

# FOCUS



News from Harvard Medical, Dental and Public Health Schools

September 2011

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Dental student Michelle Lieblich celebrates White Coat Day with senior tutor Sang Park. See photos at [focushms.com](http://focushms.com).

## A Promising Target for the Ebola Virus

*Protein essential for infection identified*



Learning how deadly Ebola enters victims' cells could lead to the first effective treatment for the virus.

MONIKA WISNIEWSKA/ISTOCK

In separate papers, two research teams report identifying a critical protein that the African Ebola virus exploits to cause deadly infections. The protein target is an essential element through which the virus enters living cells to cause disease.

The first study was led by four senior scientists: Sean Whelan, associate professor of microbiology and immunobiology at Harvard Medical School; Kartik Chandran, assistant professor at Albert Einstein College of Medicine; John Dye at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), and Thijn Brummelkamp, originally at the Whitehead Institute for Biomedical Research and now at the Netherlands Cancer Institute. The second study was led by James Cunningham, an HMS associate professor of medicine at Brigham and Women's Hospital, and also co-authored by Chandran.

"This research identifies a critical cellular protein that the Ebola virus needs to cause infection

and disease," explained Whelan, who is also co-director of the HMS Program in Virology. "The discovery also improves chances that drugs can be developed that directly combat Ebola infections."

Both papers were published in the Aug. 24 online issue of *Nature*.

### DANGEROUS INFECTIONS

The Ebola virus—and its cousin, Marburg virus—are known as the filoviruses. Widely considered one of the most dangerous infections known, Ebola was first identified in 1976 in Africa near the Ebola River, an area in Sudan and the Democratic Republic of the Congo. Infections cause severe hemorrhage, multiple organ failure and death. No one quite knows how the virus is spread, and there are no available vaccines or anti-viral drugs that can fight the infections.

By conducting a genome-wide genetic screen in human cells aimed at identifying molecules essential for Ebola's virulence, Whelan and his colleagues homed in on Niemann-Pick C1 (NPC1).

NPC1 is well known in the biomedical literature. Primarily associated with cholesterol metabolism, this protein, when mutated, causes a rare genetic disorder in children, Niemann-Pick disease.

Using cells derived from these patients, the group found that this mutant form of NPC1 also completely blocks infection by the Ebola virus. They also demonstrated that mice carrying a mutation in the NPC1 gene resisted Ebola infection. Similar resistance was found in cultured cells in which the normal molecular structure of the Niemann-Pick protein has been altered.

See "Ebola," page 6

## New Clue to Parkinson's Disease

*Shape of key protein surprises researchers*

A new study by researchers at Brigham and Women's Hospital and HMS finds that a protein key to Parkinson's disease has likely been mischaracterized. The protein, alpha-synuclein, appears to have a radically different structure in healthy cells than scientists previously thought, a finding that challenges existing disease paradigms and suggests a new therapeutic approach.

See "Parkinson's," page 6



ALYSSA KNELLER

VIDEO EXTRA

Learn more at [focushms.com](http://focushms.com).

## WARREN ALPERT FOUNDATION PRIZE SYMPOSIUM

### From Drug Delivery to Tissue Engineering

*Bioengineering and its Impact on Human Health*

#### Honoring

ALAIN F. CARPENTIER, MD, PhD

ROBERT S. LANGER, ScD

In recognition of their application of bioengineering principles to fundamental improvements in human health

Thursday, October 6, 2011, 2–5:30 pm

Joseph B. Martin Conference Center  
New Research Building, 77 Avenue  
Louis Pasteur, Harvard Medical School

#### Opening Remarks

Jeffrey S. Flier, MD  
Dean of the Faculty of  
Medicine, Harvard University

#### Award Lectures

*Bioengineering and its  
Impact on the Changing  
World of Cardiac Surgery*  
Alain F. Carpentier, MD, PhD

*Biomaterials and  
Biotechnology: From the  
Development of Controlled  
Drug Delivery Systems  
to the Foundation of  
Tissue Engineering*  
Robert S. Langer Jr., ScD

#### Invited Lectures

*Infection-Mimicking  
Polymers as a Cancer  
Vaccine*  
David J. Mooney, PhD

*Cancer Nanotechnology  
to Hepatic Tissue  
Engineering*  
Sangeeta Bhatia, MD, PhD

*DNA Nanostructures  
as Building Blocks  
for Future Therapeutics*  
William Shih, PhD

Please RSVP to events@  
hms.harvard.edu or  
617-384-8484.  
See story on page 3.

WARREN ALPERT  
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# Complex Choices

*Medicare Advantage program options may overwhelm seniors*

In a new study, researchers from Harvard Medical School's Department of Health Care Policy found that the large variety of managed care plans offered by the Medicare Advantage program may be counter-productive. Elderly patients, particularly those with low cognitive ability, often make poor decisions—or no decisions at all—when faced with an overwhelming number of complex insurance choices. Ironically, those with impaired cognition may benefit most from the more generous coverage often offered by Medicare Advantage plans.

"We are providing the most complex insurance choices to the very population that is least equipped to make these high-stakes decisions," said J. Michael McWilliams, assistant professor of health care policy and medicine at HMS and a practicing general internist in the Division of General Medicine at Brigham and Women's Hospital. "Most other Americans choose from just a few health plans, but elderly Medicare beneficiaries often have to sift through dozens of options."

The study appeared online Aug. 18 in *Health Affairs*. It will also appear in the journal's September print edition.

The Medicare Modernization Act of 2003 initiated a series of payment increases to the Medicare Advantage program. These payment hikes dramatically increased the number of private plans participating in the program and encouraged plans to compete for enrollees by offering lower premiums and more generous benefits, such as prescription drug coverage.

In order to examine the effects of these expanded choices and benefits of enrollment in Medicare Advantage versus traditional Medicare, McWilliams and his team looked at 21,815 enrollment decisions from 2004 to 2007 made by 6,672 participants in a national longitudinal survey, and compared enrollment decisions between participants with different cognition levels and different plan offerings in their area.

