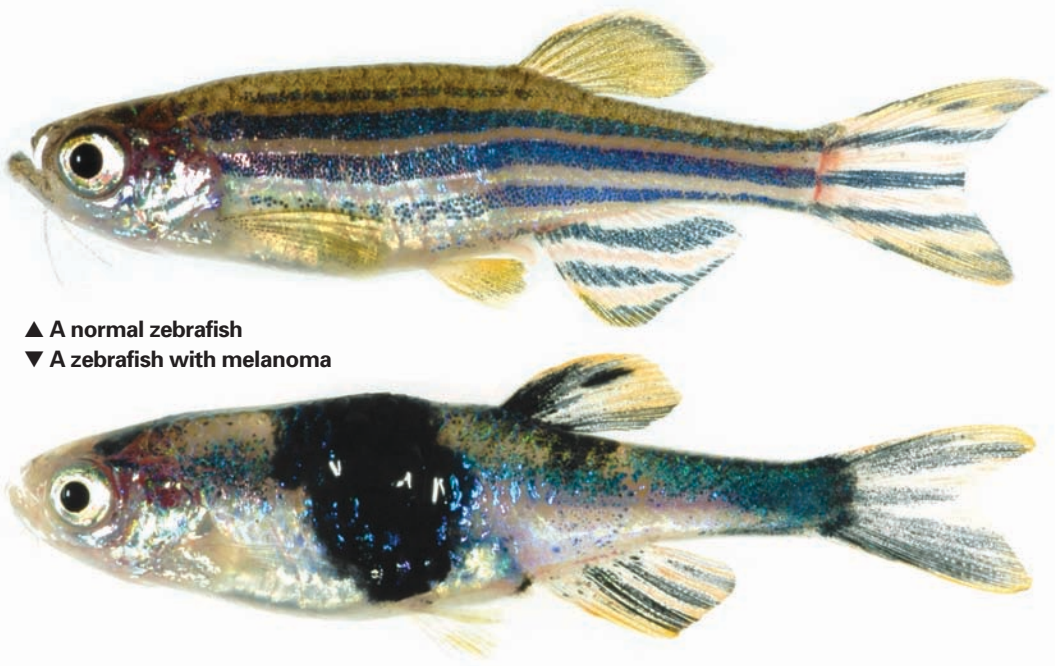
FOCUS

News from Harvard Medical, Dental and Public Health Schools

April 2011 ▶ focushms.com

Perfect MAtch "I'm beyond happy," said Stella Safo, hMS class of 2011 (with friend William Junior). See MAtch DAY, page 4



▲ A normal zebrafish
▼ A zebrafish with melanoma

Courtesy of Children's Hospital Boston

n ew Insights Into Lethal Melanomas

Zebrafish model of human tumor reveals genetics, promising drugs

Researchers at Children's Hospital Boston and collaborators from several other institutions have used a zebrafish model of melanoma to identify two important mechanisms that promote the growth of this aggressive human skin cancer, which begins in pigment-producing melanocytes.

In the first of two papers featured on the cover of the March 24 issue of *Nature*, the scientists established a new oncogene in melanoma: *SETDB1*, the first identified using a zebrafish model of the disease. In the second paper, the same Children's researchers used the model to determine that the combination of an existing arthritis drug and a new drug under study for late-stage melanomas with mutations in the gene *BRAF* may hold promise for treating some types of melanoma.

The zebrafish melanoma model was developed about six years ago, said Leonard Zon, the Grousbeck Professor of Pediatrics and director of the hospital's Stem Cell Program and senior author of both papers, "to find new genes that caused human melanoma and support the development of new drugs against a disease for which there are very few treatment options." *See "Melanoma," page 6*

The Wisdom of Crowds

Contest yields innovative strategies for conquering Type 1 diabetes

Seven research teams with fresh approaches to solving the riddle of Type 1 diabetes have received funding through an initiative that first tapped the creativity of Harvard's schools and affiliated institutions just over a year ago.

It was in February 2010 that the Harvard Clinical and Translational Science Center, known as Harvard Catalyst, launched a bold crowd-sourcing experiment called the Ideation Challenge. Some 40,000 faculty, staff and students, along with the general public, were invited to answer the question: What do we not know to cure Type 1 diabetes?

A panel of experts reviewed 190 suggestions and zeroed in on 12 outstanding responses—some of them from nonexperts, including a student at Harvard College and a human resources manager at HMS. Each of the dozen contest winners received $2,500 and agreed to release their idea and intellectual property to Harvard.

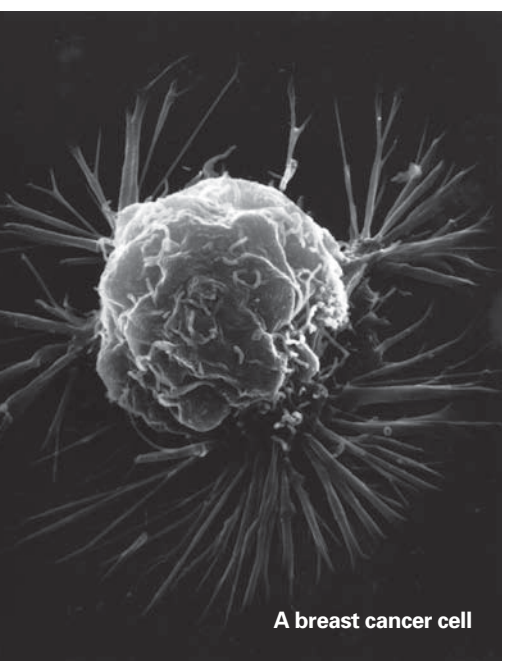
See "Type 1 Diabetes," page 6

Ulf Sirborn

Luft Award to d ean Flier

HMS Dean Jeffrey S. Flier (above, with Karolinska Institutet President Harriet Wallberg-Henriksson) received the international Rolf Luft Award in March for seminal research on insulin and leptin physiology and the mechanisms underlying their defective action in metabolic diseases.

See Notable, page 8



A breast cancer cell

National Cancer Institute

Target Identified for Aggressive Breast Cancer

Given current early detection methods for breast cancer, many people can be treated successfully. But for the 20 percent of patients with so-called triple-negative breast cancer, the outcome is bleak.

Now, however, researchers from Harvard Medical School and Baylor College of Medicine have identified a critical molecular component to the disease. Additional experiments in mice suggest potential therapies involving combinations of FDA-approved, readily available drugs.

"Whereas many basic discoveries have the potential to impact patients' lives within ten, 20 or 30 years, this has the potential to impact patients' lives within one year," said Thomas Westbrook, formerly a postdoctoral fellow at HMS and an assistant professor of biochemistry and molecular biology at Baylor College of Medicine since 2007.

