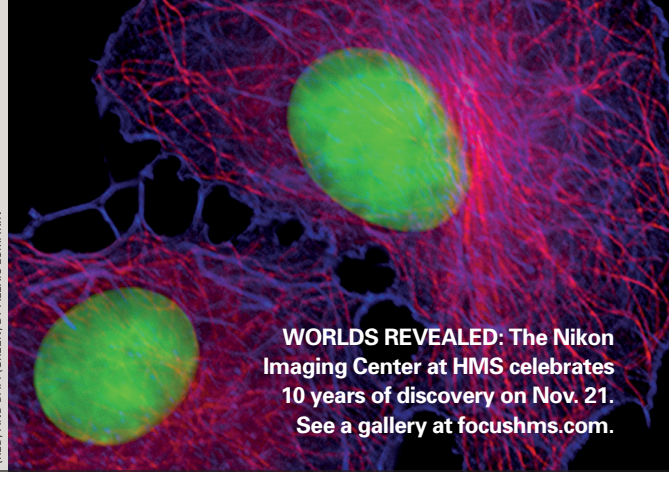
FOCUS

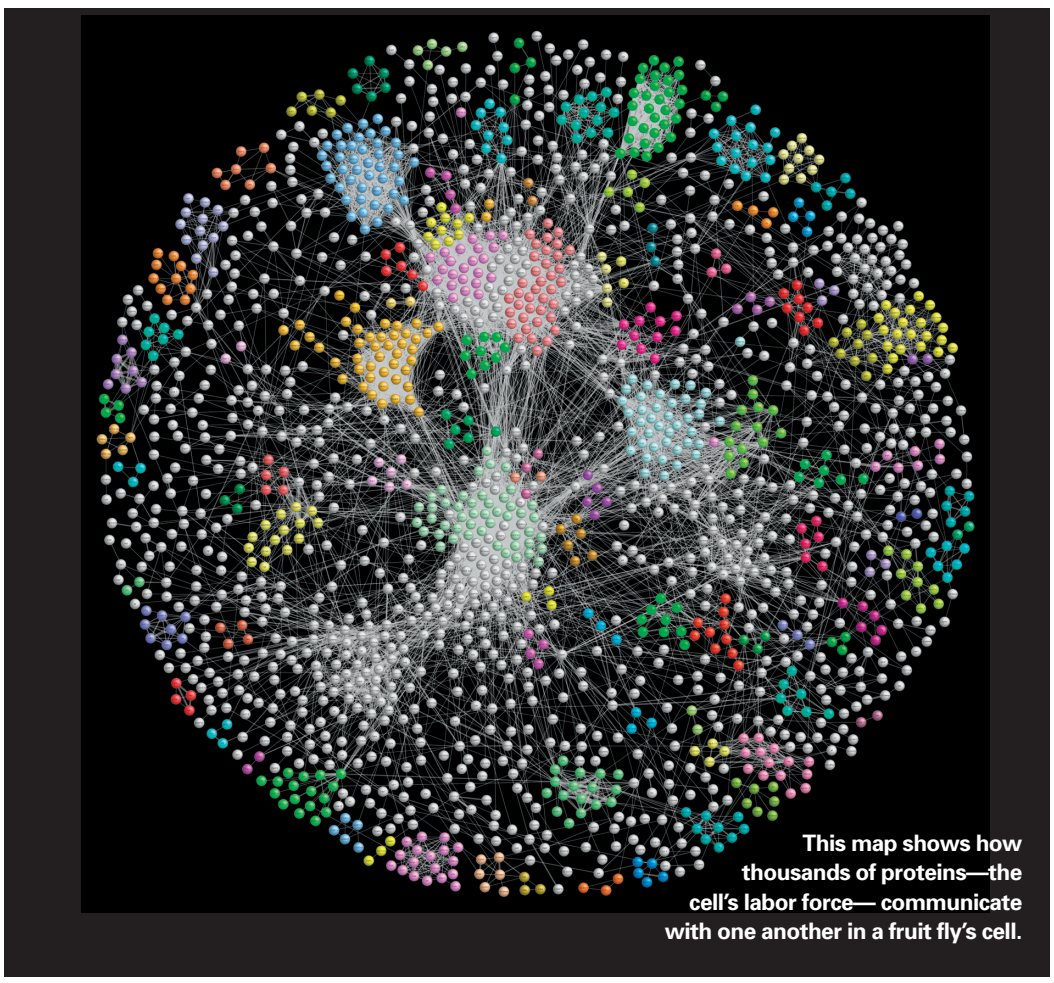
News from Harvard Medical, Dental and Public Health Schools

November 2011 ▶ focushms.com



FLUORESCENCE OVERLAY OF ACTIN (BLUE), TUBULIN (RED) AND DAPI (GREEN) BY ALEXIS LOMAKIN

WORLDS REVEALED: The Nikon Imaging Center at HMS celebrates 10 years of discovery on Nov. 21. See a gallery at focushms.com.



COURTESY ARTAVANIS-TSAKONAS LAB

This map shows how thousands of proteins—the cell's labor force— communicate with one another in a fruit fly's cell.

How do you find *Focus*?

In print, online—or both? Take a short survey at **goo.gl/FFuUS** by Dec. 2, or share your thoughts in an e-mail to Associate Dean Gina Vild at Gina_Vild@hms.harvard.edu, and help shape the future of *Focus* and other HMS communications.

Center for Primary Care Showcases Innovation

Clinicians convene from Boston and beyond to share creative solutions to health care crisis

One year following its creation, Harvard's burgeoning Center for Primary Care convened over 400 thought leaders, faculty, practitioners and students from the Harvard Medical School community and beyond to explore innovation and creative solutions to the crisis in primary care.

With practitioners, policy experts and others from across Greater Boston, and reaching as far as Group Health Research Institute in Seattle, Washington and Stanford University School of Medicine, the Oct. 13 Primary Care Innovations Conference marked the Center's first major event to bring together leaders from around the country to examine primary care innova-

See Center for Primary Care, page 8

JOEL HASKELL

CREATIVE PRIMARY CARE MODELS can protect against expensive health care crises, said Arnold Milstein, director of the Stanford Clinical Excellence Research Center.

Researchers Build Largest Protein Interaction Map to Date

Platform provides new, powerful way to explore how life and disease work

Researchers have built a map that shows how thousands of proteins in a fruit fly cell communicate with each other. This is the largest and most detailed protein interaction map of a multicellular organism, demonstrating how approximately 5,000, or one-third, of the proteins cooperate to keep life going.

VIDEO EXTRA

Watch online: Mapping the protein interactions of our distant relative at focushms.com.

The study was published October 28 in the journal *Cell*.

"My group has been working for decades, trying to unravel the precise connections among the proteins and gain insight into how the cell functions as a whole," said Spyros Artavanis-Tsakonas, HMS professor of cell biology and senior author on the paper. "For me, and hopefully researchers studying protein interactions, this map is a

See Protein Interaction Map, page 6

Bacterial Genes Tell the Tale of an Outbreak's Evolution

Deep sequencing of rare infection yields fresh insights into human defenses

Researchers at HMS and Children's Hospital Boston have retraced the evolution of an unusual bacterial infection as it spread among cystic fibrosis patients by sequencing scores of samples collected during the outbreak, since contained. A significant achievement in genetic pathology, the work also suggests a new way to recognize adaptive mutations—to see evolution as it happens—and sheds new light on how our bodies resist infection.