## TOO MANY CHOICES

The researchers found that, on average, an increase in the number of plans was associated with increased Medicare Advantage enrollment, provided the number of available plan options was fewer than 15. When the number of options surpassed 30, as it did in 25 percent of U.S. counties, such increases were actually associated with decreased enrollment. More importantly, beneficiaries with low cognitive function were substantially less likely than their peers with high cognitive function to appreciate the advantages offered by these plans, choosing to remain in the traditional Medicare program instead.

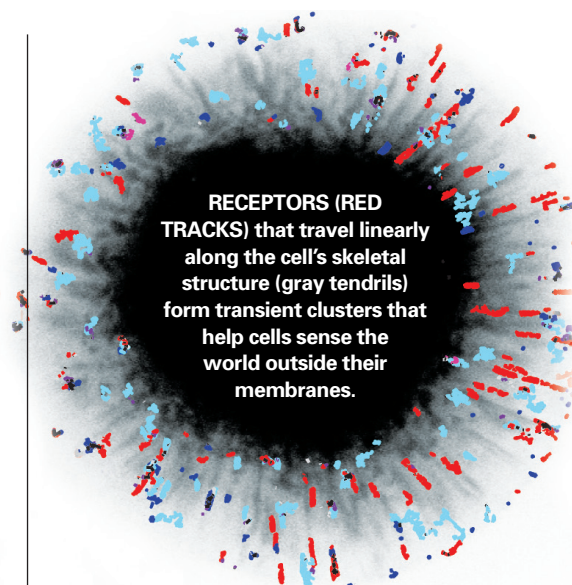
The authors suggest the reason for lower enrollment could be that beneficiaries became overwhelmed and chose traditional Medicare by default. Furthermore, elderly Medicare beneficiaries with limited cognitive abilities may have difficulty identifying the most valuable option from a complex set of Medicare alternatives. This is particularly concerning given the high and rising prevalence of cognitive impairment and dementia in the aging Medicare population.

## IMPLICATIONS FOR NATIONAL REFORM

The findings also have important policy implications as health insurance exchanges are established under the recent national health reform legislation, the Affordable Care Act. These exchanges, the authors say, could be helpful to seniors and the Medicare program if expanded to handle enrollment in Medicare Advantage plans. "Efforts to limit choice and guide seniors to the most valuable options could especially benefit those with cognitive impairments, who without more help appear to be leaving money on the table," McWilliams said. "Better enrollment decisions could in turn strengthen competition by rewarding high-value plans with more enrollees."

—Atreyee Bhattacharya

For more information, students may contact J. Michael McWilliams at [mcwilliams@hcp.med.harvard.edu](mailto:mcwilliams@hcp.med.harvard.edu).



## Molecular Meet and Greet

*Single-molecule imaging reveals how cells prepare to interact with the world*

Researchers at Harvard Medical School have discovered that structural elements in the cell play a crucial role in organizing the motion of cell-surface receptors, proteins that enable cells to receive signals from other parts of the organism.

This discovery, published in the Aug. 19 issue of *Cell*, fills a fundamental gap in the understanding of how cells relate to biochemical signals, including pharmaceuticals, and could have profound implications for drug development and the treatment of cancer and other diseases.

The findings are already prompting the design of a new lecture on cell signaling in one basic biochemistry course at HMS.

"We found that the way the receptors are organized in the membrane and the way they move around are controlled by the cytoskeleton," said Khuloud Jaqaman, instructor in the Department of Systems Biology and first author of the study. This dynamic organization promotes signaling

See "Meet and Greet," page 6



See receptors in action at [focushms.com](http://focushms.com)

## FOCUS

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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 Sept. 27, 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.

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# Warren Alpert Foundation Prize Honors Bioengineering Luminaries

*Carpentier, Langer to share award at October symposium*

The 2011 Warren Alpert Foundation Prize will be awarded to bioengineering pioneers Alain F. Carpentier and Robert S. Langer in recognition of their extraordinary contributions to medicine. The recipients, who will share an unrestricted prize of \$250,000, will be honored at a symposium Oct. 6 at Harvard Medical School.

The Alpert Prize recognizes researchers for laboratory discoveries with dramatic promise to improve human health. That spirit defines the remarkable careers of Langer, a basic scientist and engineer whose research is focused directly at the clinic, and Carpentier, a clinician whose practice has brought him to engineering.

The late Warren Alpert, a philanthropist dedicated to advancing biomedical research, established the Prize in 1987. To date, the Foundation has awarded more than \$3 million to 39 indi-

viduals. Seven honorees have also received a Nobel Prize. The valve utilized the world's first artificial valve used in clinical practice. The valve utilizes animal tissues that are chemically processed in order to prevent immunological reaction when implanted in humans and currently benefits more than 100,000 patients each year. Carpentier is also a lead developer of a fully implantable artificial heart created from biomaterials, soon to enter clinical trials. He was elected President of the French Academy of Sciences in 2011.

This prestigious award is a great honor for myself, my research team and my country," Carpentier said. "The development of biological valve prosthesis is a sterling example of the important contribution of bioengineering in the progress of surgery. We are proud that this new valve could benefit thousands of patients."

Langer, senior lecturer on surgery at HMS and the David H. Koch Institute Professor at

honored to be in the company of the previous award winners," Langer said. "My colleagues and I remain dedicated to improving patients' lives and are thrilled that the Foundation acknowledged our research with this prize."

Recent honorees of the Warren Alpert Prize include Howard Green of HMS (2010) for revolutionizing skin restoration after severe burns; Lloyd M. Aiello of the Joslin Diabetes Center (2008/2009) for averting diabetes-related blindness; Harald zur Hausen and Lutz Gissmann of the German Cancer Research Centre (2007) for linking specific types of human papillomavirus (HPV) to cancer of the cervix.

The Alpert Prize has also recognized discoveries with direct impacts on a wide spectrum of diseases, including asthma, breast cancer, hepatitis B, HIV/AIDS, leukemia and stomach ulcers.

## BREAKTHROUGHS REWARDED

Each year the Warren Alpert Foundation receives 30 to 50 nominations for the Alpert Prize from scientific leaders worldwide. Prize recipients are selected by the Foundation's scientific advisory board, composed of distinguished biomedical scientists and chaired by the dean of Harvard's Faculty of Medicine.

