

It's All in Your Head

Building better brains through
neuroengineering



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Harvard Medical School
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HARVARD
MEDICAL SCHOOL

It's All in Your Head: Building better brains through neuroengineering



Moderator

Joseph B. Martin, MD, PhD

Edward R. & Anne G. Lefler Professor of
Neurobiology
Harvard Medical School



Speakers

Clifford Woolf, MB, BCh, PhD

Professor of Neurology & Neurobiology,
Harvard Medical School
Boston Children's Hospital



Albert Edge, PhD

Associate Professor of Otolaryngology
Otolaryngology
Harvard Medical School
Massachusetts Eye and Ear Infirmary

About the Speakers

Joseph B. Martin, MD, PhD

Dr. Martin is the Edward R. and Anne G. Lefler Professor of Neurobiology at Harvard Medical School.

Dr. Martin served for ten years as Dean of the Faculty of Medicine at Harvard University from 1997 to 2007. At Harvard, in 1999, he helped establish, the Dana-Farber/Harvard Cancer Center, an innovative collaboration which brings together seven Harvard-affiliated institutions intent on reducing the burden of cancer. He also led the formation of the Harvard NeuroDiscovery Center, a virtual center of researchers working together on understanding the prevention, causes, and treatment of neurodegenerative diseases like Alzheimer's and Parkinson's disease.

Following academic appointments at McGill University, Dr. Martin was appointed chief of the neurology service at the Massachusetts General Hospital, serving from 1978-1989. From 1989-1993, Dr. Martin was Dean of the School of Medicine at University of California, San Francisco. In 1993, he was appointed Chancellor of UCSF, serving four years until his return to Harvard University in 1997.

Dr. Martin is a member of the Institute of Medicine of the National Academies, a Fellow of the American Academy of Arts and Sciences and an honorary member and past president of the American Neurological Association.

Dr. Martin is author of over 300 scientific publications and several books. The most recent is "Alfalfa to Ivy: Memoir of a Harvard Medical School Dean" published in 2011.

Albert Edge, PhD

Dr. Albert Edge is on the faculty of Harvard Medical School and investigator at Massachusetts Eye and Ear Infirmary (MEEI). He was a Postdoctoral Fellow in the Department of Biological Chemistry at Harvard Medical School, where he was an Iacocca Fellow and a Capps Scholar, and in 2003 took his current position at MEEI.

Dr. Edge works on stem cell differentiation and regeneration of the inner ear and has identified developmental pathways for converting stem cells into cochlear hair cells and neurons. The goal of his research is to develop treatments for hearing loss through the stimulation of signaling pathways.

Clifford Woolf, MB, BCh, PhD

Dr. Woolf is director of the F. M. Kirby Neurobiology Center at Boston Children's Hospital and a professor of neurology and neurobiology at Harvard Medical School. His research focuses on the mechanisms of the adaptive and maladaptive plasticity of the nervous system, and in translating the results into new therapeutics.

Dr. Woolf's research is devoted to investigating how the functional, chemical and structural plasticity of neurons is involved in both the normal adaptive functions of the nervous system and in maladaptive changes that contribute to neurological diseases. Most of his work is concentrated on sensory and motor neurons using a multidisciplinary approach spanning molecular and cell biology, electrophysiology, neuroanatomy, behavior, and genetics, with particular emphasis on the intersection between advances in basic science and its translation into new therapies.

Harvard Medicine

The following articles are selections from *Harvard Medicine*. Additional content can be found online, please visit: <http://harvardmedicine.hms.harvard.edu/>

The Discovery Channel

Why do Harvard doctors remain undaunted by the demands of discovery?

On one ridge stand scientists clutching discoveries rich with possibility; along another are physicians reaching for therapies to alleviate their patients' suffering. Between them runs an abyss, its floor strewn with abandoned drug candidates and failed clinical trials.

Into this chasm ventured two unsuspecting Harvard Medical School neurobiology professors, Clifford Woolf and Bruce Bean. After years of collaboration, the scientists wanted to use their experience in deciphering the neurophysiology of pain to develop a new generation of analgesics. Joining forces with a group of neurobiologists and clinicians, they sought venture capital. In 2006, the group launched Solace Pharmaceuticals with a plan to translate several key discoveries into new drugs – and to bridge the gaps between bench and bedside, basic and applied science, academia and the pharmaceutical industry.



O Pioneers!: Clifford Woolf (left) and Bruce Bean, who entered the discovery-to-drug adventure as experienced scientists but inexperienced entrepreneurs, weathered early setbacks before crafting a promising agreement to collaboratively develop their new pain medication with Endo Pharmaceuticals. Photo by John Soares

Neither Woolf nor Bean had attempted anything like this before, and they found that the journey from idea to drug carried a steeper learning curve and more steps – seeking a patent, licensing the technology, raising money for further testing, among many others – than either had anticipated. Nevertheless, their plan seemed to proceed flawlessly, and they quickly identified a compound that relieved pain in rats. Then came the giant hurdle of translation to human clinical trials.

“The results were beautifully clear,” says Woolf. “The drug didn’t work in humans.”