The results were published online Nov. 13 in *Nature Genetics*.

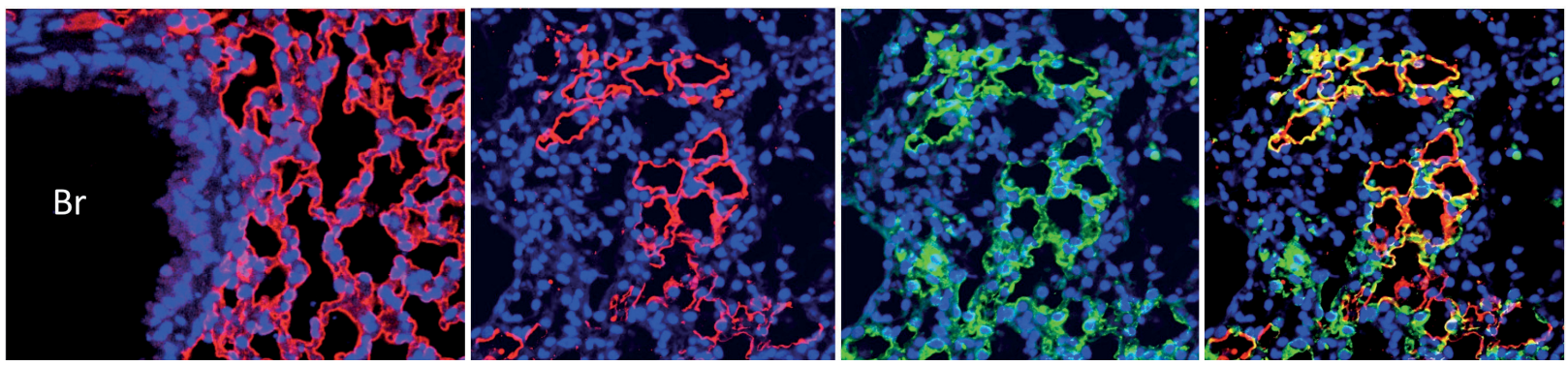
Cystic fibrosis (CF) is a hereditary disease that renders the lungs susceptible to bacterial infection. Though there is no cure for CF, it is managed with antibiotics and therapies that remove mucous from the lungs. An infection that resists antibiotics can overwhelm the body's defenses and lead eventually to respiratory failure and death, but advances in

See Bacterial Genes, page 6

INSIDE

Lung Stem Cells Offer Therapeutic Clues

Understanding mechanics of lung repair suggests new cell-based strategies for enhancing tissue regeneration



POOJA KUMAR

Healthy lung tissue (left) and at three time points during regeneration following severe damage due to infection.

Guided by insights into how mice recover after H1N1 flu, researchers at Harvard Medical School and Brigham and Women's Hospital, together with researchers at A*STAR of Singapore, have cloned three distinct stem cells from human airways and demonstrated that one of these cells can form into the lung's alveoli air sac tissue. What's more, the researchers showed that these same lung stem cells are rapidly deployed in a dynamic process of lung regeneration to combat damage from infection or chronic disease

"These findings suggest new cell- and factor-based strategies for enhancing lung regeneration following acute damage from infection, and even in chronic conditions such as pulmonary fibrosis," said Frank McKeon, HMS professor of cell biology. Other senior authors on the paper include Wa Xian of the Institute of Medical Biology in Singapore and Brigham and Women's, and Christopher Crum, director of Women's and Perinatal Pathology at Brigham and Women's Hospital. The researchers worked as part of an international consortium involving scientists from Singapore and France.

The findings were reported in the Oct. 28 issue of *Cell*.

For many years, clinicians have observed that patients who survive acute respiratory distress syndrome (ARDS), a form of airway damage involving wholesale destruction of large regions of lung tissue, often recover considerable pulmonary function within six to 12 months. But researchers did not know whether that recovery was due to lung regeneration or to some other kind of adaptive remodeling.

> **"We have found that the lungs do in fact have a robust potential for regeneration, and we've identified the specific stem cell responsible."**
>
> —Frank McKeon, HMS professor of cell biology

"This study helps clear up the uncertainty," said McKeon. "We have found that the lungs do in fact have a robust potential for regeneration, and we've identified the specific stem cells responsible."

To probe the potential for lung regeneration, Xian, McKeon and colleagues infected mice with a sublethal dosage of a virulent strain of H1N1 influenza A virus. After two weeks of infection, these mice showed a loss of nearly 60 percent of tissue in the lung air sacs, but—remarkably—by three months, the lungs appeared completely normal by all histological criteria.

These findings demonstrated true lung regeneration but raised the question of the nature of the stem cells underlying this regenerative process.

Adapting the methods for cloning epidermal skin stem cells pioneered by Howard Green, the George Higginson Professor of Cell Biology at HMS and the 2010 Warren Alpert Foundation Prize recipient, the researchers cloned stem cells from the lung airway in a dish and watched as they differentiated to unusual structures with gene profiles similar to alveoli, the cells in the lung's air sacs.

"This was startling to us," Xian said, "and even more so as we observed the same stem cell populations involved in alveoli formation during the peak of H1N1 infections in mice." The researchers genetically traced the formation of new alveoli to a discrete population of stem cells in the fine endings of the conducting airways that rapidly divide in response to infection and migrate to sites of lung damage.

The scientists were intrigued when molecular dissection of these incipient alveoli revealed the presence of an array of signaling molecules known to control cell behavior, suggesting the possibility that these molecules coordinate the regeneration process itself.

Currently the team is testing the possibility that the secreted factors they observed might promote regeneration, suggesting a therapeutic approach for conditions such as chronic obstructive pulmonary disease and even asthma. They also foresee the possibility that these distal airway stem cells could contribute to repairing lungs scarred by irreversible fibrosis, a condition resistant to present therapies.

—David Cameron

To learn more, students may contact Frank McKeon at Frank_McKeon@hms.harvard.edu.

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A Publication of Harvard Medical School Communications and External Relations

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Conflict disclosures and funding sources appear online.

Recent books written or edited by members of the HMS, HSPH and HSDM faculty, staff or students may be submitted to *Focus* at the address above. Books received by Dec. 2, 2011, 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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Junying Yuan

JOHN SOARES

Long Search for Prized Cancer Target Bears Fruit

Disabling autophagosomes, the cell's sanitation crew, may yield new approach to cancer therapy

Researchers have discovered a small molecule that disables a prized cancer target, one that many pharmaceutical and biotech companies have been investigating for years.

The findings, which also establish a chain linking the target to the tumor-suppressing gene p53, suggest a long-sought weapon against the defenses of cancer cells.

The results were published Sept. 29 in the journal *Cell*.

The cancer target is a complex that regulates the formation of autophagosomes in the cell's cytoplasm. Autophagosomes are lipid vesicles that function to dispose of old proteins and expired organelles. Like the B-movie monster "The Blob," they wrap themselves around cellular garbage and degrade the material with hydrolytic enzymes.

