinical trial in advanced GIST patients. We will examine the efficacy and imatinib/MEK inhibitor resistance mechanisms of this dual-targeting strategy and develop predictive therapeutic biomarkers using biospecimens derived from the murine models and the clinical trial. We believe that this strategy, if successful, has the potential to change the landscape of clinical practice in GIST management and has important therapeutic implications in other ETV1-dependent malignancies.

Inactivation of Neogenin in Castration-Resistant Prostate Cancer

Filippo Giancotti, MD, PhD

Once prostate cancer has become refractory to antiandrogen therapy and metastatic, it cannot be effectively cured. The molecular pathways underlying prostate cancer progression to this advanced stage are incompletely understood. We have observed that the cell adhesion receptor neogenin is inactivated in a fraction of hormone-refractory

prostate tumors. We propose to elucidate the molecular mechanisms by which loss of neogenin induces prostate cancer progression and metastasis, and to examine whether these mechanisms operate in human prostate cancer. The results of these studies may lead to the identification of novel targets for the therapy of AR-independent prostate cancer.

Quantitative Approaches for the Mechanistic Analysis of Tumor Cell Killing by Cytotoxic Lymphocytes

Morgan Huse, PhD

Cytotoxic T lymphocytes (CTLs) fight cancer by recognizing and destroying tumor cells. This proposal describes experiments aimed at learning how CTLs carry out this killing process. The information gained from our study will aid in the development of strategies to use CTLs for antitumor immunotherapy.

Combined JAK2/HSP90 Inhibition in Primary Myelofibrosis, Postessential Thrombocythemia Myelofibrosis, and Postpolycythemia Vera Myelofibrosis

Raajit Rampal, MD, PhD

The Philadelphia chromosome (Ph)-negative myeloproliferative neoplasms (MPNs) include myelofibrosis (MF), polycythemia vera (PV), and essential thrombocythemia (ET). Mutations in the JAK2 gene occur in the majority of MPN patients, which has led to efforts to target this mutation with JAK2 inhibitors. The JAK1/2 inhibitor ruxolitinib (Jakafi®) has been approved for the treatment of MF. While JAK inhibitor therapy relieves symptoms in the majority of MF patients, there is no evidence that these inhibitors can induce remission of the disease. Thus, other agents are needed that can target JAK2. Hsp90 is a protein chaperone that stabilizes JAK2. We previously demonstrated that JAK2 associates with Hsp90, and that inhibition of Hsp90 leads to degradation of JAK2. Our preliminary studies suggest that combined Hsp90/JAK2 inhibition results in more potent JAK2 inhibition. We therefore seek to determine the effect of combined Hsp90 and JAK2 inhibition in

preclinical studies and in MPN patients, with the goal of improving the outcome of patients with MPNs.

TFIH Complex Somatic Mutations as Biomarkers of Platinum Chemotherapy Sensitivity

Jonathan Rosenberg, MD

While platinum-chemotherapy has been long used in oncology, most patients do not derive dramatic benefits. Newly identified DNA repair gene mutations in urothelial carcinoma appear to be associated with high levels of sensitivity to cisplatin chemotherapy in muscle-invasive urothelial tumors. This project will determine whether these findings predict response to platinum chemotherapy drugs in metastatic urothelial carcinoma and begin to explore whether these or similar mutations in other cancer types predict platinum treatment responses. In addition, laboratory investigations will explore the molecular underpinnings of these findings. The ultimate goal of this project is to determine whether these mutations can be used to predict which tumors will respond to platinum chemotherapy, allowing better selection of patients for chemotherapy treatment.

Functional Consequences and Therapeutic Implications of RAF-dimer Signaling in Cancer

Neal Rosen, MD, PhD

Activation of the ERK signaling pathway occurs in at least half of human cancers and is controlled by a protein called RAF. RAF can exist as a single protein (monomer) or a pair of proteins bound together (dimer); in most tumors, activation occurs via dimers. Inhibitors of RAF monomers have been developed that have remarkable clinical activity in melanoma, but no inhibitors of RAF dimers currently exist. We have now identified the first known inhibitor of RAF dimers and found that it inhibits some tumors that are driven by this protein. Our grant is focused on understanding how this compound works, using this information to make better drugs, and developing these drugs as cancer therapeutics.

Investigating the Role of Transcription Factor Zbtb32 in the NK Cell Response against Tumor Establishment and Metastasis

Joseph Sun, PhD

Natural killer (NK) cells recognize and destroy transformed host cells in a process termed tumor immunosurveillance. Humans lacking NK cells or NK cell function have severe health complications due to certain cancers and viral infections. The general goals of my research program are to understand the molecular mechanisms behind NK cell responses against cancer and infectious pathogens. Because the transcription factor Zbtb32 is critical for NK cell activation and proliferation, we will investigate the role of Zbtb32 in the generation of a robust immune response against tumor establishment and metastasis. The studies in this proposal will uncover the biological pathways mediated by Zbtb32 and provide a framework for manipulating powerful NK cell responses in the clinic to target cancer.