Warren Alpert (1921-2007), a native of Chelsea, Mass., established the Warren Alpert Foundation Prize after reading about the development of a vaccine for hepatitis B. Alpert decided immediately that he would like to reward such breakthroughs, so he picked up the phone and told the vaccine's creator, Kenneth Murray of the University of Edinburgh, that he had won a prize. Alpert then set about creating the foundation.

To award subsequent prizes, Alpert asked Daniel Tosteson (1925-2009), then dean of the Faculty of Medicine, to convene a panel of experts to identify scientists from around the world whose research has had a direct impact on the treatment of disease.

The Warren Alpert Foundation does not solicit funds. It is a private, philanthropic organization funded solely by The Warren Alpert Estate.

—Bob Brody



**PIONEERS: Alain Carpentier (left) and Robert Langer will receive the 2011 Warren Alpert Foundation Prize.**

viduals. Seven honorees have also received a Nobel Prize.

"The Alpert Prize was created to reward scientists whose discoveries have made great progress in new therapies for a wide range of diseases," said Jeffrey S. Flier, Dean of the Faculty of Medicine at Harvard University and chairman of the Foundation's scientific advisory committee. "Alain F. Carpentier and Robert S. Langer's research splendidly fulfills the Prize's central mission."

## SAVING LIVES

Carpentier, head of the Department of Cardiovascular Surgery at the Hôpital Européen Georges-Pompidou in Paris, is renowned for his research on developing and implanting the first successful artificial bronchus, saving the lung of a patient with lung cancer. The cardiac surgeon also devel-

oped the world's first artificial valve used in clinical practice. The valve utilizes animal tissues that are chemically processed in order to prevent immunological reaction when implanted in humans and currently benefits more than 100,000 patients each year. Carpentier is also a lead developer of a fully implantable artificial heart created from biomaterials, soon to enter clinical trials. He was elected President of the French Academy of Sciences in 2011. This prestigious award is a great honor for myself, my research team and my country," Carpentier said. "The development of biological valve prosthesis is a sterling example of the important contribution of bioengineering in the progress of surgery. We are proud that this new valve could benefit thousands of patients."

Langer, senior lecturer on surgery at HMS and the David H. Koch Institute Professor at

## Paper Chase

RECENT PUBLICATIONS 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](http://focushms.com).

### A CERNA HYPOTHESIS: THE ROSETTA STONE OF A HIDDEN RNA LANGUAGE?

Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. *Cancer Genetics Program and departments of Medicine and Pathology, Beth Israel Deaconess Medical Center and HMS*

The authors present a unifying hypothesis about how messenger RNAs, transcribed pseudogenes, and long noncoding RNAs "talk" to each other using microRNA response elements (MREs) as letters of a new language. They propose that this "competing endogenous RNA" (ceRNA) activity forms a large-scale regulatory network across the transcriptome, greatly expanding the functional genetic information in the human genome and playing important roles in pathological conditions, such as cancer. *Cell*. 2011 Aug 5;146(3):353-8.

### MALPRACTICE RISK ACCORDING TO PHYSICIAN SPECIALTY

Jena AB, Seabury S, Lakdawalla D, Chandra A. *Department of Medicine, Massachusetts General Hospital, and HMS*

The authors analyzed malpractice data from 1991 through 2005 for all physicians who were covered by a large professional liability insurer. The proportion of physicians facing a claim each year ranged from 19.1% in neurosurgery, 18.9% in thoracic-cardiovascular surgery and 15.3% in general surgery to 5.2% in family medicine, 3.1% in pediatrics and 2.6% in psychiatry. It was estimated that by the age of 65 years, 75% of physicians in low-risk specialties had faced a malpractice claim as compared with 99% of physicians in high-risk specialties. *New England Journal of Medicine*. 2011 Aug 18;365(7):629-36.

### SIMULTANEOUS VISUALIZATION OF THE EXTRACELLULAR AND CYTOPLASMIC DOMAINS OF THE EPIDERMAL GROWTH FACTOR RECEPTOR.

Mi LZ, Lu C, Li Z, Nishida N, Walz T, Springer TA. *Immune Disease Institute and Department of Pathology, HMS*

The authors' knowledge, no structural study to date has characterized, in an intact receptor, the coupling of conformational change in extracellular domains through a single-pass transmembrane domain to conformational change in cytoplasmic domains. Here the authors examine such coupling, and its unexpected complexity, using nearly full-length epidermal growth factor receptor (EGFR) and negative-stain EM. The coupling of one conformation of an activated receptor ectodomain to multiple kinase-domain arrangements reveals previously unanticipated complexity in transmembrane signaling and facilitates regulation of receptor function in the juxtamembrane and cytoplasmic environments. *Nature Structural & Molecular Biology*. 2011 Aug 7 18(9):984-9.



ANGELA ALBERTI

ASSISTANT DEANS for Faculty Affairs Mary Walsh, left, and Carol Bates work to improve the promotions process at HMS.

## Faculty Affairs Team in Place

*Team works to improve speed, transparency of faculty promotions*

Dean for Faculty Affairs Maureen Connelly has announced the completion of her leadership team, a milestone in the efforts of the Office for Faculty Affairs to speed and streamline the promotions process for faculty at Harvard Medical School and the Harvard School of Dental Medicine.

Carol Bates, associate professor of medicine at Beth Israel Deaconess Medical Center, joined Mary Walsh, instructor in anaesthesia at Brigham and Women's Hospital, on the HMS quadrangle this summer. Both are assistant deans for faculty affairs.

Bates is a general internist who has practiced primary care internal medicine at Beth Israel Deaconess since coming to Harvard in 1988 and served as director of the Beth Israel Deaconess Primary Care Residency Program from 1992 to 2011. In her new role, Bates will oversee all aspects of the assistant and associate professor appointment and promotion processes at HMS and HSDM. She will also manage faculty development activities of the Office for Faculty Affairs, including the HMS Leadership Course, the New Junior Faculty Orientation, and the Eleanor and Miles Shore 50th Anniversary Scholars in Medicine Program.

