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News from Harvard Medical, Dental and Public Health Schools

October 2011

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VEGETABLES

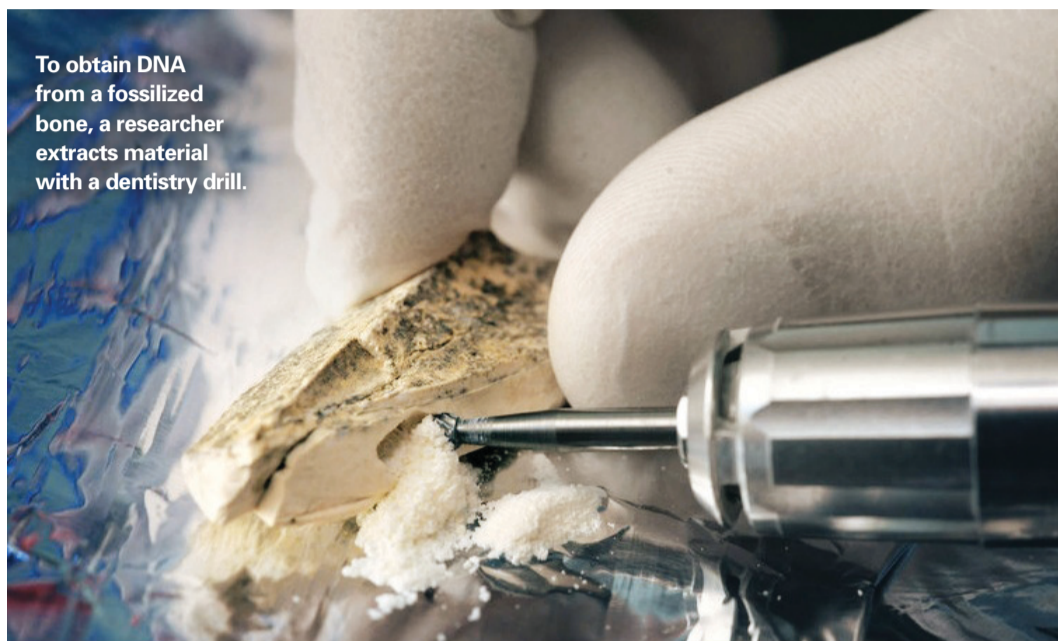
WHOLE GRAINS

HEALTHY PLATE: Harvard researchers unveil an alternative nutrition guide. Page 3

FRUITS

HEALTHY PROTEIN

BENCE VIOLA, JOHANNES KRAUSE AND FRANK VINKEN, MAX PLANCK INSTITUTE



To obtain DNA from a fossilized bone, a researcher extracts material with a dentistry drill.

DNA Reveals Asia's Waves of Migration

Shedding light on human history, lab finds Denisovans ranged from Siberia to Southeast Asia

Drawing DNA from a lone finger bone found in a cave in Siberia, an international team of researchers studying genetic patterns from modern and archaic humans has uncovered new clues about the movement and intermixing of populations more than 40,000 years ago in Asia.

Using state-of-the-art methods of genome analysis, scientists from Harvard Medical School and the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, have found that Denisovans—a recently identified group of archaic humans whose DNA was extracted last year from a pinky bone excavated in Siberia—contributed DNA not just to present-day New Guineans, but also to aboriginal Australian and Philippine populations.

The study demonstrates that, contrary to the findings of the largest previous genetic studies,

modern humans settled Asia in more than one migration. According to HMS Professor of Genetics David Reich, “Denisova DNA is like a medical imaging dye that traces a person’s blood vessels. It is so recognizable that you can detect even a little bit of it in one individual. In a similar way, we were able to trace Denisova DNA in the migrations of people. This shows the power of sequencing ancient DNA as a tool for understanding human history.”

The patterns the researchers found points to at least two waves of human migration: the first giving rise to the aboriginal populations that currently live in Southeast Asia and Oceania, and later migrations giving rise to relatives of East Asians who now are the primary population of Southeast Asia.

The study also provides new insights into where
See Migration, page 8

Systems Pharmacology Tackles Pipeline Crisis

Translational science drives key initiative

Taking aim at the alarming slowdown in the development of new and lifesaving drugs, Harvard Medical School is launching an Initiative in Systems Pharmacology, a comprehensive strategy to transform drug discovery by convening biologists, chemists, pharmacologists, physicists, computer scientists and clinicians to explore together how drugs work in complex systems.

“With this Initiative in Systems Pharmacology, Harvard Medical School is reframing classical pharmacology and marshaling its unparalleled intellectual resources to take a novel approach to an urgent problem,” said Jeffrey S. Flier, dean of the Faculty of Medicine at Harvard University, “one that has never been tried either in industry

See Systems Pharmacology, page 6

Clinical Research Network Expands Among Hospitals

Query tool transcends institutional barriers

A pilot project that allows researchers to query clinical data across institutions is expanding from five Harvard affiliated teaching hospitals to many more hospitals across the United States—enabling researchers to ask new questions about disease and patient care.

The Shared Health Research Information Network, or SHRINE, part of Harvard Catalyst, the Harvard Clinical and Translational Science Center, was launched in 2010 to help researchers overcome one of the greatest problems in population-based research: compiling large groups of well-characterized patients. By aggregating large numbers of de-identified patients, studies can have greater power and at the same time protect patient privacy. Similarly, studying multiple hospitals in parallel increases the chances that a scientific finding is real and not just a coincidence.

“We can answer questions in seconds that

See “SHRINE,” page 8

Melton Named University Professor

Stem cell pioneer honored for research, leadership and teaching

JUSTIN IDE/HARVARD UNIVERSITY



Melton

Harvard University has granted its highest honor for faculty members to stem cell pioneer Douglas Melton of Harvard Medical School and the Faculty of Arts and Sciences.

Melton, the Thomas Dudley Cabot Professor of the Natural Sciences and a co-chair of both the Department of Stem Cell and Regenerative Biology and the Harvard Stem Cell Institute, was named a University Professor on Sept. 27. A driving force behind the University’s ascendancy in stem cell research, he is also the co-master of Eliot House with his wife, Gail.