Theranostics of Neuroendocrine Tumors with Somatostatin Antagonists

Wolfgang Weber, MD

The goal of this study is to develop a new therapy for neuroendocrine tumors (a group of tumors that can arise from hormone-producing cells throughout the body). The therapy is based on a novel class of molecules (somatostatin receptor antagonists) that can selectively deliver radiation to these tumors. The study will evaluate how much radiation can be delivered safely in patients and how well tumors respond to this therapy.

SHARED RESOURCES AWARDS

Antitumor Assessment Core

Elisa DeStanchina, PhD

To initiate first-in-human clinical trials, the US Food and Drug Administration requires that animal safety studies be conducted in accordance with federal regulations for good laboratory practices (GLP). In the past five years alone, MSK investigators have developed more than 20 investigational new drugs (INDs), including biologics,

radiopharmaceuticals, and small molecule drugs, which have been cleared by the FDA for clinical trials at MSK The Antitumor Assessment Facility conducted IND-enabling safety studies for more than half of these studies in a GLP-like manner. However, similar future studies will have to be conducted under strict GLP conditions. Currently, no facility exists for conducting GLP-compliant studies at MSK; therefore, the only option available for investigators developing novel agents is to contract GLP safety studies to an outside vendor (CRO). Drug development efforts with CROs are extremely costly, frequently delayed, and often suffer difficulties in method development, technology transfer, and the initial characterization of novel agents. Thus, to maintain a competitive translational research program, MSK needs to develop internal resources to conduct GLP studies in a more cost- and time-effective way. The proposed resource will enable investigators to conduct GLP-compliant animal safety studies on-site at MSK, thereby streamlining preclinical development and reducing costs.

Computational Biology

Gunnar Ratsch, PhD

The rapid increase in speed and decrease in cost of DNA sequencing have started a revolution in genomics. While data generation is now quick and cost-effective, data transfer and storage issues currently prevent the effective use of many new data-sequencing resources. At present, researchers may lose precious time, bandwidth, and disk space by downloading and storing large-scale and commonly utilized data resources. The establishment of a one petabyte (1,000,000 gigabytes) local data storage server will solve these issues for many MSK investigators across departments by providing fast and convenient access to insight-enabling data. The resources we have targeted include the Cancer Genome Atlas, ENCODE, the 1000 Genomes Project, the Human Microbiome Project, and others.

2014

Exome Sequencing to Identify Genetic Predictors of Response to Anti-PD-1 Therapy in Patients with NSCLCs

Matthew Hellmann, MD

Immunotherapies, medicines that stimulate the body's immune system to better recognize and attack cancers, have recently shown great promise as a new treatment for patients with lung cancers. We hypothesize that the degree and type of genetic change (called mutations) in lung cancer is important for predicting and understanding which patients are most likely to benefit from immunotherapies. Using state-of-the-art genetic sequencing technology and new computational methods developed by our team at MSK, we will study tumors from patients with lung cancer to examine how mutations in cancers can be used to predict response to immunotherapies. We believe this work can lead to direct benefits to patients, by being able to identify which patients are most likely to benefit from immunotherapies, and can lead to the development of better and more personalized immunotherapies in the future.

Use of Human Pancreatic Precursor Cells to Explore the Cellular Changes Associated with the Development of Pancreatic Malignancy

Alan Hall, PhD

Pancreatic cancer is the fourth most common cause of cancer death in the United States. Mutations in K-Ras are known to be present in 90 percent of these cancers, and yet it has proven extremely difficult to target this oncogene and treat the disease. We propose to generate pancreatic cells from human embryonic stem cells and explore the effects of introducing the K-Ras oncogene on their behavior in culture. We hope to uncover a new understanding in the development of this devastating disease.

Differentiation and Function of Tumor-Associated Macrophages

Ming Li, PhD

Tumors are complex tissues that progress through the exploitation of a

supportive environment, including the immune system. In this program, we will study how a new type of tumor-infiltrating immune cell is induced and coerced to promote tumor growth. Our goal of this research is to target these cells for novel cancer immunotherapy.