See "Breast Cancer," page 6

Inside

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Von Furstenberg on Health and Beauty ■ Books ■ Professors ■ Faculty Council

In this portrait of Pablo Picasso, the differing positions of the points of light in the artist's eyes suggest their misalignment.

The eye of the Beholder

Neurobiology sheds new perspective on the artist's gaze

One of the challenges of learning to paint the world is figuring out how to collapse the three dimensions of life onto a two-dimensional canvas. Part of that difficulty is technical; the evolving artist must grasp the subtleties of paint, stroke and composition in order to depict depth and space. Another hurdle is neurological; the artist must figure out how to undermine the stereoscopic accuracy of binocular vision. In short, the artist must learn to "see" three dimensions as two before he or she can render well real-world perspective.

Or perhaps, if you're Edward Hopper, say, or Marc Chagall, Alexander Calder, or Pablo Picasso, you might rely on a natural aberration: a deficit in your stereoscopic vision.

Writing in the March issue of *Psychological Science*, Margaret Livingstone, HMS professor of neurobiology, and fellow researchers report that difficulties with stereopsis, the perception of depth generated by the brain from the sensory input of both eyes, are more common among artists than non-artists. Moreover, according to the team's assessment of photographs of established artists, artists' eyes often show misalignment, especially when compared to a control population of non-artists. Eye misalignment, a condition known as strabismus, contributes to poor stereopsis.

The unexpected advantage gained by overriding the brain's tendency to layer depth into the tandem views captured by the eyes has long been recognized by teachers of art. Budding representational artists are often counseled to close one lid and peer through a single eye at the subject of their attention. Shuttering one eye, says Livingstone, defeats stereopsis and heightens visual cues for depth, such as shading and perspective.

In their two-part study, Livingstone; Bevil Conway, HMS lecturer on neurobiology and assistant professor of neuroscience at Wellesley College; and former Wellesley student Rosa Lafer-Sousa tested stereoscopic accuracy among 403 art students from two U.S. art schools noted for their emphasis on representational rendering. They then compared those results with the same measurements for 190 non-artist peers at two universities. Next, the investigators assessed stereopsis among established artists by adapting an eye alignment test and using it to measure alignment in photographed eyes. The researchers used photographs of notable artists drawn from respected archives, the National Gallery of Art and the Smithsonian American Art Museum. As a control, the team measured eye alignment in photographs of an age- and gender-matched group of U.S. congressional representatives.

The team not only found poorer stereo accuracy among the art students as compared to the non-artists, but also found a prevalence of eye misalignment among the established artists, indicating an increased incidence of strabismus.

Does all this mean poor eye alignment is necessary for artistic success? No, cautions Livingstone, "You can get the same effect simply by closing one eye. But, at a minimum, if poor stereopsis doesn't contribute to artistic talent, it certainly doesn't detract from it." ■

—Ann Marie Menting

For more information, students should contact Margaret Livingstone, professor of neurobiology, at margaret_livingstone@hms.harvard.edu.

Paper Chase

RECENT PUBI ICATIONS FROM HMS RESEARCHERS

The index below is a selection of new studies and review articles by researchers from across the HMS community. It represents a small sample of research at **focushms.com**.

dO POsTMARkeTIn g suRveILLAn Ce sTud les RePRes en T ReAL-WORLd POPu LATIOn s?: A COMPARIs On OF PATIen T CHARACTeRIs TICs An d Ou TCOMes AFTeR CAROTId ARTeRy sTen TIn g

Yeh RW, Kennedy K, Spertus JA, Parikh SA, Sakhuja R, Anderson HV, White CJ, Rosenfield K. Cardiology Division, Department of Medicine, Massachusetts General Hospital and HMS.

To evaluate outcomes after carotid artery stenting in larger real-world populations, the Food and Drug Administration mandated that companies conduct postmarketing surveillance (PMS) studies of approved stent systems. We compared patient and procedural characteristics, in-hospital outcomes, and subsequent all-cause mortality after carotid artery stenting in PMS study participants and nonparticipants. We conclude that participants in PMS studies for carotid artery stenting have different clinical and procedural characteristics and lower mortality compared with nonparticipants. Extrapolating results from PMS studies of carotid artery stenting to larger real-world settings should be done only with great caution. *Circulation.* 2011 March 21.

syn THeTIC CIRCu IT Iden TIFIes su BPOPu LATIOns WITH sus TAIned MeMORy OF dn A d AMAge

Burrill DR, Silver PA. HMS Department of Systems Biology

Differential responses to stimuli can affect how cells succumb to disease. In yeast, DNA damage can create heterogeneous responses. To delineate how a response contributes to a cell's future behavior, we constructed a transcription-based memory circuit that detects DNA repair to isolate subpopulations with heritable damage responses. Strongly responsive cells show multigenerational effects, including growth defects and iron-associated gene expression. l ess-responsive cells exhibit increased mutation frequencies but resume wild-type behavior. These two subpopulations remain distinct for multiple generations, indicating a transmissible memory of damage. Collectively, this work demonstrates the efficacy of using synthetic biology to define how environmental exposure contributes to distinct cell fates. *Genes & Development.* 2011 March 1;25(5):434-9.

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HARVARD MEDICAL SCHOOL

Gordon Hall, Suite 001
25 Shattuck Street
Boston, MA 02115
Tel: 617-432-1589
E-mail: focus@hms.harvard.edu
Website: focushms.com

Conflict disclosures and funding sources appear online.

Recent books written or edited by members of the HMS, HSPH and HSDM faculty or staff may be submitted to *Focus* at the address above. Books received by April 20, 2011, will be featured in the next book section.

We invite letters from our readers, which should be brief and include a signature, address and daytime phone number.

Associate Dean and Chief Communications Officer
Gina Vild

Editor
Karin Kiewra

Managing Editor
R. Alan Leo

Editorial Specialist
Angela Alberti

Writing
Angela Alberti, David Cameron, R. Alan Leo, Ann Marie Menting, Michelle Pflumm, Scott Podolsky, Erica Seiguer Shenoy, Mildred Solomon, Thomas Ulrich

Art Director
Paul DiMattia

Photos/Illustrations
Angela Alberti, David Mack, R. Alan Leo, Béatrice Pautaire, Graham Ramsay, Ulf Sirborn

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RAINFOREST ALLIANCE CERTIFIED

TRAnsMIssIOn dynAMICs And COnTROL OF CHOLeRA In HAITI: An ePIdeMIC MOdeL

Andrews JR, Basu S. Division of Infectious Diseases, Massachusetts General Hospital and HMS; HSPH Center for Communicable Disease Dynamics

