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

“Lung stem cells and healing Autophagy yields cancer target”

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.

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top stories

Lung stem cells and healing
Autophagy yields cancer target

Paper Chase
Community

Learning bioinformatics
Seidman Lecture
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Bertarelli Symposium
Martin’s memoir
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The hours
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Grants
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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 innovation.

See Center for Primary Care, page 8

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

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

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

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.

“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 cell responsible.”

—Frank McKeon, HMS professor of cell biology

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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 lungs 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.

Healthy lung tissue (left) and at three time points during regeneration following severe damage due to infection.
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 finding, which also establishes 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 allowing 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 fac-

forsing 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, specific and potent autophagy inhibitor-1.

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

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 Bedin1 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.

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

Researchers have uncovered a small molecule that interferes with the protein p63 (shown binding to DNA), which is one of the most widely studied cancer suppressors.

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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 IMP Genomics.”

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.

“高高在上的金矿

在研究数据中寻找宝藏

Collaborative offers free bioinformatics training, research support

“Researcher, this may be a week’s work for you, but we can help you do it quickly and efficiently.”

—Reddy Gali, Harvard Catalyst bioinformatics educator

The winners of the 2011 Alpert Prize, Alain Carpenter (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.
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.

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 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 prescriptive 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.

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. He joined HMS in 1960 as an associate in anatomy. Promoted to professor in 1968, he received his named professorship in 1982 and retired in 1988. 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.”

—Jake Miller

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.

“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 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 focus HMS.com.)

Funding for the symposium was provided by the Bertarelli Foundation.

For more information, visit the Bertarelli Program website at www.hms.harvard.edu/bertarelli.
Focus FINAL.indd   6
Continued from page 1

Protein Interaction Map

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-author papers on the paper included Jean-Francois Raal, also a postdoctoral fellow in Artavanis-Tsakonas’s lab, and Julian Mintseris and Bo Zhao, 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, 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

Care has 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.

“I 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 anesthesia 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 Freibe, 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 thick dots 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. Matched arrows indicate less certainty.

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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 thick dots 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. Matched arrows indicate less certainty.

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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 random. 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 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. “Tami had the key insight,” said Kishony. If a mutation has any effect, it’s typically random. 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.

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tion. Previous events at the Center gathered members of the HUM 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 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 HUM 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 lead that innovation.”

—David Cameron

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Romesh Nalliah selected as a member of the American Dental Association’s Institute for Diversity in Leadership

Tarbell

Diversity in Leadership

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 Academe Medical Research (SEALM)