“While the world knows Doug Melton as a scientist who has played a

See Melton, page 5

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Slippery Slope: Cues From a Carnivorous Plant

Liquid-resistant, bio-inspired coating could repel bacteria, aid fuel transport—even de-ice windows

After a rain, the cupped leaf of a pitcher plant becomes a virtually frictionless surface. Sweet-smelling and elegant, the carnivore attracts ants, spiders and even little frogs. One by one, they slide to their doom.

Adopting the plant's slick strategy, a group of applied scientists at Harvard have created a material that repels just about any type of liquid, including blood and oil, and does so even under harsh conditions like high pressure and freezing temperatures.

The bio-inspired liquid repellence technology, described in the Sept. 22 issue of *Nature*, should find applications in biomedical fluid handling, fuel transport, and anti-fouling and anti-icing technologies. It could even lead to self-cleaning windows and improved optical devices.

"Inspired by the pitcher plant, we developed a new coating that outperforms its natural and synthetic counterparts and provides a simple and versatile solution for liquid and solid repellency," said principal investigator Joanna Aizenberg, a core faculty member at the Wyss Institute for Biologically Inspired Engineering, the Amy Smith Beryson Professor of Materials Science at the Harvard School of Engineering and Applied Sciences and co-director of the Kavli Institute for Bionano Science and Technology at Harvard University.

By contrast, current state-of-the-art liquid repellent surfaces have taken cues from a different member of the plant world. The leaves of the lotus resist water due to microtextures on the surface; droplets balance on the cushion of air on the tips of the surface and bead up.



NON-STICK SURFACE: Inspired by the meat-eating pitcher plant, a team led by Joanna Aizenberg has developed a material that repels fluids by locking in a water layer to create a slick coating.

The so-called lotus effect, however, does not work well for organic or complex liquids, or if the surface is damaged. Finally, it has proven costly and difficult to manufacture surfaces based on the lotus strategy.

The pitcher plant takes a fundamentally different approach. Instead of using burr-like, air-filled nanostructures to repel water, the plant locks in a water layer, creating a slick coating on the top. In short, the fluid itself becomes the repellent surface.

"The effect is similar to when a car hydroplanes, the tires literally gliding on the water rather than on the road," says lead author Tak-Sing

Wong, a postdoctoral fellow in the Aizenberg lab. "In the case of the unlucky ants, the oil on the bottom of their feet will not stick to the slippery coating on the plant. It's like oil floating on the surface of a puddle."

PASSING THE TEST

Inspired by the pitcher plant's elegant solution, the scientists designed a strategy for creating slippery surfaces by infusing a nano/microstructured porous material with a lubricating fluid. They call the resulting bio-inspired surfaces "SLIPS," for Slippery Liquid-Infused Porous Surfaces.

"Like the pitcher plant, SLIPS

are slippery for insects, but they are now designed to do much more: they repel a wide variety of liquids and solids," says Aizenberg. SLIPS show virtually no retention, as very little tilt is needed to coax the liquid or solid into sliding down and off the surface.

To see if the surface was truly up to nature's high standards, the team even did a few experiments with ants. In tests, the insects slid off the artificial surface or retreated to safer ground after only a few timorous steps.

The researchers anticipate that the pitcher plant-inspired technology, for which they are seeking a patent, could one day be used for medical tubing, such as catheters and blood transfusion systems, which are sensitive to drag and pressure and are compromised by unwanted liquid-surface interactions.

Other potential applications include fuel and water-transport pipes, self-cleaning windows and surfaces that resist bacteria and other types of fouling (such as the buildup that forms on ship hulls). The advance may also find applications in ice-resistant materials and may lead to anti-sticking surfaces that repel fingerprints or graffiti.

"The versatility of SLIPS, their robustness and unique ability to self-heal, makes it possible to design these surfaces for use almost anywhere," says Aizenberg. "It potentially opens up applications in harsh environments, such as polar or deep sea exploration, where no satisfactory solutions exist at present. Everything SLIPS!"

— Michael Rutter

To learn more, students may contact Professor Joanna Aizenberg at jaiz@seas.harvard.edu.

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Recent books written or edited by members of the HMS, HSPH and HSDM faculty or staff may be submitted to *Focus* at the address above. Books received by Nov. 4, 2011, will be featured in the next book section.

We invite letters from our readers, which should be brief and include a signature, address and daytime phone number.

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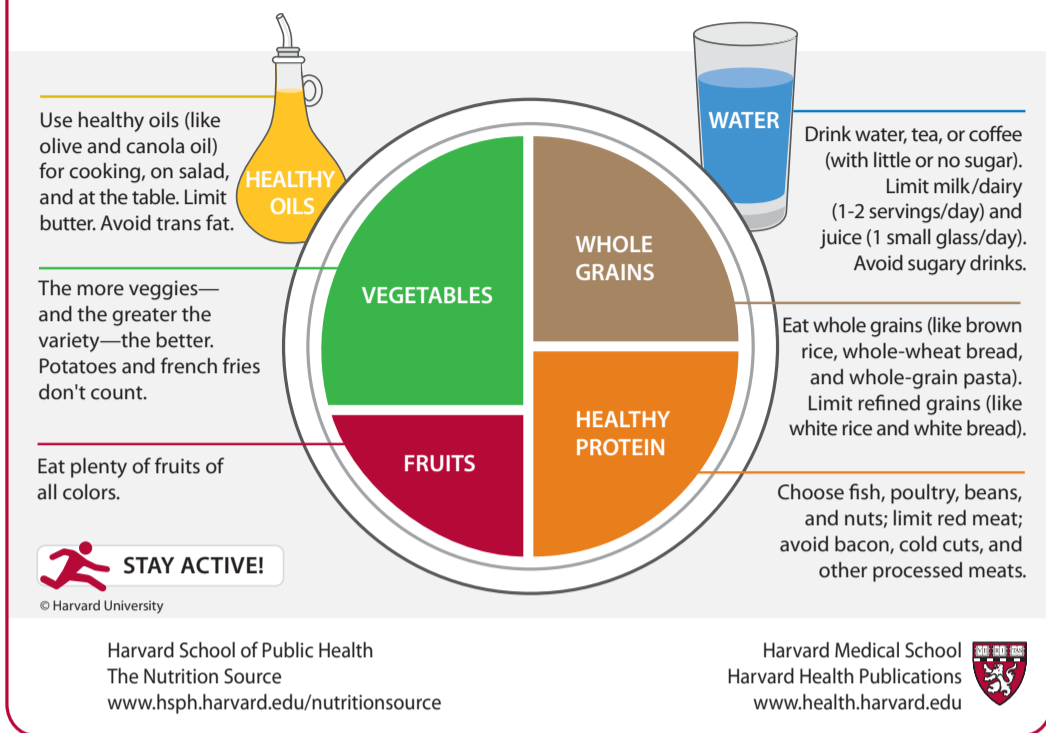
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HEALTHY EATING PLATE



The sizes of the Healthy Plate's sections suggest relative proportions of each of the principle food groups.

