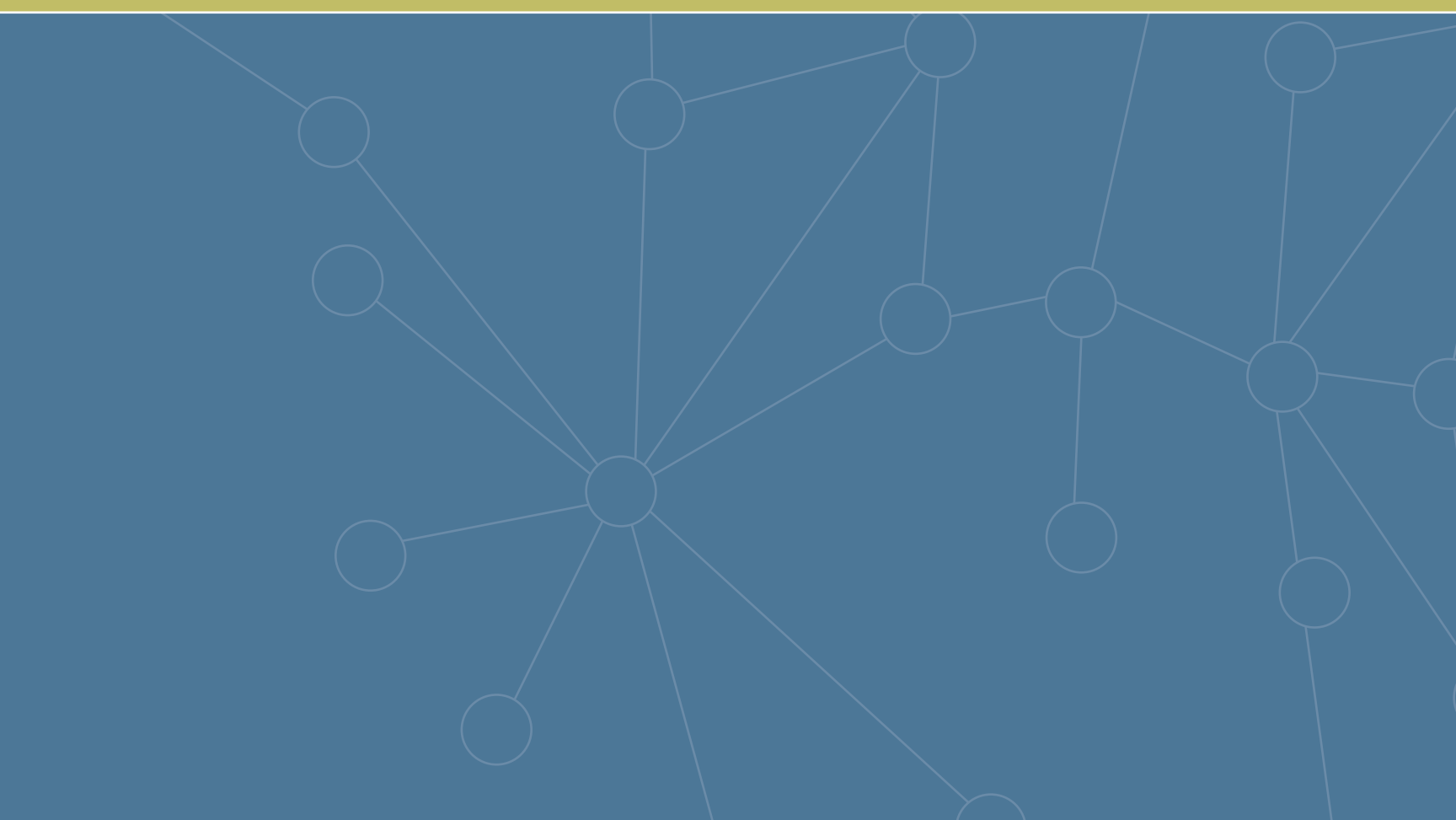


DANA-FARBER  
CANCER INSTITUTE

# DANA-FARBER CANCER INSTITUTE SCIENTIFIC REPORT 2009





ON THE COVER: PRIMARY BROWN PREADIPOCYTES GIVE RISE TO MUSCLE CELLS WHEN PRDM16 EXPRESSION IS KNOCKED DOWN. A culture of primary brown fat preadipocytes was treated with an siRNA vector targeting PRDM16. In these cultures, long, multinucleated, tube-like cells appeared that were strongly marked by green fluorescent protein (GFP), which was coexpressed from the vector. These GFP-expressing cells were stained with an antibody specific to the muscle-specific protein, myosin heavy chain, demonstrating that they were skeletal myocytes. These results suggest that brown fat precursors and skeletal muscle cells are derived from a common precursor and that PRDM16 restricts skeletal muscle gene expression and development. Staining: GFP (green), myosin heavy chain (red), and nuclei (blue).

# Message from the President of Dana-Farber Cancer Institute

Dear Friends and Colleagues:

It is a great pleasure to introduce you to the *Dana-Farber Cancer Institute Scientific Report 2009*. Since its inception, Dana-Farber has placed a unique emphasis on all forms of research relevant to the eradication of cancer while, at the same time, providing both cutting-edge and highly compassionate comprehensive cancer care. Indeed, the idea that research shall be at least half of everything we do at the Institute is part of Dana-Farber's own DNA. This underlying credo means that research is prominent in all of our strategic and daily decisions; it has also allowed us to have a far-reaching impact on all fields of cancer research that is disproportionate to our size.

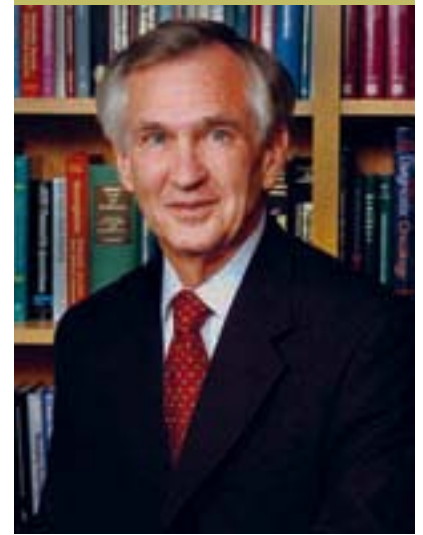
Today, we remain aggressive in our pursuit of discoveries relevant to cancer and their application to improve cancer outcomes, even as the economy has presented us with enormous challenges. It is therefore particularly gratifying to share with you the substantial research accomplishments made by our outstanding group of investigators. As is evidenced within these pages, their contributions span multiple fields of cancer research and provide insights that are both deep and broad. Their stories reflect the Institute's fidelity to the dream of its founder, Sidney Farber, MD, who believed that discoveries in the laboratory needed to be quickly and safely put to use to treat patients if advances were to be made.

We hope that this report captures the excitement we all feel in our investment in research, technology, innovation, and partnerships. Combined, they will enable us to continue to make special contributions to the worldwide campaign to conquer cancer.

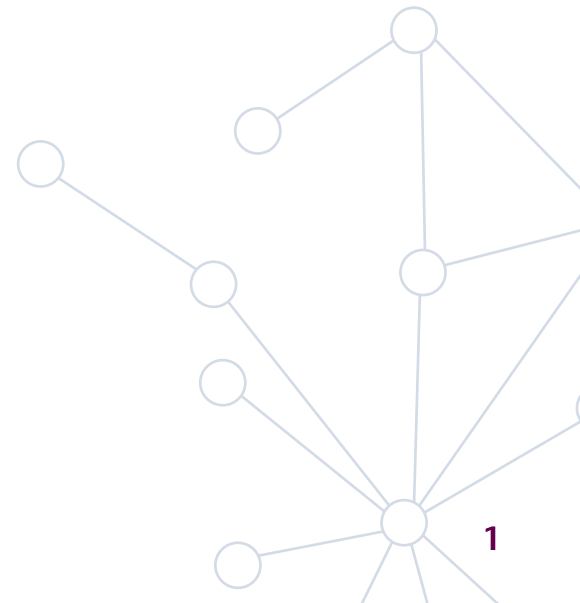
Sincerely,



Edward J. Benz Jr., MD



EDWARD J. BENZ JR., MD,  
PRESIDENT



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# What distinguishes Dana-Farber

At Dana-Farber Cancer Institute, basic, translational, clinical, and population sciences research are never far apart — physically or philosophically. It's a tradition that goes back to the Institute's founder, Sidney Farber, MD, who conceived of a facility where scientists in upper-floor laboratories would make discoveries that could be used in treating cancer patients in ground-floor clinics. Dr. Farber first saw his dream realized with the construction of the Jimmy Fund Building in 1951. The tradition continues today with the construction of Dana-Farber's new home for patient care and clinical research, the Yawkey Center for Cancer Care, which is being built next to the Richard A. and Susan F. Smith Research Laboratories. These buildings will be connected via enclosed bridges containing meeting areas to foster dynamic exchanges between physicians and scientists.

The proximity of these facilities means that, in the everyday process of going to and from work or visiting colleagues elsewhere in the Institute, wet and dry laboratory-based scientists routinely encounter the ultimate beneficiaries of their efforts — patients and their families. The interconnectedness of the scientific and clinical worlds at Dana-Farber is also reflected in the Institute's finances, where the amount spent on research is roughly equivalent to that spent on patient care.

Scientific work at Dana-Farber is based on the premise that basic and clinical investigation are complementary and reinforcing activities — and that drawing a strict demarcation between them creates a false distinction. Insights from one area invariably inform and invigorate the other. To encourage this cross-pollination of ideas, the Institute has developed an organizational framework that fosters collaborations among investigators from different disciplines.

The same attention to the underlying conditions that lead to outstanding research applies to the Institute's support of "pure science." Research undertaken to answer basic biological questions, while recognizing the inherent value of empirical efforts to expand knowledge, requires



an environment in which free, interest-fueled inquiry is encouraged. Dana-Farber's success in creating such an environment is reflected in the countless advances in the understanding of cellular and systemic processes that have occurred in its laboratories. The commitment to curiosity-driven research remains undiminished even as the Institute integrates basic, translational, clinical, and population sciences research into a well-functioning transmission system for scientific progress against cancer.

Dana-Farber's strategic investment in research is realized through creating a cadre of established scientific leaders and talented young investigators, acquiring technology at the leading edge of cancer research, encouraging collaboration among the faculty, providing resources in support of promising work, and ensuring a presiding spirit of innovation, which is the Institute's legacy. The result is an intense scientific impact on a group of diseases that continue to represent one of humanity's greatest health challenges.

What most distinguishes Dana-Farber's science, perhaps, is the preeminence of its investigators and the extent of their collaborations. The scientific community includes nationally recognized leaders in fields across the spectrum of cancer research, including Institute President Edward J. Benz Jr., MD, who serves as president of the Association of American Cancer Institutes. Among the faculty are editors of dozens of scientific journals and cancer textbooks, Howard Hughes Medical Institute investigators, officers of professional associations, and authors of some of the most often-cited research papers of the past decade. Others are scientific advisors to advocacy organizations, featured speakers at scientific conferences around the world, award-winning mentors, and elected members of professional organizations, including the National Academy of Sciences, the American Academy of Arts and Sciences, and the Institute of Medicine.

A key index of scientific stature is Dana-Farber's success in external peer-reviewed funding. In the past decade, the Institute's research revenue has grown by nearly 160 percent, to \$270 million. The Institute continues to



BARRETT ROLLINS, MD, PHD,  
CHIEF SCIENTIFIC OFFICER

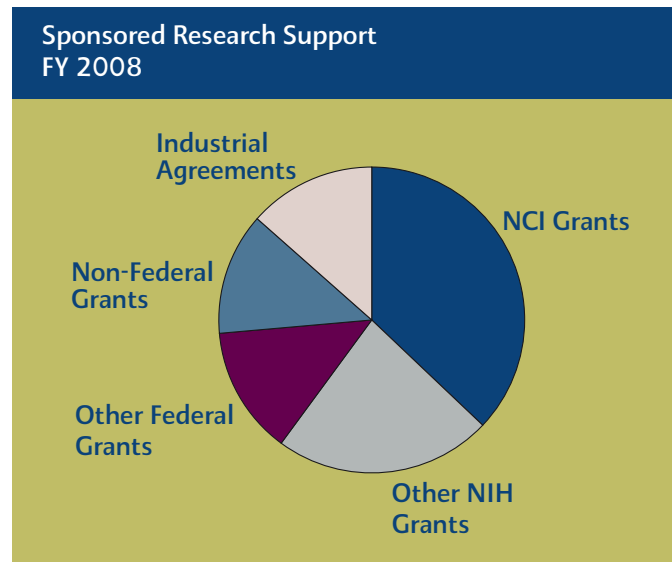
be one of the highest recipients of grant funding from the National Cancer Institute, an accomplishment that is particularly impressive considering its relatively small faculty base. Moreover, Dana-Farber scientists compete successfully for grants from such noted foundations as the Leukemia and Lymphoma Society, American Cancer Society, Bill and Melinda Gates Foundation, Susan G. Komen for the Cure, Doris Duke Charitable Foundation, Tisch Family Foundation, and Robert Wood Johnson Foundation.

Dana-Farber also has one of the largest cancer clinical trials programs in the country, with nearly 500 adult and pediatric therapeutic trials actively accruing patients. Importantly, more than one-quarter of these studies are investigator-initiated and one-third are Phase I or I/II, demonstrating our commitment to translate basic research findings to the clinic through proof-of-principle and early phase studies.

The achievements of our faculty are in part due to a special environment, where collaboration is intrinsic to the way Dana-Farber researchers work. Tangible evidence of this is the number of NIH Specialized Projects of Research Excellence (SPORE) grants — in breast cancer, multiple myeloma, lung cancer, prostate cancer, and gastrointestinal cancers, among others — and Program Project Grants awarded to Dana-Farber. It is the responsibility of the Institute’s Chief Scientific Officer Barrett J. Rollins, MD, PhD, to develop the tools and resources that Dana-Farber’s faculty need to realize their research vision, and to provide an environment that supports and rewards collaboration.

This invigorating environment is furthered through scientific partnerships with other research centers. The most significant of these is Dana-Farber/Harvard Cancer Center (DF/HCC), the largest NCI-designated Comprehensive Cancer Center in the country. DF/HCC

is comprised of more than 1,000 cancer researchers at Dana-Farber and six other Harvard-affiliated institutions who are working together with a singular goal — to find new and innovative ways to combat cancer. A related collaboration has been established between scientists at DF/HCC and the University of Massachusetts Boston (UMB). The UMB-DF/HCC Comprehensive Cancer Partnership Program enhances research in health disparities and improves research, training, and outreach opportunities for minority students, fellows, and scientists. In addition, Dana-Farber faculty access resources and scientific expertise in highly specialized fields through the Institute’s associations with the Harvard Stem Cell Institute, Harvard’s NIH Clinical and Translational Science Center, and the Broad Institute, a center of genomic research where several Dana-Farber faculty members have joint appointments. Established partnerships with pharmaceutical manufacturers have facilitated the development of new cancer drugs. Lastly, faculty enjoy the robust clinical care, clinical research, and training opportunities made possible through long-standing hospital alliances, including Dana-Farber/Children’s Hospital Cancer Care, Dana-Farber/Brigham and Women’s Cancer Center, and Dana-Farber/Partners CancerCare.



The forward-looking nature of research at Dana-Farber is embodied in the Institute’s commitment to developing the next generation of cancer science leaders. Dana-Farber faculty are recognized for their excellence in medical education, research training, and clinical training. At Harvard Medical School, Harvard School of Public Health, and Harvard College, our researchers teach graduate and undergraduate courses in basic biomedical and related sciences. They also serve as mentors for predoctoral and postdoctoral trainees at Harvard

and Harvard-affiliated institutions. Building upon a determination to increase the pipeline of future cancer researchers, the Institute supports training programs with high schools, colleges, and community groups that enable underserved students to work in Dana-Farber laboratories and begin their careers in science. Our adult and pediatric oncology fellowship programs, operated in conjunction with Children's Hospital Boston, Brigham and Women's Hospital, and Massachusetts General Hospital, are among the most sought-after opportunities for aspiring cancer physician-scientists. The combination of careful mentoring and encouragement of novel research projects has produced a corps of graduates who today are

principal investigators and institutional leaders at cancer centers around the world. This same blend of opportunity and guidance has spurred the careers of countless scientists who trained at Dana-Farber as postdoctoral fellows and graduate students.

Ultimately, Dana-Farber's support of the scientific enterprise is driven by strategic thinking and ground-level pragmatics. We have acquired the capabilities to answer the next generation of questions in cancer research. The unrivaled combination of resources and expertise available to Dana-Farber researchers ensures that the Institute will continue to lead for years to come.

## Supporting Dana-Farber's researchers

Today's researchers face many challenges, from competition for grant funding to work-life balance. Recognizing this, Dana-Farber's Office of Research seeks to continuously enhance its support services and capabilities. The office is directed by Beverly Ginsburg Cooper, MBA, senior vice president for research, and associate director of administration, Dana-Farber/Harvard Cancer Center. Ginsburg Cooper and Barrett Rollins, MD, PhD, Dana-Farber's chief scientific officer, work together to ensure that the Office anticipates and responds effectively to the needs of the Dana-Farber research community. Some of the key resources available to Dana-Farber faculty are highlighted below.

### GRANTS MANAGEMENT

The Office of Research helps investigators identify potential sources of funding through mechanisms such as a funding newsletter and web site, and by providing investigators with access to a subscription funding database. Investigators receive professional support in the preparation, submission, and management of grants through department-based Research Administration and the central Grants and Contracts Office. Dedicated grants management specialists in departments help faculty complete applications and prepare budgets. The Grants and Contracts Office reviews applications and completes the electronic submission process. Once funded, the Office of Research provides oversight to ensure that the overall grants program is compliant with federal policies, while staff help faculty manage their portfolio, providing regular status reports and projections while ensuring adherence with sponsor requirements.

### CLINICAL TRIALS SUPPORT

Dana-Farber has several well-established support offices that facilitate the conduct of clinical trials. The Clinical Trials Office, which assists faculty in preparing and gaining approval to conduct a trial, also helps in recruiting, training, and overseeing clinical research staff. The Office of Human Research Subjects provides regulatory guidance and resources to help investigators prepare protocols. It also supports the scientific review and IRB processes and helps ensure that all reviews and approvals have been completed prior to activation. The Quality Assurance Office for Clinical Trials is responsible for monitoring trials and conducting audits to ensure that appropriate standards for enrollment and data management are maintained. It also handles patient registration and the registration of trials required by external agencies. The Clinical Training and Education Office offers a wide variety of seminars and programs for clinical investigators and clinical research staff. Finally, the Clinical Trials Agreement and Budget Offices negotiate industry agreements on behalf of faculty.

### TECHNOLOGY TRANSFER AND NEW VENTURE DEVELOPMENT

Facilitating the translation of research discoveries into novel products for the detection and treatment of



BEVERLY R. GINSBURG  
COOPER, MBA, SENIOR VICE  
PRESIDENT FOR RESEARCH

cancer and related diseases is a top priority of the Office of Research. The Office of Research and Technology Ventures (ORTV) evaluates research discoveries for commercial potential and, with the Office of General Counsel, files patent applications covering promising inventions. A variety of strategies are employed to transfer Dana-Farber intellectual property to commercial entities, such as licensing to biopharmaceutical companies and facilitating the formation of start-up ventures. ORTV also facilitates the development of collaborations with pharmaceutical companies and provides advice to faculty on technology-transfer issues.

### **FACULTY DEVELOPMENT**

To help ensure that Dana-Farber's faculty thrive, the Office of Faculty Development responds to faculty needs in such areas as career development, work-life balance, and other topics that affect professional satisfaction and growth. The Gloria Spivak Faculty Advancement Fund provides awards to selected faculty who are at a critical juncture in balancing work and family demands. The Office sponsors career-enhancing seminars and new mentoring initiatives. Faculty committees provide feedback on the concerns of groups with specific needs.

### **ACADEMIC AFFAIRS**

The Office of Academic Affairs advises individual faculty on career growth issues and the promotion process. It provides guidance on activities that support the best opportunity for academic promotion, optimal timing for promotion, and preparation of promotion documents.

### **FACULTY ACTIVITIES**

The Office of Faculty Activities serves as a resource to faculty who wish to perform external professional activities. The office assesses proposed external arrangements, identifies potential conflicts of interest, and advises on how best to structure their arrangements to minimize such conflicts.

### **POSTDOCTORAL AND GRADUATE STUDENT AFFAIRS**

The education and support of postdoctoral fellows and graduate students is critical to Dana-Farber's mission. The Postdoctoral and Graduate Student Affairs Office creates a welcoming and supportive environment for postdoctoral fellows and graduate students. It supports trainees' professional development through programs on manuscript writing, grant writing, and laboratory

management, and provides professional editing services for papers, grants, and CVs. An annual retreat facilitates networking and provides a platform for fellows and students to showcase their research. A dedicated lounge is outfitted with computers, television, and information about educational programs, funding opportunities, and job and apartment listings.

### **SHARED RESOURCES AND SERVICE CENTERS**

Dana-Farber supports a wide array of shared resources and service centers.

**THE ANIMAL RESOURCES FACILITY** consists of a state-of-the-art animal housing environment for mice and rats, as well as on-site services, resources, and training needed by investigators to accomplish their animal research objectives.

**THE BIOHAZARD CONTAINMENT CORE** offers technical support in the preparation and propagation of viral stocks and cell lines, as well as phenotypic characterization of virus variants.

**THE BIOSPECIMEN REPOSITORY** provides long-term storage of clinical and research material in  $-80^{\circ}\text{C}$  and liquid nitrogen freezers, with full service pickup and delivery.

**THE BIostatISTICS CORE** provides expertise for the planning, conduct, analysis, reporting, and grant preparation of clinical, population-based, and laboratory research.

**THE CRITICAL ALARM MONITORING PROGRAM** notifies research labs when temperatures in critical freezers fall outside acceptable limits, preventing the loss of valuable material.

**THE CONNELL-O'REILLY CELL MANIPULATION CORE** offers cell processing for clinical research protocols and assists in developing and evaluating new cell-based therapies. Techniques employed include the processing of hematopoietic stem cells, preparation of tumor vaccines, and generation of T cells for adoptive immunotherapy.

**THE CLINICAL RESEARCH LABORATORY** processes, stores, and tracks pharmacokinetic, pharmacodynamic, and biomarker samples for therapeutic clinical trials.



MARK CURRY, IN THE  
FLOW CYTOMETRY CORE



**THE CONFOCAL AND LIGHT MICROSCOPY CORE** provides imaging microscopy technology, including standard fluorescence, live-cell long-term imaging, confocal, TIRF, FRET, and spectral imaging. The core also offers assistance in experimental design and optimal image collection.

**THE DATA TECHNOLOGIES CORE** provides expertise in data collection from study participants and in data management. Services include the development of online, mail, and in-person surveys, complex databases, cognitive interviewing, and focus groups.

**THE FLOW CYTOMETRY CORE** provides immunofluorescent sterile sorting, with up to nine-color simultaneous detection, and sample analysis with up to 12-color detection.

**THE HEALTH COMMUNICATION CORE** offers evidence-based communication expertise in intervention research and the recruitment and retention of patients for research studies. Services include focus groups, graphic design, writing, editing, web site design, consultation on materials, development of marketing plans, and facilitation of cancer prevention seminars.

**THE MEDICAL ARTS CORE** offers custom graphics and photography services for scientific publications and presentations, and training in the use of graphic design software.

**THE MICROARRAY CORE** provides services for genome-wide analysis of gene expression, nucleotide variation, copy number variation, and chromatin protein binding sites. Platforms include microarrays and “next generation” sequencing. Assistance with data analysis is available.

**THE MOLECULAR BIOLOGY CORE** offers automated DNA sequencing, genotyping, peptide synthesis, protein sequencing, amino acid analysis, BIAcore protein ligand assays, and mass spectrometry. DNA sequencing and genotyping services include synthesis and tracking of oligonucleotides, contig building, and publication to appropriate databases.

**THE MOLECULAR DIAGNOSTICS LABORATORY** provides microRNA expression profiling, human cell line identity verification, mutation detection for clinical research studies, and specimen processing for clinical research studies. Consultation on experimental design and data analysis is also available.

**THE MONOCLONAL ANTIBODY CORE** produces novel monoclonal antibodies for use in basic research, drug discovery, and clinical applications. Services range from cloning and scale-up of immunization antigens to purification of the resulting antibodies.

**THE RNAi SCREENING FACILITY** provides access to RNAi reagents and high-throughput screening technology. Lentiviral-based RNAi constructs against the human and mouse genomes are provided by the RNAi Consortium of the Broad Institute. The facility provides technical expertise on how to design, optimize, and perform cell-based, arrayed lentiviral RNAi screens. Lentiviral RNAi constructs against individual genes can be requested.

**THE TRANSGENIC/GENE TARGETING CORE** offers state-of-the-art instrumentation, as well as scientific and technical expertise in the area of transgenic and gene-targeted mouse models. The core provides the essential services, equipment, and reagents, and the scientific and technical expertise to generate and characterize such models.

# Translational Research



Dana-Farber is equally committed to scientific discovery and patient care. Our world-class scientists and clinical investigators work across disciplines, departments, and institutional boundaries to translate research findings into new diagnostics and therapeutics for patients. The cornerstone of translational research at Dana-Farber is collaboration: close interactions among basic scientists, computational biologists, chemists, clinical investigators, and others. The Institute also enjoys fruitful partnerships with pharmaceutical and biotechnology companies, which have the complementary resources needed to help transform promising compounds into drugs and biologics.

