

FOCUS



News from Harvard Medical, Dental and Public Health Schools

January 2012

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THAT'S SOME WALK: The molecular motor dynein doesn't just walk; it staggers like a drunken sailor. HMS biologists say that may be key to dynein's role in keeping cells healthy. See the video at focushms.com.

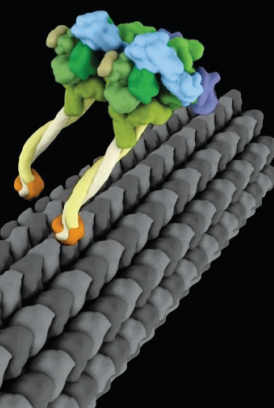


IMAGE FROM ANIMATION BY JANET IVASA

In biomedical research, astounding things happen when people from diverse disciplines work together in a coordinated way. "Be an apple in a bowl of oranges," said Frances Jensen, director of epilepsy research at Children's Hospital.



JAKE MILLER

Researchers Gather to Discuss Future Of Translational Research Education

Inaugural Kantoff-Sang Lecture draws leaders to discuss Harvard's approach to the evolving challenges of clinical and translational research education

The pace of discovery in the life sciences is breathtaking. Our understanding of human genetics, as well as the chemical and physical interactions of single molecules within cells, has advanced according to Moore's Law. Meanwhile, critical new insights show how social networks, psychology and behavioral economics impact health.

And yet, there have been painfully few equivalent advances in human health. The drug development system is stalling, health care costs continue to rise unsustainably, and poverty and politics prevent many in the world from achieving even the most basic standards of human health.

"In the 40 years that I've watched the progress of medicine and science, we have not conquered enough diseases," said Lee Nadler, HMS dean for clinical and translational research, addressing the crowd Nov. 29

See Kantoff-Sang, page 6

Aids@30 Symposium Plots End to an Epidemic

Scientists, physicians, activists and others on the front lines of the 30-year fight against AIDS gathered on Harvard's Longwood Campus on World AIDS Day on Dec. 1 to plot a strategy to achieve something that most once thought impossible: ending the AIDS epidemic.

The discussion was part of a two-day conference called "AIDS@30: Engaging to End the Epidemic." The conference, sponsored by the Harvard School of Public Health (HSPH) and held at the Joseph B. Martin Conference Center, was an effort to reflect on the many advances and milestones that have transformed AIDS from a death sentence to a manageable, chronic disease. But the conference also worked to engage those who best know the ailment to plot its end.

"We're tired of this virus, this epidemic, and now hopefully are able to plan its demise," wrote Richard Marlink, the program chair and Beal Professor of the Practice of Public Health, in a message to participants. "I, for one, do not want to be discussing AIDS at 40 years or AIDS at 50 years. The conversation starts now, for planning the end of AIDS."

Conference participants have been cheered by the
See AIDS, page 8

Study Points to Therapy For Radiation Sickness

A combination of two drugs may alleviate radiation sickness in people who have been exposed to high levels of radiation, even when the therapy is given a day after the exposure occurred, according to a study led by Harvard Medical School researchers at Dana-Farber Cancer Institute and Children's Hospital Boston.

Mouse studies of other potential therapies suggest they would be effective in humans only if administered within a few minutes or hours of radiation exposure, making them impractical for use in response to events involving mass casualties. In contrast, the larger time window for administering the two-drug regimen raises the prospect

See Radiation, page 6

Research Fellow Marc Andermann studies mouse vision in the lab of Neurobiology Professor Clay Reid.



JOHN SOARES

Mouse Brains Keyed to Speed

Slow and fast visual cues are processed in discrete regions, opening new avenues for neural research

It's hard to be a mouse. You're a social animal, but your fellows are small and scattered. You're a snack to a bestiary of fast, eagle-eyed predators, not least the eagle. You're fast too, but your spatial vision is poor — around 20/200. So what's a mouse to do?

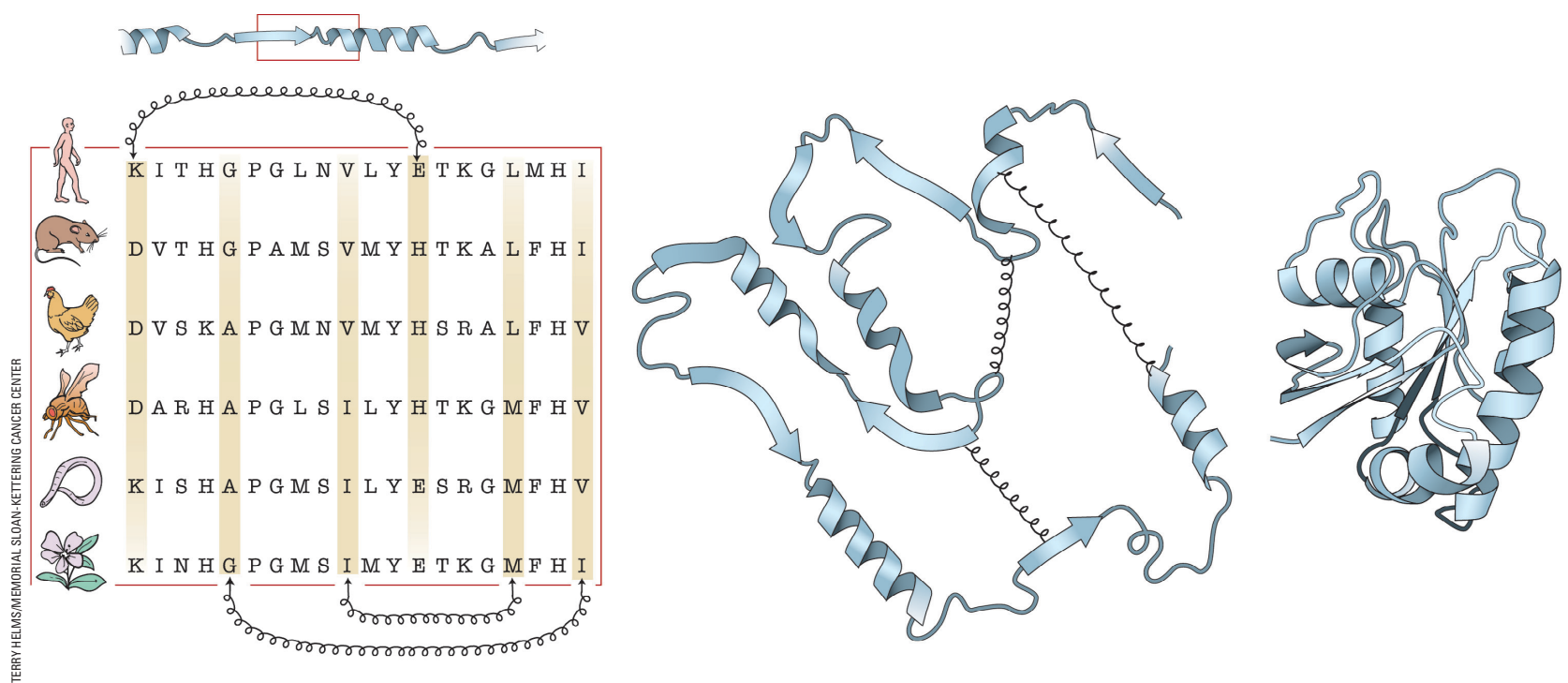
For starters, pay attention.