A Simpler Guide to Healthy Meals

Public health experts unveil Healthy Eating Plate as alternative to USDA's MyPlate

Nutrition experts at the Harvard School of Public Health and colleagues at Harvard Health Publications recently served up a simple, colorful guide to healthy meal planning. Grounded in science, the Healthy Eating Plate highlights important deficiencies in the MyPlate chart developed by the U.S. government.

"Unfortunately, like the earlier U.S. Department of Agriculture pyramids, MyPlate mixes science with the influence of powerful agricultural interests, which is not the recipe for healthy eating," said Walter Willett, Fredrick Stare Professor of Epidemiology and Nutrition, and chair of the Department of Nutrition at HSPH. "The Healthy Eating Plate is based on the best available scientific evidence and provides consumers with the information they need to make choices that can profoundly affect our health and well-being."

The Healthy Plate's section sizes suggest relative proportions of each of the food groups. They do not prescribe numbers of calories or servings per day, since these vary from person to person. The plate is consistent with guidelines of a Healthy Eating Pyramid created at HSPH in 2001

and updated in 2008.

"One of the most important fields of medical science over the past 50 years is the research that shows just how powerfully our health is affected by what we eat," said Anthony Komaroff, the Steven P. Simcox, Patrick A. Clifford and James H. Higby Professor of Medicine at Harvard Medical School and editor-in-chief at Harvard Health Publications, the consumer information division of HMS. "Knowing what foods to eat, and in what proportions, is crucial for health."

PLATES COMPARED

Comparing the Harvard Healthy Eating Plate to the USDA's MyPlate reveals shortcomings in the latter. MyPlate does not tell consumers that whole grains are healthier than refined grains, for example. Nor does its protein section indicate that some high-protein foods—fish, poultry, beans, nuts—are healthier than red meats and processed meats.

MyPlate is silent on the subject of beneficial fats. It does not distinguish between potatoes and other vegetables. It recommends dairy at every meal—even though there is little evidence that high dairy intake protects people against

osteoporosis, while substantial evidence suggests that high intake can be harmful. MyPlate says nothing about the downside of sugary drinks. Finally, MyPlate makes no mention of physical activity and weight control.

OBESITY EPIDEMIC

In contrast, science underlying the Healthy Eating Plate shows that a plant-based diet rich in vegetables, whole grains, and healthy fats and proteins lowers the risk of both weight gain and chronic disease. Helping Americans get the best possible nutrition advice is critically important as the country grapples with an obesity epidemic. In the United States today, two in three adults and one in three children are overweight or obese.

"We want people to use this as a model for their own healthy plate or that of their children every time they sit down to a meal—either at home or at a restaurant," said Eric Rimm, HSPH associate professor of epidemiology and nutrition, HMS associate professor of medicine and member of the 2010 U.S. Dietary Guidelines Advisory Committee.

—Todd Datz

Paper Chase

RECENT PUBLICATIONS FROM
HMS RESEARCHERS

The index below is a selection of new studies and review articles by researchers from across the HMS community. It represents a small sample of research at focushms.com.

GLOBAL IDENTIFICATION OF MODULAR CULLIN-RING LIGASE SUBSTRATES

Emanuele MJ, Elia AE, Xu Q, Thoma CR, Izhar L, Leng Y, Guo A, Chen YN, Rush J, Hsu PW, Yen HC, Elledge SJ. Division of Genetics, Brigham and Women's Hospital; Department of Genetics, Harvard Medical School; Howard Hughes Medical Institute.

Cullin-RING ligases (CRLs) represent the largest E3 ubiquitin ligase family in eukaryotes, and the identification of their substrates is critical to understanding regulation of the proteome. Using genetic and pharmacologic Cullin inactivation coupled with genetic and proteomic assays, the authors have identified hundreds of proteins whose stabilities or ubiquitylation status are regulated by CRLs. Findings demonstrate the broad role of CRL ubiquitylation in all aspects of cellular biology and provides a set of proteins likely to be key indicators of cellular physiology. *Cell*. 2011 Oct. 14;147-2:459-474.

ANTIDIABETIC ACTIONS OF A NON-AGONIST PPAR γ LIGAND BLOCKING CDK5-MEDIATED PHOSPHORYLATION

Choi JH, Banks AS, Kamenecka TM, Busby SA, Chalmers MJ, Kumar N, Kuruvilla DS, Shin Y, He Y, Bruning JB, Marciano DP, Cameron MD, Laznik D, Jurczak MJ, Schürer SC, Vidovi D, Shulman GI, Spiegelman BM, Griffin PR. Dana-Farber Cancer Institute and Department of Cell Biology, HMS.

PPAR γ is the functioning receptor for the thiazolidinedione class of antidiabetes drugs. These drugs are full classical agonists, but many PPAR γ -based drugs have a separate biochemical activity, blocking the obesity-linked phosphorylation of PPAR γ by Cdk5. The authors describe novel compounds that completely lack classical transcriptional agonism and block the Cdk5-mediated phosphorylation. One such compound has potent antidiabetic activity while not causing the fluid retention and weight gain that are serious side effects of many of the PPAR γ drugs. *Nature*. 2011 Sept. 4;477(7365):477-81.

ALCOHOL CONSUMPTION AT MIDLIFE AND SUCCESSFUL AGEING IN WOMEN: A PROSPECTIVE COHORT ANALYSIS IN THE NURSES' HEALTH STUDY

Sun Q, Townsend MK, Okereke OI, Rimm EB, Hu FB, Stampfer MJ, Grodstein F. Department of Nutrition, Harvard School of Public Health.