The researchers had experienced a common obstacle: molecular processes in animals don’t necessarily translate to human biology. Their drug failed in a proof-of-principle trial and never made it to more extensive phase II and III trials. Even if the drug had shown promise, other obstacles – including safety, regulatory, and financial ones – might well have derailed their work down the road. For every new drug that makes it to market, at least a hundred promising compounds fail at an experimental stage. Many biomedical researchers put the chances of a discovery surviving the trip to market more simply: it is a journey through the Valley of Death.

And academics are ill equipped to traverse that valley alone. “Medical schools aren’t set up to do small-scale proof-of-principle human clinical trials, much less large-scale ones, and scientists aren’t used to navigating regulatory issues,” says Jeffrey Flier, dean of HMS. “Those capacities lie in industry.”

But the road can be treacherous for the pharmaceutical industry as well. Nine of ten potential medicines entering clinical trials fail. High-profile, late-stage drug failures have cost Big Pharma billions of dollars and prompted the industry to seek new, innovative approaches to drug discovery and development. These approaches include closer collaborations with academic institutions, from which, says Flier, “most of the fundamental discoveries come.”

Meanwhile, many brilliant university-based discoveries with true drug-development potential “just get left on the pages of medical journals,” says Frances Jensen, an HMS professor of neurology and director of epilepsy research at Children’s Hospital Boston. “At the basic science level, scientists might do great research, get their results published in a high-profile journal, and then move on to the next fundamental experiment. Their discovery just sits on a shelf. Nobody picks it up, and nobody takes the next step of translation.”

Even when promising ideas get noticed, universities lack the resources and know-how to develop them. The continued shrinking of research dollars adds more pressure to an already competitive process. And industry is cutting budgets as well.

These forces have created what one HMS official calls “a perfect storm.” But the School is creating shelters for those willing to brave the tempest.

At the Center of Discovery

Around the time that Solace halted clinical trials of the pain medication that Woolf and Bean had developed, the National Institutes of Health was unveiling an initiative — eventually expected to surpass \$500 million a year — to address the very issues that had caused the researchers grief. Universities and medical centers around the country began to vie for a share of the funds, with the hope of using them to create clinical and translational science centers, or CTSCs, designed to ease the journey from discovery to therapy.

In 2007, Flier had barely settled in his new position as dean of HMS when he learned that the NIH would be phasing out the general clinical research center grants historically awarded to Harvard’s major teaching hospitals. Instead, HMS would have to apply for funding to create a CTSC to be shared with its hospital affiliates and the rest of the University. Flier pulled together a team that, under the leadership of Lee Nadler ’73, crafted a winning proposal for a five-year, \$117.7-million award for such a center, now known as Harvard Catalyst.

The difference between translational medicine and basic research is intent, Flier says. In basic research, scientists seek to understand fundamental biology: how a certain part of a cell works, for example, or how a molecular signal passes from cell to cell. In translational work, researchers want to frame basic science findings to capture a disease’s cause or to improve its diagnosis, treatment, management, or prevention.

“We’re still a long way from even a basic grasp of the mechanisms that underlie most human diseases,” Flier says. “Even when we have that understanding, as we do with cystic fibrosis, for example, it’s not an easy leap to therapies. Turning discoveries into effective treatments is daunting, even before you encounter issues in funding, conflict of interest, regulation, or a host of other arenas.”

To help bridge that gap, in the past few years Flier created two new posts — dean for clinical and translational research, held by Nadler, and executive dean for research, held by William Chin ’72, both of whom brought significant experience in translational research and human clinical experimentation.

“Medical schools have at their heart a desire to help patients,” says Chin. “We focus on basic research — using such model systems as mice, zebrafish, and fruit flies — because we need this information for enough insight to learn what leads to human disease in the first place. But remember, one of our primary goals is to alleviate human suffering caused by disease, and stopping at basic research would leave us short of that goal. So

while we don't require scientists to take a translational approach, we encourage them to think about it. We're also working to make the process easier for those who do."

Sometimes, adds Nadler, the hardest step is the first one. "My colleagues who are basic scientists often tell me, 'I'd really like to pursue translational research. But I don't know what the question should be or how to proceed to the answer.'"

So Nadler, under the auspices of Harvard Catalyst, has fostered initiatives aimed at helping to frame those questions. One such initiative was a recent crowdsourcing challenge that solicited ideas – and funded research projects – based on a simple question: What do we not know to cure type 1 diabetes? This question was posed to the entire community of basic researchers, disease- and patient-focused clinicians, and technology innovators, and the wisdom of the crowd provided new approaches to an old and still vexing disease. "The effort was highly successful," says Nadler, "in that it allowed people who had never worked in the field of type 1 diabetes to share their ideas."

Chin agrees that collaboration is key to the School's translational research initiatives. "We want to foster more productive multidisciplinary, interdepartmental, and cross-institutional work and team formation," he says. "We believe this will lead to more innovation and creativity."

But that goal bumps up against another hurdle to translational research – the culture of science. "When basic scientists have a translatable discovery," Jensen says, "they generally have to hand that discovery over to a translation scientist and then to a clinician." She adds that the incentives in academic medicine – journal publications, grants, awards, promotions – often reward individuals rather than teams. In contrast, translational and clinical work require more collaboration. "It's hard," she says, "for translational researchers to show their added value and get credit for their work."