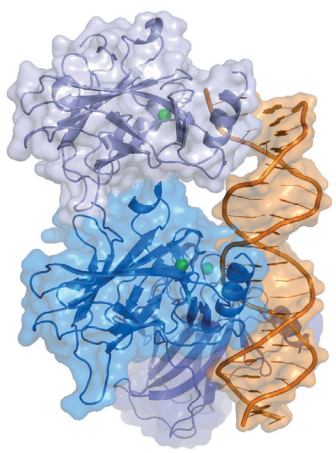
The process, called autophagy, rids cells of debris and is crucial for cell survival.

RECYCLING PROCESS

"Autophagy helps cells survive stress," said Junying Yuan, Harvard Medical School professor of cell biology and senior author on the paper. "It's like a recycling process that degrades old proteins into amino acid energy sources enabling cells to survive in difficult circumstances. It's a turnover mechanism."

When autophagy falters, life span shortens, and cancer and other diseases, such as neurodegeneration, can ensue. One such defect, in a gene called Beclin1, decreases autophagy in mammalian cells, and researchers have suspected that this leads to an increase in prostate and breast cancers.

But like so many cancer factors, autophagy can be a double-edged sword.



Researchers have uncovered a small molecule that interferes with the protein p53 (shown binding to DNA), which is one of the most widely studied cancer suppressors.

When a patient is undergoing treatment such as chemotherapy, cancer cells co-opt autophagy and use it to survive the stress of therapy. Researchers have reasoned that in certain clinical settings, briefly disabling autophagy may support and enhance treatment.

For years, pharmaceutical companies have sought to do just that. The challenge lay in identifying the precise target within a protein complex. Yuan and her colleagues developed a cell-based screening platform in which they uncovered a key mechanism of autophagy as well as a small molecule that efficiently blocks the process by degrading the protein complex on which autophagy depends. The protein beclin1, encoded by the Beclin1 gene already linked to autophagy, is a part of this complex.

They named the molecule spautin-1, for specific and potent autophagy inhibitor-1.

FOLLOW THE CHAIN

Drilling deeper, the researchers found that spautin-1 blocked the activity of USP10, a molecule that offers a kind of stay of execution for proteins on death row. Proteins marked for disposal are tagged with a marker called ubiquitin, and USP10 often removes this tag from select proteins, sparing them. Removing USP10 leaves these proteins vulnerable.

Beclin1, it turns out, regulates the activity of USP10. And the researchers connected these findings to other studies linking USP10 to p53, a gene widely known to suppress cancer.

"Knocking down Beclin1, which our small molecule does, knocks down USP10, which in turn knocks down p53," said Yuan. "They are all part of a chain."

That finding explains the earlier observation that mammals with defective Beclin1 experience increased cancer. When beclin1 is diminished, p53, which is downstream, is also diminished, and cancer thrives. However, when Beclin1 is removed altogether, the cell dies. This discovery suggests that selectively targeting autophagy during cancer therapies may greatly benefit patients.

Yuan is now collaborating with researchers at the company Roche, based in Basel, Switzerland, and at BioBay, based in Suzhou, China, to translate these findings into potential therapies.

—David Cameron

To learn more, students may contact Junying Yuan at junying_yuan@hms.harvard.edu.

ILLUSTRATION: THOMAS SPLETTSTOESSER/WIKIMEDIA COMMONS

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**.

LOW-DENSITY LIPOPROTEINS CONTAINING APOLIPOPROTEIN C-III AND THE RISK OF CORONARY HEART DISEASE

Mendivil CO, Rimm EB, Furtado J, Chiuve SE, Sacks FM. Department of Nutrition, Harvard School of Public Health.

Low-density lipoprotein (LDL) that contains apolipoprotein (apo) C-III makes up only 10% to 20% of plasma LDL but has a markedly altered metabolism and proatherogenic effects on vascular cells. The authors examined the association between plasma LDL with apoC-III and coronary heart disease in 320 women and 419 men initially free of cardiovascular disease who developed a fatal or nonfatal myocardial infarction during 10 to 14 years of follow-up and matched controls who remained free of coronary heart disease; they conclude that the risk of coronary heart disease contributed by LDL appeared to result to a large extent from LDL that contains apoC-III. *Circulation.* 2011 Nov. 8;124(19):2065-72.

THE THREE-DIMENSIONAL ARCHITECTURE OF A BACTERIAL GENOME AND ITS ALTERATION BY GENETIC PERTURBATION

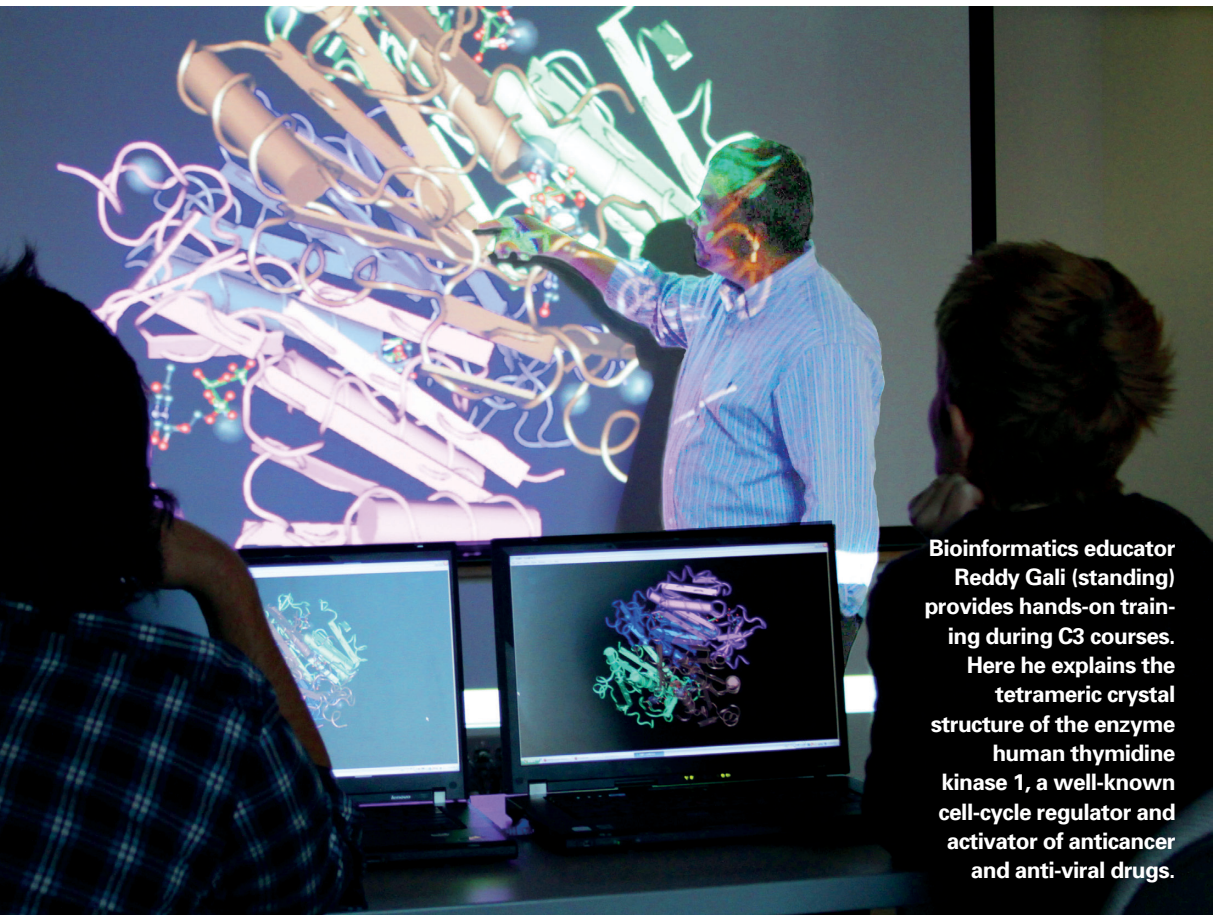
Umbarger MA, Toro E, Wright MA, Porreca GJ, Baù D, Hong SH, Fero MJ, Zhu LJ, Marti-Renom MA, McAdams HH, Shapiro L, Dekker J, Church GM. Department of Genetics, Harvard Medical School.