Observational studies have documented inverse associations between moderate alcohol consumption and risk of premature death. It is largely unknown whether moderate alcohol intake is also associated with overall health and well-being among populations who have survived to older age. The authors prospectively examined alcohol use assessed at midlife in relation to successful ageing in a cohort of US women. Data suggest that regular, moderate consumption of alcohol at midlife may be related to a modest increase in overall health status among women who survive to older ages. *PLoS Medicine*. 2011 Sept.;8(9):e1001090.



JEFF THEBAULT

LEFT TO RIGHT: Dean Joan Reede, Richard Bail, LeManuel "Lee" Bitsoi, Dean Jeffrey S. Flier, Brandon Abbs, Jennifer Kasper; not pictured is Ari Johnson, who is doing his residency at the University of California-San Francisco

For Hinton Scholars, a Jump Start on Science

After AP Biology, students set sights on college

When Superintendent of Boston Public Schools Carol Johnson gave a keynote address to students at Harvard Medical School in September, she urged them to tackle science on campus with gusto. None of her listeners had yet applied to HMS, however, let alone enrolled. Their average age was 17.

"Some of you in this room may be the first in your family to go to college," Johnson told the crowd of 10th, 11th and 12th graders, advanced placement biology students accepted to the HMS-sponsored Hinton Scholars Program. Given the enrichment opportunities Harvard offers, Johnson said, "You are not only going to college, but you will complete college—and some of you will go off to graduate school."

Applause broke out in the Tosteson Medical Education Center Amphitheater as parents, teachers and headmasters cheered on the participants, who hail from five Boston schools: Boston Latin Academy, Brighton High School, East Boston High School, Edward M. Kennedy Academy for Health Careers and the John D. O'Bryant School of Math and Science.

HMS faculty, researchers, tutors and lab assistants from both HMS and Northeastern University will help prep the public high school students for the 2012 advanced placement biology exam.

For the ninth year, Hinton Scholars will participate in labs led by graduate students. Their calendars, dotted with site visits to research labs and hospitals, also include small-group tutorials, career panel discussions, lectures and conferences. Students will attend a lecture on genetic sequencing by Ting Wu, HMS professor of genetics; visit the HMS mobile Family Van and the STRATUS Center for Medical Simulation at Brigham and Women's Hospital; and attend the spring Biomedical Science Careers Student Conference.

A panel of past participants and Harvard medical, dental and graduate students shared advice. "You have to be very committed," said one of last year's Hinton Scholars, who is now a senior at the t School. "I see life in a new way now."

The program, created by Joan Reede, dean for Diversity and Community Partnership, is named for the first African-American professor at HMS, William Hinton.

Said Superintendent Johnson: "Dr. Reede has really been instrumental, not just in selecting the right materials for our kids, but in opening the door to many opportunities in our schools with the greatest economic needs. The best way you can thank her is to do your very best work in science, graduate from high school and head to college—right here to Harvard."

—Katie DuBoff



ROBERT ROCHLIN

AP biology students—Hinton Scholars all—were urged to take advantage of HMS science enrichment programs by Carol Johnson, superintendent of Boston Public Schools (with scarf).

Service Above and Beyond

Community Service Awards honor extraordinary contributions

After proving their competence in clinics, hospitals, offices and classrooms, they put their ideals into action after hours on the local, national and global stage. At the Dean's Community Service Awards celebration on Sept. 12, five honorees were lauded for volunteer efforts that better the lives of others.

At breakfast around a conference table in the Waterhouse Room on the HMS Quad, awardees exchanged stories about educating orphans in an impoverished African nation and raising funds for a library for the people of Boston.

"We are gathered here to salute you," said Dean Jeffrey S. Flier, "as creative and tireless leaders within our School community; as selfless innovators in advancing our mission of outreach and service; and as activists and ambassadors who truly are beyond compare in campaigning for better health—and better life—right here in Boston, and around the world."

With trophies for the recipients and framed certificates for their community agencies, Flier thanked the honorees advancing the mission of HMS, which includes not only education and research, but also public service. The School contributed \$1,000 to the organizations for which they volunteer.

Dean for Diversity and Community Partnership Joan Reede, whose office has sponsored the awards since 1999, put the group's efforts into perspective.

"In today's uncertain and often trying times, community service is more important than ever," Reede said. "This service comes in many forms, and one's contributions need not be heroic or hugely financial in scope; it is about giving of your time, your talents, and making a difference."

In the intimate setting, surrounded by their invited guests, they shared the profound

Honorees

Lifetime Achievement: Jennifer Kasper, instructor in pediatrics at MassGeneral Hospital for Children, has worked with Doctors for Global Health for more than 15 years. The all-volunteer nongovernmental organization creates comprehensive global health curricula and experiential learning sites overseas for pediatric residents.

Faculty Award: Richard Bail, clinical instructor in population medicine at Harvard Vanguard Medical Associates, is the co-founder of Communities without Borders, which provides educational opportunities to orphans and vulnerable children in Zambia.

Trainee Award: Brandon Abbs, research fellow in psychiatry at Brigham and Women's Hospital, advocates for library resources through People of Boston for a Better Library.

Student Award: Ari Johnson is a co-founder of Project Muso Ladamunen, which works with mothers in Mali to help them to free themselves from the cycle of poverty and disease.

Staff Award: LeManuel "Lee" Bitsoi, MAP program director, devotes his energies to the North American Indian Center of Boston, which promotes greater self-determination, socioeconomic self-sufficiency and empowerment for the North American Indian community.

impact of their experiences on their lives and outlook. "It has been my privilege to give back to the children," said Faculty Award honoree Richard Bail. "Every time I look into their eyes, it makes it all worthwhile."

—Valerie Wencis

Melton

Continued from page 1

seminal role in the exponential growth of the new field of stem cell science, we at Harvard also know him as an untiring mentor to scientific leaders of tomorrow and as an academic who is passionate about improving undergraduate education,” said Harvard University President Drew Faust. Melton is teaching four classes this semester, including a freshman seminar.