Part of the solution, Nadler says, is to evolve the culture and incentives. "What we need is a precise question, a team of investigators with the diverse skills to solve the problem, the required tools and technologies, and incentives to bring people from disparate disciplines together. If we say we need an answer to a specific problem and then provide pilot funding for that research," he says, "we give collaborations more focus and means."

As part of its incentive-building program, Harvard Catalyst provides one-year, \$50,000 pilot grants for investigations that carry a high risk of failure yet offer big payoffs if successful. "But there's a catch," says Nadler. "You can't work with anyone you've worked with before and you must reach across the University system to find a collaborative partner." In three funding cycles thus far, the program has awarded 161 grants for innovative projects aimed at, for example, engineering resistance to epileptic

seizures, identifying biomarkers for Alzheimer's disease, and pinpointing neural indicators of dyslexia in infants.

Harvard Catalyst has also introduced practical courses in clinical research and translational medicine, including a weeklong introduction to clinical investigation, offered several times a year, and more advanced classes. Several affiliated hospitals offer training as well.

"Through such initiatives," says Chin, "we're creating a new breed of investigator. Basic scientists are engaged in learning about disease, and physicians are gaining backgrounds in basic science."

Another program that provides critical assistance to foster and advance translational research at HMS is the Technology Development Accelerator Fund, launched and operated by Harvard's Office of Technology Development. Fueled by donations raised from philanthropic sources, the Accelerator Fund is a grant-based program that enables investigators to bridge the often insurmountable development gap in order to establish proof-of-principle and to transform promising early-stage inventions into viable candidates for development, commercialization, and clinical application. The Accelerator Fund has provided seed funding for 27 projects at the level of approximately \$200,000 each.

"Our primary motivation is to accelerate the development of promising new inventions that might otherwise languish for lack of support and validation, and to ensure that they're expeditiously translated for the public good," says Isaac Kohlberg, the University's chief technology development officer. "We can't predict or pick 'winners' with certainty. It's all about planting the right seeds, nurturing the seedlings, encouraging them to blossom, and weeding when necessary. Every now and then we'll be rewarded with a prize-winning flower, but we need to seed and cultivate constantly."



Receptive Manner: Epilepsy researcher Frances Jensen found that using a safe, approved diuretic that lowers the number of chloride receptors in the brains of epileptic infants helped the babies respond to an antiseizure medication.

Photo by Patrick Bibbins

Tending the Gap

Jensen had no such assistance when she ventured into the foreign landscape of translational medicine two decades ago, on a search for a new drug to control seizures in newborns. She had long been fascinated by synaptic plasticity – how synapses, or the connections between neurons, grow with experience. Now she wanted to apply her knowledge to heal injuries to the infant brain.

Such an approach – translating findings on rodent brains into aids for human infants – requires a delicate pairing of basic researcher and clinician. “But in my department, as in many departments, the clinicians don’t know many of the basic scientists all that well,” Jensen says. The gulf between the laboratory and clinic, researcher and physician, and animal model and human patient is a major obstacle in the translational journey. Yet increasingly, people on both sides of the gap are working to bridge it.

“As clinical medicine advances and as diagnostic tools, such as biomarkers and genetics, continue their rapid evolution, we’ll discover new areas of science, ones that you have to go to the bench to study,” Jensen says. “In some cases we’re discovering that some pathways involved in one disease process are surprisingly also important in another, seemingly unrelated disease process” – or, as Jensen’s work on controlling seizures in

infants shows, that a drug intended for one disease may be effective against a vastly different disease.

Medications that control seizures in adults, for example, work only half the time in infants. From research in animal models, Jensen knew that antiseizure drugs work by targeting inhibitory synapses. But infant brains have fewer inhibitory and more excitatory synapses than adult brains do. “If you give babies a drug that targets inhibitory receptors,” Jensen says, “you’ll find they don’t have enough receptors for the drug to work.”

A number of laboratories had shown that lowering the number of chloride receptors inside infant brain cells causes them to respond to a drug that targets inhibitory synapses. It turned out that bumetanide, a long-used, federally approved diuretic, targets chloride receptors in the kidney. These receptors also are found in human brains, with the numbers found in infant brains surpassing those in adult brains. To win the U.S. Food and Drug Administration’s approval for repurposing this drug for infant epilepsy, Jensen and her colleagues had to prove that the drug targeted neural chloride receptors in animal brains, and then show that such receptors were also in the human brain.

Jensen’s team then encountered the first of several regulatory hurdles that precede clinical trials – the institutional review board, or IRB, which ensures patient safety. Because Jensen’s trial would involve three Harvard hospitals – Brigham and Women’s, Children’s, and Massachusetts General – it needed approvals from three separate IRBs. “It took about 18 months,” Jensen recalls. That process has since been streamlined through a combined IRB, thanks to Harvard Catalyst.

Jensen hopes to tap this eased process when a new mechanism she is investigating, one that blocks the progression to epilepsy, moves from animal to human studies. But since this mechanism might be a new rather than repurposed agent, yet more steps – involving, for instance, medicinal chemistry, toxicology, and drug metabolism – may be required. For those steps, academic institutions, which rarely have the needed expertise or infrastructure, often need to contract with industry.