Single-Cell Multiparametric Analysis of Lymphocyte Signaling in Health and Disease Using CyTOF

Gregoire Altan-Bonnet, PhD

B cell lymphoma is the result of abnormal proliferation and apoptosis, as well as in the in vivo maintenance of a neoplastic clone within the peripheral B cell compartment. A key driver mechanism for oncogenic transformation in lymphoma is the dysregulation of the B cell receptor-mediated signaling machinery and its synergy with other pathways (e.g., Bcl-2 and antiapoptosis). The Altan-Bonnet and Wendell labs are collaborating to characterize quantitatively such dysregulation by developing genetic mouse models of B cell lymphoma, and probing their signal transduction using single-cell phosphor profiling with mass cytometry and mathematical modeling.

Hedgehog Acyltransferase as a Target in Breast and Lung Cancers

Marilyn Resh, PhD

The project focuses on cancer pathways driven by hedgehog acyltransferase (Hhat). Hhat attaches an essential fatty acid onto a hedgehog, a protein that is aberrantly expressed in human cancers. The Resh lab has developed Hhat inhibitors and aims to use these drugs as tools to block the growth of breast and lung cancer tumors.

Unraveling Resistance to PI3K p110 Inhibitors in Breast Cancer

Mauri Scaltriti, PhD

Activating mutations of the PI3K pathway are present in up to 40 percent of breast cancer. Many of these tumors respond to specific PI3K inhibitors, but the emergence of drug resistance inevitably occurs. In this proposal, we aim to investigate the mechanisms of resistance to these agents in patients with breast cancer.

Non-Cell-Autonomous Rewiring of Mitosis by the Tumor Microenvironment

Emily Foley, PhD

Cancer cells proliferate in the midst of a complex environment composed of numerous other cell types. These neighbors have influential roles in cancer development and metastasis, and are expected to play a role in how chemotherapeutic drugs kill cancer cells. The goal of this proposal is to identify how a tumor cell's environment impacts the response to anticancer drugs, like paclitaxel (Abraxane®, Onxol®), which are commonly used in chemotherapy.

A CRISPR-Based Approach to Generate Chromosomal Rearrangements In Vivo

Andrea Ventura, MD, PhD

The main goal of this research proposal is to develop a novel strategy to engineer chromosomal rearrangements in vivo using somatic genome editing. The underlying idea is that by inducing two simultaneous double-stranded breaks at specific chromosomal locations, it should be possible to engineer a wide array of chromosomal rearrangements, including inversions, deletions, and reciprocal translocations.

NF2-Hippo in RAS-Driven cancers

James Fagin, MD

The goals of this project are to test whether the Merlin-Hippo axis promotes transformation in part through the activation of mutant Ras gene transcription in other RAS-driven tumor lineages to determine the role of upstream effectors of the Hippo pathway on thyroid and pancreatic RAS-induced tumorigenesis in vivo, and to test whether pharmacological interference with the YAP-TEAD transcriptional complex will attenuate the phenotype.

BRCA Pathway Defects in Sporadic Breast Cancer

Simon Powell, MD, PhD

The major goal of this project is to define the nature of homologous recombination (HR) deficiency in breast cancers, and potentially in other cancer types in the future. Genomic

landscape assays (genomic scars) have been developed by both Myriad Genetics and other academic groups to provide a readout of homologous recombination repair. Chromosomal breaks and chromatid breaks are responsible for the initiation of these landscape changes, which can arise from HR deficiency, but these changes can also occur from other sources of genomic instability

Dissecting the Mechanism of DDR Signaling: Mining the Nbs1/Mre11 Interface

John Petrini, PhD

With the support of the Geoffrey Beene Cancer Research Center, we will use state-of-the-art genetic tools to understand the mechanism by which cells sound the alarm when chromosomes are damaged. This alarm sets in motion an array of processes that help cells survive and repair damage to chromosomes. The detailed information we gather in this effort will ultimately allow us design tools to disable the alarm in cancer cells, making them more vulnerable to DNA damaging therapies, such as radiation and chemotherapy.

Noninvasive Detection of Glutamate Pool Metabolism Using Hyperpolarized MRI

Kayvan Keshari, PhD

Metabolic reprogramming can be observed in the change in substrate uptake and utilization of cancer cells. Glutamine and the subsequent glutamate that is metabolized in the cell can provide a source of both carbon and nitrogen for proliferating cells to meet their growing needs. Until recently, it was difficult to noninvasively image these changes in cancer cell metabolism as well as the flux through different pathways. To address this, we propose developing molecules using hyperpolarized MRI to interrogate these pathways and extend them to a better understanding of tumor metabolism in vivo.

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gene transcription in other RAS-driven tumor lineages to determine the role of upstream effectors of the Hippo pathway on thyroid and pancreatic RAS-induced tumorigenesis in vivo, and to test whether pharmacological interference with the YAP-TEAD transcriptional complex will attenuate the phenotype.