The authors have determined the three-dimensional (3D) architecture of the Caulobacter crescentus genome by combining genome-wide chromatin interaction detection, live-cell imaging, and computational modeling. Using chromosome conformation capture carbon copy (5C), the authors derive 13 kb resolution 3D models of the Caulobacter genome. The resulting models illustrate that the genome is ellipsoidal with periodically arranged arms. The parS sites, a pair of short contiguous sequence elements known to be involved in chromosome segregation, are positioned at one pole, where they anchor the chromosome to the cell and contribute to the formation of a compact chromatin conformation. Collectively, the data suggest that genome folding is globally dictated by the parS sites and chromosome segregation. *Molecular Cell.* 2011 Oct. 21;44(2):252-64.

INHIBITION OF PYRUVATE KINASE M2 BY REACTIVE OXYGEN SPECIES CONTRIBUTES TO ANTIOXIDANT RESPONSES

Anastasiou D, Poulogiannis G, Asara JM, Boxer MB, Jiang JK, Shen M, Bellinger G, Sasaki AT, Locasale JW, Auld DS, Thomas CJ, Vander Heiden MG, Cantley LC. Beth Israel Deaconess Medical Center.

Control of intracellular reactive oxygen species (ROS) concentrations is critical for cancer cell survival. The authors show that, in human lung cancer cells, acute increases in intracellular concentrations of ROS caused inhibition of the glycolytic enzyme pyruvate kinase M2 (PKM2) through oxidation of Cys(358). Besides promoting metabolic changes required for proliferation, the regulatory properties of PKM2 may confer an additional advantage to cancer cells by allowing them to withstand oxidative stress. *Science.* 2011 Nov. 3.



KERRY FOLEY

Bioinformatics educator Reddy Gali (standing) provides hands-on training during C3 courses. Here he explains the tetrameric crystal structure of the enzyme human thymidine kinase 1, a well-known cell-cycle regulator and activator of anticancer and anti-viral drugs.

Panning for Gold in Research Data

Collaborative offers free bioinformatics training, research support

Hidden knowledge lurks in the massive data sets generated by high-throughput technologies like the microarray, which can measure the expression of tens of thousands of genes simultaneously. A bioinformatics services program at Countway Library of Medicine, in collaboration with Harvard Catalyst, the Harvard Clinical and Translational Science Center, trains researchers and students to use powerful software, algorithms and databases. These tools can find nuggets of gold in rivers of research data—a mutated protein sequence that raises the risk of colon cancer, for example, or a new target for an existing drug.

Bioinformatics is the application of computer science and information technology to the generation of knowledge about medicine and the life sciences. Common activities include comparing gene expression under different conditions, such as before and after the application of a drug; mapping, aligning and analyzing DNA and protein sequences; or mining the genomes of a patient population, thousands of medical records or the global research literature for fresh insights.

Although bioinformatics was primarily used in genetics in the past, "Bioinformatics has become a core tool for every field of biology, including clinical research," says David Osterbur, public and access services librarian and head of the bioinformatics services team based at Countway. The group is known as C3 Bioinformatics (C3 stands for Countway, the Center for Biomedical Informatics, and Harvard Catalyst). The C3 collaboration is a dream team of bioinformatics experts in genetics, molecular and cellular biology, clinical medicine, software engineering and library science.

WORKSHOPS AND CONSULTS

In the true spirit of a library, Osterbur's team offers nearly 30 different training workshops, as well as private consultations, all free of charge. Classes include "BLAST Tips and Tricks," "Illumina Microarray Data Analysis Using R/Bioconductor" and "Next Generation Sequencing Analysis Using JMP Genomics."

"What may have taken a researcher a week to do, with frustrating results, we can usually help them do in a couple of hours."

— Reddy Gali, Harvard Catalyst bioinformatics educator

In the five years since Osterbur founded this program, thousands of Harvard researchers and students have taken hands-on courses and found them indispensable. Reddy Gali, a Harvard Catalyst bioinformatics educator, does much of the teaching and often works one-on-one with researchers.

After consulting with Gali on how to do microarray and "nano string" data analyses, Oleg Butovsky, a research fellow in neurology at Brigham and Women's Hospital, discovered therapeutic targets in the peripheral immune system that he said can potentially slow development of amyotrophic lateral sclerosis, or ALS. For his critical assistance, Gali will be acknowledged as a co-author of a paper on Butovsky's findings.

Amanda Nottke, an HMS postdoctoral student in pathology, consulted with Osterbur on how to perform a search in a sequence alignment algorithm called ClustalW. She had tried using other tools on her own with no luck, but after meeting with Osterbur for an hour, she left with a solution.

"What may have taken a researcher a week to do, with frustrating results, we can usually help them do in a couple of hours," Gali said.

HIGHLY RESPONSIVE

C3 Bioinformatics is a critical resource that increases researchers' efficiency, points out Douglas MacFadden, director of informatics technology for the Center for Biomedical Informatics, the research arm of the library's bioinformatics enterprise. Making up the team are he, Gali, Osterbur and Paul Bain—a reference and education librarian whose expertise includes data-access tools for eukaryotic and other species, including the Ensemble browser, the University of California Santa Cruz genome browser, and BioMart.

"We can be highly responsive to the changing needs of Harvard's community and in a matter of months develop a new course to teach precisely what our researchers need," said MacFadden. For example, after people started clamoring to learn next-generation sequencing, the C3 team designed a course and offered it for the first time on October 27, 2011.

Most researchers don't have the time to sit down and teach themselves how to use these complex tools. They can hire a consultant to perform data analyses, or they can turn to C3 Bioinformatics and learn how to do it.

Bioinformatics tools are constantly changing, becoming ever more powerful. Microarray was new in the late 1990s, says Osterbur. Today, it is about to be eclipsed by next generation sequencing technology.

Starting with this year's incoming class, as part of the new Scholars in Medicine Program, all medical students are required to conduct a research project. The bioinformatics staff and reference librarians will introduce them to the Countway's rich resources and explain how to manage their research.