Official projections of the cholera epidemic in Haiti have not incorporated existing disease trends or patterns of transmission, and proposed interventions have been debated without comparative estimates of their effect. We used a mathematical model of the epidemic to provide projections of future morbidity and mortality, and to produce comparative estimates of the effects of proposed interventions. We conclude that a decline in cholera prevalence in early 2011 is part of the natural course of the epidemic, and should not be interpreted as indicative of successful intervention. Substantially more cases of cholera are expected than official estimates used for resource allocation. Combined, clean water provision, vaccination and expanded access to antibiotics might avert thousands of deaths. *Lancet.* 2011 March 16.

sHORTCuTs TO MAkIng CARdIOMyOCyTes

Xu H, Yi BA, Chien KR. Cardiovascular Research Center, Massachusetts General Hospital; Harvard Stem Cell Institute, Department of Stem Cell and Regenerative Biology, Harvard University

The adult human heart lacks sufficient regenerative capacity to recover after a myocardial infarction. Cell-based therapy has emerged as a potential treatment for the failing heart; however, a key issue for the success of future cell-based therapies is the ability to obtain patient-specific high-quality cardiomyocytes in a fast and efficient manner. Recent progress has been made towards this goal using reprogramming-based approaches. *Nature Cell Biology.* 2011 March;13(3):191-3.

X CHROMOsOMe dOsAge COMPensATIOn vIA enHAnCed TRAnsCRIPTIOn AL eLOngATIOn In *Drosophila*

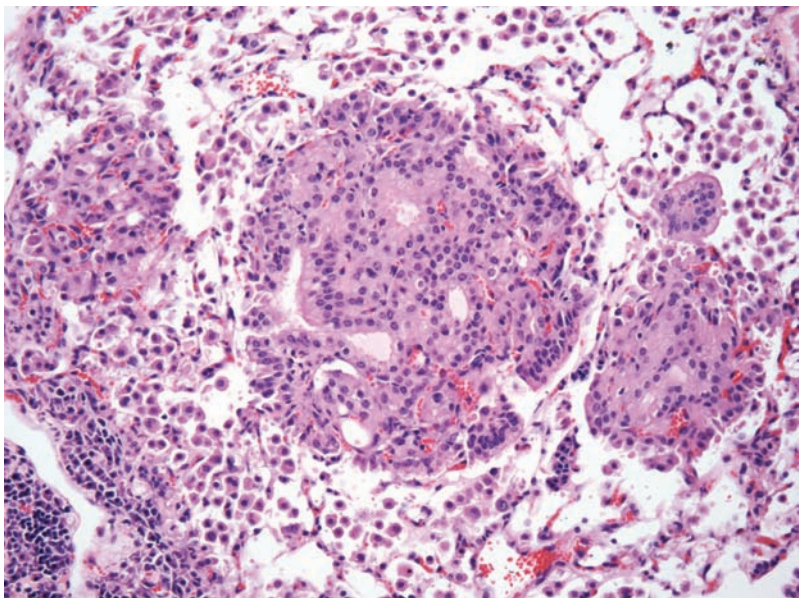
Larschan E, Bishop EP, Kharchenko PV, Core LJ, Lis JT, Park PJ, Kuroda MI. Division of Genetics, Department of Medicine, Brigham and Women's Hospital

The evolution of sex chromosomes has resulted in numerous species in which females inherit two X chromosomes but males have a single X, thus requiring dosage compensation. MSl (male-specific lethal) complex increases transcription on the single X chromosome of *Drosophila* males to equalize expression of X-linked genes between the sexes. Results indicate that the MSl complex enhances transcription by facilitating the progression of RNA Polymerase II across the bodies of active X-linked genes. Improving transcriptional output downstream of typical gene-specific controls may explain how dosage compensation can be imposed on the diverse set of genes along an entire chromosome. *Nature.* 2011 March 3;471(7336):115-8.

ReLATIOnsHIP BeTWeen quALITy OF CARe And negLIgenCe LITIgATIOn In nuRsIng HOMes.

Studdert DM, Spittal MJ, Mello MM, O'Malley AJ, Stevenson DG. Melbourne School of Population Health, University of Melbourne; HMS Department of Health Care Policy

It is unclear whether high-quality health care institutions are less likely to be sued for negligence than their low-performing counterparts. We linked information on tort claims brought against 1,465 nursing homes between 1998 and 2006 to 10 indicators of nursing home quality drawn from two U.S. national data sets. We conclude that the best-performing nursing homes are sued only marginally less than the worst-performing ones. Such weak discrimination may subvert the capacity of litigation to provide incentives to deliver safer care. *New England Journal of Medicine.* 2011 Mar 31;364(13):1243-50.



Beth Israel Deaconess Medical Center

Multiple independent lung tumors metastasized from breast cancer in PinX1 mutant mice. t hat's a rare development in single-gene knockout mouse tumor models, says r oderick Bronson, an hMS lecturer on pathology who collaborated with researchers at Beth Israel Deaconess Medical c enter.

Focus on u nderstanding Cancers

HMS affiliates are advancing our understanding of cancer to improve human health

MuTABLe Lung TuMORs sHed LIgHT On ResIsTAnCe

A detailed analysis of lung tumors that became resistant to targeted drugs has revealed two previously unreported resistance mechanisms. In the March 23 *Science Translational Medicine,* investigators from Massachusetts General Hospital Cancer Center and HMS also describe how the cellular nature of some tumors actually changes in response to treatment and find that resistance-conferring mutations can disappear after treatment is discontinued. The findings support the importance of monitoring the molecular status of tumors throughout treatment.

"It is really remarkable how much we oncologists assume about a tumor based on a single biopsy," said lead author Lecia Sequist, HMS assistant professor of medicine at Mass General.

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death, and in about 12 percent of patients the tumor is driven by a mutation in the epidermal growth factor receptor (EGFR). Targeted drugs called tyrosine kinase inhibitors (TKIs) block EGFR activity and can halt the growth of such tumors, but resistance usually develops.

To better understand why, the research team analyzed the genotype and the phenotype of tumor samples from 37 NSCLC patients, taken both before TKI treatment and when resistance first appeared. The results validated previously reported mechanisms of resistance and identified two more genetic changes: mutations in another oncogene called *PIK3CA* and overproduction of the EGFR molecule itself.

▲TeLOMeRASe InHIBITOR PInX1 seen TO su PPRess TuMORs

It's been nearly 10 years since Beth Israel Deaconess Medical Center scientists Kun Ping Lu and Xiao Zhen Zhou discovered PinX1, the first potent endogenous protein shown to inhibit telomerase in mammals

Now the scientific team has discovered a critical new function for this telomerase inhibitor.

The investigators reported March 23 in the J*ournal of Clinical Investigation* that low levels of PinX1 contribute to cancer development, providing the first genetic evidence linking telomerase activation to chromosome instability and cancer initiation, and suggesting a new avenue of treatment for cancers.