FRONTIERS THROWN OPEN

Melton becomes the Xander University Professor. Melton initially established himself as a researcher by bringing the tools of molecular biology to bear on the field of developmental biology in frogs, but he switched his focus to the infant field of stem cell biology and regenerative medicine when his young son was diagnosed with Type 1 diabetes. Since then, Melton has dedicated his career to using stem cell biology to search for a cure for diabetes, which was also diagnosed in his daughter.

“A brilliant scientist and pioneering advocate for embryonic stem cell research, Doug has thrown open the frontiers of his field,” said Dean of the Faculty of Medicine Jeffrey S. Flier. “The story of how he turned his attention to regenerative medicine after his own son was diagnosed with Type 1 diabetes illuminates both the power and the humanity of our mission.”

In 2004 with David Scadden, HMS’s Gerald and Darlene Jordan Professor of Medicine, Melton launched the Harvard Stem Cell Institute, which today boasts more than 80 principal investigators and more than 800 scientists scattered across the science departments, Schools and affiliated hospitals at Harvard. Such a collaborative, interdisciplinary effort would have been unthinkable when Melton came to Harvard in 1981, after undergraduate studies at

the University of Illinois and a PhD in molecular biology earned as a Marshall Scholar at Cambridge University in England.

Three years ago, Melton and Scadden were named co-chairs of the Department of Stem Cell and Regenerative Biology, Harvard’s first inter-School department. Based in both the FAS and HMS, the department has launched an undergraduate concentration in regenerative biology, introducing a new generation of students to the possibilities of stem cell science.

A RARE DISTINCTION

“This is a tremendous honor, for which I am very grateful. There are a number of great research institutions with outstanding scientists,” he said. “But what sets Harvard apart is the quality of its students, undergraduates, graduate students and postdoctoral fellows. I especially enjoy teaching undergraduates because of their almost palpable desire not only to learn, but also to expand the frontiers of learning.”

Melton was one of two University Professors named Sept. 27; the other was Rebecca Henderson, the Senator John Heinz Professor of Environmental Management at Harvard Business School. Their appointments bring to 25 the number of University Professors among Harvard’s entire faculty.

Melton became the third university professor currently at HMS. Marc Kirschner, founding chair of the Department of Systems Biology, was named John Franklin Enders University Professor in 2009. Paul Farmer, chair of the Department of Global Health and Social Medicine, was named Kolokotronis University Professor in 2010.

—From the Harvard Gazette

HMS~PORTUGAL PROGRAM INVITES COLLABORATIVE GRANT PROPOSALS



The Harvard Medical School–Portugal Program in Translational and Clinical Research and Health Information seeks applications for

Collaborative Research Grants for Harvard-affiliated investigators working with scientists at Portuguese medical schools and biomedical research institutions.

The program, a collaboration between HMS and Portuguese universities and medical schools, issued this third annual call in September. The final deadline is Nov. 16.

Successful applicants will be involved in collaborative biomedical research relevant to human disease; they must include at least one research group at Harvard and at least two from different institutions

in Portugal. Applications that include a translational or clinical research component are especially encouraged.

A typical award will provide in direct costs up to \$160,000 a year for the Harvard groups and up to 100,000 euros annually for each Portuguese group. Grants will run for two years, with the possibility of extension to a third. This year, grants for three projects will be awarded. All investigators with a Harvard appointment are eligible, including those from HMS and HMS-affiliated hospitals and research institutions.

—Jake Miller

For more information, visit the HMS-Portugal Program at www.hmsportugal.pt/portal/server.pt/community/Calls or e-mail patrodrigues@hmsportugal.pt.

VIDEO EXTRA

Harvard Medical School in Motion

HMS is moving in new directions, propelled by the expertise and energy of its faculty, staff and students. Learn how these innovators are shaping the future of biomedicine.

www.youtube.com/harvardmedicalschoo



LEONARD RUBENSTEIN

Modell Immunology Prize Recognizes Lysosome Research

HMS graduate student Salil Garg received the 2011 Jeffrey Modell Prize, presented annually since 2000 for the best dissertation and overall contribution to the Harvard Graduate Program in Immunology.

Garg, who earned a doctorate in 2010 and plans to finish his medical degree in 2012, used the technique known as RNA interference to screen for novel genes used by the immune system to control the digestion and processing of invading microbes within compartments called lysosomes for presentation to immune T cells.

After a residency in pathology, Garg plans a career in basic science, aiming to bring advances in cellular and molecular immunology to bear on the diagnosis and treatment of human diseases.

—Karin Kiewra



STEVE LIPOFSKY

LEFT TO RIGHT: Vicki and Fred Modell, and MD/PhD student Salil Garg. Garg was honored by the couple, who funded an endowment to recognize excellence in immunology in honor of their late son, for whom the Jeffrey Modell Immunology Center at HMS is named.

Specialty Is Seen to Guide Referrals

Primary care physicians and specialists use different criteria to decide whom their patients see

referrals are initiated by specialists, not just primary care physicians.” The paper was released online by the *Journal of General Internal Medicine* on Sept. 16.

Barnett and team examined reasons why primary care and specialist physicians choose certain specific colleagues to refer to, and how those reasons differ by specialty. Using a web-based survey, they asked 616 physicians, who treated 46,937 Medicare patients in 2006, about their referral and information-sharing relationships with other physicians of any specialty.

...AND EXPERTISE

The researchers first identified referral relationships for each physician. They then asked respondents to identify the two most important reasons for choosing a specific physician the last time they referred a patient to him or her. The researchers grouped reasons for referral into three categories: patient experience with physician, patient access and physician-to-physician communication.

Clinical expertise was excluded from the list of criteria because in pre-testing, physicians uniformly chose it as the most important reason for referral. Excluding expertise as a criterion enabled researchers to examine how physicians choose among physicians of similar quality.

To date, much of the work looking at the referral process has focused on primary care physicians as the sole source for referrals, consistent with their role as coordinators of care.

—Jake Miller

For more information, students may contact Bruce Landon at landon@hcp.med.harvard.edu.



LEONARD RUBENSTEIN

Primary care physicians and specialists use different criteria for choosing the doctors to whom they refer patients, researchers from Harvard Medical School, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center said in the first study to explore how referral decisions differ by specialty.

The study is part of a larger effort to understand how and why physicians make referrals.

