

One collective force dedicated to the fight against cancer

Fusion vaccine may prove potent in renal cell cancer

Renal cell cancer (RCC) is a life-threatening malignancy considered incurable in the metastatic setting. While standard chemotherapy has proved largely ineffective, biological-based treatments, such as vaccines, do hold promise. In prior studies, for example, fusion vaccines – made of dendritic cells fused with tumor cells, both derived from the patient – were well-tolerated and demonstrated clinical response in a subset of patients. David Avigan, MD (BIDMC), is now leading a clinical trial to confirm the safety of fusion cell vaccination, to investigate its impact in combination with GM-CSF, a protein that stimulates the immune system, and most importantly, to test whether vaccination following surgery improves its efficacy.

Avigan trial *continued on page 4*

Divide-and-conquer strategy drives breast cancer breakthroughs

Pulling a page from ancient Rome’s military handbook, investigators in the DF/HCC Breast Cancer Program are deploying a divide-and-conquer strategy in the battle against breast cancer. Rather than mounting a one-strike-fits-all assault against a heterogeneous enemy, scientists are dividing the enemy into smaller, more homogeneous adversaries – whose unique vulnerabilities can be exploited with greater tactical precision.

“Breast cancer is not just one disease, but a diversity of distinct entities,” says program leader J. Dirk Iglehart, MD (DFCI). “This realization is changing the way we do translational science.” Based on genetic data, the program classifies life-threatening breast tumors into three broad subtypes: hormone-receptor positive, HER2-positive, and triple negative. Clinical trials initiated within DF/HCC are now testing an array of innovative subtype-specific therapies – and applying them preoperatively, when safe and feasible – resulting in some profound improvements, says Iglehart.



Breast cancer specialist Paula Ryan, MD, PhD, and basic scientist Leif Ellisen, MD, PhD, are co-investigators on a phase II trial of cisplatin for triple negative breast cancer. (Photograph by Joshua Touster)

Overcoming resistance in receptor-positive disease

Hormone receptor-positive breast cancer accounts for approximately 60 percent of all breast tumors. The hallmark of these tumors is a high number of estrogen receptors (ER) and/or progesterone receptors (PgR), which stimulate cell growth when bound by these hormones. Their hormone dependency renders these tumors vulnerable to targeted endocrine therapies, including tamoxifen and aromatase inhibitors that deprive tumors of estrogen. But although aromatase inhibition (AI) has demonstrated “a modest disease-free survival benefit” compared with tamoxifen, explains breast cancer specialist Paula Ryan, MD, PhD (MGH), resistance remains a critical problem. Thus she and co-investigator Paul Goss, PhD (MGH) –

Breast cancer *continued on page 6*

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siRNA knockdowns turn up intriguing HER2 targets

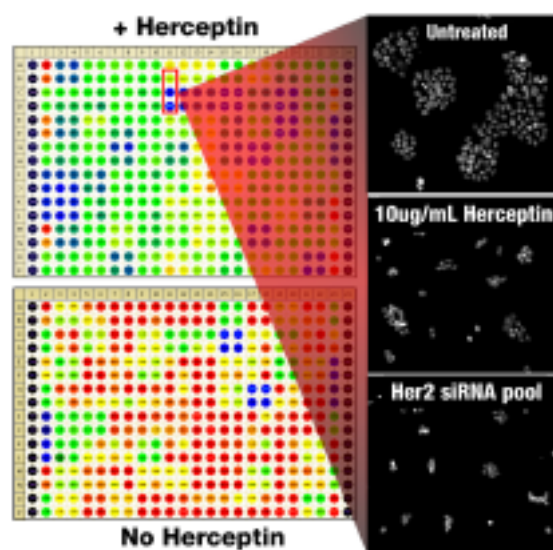
At best, only 20 to 30 percent of women with HER2-positive breast cancer respond to trastuzumab. This grim reality has prompted the Breast Cancer Program to search for new drug targets that, when inhibited, might synergize with trastuzumab to yield better outcomes during initial treatment. In one SPORE (Specialized Program of Research Excellence) project, Randy King, MD, PhD, associate professor of cell biology at HMS, is using siRNA technology to do just that. Rather than looking for all possible needles in the genomic haystack, however, King is aiming at known cancer culprits – kinase genes – whose products lend themselves to small-molecule inhibition and thus more rapid translation into therapies.