"Although telomerase is activated in 85 to 90 percent of human cancers, little has been known about the significance of telomerase activation in chromosome instability and cancer initiation," explains Lu, the paper's senior author and HMS professor of medicine at BIDMC. "We have discovered, for the first time, a novel role for abnormal telomerase activation in cancer initiation. This suggests that telomerase inhibition using PinX1 or other small molecules may be used to treat certain cancers with activated telomerase."

Notably, the discovery that most PinX1-mutant mouse tumors share tissues of origin with human cancer types linked to alterations in chromosome 8p23 suggests a possible role for deregulation of the PinX1-telomerase complex in treating several common carcinomas, including breast, lung, liver and gastrointestinal cancers.

MuLTIPLe MyeLOMA gen OMe yIeLds unexPeCTed InsIgHTs

Scientists have unveiled the most comprehensive picture to date of the full genetic blueprint of multiple myeloma, a form of blood cancer. A study of the genomes from 38 cancer samples has yielded new and unexpected insights into the events that lead to this form of cancer and could influence the direction of multiple myeloma research. This work, led by scientists at the Broad Institute of MIT and Harvard and Dana-Farber Cancer Institute, appeared March 24 in *Nature.*

Multiple myeloma is the second most common blood cancer in the United States, with about 20,000 new cases diagnosed in this country each year.

The emerging genome-wide picture of multiple myeloma reveals genes never before associated with cancer as well as multiple mutations that disrupt just a handful of common pathways, or chains of chemical reactions that trigger a change in a cell. Individually, each mutation is fairly uncommon and might have remained undiscovered had researchers not looked at such a large collection of samples.

"Already, we can see that mutations are funneling into a limited number of pathways," said co-senior author Todd Golub, director of the Broad's Cancer Program and Charles A. Dana Investigator in Human Cancer Genetics at Dana-Farber Cancer Institute. "This is a demonstration of the value of looking at more than just a single tumor at great depth." ■

—From the news offices of Mass General, Beth Israel Deaconess and Dana-Farber

Compost It

HMS prepares to celebrate Earth Day, removes food from waste stream

It was 20 degrees outside, but the compost piles were steaming at Brick Ends Farm, in Hamilton, Mass. Harvard students toured the farm on March 26 to learn about post-consumer composting and discover what happens to apple cores and soup containers after they leave Harvard's cafeterias.

The tour was part of the gearing-up for Earth Day on April 22. All month long, Harvard's faculty, students and staff will be raising awareness of sustainability. At HMS, the focus is on "post-consumer" composting in the Courtyard and Atrium cafes. On April 18, HMS Campus Operations, Restaurant Associates and Harvard's Office for Sustainability will provide information and a video in the cafes, where volunteer "composting ambassadors" will demonstrate how to compost correctly, creating a waste stream of food scraps, napkins and compostable take-out containers.

Angela Alberti

At Brick ends f arm, h arvard students get a tour of the compost fields from Peter Britton, who founded the farm in 1975 to improve local farmland and divert food waste from landfills.

"To be successful, everyone must make a conscious behavior change," said Longwood Sustainability Manager Claire Berezowitz. At HMS, cafeterias compost waste from food production, but a challenge, Berezowitz said, is to recognize and dispose of non-compostables, such as coffee cups from outside vendors. For inspiration, she points to the Harvard School of Public Health, which kept 103.3 tons of material out of landfills last year, saving $2,289 in trash-hauling fees.

Composting has benefits beyond the environmental and financial. At Brick Ends Farm, the product is bagged by Bass River, an organization for disabled adults. Bag labels were designed by patients from Children's Hospital Boston through Kidz B Kidz, a non-profit children's art group.

Proceeds go to Children's to fight childhood cancers, said Kidz B Kidz co-founder Jan Weinshanker. The 20-pound bags were set to go on sale in April at local grocery and garden stores. ■

—Angela Alberti

For a full list of Harvard-wide Earth Day events, visit green.harvard.edu.

Angela Alberti

Match d ay 2011

f rom left: c elebrating family-style are Varsha Keelara; her mother, c haya Gopalan; Keelara's financé, Shyam t anguturi; and t anguturi's parents, Satyan and Kusama. t anguturi and Keelara matched as a couple to Brigham and Women's h ospital—Keelara in internal medicine, t anguturi in internal medicine and the joint h arvard r adiation Oncology Program.

Ada Gropper, who matched at Brigham and Women's h ospital in internal medicine, celebrates with Sasha c lifton, who will head to a t ufts University family medicine residency at c ambridge h ealth Alliance.

Medical schools across the country hosted annual Match Day ceremonies on March 17, during which 16,559 medical school seniors learned where they are going to spend the next three to seven years for their residency training. At HMS, approximately 170 seniors matched to residency programs across the country, with the greatest number matching in internal medicine.

Family medicine program matches increased the most at HMS. This trend held true nationwide, with family medicine programs experiencing the strongest growth in the number of positions filled, according to the National Residency Matching Program (NRMP). Pediatrics, internal medicine, emergency medicine, anesthesiology and neurology also increased in popularity. The most competitive fields, according to the NRMP, were dermatology, orthopaedic surgery, otolaryngology, plastic surgery, radiation oncology, thoracic surgery and vascular surgery.

The 2011 match offered more than 23,000 first-year residency positions, and more than 95 percent of those were filled. Nationwide, 81 percent of those students matched to one of their top three choices.

The NRMP is a non-profit organization sponsored by several national medical societies in order to provide an orderly and fair way to match applicants to U.S. residency positions. ■

—Angela Alberti

Toward Better Child Care

Summit yields strategies for change

From saving lives to expanding knowledge to shaping global policy, the challenges of a career at HMS and its affiliates are immense and rewarding. But for faculty, staff and students balancing work and family, another challenge can be overwhelming: arranging child care in a community where demand far outstrips supply.

That challenge drew 180 participants on Jan. 25 to "Child Care Summit: Future Directions," organized by the Joint Committee on the Status of Women at HMS and the Harvard School of Dental Medicine with the HMS Office for Faculty Affairs and Provost's Office at Harvard University. On March 15, summit organizers shared conclusions from the summit and next steps toward addressing child care needs across the HMS community.

"We are energized by the combined efforts of everyone who contributed to this work," said Susan Farrell, faculty chair of the Joint Committee and assistant professor of medicine at Brigham and Women's Hospital. "And we will be moving forward in three important ways."

The Joint Committee spelled out those ways in a letter, announcing that it would support the creation of a consortium of child care champions across institutions; explore with HMS leadership efforts to address child care issues; and convene a subcommittee to guide ongoing work. The authors also summarized recommendations that emerged from breakout sessions at the summit, from expanding options for flexible work hours to building information networks across institutions. ■

—R. Alan Leo

To read the full report from the Child Care Summit, or to learn more about the Joint Committee on the Status of Women, including how to join, visit www.hms.harvard.edu/jcsw.