SHARED RESOURCES AWARDS

Automated High-Throughput DNA Extraction Facility Dedicated to Research Studies

Rajmohan Murali, MBBS, MD, FRCPA

Dr. Murali would like to establish an automated, research-dedicated DNA extraction facility that will be operated by the Pathology Core. The facility will be shared by all investigators at MSK whose projects require DNA extraction from tissue and blood. Automation will be crucial to support the high-bandwidth and volume demands of next-generation assays.

A Validated Laboratory Information System for Integrated Management of Preclinical Projects

Elisa DeStanchina, PhD

The resource requested in this application is a validated preclinical laboratory information system, which consists of computers, network servers, software licenses, and crucially, a US Food and Drug Administration-compliant validation package for GLP studies. The system will capture, analyze, and link drug-testing data from multiple instruments and locations, improving collaboration and streamlining interdisciplinary studies at all levels of research and preclinical development within the center.

2015

Role of the Cohesin Complex in Leukemic Transformation

Ross Levine, MD

Programmed cell death plays important roles in normal biology, and its deregulation impacts various human diseases, including cancer. Recent progress has established that in addition to apoptosis (which is the best-established mode of programmed cell death), there are also other forms of

programmed cell death. Ferroptosis is a newly emerged programmed necrosis process that is implicated in various biological and pathological conditions. The overall goal of this proposal is to investigate the mechanisms of ferroptosis and its potential involvement in cancer and cancer treatment, which are poorly understood currently.

Dissecting the Role of Cancer Metabolism on the Tumor Microenvironment

Joao Xavier, PhD

Although metabolic alterations and interactions with stromal cells are both considered hallmarks of cancer, cancer metabolism and the tumor microenvironment remain separate areas of research. This project investigates the intricate link between cancer metabolism and microenvironment. We combine computational models with experiments to determine how the extracellular metabolites produced by cancer cells alter the phenotypes of tumor-associated macrophages, which then impact tumor development, progression, and metastasis.

Targeting the Oncogenic eIF4A RNAhelicase in Cancer

Hans Guido Wendel, MD

We discovered that an RNA unwinding enzyme called eIF4A is a new and exciting drug target in leukemia and potentially other cancers. The natural product silvestrol is a selective inhibitor of eIF4A. However, the compound is purified from the *Aglaia silvestris* plant in Malaysia in small quantities and is not suitable as a clinical drug. Together with MSK chemist Derek Tan, we will develop synthetic analogues of silvestrol and ensure that they retain the anticancer activity and specificity of silvestrol. The goal is to develop compounds that can lead to new clinical drugs against this exciting target.

Modulators of BRCA1 and BRCA2 Function

Maria Jasin, PhD

By providing a mechanism for cells to acquire mutations in tumor-relevant genes, ongoing genomic instability promotes tumor initiation, progression, and metastasis. Not surprisingly then,

many tumor suppressors, including the breast and ovarian susceptibility genes *BRCA1* and *BRCA2*, are DNA repair genes. Our aim in this grant is to investigate potential modulators of *BRCA2* function that may be important for tumor suppression.

Identifying Suppressors of Tet Mutation in Development and Disease

Mary Goll, PhD

The ten-eleven translocation protein TET2 is one of the most commonly mutated genes in myeloid leukemias. Mechanistically, TET proteins are important for removing methyl groups from DNA. Mutation of TET enzymes can lead to aberrant accumulation of DNA methylation, which can interfere with normal gene expression and promote abnormal cell states. The goal of this project is to use the hematopoietic system of the zebrafish embryo as a model system to identify chemical and genetic alterations that promote normal gene expression in cells that are compromised for TET activity.

Modeling Pancreatic Ductal Adenocarcinoma through Gene Editing in Human Embryonic Stem Cells

Danwei Huangfu, PhD

Pancreatic ductal adenocarcinoma (PDAC) is one of the most deadly cancers, largely because of delayed diagnosis. We propose modeling pancreatic cancer using human embryonic stem cells (hESCs) based on our ability to perform sophisticated genetics in hESCs and to generate pancreatic cells from hESCs through directed differentiation. We will model early preinvasive lesions, known as PanINs, to better understand the cancer cells of origin and to further study the genetic regulators of the transition from early PanINs to PDAC.

Uncovering the Role of SYNCYRIP in Myeloid Leukemia Stem Cells

Michael Kharas, PhD

Our proposal will utilize novel mouse models to understand the role of SYNCYRIP in normal and malignant hematopoietic cells. Our second aim will dissect how SYNCYRIP modulates critical transcription factors associated

with myeloid leukemia. Overall, these studies will provide evidence that SYNCYRIP is required for human leukemia and uncover mechanisms of leukemogenesis, providing a novel therapeutic strategy in leukemia.