## Targeting the PI3 kinase pathway

Dana-Farber's interactive approach is exemplified by work on the PI3 kinase (PI3K) pathway, from the discovery of PI3K in the laboratory to clinical trials testing PI3K inhibitors in patients with cancer. Key nodes of the PI3 kinase intracellular signaling pathway are frequently mutated in cancer, particularly in solid tumors of the colon, breast, lung, and brain, as well as sarcomas. Since the 1980s when Thomas Roberts, PhD, co-chair of the Department of Cancer Biology, codiscovered PI3K, scientists have been hunting for a component of the kinase that could be targeted precisely — like Achilles' heel — to shut down unrestrained cell growth of PI3K-driven tumors.

Roberts and Jean Zhao, PhD, also of the Department of Cancer Biology, subsequently found such a target: a catalytic subunit of PI3K, termed p110 $\alpha$ , which is encoded by the *PIK3CA* gene. In their landmark study, Roberts and Zhao knocked out *PIK3CA* in mouse cells and discovered that the cells remained stubbornly resistant to oncogenic transformation, providing strong *in vitro* evidence that p110 $\alpha$  might represent a selective therapeutic target. They went on to show that formation of tumors arising from inactivation of the tumor suppressor PTEN was blocked by the knock-out of the *PIK3CB* gene encoding p110 $\beta$ , marking that protein as a potential drug target as well.

Expanding on this work, Kwok-Kin Wong, MD, PhD, of Medical Oncology at Dana-Farber, and colleagues from Massachusetts General Hospital investigated the role of *PIK3CA* mutations *in vivo* (see story, page 14). Wong genetically engineered mice to express in lung epithelia the p110 $\alpha$  activating mutation known as H1047R and then demonstrated that this

PICTURED ABOVE (FROM TOP):  
PHILIP KANTOFF, MD, CHIEF  
CLINICAL RESEARCH OFFICER,  
AND GEOFFREY SHAPIRO, MD, PHD,  
DIRECTOR, EARLY DRUG DEVELOPMENT  
CENTER

mutation is indeed causal. When Wong then treated the mice with a PI3K inhibitor developed by Novartis, the tumors regressed dramatically. Independently, Zhao obtained similar data for breast tumors driven by the oncogenic *PIK3CA* in vivo.

Dana-Farber now has four different PI3K-inhibiting drugs (two from Novartis, one each from Genentech and Exelixis) in clinical trials, with more on the way, says George Demetri, MD, whose laboratory colleagues in the Sarcoma Disease Center have demonstrated that PI3K pathway blockade is a promising therapeutic strategy for gastrointestinal stromal tumors that become resistant to imatinib (Gleevec) and sunitinib (Sutent). “Dana-Farber is one of the few places in the world with this number of PI3K inhibitors in actual patient trials,” remarks Demetri. “It reflects the commitment we’ve made to translational research, as well as the medical and scientific power we bring to collaborations with industry.”



JEAN ZHAO, PHD, AND THOMAS ROBERTS, PHD

## Identifying targets for therapy

Four projects illustrate the unique scientific capabilities of Dana-Farber and how we are accelerating the pace of translational research and bringing new hope to patients.

### TARGETING B-CELL RECEPTOR PATHWAYS IN DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphomas (DLBCLs) have similar features under the microscope, says physician-scientist



MARGARET SHIPP, MD

Margaret Shipp, MD, of the Department of Medical Oncology. But subtypes of the disease, which is the most common type of non-Hodgkin’s lymphoma (NHL), behave differently in response to treatment. Shipp suspected that identifying unique molecular signatures of these tumors might provide insight into their survival pathways. In previous research, her long-time collaborator, Stefano Monti, PhD, of the Broad Institute, had conducted gene expression profiles of DLBCL samples. In interpreting the data, they found a significant subset, named the BCR-type, with a distinctive signature: increased expression of components of the B-cell receptor (BCR) signaling pathway.

A key node in the pathway, spleen tyrosine kinase (SYK), relays signals downstream and plays a major role in low-level, or tonic, BCR signaling. Because SYK has been found to be crucial to survival, Shipp hypothesized that BCR-type tumors might depend on tonic BCR signaling and that a SYK inhibitor — which Rigel Pharmaceuticals had already developed and tested in clinical trials for another indication — might offer a new rational therapy. To find out, the Shipp group, led by Linfeng Chen, PhD, treated a panel of DLBCL cell lines and primary tumors

“Given Margaret’s elegant correlative laboratory data, we expected a subset of patients to respond based on their subtype,” says LaCasce.

with the SYK inhibitor and showed that it induced apoptosis by shutting down tonic BCR signaling. Moreover, the responsive cell lines and tumors were identified by transcriptional profiling as the BCR-type, which comprises up to 50 percent of all DLBCLs.

Within months of her preclinical work, Shipp partnered with Dana-Farber oncologist Ann LaCasce, MD, of the Department of Medical Oncology, and Rigel Pharmaceuticals to conduct the first clinical trial of an oral SYK inhibitor in patients with NHL. “Given Margaret’s elegant correlative laboratory data, we expected a subset of patients to respond based on their subtype,” says LaCasce, who oversaw the Dana-Farber patients on the Phase III multicenter trial. “The drug induced a response in 21 percent of patients with DLBCL — exciting results, considering that many of these patients had rapidly advancing disease,” says LaCasce. Shipp and pathology colleagues are now searching for biomarkers of BCR-dependent DLBCLs, which will help identify subtypes in real time and predict which patients will respond to this targeted therapy.

### TARGETING BRAF IN PEDIATRIC LOW-GRADE ASTROCYTOMAS

“Brain tumors have surpassed leukemias as the leading cause of cancer-related death in children,” says Charles Stiles, PhD, co-chair of the Department of Cancer Biology. The most common of these tumors are low-grade astrocytomas (LGAs). Some LGAs are curable with surgery and chemotherapy; others, however, arise within inoperable regions of the brain, and the side effects of cytotoxic drugs in growing children can be severe. In addition, LGAs frequently recur after surgery or drug treatment, and these tumors can be fatal. The Pediatric Low-Grade Astrocytoma Program (PLGA) at Dana-Farber seeks to find nontoxic targeted therapeutics. Stiles and Kieran, along with collaborators Keith Ligon, MD, PhD, and Levi Garraway, MD, PhD, both of the Department of Medical Oncology, have made major



CHARLES STILES, PHD (LEFT), AND MARK KIERAN, MD, PHD

progress. Recent studies from the PLGA Program and other laboratories identified two separate abnormalities in the *BRAF* oncogene, which together account for as many as 50 percent of pediatric LGAs. To help Stiles and Kieran analyze archival LGA tissue for *BRAF* abnormalities, Ligon and Garraway adapted genomic technologies to work with the paraffin-embedded samples that comprise the majority of LGAs. Ligon’s “paraffin-friendly” fluorescent in situ hybridization (FISH) assay detects the most common *BRAF* abnormality, while Garraway’s OncoMap (see story, page 21) finds the less common one. In addition, OncoMap can identify point mutations in the other 50 percent of LGAs that are genetically normal for *BRAF*. Investigators are now working to convert paraffin-based FISH and OncoMap assays into CLIA-certified tests, upon which clinical decisions can be made, says Stiles, who also plans to establish a nationwide *BRAF* mutation database for pediatric LGAs. “We want to identify the children with *BRAF* mutations, in the hope that targeted drugs will be available in a few years,” he says.

Since *BRAF* mutations in pediatric LGAs are identical to those found in a high percentage of adult malignant melanomas, data from ongoing Phase I studies of *BRAF* inhibitors in adults will greatly reduce the lead time to clinical trials in children, explains Stiles. “LGAs grow slowly, and even if they recur after initial treatment, the interval is measured in years,” he adds. “For some of these kids, this may be plenty of time.”

## OVERCOMING RESISTANCE TO EGFR INHIBITORS

Non-small cell lung cancer is the leading cause of death from cancer in the United States. One of the most common activating mutations found in this type of lung cancer is L858R, located in the tyrosine kinase domain of the epidermal growth factor receptor gene (*EGFR*). Although patients with *EGFR* mutations are very responsive to tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, cancer cells ultimately develop resistance to TKIs, primarily through an acquired secondary mutation known as T790M. Overcoming the resistance conferred by T790M has become a major clinical challenge.

In a recent study, Kwok-Kin Wong, MD, PhD, of the Department of Medical Oncology, who specializes in lung cancer models, and clinical investigator Geoffrey Shapiro, MD, PhD, of the same department, teamed up to search for an alternative therapeutic strategy for patients who develop resistance to TKIs. Wong began by genetically engineering mice to express mutant human *EGFR* with the T790M-L858R compound mutation (*bEGFR TL*) and then demonstrated that it is both oncogenic and essential to tumor maintenance.

Wong tried treating the *bEGFR TL* mice with neratinib (HKI-272, from Wyeth), based on studies showing that the newer “irreversible” TKIs could block T790M. If he was expecting a robust response, he was to be disappointed. “It turned out that neratinib alone was not that potent,” says Shapiro, whose laboratory collaborated with Wong and conducted parallel experiments in cell lines with similar results. “There was still residual downstream signaling related to PI3K and mTOR,” he explains. Subsequently, the two investigators decided to treat the mice with neratinib and the mTOR inhibitor rapamycin. To their great satisfaction, the combination therapy inhibited *EGFR* and downstream signaling as well, resulting in dramatic tumor regression.

“The results seen in Kwok’s mouse models will be extremely useful in predicting outcomes of various treatments as we now move ahead with clinical trials,” says Shapiro, who directs the Early Drug Development Center (EDDC) at Dana-Farber, where the majority of Phase I and proof-of-mechanism studies at the Institute are conducted. In fact, EDDC will soon be launching a trial combining neratinib with Wyeth’s mTOR inhibitor, temsirolimus. “The mission of the EDDC is to harness as much science as possible from Dana-Farber laboratories and to convert discoveries into trials for our patients,” declares Shapiro. “Our work with Kwok is a prime example of that.”



GEOFFREY SHAPIRO, MD, PHD (RIGHT), TALKING WITH PATIENT SHAUN FARRELL AND ALAN D'ANDREA, MD



A. THOMAS LOOK, MD (LEFT), RANI GEORGE, MD, PHD (FRONT RIGHT), WITH JEONG-SOO LEE, PHD (BACK LEFT), RODNEY STEWART, AND JOHN KANKI, PHD

### A NEW APPROACH IN NEUROBLASTOMA

Neuroblastoma (NB), another serious pediatric cancer, is especially dangerous in children over the age of 18 months and those with disseminated disease, says A. Thomas Look, MD, vice chair for research in the Department of Pediatric Oncology. Although survival has improved with intensive chemotherapy, treatment causes long-term effects, adds translational investigator Rani George, MD, PhD, also of Pediatric Oncology, whose laboratory is collaborating with Look's to discover new genetic abnormalities in NB that may lead to better and less toxic treatments.

In previous SNP array analyses of NB tumor samples, George and Look had found that anaplastic lymphoma kinase gene (*ALK*) was amplified, leading them to wonder whether *ALK* played a major role in NB. With the help of Matthew Meyerson, MD, PhD, of the Department of Medical Oncology and co-director of the Center for Cancer Genome Discovery, they sequenced *ALK* in 93 primary tumors from high-risk patients and identified five previously unknown mutations, including F1174L, which was the most common and found to activate signaling by the *ALK* cell surface receptor.

"These mutations change the structure of the kinase," says Look, "so that the *ALK* receptor is no longer

dependent on a ligand for activation — thereby removing the mechanism for controlling powerful growth signals." He and George hypothesized that when tumor cells mutate and constitutively activate *ALK*, the receptor becomes oncogenic. To test their hypothesis, George turned to chemical biologist and colleague Nathanael Gray, PhD, of the Department of Cancer Biology and member of the Initiative in Chemical Biology, who had developed a compound, TAE684, which would allow investigators to chemically inhibit *ALK* in NB cell lines (see story, page 13). Not only was the F1174L mutation especially sensitive to the *ALK* inhibitor, but also siRNA knockdown of *ALK* with activating mutations, particularly F1174L, caused tumor cell death, "implying that this mutation is one of the major abnormalities mediating growth and proliferation in neuroblastoma cells," explains George.

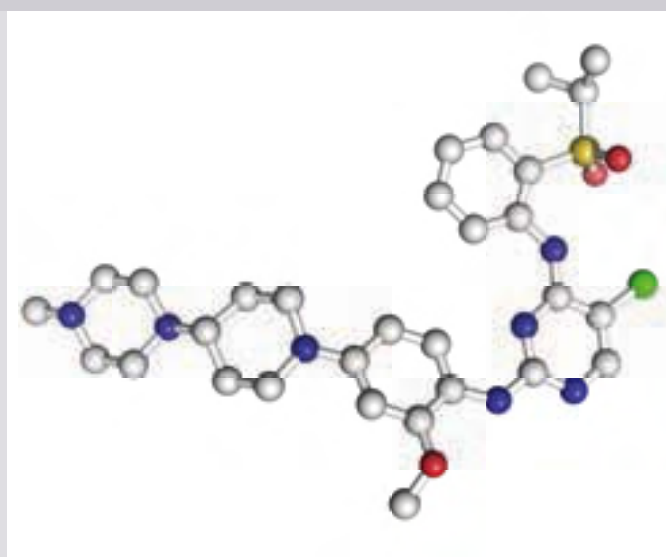
Fortunately, since drug companies had already introduced an *ALK* inhibitor in adult clinical trials, a Children's Oncology Group (COG) clinical trial can soon begin enrolling neuroblastoma patients with *ALK* mutations. "I'm so gratified that all our work in the laboratory has led to a target that we can not only exploit clinically, but also study in more detail to expand our knowledge of neuroblastoma," says George.

## Tinkerer turned chemist

As a boy, Nathanael Gray, PhD, was fascinated with LEGOs. “Assembling complicated structures from simple ones was very gratifying to me,” says the assistant professor in the Department of Cancer Biology. He even imagined becoming a professional LEGO designer. As that dream faded, he channeled his passion into a career in chemistry, not such an unlikely choice. Chemical elements — like the interlocking toy bricks the young Nathanael snapped together into elaborate skyscrapers — constitute the basic building blocks from which medicinal chemists construct complex compounds.

Gray became familiar with organic chemistry by working in his godfather’s laboratory at the University of California at Berkeley, where he later earned a PhD in chemistry. While the director of biological chemistry at the Novartis Research Foundation, he led a team that designed inhibitors of kinases that become deregulated in cancer.

In 2005, Dana-Farber recognized a rising star and recruited Gray as part of a strategic investment in chemical biology — expertise that is crucial to translational research, says Thomas Roberts, PhD, co-chair of Cancer Biology. “With the addition of chemical biology skills to our armamentarium, Dana-Farber can now translate basic cancer discoveries into small molecules, which



**CHEMICAL STRUCTURE OF THE ALK INHIBITOR TAE684.** Chemical structure of TAE684, an ALK inhibitor, is shown as a ball and stick diagram. Atoms are colored by element: carbon (grey), nitrogen (blue), chlorine (green), sulfur (yellow), and oxygen (red).



NATHANAEL GRAY, PHD

previously had been the sole domain of the biotech and pharmaceutical industries.”

Gray oversees a laboratory of medicinal chemists and biologists who synthesize small molecule inhibitors and use a variety of screens and assays to improve their potency, selectivity, and biological function. The overriding goals of his lab are to rigorously validate the mechanisms and targets of compounds, and to kindle the interest of biopharmaceutical companies in turning these compounds into new cancer drugs. His lab recently used an inhibitor of ALK to demonstrate that this kinase may be an appropriate target in lung cancer and neuroblastoma (see story, page 12).

Early pharmacological validation gives companies the data they need to pursue new therapies and shortens the drug discovery timeline, explains Gray. “Doing this up-front work for companies helps bring new agents to clinical trials more quickly.”

## Mouse models play pivotal role in testing combination therapies

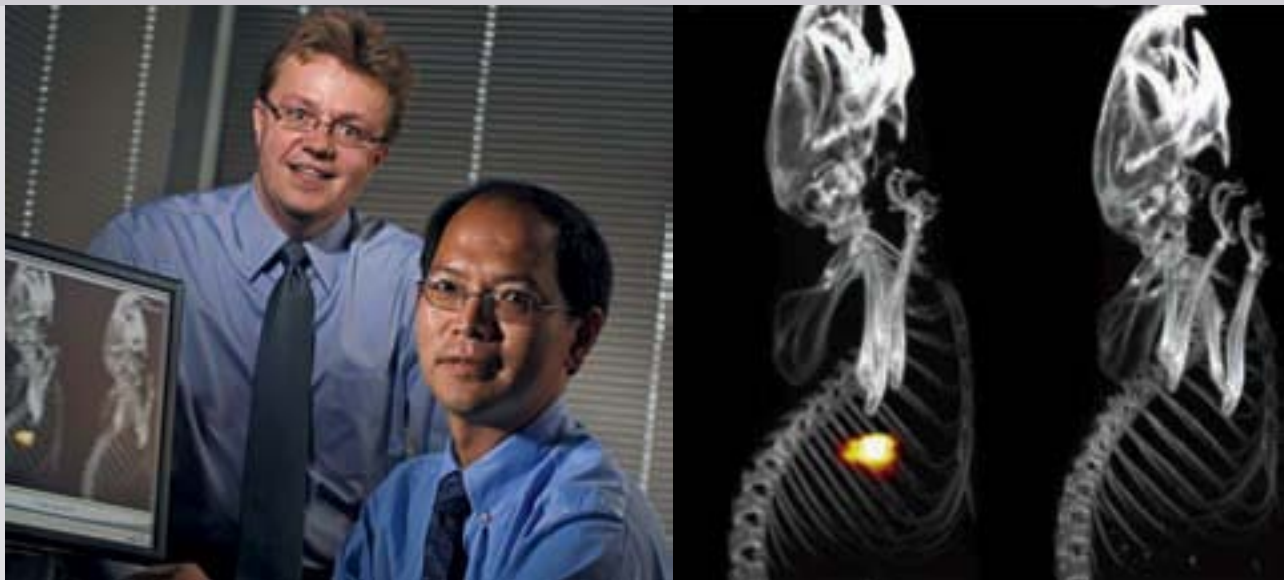
Sophisticated animal models, like the mice genetically engineered by Kwok-Kin Wong, MD, PhD, play numerous supporting roles in translational research: revealing whether particular genetic alterations are tumorigenic, informing the selection of patients for targeted therapies already developed, and providing another level of preclinical screening and validation, besides cell lines, to hasten the development of new drugs for patients.

Increasingly, as clinicians inch closer to defining a patient's cancer based on their genotype — or, at least, on their known oncogene status — mouse models that recapitulate the genetic complexity of human cancers are taking center stage in translational research. “Figuring out which specific combination of targeted therapies works best for which genotypes will become crucial in personalized medicine,” asserts Wong, whose research focuses on lung cancer.

Yet the number of patients genetically qualified for such combination studies is small and the process

prohibitively time-consuming and expensive, he explains. Complex animal models, however, which carry several mutations that collectively lead to cancer, offer an elegant and pragmatic platform in which to test myriad targeted compounds simultaneously, says Wong, whose genetic engineering technique can be readily adapted to create models of any cancer type. “When we mix mutations in the mouse, we can study in a meaningful manner how these impact or attenuate response to different therapies.” He and colleagues are now testing the combination of a PI3K inhibitor and a MEK inhibitor in mice whose lung tumors harbor *K-ras* mutations and concurrent loss of a tumor suppressor, such as p53 or Lkb1.

“Our preclinical studies may determine whether a drug is likely to be efficacious and therefore a good candidate for a clinical trial,” adds Wong. “That’s the power of these genetically engineered mouse models: helping us sort out which compounds we should bring to patients.”



LEFT: PASI JÄNNE, MD, PHD (LEFT), AND KWOK-KIN WONG, MD, PHD

RIGHT: PI3K INHIBITOR INDUCES TUMOR REGRESSION IN MICE EXPRESSING A PI3K ACTIVATING MUTATION. A mouse expressing the PI3K p110 $\alpha$  activating

mutation H1047R was serially imaged using 18FDG PET-CT. Before treatment (left image), a lung tumor was visualized; the tumor dramatically reduced in size after four days of treatment with the PI3K inhibitor NVP-BEZ 235 (right image).

# Advancing translational research through institutional resources

In recent years, Dana-Farber has invested in initiatives that provide the organizational framework and resources needed to support outstanding translational research. “The overall strategy behind this considerable institutional support is to facilitate productive relationships, internally and externally, that lead to the highest-caliber clinical trials,” says George Demetri, MD, of the Department of Medical Oncology and director of the Ludwig Center for Cancer Research at Dana-Farber. “Our aim is to decrease drug development time from twenty years to five by making these connections work effectively, and ultimately to ensure that the best science ideas from the lab are converted quickly to the clinic.”

## THE LUDWIG CENTER FOR CANCER RESEARCH AT DANA-FARBER

The first of only six of its kind in the United States, the Ludwig Center at Dana-Farber represents an expansion of the philanthropic vision of American business magnate Daniel K. Ludwig, who bequeathed his fortune to cancer research. Under the direction of Demetri, and supported by an endowment in perpetuity, this academic research center helps to translate scientific discoveries from the laboratory into the clinic as rapidly as possible. This is achieved by fostering collaborations among a multidisciplinary group of investigators and facilitating access to new therapies and technologies for preclinical and early clinical research.

Among other achievements, the Ludwig Center has been instrumental in developing novel inhibitors for the treatment of gastrointestinal stromal tumor (GIST). Approximately 90 percent of patients benefit from first- and second-line treatment with tyrosine kinase inhibitors (TKIs), such as imatinib (Gleevec) or sunitinib (Sutent), which block the activated oncoproteins KIT and PDGFRA; however, resistance to TKIs evolves when tumors acquire secondary mutations in the target kinase. Demetri and the team at Dana-Farber, in collaboration with colleagues at Brigham and Women’s Hospital, sought to inhibit these oncoproteins by targeting HSP90, a molecular chaperone that escorts “client” proteins and ensures their proper folding, localization, stability, and



GEORGE DEMETRI, MD

degradation. Since HSP90 appears to protect the mutant KIT oncoproteins from normal degradation, investigators reasoned that HSP90 might be a good therapeutic target in GIST and other cancers. A preclinical study validated HSP90 as a target and found that inhibition of the molecule dramatically inactivated KIT oncoproteins in imatinib-resistant GIST cell lines. Later, in collaboration with Infinity Pharmaceuticals, Demetri and Andrew Wagner, MD, PhD, also of the Department of Medical Oncology, and colleagues conducted the first Phase I clinical trial of an HSP90 inhibitor specifically targeting patients with TKI-resistant GIST and other sarcomas. The inhibitor was generally well tolerated and showed evidence of efficacy. This trial led to an international Phase III study in GIST, currently underway, a Phase II trial in lung cancer, and a Phase I study in breast cancer.

The initial focus of the Center — developing molecularly targeted therapies for GIST and other sarcomas — has since expanded to encompass therapeutic initiatives in melanomas and lung cancers. “Our center has a uniquely dedicated focus on translational science and clinical opportunities,” says Demetri. “The driving force, design,



ANDREW KUNG, MD, PHD

and academic control of clinical trials rests firmly in the hands of Dana-Farber. The Ludwig endowment gives us the certainty of continuity, long-term vision, and commitment to do this work.”

### IMAGING IN TRANSLATIONAL RESEARCH

“Imaging technology is a powerful tool in translational research,” says Annick Van den Abbeele, MD, chair of the Department of Imaging and director of Dana-Farber’s Center for Biomedical Imaging in Oncology, or CBIO (see page 59). “Integrating our preclinical and clinical imaging research activities in CBIO will help us evaluate promising new drugs more efficiently and translate them more rapidly into clinical trials and practice.” A critical component of CBIO is the Lurie Family Imaging Center, directed by Andrew Kung, MD, PhD, of Pediatric Oncology. The Center offers state-of-the-art technologies, techniques, and expertise for conducting small animal experiments. In the facility, all imaging equipment is located inside the animal housing barrier. Miniaturized versions of X-ray, CT, PET, SPECT, MRI, and ultrasound equipment are available, as well as a full range of clinically relevant radiotracers. Optical imaging provides an additional research tool for studying molecular targets in living animals. “These imaging modalities

will help investigators understand not only whether a drug impacts tumor growth, but also whether a drug modulates its target *in vivo*,” explains Kung. “Imaging is non-invasive and nonlethal, so it gives us the ability to conduct longitudinal studies using smaller numbers of mice to obtain significant results in a matter of days instead of weeks.”

### CLINICAL RESEARCH INSTITUTE

As part of a strategic effort to enhance the quality and impact of its clinical trials, Dana-Farber recently founded the Clinical Research Institute (CRI) under the direction of Philip Kantoff, MD, chief clinical research officer. An educational program, directed by Harold Burstein, MD, PhD, of Medical Oncology, offers an intensive two-month training program between the first and second year of fellowship, followed by several hours of coursework per week. Classes and hands-on workshops focus on how to write and conduct clinical protocols. Over time, says Kantoff, CRI will provide training and credentialing for all Dana-Farber clinical investigators.

In addition, CRI offers consultative services to enhance the scientific design of investigator-initiated trials. “Before the protocol is written, the investigator presents the study concept before a multidisciplinary team of experts, who give their feedback and advice,” explains Kantoff. CRI’s research navigator then facilitates the execution of clinical trials by linking investigators with services needed for the trial.

“The intent is to elevate the quality and efficiency of clinical research at Dana-Farber,” says Kantoff. “Ultimately, we hope to create a new generation of clinical trials that will guide us toward personalized cancer medicine, an area where we expect to play a leading role.” Many of the novel trials emerging from the efforts of CRI will be conducted in the Early Drug Development Center (EDDC), directed by Geoffrey Shapiro, MD, PhD. “CRI and EDDC represent two cornerstones of the larger clinical trials infrastructure we have built at Dana-Farber to improve outcomes for cancer patients,” says Kantoff.

# Genomics



The genetic language of cancer represents one of nature's most complex codes. To help break this biological cipher, Dana-Farber has created an environment where ingenuity and collaboration meet advanced technologies. Like cryptographers applying a key to crack a secret document, researchers are applying sophisticated genomic techniques to decrypt the cancer code and translate new discoveries to the clinic.