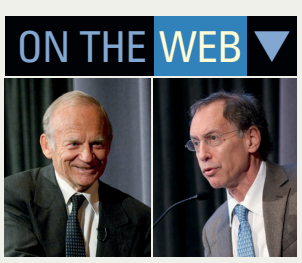
"Medical students typically learn about nucleic acids and sequence alignment, and why those analyses are done," said Osterbur, "but no class teaches them how to actually do these things."

That's where C3 comes in. "This is stuff you can only learn hands-on, at the computer," Osterbur said. "That's where it comes alive." Best of all, participants leave class knowing what to do next with all that raw data.

—Ellen Barlow

Learn more at the C3 Bioinformatics website at hms.harvard.libguides.com/c3bioinformatics.

SUZANNE CAMARATA



The winners of the 2011 Alpert Prize, Alain Carpentier (left) and Robert Langer, led a symposium on the foundations and frontiers of bioengineering at the 11th annual Warren Alpert Foundation Prize Symposium. Bioengineering luminaries from Boston and beyond discussed everything from lab-grown transplantable livers to self-folding DNA origami. Read the full story, "Foundations and Frontiers of Bioengineering," online at **focushms.com.**

Federalism and Health Care

Can states share responsibility for national reform?

RICK REINHARD

Weil

When a contentious 111th Congress passed the Patient Protection and Affordable Care Act (PPACA) in March of 2010, the final legislation included strong language that spelled out a leading role for states in creating a variety of experimental models for health reform.

In theory, a diverse mix of state policies would serve as a kind of laboratory of democracy, testing different approaches to regulating and providing health care and allowing states to tailor their policies to their citizens' values and local circumstances.

But according to Alan Reed Weil, executive director of the National Academy for State Health Policy, in reality, the fiscal, legal, political and power structures of federalism as we know it severely limit the possibilities of any real diversity of policy among the states. Weil presented his views at the 11th annual Marshall J. Seidman Lecture in Health Policy, sponsored by the HMS Department of Health Care Policy.

Weil's argument drew on analyses of other national reform efforts from the recent past, including welfare reform and both the No Child Left Behind and the Race to the Top educational reform initiatives. He also shared insights on how the congressional statute of the PPACA was transformed into regulations and discussed research on how states are implementing those regulations.

For example, despite Congress's clear mandate that states be given leeway in developing their own policies as they implement the PPACA, the legal regulatory framework that dictates their relationship with the national government gives the last word in defining policy to the federal administrative agency. As a result, a few pages of suggestive, evocative statute become hundreds of pages of proscriptive regulations. If states interpret the legislation differently than, say, the Department of Health and Human Services, HHS automatically wins.

This isn't a function of health policy; it's just the way our federation has evolved, Weil said. Since there are very few constitutional restraints on the power of the federal government, the only real restraints are political. There is no legal framework for mandating state autonomy in implementing national legislation like the PPACA. Weil, who was an appointed member of President Clinton's Advisory Commission on Consumer Protection and Quality in the Health Care Industry, pointed out that this is not a left or right-wing issue: many conservative proposals, like national tort reform, would also result in rising concentrations of authority with the national government.

It also doesn't help the chances for diverse state experimentation that most of the states are struggling financially and can only afford to do what the federal government provides resources to do.

Weil provocatively titled his talk "Can American Federalism Survive Health Reform."

His answer?

"The federation will survive," Weil said, "but it may demonstrate itself too weak to tackle the problems we face as a country."

To view the talk online, visit the Health Care Policy website: www.hcp.med.harvard.edu.

—Jake Miller

Professor Ito Captures Congressional Gold Medal

Susumu Ito, the James Stillman Professor of Comparative Anatomy *Emeritus* at HMS, was honored with the Congressional Gold Medal in November for exemplary service during World War II. Ito, a forward observer for his artillery unit, was part of a now legendary 1944 mission to rescue the Lost Battalion of the 36th Division, surrounded by German forces in the Vosges Mountains.

The Congressional Gold Medal is one of the highest of all civilian honors, presented for outstanding service to the nation. At a ceremony at the U.S. Capitol, Ito and thousands of Japanese American soldiers of the 100th Infantry Battalion, the 442nd Regimental Combat Team and the Military Intelligence Service were honored, with Ito and two others chosen to represent these three units.

Ito, the child of California sharecroppers—who were interned by the U.S. government with other Japanese Americans during the war—is an expert on acid secretion by gastric parietal cells and the rapid repair of the gastric mucosa after its destruction. Ito joined HMS in 1960 as an associate in anatomy. Promoted to professor in 1969, he received his named professorship in 1982 and retired in 1990. Now 92, Ito still enjoys using the electron microscope to read lab tissue samples.

"For my fellow Nisei veterans and me, to serve in the military was an honor and opportunity to demonstrate our patriotism," Ito said. "We who are still able to be here accept the Congressional Gold Medal with pride and humility."

—Katie DuBoff

BRENDAN HOFFMAN/GETTY

VIDEO EXTRA

For a video of Ito on CNN, visit goo.gl/hXjTr

Bioengineering for Hearing, Sight and Mobility

Bertarelli Symposium highlights new collaborations for tackling neurological disorders

As breakthroughs in basic biomedical science make their way from researchers' labs to patients' bedsides, the skills of engineers play an increasingly crucial role.

Engineers might help an otologic surgeon develop new diagnostic tools for imaging the bone-encased inner works of the ear, for example, or develop massively parallel testing structures that allow stem-cell researchers to identify chemical and microenvironmental factors that can reactivate a sensory neuron's ability to replace itself. They might also develop new tools for drug delivery and brain-machine interfaces to restore hearing, sight or motor function in patients with neurological disorders.

These and other research projects were presented at the inaugural Bertarelli Neuroengineering Symposium at HMS on Oct. 28 and 29. Researchers from HMS and École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland, along with keynote speaker John Donoghue, a professor of neuroscience from Brown University, spoke about their work, including collaborations now underway between HMS and EPFL, to tackle these and other challenges.

STEVE GILBERT

HMS Neurobiologist Lisa Goodrich discusses the challenges of regenerating auditory hair cells.

This first scientific symposium is a key element of the Bertarelli Program's educational goals. Launched in October of 2010, the program is a joint effort between HMS and EPFL, one of the premier European schools of engineering and science. The program aims to accelerate the pace of translating developments in the basic biomedical sciences, including genetics, biophysics and neurology, into improved health and quality of life for people with neurological disorders.

"In addition to our colleagues at the Harvard School of Engineering and Applied Sciences and at our affiliated hospitals," said Dean of the Faculty of Medicine Jeffrey S. Flier in his welcoming remarks, "we at Harvard Medical School are fortunate to have collaborations like this, which allow us to take advantage of the unique skills of our colleagues around the world."

Earlier in the week the Bertarelli Program in Translational Neuroscience and Neuroengineering announced the recipients of the Program's inaugural round of research grants. Six projects were funded for a total of $3.6 million. Five of the projects focus on hearing loss; the sixth grant will explore the use of a combination of gene therapy, pharmaceutical and engineering tactics to restore the ability to walk in patients with spinal cord injuries. (For more information about these projects, visit focushms.com.)