Ferroptotic Cell Death, Mechanisms and Role in Cancer

Xuegun Jiang, PhD

Programmed cell death plays important roles in normal biology, and its deregulation impacts various human diseases, including cancer. Recent progress has established that in addition to apoptosis (which is the best-established mode of programmed cell death), there are also other forms of programmed cell death. Ferroptosis is a newly emerged programmed necrosis process that is implicated in various biological and pathological conditions. The overall goal of this proposal is to investigate the mechanisms of ferroptosis and its potential involvement in cancer and cancer treatment, which are poorly understood currently.

The Role of Aneuploidy in Tumor Development

Robert Benezra, PhD

Whole chromosome losses have been known to be a hallmark of tumor aggressiveness for over a century, but whether they are a cause or consequence of tumor proliferation and spread is still poorly understood. We have devised a genetic strategy to induce the loss of individual chromosomes and have found that, in both mouse and human cells, the loss of four individual chromosomes in each case leads to reduced fitness in cell culture but dramatically enhanced ability to form tumors in mice. With the help of the Beene Foundation, we will now try to understand the molecular mechanisms underlying this enhanced tumorigenic potential, with the ultimate goal of identifying novel targets for therapeutic intervention.

Mitotic Stress Response and Cancer

Meng Fu Bryan Tsou, PhD

Drugs that target cell division have been widely used for cancer chemotherapy, but the underlying mechanism is not clear. We have

developed novel reagents and approaches to fully understand how cells sense and respond to cellular dysfunction or stresses that occur specifically during cell division.

Molecular Characterization and Novel Therapeutics in Malignant Peripheral Nerve Sheath Tumor (MPNST)

Ping Chi, MD, PhD

Malignant peripheral nerve sheath tumors (MPNSTs) arising from the cellular component of the peripheral nerves represent a group of highly aggressive soft tissue sarcomas with limited treatment options. They can occur in the setting of type I neurofibromatosis (NF1-associated), sporadically, or in association with prior radiotherapy (RT-associated). Using comprehensive genomic approaches, we and others have recently discovered that the majority of MPNSTs have an inactivation of three tumor suppressor pathways, including NF1, CDKN2A (INK4A/ARF), and polycomb repressive complex 2 (PRC2). Here, we propose to use multidisciplinary and integrative approaches to dissect the transcriptional dysregulation mediated by PRC2 pathway loss in MPNST pathogenesis, to examine the influence of PRC2 loss on the tumor microenvironment, and to explore the therapeutic vulnerability of PRC2 loss in MPNSTs, with the goal of clinical translation of novel therapeutic developments for this difficult disease.

2016

A Novel Approach for the Identification of MicroRNA Targets In Vivo

Andrea Ventura, MD, PhD

The goal of this proposal is to overcome these limitations by developing a novel system for the unbiased identification of miRNA/mRNA interactions in a cell and tissue-specific manner in vivo. The new method we propose developing (Halo enhanced Ago2 pulldown) takes advantage of the recently developed Halo-Tag, a modified bacterial haloalkane dehalogenase designed to covalently bind a substrate that is not normally present in mammalian cells.

Mechanisms of PGBD5 Transposase-Induced Transformation of Rhabdoid Tumors

Alex Kentsis, MD, PhD

Specific aim 1: Define molecular mechanisms of PGBD5-induced DNA transposition and cell transformation using functional genomics and epigenomics. Mutation of regulatory DNA elements and dysregulation of gene expression are inherently linked to chromatin accessibility. Here, using inducible alleles of PGBD5 and functional genomic approaches, we will determine the targeting and DNA repair mechanisms that are required for PGBD5-induced transformation and establish its regulatory mechanism

Therapy-Related Myeloid Neoplasms: Characterization of Mutation Order and Clonal Dynamics in Response to Therapy during Disease Transformation

Elli Papaemmanuil, PhD

Aim 1: To study the molecular mechanisms leading to the development of therapy-related leukemia whilst on therapy for neuroblastoma in children. Aim 2: To evaluate the utility of gene-based molecular profiling in the clinical setting to support early diagnosis of therapy-related disease in patients treated for neuroblastoma.

Nucleosome Remodeling in DNA Damage Response

Jayanta Chaudhuri, PhD

DNA double-strand breaks (DSBs) constitute one of the most toxic cellular lesions, with a single unrepaired DSB potentiating cell death or tumor-initiating chromosomal translocations. Yet in B cells undergoing class switch recombination (CSR), DSBs are deliberately introduced into the immunoglobulin heavy chain locus by the DNA deaminase activation-induced cytidine deaminase. An efficient DNA damage response pathway rapidly senses and repairs the DSBs to complete CSR and preserve genomic integrity. While many of the DNA repair pathways operating during CSR have been elucidated, the role of nucleosomes in sheltering the genome from DNA damage and the requirement of nucleosome remodeling

in DDR are poorly understood. We have recently identified the ATPase CHD4 as a novel effector of CSR. In this proposal, we will assess the role of CHD4 in recruiting AID to DNA and determine its function in DNA repair in B cells.