Captains of Industry

To better his chances of catching the eye of an industry collaborator, Randall King tapped a special gap-funding program to research improvements to the uptake and potency of a compound that could help degrade proteins linked with Alzheimer’s disease.

King and Finley were exploring why ubiquitin, a small regulatory protein that normally helps neurons dispose of misfolded proteins, sometimes fails. Wayward proteins accumulate, forming the signature plaques of neurodegenerative diseases. Finley, an

HMS professor of cell biology, and King, an HMS associate professor of cell biology, discovered that, in cell cultures, the enzyme Usp14 slows the degradation of an Alzheimer's disease-linked protein. So the researchers began to hunt for a Usp14 inhibitor.

They worked with Byung-Hoon Lee, an HMS research fellow in cell biology who, using the School's Institute of Chemistry and Cell Biology-Longwood screening facility, developed a high-throughput-screening assay to search for molecules that inhibited only Usp14. The strongest candidate, christened IU1, easily entered both mouse and human cells in cultures and boosted ubiquitin's beneficial activity. Although the results were good, they weren't attractive enough for investors. "Pharmaceutical companies tend to have a weak appetite for risk," says King.

To make their invention more viable for development and commercialization, the researchers needed to demonstrate that the molecule could penetrate neurons. And they needed to boost the molecule's potency. Those steps required more medicinal chemistry than they could provide. It was a perfect project for the Accelerator Fund. Kohlberg, who oversees the program, says this early stage of technology development is where many promising university technologies run aground. "The Accelerator Fund enables early innovations to achieve preliminary validation," he says, "and selects early-stage technologies that manifest significant translational promise."

King and Finley now have a compound that not only can cross the blood-brain barrier but is also ten times more potent than the previous compound. "That work made the innovation more attractive to potential industry partners," says King. As a result, OTD identified potential partners, held discussions with a number of industry groups, and recently concluded a major agreement with a biotech company, Proteostasis Therapeutics, for the development and commercialization of this technology.

"This progress would have been impossible without the Accelerator Fund," Kohlberg says. "The fund not only supported the project, enabling the key medicinal chemistry work to be done, but also devised an effective intellectual property strategy and undertook a dedicated marketing and licensing program. All of these steps culminated in our now having a strong industry partner that's committed to the commercial development of this technology and that can, we hope, take it to the clinic in the near future." If all goes well, Finley points out, it will still be two to three years before the scientists can test their molecule in human studies.

Doctoring Peppers

Even after their disappointing first attempt, Clifford Woolf and Bruce Bean wanted to see their work result in pain medications. As they pondered new approaches, they came up with chili peppers.

Bean knew that capsaicin, the molecule that puts the sizzle in certain peppers, opens a channel called TRPV1 in pain-sensing nerve cells. A scientist seeking to alleviate pain in a research model would normally try to block this channel. But Bean and Woolf realized they could also use capsaicin as a way to guide and deliver a painkiller inside pain-sensing neurons without affecting muscles or other neurons. When considering which pain medication to pair with capsaicin for delivery, the researchers hit upon QX-314, a derivative of the common anesthetic lidocaine. Their vision: a capsaicin/QX-314 package delivered through local injection to ease the pain of childbirth and postsurgical pain.

The time seemed ripe to pursue an industry partner for development and commercialization. This time, OTD identified and held discussions with a number of established companies with relevant expertise. Those led to the negotiation and conclusion of a major licensing and collaboration agreement with Endo Pharmaceuticals, which will navigate the regulatory hurdles when it comes time to apply for safety trials in humans, possibly next year.

The imperatives of translational medicine and the importance of collaborating with industry are inextricably related, Kohlberg says. “With rare exception,” he adds, “it’s only through licensing and collaboration with industry partners that early-stage inventions made in academic labs can reach fruition and culminate in a new FDA-approved drug. And such a culmination in therapy represents in many ways the ultimate fulfillment of our core mission to serve the public interest.”

Another important feature of agreements with industry relates to intellectual property rights and the right to publish. “When industry funds research in our laboratories, we expect to be able to publish those findings,” says Flier. Industry has traditionally sought to sequester results as proprietary as often and as long as possible. More and more, though, industry realizes it’s important to publish results, and researchers acknowledge the need for patent protection.

“The right to disseminate research results is sacrosanct,” Kohlberg says. “In all of our agreements with industry, we make certain that the right to publish is inviolable – it is absolutely protected and guaranteed.”

Previously, industry and academia each believed it could do everything alone. “In the past, partnering with industry was a bit frowned upon,” Jensen recalls. “But actually, it’s a necessary relationship. How else can drugs get to patients? Medical schools aren’t set up to make drugs.”

As for Woolf and Bean’s first failed trek, not all was lost. In the reverse of a spinout, Woolf brought one of Solace’s programs back into his laboratory for further

development. The path across the formerly formidable Valley of Death might just turn out to be a two-way street.