Remarkably, the capacity of these technologies to analyze cancer genomes at higher resolution and greater depth is increasing 10-fold, 100-fold, or more every year, says Matthew Meyerson, MD, PhD, of the Department of Medical Oncology. Even before their translational utility was proven, Dana-Farber began investing institutional resources in these technologies through its partnership with the Broad Institute and the development of the Dana-Farber Center for Cancer Genome Discovery (CCGD), directed by Meyerson and William Hahn, MD, PhD, also of Medical Oncology.



## Combining genomic approaches to decrypt the cancer code

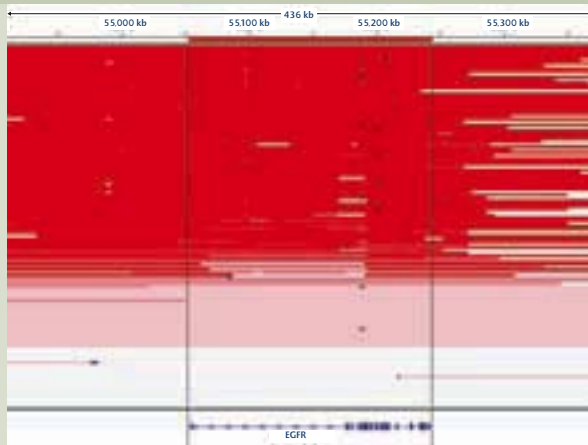
While some investigators are mapping the structural alterations in the cancer genome, others are searching for new oncogenes that fuel tumors.

### MAPPING CANCER'S ALTERED GENOME

The most comprehensive of the efforts to map structural alterations is The Cancer Genome Atlas (TCGA), a nationwide research network of more than a dozen institutions, including Dana-Farber and the Broad Institute. Its goal is to fully characterize the architecture of the cancer genome. The first published paper of the TCGA pilot project, led by Lynda Chin, MD, of the Department of Medical Oncology, and Meyerson, focused on an integrative analysis of DNA copy number variations, gene expression, and DNA methylation aberrations in 206 glioblastoma tumor samples, as well as nucleotide sequence aberrations in 91 samples.

Interim analysis revealed alterations in three core pathways (RB, p53, and RTK/RAS/PI3K) and somatic mutations in three genes (*ERBB2*, *NF1*, and *PIK3R1*) not previously associated with glioblastoma. "No one had looked at this cancer in enough specimens and in high enough resolution before to derive that information," says Meyerson. Moreover, because PI3K inhibitors are already in development, adds Chin, "the *PIK3R1* discovery may soon

PICTURED ABOVE (FROM TOP):  
LYNDA CHIN, MD,  
WILLIAM HAHN, MD, PHD,  
AND MATTHEW MEYERSON, MD, PHD



**EPIDERMAL GROWTH FACTOR RECEPTOR GENE IS ACTIVATED IN MANY GLIOBLASTOMA SAMPLES.** The epidermal growth factor receptor gene, *EGFR*, was analyzed in glioblastoma samples using SNP array and DNA sequence data. Each sample is a thin horizontal line. The *EGFR* copy number is indicated by the intensity of line; amplification as dark red lines, internal deletions within the gene by lighter shades of red or white stretches within the line. Mutations are shown as blue dashes. Courtesy of Matthew Meyerson, Wendy Winckler, and Gad Getz.

lead to new clinical trials in glioblastoma and enable stratification of patients based on their *PIK3R1* status.”

One of the most exciting insights from the interim analysis came from integrating the sequencing and DNA methylation data with treatment information. Combining these data sparked a new hypothesis for the mechanism of resistance to temozolomide (Temodar, a standard treatment for glioblastoma): the tumor cell bypasses the drug by inactivating DNA repair machinery.

Their ultimate goal is to sequence and map every base pair of the cancer genome across a large collection of samples from ovarian, lung, and other tumors and disseminate the data to the research community.

**FINDING MUTATIONS THAT MATTER**

Not all genetic mutations play an essential role in carcinogenesis. The goal of Project Achilles, led by William Hahn, MD, PhD, in collaboration with Meyerson, Levi Garraway, MD, PhD, Kornelia Polyak, MD, PhD, of the Department of Medical Oncology, and Todd Golub, MD, of Pediatric Oncology, is to find and exploit cancer’s vulnerabilities using integrative genomic approaches.

“Each genomic approach is powerful, but gives you only one dimension of information,” explains Hahn.

“By combining different approaches, you quickly find a small set of genes — and in some cases, just one gene — that satisfy all criteria” for the development of cancer.

In one study, Hahn and colleagues, including post-doctoral fellow Ron Firestein, MD, PhD, in Hahn’s lab and clinical fellow Adam Bass, MD, in Meyerson’s, set out to find the genes required for full transformation to colon cancer. At Dana-Farber’s RNAi facility and at the Broad, investigators used RNA interference to conduct two loss-of-function screens: one for genes essential for proliferation, the other for those that regulate the Wnt/beta-catenin pathway (implicated in virtually all colon cancers), resulting in a subset of genes at the intersection of the two screens. Next, they determined which genes of this subset were also amplified in colon cancer specimens. Using high-density SNP arrays — originally designed for genome-wide detection of single nucleotide polymorphisms (SNPs) associated with disease, but modified by Meyerson to assess copy number variations — a single gene emerged from the SNP arrays, *CDK8*, a new oncogene mutated in up to 50 percent of colon cancers.

The investigators applied a similar rationale to hunt for breast cancer oncogenes. They added another tool from the genomic arsenal, thanks to Marc Vidal, PhD, of the Department of Cancer Biology and director of Dana-Farber’s Center for Cancer Systems Biology. Vidal had compiled a library of open reading frames (ORFs), the coding sequences of genes. While short interfering RNAs allow investigators to knock down genes of interest, ORFs allow them to overexpress genes to screen for gain-of-function mutations, a common occurrence in breast cancer. Integrating RNAi, the ORF library, and high-density SNP arrays, they discovered the oncogene *IKBKE*, which is mutated in 30 percent of breast cancers. Since the products of *CDK8* and *IKBKE* are kinases, which lend themselves to small-molecule inhibition, these two discoveries alone could have an impact on patients.

“We’re able to do this research because we have resources at Dana-Farber and the Broad that do not exist anywhere else,” notes Hahn. “It feels almost effortless, because we’re all collaborating.”

# Modeling resistance in the laboratory

When Pasi Jänne, MD, PhD, was a fellow, the Dana-Farber/Partners clinical oncology fellowship suited him perfectly; it integrated his two major interests, science and medicine, while introducing him to distinguished mentors like Bruce Johnson, MD, of the Department of Medical Oncology. The difficult part, he found, was having to tell patients that their lung cancer had relapsed. Today, as a thoracic oncologist and clinical researcher, Jänne is bringing new hope to patients by uncovering the mechanisms of resistance in lung cancer and designing more effective therapies.

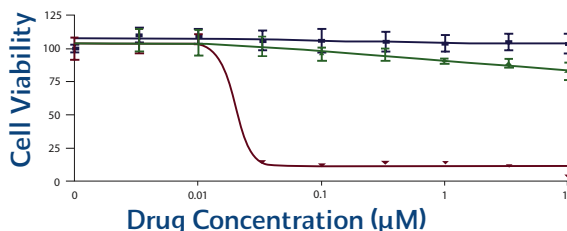
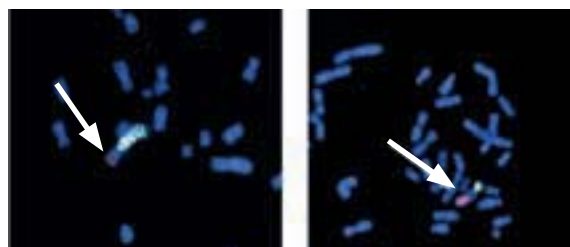
The drugs gefitinib (Iressa) and erlotinib (Tarceva), which inhibit the epidermal growth factor receptor (EGFR), initially work in patients with *EGFR* mutations, but then fail as the tumors become resistant to treatment. Studying exactly how this happens, however, is no easy matter, explains Jänne, because patients do not routinely undergo repeat biopsies that can be analyzed for genetic changes.

To circumvent the problem, he and colleagues modeled resistance in the laboratory, by treating *EGFR*-mutant cells with gefitinib and isolating those that became resistant. Investigators then compared the resistant cells to gefitinib-sensitive cells, deploying three different techniques: genome-wide copy number analysis (using the high-density SNP arrays adapted by Dana-Farber colleague Matthew Meyerson, MD, PhD), RNA expression profiling and proteomic analysis. “All three independent approaches pointed us in the same direction,” says Jänne, recalling the excitement of an entirely unexpected discovery — amplification of the *MET* kinase gene, which provided an alternate pathway for tumor growth.

Within a year, he had begun enrolling patients in a multicenter clinical trial combining Tarceva with a *MET* inhibitor. “We were hopeful of finding something new for patients,” he says, “and we did!”



LEFT: PASI JÄNNE, MD, PHD (LEFT), AND BRUCE JOHNSON, MD



- EGFR inhibitor (Gefitinib)
- ▲ MET inhibitor (PHA665752)
- ▼ EGFR + MET inhibitors

RIGHT: EGFR-INHIBITOR-RESISTANT CELL LINE EXPRESSES A FOCAL AMPLIFICATION OF *MET* AND IS SENSITIVE TO A COMBINATION OF EGFR AND MET INHIBITORS.

**Top** – An *EGFR* mutant lung cancer cell line was selected for resistance to the EGFR inhibitor, gefitinib, and analyzed for expression of the *MET* gene by fluorescence in situ hybridization (FISH). The gefitinib-sensitive cell line (left panel) contained a single copy of *MET* (arrow),

while the resistant cell line (right panel) contained a focal amplification at the *MET* locus (arrow). The image on the right was photographed with a lower sensitivity. FISH probes: red – *MET*, orange – *EGFR*, and green – CEP 7, a centromere marker.

**Bottom** – The gefitinib-resistant *EGFR* mutant cell line was treated with either the EGFR inhibitor gefitinib, a *MET* inhibitor (PHA-665752), or a combination of the two. Viability relative to untreated cells was assessed by colorimetric assay after three days.

# Identifying drug candidates through gene expression screening

A decade ago, Dana-Farber pediatric oncologist and researcher Todd Golub, MD, pioneered the use of DNA microarrays to classify cancers based on their gene expression signatures, a technique used worldwide today. Recently, with colleague Kimberly Stegmaier, MD, a former postdoc in his lab, Golub finessed this technique into an unconventional drug discovery tool. Known as gene expression-based high-throughput screening (GE-HTS), this approach makes ingenious use of genomics to identify anti-tumor compounds even when their molecular targets are unknown or considered undruggable.

This approach makes ingenious use of genomics to identify anti-tumor compounds, even when their molecular targets are unknown or considered undruggable.

In GE-HTS, investigators first define the gene expression signature of a desired biological state, such as differentiation, and then screen a library of small molecules for compounds that induce this target signature and corresponding phenotype.

In collaboration with the Broad Institute, where Golub is director of the cancer program, Stegmaier

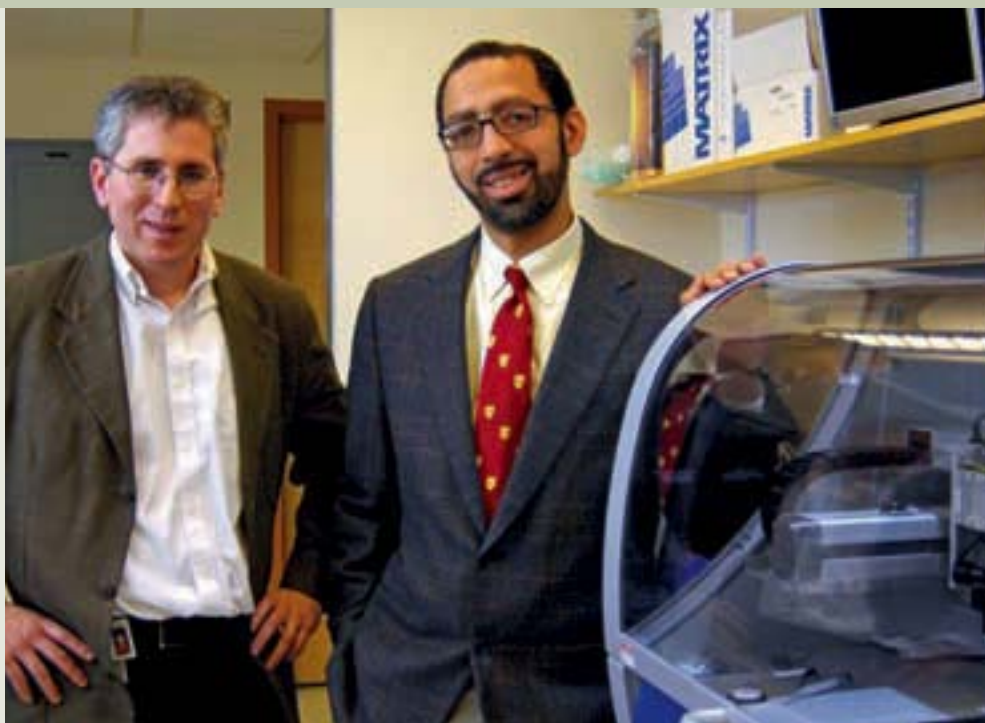
and colleagues demonstrated the feasibility of GE-HTS in a landmark study of acute myeloid leukemia (AML), a cancer in which white blood cells fail to mature.

After comparing gene expression profiles of undifferentiated AML cells with their mature myeloid counterparts, the investigators selected a core signature of five genes that collectively acted as a surrogate for the differentiation phenotype. “The tricky part,” says Stegmaier, “was figuring out how to quantify the expression of this collection of genes affordably in 384 wells,” the format of small-molecule libraries. Of the technologies available at the time, Stegmaier and Golub chose mass spectrometry, building on an assay used by Levi Garraway, MD, PhD, (see story, page 21) to measure mRNA levels after cells were exposed to 1,700 small molecules provided by the Broad. This work led to identification of candidate compounds that reliably reproduced the target signature. Based upon the results of this screen, Dana-Farber investigators are now collaborating with industry partners to test a new drug for patients with AML.

With recent enhancements to bead-based Luminex technology, investigators gain the capacity to analyze expression of up to 500 genes simultaneously, increasing both the sensitivity and specificity of screening and enabling the study of increasingly intricate gene expression patterns induced by small molecules, says Stegmaier, of the Department of Pediatric Oncology. “This opens up new possibilities in predicting synergy between compounds, screening for very complex biological signatures, and analyzing multiple phenotypes in a single screen.”



LEFT: TODD GOLUB, MD  
RIGHT: KIMBERLY STEGMAIER, MD



MATTHEW MEYERSON, MD, PHD (LEFT), AND LEVI GARRAWAY, MD, PHD, WITH THE ROBOTIC NANODISPENSER

## OncoMap: profiling tumor DNA

In a laboratory bay on the 15th floor of the Dana building, a robotic nanodispenser hums mechanically in the background as a mass spectrometer churns out genotyping data. Though mass spectrometric genotyping has typically been used to find single nucleotide polymorphisms in germline DNA, researchers here at Dana-Farber are applying the technology to ferret out known point mutations in tumor DNA for which targeted therapies already exist or are in development. This novel screening approach, called OncoMap, is the brainchild of physician-scientist Levi Garraway, MD, PhD, of the Department of Medical Oncology and a member of the Center for Cancer Genome Discovery, who developed the technique in collaboration with the Broad Institute.

Garraway, who specialized in tropical parasites for his PhD, never planned to become a cancer researcher. But as an MD/PhD student, he faced a career crossroads when his scientist father was suddenly diagnosed with prostate cancer. “Since that day,” says Garraway, “the guiding theme of my career has been translating molecular and genetic understanding of cancer into the clinic.”

Following a research fellowship at Dana-Farber, Garraway joined the faculty in 2005, started his own lab, and began searching for a cost-effective way to profile mutations in many different tumor types. “We realized, in principle, that we could adapt mass spectrometric genotyping to extract highly relevant information from tumors that might guide therapy choices and yet cost only pennies per genetic variant,” says Garraway. Still, demonstrating the value of the OncoMap approach was another matter. He and colleagues, including Matthew Meyerson, MD, PhD, of Medical Oncology, initially tested the technology by scouring cancer DNA for 238 known mutations in 17 oncogenes. Their work culminated in a eureka moment as the first wave of data streamed off the robots, transforming principle into reality. “We were observing mutations in tumor types we would never have expected, a priori,” says Garraway. “It was an exceedingly satisfying moment.” With the addition of institutional resources for large-scale mutation profiling, OncoMap has now expanded into numerous other scientific and clinical research projects. “By systematically profiling diverse tumor collections for critical mutations, we hope to enable definitive advances in molecular oncology and, ultimately, to promote personalized cancer medicine,” says Garraway.

# Computational Biology



Soon after the sequencing of the human genome, Dana-Farber foresaw the need for building a strong capability in computational biology, an academic discipline deemed essential to personalized medicine. Computational biologists, who apply quantitative and computer science skills to answer biological questions, specialize in analyzing, interpreting, and managing complex, high-dimension data sets.



## Applying quantitative sciences and information technologies to answer biological questions

Featured here are two examples where computational biology is helping to make sense of an increasingly information-rich environment.

### INSIGHTS INTO STEM CELL DIFFERENTIATION

The laboratory of stem cell biologist Stuart Orkin, MD, chair of the Department of Pediatric Oncology, identified a novel enzyme that safeguards the identity and pluripotency of embryonic stem (ES) cells. Together with computational biologist Guo-Cheng (“GC”) Yuan, PhD, of the Department of Biostatistics and Computational Biology, Orkin is defining the novel mechanisms that regulate cellular identity and cell-fate switching during ES cell development. These rely on an understanding of the molecules that play essential roles in development and in the proliferation of tumor cells.

Histones, the spool-like proteins around which DNA winds to form chromatin, are critical to embryonic development because they undergo methylation and other epigenetic modifications that affect gene expression. Enzymes, called methyltransferases, transfer a methyl group onto the tails of histones at fixed locations on chromatin. This marks the gene at that site for repression or activation, depending on where methylation occurs in the histone. One of the protein complexes that synthesize these methylation marks is Polycomb repressive complex 2 (PRC2), which acts as a master epigenetic regulator of ES cells. To maintain pluripotency of the cell, PRC2 binds to developmental genes and mediates methylation via the EZH2 methyltransferase within the complex, thereby repressing differentiation genes. When the cell is destined to develop into different lineages, however, PRC2 deassociates from its target genes, allowing them to be fully expressed and for differentiation to occur.

PICTURED ABOVE (FROM TOP):  
JOHN QUACKENBUSH, PHD,  
AND XIAOLE (SHIRLEY) LIU, PHD

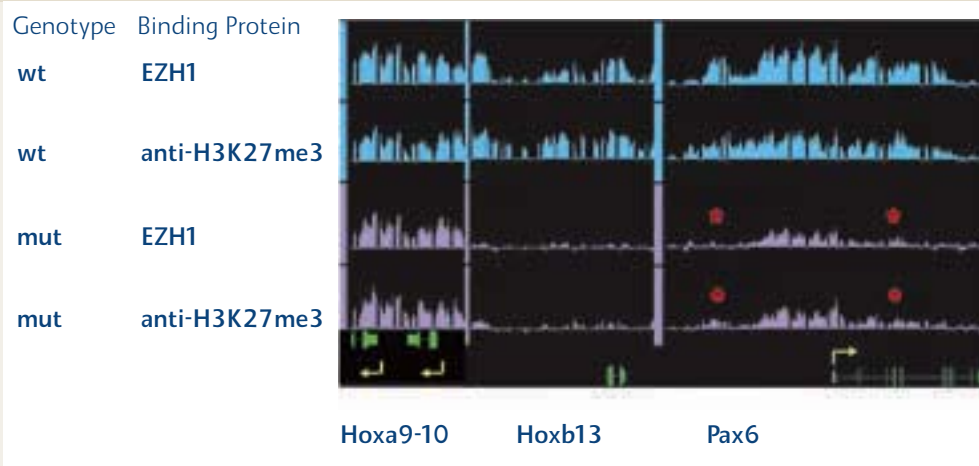
Until recently, scientists believed that EZH2, which is upregulated in some cancers, was the only enzyme directly responsible for methylation on histone H3 lysine 27 (H3K27). Then Xiaohua Shen, PhD, a research fellow in the Orkin laboratory, identified a new methyltransferase, EZH1, which is homologous to EZH2 and able to transfer methylation marks to H3K27. After interrogating a 45-million-probe microarray to locate the marks and target genes of both EZH1 and EZH2, Orkin turned to Yuan to analyze the enormous data set. “Traditional biochemical and molecular analyses are rudimentary compared to what a true computational biologist can do,” says Orkin.

Yuan and his postdoctoral fellow, Yingchun Liu, PhD, sifted through the dizzying array of numbers in order to find the loci where the EZH proteins bind, to map these loci to their chromosomal locations, and to search complex databases to uncover the genes at those sites. They also assessed whether the binding sites of EZH1 correspond to the same genomic regions as the H3K27 marks; indeed, both EZH1 and EZH2 colocalize with H3K27 on chromatin. Genome-wide study and

computational analysis thus confirmed biochemical and genetic evidence that EZH1 compensates for, and complements, EZH2 by targeting the same genes. Interestingly, in cells lacking EZH2, only one-third of target genes retained H3K27 marks due to the presence of EZH1. These genes were more often associated with lineage differentiation, while genes losing H3K27 marks were associated with non-developmental functions.

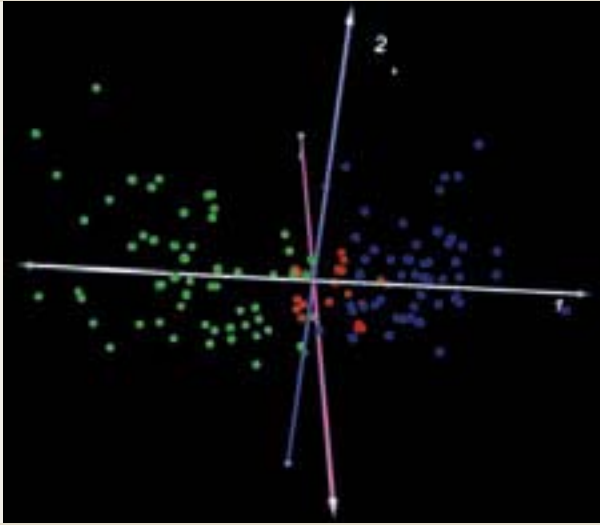
“Other scientists believed that EZH1 has no role whatsoever,” says Orkin, who is renowned for defining the transcription factors governing differentiation. “But with GC’s help, we made a solid case to the contrary. This collaboration gave us real confidence in our data and insight into the function of these genes.”

More exciting work will happen in the next step of this research, says Yuan. “The real question is: how does EZH1 know which set of genes to target when EZH2 is depleted?” It’s a mystery he hopes to help solve using a new computational method he developed for other purposes, but has since adapted to study Polycomb binding.



**TILING ARRAY ANALYSIS REVEALS THAT EZH1 COLOCALIZES WITH H3K27ME3 ON CHROMATIN.** DNA was purified from embryonic stem cells (ESC) and incubated with either EZH1 or an anti-H3K27me3 monoclonal antibody. The DNA that bound to the protein then was analyzed by tiling array. When *Ezh2* wild-type (wt) DNA was analyzed, many genetic regions bound to anti-H3K27me3 (row 2, three representative genetic loci are shown). Although EZH2 had been thought to be the only histone methyltransferase responsible for the H3K27 trimethylation, about 1,000 genes isolated from *Ezh2* mutant (mut) ESC still bound to the anti-H3K27me3 mAb (row 4, e.g., *Hoxa9-10* and *Pax6*).

In both *Ezh2*wt and *Ezh2*mut DNA, anti-H3K27me3 binding strongly correlated with EZH1 binding (compare row 1 with row 2, and row 3 with row 4), demonstrating that the same DNA loci that bind to EZH1 are trimethylated on H3K27. These results suggest that EZH1 partially compensates for, and complements, EZH2 by trimethylating a subset of the genes that are targeted in *Ezh2*wt mice. Annotated gene locations (green bars), transcription directions (yellow arrows), and regions with partial H3K27me3 loss (red asterisks) are shown. The plot was generated by Affymetrix Integrated Genome Browser (IGB).



OVARIAN CANCERS CAN BE SUBTYPED BASED ON GENOME-WIDE GENE EXPRESSION PROFILING. Ovarian cancer samples were evaluated by genome-wide gene expression profiling and the data subjected to principal component analysis. The ovarian cancer samples grouped into three distinct classes, shown here in red, blue, and green.

“The identification of EZH1 as a novel methyltransferase acting on H3K27 demonstrates the diversity in mammalian Polycomb repressive complexes,” explains Orkin. “This discovery should set the stage for new developments in the role of chromatin in stem cell pluripotency and cancer biology.”

### PROFILING OVARIAN CANCER

One day, after consoling yet another patient whose ovarian cancer had stubbornly resisted platinum agents, clinical investigator Ursula Matulonis, MD, of Medical Oncology, sought the expertise of computational biologist John Quackenbush, PhD, of Biostatistics and Computational Biology. She wanted to apply modern molecular techniques, such as DNA microarrays, to understand platinum resistance in ovarian cancer, the most deadly gynecologic malignancy. The cross-disciplinary partnership that the two investigators forged that day has reached beyond the laboratories of Dana-Farber to produce the largest set of ovarian cancer genomic profiles to date.

