A Promising Target for the Ebola Virus

Protein essential for infection identified

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

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See “Parkinson’s,” page 6
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 counterproductive. 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 less likely 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 mewilliams@hsp.harvard.edu.
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 individuals. 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. Flatt, 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 developed 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 the Massachusetts Institute of Technology, is known widely for his advancements in both drug delivery and tissue engineering. He has developed polymers to deliver drugs continuously at sustained levels, and he has engineered blood vessels and vascularized skeletal muscle tissue. The world’s most cited engineer, Langer holds more than 1,700 granted patents and is the youngest person to be elected to all three National Academies. Other recognitions include the National Medal of Science, the Charles Stark Draper Prize and the Albany Medical Center Prize in Medicine and Biomedical Research; he is to receive the American Chemical Society Priestley Medal in 2012.

“I am very grateful to the Warren Alpert Foundation for recognizing my work, and I am 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 (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 work 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.
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 anesthesiology 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 anesthesiology 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 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.”

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 each 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.

**NEW JUNIOR FACULTY ORIENTATION**

October 11, 2011, 11-2 p.m., Waterhouse Room, Gordon Hall
25 Shattuck St., Boston
E-mail: hmsfa_programs@hms.harvard.edu

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 McNeill.

_— R. Alan Leo_
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

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**CALENDAR OF EVENTS**

<table>
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<th>September 19-23</th>
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<tr>
<td><strong>MARKET:</strong> How Employment Works in a Down Economy</td>
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<tr>
<td>2:30-4:00 PM</td>
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<td>Pfizer Lecture Hall, B23 Mallinckrodt</td>
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<td>Chemistry Building</td>
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<tr>
<td>12 Oxford St., Cambridge</td>
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<td>Keynote: Dave Jensen, columnist, AAAS</td>
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<tr>
<td>Science Careers</td>
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<tr>
<td>Gain advice on managing careers in the life sciences.</td>
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<td>Registration required; visit postdoc.hms.harvard.edu</td>
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**Postdoc Research Day**

3:00-5:00 PM
Courtyard Cafe, 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.*

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**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 academia, and discovery. At a reception in the Modell Atrium, poster-session travel award recipients will be announced.*

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**Secrets of the Recessionary Job**

9.22

*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.**

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**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.

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**THE HMS CURRICULUM FELLOWS**

Back row, from left: Narveen Jandu; Johanna Gutleuer; Catherine Dubreuil; Ondra Kiebasa; and Randall King, founding member of the CFP Faculty Advisory Committee. Front row: Lalithaya Steele; Leah Braull; David Van Vactor, program director; and Heather Doherty. Gutleuer and Steele will complete their fellowships in 2012, the rest in 2013.

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**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 academia had 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 (IBBS) Program gradute, 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

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**SYMPOSIUM:**

Postdoc Andrea Tentner studies embryonic development through the lens of zebrafish. She says, “Patterns of cellular asymmetry during zebrafish embryogenesis can be used for attending scientific conferences.”

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**FOCUS 5**

SEPTEMBER 2011
fossils.com
Ebola
Continued from page 1

In other words, targeting NPC1 has real therapeu- tic 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 Cunn- ingham and Chandra, 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 propels it 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 mole- cules that target NPC1 and inhibit Ebola virus infection have the potential to be developed into anti-viral drugs.”

—Robert Cooke and Lori Shanks

For more information, students may contact Sean Whelan at sean_whelan@hms.harvard.edu.

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 Pro- fessor 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 exqui- site 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 hap- pened 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 disrupt the structure of most other proteins.

Consider what happens when an egg is boiled: the liquid proteins of the egg white are precipi- tated 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 con- geal when boiled. This apparent hardiness made alpha-synuclein easy to work with in the lab. Sci- entists 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 engi- neered 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 “mono- meric” 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.”

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

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

Jaquaman and Gaudenz Danuser, HMS profes- sor 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 recep- tor 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 communica- tion system with the world outside their membrane. The cytoskeleton, which includes a fine meshwork of actin fibers and an array of radi- ating 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 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-molecular 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 fleetingy 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.

CLUES TO DRUG RESISTANCE

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.

When the corridors did bubble 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.

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’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.

“So, 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 dribbled 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 untypically 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, he 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 crvice. Still not satisfied, we scrutinize their urine, stool and pleuritis. 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 under-appreciated way. How do we better care for patients who fear us?
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 Mentor” 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 initially focus on traditional tenure-track positions on faculties at colleges and universities or positions in industry, they are exposed to various other opportunities including 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.”

“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

For more information about the OPF, please visit postdoc.hms.harvard.edu. Postdoctoral fellows may contact Jim Gould at postdoc.office@hms.harvard.edu.

Notable
For details, visit focushms.com.

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