Walsh has been part of the Medical School community since 2002, training in the anaesthesiology department at Brigham and Women's, and joining the Office for Faculty Affairs in 2007 as a program director for faculty appointments. She was appointed assistant dean in 2010, overseeing the professorial appointments and promotion processes for faculty at HMS and HSDM. Her responsibilities include providing guidance to faculty participating on search and evaluation committees for senior faculty appointments as well as serving as a source of expertise and advice on all content, technical and administrative details related to senior promotions. Walsh works closely with Harvard University on faculty hiring systems and is leading the implementation of the streamlining of the professorial promotion process.

Through outreach efforts that include presentations at affiliated institutions and a promotions hotline (OFA\_promotions@hms.harvard.edu or 617-432-7112), Bates, Walsh and other senior staff in the Office for Faculty Affairs work to educate faculty members about the promotions process and allay concerns.

A common misconception involves areas of excellence, Walsh said. A faculty member may feel locked into the area—research, clinical or education—emphasized in his or her first promotion. In fact, Walsh said, a scholar's focus can change as each develops new skills and interests. "The promotion criteria are more flexible than people think," Walsh said. "The structure is meant to reflect to reflect the breadth of each faculty member's academic activities."

Bates noted that another misconception involves the tenor of promotion committee reviews. "There's a perception that evaluators are looking for flaws," she said, "but it's been my experience that the review is in fact a celebration of the individual."

—R. Alan Leo

## Developments in promotion process for HMS and HSDM

*As academic year 2011 drew to a close, the Office for Faculty Affairs reported significant strides in streamlining the promotions process*

### INCREASED NUMBER AND QUICKER PACE

- Faculty promotions increased 28 percent in 2010-11 over the previous academic year; promotions to the rank of professor increased 43 percent.
- The average length of the HMS portion of the professorial evaluation has decreased by seven months since 2005, from 16 months to nine.
- With 51 cases for promotion to professor being evaluated by the new senior promotion process since April 2011, the streamlining of senior promotions is well under way.

### COMMITMENT INCREASES FACULTY DIVERSITY

- The number of women professors increased to 150; women now make up 16 percent of the senior faculty. The second and third African-American women professors appointed at HMS were promoted in this academic year.
- Underrepresented minority (URM) faculty now constitute 5 percent of faculty and 5 percent of promotions at every rank except that of professor, for which promotions of URM faculty constitute 5 percent.

### EFFICIENCY BENEFITS DEPARTMENTS, CANDIDATES

- All promotion committees now use a paperless system for candidate reviews.
- The Promotions, Reappointments and Appointments Committee introduced a new system for approval of assistant professor candidates, including review and approval prior to in-person meetings, thereby increasing the number of candidates that can be considered each month.



ANGELA ALBERTI

Junior faculty learned about the new promotions process at a June luncheon with panelists (from left) Faculty Affairs Dean Maureen Connelly, Genetics Chair Cliff Tabin, Faculty Affairs Assistant Dean Mary Walsh and Health Care Policy Chair Barbara McNeil.

### NEW JUNIOR FACULTY ORIENTATION

October 11, 2011, 3–5 p.m.  
Waterhouse Room, Gordon Hall  
25 Shattuck St., Boston  
e-mail: hmsafa\_programs@hms.harvard.edu



ALEX GRIMM

## Happy 375th Birthday, Harvard

*Save the date: October 14*

Celebrate Harvard's 375th birthday Friday evening, October 14, with faculty, staff, students and alumni from every school. The medical, dental, and public health communities will gather at HMS and HSPH for refreshments; shuttle services will help transport people to Cambridge (details to follow). There, all will enjoy fabulous desserts, a memorable musical performance

and a dance party backed by a popular cover band.

Roving about will be student performers—dancers, musicians, soloists and a cappella groups. A costume parade led by HMS participants will proceed from Dudley House to a Tercentenary Theatre transformed by lighting and special effects, near the Old Yard where English settlers created this country's first college.

Revelers will enjoy the sublime strains of cellist Yo-Yo Ma, '76, as well as music from the Harvard-Radcliffe Orchestra and a chorus of students. Don't miss the 15-by-18-foot red velvet birthday cake by Flour bakery chef and Harvard alumna JoAnne Chang, '91, and treats from Taza chocolate and other local providers.

*For details on this event, including transportation, and other events and programs for this year, visit 375.harvard.edu.*

# Celebrating Postdoctoral Fellows

National Postdoc Appreciation Week is Sept. 19-23

Postdoctoral fellows from HMS and HSDM are expected to converge on the Quad for the third annual National Postdoc Appreciation Week, September 19-23. Postdocs will meet and mingle, discover one another's research through talks and a poster session, learn about the state of academe-industry relations from an HMS leader who knows that landscape well, and explore job opportunities for scientists-in-training with a doctoral degree in the basic sciences.



The event at HMS, organized by the Office for Postdoctoral Fellows (OPF), was spearheaded in 2009 by the National Postdoctoral Association (NPA) to recognize the important contributions postdocs make to scientific research. The celebration evolved from a single day to several days in 2010, when the U.S. House of Representatives passed a resolution recognizing National Postdoc Appreciation Week.

"The week allows us an opportunity to bring the postdocs together and celebrate their significant contributions," said Jim Gould, director of the OPF since June and, up until then, a postdoc himself.

Tuesday through Friday, these informative events will unfold (see program calendar):

- **At Hot Talks**, postdocs will enjoy a pizza lunch

while hearing about research by peers who, in discussing their research projects, aim to polish their presentation skills. Participants are invited to offer comments and ideas during this informal meeting of minds;

- **On Postdoc Research Day**, postdocs will showcase their work at a poster session to gain recognition for the important scientific contributions they make to research on the Quad;
- **At "Academic-Industry Interactions: New Frontiers,"** keynote speaker and HMS Executive Dean for Research William Chin will discuss academic-industry relationships and their importance to research funding, collaboration and discovery. Prior to joining HMS, Chin served as senior vice president for discovery research and clinical investigation at Eli Lilly and Company. At a reception to follow, travel awards will be presented for best posters from the previous day;
- **At "Secrets of the Recessionary Job Market: How Employment Works in a Down Economy,"** keynote speaker Dave Jensen, Science Careers columnist at the American Association for the Advancement of Science (AAAS), will offer practical advice on managing careers in the life sciences and navigating today's job market. OPF will cosponsor this and future events with a revitalized Faculty of Arts and Sciences Office of Postdoctoral Affairs.