Or specifically, pay attention to small, slow-moving shapes — like other mice — and big, fast ones — the

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Evolution Reveals Missing Link Between DNA and Protein Shape

Fifty years after the pioneering discovery that a protein's three-dimensional structure is determined solely by the sequence of its amino acids, an international team of researchers has taken a major step toward fulfilling the tantalizing promise: predicting the structure of a protein from its DNA alone.

The team at Harvard Medical School, Politecnico di Torino / Human Genetics Foundation Torino (HuGeF) and Memorial Sloan-Kettering Cancer Center in New York (MSKCC) has reported substantial progress toward solving a classical problem of molecular biology: the computational protein folding problem. The results were published Dec. 7 in the journal *PLoS ONE*.

In molecular biology and biomedical engineering, knowing the shape of protein molecules is key to understanding how they perform the work of life, the mechanisms of disease and drug design. Normally the shape of protein molecules is determined by expensive and complicated experiments, and for most proteins these experiments have not yet been done. Computing the shape from genetic information alone is possible in principle. But despite limited success for some smaller proteins, this challenge has remained essentially unsolved. The difficulty lies in the enormous complexity of the search space, an astronomically large number of possible shapes. Without any shortcuts, it would take a supercomputer many years to explore all possible shapes of even a small protein.

"Experimental structure determination has a hard time keeping up with the explosion in genetic sequence information," said Debora Marks, a mathematical biologist in the Department of Systems Biology at HMS. Marks worked closely with Lucy Colwell, a mathematician, who recently moved from Harvard to Cambridge University. They collaborated with physicists Riccardo Zecchina and Andrea Pagnani in Torino in a team effort initiated by Marks and computational biologist Chris Sander of the Computational Biology Program at MSKCC, who had earlier attempted a similar solution to the problem, when substantially fewer sequences were available.

"Collaboration was key," Sander said. "As with many important discoveries in science, no one could provide the answer in isolation."

The international team tested a bold premise: That evolution can provide a roadmap to how the protein folds. Their approach combined three key elements: evolutionary information accumulated for many millions of years; data from high-throughput genetic sequencing; and a key method from statistical physics, co-developed in the Torino group with Martin Weigt, who recently moved to the University of Paris.

Using the accumulated evolutionary information in the form of the sequences of thousands of proteins, grouped in protein families that are likely to have similar shapes, the team found a way to solve the problem: an algorithm to infer which parts of a

Studying related proteins, researchers identified pairs of amino acid residues (left) that seemed to change in lock-step in the evolutionary record. These co-varying pairs indicated points on protein (middle) likely to be in contact after folding, giving researchers enough clues to create a computational model of the protein's three-dimensional structure (right).

protein interact to determine its shape. They used a principle from statistical physics called "maximum entropy" in a method that extracts information about microscopic interactions from measurement of system properties.

"The protein folding problem has been a huge combinatorial challenge for decades," said Zecchina, "but our statistical methods turned out to be surprisingly effective in extracting essential information from the evolutionary record."

With these internal protein interactions in hand, widely used molecular simulation software developed by Axel Brunger at Stanford University generated the atomic details of the protein shape. The team was for the first time able to compute remarkably accurate shapes from sequence information alone for a test set of 15 diverse proteins, with no protein size limit in sight, with unprecedented accuracy.

"Alone, none of the individual pieces are completely novel, but apparently nobody had put all of them together to predict 3-D protein structure," Colwell said.

To test their method, the researchers initially focused on the Ras family of signaling proteins,

See "Folding," page 8

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Recent books written or edited by members of the HMS, HSPH and HSDM faculty, staff or students may be submitted to *Focus* at the address above. Books received by Jan. 31, 2012, will be considered for 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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Novel Target Identified for Aggressive Cancer Gene

Findings from the HMS Department of Genetics may open door for new treatments for particularly dangerous forms of breast and prostate cancer

Researchers have found a way to kill human cells hijacked by a genetic accelerator that puts cancer cells into overdrive: the Myc oncogene. The discovery reveals new drug targets for Myc-driven cancers, which tend to be particularly aggressive.

The results were published online Dec. 8 in *Science*.

In its non-cancerous, healthy form, Myc oversees how genetic information is translated into proteins, typically those involved in growing new cells. But mutations can cause Myc to become hyper-activated, or oncogenic, and when that happens, cells divide uncon-

To find the genes, Elledge and Westbrook used a method that relies on tiny RNA molecules (dubbed short-hairpin RNA or shRNAs) that block the activity of specified genes. The scientists used those shRNAs in experiments with human breast epithelial cells in which Myc could be selectively hyper-activated. Each cell in the experiment contained just one silenced gene. If the cell died when Myc's cancer activity was triggered, then that silenced gene was clearly one Myc needed to form tumors.

Altogether they tested nearly 75,000 shRNAs, and ultimately

One standout among the new candidates was the gene SAE2. Myc-activated cells in which SAE2 is depleted are unable to build normal spindles — the internal structures that guide mitosis. This suggests the cells die because they're not able to divide correctly. The researchers determined that SAE2 depletion blocks Myc's ability to activate genes involved in spindle formation.

BUILDING THE CASE

To add more weight to their findings, the two research teams confirmed that SAE2 depletion slows growth rates of human, Myc-driven breast cancer cells both in a dish and after transplantation into immune-compromised mice. Finally, the researchers stratified gene expression data for nearly 1,300 breast cancer patients according to whether Myc activity was high or low. Consistent with their prior findings, they found that Myc-high patients fared better in terms of metastasis-free survival if they had naturally low SAE2 levels, while among Myc-low patients, SAE2 levels made no difference.