Funding for the symposium was provided by the Bertarelli Foundation.

—Jake Miller

For more information, visit the Bertarelli Program website at ***www.hms.harvard.edu/bertarelli.***

Protein Interaction Map

Continued from page 1

dream come true."

While genes are a cell's data repository, containing all the instructions necessary for life, proteins are its labor force, talking to each other constantly and channeling vital information through vast and complicated networks to keep life stable and healthy. Humans and fruit flies are descended from a common ancestor, and in most cases, both species still rely on the same ancient cellular machinery for survival. In that respect, the fruit fly's map serves as a sort of blueprint, a useful guide into the cellular activity of many higher organisms.

Understanding how proteins behave normally is often the key to their disease-causing behavior.

INTRA-CELLULAR CONVERSATIONS

For this study, Artavanis-Tsakonas and his colleagues provide the first large-scale map of this population of proteins. Their map, which is not yet fully complete, reveals many of the relationships these myriad proteins make with each other as they collaborate, something which, to date, has been to a large degree an enduring mystery among biologists.

"We already know what approximately one-third of these proteins do," Artavanis-Tsakonas said. "For another third of them we can sort of guess. But there's another third that we know nothing about. And now through this kind of analysis we can begin to explore the functions of these proteins. This is giving us extraordinary insight into how the cell works."

One significant use for such a map is to assess how a cell responds to changes in metabolic conditions, such as interactions with drugs or in conditions where genetic alterations occur. Finding such answers might lead to future drug treatments for disease, and perhaps to a deeper understanding of what occurs in conditions such as cancer.

"This is of extraordinary translational value," Artavanis-Tsakonas said. "In order to know how the proteins work you must know who they talk to. And then you can examine whether a disease somehow alters this conversation."

A pivotal part of this research involved a scientific technique called mass spectrometry, which is relatively new to the science of biology. The ultra-precise mass spectrometry experiments were done by HMS professor of cell biology Steven Gygi. Mass spectrometry is used to measure the exact weight (the mass) and thus identify each individual protein in a sample. It is a technique originally devised by physicists for analyzing atomic particles. But in recent years mass spectrometry was adapted and refined for powerful new uses in basic biological research.

Other studies using similar techniques to date have focused on small groups of related proteins or single-celled model organisms such as bacteria and yeast.

Despite the huge amount already known about the fruit fly and its genetic endowment, much about the function of thousands of proteins remains a mystery. This map, however, now gives researchers precise clues about their function. Filling in the detailed protein map may help scientists gain important insights into the process of development, that is, how a creature is put together, maintained and operated.

"Our analyses also sheds light on how proteins and protein networks have evolved in different animals," said K. G. Guruharsha, a postdoctoral fellow in Artavanis-Tsakonas's lab and a first author on the paper.

Co-lead authors on the paper included Jean-Francois Rual, also a postdoctoral fellow in Artavanis-Tsakonas's lab, and Julian Mintseris and Bo Zhai, both research fellows in Gygi's lab.

Also important in this effort was the work of K. VijayRaghavan, at the National Centre for Biological Sciences in Bangalore, India. Similarly, crucial contributions to this work also came from the University of California, in Berkeley, where Susan E. Celniker collaborated through her studies in the Berkeley Drosophila Genome Project.

—Robert Cooke

To learn more, students may contact Spyros Artavanis-Tsakonas at artavanis@hms.harvard.edu.

Bacterial Genes

Continued from page 1

care have increased the median life expectancy for Americans born with CF from six months in 1959 to nearly 40 years today.

Despite constant vigilance, outbreaks pose a particular risk at CF treatment centers, where otherwise rare strains of bacteria can spread between patients. In the 1990s, one such outbreak spread among CF patients followed at a single CF center in Boston. Thirty-nine people were infected with the strain, later identified as a new species of bacteria, *Burkholderia dolosa.*

The hospital implemented new infection control measures and has not seen a new case in more than six years. But the outbreak presented researchers with a rare opportunity: a new pathogen with a closed circle of infection and abundant samples collected over the span of a decade.

THE MICROBE HUNTERS

Roy Kishony was looking for just such a bug. The HMS professor of systems biology studies bacterial evolution, exploring such questions as how antibiotic resistance arises. Many of his experiments are conducted in the lab: Grow bacteria in a test tube, add just enough antibiotic to challenge it, and look for genetic changes over time. But people aren't test tubes, and Kishony wanted to investigate how a pathogen evolves in a natural context.

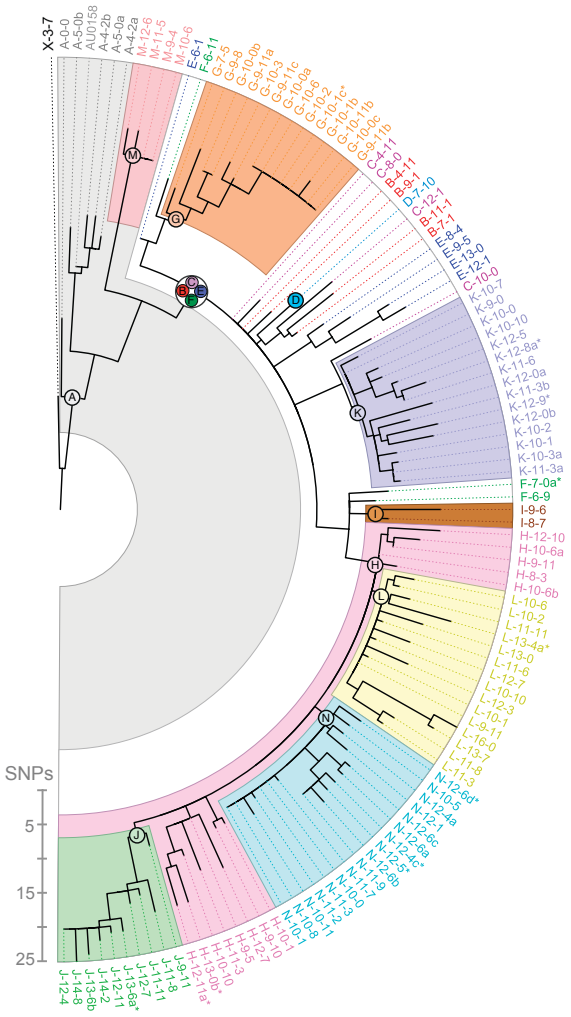
"Imagine if you could interrogate the bacteria," said Kishony, principal investigator on the study. "You would ask, 'What do you find most challenging in the human body?'"

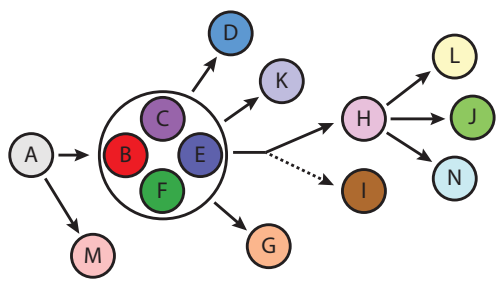
In search of a good model system, Kishony and his graduate student Jean-Baptiste Michel consulted clinicians and found their way to Alex McAdam, an associate professor of pathology at Children's Hospital Boston who suggested *B. dolosa.* "I thought it would be interesting," McAdam said, "because we could also see how the organism changed during the course of an outbreak."