Postdocs at HMS are engaged in mentored, advanced training, and many aim to run independent laboratories, according to Gould. The OPF's goal is to serve the roughly 800 postdocs across six basic science departments on the Quad and often collaborate with the School's affiliates to reach another 4-5,000.

"We're giving postdocs a forum in which they can be at work, surrounded by other postdocs," Gould said, "but also take a break from the bench to foster a community."

See "Celebrating Postdocs," page 8

## Training Tomorrow's Teachers

*Curriculum Fellows Program is first at graduate level*

Not so long ago, PhD-trained scientists eager to explore careers in science education rather than traditional tracks into research and academe trod an uncertain path. Today they need look no further than the three-year Curriculum Fellows Program at HMS, perhaps the first graduate-level program centered solely on education and its best practices.

The seed of the idea for the program took root in 2003, when Randall King, an associate professor of cell biology, needed an extra set of hands to help him revamp a course in cell biology and biochemistry for medical students at HMS. The ideal person, he realized, would have PhD training, grounding in basic science and a deep interest in education. He found her in a recent Biological and Biomedical Sciences (BBS) Program graduate, Jennifer Stanford.

The success of that experiment led Professor of Cell Biology David Van Vactor to propose a pilot program in 2006 to help train a new generation of teachers and leaders in science education. The HMS Dean's Office and the preclinical departments, which would benefit from fellows' efforts, agreed to provide crucial support.

Today, Van Vactor directs a program in full flower. The original six alumni have gone on to teaching and curriculum development positions, he said—serving, for example, as a lecturer in biology at Tufts University, as an education outreach coordinator in science, technology, engineering and mathematics at Johns Hopkins University, and as director of Science Alliance, an education and training program at the New York Academy of Sciences.

See "Tomorrow's Teachers," page 8

## CALENDAR OF EVENTS

National Postdoc Appreciation Week | September 19-23

9.20

### HOT TALKS 2011

Noon-1:00 PM  
Cannon Room, Building C  
Come for pizza and hear about exciting new work by exceptional HMS postdocs, who aim to gain feedback and hone their presentation skills.

9.21

### POSTDOC RESEARCH DAY

3:00-5:00 PM  
Courtyard Café,  
Warren Alpert Building

Attend a poster session showcasing the work of HMS and HSDM postdocs. Winners will receive travel awards to be used for attending scientific conferences.

9.22

### ACADEMIC-INDUSTRY INTERACTIONS:

#### NEW FRONTIERS

4:00-5:00 PM  
Armenise Auditorium,  
200 Longwood Ave.  
Keynote: William Chin,  
MD, Executive Dean

for Research, HMS  
Hear an HMS leader describe academic-industry relationships today and their importance to research funding, collaboration with academe, and discovery. At a reception in the Modell Atrium, poster-session travel award recipients will be announced.

9.23

### SECRETS OF THE RECESSIONARY JOB

### MARKET: How Employment Works in a Down Economy

2:30-4:00 PM  
Pfizer Lecture Hall,  
B23 Mallinckrodt  
(Chemistry Building)  
12 Oxford St., Cambridge  
Keynote: Dave Jensen,  
columnist, AAAS  
Science Careers  
Gain advice on managing careers in the life sciences.

Registration required; visit  
[postdoc.hms.harvard.edu](http://postdoc.hms.harvard.edu).



**THE HMS CURRICULUM FELLOWS**  
**Back row, from left:** Narveen Jandu; Johanna Gutlerner; Catherine Dubreuil; Ondra Kielbasa; and Randall King, founding member of the CFP Faculty Advisory Committee.  
**Front row:** Latishya Steele; Leah Brault; David Van Vactor, program director; and Heather Doherty. Gutlerner and Steele will complete their fellowships in 2012, the rest in 2013.

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## Ebola

*Continued from page 1*

In other words, targeting NPC1 has real therapeutic potential. While such a treatment may also block the cholesterol transport pathway, short-term treatment would likely be tolerated.

In the accompanying paper, Cunningham's group describes such a potential inhibitor.

### SCREENING COMPOUNDS

Cunningham and his group at Brigham and Women's investigated Ebola using a robotic method developed by their colleagues at the National Small Molecule Screening Laboratory at HMS to screen tens of thousands of compounds. The team identified a novel small molecule that inhibits Ebola virus entry into cells by more than 99 percent.

The team then used the inhibitor as a probe to investigate the Ebola infection pathway and found that the inhibitor targeted NPC1.

This finding builds on a 2005 paper by Cunningham and Chandran for which Whelan was also a collaborator. In that study, Whelan and his group discovered how Ebola exploits a protein called cathepsin B. This new study completes the puzzle. It now seems that cathepsin B interacts with Ebola in a way that preps it to subsequently bind with NPC1.

"It is interesting that NPC1 is critical for the uptake of cholesterol into cells, an indication of how the virus exploits normal cell processes to grow and spread," said Cunningham. "Small molecules that target NPC1 and inhibit Ebola virus infection have the potential to be developed into anti-viral drugs."

—Robert Cooke and Lori Shanks

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*For more information, students may contact Sean Whelan at [sean\\_whelan@hms.harvard.edu](mailto:sean_whelan@hms.harvard.edu).*

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## Parkinson's

*Continued from page 1*

"Our data show that alpha-synuclein was essentially mistakenly characterized as a natively unfolded protein that lacked structure," said Dennis Selkoe, the Vincent and Stella Coates Professor of Neurologic Diseases and senior author of the paper, published online Aug. 14 in the journal *Nature*. "We think this discovery has fundamental importance for understanding both how alpha-synuclein normally functions and how it becomes altered in Parkinson's."