R. Alan l eo

On Jan. 25, a child care summit drew about 180 participants from across the h arvard community to the Joseph B. Martin c onference c enter.

Photos courtesy of Blinden-Museum an der Johann-Agust-Zeune-Schule fur Blinde, Berlin

Models of racial types (near left) served as teaching aids in racial hygiene classes at the Berlin School for the Blind, where students (far left) were taught Gregor Mendel's principles of inheritance and their applications to heredity. In Nazi Germany, German-born blind children were urged to submit to sterilization.

d eadly Medicine: Creating the Master Race

Exhibit explores lessons in eugenics from the Nazi era

How can it be that physicians and nurses worked actively in collaboration with government leaders to sterilize and kill "undesirables" during the Nazi era? How did these health care professionals come to subordinate their obligation to individual patients to a perceived obligation to the state-as-patient? What were the intertwined ideological and scientific origins of "racial hygiene"? And what lessons might we draw for contemporary medicine and society?

These questions that will confront visitors to "Deadly Medicine: Creating the Master Race," an exhibition by the United States Holocaust Memorial Museum that opens April 14 at the Countway Library. Harvard Medical School has partnered with the museum to bring the exhibition and its provocative questions to health care professionals in training, including students of medicine, nursing, law and public health, as well as their faculties, staff members and the public. To inspire and lead debate, the museum and HMS will sponsor related public forums and events on campus and across Boston.

Few adults are ignorant of the virulent anti-Semitism of the Third Reich and the Nazis' attempted annihilation of Europe's Jews. Most are familiar with the horrors of medical experimentation attached to the concentration camps, and the name Josef Mengele remains a notorious synonym for monster-physician. What far fewer people know is that, in the Nazi era, the medical profession and its opinion elites played a central role in conceiving and promoting the concept of "racial hygiene," which became the ideological foundation for Hitler's efforts to purify the German nation. Indeed, a symbiotic relationship existed between medical professional elites and the Nazi regime: Nazi policies supported public health measures that many physicians already had come to embrace years before, while the profession's imprimatur and active involvement became the literal means of effecting Hitler's plans.

For example, in addition to eliminating "non-Aryans"—Jews, Gypsies and others who differed from Nazi stereotypes of the ideal German—it was seen as important for the health of the nation to eradicate "feeblemindedness," physical deformity, alcoholism, blindness and deafness. More than 400,000 German men and women were sterilized, many through orders issued by "heredity health courts" comprising geneticists, physicians and anthropologists, who offered a patina of respectability to the unconscionable process. Likewise, convinced that maintaining "non-productive" members of society within institutions at government expense was a waste of resources, Hitler instituted a secret, so-called euthanasia program that some physicians and nurses helped implement. More than 200,000 Germans, including 5,000 children, were killed between 1935 and 1945. These murders of German citizens began before and continued during the Holocaust.

Of course, not all health care professionals supported

See "Deadly Medicine," page 8

Guest essay by Mildred Solomon and Scott Podolsky

Solomon is an associate clinical professor of medical ethics in the departments of Global Health and Social Medicine (GHSM) at HMS and of Anesthesia at Children's Hospital Boston, and director of the Fellowship in Medical Ethics within the HMS Division of Medical Ethics. Podolsky is an assistant professor of social medicine in GHSM and director of the Center for the History of Medicine at Countway Library. The opinions expressed are those of the authors and not necessarily those of Harvard Medical School, its affiliated institutions or Harvard University.

Of what relevance to medicine today are the lessons of eugenics? Join this month's discussion at the hMS Idea Lab, a virtual laboratory for sharing opinions on research, academic medicine, medical education and more.

s CHed u Le OF ev en Ts

From April 14 through July 17, "Deadly Medicine: Creating the Master Race" will present long-hidden documents, rarely seen photographs and historical film footage to illustrate the role that physicians, public health officials, scientists and academics played in implementing the Nazis' program of "racial hygiene." During the 14-week run, the United States Holocaust Memorial Museum and HMS will also sponsor programs open to academics and the public. For additional information, see www.ushmm.org/deadlymedicineboston.

d eadly Medicine: Creating the Master Race
All events are in Boston.

April 14, Thursday
5:30 p.m.
exhibition Opening
Countway l ibrary of Medicine, 10 Shattuck St.
7 p.m.
Public Program and Reception: "Why d eadly Medicine Matters Today: Medical ethics in the s hadow of the Holocaust."
Joseph B. Martin Conference Center, 77 Ave. l ouis Pasteur.

April 27, Wednesday
4–6:30 p.m.
Public Program: Ackerman s ymposium: "g enetic d eterminism Then and n ow: Confronting the Legacy of eugenics."
Carl Walter Amphitheater, Tosteson Medical Education Center, Harvard Medical School, 260 l ongwood Ave.

May 12, Thursday
7 p.m.
Public Program: "When the s tate Makes d emands: Medical Professionalism, d ual Loyalty, and Human Rights."
Carl Walter Amphitheater, Tosteson Medical Education Center, Harvard Medical School, 260 l ongwood Ave.

In addition, the Center for the History of Medicine at Countway will mount a companion exhibit, "Galton's Children: The Rise and Fall of the Eugenics Movement," a display of library holdings tracing the history of eugenics in concept and practice.

For information on exhibit-related events at the Countway l ibrary of Medicine, visit www.countway.harvard.edu. For questions about scheduling group visits to the exhibition, contact Francesca Holinko at fholinko@hms.harvard.edu.

Melanoma

Continued from page 1

Melanoma has a poor prognosis when diagnosed late. In the United States, there were about 68,000 new cases and 8,700 deaths in 2010.

Mutations in *BRAF,* a core characteristic of the Zon lab's model, are seen in about 50 to 60 percent of human melanomas. But *BRAF* mutations are also seen in benign moles and are by themselves insufficient to cause cancer; other mutations must also be present. The team set out to pinpoint other candidates in a region of chromosome 1 called 1q21 in which a stretch of 54 genes are amplified in about 30 percent of melanoma patients. Of those 54, *SETDB1* stood out: It was the only gene there that worked with *BRAF* to fuel tumor development.

By THe nuMBeRs

"Along with being a creative approach, it was truly a brute force scientific effort to home in on *SETDB1,*" said Zon, a Howard Hughes Medical Institute investigator. "We looked at each of the genes in this region one by one, and between discovery and validation, ultimately assayed more than 2,100 tumors from more than 3,100 fish."

SETDB1 encodes an enzyme that helps turn other genes on or off and is overactive in breast, ovarian, liver and numerous other tumors. Because in the model the level of a tumor's malignancy rose with the level of *SETDB1* activity, the gene could be a valuable target for prognostic testing, Zon said, and for designing new melanoma treatments.