In collaboration with Ben Neel, MD, former member of the DF/HCC Breast Cancer Program and current director of the Ontario Cancer Institute, King is hunting for kinase genes that when knocked down by siRNAs prevent the proliferation or survival of *HER2*-over-expressing cells. The project may also uncover new insights about the biology of HER2-associated signaling pathways.

In the primary screen, King and colleagues muted expression of approximately 600 kinase (and some phosphatase) genes to see which ones affect

growth in HER2-positive cell lines; in parallel, they conducted the same assays in the presence of trastuzumab. In vitro, trastuzumab inhibits cell proliferation by about 40 percent, giving investigators a handy yardstick by which to measure additional growth inhibition by siRNA knockdown.

Although one objective of this work is to identify genes that induce cell death in the presence of trastuzumab but not in its absence, the screen has also turned up genes that inhibit proliferation of *HER2*-amplified cells independent of trastuzumab. The 100 most effective genes found in the first screen are now being validated in secondary screens in a variety of HER2 positive cell lines to confirm their selectivity for *HER2*-amplified cells. Those validated are then tested across a panel of other breast cancer cell lines – including HER2-negative. “We’re characterizing the results from these kinase screens to understand whether we’ve found any genes specific for *HER2*-over-expressing cells,” says King. “And we’re still wrestling with that question.”



HER2-positive breast cancer cells transfected with siRNAs are grown in the presence or absence of Herceptin for four days. Then cell viability and number are measured.

Validation: the hard work ahead

The real challenge, he says, is winnowing down genes to a subset that are truly selective to the HER2 pathway and physiologically relevant. “We’re being very careful in confirming that the effects of a given siRNA are indeed due to a knockdown of the intended target, as opposed to the so-called “off-target phenomenon.” Because siRNAs are only 21 nucleotides long, they can occasionally hit the same sequences

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Produced by the
DFCI Communications Department

More on Cores

High-Throughput Polymorphism Detection Core

Directors: David Hunter, MPH, ScD (HSPH),
and David Kwiatkowski, MD, PhD (BWH)

The High-Throughput Polymorphism Detection Core provides services to investigators conducting molecular analyses of somatic DNA collected as part of a wide range of investigations. This includes high-throughput assays of specific gene mutations and polymorphisms (SNPs) in the many situations where previously

defined specific nucleotide alterations are of interest. For more information, call 617-355-9005.

Specialized Histopathology Services Core

Directors: Jon Aster, MD, PhD (BWH), and
Anat Stemmer-Rachamimov, MD (MGH)

The Specialized Histopathology Services (SHS) Core provides technical

on other genes. To lower that likelihood, King is using four different siRNAs in the secondary screens, each one aimed at a distinct region of the gene of interest. "If we find that all four siRNAs give us the same phenotype, it's much more likely the consequence of knockdown of the intended gene than of off-target effects."

The second round of screening also provides a more information-rich read-out, measuring both cell number and metabolic activity simultaneously, thus allowing investigators to correlate the two. Moreover, King plans to use time-lapse microscopy to characterize how cells respond when a particular kinase gene is knocked down. "Sometimes cells round up and die right away, or flatten out and just sit there," says King, who uses time lapse routinely in his other research. "Observing cells over time gives us more insight into the potential mechanisms by which loss of gene function might be inhibiting proliferation."

Will future avenues of investigation screen kinase genes in trastuzumab-resistant cell lines? Or in combination with lapatinib? "These are all interesting questions," acknowledges King. "But validating these genes is where the hard work lies right now."

— Lonnie Christiansen

and professional pathology services in a variety of experimental organisms and human tissues. Specific services include routine processing, embedding, cutting, and staining of tissue sections; and the development, implementation, and interpretation of *in situ* tests for RNAs and proteins. The SHS Core also assists with experimental design, test development, and test interpretation. For more information, call 617-278-0080 (Longwood Area) or 617-726-5510 (MGH).