"This study show us that Myc-driven cancers become addicted to unique sets of proteins that are not required in normal, non-cancerous tissues," said Westbrook. "And many of these cancer vulnerabilities are enzymes, giving us new, rapid directions for treatments for these notoriously bad cancers."

Taken together, these findings suggest that disabling SAE2 and similar enzymes is a new therapeutic strategy for patients with Myc-driven cancer, the researchers concluded in the paper. According to Elledge, future research will look at the consequences of inactivating these genes in animals. "We'd also like to delve more into the mechanism," Elledge said. "We'd like to know more specifically which proteins Myc depends on — if we can hit those targets with drugs, we might be able to turn Myc off and kill cancer cells selectively."

—Charles W. Schmidt

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

Paper Chase

RECENT PUBLICATIONS
FROM HMS RESEARCHERS

This selection of new studies and review articles by researchers from across the HMS community represents a small sample of research at focushms.com.

COMBINATORIAL PATTERNING OF CHROMATIN REGULATORS UNCOVERED BY GENOME-WIDE LOCATION ANALYSIS IN HUMAN CELLS

Ram O, Goren A, Amit I, Shores N, Yosef N, Ernst J, Kellis M, Gymrek M, Issner R, Coyne M, Durham T, Zhang X, Donaghey J, Epstein CB, Regev A, Bernstein BE. Broad Institute; Howard Hughes Medical Institute; Massachusetts General Hospital; Harvard Medical School.

Hundreds of chromatin regulators (CRs) control chromatin structure and function by catalyzing and binding histone modifications, yet the rules governing these key processes remain obscure. The authors present a systematic approach to infer CR function: ChIP-string, a meso-scale assay that combines chromatin immunoprecipitation with a signature readout of 487 representative loci. The work provides a multiplex method that substantially enhances the ability to monitor CR binding, presents a large resource of CR maps and reveals common principles for combinatorial CR function. *Cell*. 2011 Dec. 23;147(7):1628-39.

THE CYC8-TUP1 COMPLEX INHIBITS TRANSCRIPTION PRIMARILY BY MASKING THE ACTIVATION DOMAIN OF THE RECRUITING PROTEIN

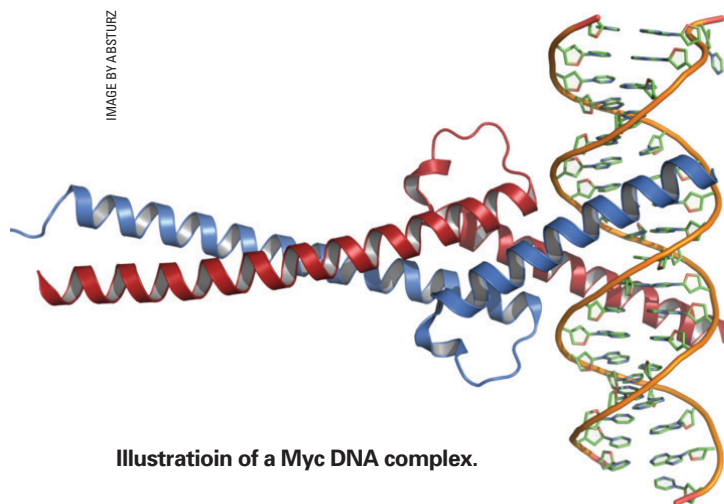
Wong KH, Struhl K. HMS Department of Biological Chemistry and Molecular Pharmacology.

The yeast Tup1-Cyc8 corepressor complex is recruited to promoters by DNA-binding repressors, but the mechanisms by which it inhibits expression of genes involved in various stress pathways are poorly understood. ... Cyc8-Tup1 regulates transcription primarily by masking and inhibiting the transcriptional activation domains of the recruiting proteins, not by acting as a corepressor. The authors suggest that the corepressor function of Cyc8-Tup1 makes only a modest contribution to expression of target genes, specifically to keep expression levels below the nonactivated state. *Genes & Development*. 2011 Dec. 1;25(23):2525-39.

A GENOMIC STORM IN CRITICALLY INJURED HUMANS

Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, Hayden DL, Hennessy L, Moore EE, Minei JP, Bankey PE, Johnson JL, Sperry J, Nathens AB, Billiar TR, West MA, Brownstein BH, Mason PH, Baker HV, Finnerty CC, Jeschke MG, López MC, Klein MB, Gamelli RL, Gibran NS, Arnold B, Xu W, Zhang Y, Calvano SE, McDonald-Smith GP, Schoenfeld DA, Storey JD, Cobb JP, Warren HS, Moldawer LL, Herndon DN, Lowry SF, Maier RV, Davis RW, Tompkins RG, and the Inflammation and Host Response to Injury Large-Scale Collaborative Research Program. MGH and HMS.

Human survival from injury requires an appropriate inflammatory and immune response. The authors describe the circulating leukocyte transcriptome after severe trauma and burn injury, as well as in healthy subjects receiving low-dose bacterial endotoxin, and show that these severe stresses produce a global reprioritization affecting >80% of the cellular functions and pathways, a truly unexpected "genomic storm." Similarities in gene expression patterns between different injuries reveal an apparently fundamental human response to severe inflammatory stress. Based on these transcriptional data, the authors propose a new paradigm for the human immunological response to severe injury. *Journal of Experimental Medicine*. 2011 Nov. 21;208(13):2581-90.



trollably and form tumors.

Myc-dependent cancer cells are addicted to the oncogene, to the extent that they'll die if it's disabled. Scientists have long tried to exploit this vulnerability in drug development. However, in its protein form, Myc is a notoriously difficult target, mainly because it lacks efficient binding sites for drug compounds.

THE HELP

So Stephen Elledge, the Gregor Mendel Professor of Genetics and Medicine at Harvard Medical School, and a senior author on the paper, and his collaborator and co-senior author Thomas Westbrook, an assistant professor at the Baylor College of Medicine, opted for a different approach. They aimed to suppress Myc by disabling its helper genes rather than the oncogene itself. Taking advantage of "synthetic lethality," or the cell-killing effect of having two incompatible mutations in a shared pathway, they hoped to mimic the success seen in studies of genes associated with inherited breast cancer.

"Myc-driven cancers become addicted to unique sets of proteins, ... giving us new, rapid directions for treatments for these notoriously bad cancers."