BRAF abnormalities also led to the recognition that zebrafish on the way to developing melanoma harbor excess numbers of immature "embryonic" cells called neural crest cells, raising the fishes' risk of later cancer formation. Zon and a second research team used the zebrafish to screen 2,000 chemicals for candidates that would suppress these excess cells. Zon and his colleagues found that a compound that interfered with dihydroorotate dehydrogenase (DHODH), an enzyme involved in neural crest cell development, showed promise.

The team turned to leflunomide, a DHODH-inhibitor approved to treat arthritis. In the zebrafish model, leflunomide knocked down expression of several genes overexpressed in both melanomas and neural crest cells, while in rats it prevented neural crest stem cells from renewing themselves. Leflunomide also stopped the growth of cultured cells from human melanomas and caused regression of human tumors transplanted into nude mice.

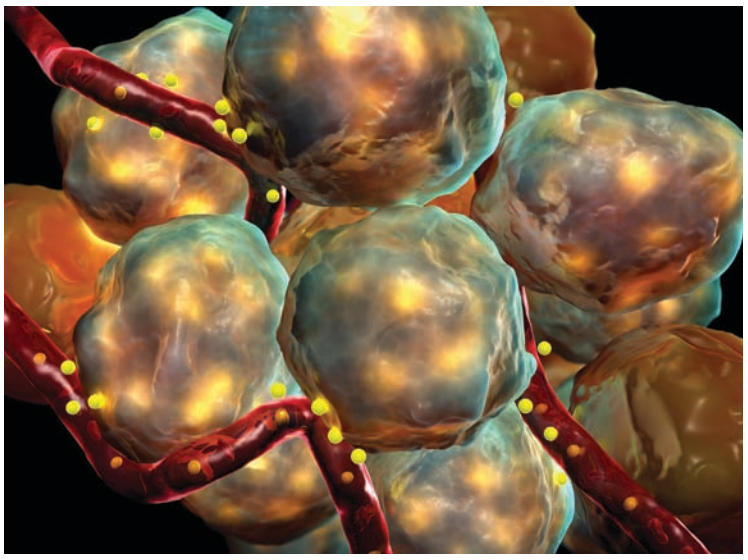
According to Zon, "We realized that a combined blockade of DHODH and *BRAF* would cooperate to suppress melanoma growth by targeting both the fate and the growth of melanoma precursors."

The researchers then tested in mice a combination of leflunomide and a *BRAF* inhibitor developed by Plexxikon that is in late-stage clinical trials. The combination of drugs led to an almost complete abolition of tumor growth; 40 percent of the mice experienced a near complete tumor regression.

"The combination of the two drugs was more effective than either drug alone, and allowed us to use lower doses of each," said Zon, who has begun planning a clinical trial. "It will be interesting to put them into the clinic together." ■

—Thomas Ulrich

For more information, students may contact Leonard Zon at zon@enders.tch.harvard.edu.



David Mack / Science Photo Library

t his computer artist's rendering depicts pancreatic islets of Langerhans cells, including beta cells, which are destroyed by an errant immune system in t ype 1 diabetes. Beta cells help regulate blood-glucose levels by secreting the hormone insulin, which stores glucose as glycogen in the muscles

Type 1 Diabetes

Continued from page 1

In November, proposals for research to explore several of the dozen winning ideas were solicited by the Harvard Institute of Translational Immunology, or HITI. From a pool of 31 entries, seven were deemed as most worthy of pilot funding. The pilot grant program, supported by $1 million from the Leona M. and Harry B. Helmsley Charitable Trust, is HITI's first effort to convene multidisciplinary translational and clinical investigators from across Harvard to study immune-mediated diseases.

According to HITI Co-directors Arlene Sharpe, the George Fabyan Professor of Comparative Pathology, and Larry Turka, HMS lecturer on medicine at Beth Israel Deaconess Medical Center, the goal of these seven research projects is three-fold: to better understand the origins of these diseases, to formulate immune-based assays to support human clinical trials and improve diagnostics, and, ultimately, to develop novel therapies.

Most of the winning entries involve the creation of new, multidisciplinary teams that introduce new investigators to the study of Type 1 diabetes.

"The assembly of these groups is in itself an important metric of success," said Eva Guinan, director of the Harvard Catalyst Linkages Program.

seven PROj eCTs An d THeIR LeAd eRs

» **Harvey Cantor,** Baruj Benacerraf Professor of Pathology, Dana-Farber Cancer Institute (DFCI), will use novel strategies to expand populations of the recently identified suppressor T cell CD8+ Treg and examine the potential therapeutic effects of this cell type on the progression of Type 1 diabetes.

» **Stephen Elledge,** Gregor Mendel Professor of Genetics and Medicine, HMS, and professor of medicine, Brigham and Women's Hospital (BWH), will use the tools of synthetic biology to create a copy of the human proteome in small pieces, with the goal of identifying parts of the proteome recognized by antibodies in people with Type 1 diabetes.

» **Richard Lee,** professor of medicine, BWH, and Douglas Melton, Thomas Dudley Cabot Professor of Natural Sciences, Stem Cell and Regenerative Biology, Faculty of Arts and Sciences (FAS), will endeavor to engineer cells that can monitor blood glucose, allowing patients to strive for normal control without having to prick their fingers frequently to test their blood.

» **Towia Libermann,** associate professor of medicine, Beth Israel Deaconess Medical Center, will identify new genomic biomarkers in the blood of mice that model human Type 1 diabetes prior to the destruction of pancreatic islet cells and the resulting onset of disease. These biomarkers, once validated in patients, will enable monitoring of pre-diabetic patients and others at high risk for the disease so that pre-emptive therapy can be applied.

» **David Mooney,** Robert P. Pinkas Family Professor of Bioengineering, FAS/School of Engineering and Applied Sciences, and Kai Wucherpfennig, professor of neurology, DFCI, plan to use novel nanomaterials that will leverage regulatory T cells' ability to inhibit immune system attacks on insulin-producing cells and thus prevent Type 1 diabetes.

» **Martin Yarmush,** senior lecturer on surgery and bioengineering (formerly the Helen Andrus Benedict Professor), HMS, and director, Center for Engineering in Medicine, Massachusetts General Hospital, will take advantage of molecular biology and microfabrication techniques in order to detect autoantibody levels with great sensitivity. This would enable the detection of the onset of Type 1 diabetes far earlier, allowing the use of interventions designed to deter disease progression.

» **Qiao Zhou,** assistant professor of stem cell and regenerative biology, FAS, and Jason Gaglia, instructor in pathology, Joslin Diabetes Center, aims to convert non-beta cells in the pancreas into fully functional beta cells with normal insulin release, thus replenishing populations destroyed in patients with Type 1 diabetes. ■

Breast Cancer

Continued from page 1

The research was published on March 4 in the journal *Cell.*

Triple-negative breast cancer is an aggressive disease with few therapeutic options. Patients with such tumors can be treated only with chemotherapy. If the cancer spreads, the median survival rate is one year.