HHMI selects nation's top scientists

Matthew Freedman, MD (HMS), David Pellman, MD (DFCI), and Bernardo Sabatini, MD, PhD (HMS), were recognized by the Howard Hughes Medical Institute as leaders in cancer research.

Pellman and Sabatini were chosen as two of 56 researchers nationwide to become part of the newest crop of HHMI investigators. The Institute has committed more than \$600 million collectively to these investigators so that they may tackle their most ambitious and risky research ideas.

Freedman was one of 19 researchers to receive an Early Career Physician Scientist award. The award of \$375,000 over five years supports scientists who bridge the gap between basic and clinical research and are less than two years into a tenure track position. The idea is to give these promising individuals a boost during a vital time in their careers.



Matthew Freedman, MD



David Pellman, MD



Bernardo Sabatini, MD, PhD

Two DF/HCC members honored at ASCO annual meeting

Jay Harris, MD (DFCI), and Bruce Johnson, MD (DFCI), were honored recently at the 2008 meeting of the American Society of Clinical Oncology (ASCO) for their outstanding accomplishments in cancer research.

Harris was chosen as the annual Gianni Bonadonna Breast Cancer Award recipient. This \$10,000 award recognizes an active clinical or translational researcher with a distinguished record of accomplishments in advancing the field of breast cancer research. He will accept the award and present his upcoming lecture, "Local Treatment of Breast Cancer: Looking Backward to Gaze Forward," at the upcoming 2008 Breast Cancer Symposium being held Sept. 5–7 in Washington, D.C.



Jay Harris, MD



Bruce Johnson, MD

Johnson was awarded the ASCO Cancer Foundation's newest grant, the Translational Research Professorship. He, as well as Everett Vokes, MD (University of Chicago), will receive \$500,000 over five years to support continued efforts to bring advances in basic sciences into the clinical area, and to serve as a mentor for other translational researchers.

Why this study is important

This phase I/II trial is one of a new generation of cancer vaccine studies looking at ways to “manipulate the environment” in the patient to better respond to the vaccine, explains Avigan. “We wanted to take advantage of improved outcomes in metastatic disease following nephrectomy, due in part to the increased immune effects of removing bulk lesion from the patient.” His hope is that the combination of vaccination and surgery will improve immunologic response and clinical outcomes.

Patients with previously untreated metastatic RCC who have undergone nephrectomy (or resection of other accessible lesions) receive three vaccinations

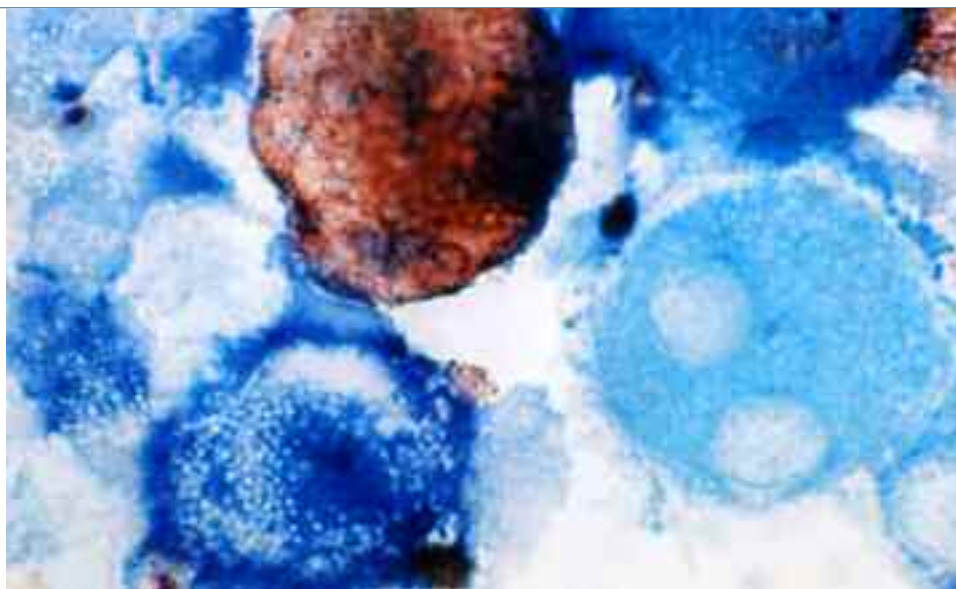
of fused cells by subcutaneous injection at three-week intervals, starting one to two months after surgery. One cohort, now closed, received the vaccine alone, and those who tolerated it proceeded to the



David Avigan, MD

second cohort. All subjects enrolled on the study since the first cohort closed received both the vaccine and GM-CSF.