Although their pilot project was limited by the small number of fresh-frozen tumor samples available, serendipitous events enabled the two investigators to dramatically scale up their joint effort. Quackenbush happened to meet a former colleague, now at Illumina, who had developed a new gene expression assay for paraffin-embedded tissues. Meanwhile, Matulonis was working with pathologists Ronny Drapkin, MD, PhD, of Medical Oncology, and Michelle Hirsch, MD, PhD, of Brigham and Women’s Hospital, who had recently used paraffin-embedded tissues from a tumor bank to build a tissue microarray — a paraffin block of 100 or

more microtumor cores on a single slide. Quackenbush and Matulonis quickly recognized the power of combining these two new resources. “We thought that if the results of our gene expression assays could be confirmed using a simple antibody test on the tissue microarray,” says Quackenbush, “we might have a test with the potential for immediate clinical impact.”

With the pathologists joining the partnership and Illumina on board, the study began in earnest. Quackenbush’s team extracted DNA and RNA from the same tumor samples used to create the tissue microarray and sent the purified nucleic acids to Illumina. The company generated data on mRNA, microRNA, copy number variation, and DNA methylation, which it returned to Dana-Farber for analysis.

Discoveries deriving from these data — such as markers indicating that a patient is likely to become platinum-resistant or platinum-sensitive — may lead to more effective diagnostics and treatments. One early discovery showed that tumor samples separate into distinct molecular subgroups, a finding which may guide future treatment of patients with ovarian cancer. Investigators are now examining whether these subgroups are associated with outcomes or other clinical measures. The team is also analyzing RNA and microRNA (which can bind to mRNA, targeting it for degradation) to look for anti-correlations, instances where an increase in microRNA decreases mRNA. “Integrating these two types of data may provide more complete information than analyzing either type alone,” Quackenbush explains. “Most importantly, Dana-Farber now has the ability to address basic questions about ovarian cancer.”

# Designing tools to unravel transcription factor interactions genome-wide

As a PhD graduate from Stanford University, computational biologist Xiaole (Shirley) Liu set her sights on joining an institution with a biology specialty, first-rate mentors, and the resources needed to start her career. In 2002 she joined the Department of Biostatistics and Computational Biology at Dana-Farber.

One of Liu's earliest mentors at Dana-Farber was physician-scientist Myles Brown, MD, now a colleague and frequent collaborator. The Brown lab, which studies the function of hormone receptors in human cancers, had recently conducted a genome-wide analysis of the interactions between estrogen receptor (ER) and the DNA sequences it recognizes. ER, a transcription factor that is overactive in about 70 percent of breast tumors, binds to specific DNA sequences called cis-regulatory elements, and acts as a master on-off switch for target genes. The sophisticated technology Brown used in the study contained probes for all the non-repetitive human genome sequences at 35-base-pair resolution, resulting in an avalanche of data.

Brown turned to Liu to tunnel through the data to locate all of ER's binding sites and the genes they up- or downregulate. Liu and colleagues designed data analysis and modeling algorithms specifically for the project. Using these tools, they discovered several thousand authentic ER binding sites in previously unexplored regions of the genome and mapped these sites to the genes they control. Surprisingly, the vast majority of these binding sites occurred not

in promoters, but in enhancers, tens to hundreds of kilobases away from their targets.

Furthermore, through integrative modeling of myriad data sets (e.g., binding, gene expression, and genomic sequences), Liu's group showed for the first time that even ER binding sites distant from genes are still functional. Later studies from other groups validated these findings and demonstrated that transcription factor binding to thousands of enhancer regions in the genome is the norm, not the exception.

Liu and colleagues also analyzed the enriched sequence patterns around ER binding sites and identified ER's collaborating partners, other transcription factors that cooperate with ER and correlate with the ER level in breast tumor samples. Remarkably, the collaborating partners for upregulated genes were distinct from those for late-response downregulated genes.

"Biologists can generate massive amounts of data in a few weeks," says Liu, "but analyses can take months or even longer." The ER data set, for example, took three postdoctoral fellows almost two years to unravel. Liu and colleagues are now building tools to automate the process and to create a knowledge base for storing genome-wide interaction data. Called the cistrome (cis-elements bound by transcription factors across the genome), these tools will soon be available to Dana-Farber scientists through a web server and, in a year, to investigators worldwide.

# Immunology



For years, Dana-Farber has been a leader in immunology research, evaluating fundamental questions in immune development, antigen recognition, and immune responses to cancer, autoimmune disease, and HIV. Recently, several faculty members have made paradigm-changing discoveries in antigen presentation and recognition; others are applying those insights to the development of new kinds of cancer vaccines and therapeutic antibodies.

## Promoting immunological self-tolerance

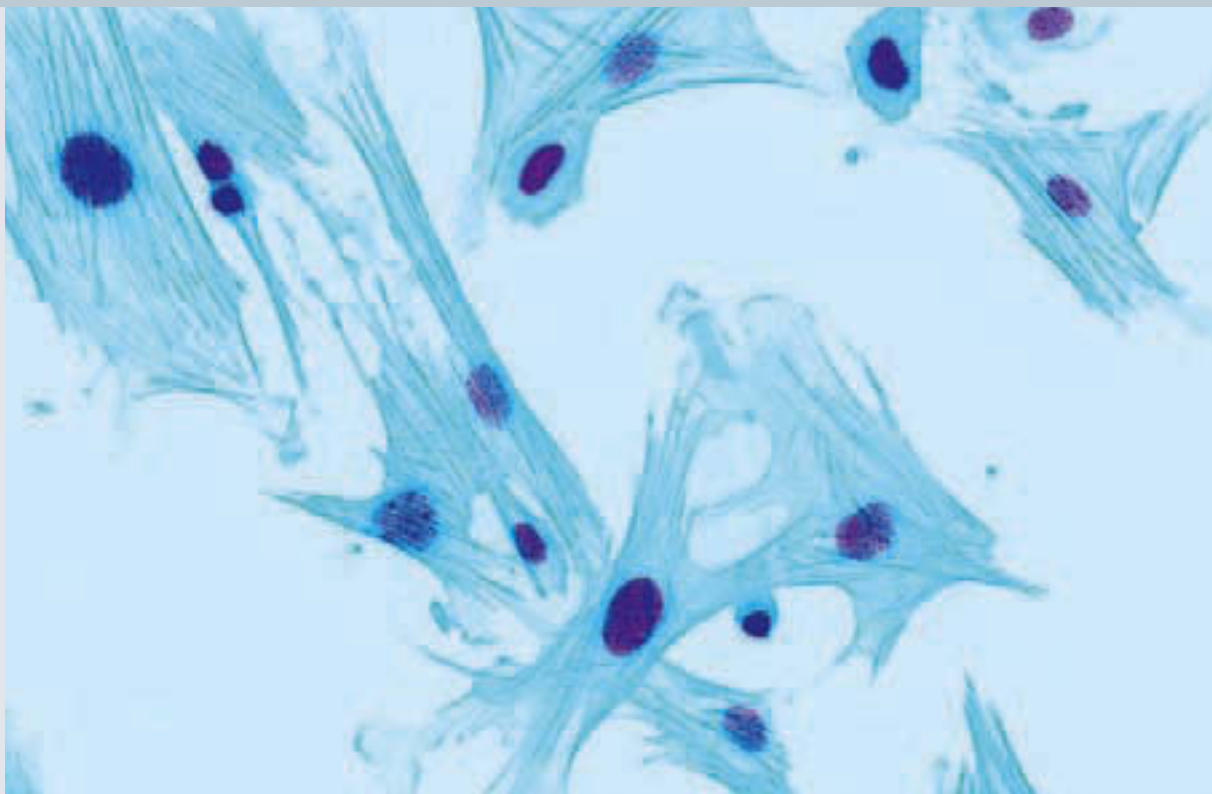


For more than a decade, says Shannon Turley, PhD, she has had a passion for dendritic cells, the “most potent” of the professional antigen-presenting cells (APCs) involved in adaptive immunity. Not only has she trained in dendritic cell biology, her laboratory in the Department of Cancer Immunology and AIDS has focused primarily on understanding the role of dendritic cells in immunity and tolerance, as well as their implications for autoimmune diseases and tumor immunology. Small wonder, then, that her recent findings — which challenge the supremacy of the dendritic cell in immune regulation — were hard to believe at first.

Turley and colleagues sought to understand how dendritic cells induce T-cell tolerance to self-antigens in the intestine, which is teeming with microorganisms; little has been known about tolerance induction in organs exposed to the environment. Self-tolerance, which is crucial to preventing autoimmune diseases, is promoted by the immune system through the mechanisms of central tolerance, which takes place in the thymus, and peripheral tolerance, which occurs in secondary lymphoid organs, such as lymph nodes and spleen. As T cells develop in the thymus, they are “educated” to ignore self-antigens; as they enter the circulatory system, peripheral tolerance controls any remaining self-reactive T cells that may have escaped central tolerance. Dendritic cells play a role in both mechanisms by cross-presenting antigen-MHC complexes to T cells. Cross-presentation is the process of internalizing exogenous antigen (which originates from outside the cell), breaking it down, and then coupling it with MHC for display on the surface of the cell.

In her study, Turley indeed found dendritic cells in the gut and gut-associated lymphoid tissues. She also found that they cross-present intestinal self-antigens, but are not essential for inducing tolerance. To everyone’s

PICTURED ABOVE (FROM TOP):  
SHANNON TURLEY, PHD,  
GLENN DRANOFF, MD, AND  
WAYNE MARASCO, MD, PHD



LYMPH NODE  
STROMAL  
CELLS STAINED  
FOR SMOOTH  
MUSCLE ACTIN

To everyone's astonishment, lymph node stromal cells — previously overlooked in immunological tolerance — were found to promote the elimination of T cells that react to intestinal self-antigens.

Turley. "As circulating self-reactive T cells brush by, they become functionally tolerized or silenced. We had thought that dendritic cells were the *only* players responsible for peripheral tolerance," she adds. "Now we know that the stromal cells we discovered are equally, if not more, important."

astonishment, lymph node stromal cells — previously overlooked in immunological tolerance — were found to promote the elimination of T cells that react to intestinal self-antigen. Moreover, unlike dendritic cells, they do so through direct presentation, the process of displaying endogenous antigens (which originate from inside the cell).

"Lymph node stromal cells actually express these intestinal antigens and present them in MHC complexes in every lymph node of the body," marvels

Follow-up studies from other laboratories have since confirmed Turley's results and reported a much more generalized mechanism of tolerance induction for lymph node stroma. "This was fantastic for us," says Turley. "When we made the first discovery, it was so surprising, so unexpected, that we wanted others to find the same results." Further research from her laboratory and others has shown that these lymph node stromal cells directly present specialized antigens associated with other bodily organs, including the skin, eye, and pancreas, as well as tumors. Today, the Turley laboratory is seeking to understand the molecular underpinnings of this new mechanism of peripheral tolerance, while also investigating the roles that lymph node stroma may play in autoimmunity and tumor immunology.

Turley now sees these stromal cells, which have become a major focus of her laboratory, as a "risk-free" mechanism for promoting tolerance. Dendritic cells, which are exposed to bacteria, viruses, and other pathogens, become immunogenic over time and lose their capacity to induce tolerance. "They can protect us against pathogens, but stromal cells appear to be dedicated to promoting self-tolerance," she explains.

## New strategies in tumor vaccines

Glenn Dranoff, MD, knows this for sure: if immune T cells are present in tumors, cancer patients have a better chance of benefiting from surgery, radiation, or chemotherapy. “The work has become quite convincing in the last five years, where it is now clear that whether it is colon, ovarian, lung or breast cancer, or lymphoma, melanoma or kidney cancer, the people who live the longest and have the best response to treatment are those whose tumors show evidence of an immune response,” Dranoff says.

Unfortunately, most patients do not have an appreciable T-cell response, and that is where tumor vaccines come in. Dranoff, of the Department of Medical Oncology, is a leader in finding ways to boost anti-tumor immune responses. His approach of engineering a patient’s own tumor cells to produce the immunostimulatory cytokine, GM-CSF, has been clinically tested so far in nine different kinds of cancers. In each case, the vaccine elicited an increased T-cell response to tumors.

But stimulating the immune system is not enough, Dranoff has found. Not all T cells are helpful: some are devoted to killing cancer cells, while others shut off the immune response, partly to protect against harmful autoimmune reactions. “Every time the immune system gets a signal to start a reaction, as with a vaccine, it also has signals built in to ultimately turn off that response,” he explains. “And in cancer patients, their immune system has a lot of these control points triggered to turn off the response, because in many ways their tumor is part of themselves.”

In the past year, Dranoff and colleagues have reported on two approaches to get around the shutdown response by using combinatorial vaccines. In one, they used an antibody to block temporarily the action of the negative regulatory receptor, CTLA4, after vaccination. Through a study of 20 patients, they found that those who developed the highest ratio of killer cells to regulatory cells responded the best. “CTLA4 antibodies are being tested widely now and we may find out in the near future whether or not they reach the level of activity that’s going to be required to seek FDA approval,” Dranoff says. In another combination approach, they

found that giving a vaccine shortly after bone marrow transplant preferentially promotes the formation of killer T cells over negative regulatory T cells.

Other work has focused on identifying the tumor-specific proteins that are most likely to trigger a successful T-cell response. Using sera from patients who responded well to immunization, Dranoff and colleagues identified antibodies to MICA, a protein that appears on the outer surface of stressed or damaged cells and tags them for destruction by killer T cells. In additional studies, they found a soluble form of MICA in blood that acted to suppress the anti-tumor immune response. The therapy-induced antibodies overcame this immune suppression and boosted cytotoxic T-cell responses.



KAI WUCHERPFENNIG, MD, PHD

Now, Dranoff is working with Kai Wucherpfennig, MD, PhD, of the Department of Cancer Immunology and AIDS, to isolate and analyze the anti-MICA antibodies. Wucherpfennig, who has made major contributions to the basic understanding of how immune cells recognize antigens at the molecular level, recently developed a technique to isolate the one in ten thousand immune cells that reacts to a specific antigen. Using blood samples from immunized patients, the researchers are looking for the proverbial needle in a haystack, Wucherpfennig says. If they are successful, it will give them the ability to produce a recombinant anti-MICA antibody in unlimited amounts that can be rigorously tested for anti-tumor activity.



**CRYSTAL STRUCTURE OF THE NEUTRALIZING F10 ANTIBODY-HEMAGGLUTININ H5 COMPLEX.** The H5 protein is composed of three monomers, depicted in green, blue, and yellow. The highly mutable H5 mushroom cap region, where most anti-influenza antibodies bind, is shown at the top of the structure; the highly conserved stem region is at the bottom. The F10 antibody (red) binds to a pocket within the H5 stem region that is critical in the large structural reorganizations required for postattachment membrane fusion. When bound by F10, these structural reorganizations cannot occur, and thus viral entry into the host cell is prevented.

## Developing a common influenza vaccine

One of the most successful pathogens ever, the influenza virus is easily spread and potentially deadly. Waves of pandemics arise when the virus mutates the hemagglutinin (H) protein in its outer coat, producing new strains that bypass the immunity to previous versions. Currently, vaccines must be given every year and tailored to the prevailing H strain to be effective. For a long time, the goal of a common flu vaccine, a one-time shot that would silence all strains, has been elusive.

Wayne Marasco, MD, PhD, and Jianhua Sui, MD, PhD, a fellow in his laboratory in the Department of Cancer Immunology and AIDS, are bringing that goal closer to reality. In recent work, Marasco's lab screened a library of 27 billion different antibodies, developed previously in his laboratory, with the hemagglutinin protein from the highly pathogenic avian influenza virus or "bird flu." He found ten antibodies that potently inhibited infection in mice. Unlike most previously isolated antibodies, the new ones did not block the attachment of the virus to the cell, but instead stopped its internalization. Even more surprising, the antibodies blocked the infectivity of other influenza variants that have a different hemagglutinin subtype, including the 1918 pandemic flu virus.

Cross-reactivity between different hemagglutinin subtypes was a very unusual finding. To understand how that could happen, Marasco turned to Robert Liddington, PhD, a crystallographer at the Burnham Institute for Medical Research. When he analyzed the crystal structure of the antibody-hemagglutinin complex, Liddington found that

the antibody bound to an unusual, and usually hidden, region of the hemagglutinin protein. Knowing the exact spot recognized by the antibodies, the researchers then compared that to other hemagglutinin proteins whose sequences were available in public databases. "That was the moment we realized that this was a highly conserved region present in all influenza A viruses," Marasco says. "For the next several months, we worked closely with the Centers for Disease Control (CDC) to prove that what looked like a broadly cross-reactive antibody in silico was confirmed by biological data."

Marasco's work, published in February 2009, was especially timely with the news of the H1N1 (swine) flu breaking shortly after. In April, he was on vacation when he got a phone call from the CDC. "It was about the new outbreak," he said. "It [the H1N1 virus] happened to be of the same class that our antibodies recognize. Can you imagine? How often in one's research career does something like that happen, a new pandemic emerging on the heels of a major therapeutic advance in the field?"

While it is still too early to say definitely that Marasco's antibodies provide protection against the new H1N1 pandemic strain in vivo (those experiments are underway), they do block infection in tissue culture studies. Meanwhile, Dana-Farber is in the process of licensing the finding to a major pharmaceutical company, and the NIH is supporting Marasco's lab to develop the antibodies and wants to stockpile them in case of a pandemic outbreak.

# Metabolic Regulation and Disease



Basic researchers at Dana-Farber are busy exploring fundamental questions of biology: How do cells grow and divide? How do they turn from normal to cancerous? How can that process be stopped? Sometimes the search leads to findings that may not seem directly relevant to cancer, such as when investigators chasing a basic understanding of how cells live, develop, and die stumble upon potential therapies for obesity and diabetes. Even then, however, such discoveries may not be as foreign as they appear. Metabolic diseases contribute to an increase in the incidence and lethality of cancers and, thus, treating one may prevent the other.

## Exploring energy metabolism

Bruce Spiegelman, PhD, acknowledges that his work represents an untraditional area of Cancer Biology, the department in which he is a professor. “When I first came to Dana-Farber, I had a strong focus on cell differentiation, which is part of the cancer problem,” he says, “and I used fat cells as a model system.” Over time, Spiegelman became interested in the control of energy metabolism. Metabolic disease accounts, at least in part, for the rising incidence of cancer despite improvements in treatment during the last two decades, he explains. Today, a major focus of his laboratory is studying how gene transcription regulates energy homeostasis, which has application to the development of new therapies for obesity, diabetes, cardiovascular and neurodegenerative disorders, as well as cancer.

In a 2008 paper published in the journal *Nature* — and lauded by the journal *Science* as one of the year’s top 10 scientific breakthroughs — investigators in the Spiegelman laboratory, including first author Patrick Seale, PhD, completely overturned conventional dogma regarding the origin of brown fat. Previously, scientists believed that white fat cells, which store calories, and brown fat cells, which burn energy, arise from the same progenitor. Instead, says Spiegelman, “Brown fat is derived from muscle precursors, not at all from the white fat cell lineage.” Through a series of biochemical and in vivo genetic studies, the Spiegelman group traced the lineage of brown fat cells and discovered that these cells share a common precursor with skeletal muscle cells, and that a protein known as PRDM16 acts as a cell-fate switch between the two. Astonishingly, RNAi knockdown of PRDM16 in brown fat cell precursors of mice induced the development of skeletal muscle cells — a “pretty outrageous result,” remarks Spiegelman, who observed the

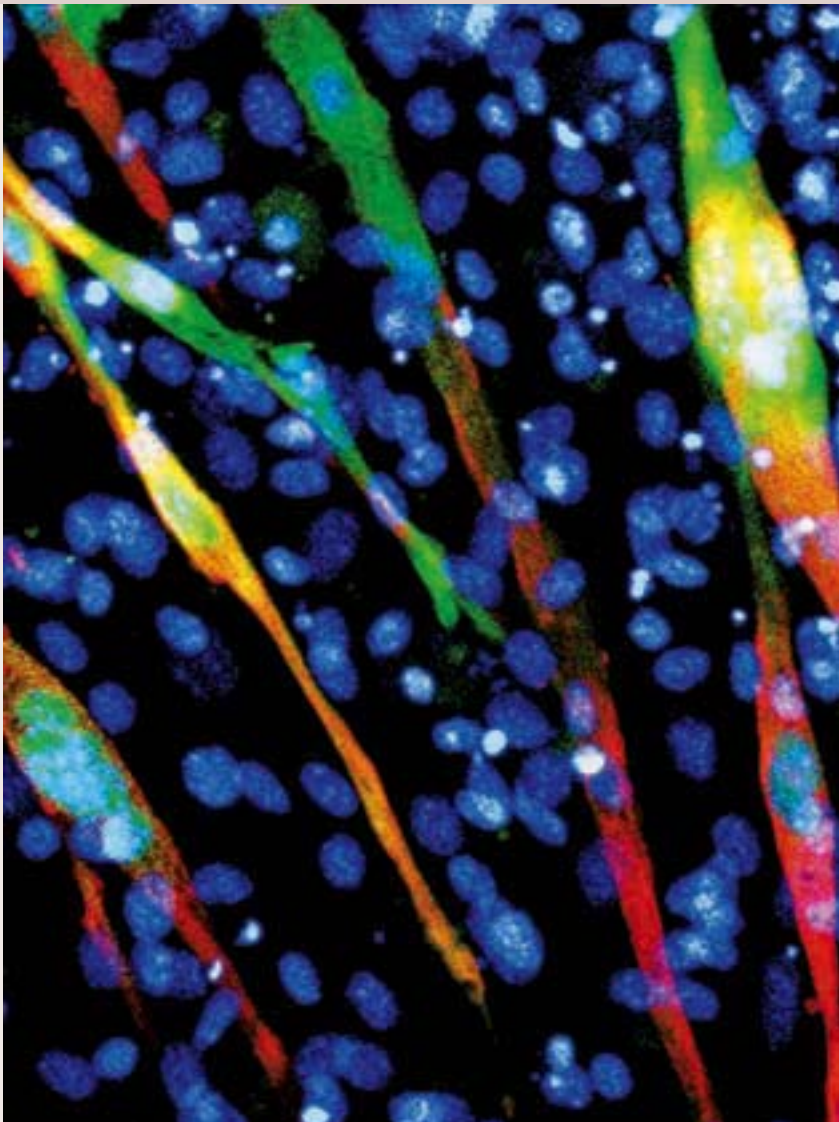
PICTURED ABOVE (FROM TOP):  
BRUCE SPIEGELMAN, PHD,  
AND NIKA DANIAL, PHD

multinuclear, tubular muscle cells under the microscope. If confirmed in future studies in the whole mouse or in humans, this unexpected connection between brown fat and skeletal muscle may present an entirely new approach to the treatment of obesity, says Spiegelman. “That’s what we’re really excited about.”

In studies of ischemia and hypoxia, investigators in his lab also discovered a novel transcriptional pathway of angiogenesis that bypasses — and appears to complement — the canonical pathway known as hypoxia inducible factor (HIF)-1 $\alpha$ . Until this finding, it was thought that when a cell experiences a crisis, the HIF-1 $\alpha$  pathway stimulates vascular endothelial growth factor (VEGF) to develop new blood vessels to protect the cell from injury. In experiments in cultured muscle cells and in the skeletal muscle of mice, however, investigators found that a lack of nutrients and oxygen

induced the transcriptional coactivator PGC-1 $\alpha$  to stimulate VEGF (the PGC-1 $\alpha$  protein activates transcription factors that regulate energy metabolism). “We discovered a separate regulatory pathway, independent of HIF-1 $\alpha$ , which leads to induction of the same growth factors through PGC-1 $\alpha$ ,” explains Spiegelman.

So, why would the cell choose one pathway over the other? “We think the two pathways are complementary,” he responds, “and that the HIF-1 $\alpha$  pathway depends on the relative oxygen tension in the cell, while the PGC-1 $\alpha$  pathway depends on its relative energy charge.” Although this research was conducted exclusively in skeletal muscle cells, Spiegelman predicts that PGC-1 $\alpha$  is likely to function similarly in other cells. Whether it plays a role in the vascularization of tumor cells has yet to be studied.



PRIMARY BROWN PREADIPOCYTES GIVE RISE TO MUSCLE CELLS WHEN PRDM16 EXPRESSION IS KNOCKED DOWN. A culture of primary brown fat preadipocytes was treated with an siRNA vector targeting PRDM16. In these cultures, long, multinucleated, tube-like cells appeared that were strongly marked by green fluorescent protein, which was coexpressed from the vector. These GFP-expressing cells were stained with an antibody specific for the muscle-specific protein, myosin heavy chain, demonstrating that they were skeletal myocytes. These results suggest that brown fat cells and skeletal muscle cells are derived from a common precursor and that PRDM16 restricts skeletal muscle gene expression and development. Staining: GFP (green), myosin heavy chain (red), and nuclei (blue).

## New role for BAD yields novel diabetes therapy

Ever since she was a postdoctoral fellow in the laboratory of the late Stanley Korsmeyer, Nika Danial, PhD, has been intrigued with BAD (BCL-2 associated death promoter), a member of the BCL-2 family of proteins known to regulate apoptosis, a process that many cancer cells escape. Like an alert sentinel, BAD senses cellular damage and communicates this information to the mitochondria, which in turn, release apoptogenic factors

Genetic experiments showed that mice lacking the BAD protein had fasting hyperglycemia and impaired glucose tolerance, features characteristic of type 2 diabetes.

leading to destruction of the damaged cell. But, Danial was curious about the biology of BAD and whether the protein might play a nonapoptotic role in healthy cells.

She and colleagues embarked upon a series of biochemical studies of the proteins to which BAD binds at mitochondria, she says, and “literally stumbled” upon glucokinase (GK, an enzyme that facilitates phosphorylation of glucose), suggesting a new role for BAD in the metabolism of glucose. Moreover, genetic experiments showed that mice lacking the BAD protein had fasting hyperglycemia and impaired glucose tolerance, features characteristic of type 2 diabetes.