When it comes to proteins, function follows form. A protein consists of a chain of chemical building blocks (amino acids), typically folded into an exquisite three-dimensional structure. Each twist and turn in the chain contributes to the protein's unique properties and behavior, so it's critical for scientists to accurately describe the arrangement of folds. But sometimes, they get the entire pattern wrong.

The new study suggests that's just what happened with alpha-synuclein, the protein that forms clumps called Lewy bodies in the brains of patients with Parkinson's and in certain related disorders. Scientists have long assumed that alpha-synuclein occurs in healthy cells as a single, randomly coiled chain that resembles a writhing snake. Selkoe's team has proven, however, that the structure is far more orderly and sophisticated.

### NEW TREATMENT STRATEGY

"This will open some new therapeutic doors," said first author Tim Bartels, a postdoctoral researcher in Selkoe's lab. "Everybody thought the protein was unfolded, so pharmaceutical companies have focused on preventing unfolded alpha-synuclein from aggregating."

Bartels recommends a new strategy—keeping the folded form of the protein stable.

How did the true structure of alpha-synuclein in healthy cells evade researchers for so long? Scientists knew that alpha-synuclein was abundant in the brain before they made the connection between the protein and Parkinson's disease in 1997. Experiments in the mid-1990s indicated the protein was stable when exposed to conditions that typically

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**"I did my PhD on alpha-synuclein, and—like the rest of the world—I assumed that it occurs natively as a monomeric, unfolded protein, so I was shocked."**

—First author Tim Bartels, a postdoctoral fellow in the lab of Dennis Selkoe

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disrupt the structure of most other proteins.

Consider what happens when an egg is boiled: the liquid proteins of the egg white are precipitated by the heat and congeal into a dense white mass. But alpha-synuclein seemed to behave like an egg that remains entirely viscous despite many minutes on the stove. It didn't precipitate and congeal when boiled. This apparent hardness made alpha-synuclein easy to work with in the lab. Scientists could boil the protein, even douse it with detergents and other rather harsh chemicals, while ostensibly leaving its structure intact.

Bartels and Selkoe wondered whether labs might be overlooking important aspects of the protein's natural biology by handling it so roughly, so they designed experiments to probe alpha-synuclein's behavior using gentler methods. They also bucked a trend by working with protein gathered from human cells rather than from engineered bacteria. The goal was to gain new insight into alpha-synuclein's clustering behavior.

### SURPRISING STRUCTURE

The initial data took them by surprise. Single, isolated chains of alpha-synuclein—the "monomeric" form of the protein—were absent from their cellular samples.

"I did my PhD on alpha-synuclein, and—like the rest of the world—I assumed that it occurs natively as a monomeric, unfolded protein, so I was shocked," said Bartels.

Using special gels and other methods that are less disruptive to a protein's form, the team conducted additional experiments to explore the structure of alpha-synuclein in healthy blood and brain cells. The native protein was exactly four times the predicted weight of a single alpha-synuclein chain, suggesting that cells package four alpha-synuclein chains together as a "tetrameric" unit. Applying sophisticated equipment and techniques, the team validated the molecular weight of the package, confirmed that it consists solely of

alpha-synuclein chains and showed that these four chains have orderly twists.

The researchers observed tetrameric alpha-synuclein to be the dominant form of the protein in healthy human cells, and remarkably resistant to aggregation. The tetramers maintained their original structure for 10 days, the entire length of the experiment, while the team monitored their samples for clustering behavior. In stark contrast, alpha-synuclein monomers began to form clusters after a few days and ended up as large aggregates called amyloid fibers. The Lewy bodies that accumulate in the brains of patients with Parkinson's consist mainly of such amyloid fibers.

"We hypothesize that the folded protein must disassemble into monomers before large pathological aggregates can form," said Selkoe, who is also co-director of the Center for Neurologic Diseases at Brigham and Women's. "If we can keep alpha-synuclein tetrameric and soluble, we might be able to prevent the neuronal degeneration of Parkinson's disease from progressing—or perhaps from even developing."

The finding could also prove useful in the quest for new diagnostics. Perhaps ratios of tetrameric protein to monomeric protein in blood cells, serum or spinal fluid will correspond to different propensities or stages of the disease.

Finally, the discovery of the folded tetramers should help labs to uncover the function of alpha-synuclein in healthy cells, which is still much debated. This functional knowledge should, in turn, contribute to researchers' understanding of Parkinson's and other diseases characterized by the formation of Lewy bodies rich in aggregated alpha-synuclein.

—Alyssa Kneller

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*For more information, students may contact Dennis Selkoe at [selkoe@rics.bwh.harvard.edu](mailto:selkoe@rics.bwh.harvard.edu).*

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## Meet and Greet

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function by encouraging receptors to cluster, even if briefly, she said.

Jaqaman and Gaudenz Danuser, HMS professor of cell biology, working with Sergio Grinstein from the Hospital for Sick Children in Toronto as well as colleagues at the University of Alberta, Edmonton, studied the motion of CD36, a receptor in human macrophages, a type of white blood cell that plays a role in immune response. CD36 detects oxidized LDL (oxLDL), a lipoprotein implicated in atherosclerosis.

Receptors are like the antennas in a cell's communication system with the world outside their membrane. The cytoskeleton, which includes a fine meshwork of actin fibers and an array of radiating microtubules, gives the cell its shape.

### FUNCTIONAL CLUSTERS

Like many receptors, CD36 can't work alone; a group of receptors must cluster together to send a signal into the cell. Until now, very little was known about how those functional groups of receptors formed. The cell and receptors were thought to wait "at rest" until a chemical signal happened to appear, causing receptors to coalesce.

This study reveals a much more dynamic "before" picture, with structures that precondition the cell to respond to signals. The researchers say that their work clearly demonstrates how "resting"

receptor movements are functionally relevant to the transmission of signals into the cell.

Grinstein, a senior scientist at Toronto's Hospital for Sick Children whose interests include understanding how macrophages work, approached Danuser for imaging and analysis expertise. Grinstein wanted to study CD36 at the single-molecule level in live cells and in real time under a microscope.

Using an automated particle-tracking algorithm she had developed to overcome the challenges of imaging such minute, complex interactions, Jaqaman analyzed these single-molecule movies to dissect the receptor behavior and its regulation.