The vaccine contains patient-derived antigen-presenting dendritic cells and the patient's own tumor antigens, a fusion that Avigan believes can provoke a broad-based immunologic response that makes it



Fusion of renal carcinoma and dendritic cells stained for Cytokeratin (red) and CD86 (blue) 100zx.

more difficult for the tumor to escape detection. Tumors have evolved strategies to evade, mute, or disable the immune system, and fusion vaccines are an attempt to “re-educate” immune cells so that they can more effectively recognize tumor cells and eradicate them. “The vaccine is also created outside the patient,” he adds, “and thus away from the inhibitory influences of the tumor.” The addition of GM-CSF, which has been studied in other vaccine trials as well, is part of the effort to amplify response to the vaccine and may even recruit other dendritic cells in the patient, suggests Avigan.

Before and after vaccination, investigators count the patient's tumor-reactive lymphocytes to determine whether the vaccine induced a rise in the number of these cells. “We quantify immunologic response by measuring the expression of these cytokines for their ability to become functionally active again,” says Avigan.

Since some investigators hypothesize that debulking the tumor might also decrease the number of regulatory cells (involved in immunosuppression), the study is measuring those as well. “But our main focus is evidence of regression after vaccination,” says Avigan.

The open-label study, which began accruing patients in 2004, is ongoing, but preliminary evidence of immunologic and disease response has been seen in some patients, says Avigan. “Our hope is to extend that phenomenon into clinically meaningful outcomes that result in stable disease or eradication.”

— Lonnie Christiansen

Protocol title: Vaccination of Patients with Renal Cell Cancer with Dendritic Cell Tumor Fusions and GM-CSF

Principal Investigator: David Avigan, MD

Mark your calendars for RNAi: from Mechanism to Medicine

The UMass Boston/DF/HCC Partnership's Annual Cancer Symposium will be held on Oct. 7. Keynote speaker Craig Mello, PhD (UMass), will visit the Joseph B. Martin Conference Center at Harvard Medical School to present his RNAi research to the DF/HCC community. Mello, along with colleague Andrew Fire, PhD (Stanford), was

awarded the Nobel Prize in 2006 for his discoveries related to RNA interference. There will be a reception for Mello immediately following the presentation. Seating will be limited, and registration is required. For more information about this event, visit the DF/HCC online calendar: www.dfhcc.harvard.edu/calendar.

Seeking higher survival rates and lower side effects in pediatric ALL

Children newly diagnosed with acute lymphoblastic leukemia (ALL) typically receive a two- to three-year regimen of chemotherapy drugs. While this treatment results in event-free survival for the majority of young patients, 15 to 20 percent of children relapse and have poor outcomes; in addition, drug toxicities negatively affect their quality of life. A clinical trial, led by Lewis Silverman, MD (DFCI/CHB), is testing whether an alternate preparation of asparaginase reduces its side effects, and whether a risk-stratified approach to therapy based on minimal residual disease (MRD) leads to better survival rates.

Why this study is important

In this randomized phase III trial, investigators are comparing the efficacy and safety of two different preparations of asparaginase in combination with other chemotherapy drugs. Asparaginase is a universal component of therapy for childhood ALL, but is associated with many side effects including allergic reactions, pancreatitis, and thrombosis. One cohort receives standard *E.coli* asparaginase by intramuscular injection every week for 30 weeks; another receives PEG-asparaginase intravenously through a central line every two weeks. Previous studies have shown that polyethylene glycosylated (PEG) asparaginase – a preparation in which asparaginase is encapsulated within a polyethylene barrier – lasts longer in the body and may be less allergenic than the standard *E.coli* preparation. Moreover, while *E.coli* asparaginase can only be given as an intramuscular injection in the U.S., PEG asparaginase has recently been approved for intravenous administration. “Our hope is to reduce the rate of allergy to asparaginase so that more patients can receive effective doses,” says Silverman. “Children also benefit by not having to get a painful intramuscular injection every week.”