“Patient referrals have strong implications for both the cost and the quality of care,” said Bruce Landon, professor of health care policy at HMS. A referral can trigger a cascade of diagnostic tests, follow-up visits and procedures.

The findings suggest that any interventions to influence referral practices ought to be tailored by speciality, the researchers said.

PATIENT ACCESS OR PATIENT EXPERIENCE?

The study, led by Michael Barnett, now a first-year resident in internal medicine and primary care at Brigham and Women's, reports that primary care physicians are more likely to cite reasons related to patient access (such as availability of appointments) or physician-to-physician communications (such as a shared electronic records system), whereas medical or surgical specialists cite reasons related to patient experience with the chosen physician. For example, specialists are more likely to refer to doctors with whom previous patients report positive experiences.

“It's clear that primary care physicians have different priorities than other physicians when choosing a specialist,” Barnett said. “This is particularly important since we found that many

Systems Pharmacology

Continued from page 1

or academia.”

Modern drug discovery has focused on the interaction between a candidate drug and its immediate cellular target. That target is part of a vast and complex biological network, but because studying the drug in the context of a living system is profoundly difficult, scientists have largely avoided this approach.

As a result, predicting the effects of a particular candidate drug in humans is currently all but impossible, and many initially promising drugs have been found to lack efficacy or to have unsupportable levels of toxicity—typically at a late stage of a clinical trial, at a cost of years of effort and up to \$1 billion.

“Right now in the world of drug discovery, it's as if we have a map of a highway system that only contains small pieces extending a few miles here and there, without any connectivity on a large scale,” said Marc Kirschner, the John Franklin Enders University Professor of Systems Biology and chairman of the HMS Department of Systems Biology. “If you try to plan a trip on such fragmentary information, you'll fail. It's our inability to develop a coherent picture that has stymied drug discovery for so long.”

As drug makers exhaust the most promising candidate areas, the number of new drugs brought to patients has actually decreased in recent years, even as the cost of discovery has soared.

A better understanding of the whole system of biological molecules that controls medically

important biological behavior, and the effects of drugs on that system, will help industry identify the best drug targets and biomarkers. This will help to select earlier the most promising drug candidates, ultimately making drug discovery and development faster, cheaper and more effective.

“Through this new initiative, we will develop large-scale models of biological systems and networks that should more accurately predict drug efficacy,” Kirschner added.

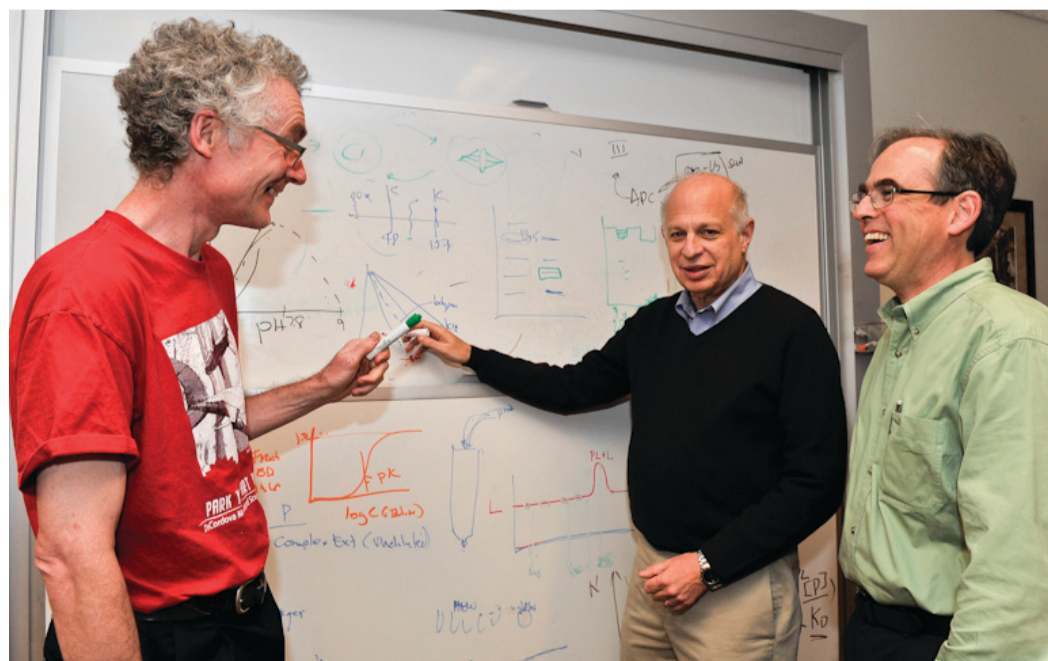
THE SYSTEMS APPROACH

The science of analyzing specific biological processes within the context of an entire living system,

called systems biology, is relatively new. Harvard Medical School is a world leader in this area, having established one of the first department-level programs in 2003.

Building on this success, Harvard's new effort will apply systems biology's innovative approaches to the understanding and prediction of drug activity, drawing on the vast range of biomedical expertise available at the School and its affiliated teaching hospitals and research institutes.

Led by Kirschner and systems biology professors Peter Sorger and Tim Mitchison, the Initiative in Systems Pharmacology will include faculty from a broad array of disciplines: systems biology,



STEVE LIPOFSKY

Systems Biology faculty (from left) Tim Mitchison, Marc Kirschner and Peter Sorger will lead the multi-disciplinary Initiative in Systems Pharmacology.

cell biology, genetics, immunology, neurobiology, pharmacology, medicine, physics, computer science and mathematics. The initiative will be fueled by a strong and diverse group of existing faculty and new recruits who will be based in several departments, and will be supported by an ambitious fundraising effort. New approaches could include use of chemical biology to develop probes of biological pathways and failure analysis on unsuccessful drugs, similar to how the aviation industry scrupulously analyzes accidents to learn what went wrong. Such a practice is not common in today's pharmaceutical industry.

Other projects currently under way at HMS will be expanded through the new initiative.

For example, Sorger and Mitchison collaborate with Ralph Weissleder, HMS professor of radiology and director of the Center for Systems Biology at Massachusetts General Hospital, to probe the mechanism by which anti-cancer drugs kill tumor cells in patients and thereby make the effects of treatment more predictable. "What's amazing is how little we know about how even existing drugs really work," Sorger said. "A systems approach could help tailor existing treatments to specific patients, and find new uses for therapies we already have."