### THREE KINDS OF MOTION

The movies reveal three kinds of motion by the receptors, which are sensitive to strands of the cytoskeleton's actin meshwork adjacent to the cell surface. As receptors roam about, they bump into these strands, slowing, stopping or changing direction. Some wander freely about the surface of the cell. Others become temporarily stuck inside a pocket of the mesh, as if trapped in a cage. Finally, some of the receptors travel linear paths.

These paths follow elongated "corridors" alongside the cell's microtubules, another part of the cell's cytoskeleton, radiating in more-or-less straight lines from the nucleus.

How the corridors form remains a mystery. The researchers suspect that they emerge from interactions between microtubules and actin, which remove actin strands from the path of the receptors.

In these narrow corridors free of actin strands, receptors scurry to and fro with more freedom, regularly bumping into one another, forming clusters that stick together fleetingly and then drift apart.

The researches suspected that these pre-formed clusters aid in signaling, so to test that theory, they disrupted the cytoskeleton. Sure enough, when the corridors disappeared, the cell no longer responded effectively to oxLDL.

Jaqaman compares the receptors in linear paths to people in the hallway of an office building. "People in the hallway are much more likely to bump into and chat with colleagues than people who stay in their offices all day, like receptors trapped in actin cages, or people wandering around the city, like receptors wandering freely around the cell surface," she says.

### CLUES TO DRUG RESISTANCE

Jaqaman and Danuser stress that the mechanical nature of these structures—and how they relate to the cell's chemical and mechanical environment—may be key to understanding how healthy and unhealthy cells function, replicate and grow. For example, it is well known, they said, that tumors are mechanically stiffer than normal tissues. In one provocative scenario, Danuser speculates that the broad variation in the mechanical properties between cancer tissues in different patients may be a key reason for the variable success of cancer chemotherapies that target cell-surface receptors.

"While most current research focuses on the study of oncogenes and tumor suppressors, it might be just the intrinsic change in cancer-tissue mechanics that leads to the change of signaling," Danuser said. "I think we absolutely have to look into that."

—Jake Miller

*For more information, students may contact Khuloud Jaqaman at [khuloud\\_jaqaman@hms.harvard.edu](mailto:khuloud_jaqaman@hms.harvard.edu).*

## FORUM



BLEND IMAGES/VEER.COM

## When Our Patients Fear Us



Sameer Chopra

"I never go to doctors," Mr. S announced defiantly. But he then looked away, his eyes betraying anxiety.

"Well," I said, "what brings you here tonight?"

Mr. S was my last new patient on a busy call shift at our community hospital in Jamaica Plain. At 57, he was the youngest person I admitted that evening by nearly two decades. As with my earlier admissions, his entire reason for coming to the hospital—however complicated or nuanced—had been condensed by the emergency room into a single word that flashed on my pager: "hematuria."

Though bloody urine may sound alarming, physicians most often use the term to refer to the microscopic amount of blood that enters the urine in the setting of a kidney stone, urinary tract infection or enlarged prostate. Beets and certain medications can also give the urine a pinkish hue, which patients sometimes mistake for blood. I contemplated a short list of explanations for Mr. S' hematuria, all benign.

Unexpectedly, his initial lab tests revealed profound anemia and significant renal dysfunction. I reviewed Mr. S's electronic medical record for prior measurements of hematocrit and creatinine to assess his normal baseline, but none had been logged in more than six years. In fact, his entire record was blank aside from a handful of notes by a dermatologist who once treated his psoriasis. I frowned. The current status of most of his body—from DNA to organ—was unknown.

When I arrived at his room, I thought I was in the wrong place. My "youthful" 57-year-old patient appeared haggard and emaciated, his body an awkward skeleton outlined by a loosely-draped sheet. He had a salt-and-pepper beard and dark eyes set deeply between hollow temples.

"Did you just move back to the area?" I asked.

"No, I've lived around here most of my life," he replied. "Why?"

"We don't seem to have any recent medical information on you in our system," I said. "Do you have a primary care physician at some other hospital?"

That's when Mr. S told me he never goes to doctors, and I asked why tonight was different.

Mr. S said that he had come to the hospital because he could no longer urinate. And when his urine did dribble out at inconvenient times, day and night, it looked like frank blood. He pointed at the plastic serpent that ran from beneath his sheet to a collection bag at the foot of his bed. The content, unnatural and cranberry-colored, was hardly the microscopic hematuria I had expected.

My concern grew with each fresh detail. In addition to his difficulty urinating, Mr. S had unintentionally lost more than 40 pounds in the past year. He also complained of debilitating fatigue. Despite months of concerning symptoms, Mr. S had refused to seek medical assistance.

I was perplexed. In every way, Mr. S seemed like a normal guy. He worked as a technician for a mobile phone company. In his free time, he took care of his elderly mother. But when it came to seeing doctors, he had kept his distance until one essential part of his body had stopped working.

Many of my male patients don't like coming to the hospital. They tell me how anxious they become around doctors, nurses and "sick people." Yet begrudgingly, they show up for yearly physicals, give blood for a cholesterol test, lie still for the ultrasound that looks for a bulge in their aorta, and agree to the invasive colonoscopy that hunts pre-cancerous polyps. They are the minimalists who interact with the medical system just enough to circumvent a longer, more protracted interaction—with that same system.

Mr. S had somehow evaded us for much of his adult life.

Should I have been surprised? We physicians may be much to blame. We interrogate our patients intimately, determined to turn up some small diagnostic clue like a coin on a beach. We examine their bodies' every nook and crevice. Still not satisfied, we scrutinize their urine, stool and phlegm. We insert tubes where nature never intended. We prescribe drugs that often lead to new symptoms. We tell patients they have cancer or heart failure and then inquire ridiculously, "Do you have any questions?"

We do all this and expect our patients to just trust us. We believe that in the end, their sacrifices are marginal. But are they really? How much humanity should people routinely give up when they become patients? Mr. S's refusal to seek medical care reminded me how much I expect from my patients, and how much I take for granted.

Ultimately diagnosed with stage IV bladder cancer, Mr. S has since passed away. His story is an unfortunate example of what can happen when the medical system fails in one important but underappreciated way. How do we better care for patients who fear us?