At the same time, a significant objective of this trial is to use MRD as a new biomarker to identify patients at high risk of relapse and to intervene early with more intensive treatments. After one month of chemotherapy, up to 98 percent of children achieve complete remission (that is, in a bone marrow sample, no leukemia cells can be seen under the microscope). But if chemotherapy is stopped at this point,

says Silverman, 100 percent of patients will relapse. “Even though you cannot see leukemia cells, a lot of residual disease is left behind following the initial induction phase” – thus the need for a two- to three-year drug regimen.

As more sensitive techniques such as PCR were developed that could measure “invisible” MRD, Silverman and colleagues began correlating MRD levels with outcomes. “We found that about 15 percent of patients with high levels of MRD at the end of the first month of treatment had a very high chance of subsequently relapsing. Now, for the first time, we are acting on that information in this clinical trial.”

At the time of diagnosis, probes are developed from patients’ bone marrow and peripheral blood samples and used at the end of induction to measure MRD; these tests can detect one leukemia cell

in 100,000 normal cells, says Silverman. Those patients with high levels of MRD, about 15 percent, are then assigned to a different treatment arm of the study, which includes additional chemotherapeutic agents not typically given to newly diagnosed ALL patients.

The study is also using MRD and other factors to try to reduce

long-term side effects of cranial radiation. Although it is effective in preventing relapses in the brain and spinal fluid, cranial radiation is associated with secondary brain tumors and the risk of learning disabilities. Only patients at highest risk of relapse receive this additional treatment.



Lewis Silverman, MD

– Lonnie Christiansen

Protocol title: Pegasparaginase or Asparaginase and Combination Chemotherapy in Treating Young Patients with Newly Diagnosed Acute Lymphoblastic Leukemia

Principal Investigator: Lewis Silverman, MD

an international expert on endocrine therapy and leader of the Breast Cancer Program – have embarked on several novel studies to thwart the tumor’s development of resistance and improve patients’ progression-free survival.

In one study, investigators are attempting to suspend or delay resistance by administering the aromatase inhibitor letrozole intermittently. This on-off strategy is premised on the observation that as tumor cells become chronically estrogen-deprived, they develop hypersensitivity to the hormone. Just how this happens is unclear, notes Ryan. “When all estrogen-sensitive cells in the tumor are eliminated, that may leave only drug-resistant clones,” she hypothesizes. “If we interrupt AI, we hope to retain some intratumoral heterogeneity,” which may control the growth of drug-resistant cells.

A unique aspect of this study is the use of CA 15-3 as a tumor marker to help determine, in combination with scans and monthly clinical evaluation, when to make changes in therapy. “Once we’ve seen that patients have responded to AI, we stop their therapy and watch the marker,” explains Ryan. “If it goes up 25 percent, we put them back on the drug.” This process is repeated in a cyclical fashion, using the tumor marker to dictate when to halt or reintroduce letrozole.

In another trial, Ryan and Goss are attacking the problem of endocrine resistance by testing one of the antibodies to the insulin-like growth factor 1 receptor (IGF-1R) in combination with the aromatase inhibitor exemestane, compared with exemestane alone. Underlying this study is the hypothesis of “crosstalk” between the estrogen receptor and IGF-1R pathways as a possible mechanism of resistance. The primary objective of the study – the first to evaluate an IGF-1R antibody in patients with breast cancer – is to see whether blocking crosstalk

increases progression-free survival in women with metastatic hormone-positive disease, which has no cure.

Armed antibodies and other targeted treatments for HER2-positive breast cancer

About 20 percent of breast tumors overexpress the human epidermal growth factor receptor 2 (*HER2*) gene. Until the emergence of HER2-targeted therapies a decade ago, these tumors were very difficult to treat, says Eric Winer, MD, director of the Breast Oncology Center at DFCI and one of the first investigators to conduct preoperative trials using the HER2 antibody trastuzumab (Herceptin) for early-stage HER2-positive breast cancer. Herceptin remains a remarkable drug, says Winer, but in women with metastatic disease, the cancer almost always finds a way to grow in spite of continued Herceptin treatment. And scientists do not fully understand its mechanisms of resistance. “In some patients, the disease is entirely refractory to the drug; in other patients, it continues

may cross the blood brain barrier – to overcome the problem.