From that conversation grew a robust collaboration among a diverse team of scientists and clinicians, including Kishony's lab, McAdam and Greg Priebe, assistant professor of anesthesia at Children's and a microbiologist at the Channing Laboratory at Brigham and Women's Hospital, as well as collaborators in Michigan and Virginia. The team set out to sequence the genomes of 112 *B. dolosa* isolates taken from 14 of the infected patients, mapping genetic changes over time to reveal both the route of the infection's spread and which genes faced the greatest selective pressure — in other words, how the bacteria evolved when challenged by human defenses and medical treatment.

Every time a cell divides, small copying errors can introduce slight changes in the new DNA. Some of those changes affect the cell's machinery, and some do not. To identify selective pressure on genes over generations, scientists compare the number of significant changes to the number of those that had no effect—a measure called the dN/dS ratio.

"That's where we ran into a bit of a snag," said Michel, now a postdoctoral fellow at Harvard





Phylogeny of a bacterial outbreak

Deep sequencing of *B. dolosa* suggested the most likely phylogenetic tree (left) of 112 isolates taken from 14 patients. Each isolate is represented by a thin dashed line, and labels denote patient and time. For example, C-14-5 was recovered from patient C, fourteen years and five months after the first isolate. The researchers extrapolated a likely network of infection (above) by inferring the last common ancestors of strains from each patient. Dashed arrows indicate less certainty.

TAMI LIEBERMAN ET AL

University and visiting faculty at Google, who analyzed the data with Tami Lieberman when both were graduate students in systems biology. When Michel and Lieberman, who share credit as first authors on the *Nature Genetics* paper, crunched the numbers on their *B. dolosa* samples, the dN/dS ratio was 1.0. Across the genomes of their entire sample set, the changes appeared perfectly random.

"It wasn't a small effect," Lieberman said. "It was no effect." But the finding defied previous observations and common sense—bacteria face pressure from antibiotics, pressure from the immune system, pressure from one another. Even in test tubes, bacteria evolve.

ANOTHER TACK

Maybe, Lieberman suggested, they were asking the wrong question. What if the genome-wide dN/dS ratio was a red herring, when what they really wanted to know was what was happening to specific genes? "Tami had the key insight," said Kishony. If a mutation has any effect, it's typically harmful. Randomly tune your car, and you're apt to get a broken car. In a gene pool, purifying selection weeds out those harmful changes even as positive selection spreads helpful ones. Average those positive and negative effects, and both might disappear.

Sure enough, when Lieberman and Michel analyzed the same data another way—separating genes that had mutated in multiple patients from those that had mutated just once—most genes registered a dN/dS of slightly less than one, evidence of widespread purifying selection. Seventeen genes scored much higher, strong evidence of positive selection. Tellingly, bacteria from different patients showed pressure on the same genes, which evolved in similar ways.

"These data told us what the pathogen experiences as its main challenges," Kishony said. Some of those challenges were expected: Genes linked to antibiotic resistance, cell adhesion and immune response faced pressure to adapt.

One of the most striking findings among such genes was a stop codon, seen in about 70 percent of the strains, in a previously unstudied enzyme linked to genes involved in the synthesis of lipopolysaccharide (LPS), also known as endotoxin. The Priebe lab and collaborators had previously observed an unusual degree of LPS variation among *B. dolosa* strains and now had a genetic mechanism to explain it. "That finding was a real 'aha' moment for me," said Priebe, who suggested that the enzyme could be disappearing as the bacteria adapted to evade the immune system, adhere to its host or improve a function still undiscovered.

But other challenges were a surprise, for example propelling furious changes in genes linked to growth under low-oxygen conditions typical of the lung of a CF patient. "This method suggests therapeutic directions we didn't know were important," Michel said, "and drug targets we didn't know existed."

The team's findings could help researchers better understand a pathogen's strengths and weaknesses, the mechanisms by which it adapts to our defenses, and potential targets for new therapies. The researchers next hope to study the diversity generated by a pathogen's evolution within a single patient, to learn more about the different challenges posed throughout the human body.

The questions are still evolving.

—R. Alan Leo

To learn more, students may contact Roy Kishony at Roy_Kishony@hms.harvard.edu.

JONATHAN KIM/GETTY

Two Liters Negative

Restricting intern hours has reshaped medical education, but is it a change for the better?

Chopra

Something peculiar happened during my first inpatient oncology rotation as a senior resident. At exactly 6 p.m., the on-call intern stopped admitting patients. She stopped receiving pages about new patients in the emergency department, patients being moved out of the medical intensive care unit and patients being transferred to our team from outside hospitals. A short while later, after she "signed out" her patients to a peer, she stopped receiving pages altogether. Instead, she went home and had dinner.

In July 2011, medical internship changed in a profound way. Driven in part by the 2008 Institute of Medicine report *Resident Duty Hours: Enhancing Sleep, Supervision, and Safety,* the Accreditation Council for Graduate Medical Education (ACGME) implemented new duty-hour regulations for residency programs across the country. Under the new rules, interns are no longer able to stay at the hospital for more than 16 hours at a stretch, thereby eliminating the lengthy overnight call shifts that many physicians had considered the *sine qua non* of medical internship. The regulations are an extension of sweeping changes introduced in 2003, when the ACGME enacted duty-hour standards limiting overnight call shifts to 30 continuous hours and the resident work week to 80 total hours.

While aspects of the ACGME proposal were well received when first unveiled in July 2010, the specific restrictions on intern shift duration were not as popular. In a nationwide survey of residency program directors, 79 percent of respondents disagreed with the proposed 16-hour limitation for interns. A survey of house officers across medical specialities suggested that residents similarly shared concerns about the new restriction, with many "expressing alarm that education and experience will be severely limited by the lack of traditional 24-hour call periods." Nearly half of responding residents doubted that the changes would have a positive effect on their education.

Why the skepticism? I suspect that anyone who was an intern prior to 2011 could readily answer this question. On a typical day/night at the hospital as the on-call intern, I observed the often unpredictable course of unstable angina and acute leukemia. I was there to see the normal results of the ultrasound I had ordered for my patient with suspected cholecystitis and reconsider my differential diagnosis for her abdominal pain. At the bedside of a patient with congestive heart failure, I assessed whether any of my interventions eased his breathing. Although physically and mentally challenging, the long call shifts were my chance to learn, experiment and struggle—the sort of critical, immersive experience I needed to build my basic competency as a physician.

Unfortunately, the extended call shifts of internship have been replaced by shorter day and night shifts and more frequent sign-outs among interns. Certainly sign-outs are an integral part of medicine for trained physicians—no one can or should stay at the hospital long enough to provide patient care from admission to discharge. However, increased sign-outs are a reminder that something important has been lost. For the on-call intern, does hearing about what happened to a patient overnight have the same educational value as actually being at the bedside? For the night intern, is it possible to glean the deeper meaning behind the list of seemingly mundane checkboxes on the sign-out for a patient he or she has never met? Can medicine really be learned from the completion of tasks such as "diuresis goal: two liters negative" and "follow-up midnight electrolytes"? Beyond the educational compromises, I fear that increased sign-outs could also adversely influence the culture of medicine. Rather than being a necessary evil that allows interns to go home and rest when they are not on call, will the sign-out become an end in and of itself, a daily ritual that symbolizes the endless passing of responsibility for patients back and forth between physicians, none of whom can truly call themselves a patient's doctor?