— Thomas Westbrook, assistant professor at the Baylor College of Medicine and co-senior author

found 403 potential candidates; some familiar to the field of Myc biology and some not. "These genes aren't oncogenes in and of themselves, but they do code for proteins that Myc relies on to cause cancer," said Elledge, who is also a professor of medicine at Brigham and Women's Hospital. "We see them as potential targets for drug therapy — even if you can't target Myc, you can target these other genes and inactivate its effects."



Members of the HMS Class of 2014 perform “Don’t Stop Achievin’” in the Second Year Show.

STEVE GILBERT

Second-Year Show: The Hangoverdose

Will there be a class of 2015?

In *The Hangoverdose*, the 105th original musical by Harvard Medical School, the Class of 2014 keeps the tradition of lampooning favorite faculty and staff alive and well. And in thwarting an evil genius’s diabolic plot, the show’s lead characters also ensure that the School community will live to see a 106th show.

When that evil genius turns out to be none other than Chair of Global Health and Social Medicine Paul Farmer (as portrayed by Will Johnson), the audience knows no one will be safe from barbed dialogue. In the script by head writers Andrew Le, Matthew Canver and Samyukta Mullangi, targets range from Dean Jeffrey S. Flier (Nworah Ayogu) to Atrium Café manager Franceny Bedoya (Samyukta Mullangi).

Just days before the start of the new academic year, Dean for Medical Education Jules Dienstag (Shaan Ghandi) receives the news that “there won’t be a Class of 2015.” That’s because first-year course manager Evan Sanders (Alan Carlotto) has gone missing after a night of drunken debauchery. As everybody knows, without Sanders, there can be no classes.

Charged with tracking down Sanders, Associate Professor Randy King (Peter Rozman) recruits a posse made up of Dean for Students Nancy Oriol (Julia Rudolf), Professor Joel Hirschhorn (Josh Niska) and Associate Professor Rick Mitchell (Winn Seay). Clues lead to familiar places as well as strange ones.

GLEE-FUL TRIBUTE

It’s in the Partners in Health Lair that our heroes encounter their opposing number in Farmer’s villainous scheme: Professor David Jones (Matthew Canver), Associate Professor Katharine Treadway (Kate Coyle), Associate Professor Beverly Woo (Lisa Siu) and the aforementioned barista and new mom, Bedoya. Game on!

With directors Johnson, Rozman and Rudolf doing double duty, executive producers Mohammed Karim and Phillip Kim keep the action brisk, with more than 100 actors, singers and dancers performing with a 13-piece orchestra conducted by Stephen Allsop. Song-and-dance numbers and video interludes give everyone time in the limelight. The ensemble brings the curtain down on Act I with “Don’t Stop Achievin’,” a Glee-inspired tribute to Type A personalities on stage and in the seats.

In Act II, the plot thickens, as friends of Sanders learn that Farmer aims to siphon off every cent of the School’s funds for the Partners in Health empire. A skirmish ensues, but the PIH crew handily routs the would-be rescuers.

Retreating to Gordon Hall, the demoralized heroes get encouragement from Associate Professor Julian Seifter (David Blauvelt) and his song “Nephron Gonna Give You Up.” But it’s Oriol (Rudolf) who belts out the night’s best solo, “You Make Me Feel Like I’m Hardly a Woman.”

After picking up martial arts training at Schwartzstein’s dojo — with sensei Professor Richard Schwartzstein (David Obert), reminding his pupils to “WORK THE PROBLEM” — the good guys are ready for a rematch at the PIH Lair. They recruit reinforcements, including Human Body course co-directors Cynthia McDermott (Carla Heyler) and Trudy Van Houten (Melissa Bellomy), the best comic pair since Laverne and Shirley, and a Dental School army led by students Bernard Boback and Miguel Ortiz (playing themselves).

Thus Sanders’ rescue is ensured — and just in time, because he’s got to get to the Atrium to stop his ladylove, New Pathway course administrator Kristin O’Neil (Megan Koster) from marrying someone else — the very fear that led to his fateful binge. Happily, O’Neil, “the one who looks like Sarah Silverman, but hotter,” has been hoping for just this outcome. The cast ends on a high note, with some serious shufflin’ to the HMS Party Rock Anthem. Rock on.

—Michael Rafferty

Rhodes Scholar Looks to Large Scale Responses

As a teen, two concussions from hockey and ski racing left David Obert struggling to concentrate, unable to stay awake in class and in peril of being unable to finish high school. Now the HMS second-year student has been named a 2012 Rhodes Scholar, one of 83 men and women from 14 countries and regions around the world to win the prestigious award.

Obert, a native of Edmonton, Alberta and a graduate of McGill University in Montreal is one of three representatives from the prairie region of Canada. He was nominated for the Rhodes by Harvard Medical School.

Created in 1902 by the will of British philanthropist Cecil Rhodes, the scholarships cover all costs for two or three years of study at Oxford. Winners are selected on the basis of high academic achievement, personal integrity, leadership potential and physical vigor, among other attributes.

At Oxford, Obert plans to pursue a double master’s degree in public policy and global health science.

Obert spent the summer working on a joint Harvard/NATO study examining how foreign militaries contribute to health sector stabilization in fragile states. Specifically, he focused on a case study examining the military response to the 2010 Haitian earthquake as it related to human health. He worked with Vanessa Kerry, instructor in medicine at Massachusetts General Hospital and director of the Global Public Policy and Social Change Program in the Department of Global Health and Social Medicine, and Margaret Bourdeaux, a core faculty member of Brigham and Women’s Hospital’s Division of Global Health Equity.

Obert says he has always had an interest in how the world works on a macro scale — seeing the geopolitical landscape and watching how large organizations and governments interact.

“I could see myself having a career a little bit like my supervisors from the summer,” he said. “I’d love to have the clinical side and patient contact — which brought me to medicine in the first place — but also be able to make an impact on another level, helping shape how big organizations work and how large scale responses to health needs are rolled out.”

—Jake Miller



COURTESY/DAVID OBERT

David Obert at the Kibale Health and Conservation Centre in Kibale, Uganda

Health Care Reform: The Moral Obligation



“A medical degree opens a lot of doors for people. Keep those doors wide open because, boy, do we need you.”