This startling discovery led to a series of experiments to figure out how BAD toggles between its two functions. To their surprise, the BH3 domain of BAD controls both apoptosis and glucose metabolism, says Danial, now assistant professor in the Department of Cancer Biology. Like a master switch, the phosphorylation status of the BH3 domain regulates the ligands to which BAD can bind and, thereby, determines whether the cell signals through the apoptotic or the metabolic pathway.

When investigators created a genetic mutant of BAD whose BH3 domain could not be phosphorylated, the mutant could bind only to its pro-apoptotic partners and proved incompetent for metabolic function, explains Danial. Conversely, a genetic mutant whose BH3 domain was constitutively phosphorylated could bind only to GK, required for glucose metabolism, and could not induce apoptosis.

These unusual findings sparked a new idea. “If we could mimic the phosphorylated BH3 domain through genetic or pharmacologic maneuvers,” explains Danial, “we could stimulate BAD’s metabolic function without sensitizing cells to apoptosis.” To test this hypothesis, Danial’s laboratory collaborated with Loren Walensky, MD, PhD, of the Department of Pediatric Oncology, who turned the amino acid sequence of the constitutively phosphorylated BH3 domain of BAD into a peptide-mimetic compound. Danial’s lab then tested the compound in defective beta cells of the pancreas, which in type 2 diabetes become incapable of secreting insulin in response to glucose. Strikingly, the compound restored glucose metabolism and insulin secretion in the faulty cells. “This demonstrates that the BH3 domain is not only required, but also sufficient for BAD’s function in glucose homeostasis,” Danial emphasizes. “And, remarkably, it opens up a whole new therapeutic strategy for diabetes based on mimicking the function of a domain that nature has already designed to activate GK.”

Ongoing animal model studies using both genetic and pharmacologic manipulations of BAD’s metabolic function are beginning to show promise as well. The mimetic compounds that emerged from this collaboration between biologists and chemists have the potential to serve a dual therapeutic purpose, observes Danial. “They may help control blood glucose while preventing apoptosis in the cell,” thus eliminating some toxicity problems. “We hope this novel therapeutic strategy will have significant implications for type 2 diabetes.”

# DNA Repair



Using radiation to shrink tumors has long been a mainstay of cancer treatment, with ever more powerful, precise machines delivering beams that break DNA and, as a result, kill cells. Now, scientists are also focusing on the other half of the equation — rendering cancer cells more vulnerable to the DNA-damaging effects of radiation. “Tumors become resistant by repairing the DNA damage to their cells,” explains Alan D’Andrea, MD, chief of the Division of Genomic Stability and DNA Repair in the Department of Radiation Oncology. Cells are naturally equipped to repair broken DNA; cancer cells can exploit this mechanism, activated by several DNA repair “pathways,” to counteract the gains of radiation treatment. D’Andrea and his colleagues have identified specific pathways critical to the DNA repair process. An emerging strategy is to give drugs that block those pathways along with radiation therapy.

## Discovering a role for histone methylation in DNA repair

The tumor suppressor gene *Tip60*, which is often abnormal in breast and prostate tumors, is a significant factor in a tumor’s sensitivity to radiotherapy. The ability of radiotherapy to kill tumors is critically dependent on whether or not the tumor can repair the DNA double strand breaks (DSBs) induced by ionizing radiation, explains Brendan Price, PhD, of Radiation Oncology. Previous research in the Price laboratory had demonstrated that the Tip60 enzyme, an acetyltransferase, is a key upstream regulator of the DNA damage response pathway: it acetylates the ATM kinase, the central signaling protein that initiates the cascade of events leading to DSB repair. This was the first time anyone had shown acetylation is required to activate a kinase.

Since little was known about what activates Tip60, Price looked upstream of the enzyme to elucidate its molecular mechanisms. He knew that Tip60 contains a chromodomain (a protein module associated with chromatin regulation) that is predicted to bind to methylated lysine residues that function as docking sites for regulatory proteins. He also knew that the most likely place to find methylated lysine residues is on histones.

His first step was to introduce mutations into Tip60’s chromodomain to investigate the effect in cells. He found that the enzyme’s acetyltransferase activity was abolished, thus disrupting ATM signaling. In search of the histone binding site, investigators then synthesized dozens of peptides, derived from

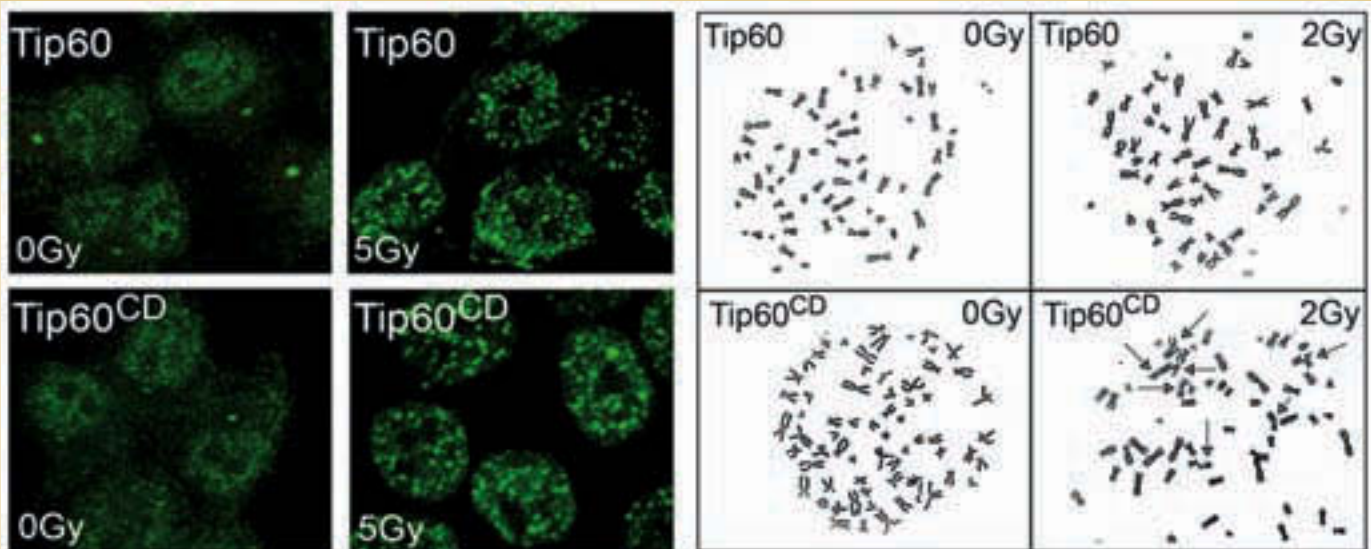
PICTURED ABOVE (FROM TOP):  
ALAN D’ANDREA, MD,  
AND BRENDAN PRICE, PHD

methylated lysines, to see which could attach to the chromodomain and activate Tip60. The lab discovered that Tip60's chromodomain has specificity for binding to H3K9me3 (histone H3 trimethylated on lysine 9), and that this direct interaction with histone methylation is required for turning on Tip60. "This finding is important because it demonstrates for the first time that histone methylation is required for DNA repair," says Price. This research also shows that rather than merely recruiting essential proteins to the damaged DNA, histone methylation in fact regulates Tip60's acetyltransferase activity, he explains.

These novel findings suggested that blocking the interaction between Tip60's chromodomain and its histone methylation site would increase the sensitivity of cells to radiation, says Price. Investigators tested this hypothesis from two angles: they mutated Tip60's chromodomain in tumor cells and irradiated them, finding there was no ATM signaling and that cells had become five to six times more sensitive to radiation; they also reduced levels of H3K9me3 to about 10 percent of normal, which resulted in defective ATM signaling and cells that were much more susceptible to radiation. These and other experiments demonstrate that methylation of the histones can be modulated, says Price, either

by inhibiting demethylases (which remove methylation) to increase signaling in the cell, or by inhibiting methyltransferases (which catalyze methylation) to decrease signaling in the cell. These discoveries suggest that H3K9me3 could be exploited as a biomarker for predicting the sensitivity of tumors to radiation therapy, with low levels of histone methylation indicating that radiation is likely to be an effective therapy, says Price.

This work might also lead to a novel approach to radiation therapy, one which hinges on exploiting the differences in histone methylation patterns between the tumor and the normal tissue surrounding it. For example, when the tumor has very high levels of H3K9me3 compared to adjoining tissue, explains Price, it is much more efficient in turning on Tip60 and repairing DSBs. "If we could target that tumor with a methyltransferase inhibitor, we might be able to decrease methylation levels and thus sensitize these tumor cells to ionizing radiation." Alternatively, a demethylase inhibitor targeted to normal cells might increase their methylation levels and provide some protective resistance to radiation. "In this case, we could deliver more radiation to the tumor and therefore improve the therapeutic response," says Price. Price and his team, including Yingli Sun, PhD, and Ye Xu, PhD, are currently working toward that goal.



**TIP60'S CHROMODOMAIN IS ESSENTIAL TO MAINTAIN GENOME STABILITY.** LEFT: Tip60 and Tip60 with a mutated chromodomain (Tip60<sup>CD</sup>) are both recruited to DNA double strand breaks (DSBs) caused by exposure to 5Gy of ionizing radiation.

RIGHT: Analysis of chromosomes from cells expressing Tip60 or Tip60<sup>CD</sup> reveals numerous chromosomal aberrations in the irradiated Tip60<sup>CD</sup> cells (arrows) due to defective DSB repair.

# Population Sciences



Certain racial and economic groups — African Americans, Hispanics, and the poor — have consistently been shown to be at greater risk for cancer, have less access to quality care, and often have worse outcomes than the rest of the population. While genetic differences may partly explain why cancer rates vary among ethnic groups, more needs to be done to identify the causes of these disparities, lower obstacles to cancer screening and prevention services, and ensure that all patients receive equal high-quality care.



Reducing inequities in cancer screening, diagnosis, treatment, and follow-up care, so no group is at a disadvantage, is one of the prime missions of Dana-Farber. “We’re interested in disparities across the entire trajectory of disease, from the point at which a patient’s cancer is first detected to the conclusion of treatment and, after that, to life as a cancer survivor,” says Jane Weeks, MD, MSc, chief of Population Sciences in Medical Oncology and director of the Institute’s Center for Outcomes and Policy Research.



## Deciphering disparities in diagnosis and treatment

Investigators are leading a variety of studies to uncover the sources and extent of disparities and to identify ways of eliminating them.

### UNDERSTANDING CANCER CARE DIFFERENCES AMONG INSURED POPULATIONS

Deborah Schrag, MD, MPH, is leading a project that focuses on the quality of cancer care provided to patients insured by state Medicaid programs. Researchers are examining whether such patients receive care that is timely and similar to that provided to patients with private insurance. They are also investigating whether treatment outcomes for Medicaid patients are worse than for those who are privately insured.

Schrag’s team is analyzing data on thousands of patients insured by Medicaid, Medicare, or both when they were diagnosed with cancer. The researchers are scrutinizing the data to determine if poor and elderly people — covered by Medicaid and Medicare, respectively — tend to be diagnosed with more advanced cancers than people with private insurance. Since early detection and diagnosis can be critical to successful cancer therapy, the study may give insights into why treatment often produces less favorable results among these

PICTURED ABOVE (FROM TOP):  
JANE WEEKS, MD, MSc,  
DEBORAH SCHRAG, MD, MPH,  
AND GLORIAN SORENSEN, PHD, MPH

The study may give insights into why treatment often produces less favorable results among disadvantaged minorities and the elderly.

groups. By examining whether racial or ethnic differences persist among patients with similar public insurance, the research will also help specify the root cause of such disparities.

The researchers have linked cancer registry information to Medicaid, Medicare, and hospital admission data in two states. “Joining Medicare and Medicaid claims with tumor registry records offers an inexpensive, timely way to monitor

the caliber of cancer care delivery,” Schrag remarks. “Discrepancies in care will help us identify areas where interventions can equalize services for all patients.”

Another project, the Gear Up for Health Study, tested a new approach to weight loss and smoking reduction among long-haul truck drivers. The study examined whether providing telephone counseling to drivers could help them lose weight and decrease tobacco use. “The rate of tobacco use among truck drivers is 40 percent, about double the national average,” says Glorian Sorensen, PhD, MPH, who led the study in collaboration with the International Brotherhood of Teamsters. “Drivers are also more likely than the average American to be overweight.”

Because a trucker’s working environment — long hours of little physical activity, boredom, deadline pressure — may contribute to health problems, the intervention was geared specifically to those conditions. “It was clear that a generic weight loss and smoking cessation program was unlikely to be effective.” Sorensen says, “so the messages delivered by the telephone counselors were designed to reflect the reality of the drivers’ work setting.” The researchers found that the intervention had a significant impact on smoking cessation among the drivers, but wasn’t

effective in weight reduction. The results show that phone counseling can be effective for tackling some of the job-related health problems experienced by truckers, but that other approaches may be necessary to deal with other issues.

### THE ROAD TO BETTER TREATMENT DECISIONS

Schrag and Sorensen’s projects are part of a larger trend in population sciences that extends beyond documenting the prevalence of inequities to defining the causes of inequities and ways to overcome them.

As a recent study shows, the “apparent” reason for a health care disparity isn’t always the right one. The question to be answered was why elderly patients with colorectal cancer are much less likely to receive adjuvant chemotherapy than are their younger counterparts. To Weeks, the reason seemed obvious: “These patients never get a chance to talk with their oncologists, because surgeons think they’re too old and don’t refer them.”

In fact, the study showed that virtually all patients, regardless of age, had the opportunity to consult with an oncologist, though some chose not to do so. By correlating data from thousands of medical records, Weeks and fellow researchers found that in two-thirds of the instances in which patients did not receive chemotherapy, oncologists had deemed the treatment unnecessary. The doctor’s decision was influenced, in part, by uncertainty over the effects of chemotherapy in older patients.

This study was undertaken by the Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium, which was formed to identify flaws in the cancer care system and identify ways of correcting them. The results point to the need for clinical trials that focus on the effects of chemotherapy in older patients. Such studies, plus education for oncologists on the risk-benefit ratio of therapy, may lead to better, more consistent treatment decisions.

# Surgical Oncology



In the search for more effective cancer treatments, the development of multimodality strategies has become key to improved outcomes. The research conducted by surgical oncologists extends from understanding tumor biology to novel treatment approaches that combine surgery, chemotherapy, and radiation therapy. The surgical oncology team at Dana-Farber, along with colleagues at Brigham and Women's Hospital, are advancing our understanding of the pathogenesis and treatment of breast cancer.



## Teaming up for innovative clinical trials

You can compare a team that runs today's multidisciplinary breast cancer clinical trials to a musical quartet, says J. Dirk Iglehart, MD. "The musicians have to play in sync; if one misses, the melody may be lost," he says. When conducting a clinical trial, everything has to work perfectly, from the time the patient consents to participate until the data are analyzed. "We work together to get answers that will allow us to improve outcomes for patients."

Iglehart, a member of Cancer Biology at Dana-Farber and surgical oncologist at Brigham and Women's Hospital, serves as director of the Women's Cancers Program. He oversees a team of surgeons, medical oncologists, radiologists, pathologists, epidemiologists, and basic scientists determined to find new ways to understand, prevent, and treat breast and gynecologic cancers.

As the investigators teamed up, they recognized that the traditional course of breast cancer treatment made it difficult to fully assess the effectiveness of an innovative therapeutic drug. "When surgeons removed tumors before therapeutic drugs were given, there was no measurable disease after surgery, so we didn't know if the drug was working," says Iglehart. Since there was no data to indicate whether patients did better if the tumor was removed first, the team decided to turn things around and started administering the drug first. "A typical preoperative trial may go from two months to four months prior to surgery, a delay which doesn't appear to make a difference to the patient's outcome," he emphasizes. After surgery, the patient continues with a normal chemotherapy regimen.

PICTURED ABOVE (FROM TOP):  
J. DIRK IGLEHART, MD,  
AND MONICA BERTAGNOLLI, MD,  
CHIEF OF SURGICAL ONCOLOGY,  
BRIGHAM AND WOMEN'S HOSPITAL,  
AND CHAIR, NCI CANCER AND  
LEUKEMIA GROUP B (CALGB)

“Twenty percent treated only with cisplatin achieved a complete pathologically confirmed disappearance of their disease,” Iglehart notes. This result was unexpected and highly significant.

molecular profiling when evaluating treatment outcomes. By integrating such profiles with treatment response data, Dana-Farber researchers and their colleagues were among the first to identify four distinct molecular subtypes of breast cancer, each with a different treatment response profile.

Such studies are enabled by a set of resources available at Dana-Farber and Brigham and Women’s Hospital. The cancer research information system, known internally as CRIS, stores clinical, treatment, and outcomes data for cancer patients treated through Dana-Farber/Partners CancerCare. CRIS was started in 1997 by Jane Weeks, MD, MSc, of Medical Oncology. Complementing CRIS, surgical pathologist Andrea Richardson, MD, PhD, of Brigham and Women’s Hospital, developed a tumor tissue bank. One of the largest of its kind, the bank has 3,000 frozen breast cancer specimens available for molecular analysis. A blood sample bank is yet another part of the investigative toolkit, funded by the Nancy Lurie Marks Foundation and led by Richardson and Penelope Miron, PhD, of Cancer Biology. “Getting a sample of the patient’s normal DNA is critical,”

The value of this approach was demonstrated in a study led by Judy Garber, MD, MPH, of Medical Oncology. As reported in 2008, the study preoperatively treated “triple-negative” patients whose tumors were negative for estrogen receptor (ER) protein, the HER2 cell-surface receptor, and the ER-related receptor for progesterone. “Twenty percent treated only with cisplatin achieved a complete pathologically confirmed disappearance of their disease,” Iglehart notes. This result was unexpected and highly significant.

This study also highlighted the critical importance of

Iglehart points out. “And the only way you’ll ever discover a blood test for breast cancer is to get serum from lots of people with cancer.”

Importantly, specimen data from the tissue and blood banks are integrated with the outcomes data in CRIS. “Now you can really ask, is there a marker in the blood that went down after the treatment?” Iglehart says. “Is there a gene in the body that predisposes a patient to a given response to the drug? Is there a gene in the tumor that was hit by the drug, and did it get inhibited? And what happened to the patient? You can put it all together, sometimes without having to conduct a new trial.”

“This really is a sea change in cancer research,” Iglehart declares. “We are developing drugs that are more and more targeted to hit specific molecular pathways.” He gives the example of the PI3 kinase (PI3K) pathway, which affects many cellular growth signals. Scientists at Dana-Farber, including Thomas Roberts, PhD, and Jean Zhao, PhD, have done major work in understanding this pathway, and companies are developing drugs that inhibit PI3K (see story, page 8). Eric Winer, MD, chief of the Division of Women’s Cancers in the Department of Medical Oncology, and Ian Krop, MD, PhD, also in the Division, are conducting trials of PI3K-inhibiting drugs in women with advanced breast cancer and, preoperatively, in women with earlier stages of breast cancer, including tumors that are HER2-positive and appear to rely on PI3K for their growth. Winer and Krop will test PI3K inhibitors in women whose breast cancers have become resistant to the HER2-targeting drug trastuzumab (Herceptin) and will combine PI3K inhibitors with trastuzumab in women prior to surgical excision. Now, the basic scientists will learn whether their results in the laboratory and in animals actually predict efficacy in people.

“In the next 20 or 30 years, we will cure or significantly reduce the burden of several subtypes of breast cancer,” Iglehart sums up. “We’ll be able to identify the subtypes and treat them selectively, improving outcomes, and reducing toxic effects. It won’t be easy, but it will be an exciting time in clinical research.”

# Department of Biostatistics and Computational Biology

The Department of Biostatistics and Computational Biology is the home of researchers trained in quantitative sciences. Their mission is to advance cancer research and cancer treatment, both directly and by providing their expertise through collaboration.

## DEVELOPING AND APPLYING QUANTITATIVE METHODS FOR CANCER RESEARCH

Today, quantitative ideas are part of the foundations of cancer research, because of the variation in etiology and response to therapy and the prominent role of data-intensive technologies in high-throughput biology, imaging, and elsewhere. In parallel, computational ideas are entering clinical activities: probabilistic risk assessment algorithms and genomic approaches to guiding treatment are just two examples. Increasingly, oncologists use tools and interpret research results that rely heavily on complex statistical and computational approaches.

To meet these challenges, the Department's faculty conduct basic research in statistical and computational methods for clinical and translational research, population-based studies, and cancer biology. They also develop software for research and clinical applications, and perform high-throughput genomic experiments guided by their computational insights. All members collaborate extensively in interdisciplinary research, providing expert advice on experimental design, data collection, data storage, data integration, as well as data analysis of clinical, laboratory, and population-based studies.

## RESEARCH TEAM

Currently, the Department is comprised of 26 faculty, 4 research associates, 12 research fellows, 15 MA biostatisticians and 12 bioinformaticians. In addition, there are at least 10 graduate students working with faculty members at any time. During 2009, Department members authored or coauthored more than 100 peer-reviewed publications.

## NATIONAL ROLE IN CLINICAL TRIALS AND OUTCOMES STUDIES

Reflecting their national prominence in supporting multicenter clinical trials, members of the Department have supported the Eastern Cooperative Oncology Group (ECOG), a consortium with more than 350 hospitals and treatment centers throughout the United States, for many years. Funded by the National Cancer Institute to conduct multicenter clinical trials in adult malignancies, ECOG maintains a database of more than 110,000 cancer cases and is conducting active follow-up on more than 20,000 patients who have participated in clinical trials. The Statistical Center of ECOG is currently led by Robert Gray, PhD.

The International Breast Cancer Study Group (IBCSG) is a network of institutions in Europe, South America, Australia, New Zealand, Asia, and South Africa. Since 1977, IBCSG has conducted large, randomized Phase III clinical trials evaluating the timing and duration of chemotherapy and the role of endocrine therapy as adjuvant treatment for breast cancer. IBCSG is considered to be a leader in the field of tailored treatment approaches for specific subpopulations of patients with breast



GIOVANNI  
PARMIGIANI, PHD,  
CHAIR



DAVID HARRINGTON,  
PHD, CHAIR THROUGH  
SUMMER 2009



cancer. For many years, the Statistical Center was led by Richard Gelber, PhD; it is now directed by Department member Meredith Regan, ScD.

Members of the Department also work closely with the AIDS Clinical Trial Group, and are coordinating statistics for studies of pediatric AIDS as well as immunologic markers of human immunodeficiency virus (HIV) infection.

The Department is similarly committed to observational studies of outcomes in cancer. For example, the Cancer Care Outcomes Research and Surveillance Consortium, or CanCORS, is a prospective follow-up study of 10,000 patients newly diagnosed with colorectal or lung cancer. The Statistical Coordinating Center for CanCORS is led by David Harrington, PhD, former department chair.

In all these areas, faculty pursue an active agenda of methodological investigations. For example Yi Li, PhD, is using data from ongoing trials to develop statistical tools for identifying patients who will respond to specific chemotherapy treatments. In 2006, the Department recruited Armin Schwartzman, PhD, an expert in multivariate and high-dimensional data analysis, who is rapidly developing a cutting-edge research program in signal and image analyses as they apply to cancer.

### **DANA-FARBER/HARVARD CANCER CENTER**

Faculty and staff statisticians play central roles in the development of all clinical research protocols at Dana-Farber/Harvard Cancer Center (DF/HCC), the largest NCI-designated Comprehensive Cancer Center in the country. Faculty serve as members of DF/HCC's Scientific Review Committee as well as the Institutional Review Board.

DF/HCC's Biostatistics Core is located at Dana-Farber and is directed by faculty member Paul Catalano, ScD. The core provides consultation and assistance to Cancer Center members in all DF/HCC Research Programs.

### **RESEARCH AND COLLABORATION IN COMPUTATIONAL BIOLOGY**

In 2008, John Quackenbush, PhD, established the Center for Cancer Computational Biology (CCCB) at Dana-Farber. This research center provides broad-based support for the analysis and interpretation of genomic and other large-scale data. In doing so, CCCB furthers basic, clinical, and translational research by providing new ways of understanding human cancer. The Center is focused on developing new methods for

improving the analysis and interpretation of genomic data through the integration of diverse data types. As such, the Center provides Dana-Farber investigators with state-of-the-art assistance in the collection, management, analysis, and interpretation of large-scale data. It also provides software, services, and training in order to assist investigators in advancing their personal research.

The faculty also pursue an active program of independent research in the computational biology of cancer. For example, Quackenbush created an integrated clinical and research data portal that will serve as the basis for the personal genomics initiative at the Institute, and created a new web-based resource, GeneSigDB, that brings together more than 500 published genomic signatures. Guo-Cheng Yuan, PhD, developed a computational method, called N-score, to predict the positions of nucleosomes in the genome. Cheng Li, PhD, continued expanding his own DChip, one of the most widely used genomic analysis tools. Xiaole (Shirley) Liu, PhD, developed novel tools for exploring the mechanisms of gene regulation, including the MACS algorithm for analysis of ChIP-seq data. Lastly, Giovanni Parmigiani, PhD, who joined the Department in 2009, continues his work on computational approaches for identifying families at risk of inherited susceptibility to cancer, which has yielded widely used algorithms such as BRCAPro, PancPro, and MMRpro.

### **TEACHING THE NEXT GENERATION OF BIostatISTICIANS AND COMPUTATIONAL BIOLOGISTS**

The Department has a close partnership with the Department of Biostatistics at Harvard School of Public Health, where the majority of the faculty have primary academic appointments. Department faculty are leaders of training grants and curriculum development initiatives, direct research, and teach in the doctoral program there, as well as the undergraduate degree program in statistics at Harvard College.

### **AWARDS OF NOTE**

Two department faculty members received significant awards in the last year: Marvin Zelen, PhD, founding chair of the Department, received the American Cancer Society's Medal of Honor, the highest honor bestowed by the ACS in recognition of outstanding contributions to cancer control in three categories; and Richard Gelber, PhD, was a corecipient of the Brinker Award, one of the most prestigious awards given for breast cancer research and supported by Susan G. Komen for the Cure.