THRee key enzyMes

The complexity of triple-negative breast cancer renders it difficult to treat. The disease is extremely heterogeneous, characterized by hundreds of genetic mutations. Without knowing the critical molecular switches that power this type of breast cancer, researchers have no way to develop targeted therapies.

The HMS-Baylor College of Medicine team reports that an enzyme called tyrosine phosphatase PTPN12 was knocked out in 60 percent of nearly 200 triple-negative breast cancers tested. This phosphatase belongs to a class of enzymes that keeps cell-growth pathways in check and cancer at bay.

The team identified the critical enzyme by looking in petri dishes for proteins whose absence caused normal breast cells to become cancerous.

"We were looking for genes that pushed the cells over the edge," explained Stephen Elledge, the Gregor Mendel Professor of Genetics and a professor of medicine at Harvard Medical School.

One of tyrosine phosphatases' primary jobs is to turn off another group of enzymes critical for growth called receptor tyrosine kinases. The researchers reasoned that, if they could identify the enzymes that were switched on in the absence of PTPN12, they could pinpoint critical drug targets that might be used to develop therapies for patients with triple-negative breast cancer.

To identify these proteins, the team turned to HMS Professor of Cell Biology Steven Gygi. By taking a look at all proteins activated in cells lacking PTPN12, the researchers found two enzymes crucial for breast cancer's progression, or metastasis, EGFR and HER2.

In addition, the team used biochemical methods to identify a third receptor enzyme, called PDGFR-ß, that was also regulated by PTPN12.

Together, these results suggest that the improper activation of these three tyrosine kinases could be the major cause of triple-negative breast cancer.

"We've grabbed a molecular foothold in triple-negative breast cancer," said Westbrook, who discovered PTPN12 as a postdoctoral fellow in Elledge's laboratory. "We are now starting to understand the disease better. Even more important, we have a rationale for a combined drug therapy for the disease."

Their idea: to treat the disease, turn off the trio of enzymes with drugs.

FdA-APPROved OPTIOns

To test their strategy, the team took advantage of two drugs already being used to battle other types of cancer: laptanib (Tykerb), which turns off EGFR and HER2, and sunitinib (Sutent), which turns off PDGFR-ß.

The team treated mice with triple-negative breast cancers with either sunitinib or laptanib, or both. In mice treated with sunitinib alone, tumors shrank by nearly 80 percent. But in mice treated with both drugs, tumors shrank by more than 90 percent—and life expectancy more than doubled.

These results suggest that sunitinib and laptanib (or similar drugs) together may be a promising therapy for people with triple-negative breast cancer. And because both drugs are already FDA-approved and sitting on pharmacy shelves, they can be tested immediately in these patients.

"This research underscores the relation of basic bench science to human health," said Elledge. "If you know what's driving the cancer, you can think about targeting that for therapy."

The team hopes to launch a phase II trial for triple-negative breast cancer by the start of 2012. ■

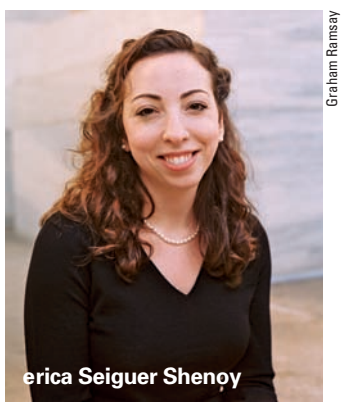
—Michelle Pflumm

To learn more, students may contact Stephen Elledge at selledge@genetics.med.harvard.edu.

Béatrice Pautaire/iStockphoto

When Medicine Has n othing More to Offer

The transition to end-of-life care tests patient and doctor



Graham Ramsay

erica Seiguer Shenoy

"My mentor held the patient's hand and spoke to him, asking gently: Was he in pain? d id his family understand the extent of his illness? d id he need to speak with anyone? Was he at peace?"

I pulled back the curtain to reveal my patient, dying quietly on a gurney.

Death had stalked him. Almost a year earlier, as his wife was dying of metastatic cancer, he himself began to develop symptoms that could not be ignored: night sweats, malaise, fevers. As his wife's primary caregiver, he stayed with her to the end. And despite attempts to properly evaluate his new symptoms, he missed most of his own medical visits, the short time with his wife too precious.

Days after his wife's death, he came to the clinic and was admitted quickly for dehydration and expedited evaluation. In such situations, I have learned to hope for infection as the cause; the alternative almost always is cancer. The diagnosis was grim: Stage IV Hodgkin's lymphoma. Over the next year, he went from one chemotherapy regimen to the next, each failing to slow the progression of disease. Most days he was hopeful, and sometimes his optimism troubled me. How could he feel so well when the PET scans clearly indicated he was losing this battle?

By the time he had reached the final chemotherapeutic option—at this stage his treatment could be considered "extreme salvage"—the reality of his imminent death had begun to set in. Clearly, if this treatment failed him, and odds were it would, we had nothing more to offer.

Nothing more to offer. To this nascent clinician, the concept seemed foreign. Even in the age of antibiotic resistance, we can almost always do something, irrespective of the diminishing returns.

The patient's health declined rapidly, and symptom management, or palliation, became the goal of his care. A few days before his final admission, he had sounded upbeat as he described a steak meal, a stark contrast to how we found him, awaiting admission for end-of-life care.

On the gurney, he was groggy, a side effect of medications to ease his pain and nausea. His face was gaunt. He looked feeble, a shadow of the stocky, healthy man he had been so recently. At first, he did not appear to recognize us, and I feared that I would not get a chance to say goodbye, or that he would be too confused or withdrawn to comprehend. My mentor, who had known the patient and his wife for the better part of a decade, held his hand and spoke to him, asking gently: Was he in pain? Did his family understand the extent of his illness? Did he need to speak with anyone? Was he at peace?

I wanted to say more to him, but in the moment it was all I could do not to cry. Cry for my patient—the stoic, the optimist, the young widower who only a year earlier had lost his closest love. But cry also for myself, for my helplessness to stop a process that was moving forward, over which I had no control.

And so I cried.

He was admitted to the hospital. For months he had delayed assigning a health care proxy, but I watched again as my mentor kindly persuaded him. His code status was also established, and he transitioned to comfort care.

A few days later, he transferred to a hospice close to home, and a week to the day after his admission, as he lay peacefully with his family by his side, death drew closed its curtain. ■

—Erica Seiguer Shenoy, MD–PhD '07, is a fellow in infectious disease at Massachusetts General Hospital and Brigham and Women's Hospital.

The opinions expressed in this column are not necessarily those of Harvard Medical School, its affiliated institutions or Harvard University.