— JudyAnn Bigby, Massachusetts Secretary of Health and Human Services, delivering the 2011 Poussaint Lecture.

shown the benefits of the state’s health care reforms; as the unemployment rate rose, Commonwealth Care, a key facet of the reform, did exactly as intended, providing access to insurance even when individuals didn’t have access to an employer-sponsored plan. Simultaneously, employers did not drop their insurance offerings, as many had feared they would. As a result, the percent of uninsured in the commonwealth has decreased, though it has increased elsewhere. Bigby also noted that the plan has improved access to care for women (whose health affects their families, therefore making a major impact on society) and has significantly increased of the probability of an individual having a primary care physician.

Bigby noted that health care funding remains an issue, and said we must identify cost challenges and take advantage of technologies that can improve care and reduce cost, but are not being widely used.

During her lecture, Bigby acknowledged the impact of her then-professor, Faculty Associate Dean for Student Affairs Alvin Poussaint, who was in the audience. She thanked him for his encouragement throughout her studies — including supporting her leave of absence to deliver and care for her first child before returning to her studies, letting her know that she could truly “have it all.”

Dean for Diversity and Community Partnership Joan Reede thanked Bigby for her powerful words and asked if she had any advice to share with the aspiring physicians in the crowd.

“It’s a wide open field,” Bigby began. “A medical degree opens a lot of doors for people. Keep those doors wide open because, boy, do we need you!”

Poussaint, for whom the distinguished lecture is named, closed the event by thanking Bigby for her presentation, adding how delighted he was to witness the inspiring work she has been doing throughout her career. “She represents the dream we have for our students,” he said.

—Valerie Wencis

JudyAnn Bigby, Massachusetts Secretary of Health and Human Services, believes that everyone has a right to affordable health care. She shared her vision for achieving that goal at her talk at the eighth annual Alvin F. Poussaint, MD, Visiting Lecture, “Health Care Reform: The Moral Obligation.”

Bigby provided the HMS community with an overview of what has happened since Massachusetts enacted health care reform in 2006, and what direction she sees it taking in the future.

Outlining the steps needed to make healthcare attainable for all, Bigby acknowledged the difficulty of the task.

“There is no silver bullet,” Bigby said, “There is a lot of work to be done.”

According to Bigby, with the amount of money currently being spent on health care, one would assume that the U.S. ranks high in health quality. However, Bigby noted, citing a recent survey of member nations of the Organization for Economic Cooperation and Development, while the U.S. ranks highly for cancer care and in-hospital care, and its mortality from stroke rate is low, it ranks only 28 out of 35 for overall life expectancy and 31 out of 35 for infant mortality. Fifty-nine percent of the population reports problems accessing care.

Bigby noted that recent economic downturn has

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Notable

For details, visit focushms.com.

Elazer Edelman is the recipient of the 2011 Katz Prize in Cardiovascular Research ■ **Shelley Hurwitz** elected to the International Statistical Institute ■ **Donald Ingber [1]** receives the 2011 Holst Medal ■ **American Society of Tropical Medicine and Hygiene** awards the Bailey K. Ashford Medal to **Louise Ivers [2]** ■ **Joan Miller** is a recipient of a Greater Boston Chamber of Commerce 2012 Pinnacle Award ■ **R. Michael Scott [3]** awarded the Franc D. Ingraham Distinguished Service Award by the American Association of Neurological Surgeons ■ **Amar Sahay** receives a Janett Rosenberg Trubatch Career Development Award and **Margaret Livingston [4]** receives the Mika Salpeter Lifetime Achievement Award from the Society for Neuroscience.



Harvard Catalyst Recognized for Best Practices in Human Research

Regulatory leaders at Harvard Medical School have received a national award for best practices in human research.

Harvard Catalyst | The Harvard Clinical and Translational Science Center received the Health Improvement Institute’s 2011 Award for Best Practice in Human Research on Dec. 15 in recognition of its framework to smooth the review of proposed multicenter human studies, including clinical research, social or behavioral studies

or research using human tissues.

“While I take great pride in Catalyst’s ability to foster collaboration among researchers, I’m especially gratified that this award recognizes the value of collaboration for research participants,” said Barbara Bierer, HMS professor of medicine at Brigham and Women’s Hospital and director of the Regulatory Knowledge and Support Program at Harvard Catalyst.

The framework, known as the Master Common Reciprocal IRB Reliance

Agreement, reduces the administrative burden on Institutional Review Boards (IRBs), increases the efficiency of review and facilitates best practices for research participants by preventing disparities among protocols and informed consent forms that often occur in multi-board reviews.

Investigators proposing multicenter studies may request “ceded review,” by which the IRBs on a multicenter study rely on the review of only one IRB. The IRBs at participating institutions may

elect to do so case by case.

This agreement applies not only to new protocols, but can also be used if an investigator wishes to add a new site to an existing trial. While not all studies will be eligible for single IRB review, the hope is that this reliance agreement can reduce duplicative IRB review and so promote, even accelerate, collaborative research efforts among investigators at the participating institutions.

“The agreement’s success required participating institutions to cooperate in

new ways,” said Sabune Winkler, director of regulatory affairs operations at Harvard Catalyst. “This award is a testament to their leadership and vision.”

“The Award program offers positive recognition for excellence in the field of human research protection,” said Dr. Peter Goldschmidt, president and founder of the Health Improvement Institute. “This year’s awards continue the high standard that we have seen since the program began.”

— R. Alan Leo

Kantoff-Sang

Continued from page 1

at the inaugural Kantoff-Sang Lecture, an event that honors Philip Kantoff, professor of medicine at Dana-Farber Cancer Institute, in memory of Heng-Kang Sang, who was Kantoff’s patient. Senior leaders, educators and researchers from Harvard University, Harvard Medical School, Harvard School of Public Health and Harvard-affiliated hospitals presented a series of talks and a panel discussion focusing on clinical and translational research education and on the challenges and opportunities inherent in the current ecosystem of biomedicine and human health.

CATALYST AT THE HEART

Speakers and panelists also addressed the challenges of educating and training a new generation of physicians and scientists who will translate scientific knowledge into innovative treatments, and the challenge of ensuring that such potential treatments are available to people everywhere.

Jeffrey S. Flier, dean of Harvard Medical School, described new programs that HMS has undertaken to facilitate translational and clinical research. At the heart of many of these efforts is Harvard Catalyst | The Harvard Clinical and Translational Science Center.

Alan Garber, provost of Harvard University

“Catalyst has given me huge hope that this is a solvable problem. Being able to point to examples of success just makes it easier to build on to other successes, to encourage people that it can be done.”