And in the lab of Systems Biology Professor Roy Kishony, scientists research the evolutionary forces that shape the emergence of antibiotic-resistant bacteria, seeking strategies for developing combination therapies to slow or reverse the spread of drug resistance.

The initiative will also include a new educational program, one that develops a new generation of students, postdoctoral fellows and physician-scientists. "The goal is to train students to be future leaders in systems pharmacology and therapeutic discovery in both academia and industry," Mitchison said.

TRANSFORMING THERAPEUTICS

The Initiative in Systems Pharmacology is a signature component of an HMS Program in Translational Science and Therapeutics. There are two broad goals: first, to increase significantly our knowledge of human disease mechanisms, the nature of heterogeneity of disease expression in different individuals, and how therapeutics act in the human system; and second—based on this knowledge—to provide more effective translation of ideas to patients by improving the quality of drug candidates as they enter the clinical testing and regulatory approval process, aiming to increase the number of efficacious diagnostics and therapies reaching patients.

"Systems pharmacology is the first and a key pillar of Translational Science and Therapeutics at Harvard Medical School," said William Chin, the Bertarelli Professor of Translational Medical Science, executive dean for research at HMS and former head of research for Eli Lilly & Co.

"We intend to harness all the strengths of HMS to gain a deeper understanding of the cause and nature of disease, addressing some of the most vexing questions that continue to impede the development of new drugs," Chin said. "We will focus our strengths and resources on translating such knowledge into new classes of life-saving medicines."

—R. Alan Leo



Listen to a conversation about the Initiative in Systems Pharmacology with Marc Kirschner, chair of the HMS Department of Systems Biology, at focushms.com.

FORUM

After Residency, a New Outlook

Residency is challenging. Residents are strapped with constant demands, serve as first responders to all clinical emergencies and shepherd patients through each step of their journey from admission to discharge, all while still in training. As a house officer at Beth Israel Deaconess Medical Center, I enjoyed my job, but my favorite parts of residency—the teamwork, patient care, and opportunity to spend time with my patients—were under constant fire from the pressures I felt as a resident.

I can happily say to the attendings who told me it gets better: You were right. This year, I became an assistant professor at New York University School of Medicine, and while most of my time is spent on research, I care for hospitalized patients about two months a year in two-week blocks. I feel more fulfilled than ever as a doctor: It is tremendous fun to care for patients in a team with house officers and medical students, to teach them about medicine, and to finally lead a team. Above all, I feel much more in touch with my patients, their families and their experiences and struggles. In just my first two-week block, I found three stories especially touching.

'TAKE CARE OF YOUR SISTER'

Ms. Cantor was a 74-year-old with Parkinson's disease admitted after falling at home. Medically, it was clear that her Parkinson's had progressed. But rather than discuss medications, she wanted to talk about her sister, a neurologist who passed away several years ago from ovarian cancer. "Have a seat," she beckoned, gesturing to her bed. "No need for us both to end up in here," she quipped in reference to my lower back, which I had bent awkwardly to hear. As I sat, she regaled me with stories of her and her sister's time together; how she had taken to heart her mother's command, from an early age, to "take care of your younger sister;" and how devastated the two sisters were when they learned of the cancer.

I was touched when her visiting friend, a retired physician herself, tugged me aside. "Can we have a podiatrist take a look at her feet? She is not taking care of herself at home," she said with deep concern. We examined Ms. Cantor's toenails, which now looked quite neat and clean. "Maybe one of the nurses trimmed them for her," I offered. Mrs. Cantor's friend didn't care—she was relieved, but not as much as I was moved by all of the love and affection in the room.

I will never forget Mr. Ford either. An energetic 88-year-old former pilot, he told me in our first meeting that he was the lone survivor of a World War II plane crash. He was admitted with anemia, but a colonoscopy revealed colon cancer. "I don't understand what's happening," he said. "Could it be wrong? Maybe it's not cancer." He was in a daze after receiving the news and grasped for certainty and familiarity. We sat and talked about the diagnosis, the range of possible treatments and the assurance that he had on his side a team of doctors thinking critically about his care.

Over the next few days, I was impressed to see his resoluteness, natural optimism and energy remain visible. While I had many younger patients, none of them got as much exercise in the hospital as Mr. Ford, who frequently walked up and down the medical floor halls to stay active. Reflecting back on my time with Mr. Ford, I am sure it was no coincidence that he survived that plane crash. Had I still been a resident, I might have missed many of his stories—and the opportunity to get to know him better.

'I WISH THERE WAS A CURE'

Finally, there was Ms. Fernandez. Her 25-year-old body had been ravaged by lupus, and the disease had pillaged one organ after the next. She was now admitted with a complication of treatment. When we first met in her hospital room, she wore the familiar expression of a patient who has been through too much. I met her mother and brother the following day, and they were frantic with concern. "I don't understand any of this," her brother said. "What's going on?" her mother echoed.

While these moments are challenging, I welcome them. I find it rewarding to help patients and families understand their illness. In plain language, I explained Ms. Fernandez's recent treatment course, the nature of the complication, and our plan to remedy it. After a few more questions, her family seemed to have a better sense of what was happening, but her mom's eyes still said everything. "I wish there was a cure for lupus," she said. "I do too," I responded, and said goodbye.

Becoming an attending has been more fulfilling than I ever imagined. It has also been my clearest reminder in years about our responsibility to our patients, the importance of the non-medical parts of patient care, and the serious role we play in the lives of our patients and their families.



Joseph Ladapo

ROSE LINCOLN/HARVARD UNIVERSITY

—Joseph Ladapo, HMS '08, is an assistant professor of medicine at the NYU School of Medicine. The names used in this column are pseudonyms, and the opinions expressed are not necessarily those of Harvard Medical School, its affiliated institutions or Harvard University.

Migration

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the ancient Denisovans lived. Mark Stoneking, a professor at the Max Planck Institute and senior author of the paper, said Denisovans must have inhabited a vast ecological and geographic range, from Siberia to tropical Southeast Asia.

“The fact that Denisovan DNA is present in some aboriginal populations of Southeast Asia but not in others shows that there was a checkerboard of populations with and without Denisova material more than 44,000 years ago,” Stoneking said.