# Department of Cancer Biology

The Department of Cancer Biology focuses on fundamental problems in biology of relevance to cancer.

## RESEARCH GOALS AND THEMES

The overarching goal of the Department is to translate laboratory findings into the development of new therapeutic strategies. Departmental strengths in the leading-edge technologies of structural, systems, and chemical biology facilitate the translation of biology-based investigations in neurobiology, women's cancers, and energy homeostasis. Expertise in signal transduction and cell cycle control has contributed directly and indirectly to a new generation of targeted therapeutics for cancer (a.k.a. "smart drugs"), such as imatinib (Gleevec) and gefitinib (Iressa).

## DEPARTMENTAL GROWTH

The Department has grown over the past three years, as measured both by grant support and number of independent faculty. Collectively, the research support portfolio grew to more than \$30 million for fiscal year 2008, compared to \$28 million for 2005. Six new faculty have joined the department since 2006, bringing the number of independent department faculty to 21. Ulrike Eggert, PhD, and Nathanael Gray, PhD, were recruited as part of the Dana-Farber strategic plan initiative in Cancer Chemical Biology. The addition of Alexander (Sasha) Gimelbrant, PhD, and Jean Zhao, PhD, adds to a growing research focus in women's cancers. Suzanne Gaudet, PhD, augments the Department's systems biology expertise, while Pere Puigserver, PhD, rounds out the energy homeostasis group.

## STRUCTURAL BIOLOGY

Michael Eck, MD, PhD, specializes in X-ray crystallography of kinases. In collaboration with investigators from Dana-Farber/Harvard Cancer Center's Lung Cancer Program, Eck has determined the structure of patient-derived *EGFR* mutants to propose mechanisms of tumor response to therapy and drug resistance. Jarrod Marto, PhD, develops mass spectroscopy techniques to optimize detection and characterization of phosphoproteins. William Shih, PhD, constructs nanoscale objects and nanomechanical devices based on DNA molecules. He uses these to interrogate and modulate the operation of cells.

## SYSTEMS BIOLOGY

Marc Vidal, PhD, director of Dana-Farber's Center for Cancer Systems Biology, uses powerful techniques in genetics and computational biology to map the genetic and protein networks that control cell behavior. He applies this information in a predictive manner to identify new pathways for therapeutic intervention. Suzanne Gaudet, PhD, takes a quantitative approach to measuring and analyzing the response of single cells to drugs and other extracellular signals.

## CHEMICAL BIOLOGY

The chemical biology group brings departmental expertise in early-stage drug discovery and translates insights on protein structure and function into entry-level screens for new cancer therapeutics. Eggert identifies new drug targets through the parallel approaches of small-molecule and genome-wide RNAi screening. Gray develops libraries of small-molecule kinase inhibitor compounds and collaborates widely with disease program investigators. Their goal is to use these libraries to define therapeutic targets in tumors (see story, page 13).



THOMAS ROBERTS,  
PHD, CO-CHAIR



CHARLES STILES, PHD,  
CO-CHAIR



### NEUROBIOLOGY

Another group of Cancer Biology faculty focuses on the genetics of brain development. Qiufu Ma, PhD, identifies and characterizes transcription factors that regulate the formation of sensory neurons and create neural networks for the perception of pain. Charles Stiles, PhD, focuses on genes that direct the formation of the glial lineages in the brain, while Rosalind Segal, MD, PhD, describes interactions between cells in the brain that lead to cell proliferation or migration. The outcomes of these studies will lead to new insights about treatments for brain cancer, one of the most deadly and untreatable forms of cancer.

### WOMEN'S CANCERS

The biology of women's cancers, particularly breast cancer, is another area of focus for faculty in the Department. J. Dirk Iglehart, MD, is the principal investigator of the DF/HCC Breast Cancer Specialized Programs of Research Excellence (SPORE), which aims to translate basic science findings into new clinical treatments for breast cancer (see story, page 37). David Livingston, MD, who is also deputy director of DF/HCC, defines the functions of breast cancer susceptibility genes, *BRCA1* and *BRCA2*. Thomas Roberts, PhD, and Zhao determine the specific roles of PI3K isoforms in diverse cellular pathways such as growth, metabolism, and transformation. Peter Sicinski, MD, PhD, characterizes the roles of cell cycle regulators in cancer, and Gimelbrant probes the mechanisms of epigenetic silencing of gene expression.

### ENERGY HOMEOSTASIS

Energy homeostasis is the area of investigation for Bruce Spiegelman, PhD, Nika Danial, PhD, and Puigserver. Spiegelman defines the transcriptional programs governing development of adipocytes, as well as their roles in regulating energy balance and homeostasis. Danial determines the functions of BCL2 family proteins that operate at the intersection of metabolic and cell death pathways. Puigserver identifies the transcriptional mechanisms that regulate metabolic and longevity pathways (see stories, pages 30-32).

### TEACHING THE NEXT GENERATION OF SCIENTISTS

Teaching is an important complement to our research activities. Collectively, the Department has trained 307 postdoctoral fellows and graduate students during the past three years. Students from many Harvard-based graduate programs — including Biomedical and Biological Sciences, Biophysics, Virology, and Neurobiology — complete their doctoral theses in the Department's many laboratories. Graduate students and postdoctoral fellows participate in informal weekly seminars and the annual departmental retreat. Stiles and Segal also codirect a Harvard-wide training grant in cancer biology from the National Cancer Institute.

# Department of Cancer Immunology and AIDS

The Department of Cancer Immunology and AIDS investigates fundamental questions in the development and expression of immune responses in cancer and autoimmune disease, as well as the closely related problem of acquired immunodeficiency syndrome (AIDS).



HARVEY CANTOR, MD,  
CHAIR

## RESEARCH GOALS AND THEMES

Research goals of the Department include understanding the requirements for effective innate and adaptive host immune responses, and the development of adoptive cellular therapies and vaccines against cancer and AIDS. These efforts are enhanced by collaborative relationships within Dana-Farber/Harvard Cancer Center's Cancer Immunology Program, where Kai Wucherpfennig, MD, PhD, and Glenn Dranoff, MD, (a member of the Department of Medical Oncology) serve as co-leaders. A cornerstone of the department's mission is training graduate students and postdoctoral fellows. Two NIH-funded training grants, led by Department Chair Harvey Cantor, MD, support postgraduate training in cancer immunology and AIDS research.

Faculty research interests include hematopoiesis and lymphocyte development; innate immunity; antigen-presenting cells; T-cell activation; the Th1 response; regulatory T cells; tumor cell metastasis; cancer vaccines and immunotherapy; human monoclonal antibody-based immunotherapy; viral entry; mechanisms of HIV integration and HIV replication and pathogenesis; and AIDS vaccines.

## HEMATOPOIESIS AND LYMPHOCYTE DEVELOPMENT

Koichi Akashi, MD, PhD, studies differentiation of hematopoietic stem cells into different lineages with particular emphasis on prospective definition of key differentiation intermediates. He has isolated the common lymphoid progenitor that gives rise to T cells, B cells, and NK cells, the common myeloid progenitor that gives rise to all myeloid lineages, and has identified myeloid progenitors with more restricted differentiation potential.

Harald von Boehmer, MD, PhD, studies early steps in T-cell differentiation. Von Boehmer and colleagues have identified T-cell precursors in peripheral blood prior to their entry into the thymus. These circulating T-cell progenitors (CTPs) were found at the same frequency in *Foxn1* (*nu/nu*) thymus-deficient mice and wild-type mice, indicating that they were prethymic rather than post-thymic. Thus, CTPs represent committed T-cell precursors linking extrathymic with intrathymic lymphopoiesis in adult mice.

In the thymus, signaling through the T-cell antigen receptor leading to elimination (negative selection) or differentiation (positive selection) of developing thymocytes generates a self-tolerant T-cell repertoire. Cantor has shown that the serine-threonine kinase MINK connects the T-cell receptor to a signaling pathway that mediates negative, but not positive, selection. Analysis of this pathway indicates that MINK-dependent elimination of self-reactive thymocytes is associated with downstream activation of Jun kinase and enhancement of expression of the pro-apoptotic molecules, Bim and BimEL.



Carl Novina, MD, PhD, and Wucherpfennig study the role of microRNAs (miRNAs) in T-cell development and T-cell-mediated immune responses. They have shown that two particular miRNAs are highly upregulated during T-cell development in the thymus, but not expressed or expressed at low levels in mature T cells. Current efforts are focused on defining the targets of these miRNAs and their function in normal lymphoid development as well as in leukemias.

### **CANCER VACCINES AND IMMUNOTHERAPY**

Using a pancreatic tumor cell model, Shannon Turley, PhD, studies how the activity of tumor-infiltrating T cells can be increased. Turley is now examining whether cytokine-cytokine receptor complexes can induce tumor regression.

Dranoff is developing cancer vaccines with autologous tumor cells engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF). This approach has been translated to clinical trials in multiple cancers and has shown consistent induction of coordinated humoral and cellular immune responses that effectuated substantial tumor destruction. Dranoff also showed that some patients who responded to tumor vaccination or CTLA4 antibody blockade developed high-titer antibodies to the NKG2D ligand MICA. These reactions contributed to tumor destruction by antagonizing immune suppression and augmenting antitumor cytotoxicity (see story, page 28).

### **HIV/AIDS RESEARCH**

Studies of mechanisms of HIV-1 integration by Alan Engelman, PhD, unveiled LEDGF, a molecular tether that targets HIV-1 to integrate evenly along transcription units, as a critical gene-targeting factor. His work yielded the first three-dimensional structure of a crucial cell factor bound to a retroviral enzyme.

Dana Gabuzda, MD, studies molecular mechanisms of the interaction of retroviruses with T-cell subsets and the important functional division of labor among subpopulations of monocytes that mediate inflammatory responses. These studies have interesting implications in the twin areas of anti-cancer and antiviral immunotherapy. Gabuzda also clarified some of the factors underlying HIV cellular tropism.

Joseph Sodroski, MD, discovered a form of innate intracellular immunity against retroviruses mediated by members of the tripartite motif (TRIM) family of proteins. Defining the mechanism by which endogenous proteins, including human

TRIM5a, might be enhanced in order to restrict HIV-1 infection in macrophages and microglia has the potential to reverse HIV-1-associated dementia and to have a tremendous impact on HIV-1-associated neurological disorders.

Ruth Ruprecht, MD, PhD, works on AIDS and cancer vaccines and recently demonstrated the ability of overlapping peptides to function as broadly applicable vaccines to defined antigens.

### **IMMUNE MECHANISMS IN TUMOR DEVELOPMENT AND AUTOIMMUNE DISEASE**

Martin Hemler, PhD, developed an integrin CD151-deficient mouse, which displays impaired tumor-induced angiogenesis and inhibition of breast cancer growth. Von Boehmer showed that APC mice, which develop a high frequency of gastrointestinal cancers, manifest a thymic defect that leads to regulatory T-cell abnormalities. Turley has generated transgenic mice with NF $\kappa$ B selectively activated or inhibited to examine the impact of dendritic cell maturation on tumor growth. Koichi Kobayashi, MD, PhD, delineated an important role for Birc1e in the inflammasome. Cantor defined the role of type I interferons in regulating development of Th1 and Th17 sublineages in CD4+ T-helper cells; this has important implications in the treatment of autoimmune disease. Wucherpfennig determined the first crystal structure of a T-cell receptor from a human autoimmune disease bound to its self-peptide/MHC target, revealing an unusual topology of peptide/MHC binding that may explain why some autoreactive T cells escape negative selection in the thymus.

### **ANTIVIRAL MONOCLONAL ANTIBODY IMMUNOTHERAPY**

Wayne Marasco, MD, PhD, was the first to isolate human neutralizing Abs against SARS-CoVs. Marasco is currently studying the structural and functional basis of broad-spectrum neutralization against avian and human influenza A viruses, with an eye toward developing a universal vaccine against all influenza viruses (see story, page 29).

# Department of Imaging

The Department of Imaging provides state-of-the-art technologies for imaging-based research, diagnostics, and drug development.

## RESEARCH FOCUS

The Department focuses on the development and validation of imaging as a biomarker through the use of the latest imaging technologies and techniques across each of its cancer-focused imaging modalities. It is dedicated to supporting translational molecular imaging research. This is achieved through facilitating interdisciplinary collaborations between disease-focused clinical investigators and basic scientists on clinical and preclinical imaging studies. Faculty are also active in developing innovative image data-management protocols and participating in developing data-mining strategies to better inform clinical decision-making through their research efforts.

To support its expanding research portfolio, the Department recently recruited radiologists Mizuki Nishino, MD, Katherine Krajewski, MD, and Katherine Zukotynski, MD, as well as Yuchuan Wang, PhD, a preclinical imaging physicist, and Tianliang Gu, PhD, a clinical MRI physicist. In addition, Mengye Guo, PhD, a biostatistician who was jointly recruited with the Department of Biostatistics and Computational Biology, develops the formal statistical design and analysis of imaging in clinical and preclinical trials.

## PARTICIPATION IN NATIONAL GROUPS

Department faculty belong to various imaging consortia and working groups. This includes the American College of Radiology Imaging Network (ACRIN), NCI Imaging Response Assessment Teams, Radiological Society of North America Imaging Biomarkers Roundtable and Quantitative Imaging Biomarker Alliance, CTEP Phase II Clinical Trial Design Working Group, CALGB Imaging Committee, the VIEW Consortium (QARC, ACRIN, CALGB) Imaging Standards Committee, National CTSA Imaging Working Group, and Society of Nuclear Medicine Clinical Trials Network.

## EVALUATING TUMOR RESPONSES

The Department pioneered the use of FDG-PET to evaluate response to tyrosine kinase inhibitors (TKIs) in gastrointestinal stromal tumor (GIST) patients. This activity has continued in the clinical trials of successive TKIs, including sunitinib, dasatinib, nilotinib, and lapatinib. The use of FDG-PET has also been extended to other cancers trials, including non-GIST sarcomas, metastatic breast cancer, lung cancer, and melanoma. The Department has had a very active role in defining the use of FDG-PET in clinical oncology trials within the global imaging community, particularly with regard to the standardization of multicenter trials.

Nishino recently received an RSNA Research Scholar Grant to evaluate new methods of assessing response to erlotinib in women with adenocarcinoma, using CT imaging to measure chronological changes in tumor size, volume, and density. She is also actively involved in evaluating the recently updated RECIST 1.1 for lung cancer.

## EXPANDING THE USES OF PET

The Department has successfully expanded the mechanisms that can be measured in vivo with PET by introducing the use of new radiopharmaceuticals. For example, in collaboration with Dana-Farber's Multiple Myeloma Program, PET with sodium fluoride (NaF-PET) was used to evaluate bone mineralization in osteonecrosis of the jaw compared to conventional CT, MRI, and FDG-PET



ANNICK D. VAN DEN  
ABBEELE, MD, CHAIR



imaging. The Department also collaborated with Geoffrey Shapiro, MD, PhD, of Medical Oncology and director of the Early Drug Development Center, and Ann LaCasce, MD, also in Medical Oncology, to conduct the first multicenter trial using fluorinated thymidine (FLT-PET).

The first FDG-PET screening trial of high-risk populations was conducted by department faculty in collaboration with Judy Garber, MD, MPH, and colleagues in the Division of Population Sciences in Medical Oncology. The study demonstrated promising results in detecting asymptomatic cancer in patients with Li Fraumeni syndrome.

Dana-Farber is an executive member of the Biomedical Imaging Core Resource that oversees the clinical and research activities of the cyclotron facility recently established at Brigham and Women's Hospital. This facility serves as a critical resource for new PET tracers for oncologic applications.

### **DEVELOPING MODALITIES FOR EVALUATING TUMOR VASCULARITY, PERFUSION, AND PERMEABILITY**

The Department of Imaging is addressing the needs to evaluate the vascularity, perfusion, and permeability of tumors in response to antiangiogenic therapies used in clinical trials and, more recently, in clinical practice. This is being done in collaboration with investigators in Medical Oncology. Pamela Dipiro, MD, director of CT Imaging, and Jeffrey Yap, PhD, senior diagnostic physicist and director of the Clinical Imaging Center, have established the use of multi-slice CT perfusion imaging in collaboration with F. Stephen Hodi, MD, from Medical Oncology, a melanoma expert. Jyothi Jagannathan, MD, and Tianliang Gu, PhD, an MRI physicist, have established dynamic contrast-enhanced MRI imaging (DCE-MRI) to evaluate tumor perfusion and permeability effects in clinical trials being conducted in patients with brain tumors by Patrick Wen, MD, sarcomas by Andrew Wagner, MD, and metastatic breast cancer by Ian Krop, MD. Diffusion-weighted imaging (DWI) is also being used to measure the diffusion of water in brain tumors. Don DiSalvo, MD, director of ultrasonography, is developing dynamic contrast enhanced (DCE) ultrasonography with the use of novel microbubbles.

### **RESOURCES TO SUPPORT IMAGING RESEARCH**

A new Dana-Farber imaging center — the Center for Biomedical Imaging in Oncology (CBIO) — is led by Department Chair Annick Van den Abbeele, MD. CBIO is dedicated to facilitating the bidirectional translation of imaging research in cancer and the realization of personalized medicine. Features of the CBIO

include: a clinical imaging research arm directed by Yap, and a preclinical imaging research program and the newly established Lurie Family Imaging Center directed by Andrew Kung, MD, PhD, of Pediatric Oncology.

Van den Abbeele serves as the Dana-Farber site director for the Dana-Farber/Harvard Cancer Center's Tumor Imaging Metrics Core. This facility provides timely standardized and longitudinal radiological measurements of treatment response of subjects enrolled in clinical trials.

Van den Abbeele is a member of the Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) Imaging Steering Committee and chairs the DF/BWCC Research Subcommittee. The goals of this committee are to optimize, expand, and coordinate the clinical and research aspects of the DF/BWCC Cancer Imaging Program.

The department's dedicated laboratory for multicenter imaging trials provides study design, imaging protocol development, PET/CT scanner evaluation and qualification, quality control and archival of imaging data, diagnostic review of images, centralized quantitative image analysis, and scientific interpretation of final imaging results.

### **TRAINING THE NEXT GENERATION**

All imaging procedures are performed under the supervision of board-certified radiologists/nuclear medicine physicians. Radiology/nuclear medicine residency and fellowship training, as well as a radiology clerkship program for Harvard Medical School (HMS) students, are offered. Dana-Farber Imaging is a member of the Joint Program in Nuclear Medicine (JPNM) at HMS. It also serves as a radiologic technologist clinical training site for a number of local undergraduate and postgraduate radiological sciences programs.

### **OF NOTE**

Van den Abbeele and Yap have participated in various NCI working groups. They coauthored the NCI Consensus Recommendations on the use of FDG-PET in clinical trials and the CTEP considerations for the use of imaging in Phase II treatment trials in oncology. Van den Abbeele and Yap also serve as site co-directors for the Harvard's NIH Clinical and Translational Science Center Imaging Consortium, and Yap is the director of education for the Imaging Consortium.

# Department of Medical Oncology

The Department of Medical Oncology seeks to gain insights that lead to the prevention of cancer and to improve diagnosis and treatment of adult patients with cancer. The Department engages in a broad range of basic and clinical research, patient care, and teaching.



JAMES GRIFFIN, MD,  
CHAIR

## RESEARCH FOCUS

The Department of Medical Oncology is committed to offering compassionate care, cutting-edge clinical and basic research, and outstanding training opportunities for basic and clinical investigators. More than 200 faculty are organized into seven divisions: General Oncology (Lawrence Shulman, MD); Hematologic Malignancies (Robert Soiffer, MD); Hematologic Neoplasia (Kenneth Anderson, MD); Molecular and Cellular Oncology (Myles Brown, MD); Population Sciences (Jane Weeks, MD, MSc); Solid Tumor Oncology (Philip Kantoff, MD); and Women's Cancers (Eric Winer, MD). Division chiefs play key roles in departmental operations, planning, promotions, recruitment, and administration. Robert Mayer, MD, vice chair for academic affairs, and Edwin Alyea, MD, chief of inpatient operations, perform key administrative functions.

## MULTIDISCIPLINARY DISEASE CENTERS

Clinical trials and patient care are conducted in 14 interdisciplinary disease centers, each directed by a nationally recognized leader who is responsible for the clinical and research activities of their center. These include: Bone and Sarcoma Oncology (George Demetri, MD), Breast Oncology (Eric Winer, MD), Cancer Genetics (Judy Garber, MD), the Carole M. and Philip L. Lowe Center for Thoracic Oncology (Bruce Johnson, MD), Cutaneous Oncology (Thomas Kupper, MD), Early Drug Development Center (Geoffrey Shapiro, MD, PhD), Melanoma (F. Stephen Hodi, MD), Gastrointestinal Oncology (Charles Fuchs, MD, MPH), Gynecological Malignancies (Ursula Matulonis, MD), Head and Neck Oncology (Marshall Posner, MD), Hematologic Oncology (Robert Soiffer, MD), Hematology (Nancy Berliner, MD), the Lank Center for Genitourinary Oncology (Philip Kantoff, MD), and Neuro-Oncology (Patrick Wen, MBBS). These centers are also the focus of teaching and mentoring for the 14 first-year clinical medical oncology fellows at Dana-Farber/Partners CancerCare as well as many senior fellows. Clinical care and research involving other departments — including Radiation Oncology, the Cantor Center for Research in Nursing and Patient Care Services, and Surgical Oncology at the Brigham and Women's Hospital — also take place within the centers.

## OVERVIEW OF DEPARTMENT RESEARCH

A major departmental research theme is linking knowledge of the genes that cause cancer to the discovery and testing of new therapeutics, involving both small-molecule drugs and immune approaches. Other key themes relate to developing personalized medicine strategies by using genetic, epidemiologic, and population-based studies to determine risk and ideal treatment for individual patients.

Dana-Farber currently has nearly 400 open adult therapeutic clinical trials. It accrues several thousand patients to therapeutic and non-therapeutic clinical protocols each year. Disease center members play a major role in Dana-Farber/Harvard Cancer Center's research programs and in national cooperative group trials, such as the Cancer and Leukemia Group B (CALGB).



Through the efforts of Philip Kantoff, MD, the Institute's chief clinical research officer, Dana-Farber has formed a Clinical Research Institute to provide training and oversight of investigators involved in clinical trial research. Clinical researchers have access to a sophisticated infrastructure of cores and other facilities to help them conduct clinical trials at the cutting edge, including an outpatient research chemotherapy unit in which the most complex of clinical trials can be conducted (see story, page 16).

Department investigators focus on testing new drugs in Phase I and II trials, particularly first-in-human studies that have the potential to move the boundaries of oncology care. A particularly novel approach to clinical investigation is the Institute's development of a new faculty model in which selected physician-scientists, dedicated to translational research, are recruited specifically to undertake laboratory research that leads to new clinical trials. Part of the Center for Clinical and Translational Research, this Next Generation Program was initiated by Lee Nadler, MD, and is now led by Bruce Johnson, MD.

The Department currently houses 40 independent research laboratories. Recent laboratory recruits include Jennifer Allen, DSc, MPH, RN, Rameen Beroukhi, MD, PhD, James Bradner, MD, Ronny Drapkin, MD, PhD, Keith Ligon, MD, PhD, and David Weinstock, MD.

Highlights of faculty research activities and accomplishments are presented below.

### **DIVISION OF WOMEN'S CANCERS**

As part of the Specialized Programs of Research Excellence (SPOR) in breast cancer, a team of investigators led by Garber, Daniel Silver, MD, PhD, and Andrea Richardson, MD, PhD, conducted the first preoperative trial of cisplatin in patients with triple-negative breast cancer. The study demonstrated that the single agent cisplatin, administered for only four cycles, resulted in a pathologic complete response rate of approximately 22 percent. The study led to the development of other trials evaluating the platinum salts in patients with triple-negative breast cancers (see story, page 37), including those with *BRCA1* mutations. As part of the trial, tumor specimens were collected to look for predictors of response to therapy. Of interest, two patients were found to have a *BRCA* mutation and both had pathologic complete responses. A Phase I trial combining cisplatin with a PARP (poly (ADP-ribose) polymerase) inhibitor is now being conducted.

### **DIVISION OF MOLECULAR AND CELLULAR ONCOLOGY**

With the goal of tailoring therapy to the specific genetic changes present in a patient's tumor, several labs have made significant contributions to studies identifying genetic mutations associated with different forms of cancer. Among these were studies led by Lynda Chin, MD, and Matthew Meyerson, MD, PhD, in which a number of novel mutations in glioblastoma, the most common type of adult brain cancer, and lung adenocarcinoma, the most common form of lung cancer, were found. The glioblastoma study was part of The Cancer Genome Atlas (TCGA) project, a federally-funded effort to probe genomic changes involved in human cancer. Meyerson is principal investigator of a TCGA center at Dana-Farber and the Broad Institute, and Chin is co-principal investigator of another TCGA center at Dana-Farber/Brigham and Women's Hospital (see story, page 17).

### **DIVISIONS OF HEMATOLOGIC NEOPLASIA AND HEMATOLOGIC MALIGNANCIES**

Richard Stone, MD, and James Griffin, MD, are developing leukemia therapies that are pathophysiologically linked to mutations in the FLT3 tyrosine kinase oncogene. Martha Wadleigh, MD, is studying whether *JAK2* mutations are important pathophysiologically in polycythemia vera and other myeloproliferative disorders. Daniel DeAngelo, MD, PhD, has shown that the histone deacetylase inhibitor panabinstat is potent in treating myelofibrosis and Hodgkin's disease.