Conflicts of interest

It wasn't precisely his bout with mononucleosis that led David Knipe into a career in virology. By the time Knipe, now the Higgins Professor of Microbiology and Molecular Genetics at HMS, lost a semester of college to the illness, he had been primed to become a virologist by a string of inspiring courses and a stint in a leading-edge laboratory. But the combination of illness and inspiration sealed that deal, involving Knipe in academia-based innovation, and now, with the aid of Harvard's Office of Technology Development, a licensing agreement with a manufacturer that may produce a vaccine for herpes simplex 2, the cause of genital herpes.

In his HMS laboratory, Knipe developed a replication-deficient form of the virus. In mice, the mutant virus triggered an immune response without reproducing. Knipe's hope is to develop a vaccine for humans based on the mutant. That task – and the clinical trials to test his innovation's safety and efficacy – will fall to Sanofi Pasteur. "This vaccine needs to be tested in people," says Knipe. "Without this agreement, that wouldn't happen."

At HMS, such academic-industry partnerships are carefully tended to guard against conflicts of interest, whether real or perceived. The School's policy aims to ensure that academic research remains robust and unfettered, and that industry involvement remains collaborative and fruitful. Overall, the goal is to translate ideas into powerful new medicines, devices, and technologies, a goal underscored by Jeffrey Flier, dean of Harvard Medical School, when he announced a revamped conflicts-of-interest policy last summer.

"Neither academia nor industry alone is equipped to develop the therapies so desperately needed to eradicate diseases worldwide," says Flier. "For this reason, we are committed to encouraging collaborations between our faculty and industry while ensuring the transparency of those relationships through a policy that further codifies and enforces our high standards."

The revised policy upholds the ability of HMS faculty to license technology to pharmaceutical and biotechnology companies, hold equity in such companies, serve on their scientific boards, and establish new ventures. At the same time, the policy prohibits academic-industry links that might adversely influence the integrity of such ties. Faculty can no longer accept, for example, personal gifts or any travel and meals from industry, other than those received during allowed activities. As of July 2011, faculty members are barred from participating in industry speakers' bureaus or accepting any speaking engagement that would dictate the faculty member's presentation content.

In the realm of medical education, the policy reinforces restrictions barring sales and marketing representatives of medical drug, device, or supply companies from accessing medical students. Continuing medical education courses may no longer be sponsored by a single company, and industry advertising and exhibits at continuing medical education events are restricted.

The conflicts-of-interest policy addresses the challenges of academic-industry collaborations, says Flier, while maintaining the School's commitment to advancing research in human diseases. To review the policy, visit the Integrity in Academic Medicine website: <http://hms.harvard.edu/about-hms/integrity-academic-medicine>

– Cathryn Delude

Back from the Dead

Sound progress is being made in efforts to regenerate sensory cells.

Hearing aids and cochlear implants bring sound into the lives of many with hearing loss. Both devices compensate for missing hair cells and auditory neurons, the delicate structures of the inner ear that receive, amplify, and translate sound into electrical signals to be processed by the brain. But these devices treat the symptoms of the loss, not the cause.

Researchers at the Massachusetts Eye and Ear Infirmary (MEEI) and the Harvard Stem Cell Institute hope to offer patients another treatment option – drug cocktails that coax the inner ear into growing new sensory cells. Albert Edge, an HMS associate professor of otology and laryngology at MEEI, and his colleagues study adult stem cells of the cochlea. Although these cells initially divide and transform into sensory cells, by puberty they become inactive.

Edge's team maps the process by which these stem cells develop specific functions, identifying factors that push them toward particular fates. The Edge lab and other groups have discovered, for example, that activation of the transcription factor Atoh1 transforms cochlear stem cells into hair cells. Working at the Harvard NeuroDiscovery Center, Edge's team applied more than 100,000 chemicals one by one to cell colonies and identified roughly a hundred that boost Atoh1 levels. Next, they must validate the findings in cochlear stem cells.

"Our ultimate goal is to identify chemicals that will activate patients' endogenous stem cells," says Edge. "We may need to administer a series of compounds to the inner ear to achieve this result."

That effort would also require sophisticated vehicles for delivering drugs to the cochlea, which hides behind a blood-perilymph barrier. Led by Michael McKenna of MEEI and Jeffrey Borenstein of MIT and Draper Laboratory, a team of auditory scientists and engineers – including Sharon Kujawa and William Sewell, both HMS associate professors at MEEI – has created one possible candidate. Working in guinea pigs, the researchers are developing a remote-controlled device that sits behind the ear in the mastoid cavity and stores drugs in a reservoir. At the press of a button, the device releases the drugs, which travel through a tube that winds from the middle ear into the cochlea.

"We can use this device to infuse the inner ear with drugs that prevent the degeneration of sensory cells," says McKenna, an HMS professor of otology and laryngology. "After we learn more about the endogenous stem cells, we can tackle those too."

– Alyssa Kneller

The following articles are selections from news at Harvard Medical School

Method Sharpens Aim for Pain Relief

October 12, 2007

Imagine a shot of Novocain or an epidural block that prevents pain completely but does not numb the face or paralyze the legs. Trips to the dentist, childbirth, and surgery would be more manageable for the doctor and the patient. And since patients could be mobile more rapidly, recovery after surgery and the risk of complications might be reduced. Research by scientists at Massachusetts General Hospital and HMS has brought this milestone a step closer by selectively inhibiting pain-sensing neurons in rats without interfering with other types of nerve cells.