— Harvard Provost Alan Garber

and, until taking his current post in 2011, director of the Center for Health Policy and the Center for Primary Care and Outcomes Research at Stanford University, and a primary care physician at the Veterans Affairs Palo Alto Health Care System, emphasized the need to include sociology, psychology and economics in the spectrum of research, and noted that Harvard University excels in these areas.

When he came to Harvard, Garber said, he saw many opportunities for improving coordination across different departments and different schools. “Catalyst has given me huge hope that this is a solvable problem,” he said. “Being able to point to examples of success just makes it easier to build on to other successes, to encourage people that it can be done.”

William Chin, HMS executive dean for research and Bertarelli Professor of Translational Medical Science, said that one of the key challenges is that, despite amazing advances, medicine still has not truly overcome the complexity of disease. “To defeat more diseases,” he said, “we don’t just need to adjust the old ways of collaborating and regulating research; we need entirely new ways.” Chin said that HMS is working to develop such new

approaches through collaborations with Harvard Law School and Harvard Business School, as well as with government agencies and with industry.

The challenges that need to be solved nowadays are more complex and the exponential growth of knowledge makes it impossible for a single physician or scientist to master it all. “We have to do this as teams,” said Elliott Antman, HMS associate dean for clinical and translational research.

Speakers mentioned a variety of new programs designed to help researchers and physicians work together, including the Harvard Institute of Translational Immunology, the new initiative in Systems Pharmacology and the Wyss Institute for Biologically Inspired Engineering. In addition to building programs and infrastructure to support collaboration, these projects also focus on inherently collaborative techniques like crowdsourcing.

David Scadden, co-chair of the Department of Stem Cell and Regenerative Biology, the University’s first cross-school department, spoke about the importance of attracting new young scientists through multidisciplinary courses like his freshman seminar, “Blood: From Gory to Glory.” Students read *Dracula*, they recreate the foundational experiments of stem cell biology, and they meet people who have benefitted from stem cell therapies.

The underlying theme of the event was clear: Astounding work happens when different disciplines intersect.

“Be an apple in a bowl of oranges,” said Frances Jensen, professor of neurology at Children’s Hospital Boston. “That is how we have to be conducting ourselves.”

The event was made possible through gifts in memory of Heng-Kang Sang.

—Jake Miller

For more information about training opportunities in clinical and translational research, visit: catalyst.harvard.edu/education.html.

Radiation

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that it could become a mainstay of the response to public health threats such as a nuclear power plant accident or nuclear terror attack.

In a paper published online by the journal *Science Translational Medicine*, the scientists report the beneficial effects, in mice, of a combination of a fluoroquinolone antibiotic (similar to the commonly used human antibiotic ciprofloxacin, or “Cipro”) and a synthetic version of the natural human infection-fighting protein BPI. Mice that received the combination a day after being exposed to high doses of radiation fared far better than mice that received neither or only one of the agents. Whereas radiation exposures of that magnitude almost always prove fatal within a month, 80 percent of the mice that received the two agents were alive and apparently healthy a month into the study.

FASTER REBOUND

The study’s lead author is Eva Guinan, HMS associate professor of radiation oncology at Dana-Farber, and the senior author is Ofer Levy, HMS assistant professor of pediatrics at Children’s Hospital Boston.

The investigators also found that the ability to generate new blood cells — which can shut down in the aftermath of radiation exposure — rebounded much more quickly and vigorously in

the mice treated with fluoroquinolone and rBPI21 (the synthetic version of BPI), potentially contributing to their return to health.

“Both fluoroquinolone antibiotics and rBPI21 have been shown to be quite safe in humans,” said Levy. “Their combined effectiveness in our study involving mice is an indication that they may be equally beneficial in people.”

The research potentially represents a major step in the United States government’s efforts to build a stockpile of therapies to counter radiological dangers.

“There is great interest in creating systems for dealing with the short- and long-term health risks of a significant release of radiation, whether from an accident at a nuclear power plant, an act of terrorism or even a small-scale incident in which a CT machine malfunctions,” said Guinan. “Developing useful agents has proven difficult. Most existing drugs aren’t effective enough and must be given within a very short time frame to provide any benefit. The recent disaster at the Fukushima nuclear power plant in Japan illustrates the need for agents that can be deployed rapidly to treat large populations.”

SEVERE EFFECTS

Radiation sickness, also known as acute radiation syndrome, varies with the amount of radiation an individual receives. The first signs of the disease usually are nausea and vomiting, which can be followed by fever, dizziness, weakness, bloody vomit and stools, difficulty breathing and infection. The body’s blood-making tissue, nervous system, digestive tract, lungs and cardiovascular system all can be affected. At very high doses, radiation is usually fatal.

Within the body, the effects of heavy radiation may include leakage of bacteria and the toxins they produce into the bloodstream from the digestive tract or through broken skin. Radiation effects wreak havoc with the function of the heart and lungs, disrupt the process of blood coagulation and inflame tissue throughout the body.

When bacteria or certain toxins enter the blood under normal conditions, the body’s immune system responds by dispatching neutrophils — white blood cells — to destroy the intruders. The neutrophils release a payload of BPI (bactericidal/permeability-increasing protein), which sticks tightly to molecules called endotoxins on the surface of the bacteria. The binding not only helps BPI kill the bacteria but also blocks inflammation caused by live or dead bacteria — something that conventional antibiotics do not do.

When a person is exposed to high levels of radiation, however, the ability to generate neutrophils is almost obliterated. “It’s a perfect storm of disease-causing events,” Guinan said. “Radiation results in bacteria and endotoxins entering the bloodstream at the same time that the body’s defenses are lowered.”

The treatment approach developed by Guinan, Levy and their colleagues takes direct aim at two potential contributors to radiation sickness: bacteria and the endotoxins on their surface. “We theorized that a two-drug therapy would be most effective,” Levy said. “Others had already shown some benefit to treatment with fluoroquinolones after radiation; at least part of the benefit came from killing bacteria in the blood. The second, rBPI21, would bind to, neutralize, and ‘mop up’ the endotoxins released by the dying bacteria, thereby removing the trigger of the inflammation process.”

—Dana-Farber Cancer Institute News

Vision

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kind you see when you're running for your life. Evolve specialized regions of the brain to process such cues. And keep moving.

Those regions are the subject of imaging research at Harvard Medical School aimed at revealing how distinct brain areas respond to different visual stimuli in the visual cortex of mice. The findings not only shed new light on mammalian vision, but also open a new avenue for exploring the mysteries of the brain.