*Sameer Chopra, MD PhD, is a third-year resident in internal medicine and genetics at Brigham and Women's Hospital. The opinions expressed are not necessarily those of Harvard Medical School, its affiliated institutions or Harvard University.*

## Postdoctoral Fellows

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Another goal of the HMS/HSDM Office for Postdoctoral Fellows is to provide postdocs with the tools they need to become effective scientists. For example, an August workshop on “How to be an Effective Mentee” encouraged postdocs to nurture their relationships with faculty mentors, while a monthly “Career Discussion Hour” series features guest speakers in various fields. Gould urges postdocs to become collaborators rather than competitors, something he feels “will serve them best in the long run.”

The OPF places a strong emphasis on career exploration. Though postdocs at HMS may ini-

## “We have top notch postdocs here at HMS who are more than qualified for a variety of positions in academia, industry and the public sector.”

—James Gould, Director of the Office of Post-Doctoral Fellows

available faculty positions, many have extended their fellowships or sought a second postdoc before landing positions, Gould said.

However, postdocs have a host of valuable transferable skills—critical thinking, project management and budgeting—that make them attractive to employers in diverse fields.

Many teach science at community colleges, advance health and research policy at the federal, state and local levels, edit scientific journals, consult for pharmaceutical and biotechnology companies, or become administrative leaders in academic and faculty affairs.

“We have top notch postdocs here at HMS who are more than qualified for a variety of positions in academia, industry and the public sector,” said Gould. “This office is here to support them in whatever they decide to do.”

—Joanna Logue

For more information about the OPF, please visit [postdoc.hms.harvard.edu](http://postdoc.hms.harvard.edu). Postdoctoral fellows may contact Jim Gould at [postdoc\\_office@hms.harvard.edu](mailto:postdoc_office@hms.harvard.edu).

## Tomorrow’s Teachers

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### SPECIAL NICHE

“This is a special niche for postdoc training for someone who really wants to focus on pedagogy,” said Van Vactor, who has directed BBS since 2007. “It was unclear whether this novel approach would lead to an effective career development platform, but we saw our first fellows get good jobs that matched their career direction.”

Today, with a funding stream augmented by HMS

graduate programs and HMS affiliates, curriculum fellows partner with faculty to develop new courses, design materials, plan symposia, seminars and journal clubs, and write training grant applications. One example of their lasting impact upon HMS is the six-hour, multi-part nanocourse, which focuses sharply on a single topic, such as gene targeting strategies and techniques.

“It’s like HMS having an education lab,” said King. “The fellows interact, act as a bridge across departments, and have really innovative ideas.” Though their expertise differs widely, curriculum fellows share a sense of community, King said. He credits CFP Associate Director Johanna Gutlerner and the second postdoc-turned-curriculum fellow, Meg Bentley, for propelling the group into a solid alliance of scholars.

### DYNAMIC CLASSROOMS

All curriculum fellows gain valuable teaching experience and credentials. At first, King said, they mainly supported BBS core courses. Now they are gearing up for Phase II, in which their training will be more structured and expand beyond BBS. The fellows will forge collaborations across Harvard, including the public health and extension schools. They will also partner with institutions such as Brandeis and Framingham State, teaching undergraduates and in some cases directing their own courses.

Said King: “In Phase II, we’re asking: Can we become a leader in training faculty who are going to teach in a wide variety of scientific environments across the country?”

According to Dean for Graduate Education David Golan, who has mentored fellows himself, science is always changing, and HMS must remain on the cutting edge. “In formalizing the CFP, we’re creating an optimal training program for fellows while at the same time serving the School’s needs.”

Jennifer Stanford embodies the program’s mission. After wrapping up her Curriculum Fellowship in 2008, she became an assistant teaching professor in the Department of Biology at Drexel University, in Philadelphia. The role suits her perfectly, she said.

“The opportunities to explore and get involved in teaching and curriculum design, to work with talented educators and some of the world’s best research scientists,” Stanford said, “was a privilege that shaped my career.”

—Katie DuBoff

For information, visit [curriculumfellows.hms.harvard.edu](http://curriculumfellows.hms.harvard.edu). Interested students may contact David Van Vactor at [davie\\_vanvactor@hms.harvard.edu](mailto:davie_vanvactor@hms.harvard.edu).



ANGELA ALBERTI

James Gould, director of the Office of Postdoctoral Fellows, and Leigh Melanson, staff assistant.

tially focus on traditional tenure-track positions on faculties at colleges and universities or positions in industry, they are exposed to various other careers that may ultimately be more suitable to their strengths and interests. Given the imbalance between the boom in research funding during the Clinton administration and the tight market in

## FOCUS ONLINE

### Notable

For details, visit [focushms.com](http://focushms.com).

► **Emery Brown** receives 2011 Jerome Sacks Award for Cross-Disciplinary Research from National Institute of Statistical Sciences  
■ **Karen Costenbader**



PATRICK GILLOLEY

receives 2011 Henry Kunkel Young Investigator Award from American College of Rheumatology  
■ **Anthony**

**Hollenberg** named chief of Division of Endocrinology, Diabetes and Metabolism at BIDMC  
■ **Shuji Ogino** receives Ramzi Cotran Young Investigator Award from U.S. and Canadian Academy of Pathology  
► **Marc Schermerhorn** named chief of the Division of Vascular and Endovascular Surgery at BIDMC  
■ **Martha Jurchak, Jeffrey Karp, Jo Shapiro**

and **John Wright** of Brigham and Women’s Hospital named *Boston Business Journal* 2011 Champions in Healthcare  
■ **Pain Management Center at Brigham and Women’s** named an American Pain Society



COURTESY BIDMC

**Center of Excellence** ■ **McLean Hospital** named America’s top freestanding psychiatric hospital for 22nd year running by *U.S. News & World Report* ■ **Wyss Institute for Biologically Inspired Engineering at Harvard University** a finalist for a 2011 INDEX: Design for Life Award for lung-on-a-chip, based on technology developed by **Donald Ingber** and **Dan Dongeun Huh**