Winer and colleagues are currently heading a number of trials in patients with advanced HER2 disease whose cancer has progressed while on trastuzumab. One novel approach to overcoming resistance is the T-DM1 trial, in which patients receive a first-in-class “armed antibody” – a conjugate of trastuzumab with the potent chemotherapy drug maytansinoid. Trastuzumab serves a dual function, delivering the lethal drug directly to HER2-positive cancer cells and decreasing HER2 signaling. “So far, the conjugate has been well tolerated and associated with a remarkable amount of activity,” notes Winer. In all these studies, investigators are also correlating what they see in the tumor on a molecular level with the response seen in the patient.

Turning on death genes in triple negative tumors

Neither HER2-targeted therapies nor aromatase inhibitors are effective against

Herceptin remains a remarkable drug, but in women with metastatic disease, the cancer almost always finds a way to grow in spite of continued Herceptin treatment.

— Eric Winer, MD

to exert an effect but the cancer finds a path around the blockade.” Moreover, in about a third of patients with advanced disease, brain metastases develop despite treatment, largely because Herceptin does not reach the brain, explains Winer. His research group was the first to describe this problem and the first to conduct studies of targeted treatment with lapatinib – a dual epidermal growth factor receptor and HER2 inhibitor that, unlike Herceptin,

the third broad subtype of breast cancer, a group of aggressive tumors that lack expression of ER, PgR, and HER2. Compared with other breast cancer subtypes, these triple negative tumors – of which 80 percent are basal-like cancers – have had a poor prognosis. But recent discoveries from the laboratories of Leif Ellisen, MD, PhD (MGH), David Livingston, MD (DFCI), Andrea Richardson, MD, PhD (BWH), and others are now yielding

promising treatments for these refractory cancers.

Because up to 90 percent of women with *BRCA1*-associated breast cancer have the triple negative subtype, investigators wondered whether the tumors that harbor *BRCA1* mutations might share certain molecular features with other triple negative tumors that do not. Indeed, the gene expression profiles of a subset of triple negative tumors revealed high levels of p63, a master regulator of normal breast development that binds tightly to p73 and prevents it from inducing apoptosis. “We found that most *BRCA1*-associated cell lines had this p63/p73 signature, but only about a third of the other triple negatives had it,” says Ellisen, who is co-director of the MGH Translational Research Lab where the genetic analyses were conducted. Surprisingly, his lab also showed that high expression of p63 and p73 in the cell confers sensitivity to platinum – a cytotoxic agent rarely used in breast cancer – which effectively turns on “death genes” by activating p73 and inhibiting p63.

These and other data led Judy Garber, MD, MPH, director of the Cancer Risk and Prevention Clinic at DFCI, to propose a bold experiment: the first preoperative clinical trial of cisplatin in women with recently diagnosed triple negative breast cancer. Results of the trial were startling. “Of 28 women receiving treatment, 22 percent had complete response and another 25 percent had significant shrinkage,” says Garber, the principal investigator.

“When we looked at the genetic signature in Judy’s trial,” adds Ellisen, “we found that patients who were p63/p73 positive were about five times more likely to have a complete pathologic response from single-agent cisplatin than patients who were p63/p73 negative.” The success of the trial spawned a new cisplatin study in the metastatic setting to assess response rate and evaluate the p63/p73 signature as a predictive biomarker of response.

“We’ve been able to conduct these clinical trials because of discoveries in the lab,” says Garber. “Now, from our clinical data, scientists can go back to the bench and ask new questions. We’re really in this together.”

– Lonnie Christiansen

Grant Updates

Breakefield awarded \$5.8 million to study tumors

DF/HCC member Xandra Breakefield, PhD (MGH), will receive approximately \$5.8 million in total costs over five years to study the genetic and cellular factors contributing to the formation and progression of benign tumors in the nervous system.