"The cortex is really the crowning glory of brain evolution; it's what allows us to think and be human," said Clay Reid, HMS professor of neurobiology and senior author on a paper reporting the findings Dec. 22 in the journal *Neuron*. "And we know that one of the hallmarks of our cortex is that there are dozens of distinct cortical areas that do different things. And the best studied part of the cortex in any species, is the visual system, particularly the multiple visual areas in primates, including ourselves."

To explore how the mouse brain responded to different visual stimuli, the researchers tagged neurons in and around the primary visual cortex with a chemical that fluoresced when the neurons fired. They then showed the mice patterns that moved across a screen at different speeds, recording neural activity as the mice watched. The researchers found that the primary visual cortex contained a mix of neurons that responded to various types of stimuli, while adjacent areas were more specialized, some for larger, faster visual cues, others for smaller, slower ones.

The types of specialization made sense, the researchers said, when one considers the challenges mice face, such as identifying other mice, or navigating at high speeds. "You have to think like a mouse to ask what the different mouse visual areas might be doing," said Mark Andermann, a neurobiology postdoctoral fellow in the Reid laboratory, and lead author on the paper.

The research, among the first to examine how different cortical areas in the mouse are specialized for processing different aspects of visual inputs, draws together two key areas of brain science: On the one hand, vision studies in humans and other primates have propelled the field of cognitive neuroscience over the last half century. Scientists know today that primates, including humans, have 20 or more different areas that are specialized to perceive such things as color, motion and complex forms like faces.

At the same time, the mouse is rapidly becoming the best-studied species in neuroscience, including studies of the cortex. So discovering that, like us, mice have distinct processing streams in visual cortical areas lays the foundation for new efforts in cognitive neuroscience that can exploit the powerful genetic tools available only in the mouse. As a result, researchers can explore more deeply the neurological basis of behavior.

The mouse brain has other features that make it attractive to researchers. Where the human brain resembles a giant, wrinkly walnut, the peanut-sized mouse brain is also peanut smooth, the better for imaging. And where the human brain has about 100 billion neurons with about 5 billion in visual areas, the mouse has only 100 million neurons, with a less daunting figure of 1 million to 2 million in visual areas.

"Even though the visual cortex is more than 1,000 times smaller in mice than in humans," Reid said, "it's amazing that we have so many things in common."

—R. Alan Leo

To learn more, students may contact Clay Reid at clay_reid@hms.harvard.edu.

FORUM

The Credit Crunch

Trainees face special challenges in negotiating research authorship. Here's a way forward.



As a first-year medical student at HMS, I worked as a research assistant for a senior faculty member writing a book chapter on health care reform. While I collected and summarized articles and drafted some prose on the topic we were studying, the faculty member did the bulk of writing. I had sought experience in a new field and the respect of a potential career mentor, but much to my surprise I was also listed as a co-author. If only all research collaborations could be managed so easily and effortlessly.

Since that time, through my own experiences and those of others, I've learned that research collaborations can be fraught with unnecessary tension over perceived contributions and attribution. While credit disputes

may arise at any career stage, they pose special challenges for students and trainees. The conflicts lead to breakdowns in otherwise productive relationships between mentors and students and can dampen interest in research careers.

The literature on negotiations offers an approach to conflict resolution that may lead to greater satisfaction for students and trainees and their collaborating investigators. These concepts include:

Establish expectations early. Conflict over authorship often manifests at the preparation of the title page of a manuscript, abstract or presentation. Research collaborators have expectations and a role hierarchy regarding credit and attribution that often go unstated until a draft publication or presentation is produced. Often, too much suspense hangs over the question. Establishing roles and authorship at the outset of a project creates needed transparency about expectations.

Medical students and trainees may avoid explicit discussions of authorship because of power asymmetries. Raising the issue of authorship with a mentor who offers guidance, funding or data to facilitate one's work might be perceived as thankless. But clarity about authorship, attribution, roles and responsibilities can facilitate productivity — a shared goal for everyone.

Build in flexibility. While the best-case scenario in a collaborative effort is that a plan of work is established and executed, relative contributions often change. Unexpected efforts or insights can alter expectations about attribution and credit. In the absence of clearly defined roles or responsibilities, changes in contribution levels are often a source of added tension. If terms and the flexibility of those terms are established upfront, deviations can be discussed and resolved.

Scheduled re-negotiations about attribution, role and responsibility can strengthen collaboration by ensuring that changes in contributions are matched with changes in attribution. The best collaborative efforts in which I have been involved have included a steady and transparent dialog around authorship.

Broaden the negotiation. Discussions about attribution often get stuck on a single research product — usually a single manuscript — without consideration of the larger set of products that may emerge from a collaborative effort.

In situations where consensus is difficult to achieve, broadening the negotiation to include research products that extend or continue the research can help resolve conflicts. When the question turns on a single research product, the negotiation is "zero-sum," i.e. when one party wins, the other loses. With more research products — manuscripts, abstracts, and presentations — at play, it is more likely that all parties emerge satisfied from the negotiation.

One HMS classmate resolved an authorship dispute by accepting a secondary authorship position along with the opportunity to present the work at a national meeting. No one was fully happy, but everyone was satisfied with the outcome.

Use mediation when necessary. In many collaborations, the student or trainee feels left at the mercy of a collaborator of higher institutional rank or position. The student or trainee may fear retribution for raising concerns about attribution. While the number of "deadlock" situations will be minimal if collaborators routinely revisit the terms of their work, agreement is not always immediately possible.

Institutions can support research collaborations by designating mediators to help settle disagreements. Mediators can play a variety of roles, ranging from acting as a formal arbiter to simply providing impartial perspective. Mediation is less desirable than if collaborators achieved consensus on their own, but even the availability of such a process can empower trainees to raise concerns with more senior collaborators. At HMS, the Ombuds Office serves this role — and is frequently called upon to help resolve difficult situations.

It is not part of our academic medicine culture to so explicitly and frequently discuss attribution. In the high-minded world of research and scientific inquiry, it can seem petty, picayune and self-serving. Yet, anyone who has spent time in academic research has heard stories of immense frustration or disappointment over the assignment of credit at all levels — student, resident, fellow, junior faculty or senior faculty.

This is particularly problematic, however, at the early stages of a career, where continued interest in pursuing research may be affected by perceptions of fairness.

Without a major cultural change, implementing negotiations as I have described may be uncomfortable for students, trainees and senior investigators alike. It is, nonetheless, a change worth pursuing. Nothing short of the integrity of our collective research enterprise is at stake.