Biologic and Clinical Characterization of ERCC2 Mutations in Urothelial Carcinoma

Gopakumar Iyer, MD

Cisplatin-based chemotherapy followed by the removal of the bladder is the current standard of care treatment for patients with muscle-invasive bladder cancer. Mutations of *ERCC2* have been identified as predicting for exquisite sensitivity to cisplatin in bladder cancer. This proposal seeks to characterize the biology of *ERCC2* alterations in bladder cancer and also to initiate a clinical trial of chemotherapy without the removal of the bladder in patients with *ERCC2*-mutant muscle-invasive bladder cancer.

In Situ Analysis of Glioma Core Signaling Pathways and Their Response to Therapy

Ingo Mellinghoff, MD

The overarching goal of our project is to develop an approach to quantify intratumoral heterogeneity and spatial tumor/microenvironment interactions at the single-cell level. This question is particularly relevant to high-grade glioma, which is histopathologically heterogeneous (glioblastoma “multiforme”) and remains one of the most treatment-refractory human cancers. Genomic studies in bulk tumor samples have identified core signaling pathways in glioma, but their functional and spatial relationship is unknown.

Define Molecular Network of DOT1L-Driven Leukemia via Noncanonical Methylation

Minkui Luo, PhD

DOT1L is the sole protein methyltransferase that methylates histone H3 lysine 79 (H3K79). Strongly supported by our preliminary data, we hypothesize that DOT1L-dependent H4K5 methylation facilitates transcription via two nonexclusive mechanisms. The overall impact of the proposal lies in the expectation of

uncovering the molecular mechanism of DOT1L-derived leukemia, the exploration of novel antileukemia strategies, and the ability to overcome emerging resistance of DOT1L inhibitors via combination therapy.

Structure, Function, and Inhibition of the Ras Methyltransferase ICMT

Stephen Long, PhD

The enzyme isoprenylcysteine carboxyl methyltransferase (ICMT) methylates the carboxyl-terminus of Ras and other CAAX proteins that have an isoprenoid (farnesyl or geranylgeranyl) lipid attached. Methylation increases the hydrophobicity of modified proteins and is important for their targeting to the plasma membrane and subsequent control of cell proliferation and differentiation. For this and other reasons, ICMT has gained attention as a potential cancer target. The aims of these studies are to study the molecular mechanisms of ICMT with regard to substrate access, substrate specificity, and catalysis, and to discover ways to inhibit the enzyme. Strong preliminary data, including an X-ray structure of ICMT that is in progress and our development of antibodylike inhibitors, support the objectives of the proposal. Completion of the aims would allow more-thorough evaluation of ICMT as a cancer target. Because relatively little is known about enzymes that catalyze reactions within lipid membranes, the mechanistic principles that we discover are likely to apply to other membrane enzymes.

Investigating the roles of a long noncoding RNA that regulates p53

Adam Schmitt, MD

The Schmitt lab has discovered a new, evolutionarily conserved long noncoding RNA (lncRNA) named DINO. It is required for the p53 response to DNA damage in humans and mice. DINO-depleted human and mouse cells have impaired p53-dependent gene regulation following DNA damage and cellular defects in DNA damage-induced cell-cycle arrest, apoptosis, and senescence. Furthermore, DINO^{-/-} mice are resistant to lethal total-body irradiation similar to p53-deficient animals, illustrating the important functional role of DINO to the p53 pathway. Surprisingly,

lncRNA DINO directly binds to the p53 protein in both human and mouse cells through a mechanism that remains to be elucidated, promoting p53 protein stability. This effectively increases the cellular pool of the p53 protein and promotes p53 recruitment to regulatory elements genome-wide. While these data point to an important role for DINO in the p53 pathway, DINO's role in tumor suppression and the molecular mechanism by which DINO regulates p53 remain to be identified.

Endogenous Fungi and the Development of Graft-Versus-Host Disease

Tobias Hohl, MD, PhD

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative therapy for patients with hematologic malignancies, though this treatment modality is limited by graft-versus-host (GvH) disease. Tissue-specific inflammation and alloreactive T cell responses underlie GvH pathogenesis. In this proposal, we examine the hypothesis that the composition and diversity of intestinal fungi can regulate intestinal inflammation and GvH during human and murine allo-HCT and that pharmacologic intervention can improve GvH outcomes.