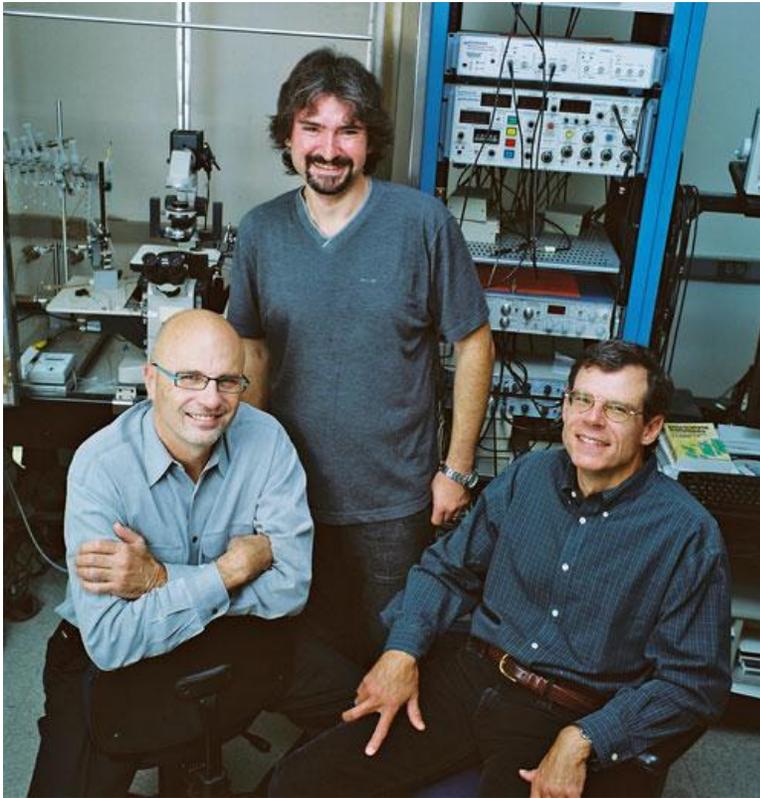


Photo by Graham Ramsay

From left, Clifford Woolf, Alexander Binshtok, and Bruce Bean blocked electrical signaling in the pain-sensing neurons of rats without interfering with either motor function or sensitivity to nonpainful stimuli.

The experimental animals received injections near the sciatic nerve and subsequently lost the ability to feel pain in their paws. But they continued

to move normally and react to touch. The injections contained QX-314, a normally inactive derivative of the local anesthetic lidocaine, and capsaicin, the active ingredient in chili peppers. In combination, these chemicals targeted only pain-sensing neurons, preventing them from sending signals to the brain.

“We’ve introduced a local anesthetic selectively into specific populations of neurons,” explained [Bruce Bean](#), HMS professor of neurobiology and an author on the paper, which appears in the Oct. 4 *Nature*. “Now we can block the activity of pain-sensing neurons without disrupting other kinds of neurons that control movements or nonpainful sensations.”

“We’re optimistic that this method will eventually be applied to humans and change our experience during procedures ranging from knee surgery to tooth extractions,” added senior author [Clifford Woolf](#), the Richard J. Kitz professor of anesthesia research at MGH.

Despite enormous investments by industry, surgical pain management has changed little since the first successful demonstration of ether at MGH in 1846. General and local anesthetics work by interfering with the excitability of all neurons, not just those that sense pain. These drugs have pronounced side effects, such as loss of consciousness in the case of general anesthetics and temporary paralysis with local anesthetics. “We’re offering a targeted approach to pain management that avoids these problems,” said Woolf.

Red Hot Research

The new work builds on research done since the 1970s showing how electrical signaling in the nervous system depends on the properties of ion channels. “This project is a perfect illustration of how research trying to understand very basic biological principles can have practical applications,” said Bean.

“Now we can block the activity of pain-sensing neurons without disrupting other kinds of neurons that control movements or nonpainful sensations.”