Breakefield and colleagues have successfully renewed this funding from the National Institute of Neurological Disorders and Strokes. The P01, entitled “Molecular Genetics of Inherited Neurological Diseases,” consists of three projects:



Molecular genetics of meningioma and NF-related disorders

James Gusella, PhD (MGH)

Mouse brain models of tuberous sclerosis

David Kwiatkowski, MD, PhD (BWH)

Vector query and therapy for TSC and NF2 lesions

Xandra Breakefield, PhD (MGH)

Miguel Sena-Esteves, PhD (MGH)

DePinho awarded \$10.8 million to study malignant gliomas

DF/HCC member Ronald DePinho, MD (DFCI), has successfully renewed funding from the National Cancer Institute to better understand the pathogenesis of glioblastoma multiforme. DePinho and colleagues

will receive approximately \$10.8 million in total costs over five years. The P01, entitled “Genetics and Biology of Malignant Glioma,” consists of three projects:



Discovering and modeling genetic events driving glioblastoma pathogenesis

Ronald DePinho, MD (DFCI)

Resistance to therapeutics directed at the EGFR/P13-K pathways in glioblastoma

Webster Cavenee, PhD (Ludwig Institute for Cancer Research)

Frank Furnari, PhD (Ludwig Institute for Cancer Research)

Identification and characterization of kinase oncogenes in glioblastoma

Lynda Chin, MD (DFCI)

William Hahn, MD, PhD (DFCI)

New Members

Congratulations to the 11 individuals who have recently joined DF/HCC:

Gregory Abel, MD, MPH (DFCI)

Leukemia Program; Outcomes Research Program

Li Chai, MD (BWH)

Leukemia Program

Toni Choueiri, MD (DFCI)

Prostate Cancer Program; Kidney Cancer Program

Irene Ghobrial, MD (HMS)

Lymphoma and Myeloma Program;
Invasion, Metastasis, and Angiogenesis Program

Hadine Joffe, MD (MGH)

Breast Cancer Program

Jan Lammerding, PhD (BWH)

Invasion, Metastasis, and Angiogenesis Program

HaeOk Lee, DNSc (UMB)

Cancer Disparities Program

Janie Lee, MD (MGH)

Outcomes Research Program;
Cancer Imaging Program

Ivan Pedrosa, MD (BIDMC)

Kidney Cancer Program

Aliyah Rahemtullah, MD (MGH)

Lymphoma and Myeloma Program

Susan Rittling, PhD (Forsyth)

Cancer Immunology Program

Harvard receives transforming NIH award

Harvard Medical School has been awarded the Clinical and Translational Science Award from the National Institutes of Health (NIH). The funding will be used to launch a Clinical and Translational Science Center (CTSC) that will transform patient-oriented research and facilitate collaborations across the Harvard schools and affiliated hospitals and universities. Harvard will receive \$23.5 million per year during this five-year award period, and Lee Nadler, MD (DFCI), and Stephen Freedman, MD, PhD (BIDMC), will direct the new center.



Lee Nadler, MD

This funding is critical to Harvard and its affiliated hospitals. With the award, Harvard will also be eligible for a new group of NIH Roadmap grants.

The CTSC will focus on building a University-wide infrastructure to support clinical and translational research and help create methods to connect and support investigators and cross-disciplinary teams of investigators. Harvard CTSC initiatives include a new Internet portal called CONNECTS that will help to navigate Harvard resources and include a “match-making” service that will allow researchers to find one another. The portal will also house SHRINE (Shared Health Resource Information Network), a database that pools information on research subjects across hospitals, giving scientists the ability to instantly analyze data from large populations.

In addition to the portal, CTSC leadership is identifying and recruiting several specialized Harvard scientists to serve as “navigators.” These investigators will act as matchmakers and consultants, helping other investigators find resources and collaborators for their translational research endeavors.

The CTSC will also distribute approximately \$8 million per year in pilot grants for early and translational studies, focusing on junior investigators who want to work across disciplines or institutions. In line with the overall goal of the CTSC, grantees will also receive support in managing these complex awarded projects.