SHARED RESOURCES AWARDS

Cancer Genomic Profiling for Precision Medicine

Zhirong Bao, PhD

We propose to acquire the RainDance RainDrop System Sense and Source instruments for the Center for Molecular Oncology to facilitate the development of plasma DNA-profiling assays that can be readily transferred to the DMP laboratory for clinical implementation as well as the further development of single-cell genomic profiling methodologies for research.

High-Resolution Living Imaging to Study Cell-Cell Interactions and Complex Tissue Formation

Zhirong Bao, PhD

With recent breakthroughs in fluorescence microscopy, high-resolution live imaging has become a powerful driving force in the study

of cells and complex tissues. Most notably, two modalities are at the cutting-edge of this revolution and are highly sought after. One is super-resolution microscopy, which allows imaging of molecular dynamics in live cells and tissues at sub-diffraction limited resolution. The other is light-sheet microscopy, which is particularly powerful for imaging developing tissues at subcellular resolution over an extended period due to its high speed and low phototoxicity.

2017

Elucidating ER Function in Hormone-Independent Breast Cancer

Sarat Chandarlapaty, MD, PhD

More than 70 percent of breast cancers are characterized by their dependence on the hormone estrogen for their growth and survival. Antiestrogens are highly beneficial in most patients with breast cancer, however, drug resistance frequently emerges over time. We have found that the estrogen receptor (ER) is still playing a critical role in such cancers despite the absence of estrogen stimulation. In this proposal, we will characterize the key partners and targets of such hormone-independent ER in order to identify new ways of treating these cancers after hormone resistance develops or to prevent hormone resistance in the first place.

Structure-Based Mechanistic Insights into CRISPR-Cas Pathways Impacting on Cancer Biology

Dinshaw Patel, PhD

Bacteria and archaea have developed RNA-guided adaptive defense systems to protect themselves against phage and viral invaders. These discoveries made initially in prokaryotes have been rapidly extended to eukaryotes, given that CRISPR-Cas represents a simple, flexible, and cost-effective way to precisely edit and manipulate the mammalian genome. Specifically, the nuclease Cas can be reprogrammed with synthetic RNAs to generate site-specific double-strand DNA breaks in mammalian cells. This powerful approach allows engineering in either precise changes to correct

genetic defects or chromosomal rearrangements that contribute to tumorigenesis, as well as develop genetically engineered mouse models of human cancer. These represent powerful tools for monitoring tumor initiation and progression and the identification of drivers of cancer metastasis.

SWI/SNF disruptions in Advanced Thyroid Tumors: Identification of Epigenome-Guided

James Fagin, MD

This project will explore how disruptions of individual components of the SWI/SNF chromatin remodeling complex, which are frequently mutated in advanced forms of thyroid cancer, lead to tumor progression and loss of differentiated properties in mouse models of the disease. The goal is to identify novel therapeutic vulnerabilities arising as a result of these changes.

Novel Embryonic Tumor Suppression Mechanism by NEPN via Direct Sequestering of Growth-Promoting Ligands and Indirect T Cell Activation in the Tumor Microenvironment

Kitai Kim, PhD

Expressing multiple tumor-causing genes in adult cells can induce tumor formation. During early-stage embryo development, multiple tumor-causing genes are highly expressed in embryonic cells to support the rapid growth of various tissues and

organs, but early-stage embryos rarely develop tumors. We hypothesize that the early embryo microenvironment contains antitumor factors and propose identifying these embryonic antitumor factors. Understanding their mechanisms may lead to the development of novel cancer therapies.

tRNA Splicing Enzymes as a Therapeutic Target for Fungal Infections in the Cancer Setting

Stewart Shuman, MD, PhD

Invasive fungal infections, especially Aspergillosis and Candidiasis, are a major cause of morbidity and mortality in people with cancer with prolonged neutropenia following chemotherapy or hematopoietic stem cell transplantation. The development of more effective treatments for these infections hinges on defining new targets for antifungal drug discovery and implementing screening to identify inhibitors. The goal of this project is to advance the case for two fungal tRNA-splicing enzymes, Trl1 and Tpt1, as antifungal targets by determining the atomic structures of the Aspergillus and Candida enzymes and their interactions with substrates, cofactors, and reaction intermediates.

Reconstructing the Evolutionary History of BRCA1-Associated Breast Cancer

Jorge Reis-Filho, MD, PhD

Inherited mutations in the BRCA1 gene are known to confer an increased risk of breast cancer. The mutations

acquired during life (i.e., somatic mutations) that are required for the development of BRCA1-associated breast cancer have yet to be fully characterized. It is currently unclear if complete loss of function of *BRCA1* is the initial step in the development of *BRCA1*-associated breast cancers or if other somatic mutations precede the complete inactivation of BRCA1. We will combine the analysis of clinical samples, single-cell sequencing techniques, and laboratory models of *BRCA1*-associated breast cancer to define the somatic mutations required for tumor development in the context of inherited *BRCA1* mutations and to determine if the order of such alterations influences the evolution of the tumor and its sensitivity to specific treatments.