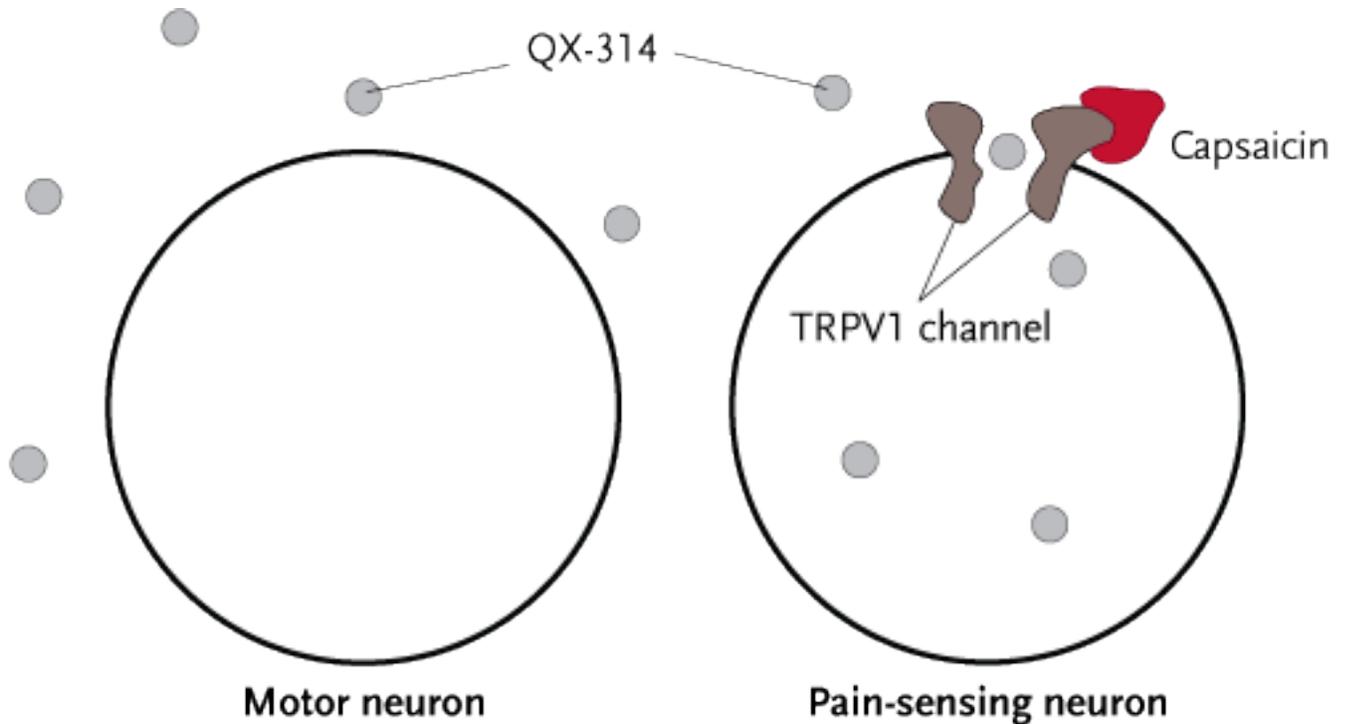
The new technique exploits the membrane-spanning protein TRPV1, which is unique to pain-sensing neurons. It forms a channel enabling large molecules to enter and exit the cell. A molecular gate typically blocks this passage, but it opens when cells are exposed to heat or the hot pepper ingredient capsaicin. Exposing the pain-sensing neurons to capsaicin leaves the channels open while other neurons are unaffected since they do not have the TRPV1 channels.

The technique also takes advantage of a property of the lidocaine derivative QX-314. Unlike most local anesthetics, QX-314 cannot penetrate cell membranes to block the excitability of the cell; it typically stays outside of neurons, where it has no effect. When pain-sensing neurons are exposed to capsaicin, however, the gates guarding the TRPV1 channels open, and QX-314 can enter the cells. Once inside, it plugs up sodium channels like any other local anesthetic molecule, interfering with neuronal communication by stopping the flow of ions and thereby shutting down electrical signals emanating from the cells.

Path to Prime Time

The team first tested its method in the petri dish. Alexander Binshtok, an instructor in anesthesia in Woolf’s lab, applied capsaicin and QX-314, separately and in combination,

to isolated pain-sensing and other neurons and measured their responses. The combination of capsaicin and QX-314 selectively blocked the excitability of the pain-sensing neurons, leaving the others unaffected.



Alyssa Kneller

Exclusive entry. Capsaicin—the active ingredient in chili peppers—opens TRPV1 channels on pain-sensing neurons, allowing the lidocaine derivative QX-314 to enter the cells. There it disrupts electrical signaling by blocking sodium channels. Other neurons do not possess TRPV1 channels, so they stay active.

Next, Binshtok injected these chemicals into the paws of rats and tested their ability to sense pain by placing them on a heat source. The animals tolerated much more heat than usual. He then injected the chemicals near the sciatic nerve and pricked the animals' paws with stiff nylon probes. The rats ignored the provocation. Although they seemed immune to pain, they continued to move normally and respond to other stimuli, demonstrating that QX-314 had failed to penetrate their motor neurons.

Before this technique can be applied to humans, however, the researchers have to overcome several hurdles. They must figure out how to open the TRPV1 channels without producing even transient burning pain before the QX-314 can enter and block the nerve cells. And they have to prolong the effect of the drug by tinkering with its formulation.

“Eventually this method could completely transform surgical and postsurgical analgesia, allowing patients to remain fully alert without experiencing pain or paralysis,” said Woolf. “In fact, the possibilities seem endless. I could even imagine using this method to treat itch, as itch-sensitive neurons fall into the same group as pain-sensing ones.”

– Alyssa Kneller

Common Genetic Variant Dampens Pain

At Least One Quarter of People Estimated to Carry Pain-tolerant Haplotype

October, 27, 2006

How we handle pain is often assumed to reveal something about our character. A person who suffers stoically or bounces back after an injury is seen as brave, while another person who constantly feels pain and remains bedridden after surgery might be branded as weak or complaining. But what if our ability to feel and tolerate pain were as programmed as our height or hair color? Our response to pain is undoubtedly more complex, but research is showing that the perception of pain varies among animals and people, and at least some of the differences are based on genetics.