Arnold Freedman, MD, is testing novel protein inhibitors that drive lymphoma growth and survival, using lymphoma biology data from the laboratories of Margaret Shipp, MD, and Anthony Letai, MD, PhD, from Hematologic Neoplasia. Ann LaCasce, MD, of Hematologic Malignancies, and Shipp have shown that the SYK inhibitor R788 can cause regression of a variety of lymphomas and CLL (see story, page 9). Jennifer Brown, MD, PhD, is studying ABT263, which inhibits the effects of BCL-2 in both lymphoma and CLL. In diffuse large B-cell lymphoma (DLBCL), Shipp has identified an overproduction of the enzyme, PKC- $\beta$ . She has also shown that the drug enzastaurin, which targets this enzyme, has significant activity against DLBCL. Freedman is studying antibody-mediated inhibition of the CD40/CD40 ligand growth/survival signal. The CD40 molecule has been shown to be an important regulator of malignant B cell growth.

Studies in the Jerome Lipper Center for Multiple Myeloma and Lebow Institute for Myeloma Therapeutics have shown that the proteasome inhibitor bortezomib, as well as the

immunomodulatory drugs lenalidomide and thalidomide, target the multiple myeloma cell in the bone marrow micro-environment to overcome drug resistance in laboratory and animal models. Clinical trials, led by Kenneth Anderson, MD, and Paul Richardson, MD, have now moved this discovery into the initial management of patients newly diagnosed with advanced myeloma. Median survival of patients with myeloma has extended from three to seven years. The next-generation proteasome inhibitor, NPI-0052, and immunomodulatory drug, pomalidomide, are more potent and can overcome drug resistance in preclinical studies, suggesting even further progress can be expected.

Using a similarly robust translational model, clinical studies in Waldenström's macroglobulinemia have also been prominent. A number of new therapies have been developed by Steven Treon, MD, PhD, some in partnership with Irene Ghobrial, MD.

Studies in the Stem Cell Transplantation Program have opened new lines of inquiry into the pathogenesis and therapy of graft-versus-host disease (GVHD), as well as into novel approaches to enhance graft-versus-leukemia (GVL) reactions. Joseph Antin, MD, and Corey Cutler, MD, are leading a trial to determine whether sirolimus-based GVHD prophylaxis will become the new standard of care to prevent GVHD. Jerome Ritz, MD, has revealed the cooperative role of B cells and T cells in generating tissue injury in chronic GVHD. In collaboration with Glenn Dranoff, MD, Vincent Ho, MD, and Robert Soiffer, MD, have developed a promising technique to use a genetically engineered autologous leukemia vaccine to stimulate the donor's immune response after transplantation. Edwin Alyea, MD, has developed a program in reduced-intensity transplantation and demonstrated that this potentially life-saving procedure can now be successfully offered to older patients.

#### **DIVISION OF SOLID TUMOR ONCOLOGY**

As part of the lung cancer SPORE, Pasi Jänne, MD, PhD, has identified *MET* amplification as a cause of resistance to EGFR inhibitors gefitinib and erlotinib, both in vitro and in non-small cell lung cancer (NSCLC) patients. The preclinical studies also demonstrated that for these resistant cancers, a combination of EGFR and *MET* inhibition is necessary to inhibit cell viability. These findings have now been translated into clinical trials that are evaluating the combination of an EGFR inhibitor (erlotinib) and *MET* inhibitor (XL184) in NSCLC patients who have developed resistance to erlotinib (see story, page 19).

Recent studies have also identified a subgroup of NSCLCs that harbor a translocation in the anaplastic lymphoma kinase (ALK) gene. Preclinical studies have demonstrated that such cancers are particularly sensitive to specific ALK kinase inhibitors. The first clinically available ALK kinase inhibitor, PF2341066, is being studied and has thus far demonstrated dramatic clinical activity in NSCLC patients with *ALK* translocations. Additional clinical trials are ongoing.

#### **DIVISION OF POPULATION SCIENCES**

A pilot study of PET/CT scan screening for patients with Li Fraumeni syndrome (LFS) was conducted by Serena Masciari, MD, and Garber. LFS is an inherited cancer syndrome originally described by Frederick Li, MD, in which children and young adults have markedly increased risks of diverse cancers, including brain tumors, breast cancer, sarcomas, and other neoplasms. Mutations in the p53 gene can be detected in 70 percent of LFS families; the lifetime cancer risk is nearly 90 percent. With Lisa Diller, MD, of Pediatric Oncology, and Annick Van den Abbeele, MD, chair of Imaging, 15 individuals with LFS were evaluated. The goal was to look for early signs of cancer in these very-high risk individuals. All patients underwent a health interview, physical examination, and basic laboratory tests. Among the asymptomatic participants, three cancers were identified. Two were thyroid cancers, both of which could be removed in their entirety and the patients should be cured. The third was a gastroesophageal junction tumor, which was treated with chemotherapy and complete surgical resection. This trial is one of the first to demonstrate that a screening modality may have a role in the management of individuals with an inherited cancer syndrome. The results of this study were reported in *JAMA*, March 2008. These investigators are now leading a consortium of investigators in applying for a grant to expand the trial to a comprehensive evaluation of children and adults with LFS.



STUART ORKIN, MD,  
CHAIR

## Department of Pediatric Oncology

The Department of Pediatric Oncology is committed to promoting laboratory research, translational investigation, and clinical studies to better understand and treat childhood cancers.

### A FOCUS ON TRANSLATIONAL RESEARCH

Research across the continuum from laboratory research to clinical trials is most likely to contribute to the development of novel therapeutics. The Department's research focus accordingly spans cancer biology, leukemia research, sarcomas, neurobiology, and chemical biology. Through Dana-Farber/Children's Hospital Cancer Care, the Department is developing unique clinical trials to improve the treatment and care of children with cancer. Leading Dana-Farber's pediatric clinical trials program is Carlos Rodriguez-Galindo, MD. The Department's clinical trials portfolio includes investigator-initiated, cooperative group, and company-sponsored trials for a variety of cancers at different stages of progression.

### VULNERABILITIES IN LEUKEMIA STEM CELLS

Scott Armstrong, MD, PhD, is focusing on acute myelogenous leukemia associated with chromosomal rearrangements of the MLL gene, an infant leukemia that is difficult to treat. His laboratory has shown that the MLL fusion products promote the formation of a self-renewing cell population called leukemic stem cells. These cells, which sustain the leukemia, express genes normally restricted to immature blood stem cells. Armstrong and colleagues are now examining ways to target these differentially expressed genes. Such approaches may lead to novel therapies.

### ATTACKING BRAIN TUMORS

Mark Kieran, MD, PhD, and Charles Stiles, PhD, co-chair of Cancer Biology, created the Pediatric Low-Grade Astrocytoma Program at Dana-Farber. Believed to be the first coordinated effort focusing on low-grade gliomas, the program has a five-year objective to identify a molecular target that can be affected with personalized therapy (see story, page 10).

Rosalind Segal, MD, PhD, who is also a member of Cancer Biology, is studying the pathways by which extracellular stimuli (such as growth factors and cell-to-cell interactions) regulate development. Segal and her group have demonstrated that neuronal precursors in the cerebellum migrate along a gradient of the growth factor brain-derived neurotrophic factor (BDNF). The lab has identified critical intracellular pathways that allow this migration and is identifying new ways in which these pathways can be selectively turned on or off. Recent studies have highlighted a role for the BDNF receptor in diverse metastatic diseases. Thus, Segal's studies may lead to new cancer drugs that block cancer cell dissemination.

### NEW APPROACHES TO SARCOMA RESEARCH

Charles Roberts, MD, PhD, is studying the role of the SWI/SNF protein complex in malignant rhabdoid tumors and other cancers. He is also investigating the mechanisms by which it controls cell growth. Roberts and his group found that aggressive cancers that arise in mice deficient in the *SNF5* gene lack widespread genome mutations. The changes that occur following *SNF5* mutation are actually epigenetic alterations, which are potentially reversible and, therefore, have important therapeutic implications for a wide variety of cancers.

Stuart Orkin, MD, is leading an effort to find new approaches to osteosarcoma, the most common primary bone tumor, using an engineered mouse model that mimics the human cancer. His team, along with Katherine Janeway, MD, seeks to define the pathways leading to metastasis and to identify novel agents that may promote differentiation of the cancer cells.

### **ADVANCING OUR UNDERSTANDING OF NEUROBLASTOMA**

Rani George, MD, PhD, performed a genome-wide analysis of neuroblastoma tumors and found multiple copies of a receptor tyrosine kinase gene, *ALK*, in up to 14 percent of high-risk neuroblastomas. In collaboration with the Broad Institute, George sequenced *ALK* in 93 primary neuroblastoma tumor samples. She discovered five different mutations, with one mutation recurring in four cases (see story, page 12).

### **GENOMIC APPROACHES TO DRUG DISCOVERY**

Kimberly Stegmaier, MD, focuses on genomic approaches to drug discovery. With the Broad Institute, Stegmaier developed a new method of chemical discovery called gene expression-based high-throughput screening (GE-HTS). This technique led to the discovery of chemicals that induce the maturation of acute myeloid leukemia (AML) cells and resulted in a clinical trial for patients with relapsed AML. Many malignancies are believed to arise from the abnormal proliferation of cells and the failure of primitive cells to differentiate. For this reason, Stegmaier is focusing on the differentiation defect in two model diseases, AML and neuroblastoma (see story, page 20).

### **ANEUPLOIDY: ATTACKING DIFFERENCES IN CANCER CELLS**

David Pellman, MD, recently developed a genome-wide imaging approach to identify genes that are essential for abnormal cell division. His goal is to find genes that are not necessary in normal cells, but are required for the survival of cancer cells. One way to distinguish cancer cells from their normal counterparts is the presence of too many centrosomes. These are cellular structures that initiate the cellular machine that distributes the chromosomes in a dividing cell. This study identified a novel drug target, the kinesin HSET. Blocking HSET kills neuroblastoma cells with extra centrosomes, but spares normal cells. This information may impact the treatment of leukemias and solid tumors, where increased centrosome numbers are common.

### **CHEMICAL BIOLOGY: A NEW FRONTIER OF MULTIDISCIPLINARY MEDICINE**

Loren Walensky, MD, PhD, is applying novel compounds to dissect and manipulate the cell signaling pathways that are integral in apoptosis in order to reactivate them to overcome cancer. Walensky inserted a chemical “staple” into a natural but otherwise unstable cell-killing peptide. This reactivated the apoptosis cell signaling pathway in leukemia cells. When the stapled peptide was injected into mice, it suppressed human-type leukemia. Compounds such as this one are now being used to study the interactions of proteins inside cells, giving scientists a “molecular toolbox” to study and to potentially treat cancer and other diseases.

### **HARNESSING THE IMMUNE SYSTEM TO FIGHT CANCER**

William Nicholas Haining, BM, BCh, is identifying the molecular characteristics of T cells associated with immunologic protection. Using gene expression profiling, Haining has demonstrated that all lymphocyte lineages in mice and humans use a common cell differentiation program during memory development. With Stegmaier, he has used GE-HTS to identify small molecules, genes, or soluble factors that direct memory differentiation in naive human lymphocytes. These studies may lead to the discovery of new immunomodulatory drugs or vaccine strategies.

### **ABERRANT SIGNAL TRANSDUCTION IN CANCER**

Andrew Kung, MD, PhD, is studying the mechanisms through which the hypoxia-inducible factor pathway allows cells to adapt to hypoxia. He is also focused on how to therapeutically target hypoxic tumor cells. Kung has developed new ways to use non-invasive imaging in order to assess molecular pathways within tumors, and has used these approaches to validate new therapies in mouse models. Kung leads the new Dana-Farber Lurie Family Imaging Center (see story, page 16) and helped establish the Institute’s Center for Biomedical Imaging in Oncology.

### **OTHER WORK**

Other exciting work by Department members, including A. Thomas Look, MD, Todd Golub, MD, and Stuart Orkin, MD, is presented in Section 2 of this report.



SUSAN BLOCK, MD,  
CHAIR

## Department of Psychosocial Oncology and Palliative Care

In 2008, Dana-Farber created the new Department of Psychosocial Oncology and Palliative Care. This was done in recognition of the growth and evolution of these fields and their centrality to cancer care.

### DEPARTMENT GOALS

The mission of the Department is to support patients of all ages who are living with a life-threatening illness, along with their families. The goals are to enhance quality of life and well-being, and to relieve suffering in all its dimensions throughout illness, survivorship, and bereavement. This is accomplished by providing expert, compassionate clinical care. The Department aims to contribute to the knowledge base guiding psychosocial and palliative interventions across the illness spectrum, train the next generation of leaders in psychosocial oncology and palliative care, and share expertise with students and colleagues in other disciplines.

### RESEARCH FOCUS

A unique feature of the Department is the focus on providing care across the life cycle. The expert interdisciplinary team of faculty and other clinicians within the department includes pediatricians, general internists, geriatricians, oncologists, psychiatrists, psychologists, social workers, nurses, chaplains, pharmacists, and physician assistants. The group shares a focus on prevention and relief of suffering, as well as promotion of quality of life for patients who are living with cancer.

The Department is organized into four clinical divisions: Adult Psychosocial Oncology; Pediatric Psychosocial Oncology; Adult Palliative Care; and Pediatric Palliative Care. Because research cuts across all four programs, research efforts are organized and integrated through the Center for Psycho-Oncology and Palliative Care Research.

Under the leadership of Holly Prigerson, PhD, the Center's research program focuses on understanding the factors affecting quality of life and quality of care of cancer patients and their family members. The general approach to research is the application of clinical epidemiology methods and perspectives of social psychology to advance understanding of the dynamics among patients, their family members, oncologists, and others involved in patient care. The Center also provides junior faculty, residents, and medical students with support in their research through mentorship, databases, measures, and analysis.

### RESEARCH ACHIEVEMENTS

Recently published, high-impact research from the Center includes:

- The associations of physician communication about end-of-life issues with improved quality of life, hospice utilization, reduced use of aggressive care, and improved caregiver bereavement outcomes
- The relationship between end-of-life communication and costs of care at the end of life
- Religious coping and its association with the receipt of intensive life-prolonging care
- The impact of young children on parents' end-of-life treatment decisions and quality of life
- The impact of terminal illness acknowledgement, religiousness, and treatment preferences on advance care planning among racial and ethnic minorities

- An empirical examination of the stage theory of grief
- Symptom assessment in pediatric palliative care
- Outcomes of pediatric palliative care programs
- Short- and long-term evaluations of palliative care educational interventions

### ONGOING RESEARCH

Prigerson has developed a research program that capitalizes on the Coping with Cancer (CwC) database, a multisite, NCI/NIMH-funded prospective, longitudinal cohort study of advanced cancer patients that is designed to investigate topics as varied as patient and family caregiver mental health, disparities in medical care, and the effects of spirituality on treatment preferences and intensity of medical care near death. The CwC has resulted in more than 50 publications in journals such as *JAMA*, *Journal of Clinical Oncology*, *Cancer*, and *Critical Care Medicine*. It has become a well-known research resource and template for advancing the evidence base in the fields of psychoncology and palliative care.

Prigerson and Block, together with Brett Litz, PhD, are developing an online intervention for bereaved family survivors of Dana-Farber patients. They have conducted studies of the effects of coping styles, particularly religious coping, on care near death. The influence of pastoral care visits, dependent children at home, and acculturation have also been identified as clinically important determinants of the aggressiveness of end-of-life care received by cancer patients. A study is currently underway to examine gender differences in communication at the end of life, and in Asian-Americans coping with cancer. Several Dana-Farber junior faculty, including Tracy Balboni, MD, MPH, Alexi Wright, MD, and Elizabeth Trice, MD, PhD, lead studies on spiritual care, communication, and ethnic disparities, respectively.

Using retrospective methods, Joanne Wolfe, MD, MPH, found that children with advanced cancer experience substantial suffering from both cancer-directed therapies and symptoms, resulting in poor quality of life. The NCI has now identified supportive care research aimed at easing suffering in cancer patients as a high priority. Wolfe and colleagues are currently conducting the Pediatric Quality of Life and Evaluation of Symptoms Technology (PediQUEST) Study at three large pediatric oncology centers: Dana-Farber/Children's Hospital Cancer Care, Children's Hospital of Philadelphia, and Seattle Children's Hospital. PediQUEST is a computerized data collection system on a tablet PC platform that tracks symptoms (using age adapted Memorial Symptom Assessment Scales) and Quality

of Life (QoL) (using the PedsQL™) in children with advanced cancer, generating feedback reports and email alerts. Using this system, Wolfe is conducting a randomized supportive care feasibility trial aimed at preliminarily assessing the effect of routinely feeding back QoL and symptom data on the child's experience of suffering. The PediQUEST system will become a powerful resource to advance supportive care research in children with cancer.

### TRAINING FUTURE RESEARCHERS

The Department offers varied educational programs for medical students, residents, fellows, and faculty. In addition to two ACGME-accredited fellowship programs in palliative medicine and psychosomatic medicine, the Department offers training for fellows in medical oncology, psychiatry, cardiology, anesthesia/pain management, and gynecologic oncology. The Department also offers extensive programs for internal medicine, pediatric, and psychiatry residents.

In collaboration with the Harvard Medical School Center for Palliative Care, the Department offers the Program in Palliative Care Education and Practice, a two-week, intensive leadership and education program designed specifically for faculty, and a three-day continuing medical education course on practical aspects of palliative care, which provides clinicians with basic and advanced palliative care competencies. For the past several years, the Department has also trained German palliative care faculty through a faculty development program in collaboration with the Ludwig Maximilian University and the German Cancer Fund.





JAY HARRIS, MD,  
CHAIR

## Department of Radiation Oncology

The Department of Radiation Oncology is committed to combining advances in clinical and laboratory research with developments in radiation physics. The goal is to promote a better understanding of the biology of cancer and normal tissues and to improve the treatment of cancer.

### RESEARCH THEMES

The unifying research aim of the Department is genomic instability in human cancer. A better understanding of this instability may lead to more tailored therapies for cancer patients. Departmental research is focused on the treatment of tumors by ionizing radiation and, ultimately, improving therapy through understanding radiation and other treatments at the molecular and cellular levels. Although the basic physical and biochemical mechanisms underlying radiation therapy are understood, the molecular and tissue-level responses that determine tumor cell fate during treatment have only recently come to light. The Department continues to make advances in the knowledge of the radiation response of cancer cells in tissue culture and within tumors.

### UNDERSTANDING CHROMOSOMAL INSTABILITY SYNDROMES

Alan D'Andrea, MD, is studying the molecular signaling pathways that regulate the DNA damage response in mammalian cells. Disruption of these pathways, by germline or somatic mutation, leads to genomic instability and cellular sensitivity to ionizing radiation, as well as defective cell-cycle checkpoints and DNA repair. These pathways are often disrupted in cancer cells, accounting for the chromosomal instability and increased mutation frequency in human tumors. D'Andrea's focus is the molecular pathogenesis of the human chromosomal instability syndromes: Fanconi anemia (FA), ataxia-telangiectasia, and Bloom syndrome. FA is an autosomal recessive cancer susceptibility disorder characterized by developmental defects and increased cellular sensitivity to DNA crosslinking agents. Thirteen FA genes have been cloned; the encoded FA proteins interact in a novel signaling pathway. Eight FA proteins form a nuclear protein complex required for the monoubiquitination of the D2 protein. Activated D2 is targeted to chromatin, where it interacts with the products of the breast cancer susceptibility genes, *BRCA1* and *BRCA2*. The Department's research program addresses several aspects of this novel signaling pathway, including: the assembly, transport, and structure of the FA protein complex; the enzymatic monoubiquitination and deubiquitination of the D2 protein; the function of the chromatin-associated FA complex in cell cycle checkpoints and homologous recombination DNA repair; and the identification of novel interacting proteins in these complexes.

### IDENTIFYING TUMOR SIGNATURES

Gerassimos (Mike) Makrigiorgos, PhD, is studying the identification and tracing of tumor signatures in cancer samples. His laboratory has a special interest in developing new technologies for cancer molecular diagnostics and molecular profiling for personalized medicine. He has developed a range of methodologies for evaluation of tumor-specific genetic changes, such as mutation and methylation. A recently developed method, COLD-PCR, has the ability to magnify traces of deleterious mutations in cancer samples containing excess normal cells so that they can be easily detected. In this way, mutation-based signatures of cancer cells can be identified and traced in small biopsies, body fluids such as plasma or sputum, and heterogeneous surgical specimens from

cancer patients. These approaches may result in an early screening test for cancer-specific genetic alterations and may contribute toward understanding the evolution and biology of tumors.

### UNCOVERING DNA REPAIR MECHANISMS

Brendan Price, PhD, has made major advances in understanding the role of the ataxia-telangiectasia gene product (ATM) as a sensor of DNA damage and a regulator of radiation resistance in the irradiated cell. He has identified the Tip60 acetyltransferase as a key regulator of the ATM protein. ATM and Tip60 exist in the cell as an inactive complex. In response to DNA damage, the ATM-Tip60 complex is recruited to sites of DNA damage. Tip60 is then activated and acetylates ATM, leading to a rapid upregulation of ATM's kinase activity. The Price lab has revealed that this activation of Tip60's acetyltransferase activity involves specific interaction between Tip60 and methylated histones adjacent to sites of DNA damage. This work shows that histone methylation can modulate the activity of acetyltransferases. It also highlights the critical importance of chromatin structure and epigenetics in mediating DNA repair processes. Further, these findings offer great potential in the rational design of combination cancer therapy specifically targeting components of the ATM-Tip60 complex and the proteins that contribute to maintaining histone methylation marks on the chromatin (see story, page 33).

Dipanjan Chowdhury, PhD, is studying two aspects of the DNA damage response. One is dephosphorylation of DNA repair proteins via phosphatases, while the other is decreased expression of repair factors via microRNAs (miRNAs). His laboratory recently made the important observation that miRNAs impede DNA repair in terminally differentiated blood cells, facilitating apoptosis. However, these miRNAs, when aberrantly expressed in progenitor cells, may induce genomic instability leading to cancer. Conversely, their expression pattern in cancer cells may impact therapeutic response and clinical outcome.

### INSIGHTS INTO PANCREATIC CANCER

Alec Kimmelman, MD, PhD, is using mouse models and in vitro human systems to study the molecular pathogenesis of pancreatic cancer. His laboratory is especially interested in defining the underlying chromosomal and genomic instability of pancreatic tumor cells. His goal is to understand the mechanism behind their intense resistance to therapy and to develop potential sensitizers to chemotherapy and radiation. Other ongoing efforts include the study of cellular metabolism in pancreatic

cancer cells and the elucidation of pathways that may lead to tumor-specific death due to altered cellular metabolism. Results from this work may provide novel vantage points of attack for this deadly disease.

### THE ROLE OF DNA REPAIR IN BRAIN TUMORS

Clark Chen, MD, is focusing on the cause and treatment of human brain tumors, including glioblastoma multiforme, and brain metastasis. The laboratory aims to integrate genomic studies of brain cancer derived from patient tumor specimens, siRNA/shRNA screening, and novel mouse models (both xenograft and transgenic). The goals of Chen's group are to: understand the role of DNA repair in brain tumor carcinogenesis and brain cancer stem cell biology; explore therapeutic approaches based on DNA repair defects incurred during brain tumor progression; develop prognostic and diagnostic biomarkers; and apply small-molecule inhibitors of DNA repair as monotherapy or in conjunction with radiation and chemotherapy for brain cancer treatment.

### OTHER RESEARCH

The Department also performs a wide range of clinical studies across disease sites, including clinical trials of new therapeutic approaches, hypothesis-generating retrospective reviews, and outcomes and health services research.





DONNA L. BERRY,  
PHD, RN, AOCN, FAAN,  
DIRECTOR

## Phyllis F. Cantor Center for Research in Nursing and Patient Care Services

The mission of the Cantor Center is to reduce the burden of cancer through scholarly inquiry and rigorous research. The focus of the Center’s research is the patient/family experience of living with a predisposition to or diagnosis of cancer, as well as survivorship issues post-treatment.

### A FOCUSED MISSION

The Cantor Center’s efforts focus on three major areas: 1) conducting innovative research on quality of life and quality of care for cancer patients and families; 2) engaging nurses and other Dana-Farber patient care staff in research; and 3) promoting the use of research evidence to ensure that patient care is of the highest standards.

### RESEARCH THEMES

Director Donna L. Berry, PhD, RN, AOCN, FAAN, along with Mary Cooley, PhD, APRN, and Jennifer Allen, ScD, MPH, RN, conduct a variety of clinical trials. The three nurse-scientists engage direct care nurses at Dana-Farber in research relevant to their fields of expertise, thereby creating a direct link between science and practice.

Berry conducts research on improving cancer symptom management by enhancing self-care, patient-clinician communication, and cancer treatment decision making. Her recent findings that the Electronic Self-Report Assessment for Cancer (ESRA-C) program significantly improved patient-provider communication about cancer symptoms and quality-of-life concerns were based in a trial conducted of adult patients with cancer. The ESRA-C is the first electronic system tested in a large randomized trial with a direct outcome measure.

Cooley is developing a decision support system and conducting a clinical trial of symptom management in lung cancer. She is also studying smoking cessation behaviors and therapies in patients with cancer and their family members.

Allen’s research focuses on developing and testing interventions to promote screening for early detection of cancer. She is also interested in understanding decision making related to the human papilloma virus vaccine.

### OF NOTE

The Center’s Grant Portfolio increased five fold in 2009, reflecting the growing success of Dana-Farber in this high-priority research area.

# Integrative Research Centers

In 2003, Dana-Farber mapped out a research strategic plan. Its goal was to promote the clinical application of our understanding about the molecular characteristics of cancer, while furthering work that generates that fundamental knowledge. To that end, cross-cutting integrative research centers were created to address the steps along the path from basic discovery to clinical application, thereby complementing the scientific work accomplished through academic departments.