SHARED RESOURCES AWARD

ITC as a Shared Instrument

Minkui Luo, PhD

The characterization of interactions between ligands and macromolecules has become a daily routine for many research laboratories at MSK. One specialized instrument with general applicability to quantify ligand-macromolecule interactions is isothermal titration calorimetry (ITC). ITC meets the broad needs of MSK laboratories for cancer research. The award allows purchasing a top-end ITC as a shared instrument among more than 20 laboratories.

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Sorted by year grant was given; publication date may differ.

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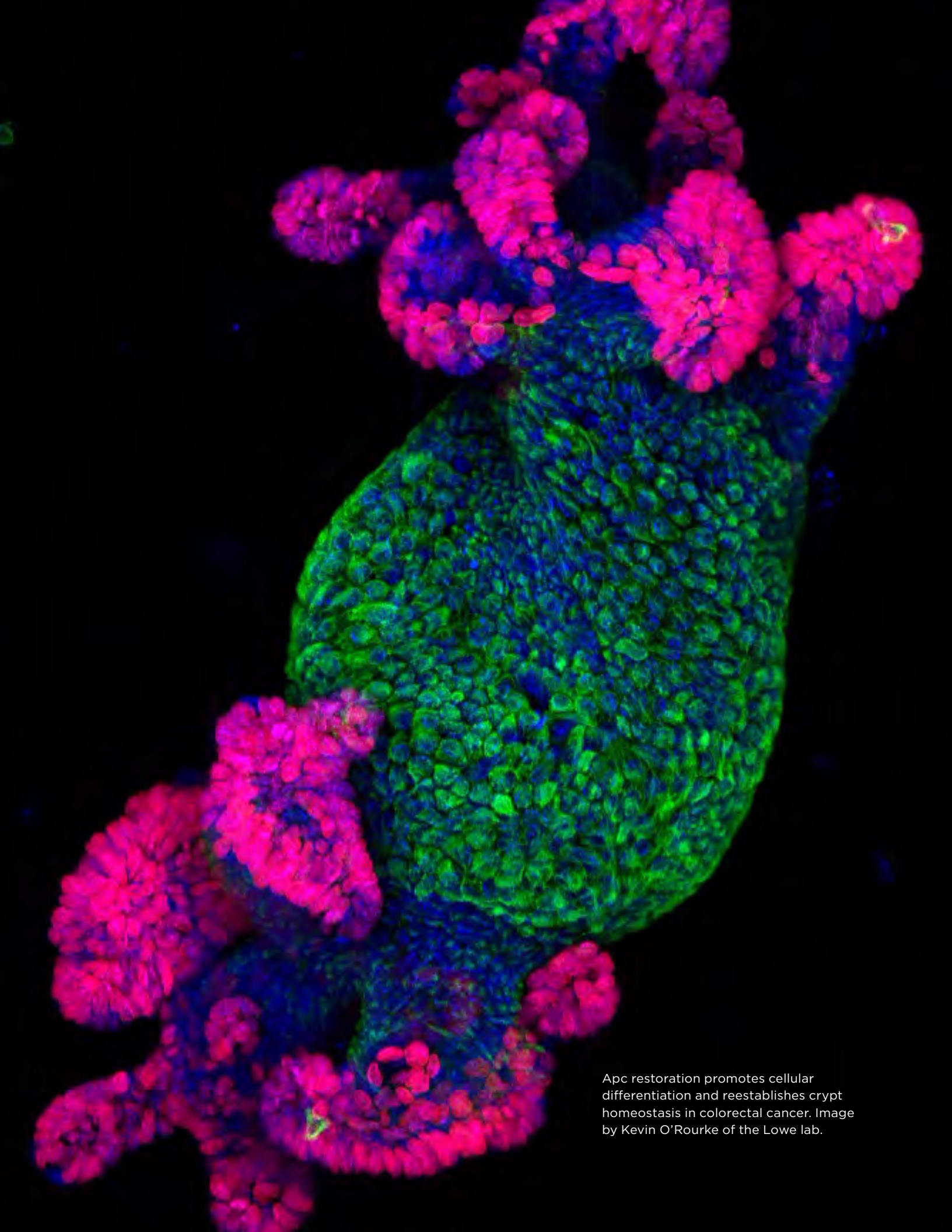
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Apc restoration promotes cellular differentiation and reestablishes crypt homeostasis in colorectal cancer. Image by Kevin O'Rourke of the Lowe lab.



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