In place of making on-call interns sign out and go home, perhaps we should let them stay at the hospital but ensure that they have the support they need to effectively take care of their patients over long stretches of time. This is what I found so valuable as an intern physician, and I was reminded this year of its importance when I became the backup as a senior resident. Otherwise, the new ACGME regulations run the risk of unintentionally withholding from interns those invaluable, formative experiences that serve as the foundation for a successful career in clinical medicine.

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

Center for Primary Care

Continued from page 1

tion. Previous events at the Center gathered members of the HMS primary care community and its affiliates to foster collaboration, strengthen education and reinforce local and national efforts in primary care.

"We are in an era where the demands on efficiency will be unprecedented," Harvard University Provost Alan Garber, a health care economist and until recently a practicing physician, told the capacity audience in Harvard Medical School's Joseph B. Martin Conference Center. "The kinds of innovations that will be rewarded are those that make care dramatically more effective and dramatically less costly."

To cultivate such innovations, the Center for Primary Care was founded in 2010 on the recommendation of a working group appointed by Jeffrey S. Flier, dean of the Faculty of Medicine. "Of all that I've had the chance to do in four years, there's nothing I'm more proud of than this Center," Flier told the crowd.

Two keynote speakers addressed the scope of the crisis in primary care and the need for innovative solutions.

CROSS-DISCIPLINARY SOLUTIONS

Arnold Milstein, director of the Stanford Clinical Excellence Research Center, began by quoting billionaire investor Warren Buffet, who has called health care a "tapeworm eating at our economic body."

In the face of that threat, Milstein said, quality primary care offers a bulwark against expensive health crises. "Primary care innovators are best positioned as near-term national rescuers," Milstein said.

To effect that rescue, Milstein said, practitioners must learn from the great innovators across many disciplines. Primary care innovators will succeed only to the extent that they break out of their circles and immerse themselves in varieties of innovation models.

He described himself as a "talent scout" seeking the very best models of primary care, detailing practices that had managed to optimize care and lower costs through team-based care, strong relationships with both patients and their families and caregivers, and creative payment structures including health insurance by the medical practice itself.

"It's not about eureka moments," Milstein said. Innovation comes from "ordinary people like us who take the time to look at great accomplishments done by others."

BUILDING A MEDICAL HOME

Robert Reid, associate medical director for health services research and knowledge translation at Group Health Cooperative in Seattle, delivered the second keynote address.

"Failure of innovation is not in the innovation itself, but in failure to deploy," said Reid, describing how his organization has worked to create a medical home, a comprehensive approach to primary care that fosters partnerships between patients and their providers to coordinate all aspects of care.

Five years ago, Reid's organization began its prototype medical home. By lengthening appointments, assembling teams of physicians, enabling electronic communication between doctor and patient, and rewarding quality of care rather than patient volume, measures of patient care improved—for example, emergency room visits dropped 39 percent—while doctor and staff burnout decreased.

DIVERSE APPROACHES

During breakout sessions, conference attendees explored a host of different innovative approaches to enhancing and redesigning primary care.

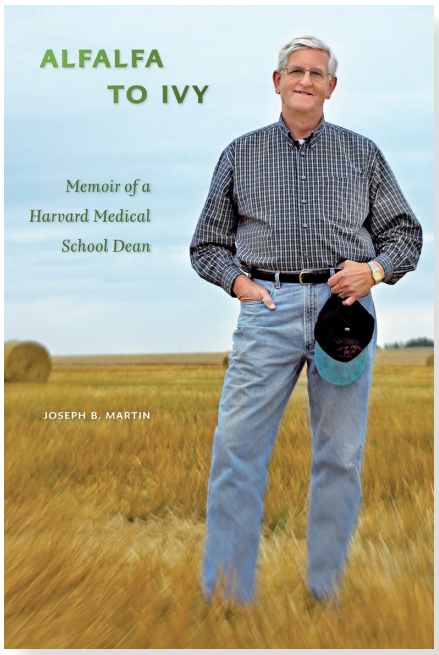
"The talent, energy, and promise from the primary care community was palpable," said Jill Bassett, executive director of the HMS Center for Primary Care. "We were thrilled to have the opportunity to bring together health care professionals from multiple disciplines, professions and over 50 different entities to celebrate the role of primary care and to move the field forward. We look forward to working together to accomplish great things."

Andrew Ellner and Russell Phillips, interim co-directors of the Center, are also primary care physicians at Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, respectively. "This conference was an extraordinary event for our community—a chance to share ideas, vision and optimism," Ellner said. "It provided many vivid examples of the type of innovations and improvements that we hope to help catalyze in our own backyard and far beyond."

Added Phillips, "The conference was a celebration of the importance of primary care, the necessity for innovation, and the capability of our community to help lead that innovation."

—David Cameron

BOOK SHELF



Alfalfa to Ivy
Memoir of a Harvard Medical School Dean

BY JOSEPH B. MARTIN

Joseph B. Martin, who served HMS as dean from 1997 to 2007, chronicles his life's journey from modest beginnings as a Mennonite farm boy to the pinnacle of U.S. academic and medical leadership. Martin—the first in his family to receive a college education—recounts his evolution, starting with his first professorial appointment, at McGill University, to his tenure as dean of medicine and chancellor of the University of California, San Francisco, to the HMS deanship. Martin also explores the creation of the Dana-Farber/Harvard Cancer Center, the redesign of the HMS medical curriculum, the planning and implementation of a new research building, and the creation of one of the country's first department-level programs in systems biology.

Because Martin, the Edward R. and Anne G. Lefler Professor of Neurobiology, witnessed and led many of the events and discoveries central to the transformation of medicine in the past 50 years, he is ideally positioned to offer here an incisive assessment of academic politics and health care in Canada and the United States. *Alfalfa to Ivy* is an important and absorbing read for anyone interested in academic and medical leadership and the history of American medicine and biomedical research.

—Angela Alberti

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Alan Cohen named neurosurgeon-in-chief and chair of Children's Hospital Boston's Department of Neurosurgery ■ **Mary Jane Houlihan** awarded the

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Cancer Liaison Physician Outstanding Performance Award from the American College of Surgeon's Commission on Cancer ■ Kamal Khabbaz elected to the American Association for Thoracic Surgery ◄ **Romesh Nalliah** selected as a member of the American Dental Association's Institute for

LIZA GREEN

Diversity in Leadership ■ **Sharon-Lise Normand** awarded the Long-Term Excellence Award by the Health Policy Statistics Section of the American Statistical Association ■ **Frank Sacks** awarded the 2011 Research Achievement Award of the American Heart Association ◄ **Nancy Tarbell** receives an Award for Excellence from the Society for Executive Leadership in Academic Medicine (SELAM)