Sachin H. Jain, MD, MBA, is a senior medical resident at the Brigham and Women's Hospital and clinical fellow in medicine at Harvard Medical School. The opinions expressed are not necessarily those of Harvard Medical School, its affiliated institutions, or Harvard University.

AIDS

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continued expansion of antiretroviral treatment to the developing world, and by new findings on how to reduce mother-to-child transmission during pregnancy and breastfeeding, on how male circumcision and vaginal gels used during sex can reduce transmission and on progress toward a vaccine.

Nonetheless, there are an estimated 34 million people infected with the AIDS virus, and many cases still go undiagnosed. “The figure is a testament not only to the challenges ahead, but also to our successes in transforming a fatal disease into a serious but manageable condition for a growing number of people with access to care,” said Jeffrey S. Flier, Dean of the Faculty of Medicine of Harvard Medical School. “Together, the scientific community will ultimately solve this problem.”

Still, just 47 percent of those in need of antiretroviral treatments get them. About the same percentage of pregnant women who need medicine get it to prevent transmission to their children.

World AIDS Day is held on the anniversary of the release of the first scientific report on the disease. In Washington, D.C., President Barack Obama declared, “We can beat this disease,” and he pledged an additional \$50 million to fight the ailment in the United States. He also promised to increase assistance to help 6 million more people gain access to antiretroviral drugs overseas.

HSPH Dean Julio Frenk introduced the event and said AIDS has been the largest public health threat in the history of humankind.

Over the decades, AIDS has generated an enormous response around the globe that stretched far beyond science and medicine. The disease and its toll touched the arts, society and even government, prompting a new generation of activism and changing the way people view sexual preference and social stigma, Frenk said.

Frenk highlighted the contributions of Harvard researchers to understanding AIDS and HIV, including Lasker Professor of Health Sciences Max Essex’s 1983 discovery that the disease was caused by a retrovirus and the 1986 discovery of a second virus, HIV2, most prevalent in West Africa. Frenk also mentioned progress to prevent mother-to-child transmission and work on AIDS policy by former HSPH Dean Harvey Fineberg. Frenk cited



HSPH Dean Julio Frenk (from left) joined Harvard Provost Alan Garber, HSPH Dean for Academic Affairs David Hunter, and HMS Dean Jeffrey S. Flier at the AIDS@30 Symposium.

AUBREY LAMERICA/HSPH

current efforts at Harvard’s affiliated hospitals, such as the work of Bruce Walker, HMS

professor of medicine and director of the Ragon Institute at Mass General, MIT and Harvard. Frenk also mentioned the work of Jonathan Mann, who was the first director of HSPH’s François-Xavier Bagnoud Center for Health and Human Rights, and who focused on social justice aspects of the disease.

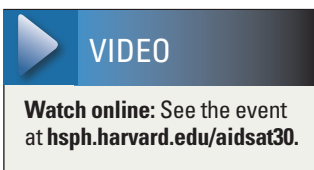
The conference featured recorded comments from former President Bill Clinton, who has targeted global AIDS through his Clinton Foundation. Clinton emphasized that although advances in the laboratory can lead to new drugs, the problem of obtaining enough resources to deliver those advances to people in need remains daunting. “AIDS is not simply a matter of health and life, it’s also a matter of resources and commitment,” Clinton said.

Harvard Provost Alan Garber said he was just starting his medical career in 1981 when the epidemic struck. Working in San Francisco General Hospital, he encountered desperately ill young men stricken with a mystery ailment that nobody knew how to treat. He recalled years later, as a resident there, that doctors knew a bit more about the disease, but still could do little.

During those years, Garber said, he and his colleagues thought they’d eventually discover the cause and have an antibiotic to treat it — or understand that it couldn’t be cured. He never anticipated a chronic disease that could be managed for years.

“I call that extraordinary progress,” Garber said. “I’m struck by how much there is still to do.”

—Alvin Powell, *Harvard Gazette*



Call for Proposals: Harvard Biomedical Accelerator Fund

Deadline is Feb. 17; grants support nascent technologies

The Biomedical Accelerator Fund is accepting proposals for early stage technologies. The pre-proposal deadline is Feb. 17, 2012.

A significant obstacle to the development and transfer of university technologies is the lack of funding for proof-of-concept and validation studies, essential steps required to demonstrate commercial potential. The Accelerator Fund, established by the Harvard University Office of Technology Development under the auspices of the Office of the Provost, is designed to overcome this barrier by providing funding assistance to faculty in the early stages of developing and validating nascent technologies originating in their labs with the goal of advancing projects beyond the bench and positioning them to attract strong industry partners who will continue to fund and develop them for commercial application and public access.

Now in its fifth year, the Accelerator has funded 33 projects from around the university with totals grants of approximately \$5.5 million. Typical awards range between \$100,000 and \$150,000 per year (direct costs only, indirect costs are waived). To learn more, visit goo.gl/odANb or contact curtis_keith@harvard.edu.

Folding

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which has been extensively studied because of its known link to cancer. The structure of several Ras-type proteins has already been solved experimentally, but the proteins in the family are larger—with about 160 amino acid residues—than any proteins modeled computationally from sequence alone.

“When we saw the first computationally folded Ras protein, we nearly went through the roof,” Marks said. To the researchers’ amazement, their model folded within about 3.5 angstroms of the known structure with all the structural elements in the right place. And there is no reason, the authors say, that the method couldn’t work with even larger proteins.

The researchers caution that there are other limits, however: Experimental structures, when available, generally are more accurate in atomic detail. And, the method works only when researchers have genetic data for large protein families. But advances in DNA sequencing have yielded a torrent of such data that is forecast to continue growing exponentially in the foreseeable future.

The next step, the researchers say, is to predict the structures of unsolved proteins currently being investigated by structural biologists, before exploring the large uncharted territory of currently unknown protein structures.

“Synergy between computational prediction and experimental determination of structures is likely to yield increasingly valuable insight into the large universe of protein shapes that crucially determine their function and evolutionary dynamics,” Sander said.

—R. Alan Leo

To learn more, students may contact Debora Marks at deboramarks@gmail.com.

Panelists (from left) Wafaa El-Sadr, Bob Grant, Sharon Hiller, John Pottage, Jr., Deborah Birx and Nancy Pardon discussed the future of HIV prevention with moderator Max Essex (not shown) at the AIDS@30 symposium.



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