The primary goals of integrative research centers are to:

- Provide a mechanism for Dana-Farber faculty from multiple departments and disciplines to focus their efforts in specific high priority areas identified by the research community
- Develop highly specialized technologies and resources that directly apply to basic science discovery and translational research
- Through collaboration, consultation, and training, make center resources and expertise available to investigators throughout Dana-Farber and beyond
- Address the concerns of special populations, such as cancer survivors and minorities who are disproportionately affected by cancer

The integrative research centers participate in a rigorous process of goal setting, monitoring of progress, and performance metrics. The Centers are considered to be a large-scale, Institute-wide experiment to determine if this kind of results-driven strategy can be successful, while coexisting alongside the more traditional open-ended, investigator-driven style of research. To date, the centers have made significant progress, as evidenced by the rapid growth in novel resources and capabilities, high scientific productivity, significant impact in their fields, and increased multidisciplinary collaboration in targeted scientific areas.

## BELFER INSTITUTE FOR APPLIED CANCER SCIENCE

Director: Ronald DePinho, MD

Cancer exhibits enormous genomic and biological complexity wherein multiple gene aberrations act to maintain the malignancy. This redundancy has hampered the development of effective single agent drugs. The Belfer Institute's mission is to convert insights gleaned from cancer genomics and biology research into effective drug development efforts that will yield the next generation of drugs and drug combinations.

The Belfer Institute at Dana-Farber consists of three multidisciplinary teams supported by powerful platforms in computational science, oncogenomics, and engineered model systems. The Discovery Team analyzes multidimensional human cancer genome data and context-specific genetic screens in vivo to identify potential therapeutic targets, which are subjected to intensive mechanistic and clinicopathological analyses. Once a highly validated and clinically credentialed preclinical therapeutic target has been defined, the Pipeline Team conducts antibody or small-molecule discovery efforts in order to generate strong preclinical therapeutic candidates, internally or in collaboration



RONALD DEPINHO, MD (LEFT), WITH KENNETH ANDERSON, MD, LYNDA CHIN, MD, AND JAMES DECAPRIO, MD

with pharmaceutical partners. The Business Development Team focuses on project management, business development, and intellectual property activities.

Dana-Farber’s Belfer investigators have led efforts to characterize the glioblastoma genome through The Cancer Genome Atlas (TCGA) pilot project (see story, page 17), and melanoma, pancreatic, and ovarian cancer genomes through international efforts. They have demonstrated that receptor tyrosine kinase coextinction is a potentially viable clinical path for brain and other cancers. The Belfer Institute’s efforts have led to three drug discovery programs with industry and two internal programs. These efforts have yielded FDA approval of six drug regimens to treat multiple myeloma. Using multiple myeloma as a guidepost, Belfer investigators are focused on developing effective drugs and combination regimens for a variety of solid tumors.

**BLAIS PROTEOMICS CENTER**

Director: Jarrod Marto, PhD

The Blais Proteomics Center develops and applies state-of-the-art proteomics, informatics, and related technologies for direct interrogation of protein expression, modification, and function in response to biological perturbation in cell-based models of human cancer and primary tissues. The Center works with other Dana-Farber integrative research centers in large-scale studies designed to leverage disparate capabilities in pursuit of novel, in-depth, and otherwise unattainable insights into human biology and disease.

Analytical capabilities in the Blais Proteomics Center include advanced protein and ultra-high-pressure peptide separations, chemical- and affinity-based enrichment techniques, along with multiple mass spectrometry platforms, including MALDI TOF/TOF, linear ion trap, Orbitrap, and quadrupole TOF instruments. In addition, bioinformatics engineers provide customized desktop and web-based software tools for the analysis of proteomics data within the context of biological pathways and networks.

Capabilities at the Blais Proteomics Center are deployed at multiple levels, including fee-for-service, focused hypothesis-driven research collaborations, and large-scale discovery or systems-level projects. Scientists in the Center routinely consult with faculty throughout Dana-Farber in planning experiments and interpreting results. Blais members also contribute to the teaching mission at Harvard Medical School and participate in outreach activities designed to introduce and train young scientists and others who may not otherwise have access to these advanced technologies.

**CANCER VACCINE CENTER**

Directors: Ellis Reinherz, MD; Glenn Dranoff, MD; and Jerome Ritz, MD

The mission of the Cancer Vaccine Center is to develop therapeutic vaccines that will enable a person’s immune system to destroy cancers. The Center pioneers technologies, integrates immunologic research with translational science, and tests vaccine candidates in clinical trials to create effective cancer vaccines. To accelerate the pace of scientific and clinical progress and to facilitate collaboration, the Center also provides expertise, consultation, and service in areas critical to the development of successful cancer vaccines. Key Center technologies include bioinformatics, nanotechnologies, mass spectrometry, structural biology, immune assessment, immunoproteomics, and immunogenomics.



JARROD MARTO, PHD



FROM LEFT: JEROME RITZ, MD, ELLIS REINHERZ, MD, AND GLENN DRANOFF, MD

The Center maintains an integrated program of scientific discovery, preclinical vaccine development, and clinical investigation.

Scientific discovery efforts include:

- Selecting cancer vaccine targets for individual cancers
- Analyzing the immunogenicity of T-cell and B-cell peptide epitopes and performing cytokine immune assessments to identify epitopes and cytokines that enhance immune responses
- Examining methods for sustaining tumor immunity.

Preclinical vaccine development and clinical investigation efforts include:

- Using antigen- and cell-based efforts in allogeneic and autologous vaccine strategies for durable, broadly effective, anti-tumor responses
- Assessing the impact of adoptively transferring immune effector cells
- Exploring the use of antibodies directed at surface components of tumors and as blockers of negative immunoregulatory mechanisms that impede immunotherapy
- Evaluating the application of nanoscale devices for the development of nanotechnology-based vaccines, including directed delivery of immune stimulants and antigens.

## CENTER FOR BIOMEDICAL IMAGING IN ONCOLOGY

**Director:** Annick Van den Abbeele, MD

**Director of Clinical Imaging:** Jeffrey Yap, PhD

**Director of Preclinical Imaging:** Andrew Kung, MD, PhD

The mission of the Center for Biomedical Imaging in Oncology is to use state-of-the-art preclinical and clinical imaging in order to accelerate translational research and develop new diagnostic and therapeutic strategies for patients with cancer. The Center has two primary components: the Lurie Family Imaging Center and a clinical research program.

The Lurie Family Imaging Center is a preclinical imaging facility equipped with a 7T MRI, microPET/CT, ultrasound, bioluminescence, and fluorescence imaging instruments, along with radiochemistry and radiotherapy capabilities. All instruments are located within a new barrier facility to allow longitudinal and cross-modality studies. This permits researchers to perform preclinical cancer biology and drug efficacy studies, incorporating highly informative noninvasive imaging endpoints.

The Center's clinical research program focuses on the development and utilization of imaging for the detection of cancer and evaluation of response to treatment. The program has an Imaging Design, Evaluation, and Analysis (IDEA) lab, a multidisciplinary functional imaging laboratory that provides study design, imaging protocol development, PET/CT scanner evaluation and qualification, quality control/archival of imaging data, diagnostic review of images, quantitative image analysis, and scientific interpretation of final imaging results for numerous institutional, national, and global multicenter cancer therapeutic trials.

The Center has created a cancer imaging program with seamless integration between preclinical and clinical imaging and across all imaging modalities. In light of the expanding role of imaging in both basic and clinical cancer research, the Center provides a critical bridge that facilitates bidirectional translation across the Institute.



FROM LEFT: JEFFREY YAP, PHD, AND ANNICK VAN DEN ABBEELE, MD, WITH SERENA MASCIARI, MD, AND IRYNA RASTARHUYEVA, MD



JOHN QUACKENBUSH,  
PHD, WITH URSULA  
MATULONIS, MD

## CENTER FOR CANCER COMPUTATIONAL BIOLOGY

Director: John Quackenbush, PhD

The Center for Cancer Computational Biology provides broad-based support for the analysis and interpretation of genomic and other large-scale data and, by doing so, furthers basic, clinical, and translational research. The Center also conducts research focused on genomic and computational biology approaches that open new ways of understanding cancer.

The Center has developed a unique bioinformatics and computational biology consulting platform that provides state-of-the-art assistance in the collection, management, analysis, and interpretation of large-scale data, with a focus on data generated using “omic” technologies. To accomplish this, bioinformatics consultants and staff work closely with investigators in designing experiments and in analyzing and interpreting the data. They assist investigators with their research and provide training in various analytical methods, as well as the use of software tools.

Recognizing that many emerging problems in genomic data analysis require the development of new methods, the Center also maintains an active research program. Focusing on integrative approaches to the analysis of genomic data, it is proactively generating data using emerging technologies. It is also developing methods and software tools that bring together information from a variety of sources, including publicly available data, to better understand the complexities of biological systems. All software and tools developed through the Center are available to the research community as a resource to accelerate research at Dana-Farber, and beyond.



MATTHEW MEYERSON,  
MD, PHD (LEFT),  
AND WILLIAM HAHN,  
MD, PHD

## CENTER FOR CANCER GENOME DISCOVERY

Directors: William Hahn, MD, PhD, and Matthew Meyerson MD, PhD

Damaged or missing bits of DNA are the engines that drive many cancer cells. By identifying the abnormal genes associated with a given cancer, we may discover abnormal proteins or pathways that would be amenable to targeted therapy. Based on this, the mission of the Center for Cancer Genome Discovery is two fold: to develop technologies focused on discovering genomic alterations that contribute to human cancer; and, in collaboration with basic, translational, and clinical investigators, to define genomic abnormalities in specific cancers, evaluate whether the genomic abnormalities have clinical significance in a therapeutic clinical trials setting, determine if genotype predicts therapeutic responses, and develop approaches to identify such mutations prospectively in cancer patients.

The Center uses multiple technology platforms to identify mutations, copy number alterations, and epigenetic modifications in cancer genomes, including gene sequencing, gene expression arrays, mass spectrometric-based genotyping, SNP arrays, and next-generation sequencing technologies. It also leverages its faculty’s long-standing collaboration with the Broad Institute, accessing its genome discovery technology platforms and data analysis tools.

Center faculty provide extensive expertise in particular genomic disciplines, such as the discovery of somatic cancer-causing mutations, tumor characterization using genomic and functional approaches, germline cancer mutations, gene expression classification of cancer, cancer epigenetics, systematic functional analysis of cancer genes using RNA interference and cDNA expression

libraries, and pathological correlates of cancer genome alterations. Together, Center faculty have created a collaborative research environment in order to accelerate advances in basic and translational cancer genomic research.

## CENTER FOR CANCER SYSTEMS BIOLOGY

Director: Marc Vidal, PhD

The Center for Cancer Systems Biology explores cancer-related biological processes from a systems perspective. Proteins, RNA, and DNA interact to form complex connections, the “interactome network.” The Center’s strategy is to generate models of this human interactome in order to answer such questions as how complex cellular systems relate to biology and how perturbations of cellular networks lead to cancer.

Systems analysis requires libraries of cloned open reading frames (ORFs, the portions of genes that encode proteins), implementation of protein-interaction analytical methods, computational resources for data analysis, and integration of disparate disciplines — biology, medicine, statistics, physics, and engineering — to codevelop experimental and computational solutions. Center members model the human interactome network with systematic protein-interaction assays, aiming to understand complex functional interactions and biological processes relevant to cancer. The resources (molecular libraries, data set resources, and reagents) and technology platforms (experimental methods and bioinformatics tools) created for the human interactome project are also used to transfer emerging systems biology technologies within and outside Dana-Farber, which allows investigators to use state-of-the-art systems biology in their study of particular cancer-related processes.

The collaborative environment of the Center fosters discovery, leverages advanced technologies, deploys resources across Dana-Farber, and communicates novel science via seminars and meetings. The Human Genetics Initiative/Center for Cancer Systems Biology Seminar Series, which is offered with the Department of Genetics at Harvard Medical School, further enhances communication.

## CENTER FOR CLINICAL AND TRANSLATIONAL RESEARCH

Director: Lee Nadler, MD

The Center for Clinical and Translational Research was established to improve the infrastructure for clinical and translational research and to develop the next generation of clinical investigators. To support the increasing number and complexity of clinical trials at Dana-Farber, the Center established the Clinical Research Center and the Clinical Research Laboratory. The Clinical Research Center provides a facility where first-in-human and proof-of-concept clinical experiments can be conducted with the highest quality and safety. The facility will double in capacity when the Yawkey Center for Cancer Care opens in 2011. The Clinical Research Laboratory was founded to ensure the accuracy and quality of specimens obtained from subjects on clinical trials. It establishes individual standard operating procedures for each clinical trial, and then processes, stores, and retrieves the human clinical research specimens, markedly improving the quality of the trial endpoints.



FROM LEFT: MARC VIDAL, PHD, WITH MICHAEL CUSICK, PHD, AND DAVID HILL, PHD



LEE NADLER, MD



BRUCE JOHNSON, MD

**NEXT GENERATION OF CLINICAL INVESTIGATORS PROGRAM**

Director: Bruce Johnson, MD

The Next Generation of Clinical Investigators Program was established to recruit, mentor, and support a cadre of promising clinical investigators. These investigators develop collaborations with other faculty at Dana-Farber and establish partnerships with industry on first-in-human and early phase clinical trials. A grant from the Dana Foundation has funded the initial group of Next Generation Investigators; additional investigators will be recruited to the program over the next several years.



PASI JÄNNE, MD, PHD

**TRANSLATIONAL RESEARCH LABORATORY**

Director: Pasi Jänne, MD, PhD

The Translational Research Laboratory (TRL), supported by a generous grant from Dunkin' Donuts, was established to define patient subsets with specific outcomes and, ultimately, to predict patient response to treatment. Technologies being offered include the isolation, enumeration, and genotyping of circulating tumor cells, determination of plasma cytokine levels, and genotypic analysis of plasma-based tumor DNA. Currently, TRL is establishing Chip-based proteomic analyses in tumor specimens.



GREGORY VERDINE, PHD

**CHEMICAL BIOLOGY INITIATIVE**

Director: Gregory Verdine, PhD

The Chemical Biology Initiative provides molecular solutions to problems posed by cancer, fostering basic biological discoveries and the translation of these discoveries into new drugs for cancer patients. Five core groups have scientific programs that focus on: the discovery of novel protein kinase inhibitors; molecules that enable dissection of chromosome management during cell division; mitochondrial events responsible for the initiation of programmed cell death; novel inhibitors of epigenetic chromatin modification and transcriptional activation; and development of new molecular platforms to target intractable targets in cancer. Members have numerous collaborations with investigators from other Dana-Farber integrative centers, Harvard-affiliated hospitals, and the Broad Institute. Recent accomplishments include:

- Discovery of inhibitors that target Abl kinase through a novel mechanism and inhibitors that target both major arms of the Tor pathway
- Discovery of small molecules that inhibit the Rho pathway
- Discovery of a new class of drugs, “stapled” peptides, and their use in targeting intracellular protein-protein interactions that drive cancer
- Discovery of a new mechanism for the induction of programmed cell death
- Discovery of a role for the protein BAD in glucose sensing and the role of molecules that rescue BAD function
- Discovery of the first potent cell-permeable inhibitors of an oncogenic transcription factor that was previously thought to be undruggable
- Discovery of potent and selective inhibitors of histone deacetylase 6.

Several molecules created by the Initiative have demonstrated efficacy in mouse models of cancer. They are undergoing extensive optimization and preclinical safety and efficacy testing in preparation for clinical evaluation in the near future.

## DANA-FARBER/BRIGHAM AND WOMEN'S CENTER FOR MOLECULAR ONCOLOGIC PATHOLOGY

Director: Massimo Loda, MD

As cancer treatment approaches an era of personalized medicine, in which care is tailored to the molecular traits of a person's tumor, success will depend on discovering distinct genetic signatures within cancer cells. The Center for Molecular Oncologic Pathology was created to advance collaborative pathology-based research projects that have the potential to result in applications for targeted cancer therapy. To achieve this end, the Center brings together faculty from Dana-Farber and Brigham and Women's Hospital with molecular oncologic pathology expertise to advance pathology-based, hypothesis-driven research. The Center also develops novel diagnostic and prognostic tests by enabling researchers to apply their knowledge of the molecular biology of cancer to pathology.

Currently, the Center is pioneering the development of quantum-dot immunohistochemistry and FISH by coupling oligonucleotide probes with fluorescent nanoparticles. The probes chosen represent molecular signatures previously identified by gene expression arrays and yield new ways of diagnosing and predicting tumor progression at initial biopsy. The Center has utilized phospho-protein immunohistochemistry to detect proteins that are active in pathways driving tumor initiation and progression, allowing prediction of patient response to kinase inhibitor therapy. Furthermore, it has developed an ex-vivo, short-term, culture model system. This system allows for pharmacodynamic profiling of a patient's tumor with preclinical prediction of response to chemotherapy. It has also generated xenograft mouse models, derived from resected primary organ-confined human tumors, that now serve as models for gene discovery or drug testing. These tools will ultimately be translated into diagnostic clinical assays, thereby providing the means to improve therapy selection for cancer patients.

## MCGRAW/PATTERSON CENTER FOR POPULATION SCIENCES

Director: Jane Weeks, MD, MSc

The McGraw/Patterson Center for Population Sciences seeks to define optimal approaches to the prevention and treatment of cancer, and disseminate these interventions to populations at large. Toward this end, the Center focuses on three major themes: identifying cancer risk, reducing health disparities, and promoting public health, particularly among high-risk and underserved populations. The Center also connects faculty from Dana-Farber and affiliated institutions who are interested in population sciences research. Based in a single location at Dana-Farber, the Center promotes collaboration with laboratory scientists and clinical researchers across disease centers and institutions to bridge knowledge gaps, share methodologic expertise, and stimulate translational science. Training the next generation of cancer-focused population scientists is another core part of the Center's mission.

One major initiative of the Center is leadership of the Institute's Cohort Studies of Patients with Cancer. This consortium of disease-specific studies enrolls patients receiving their care at Dana-Farber and follows them over time, generating a rich resource of risk-factor, clinical and outcome data, as well as annotated specimens that can be used by population science, clinical, and translational investigators.



MASSIMO LODA, MD (CENTER), WITH KEITH LIGON, MD, PHD (RIGHT), AND MATTHEW THEISEN



JANE WEEKS, MD, MSc (SEATED), WITH KASISOMAYAJULA (VISH) VISWANATH, PHD (LEFT), AND, FROM LEFT, ELANA STOFFEL, MD, MPH, SAPNA SYNGAL, MD, RINAA PUNGLIA, MD, AND STEVEN JOFFE, MD, MPH



KENNETH MILLER, MD,  
AND LISA DILLER, MD

## PERINI FAMILY SURVIVORS' CENTER

Directors: Kenneth Miller, MD, and Lisa Diller, MD

Advances in our ability to detect and treat cancer have led to greater survival rates. But we have learned that for some, cancer survival comes with a price and life is never quite the same. The Perini Family Survivors' Center was established to advance clinical care and conduct research on cancer survivorship. The Center provides care and conducts patient-oriented research in the Lance Armstrong Foundation Adult Survivorship Clinic and, for children, the David B. Perini, Jr. Quality of Life Clinic. The Center also disseminates information on the medical, emotional, and psychological challenges facing today's growing population of cancer survivors.

Currently, the Center is evaluating various methods for providing care to cancer survivors, such as: evaluation of models of survivorship care; the value of MRI in breast cancer screening for Hodgkin's disease survivors treated with chest radiation; and the efficacy of a program for transitioning children off of cancer treatment. Other studies focus on improving long-term outcome and quality of life of cancer survivors, such as: Project REACH, a prospective, clinic-based cohort study of self-reported outcomes by cancer survivors; a multicenter cohort study of 14,000 childhood cancer survivors; and an assessment of the impact of mindfulness-based stress reduction training.

# Faculty Listing

## BIostatistics AND COMPUTATIONAL BIOLOGY

### Chair

**Giovanni Parmigiani, PhD**  
Professor of Biostatistics<sup>1</sup>

### Professor

**Richard Gelber, PhD**  
Professor of Pediatrics<sup>2</sup> and of Biostatistics<sup>1</sup>

**Robert Gray, PhD**  
Professor of Biostatistics<sup>1</sup>

**David Harrington, PhD**  
Former Chair, Department of Biostatistics and Computational Biology  
Co-Leader, Biostatistics Program, DF/HCC<sup>3</sup>  
Professor of Biostatistics<sup>1</sup>

**John Quackenbush, PhD**  
Director, Center for Cancer Computational Biology  
Professor of Computational Biology and Bioinformatics<sup>1</sup>

**Lee-Jen Wei, PhD**  
Professor of Biostatistics<sup>1</sup>

**Marvin Zelen, PhD**  
Lemuel Shattuck Research Professor of Statistical Science<sup>1</sup>

### Associate Professor

**Rebecca Gelman, PhD**  
Co-Director, Biostatistics Core, DF/HCC<sup>3</sup>  
Associate Professor of Radiation Oncology<sup>2</sup> and of Biostatistics<sup>1</sup>

**Cheng Li, PhD**  
Associate Professor of Biostatistics<sup>1</sup>

**Yi Li, PhD**  
Associate Professor of Biostatistics<sup>1</sup>

**Xiaole (Shirley) Liu, PhD**  
Associate Professor of Biostatistics<sup>1</sup>

### Assistant Professor

**Meredith Regan, ScD**  
Assistant Professor of Medicine<sup>2</sup>  
Senior Research Scientist in Biostatistics<sup>1</sup>

**Armin Schwartzman, PhD**  
Assistant Professor of Biostatistics<sup>1</sup>

**Molin Wang, PhD**  
Assistant Professor of Biostatistics<sup>1</sup>

**Guo-Cheng Yuan, PhD**  
Assistant Professor of Computational Biology and Bioinformatics<sup>1</sup>

### Senior Lecturer

**Paul Catalano, ScD**  
Associate Chair, Department of Biostatistics and Computational Biology  
Director, Biostatistics Core, DF/HCC<sup>3</sup>  
Senior Lecturer on Biostatistics<sup>1</sup>

**Donna Neuberg, ScD**  
Senior Lecturer on Biostatistics<sup>1</sup>

### Senior Research Scientist

**Haesook Kim, PhD**  
Senior Research Scientist in Biostatistics<sup>1</sup>

**Sandra Lee, ScD**  
Senior Research Scientist in Biostatistics<sup>1</sup>

**Edie Toolan, PhD**  
Senior Research Scientist in Biostatistics<sup>1</sup>

**Joseph White, PhD**  
Senior Research Scientist in Biostatistics<sup>1</sup>

### Research Scientist

**Suzanne Dahlberg, PhD**  
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Research Scientist in Biostatistics<sup>1</sup>

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**Zhuoxin Sun, PhD**  
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**Hajime Uno, PhD**  
Research Scientist in Biostatistics<sup>1</sup>

## CANCER BIOLOGY

### Co-Chairs

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Professor of Microbiology and Molecular Genetics<sup>2</sup>

### Professor

**Michael Eck, MD, PhD**  
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Leader, Breast Cancer Program, DF/HCC<sup>3</sup>  
Anne E. Dyson Professor in Women's Cancers<sup>2</sup>

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Deputy Director, DF/HCC<sup>3</sup>  
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**Bruce Spiegelman, PhD**  
Stanley J. Korsmeyer Professor of Cell Biology and Medicine<sup>2</sup>

**Gregory Verdine, PhD**  
Director, Chemical Biology Initiative  
Erving Professor of Chemistry<sup>4</sup>

**Marc Vidal, PhD**  
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**Nathanael Gray, PhD**  
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**Andrea Richardson, MD, PhD**  
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**William Shih, PhD**  
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**Daniel Silver, MD, PhD**  
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**Zhigang Wang, PhD**  
Assistant Professor of Surgery<sup>2</sup>

**Jean Zhao, PhD**  
Assistant Professor of Pathology<sup>2</sup>

### Instructor

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**Vladimir Joukov, MD, PhD**  
Instructor in Medicine<sup>2</sup>

**Chrysi Kanellopoulou, PhD**  
Instructor in Medicine<sup>2</sup>

**Jean-Bernard Lazaro, PhD**  
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**Penelope Miron, PhD**  
Instructor in Surgery<sup>2</sup>

**Claire Sauvageot, PhD**  
Instructor in Neurology<sup>2</sup>

**Pengcheng Zhou, PhD**  
Instructor in Pediatrics<sup>2</sup>

### Lecturer

**Albert-Laszlo Barabasi, PhD**  
Lecturer on Medicine<sup>2</sup>

### Principal Associate

**John Genova, PhD**  
Principal Associate in Biological Chemistry and Molecular Pharmacology<sup>2</sup>

**Dennis Lynch, MD, PhD**  
Principal Associate in Medicine<sup>2</sup>

Online faculty profiles are available at: <http://www.dana-farber.org/researcher>

<sup>1</sup>Harvard School of Public Health <sup>2</sup>Harvard Medical School <sup>3</sup>Dana-Farber/Harvard Cancer Center <sup>4</sup>Harvard University

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**Paul Morrison**  
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**Debajit Biswas, DSc**

**Research Scientist**

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**Pixu Liu, PhD**  
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**Francisca Vazquez, PhD**

**Yi Zhang, PhD**

**CANCER IMMUNOLOGY AND AIDS**

**Chair**

**Harvey Cantor, MD**  
Baruj Benacerraf Professor of Pathology<sup>2</sup>

**Professor**

**Dana Gabuzda, MD**  
Professor of Neurology<sup>2</sup>

**Martin Hemler, PhD**  
Professor of Pathology<sup>2</sup>

**Ruth Ruprecht, MD, PhD**  
Professor of Medicine<sup>2</sup>

**Joseph Sodroski, MD**  
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**Harald von Boehmer, MD, PhD**  
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**Wayne Marasco, MD, PhD**  
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**Shi-Hua Xiang, PhD**  
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**Quan Zhu, PhD**  
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**Jason Pyrdol**

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**IMAGING**

**Chair**

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Co-Director, Tumor Imaging Metrics Core, DF/HCC<sup>3</sup>  
Associate Professor of Radiology<sup>2</sup>

**Professor**

**Jack Meyer, MD**  
Professor of Radiology<sup>2</sup>

**Associate Professor**

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 Professor of Society, Human Development and Health<sup>1</sup>

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