Monday, April 11
Sanders Theater, Memorial Hall, 3:30–5:00 p.m.
g reen Carpet Awards Ceremony
These annual awards recognize individuals and teams in the Harvard community who have helped the University advance its sustainability goals.

April 18-22
Courtyard and Atrium Cafes
HMs Post-Consumer Composting Launch
Featuring raffle prizes, quizzes and giveaways along with information about the new composting program.

Tuesday, April 19
HMS Armenise Amphitheater, 5:30–8:00 p.m.
"Lessons in s ustainability and Research"
Guest speaker: Nathan Phillips, director of Boston University's Center for Energy and Environmental Studies. Co-sponsored by the Association for Women in Science (Mass.).

Thursday, April 21
HSPH Kresge G-3, 12:30–1:45 p.m.
"Water and Health: A g lobal Perspective"
Featuring HSPH professors John Briscoe, James Shine and Elsie Sunderland speaking on the importance of a healthy, sustainable water supply to international public health efforts.

Monday, April 25
HMS Armenise Amphitheater, 12:30–1:30 p.m.
Bike Maintenance Clinic
Presentation from MassBike, with MASCO's CommuteWorks

Wednesday, April 27
HSPH Kresge Cafeteria, 12:30–1:30 p.m.
Hs PH "Take the s tairs Campaign"
Completion Celebration
Refreshments and prizes.

Thursday, May 26
360th Harvard Commencement
l iberian President Ellen Johnson Sirleaf, a Harvard Kennedy School alumna who played a key role in stabilizing and reviving a troubled nation that until recently was categorized as a "failed state," will be the principal speaker. For details, see the Harvard Commencement Office website, http://www.commencementoffice.harvard.edu.

Deadly Medicine

Continued from page 5

racial hygiene policies, the ideology of genetic determinism, or programs of sterilization and euthanasia. "Deadly Medicine" creates an opportunity to reflect not only on the social, political and economic determinants of these events, but also on the moral choices that individual professionals face today on a range of issues.

Visiting the exhibition and its website (www.ushmm.org/deadlymedicineboston) and participating in related forums will prompt more questions than answers. We hope that people will not view the Nazi story as an aberration of the deep past, far removed from contemporary circumstances, an impossibility anywhere else. Nazi physicians believed they were acting in the people's interest, on behalf of public health; they were blind to their own excesses. Most people are, including, and perhaps especially, esteemed professionals. Therefore, the exhibition should remind us to remain alert to our inherent biases and the possibility of committing or participating in wrongful acts that we haven't recognized as wrong.

On the other hand, it can be easy to overgeneralize and make simplistic comparisons to modern health policies. For example, the very use of the term "euthanasia" could introduce confusion, leading some people to mistakenly equate the current ethical framework in the United States for making decisions about the use of sustaining technologies near the end of life with the Nazi program of systematized murder. Careful analysis of similarities and differences between contemporary events and Nazi policies can head off overly broad generalizations and the demagoguery that could result from them. We hope that "Deadly Medicine" will foster such insight through critical analysis, self-reflection and humility. ■

AAMC Call for n ominations

The American Association of Medical Colleges invites nominations for its 2011 research and education awards, including the Flexner Award for Distinguished Service to Medical Education. Nominations are due May 2. For more information, visit www.aamc.org/initiatives/awards.

n otable

Ruhul Abid, HMS assistant professor of medicine at Beth Israel Deaconess Medical Center, will be recognized April 29 with the 2011 Werner Risau New Investigator Award in Vascular Biology. His paper, "Endothelium-dependent Coronary Vasodilatation Requires NADPH Oxidase-derived ROS," was selected as the most outstanding paper published during 2010 in the vascular biology section of the journal *Arteriosclerosis, Thrombosis and Vascular Biology*.

d onna Berry, HMS associate professor of medicine and director of the Cantor Center for Research in Nursing and Patient Care Services at Dana-Farber Cancer Institute, will accept the Oncology Nursing Society's Distinguished Researcher Award at the 2011 ONS Congress in Boston on April 28. Berry is widely recognized for her research involving patient-centered oncology care and leadership within oncology research.

Constance Cepko, HMS professor of genetics and professor of ophthalmology, has received the 2011 Alfred W. Bressler Prize in Vision Science. The prize, announced March 8 by the Jewish Guild for the Blind, recognizes her discoveries of the causes of retinal degeneration in retinitis pigmentosa (RP) and possible future therapeutic benefits to humans. The Cepko lab discovered in a mouse model of RP that cone cell death is primarily caused by a nutritional deficit resulting after rod death. Cone life can be prolonged by injecting the mice with insulin. Future applications may allow people with RP to maintain daylight and color vision longer.

j effrey s . Flier, dean of the Faculty of Medicine, received the international Rolf l uft Award from the Karolinska Institute in Sweden on March 16 for seminal contributions to the understanding of the physiology of insulin and leptin and the mechanisms underlying their defective action in metabolic diseases. Flier gave the prize lecture, "Hormone Resistance in Diabetes and Obesity: Insulin, l eptin and FGF21."

Flier's contributions to the understanding of obesity and insulin resistance have had a significant impact on lipid research, particularly in the arena of leptin action and resistance. He is credited with the groundbreaking observation that leptin is likely to be the key signal that informs the brain of the transition between the adequately nourished and the starved state. Flier has also made substantive contributions to research on the metabolic syndrome as well as on insulin action and resistance.

Previous l uft honorees at HMS include C. Ronald Kahn, Mary K. Iacocca Professor of Medicine at Brigham and Women's Hospital and Joslin Diabetes Center; Bruce Spiegelman, the Stanley J. Korsmeyer Professor of Cell Biology and Medicine at Dana-Farber Cancer Institute; and l ewis Cantley, the William Bosworth Castle Professor of Medicine at Beth Israel Deaconess Medical Center.

d onald Ingber, founding director of the Wyss Institute for Biologically Inspired Engineering at Harvard University, has been inducted into the American Institute for Medical and Biological Engineering's College of Fellows on the basis of his major contributions to cell and tissue engineering, angiogenesis and cancer research, systems biology, and nanobiotechnology. Ingber, the Judah Folkman Professor of Vascular Biology in the Department of Pathology at Children's Hospital Boston, is recognized for his pioneering efforts in the emerging field of biologically inspired engineering.

j oAnn Manson, the Elizabeth Fay Brigham professor of women's health at HMS and Brigham and Women's Hospital, recently received the 2010 Population Research Prize from the American Heart Association. The award recognizes Manson's achievement as a physician, teacher and investigator in the field of population science. Manson, who is chief of the BWH Division of Preventive Medicine, has conducted clinical trials in preventive medicine and women's health, elucidating critical biological and genetic determinants of cardiovascular disease and diabetes.