The findings appeared Sept. 22 in the *American Journal of Human Genetics*.

This research builds on previous work in which Reich and colleagues at the Max Planck Institute analyzed an ancient pinky bone uncovered by Russian archaeologists in the Siberian Denisova Cave in 2008. The Planck team, led by Svante Pääbo, sequenced the bone’s nuclear genome, and Reich led the population genetic analysis using algorithms that he and his colleagues developed.

Reporting in December 2010 in *Nature*, the team identified Denisovans as a distinct group of archaic humans, or hominins, that lived more than 30,000 years ago and contributed genes to present-day New Guineans. The findings fill in some pieces in the evolutionary puzzle that began after early humans left Africa and reinforces the view that humans have intermixed throughout history.

GENETIC FOOTPRINTS

Initiated by Stoneking, an expert on genetic variation in Southeast Asia and Oceania, the new study looks closer at the Denisovans’ genetic footprint. Using a mix of new and existing data, researchers analyzed DNA from dozens of present-day populations in Southeast Asia and Oceania, including Borneo, Fiji, Indonesia, Malaysia, Australia, the Philippines, Papua New Guinea and Polynesia.

The team’s analysis shows that, in addition to New Guineans, Denisovans contributed genetic material to Australian aborigines, a Philippine Negrito group called Mamanwa, and several other populations in eastern Southeast Asia and Oceania. The findings suggest that groups in the west or northwest, including other Negrito groups such as the Onge and the Jehai, as well as mainland East Asians, did not interbreed with Denisovans.

The researchers concluded that Denisovans interbred with modern humans in Southeast Asia at least 44,000 years ago, before the separation of the Australians and New Guineans; and that Southeast Asia was first colonized by modern humans unre-

lated to present-day Chinese and Indonesians, and these and other East Asians arrived in later migrations. This “southern route” hypothesis has previously been supported by archaeological evidence but never had strong genetic support.

Investigators from the Broad Institute of MIT and Harvard, and from Germany, India, Taiwan, Japan, Malaysia and the Netherlands, also contributed.

—Debra Ruder

For more information, students may contact David Reich at reich@genetics.med.harvard.edu.

SHRINE

Continued from page 1

would otherwise take years,” said principal investigator Isaac Kohane, professor of Pediatrics and Health Sciences Technology. “Or that you could never even ask.”

TALENT POOL

Building the network required not only technological innovation but a delicate administrative dance among five hospitals that do not routinely share clinical data for research: Brigham and Women’s Hospital, Beth Israel Deaconess Medical Center, Dana-Farber Cancer Institute, Children’s Hospital Boston and Massachusetts General Hospital.

“The success of SHRINE is the result of an extraordinary collaboration across the Harvard research community,” said Doug MacFadden, program director for SHRINE.

“Patients are treated every day, yet it can be surprisingly difficult to answer even basic questions about how well a medication is working or how often patients are diagnosed with related illnesses,” said Andrew McMurry, an informatics team lead at the HMS Center for Biomedical Informatics who helped develop SHRINE. “These clinical data can help us ask better questions on a population scale.” The collaboration required the approval of each Institutional Review Board and multiple safeguards to protect the privacy of 6 million patients.

This fall, Kohane, MacFadden, McMurry and their collaborators are working to extend the network to include Michigan Institute for Clinical and Health Research at the University of Michigan; University of Texas Health Science Center at Houston; Wake Forest Baptist Medical Center; Cincinnati Children’s Hospital Medical Center; University of California San Francisco Clinical and Translational Science Institute; and the University of Washington. The work is funded through a

Harvard Catalyst supplemental grant from the National Institutes of Health.

Authorized researchers at participating institutions can query millions of records to determine the total number of patients who meet a given set of criteria—a combination of demographics, diagnoses, medications and laboratory tests. Because counts are aggregate, patient privacy is protected. SHRINE is a federated system, meaning that each hospital maintains control of its own data.

BOON TO PATIENT CARE

Investigators who have used SHRINE call the network not only a powerful engine for research, but also a transformative tool for patient care.

Rebecca Miksad, a gastrointestinal oncologist at Beth Israel Deaconess and HMS assistant professor of medicine, is using SHRINE to find data on cancer treatment and outcomes, which improve every year. McMurry calls Miksad’s work translational research at its purest. “She’s asking: How long does it take to translate what’s known in research to what’s done in a clinical care setting?”

At his laboratory at Children’s Hospital Boston, Kenneth Mandl, associate professor of pediatrics uses SHRINE to investigate personalized therapies for patients. “Rather than relying on clinical trials data as a source of evidence, the approach is to examine the real-world experience of patients similar to ours,” said Mandl, who directs the Intelligent Health Laboratory at the Children’s Hospital Informatics Program and is on the Harvard-MIT Division of Health Sciences and Technology faculty. “This is a shift toward using large-scale observational data sets to form the evidence base.”

But to underscore the power of SHRINE, Kohane points to one study done without it. Last year, he got a call from a colleague at Stanford, Nicholas Tatonetti, who had noticed a possible link to diabetes among patients prescribed a certain antidepressant-and-statin combination. But Tatonetti didn’t have enough patient records at Stanford Medical Center for confirmation, so he reached out to Kohane and a third colleague at Vanderbilt University Medical Center. Sure enough, each researcher noticed the same correlation in their records, and the collaborators published their findings in May.

“That took months and a big Rolodex,” Kohane said. “SHRINE takes seconds and a good idea.”

— R. Alan Leo

To learn more, contact Andrew McMurry at Andrew_McMurry@hms.harvard.edu or visit catalyst.harvard.edu/services/shrine.

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of Child and Adolescent Psychiatry ■ **Jason Block** receives the Milton W. Hamolsky award for outstanding research by a junior faculty member at the National Society of General Internal Medicine conference ■ **Grace Lee** receives the 2011 Pediatric Investigator

Award from the Society for Healthcare Epidemiology of America ■ **O-GlcNAc transferase**, an essential mammalian enzyme described by **Michael B. Lazarus**, **Yunsun Nam**, **Jiaoyang Jiang**, **Piotr Sliz** and **Suzanne Walker** named The Protein Databank’s Molecule of the Month for September