Photo by Graham Ramsay

“There is a heritable component of the way we react to pain,” said Clifford Woolf (second from right), who, with lab members (from left) Michael Costigan, Joachim Scholz, and Alex Binshtok, uncovered a molecular pathway that helps determine pain sensitivity.

In a study published online Oct. 22 in *Nature Medicine*, Clifford Woolf and

colleagues identify a biochemical pathway that helps control how animals respond to pain by altering levels of neurotransmitter production. Further, the researchers reveal a genetic variation in some humans that is associated with lower pain sensitivity and a faster recovery after surgery.

“It started off as a fishing expedition,” said Woolf, the Richard J. Kitz professor of anesthesia research at Massachusetts General Hospital. His team was conducting multiple microarray analyses on cells to identify all the genes that were switched on or off by pain responses in the peripheral nerves and spinal cord of rats. From a sea of 1,500 genes that surfaced, the team was able to narrow the candidates successively, first by limiting them to genes that were upregulated for months at a time and then focusing on those shared by three different pain models. Still faced with more than 100 genes, the team then looked for genes that were part of a complex or pathway, which might be more significant than a gene acting alone. With that, the researchers found their fish: three related genes that were highly active in injured nerve cells.

The Regulator

The genes were involved in synthesizing BH4, a cofactor needed to produce critical signals in neurons, such as nitric oxide, serotonin, dopamine, and norepinephrine. This molecule had been well studied, but not as a regulator of pain. Woolf said that BH4 is known to play a necessary role in the synthesis of these signals. But “what wasn’t appreciated is if you have more of the cofactor, you get more of the reaction,” he said. It was possible that too much BH4 might lead to neuropathic pain, which some people experience after nerve damage, injury, or medical conditions like arthritis and diabetes.

Models for pain sensitivity measure the threshold at which an animal withdraws its hindpaw when exposed to a stimulus like touch or cold. When the animals have a nerve injury elsewhere in the body, they become hypersensitive to these signals. “Sensory information in undamaged axons is interpreted as pain,” Woolf said. Woolf’s team found that BH4 and its related enzymes were upregulated in these animals and that injecting a drug that inhibits GTP cyclohydrolase, one of the enzymes involved in producing BH4, could return the rats to normal sensitivity. “It didn’t make them unreactive; it just removed the abnormal pain hypersensitivity,” Woolf said. Injecting BH4 into normal rats could also make them extra sensitive to pain.

The Less Sensitive Type

Meanwhile, Mitchell Max, a co-author on the paper and chief of clinical pain research at the National Institute of Dental and Craniofacial Research, was also looking for causes of pain hypersensitivity, but from a different angle. Max had learned that pain sensitivity was about 50 percent heritable in mice and rats. He wanted to explore the genetic basis of pain in humans and to bring some of the growing molecular knowledge about pain in animals to bear on human genetics. Max identified a large pain study in humans that offered data on patients’ responses to pain, collected blood samples from the patients, and began scanning their DNA for differences in the most likely pain genes. Unfortunately, “it was a total bust,” he said.

“Here we’ve got a mutation that’s actually adaptive; it protects you. There are people out there who are not insensitive to pain, but just feel less pain than others.”

He talked with Woolf's group, knowing that they had been performing a series of microarray studies. They suggested their top gene candidates, including those in the BH4 pathway. Using data from a group of 168 people who had undergone spinal-disk surgery as a treatment for sciatica, Max's team discovered a genetic variation that seems to protect against undue pain: a haplotype of the gene encoding GTP cyclohydrolase (GCH1) that was associated with less pain a year after surgery. The variant is common – 25 to 30 percent of people have at least one copy. In another cohort of 400 people who were tested for responses to experimental pain, those who carried two copies of the protective haplotype were significantly less sensitive to pain.

To determine how the genetic variation works, the team examined blood cells of patients from the first cohort and found that cells of patients with the protective haplotype produced less BH4 when they were stimulated with a drug that leads to the transcription of GCH1. Presumably, the genetic variation works in neurons in the same way. "The gene is fine, but it doesn't respond in the same way to transcription factors," Woolf said. A subtle change in GCH1 could have wide-ranging effects on the dynamics of neurotransmitter production, keeping a cell from responding too aggressively to stimuli.

Woolf said that certain people who tolerate unpleasant conditions, such as having their arm placed in a bath of ice water, often fare better after surgeries. "We now think it's because those individuals really do feel less pain," he said. Though most genetics has focused on mutations that cause disease, "here we've got a mutation that's actually adaptive; it protects you. There are people out there who are not insensitive to pain, but just feel less pain than others."

Max said that genetic studies can help translate basic research in pain into drug development: a protective phenotype offers evidence that this pathway is important in humans. Woolf is involved in a company, Solace Pharmaceuticals, that will be looking for ways to target this pathway chemically in humans. The researchers speculate that many other genetic variations underlie the pain response, and it will be interesting to see whether some of the behavioral and lifestyle differences among people can be explained by their differing abilities to feel pain.

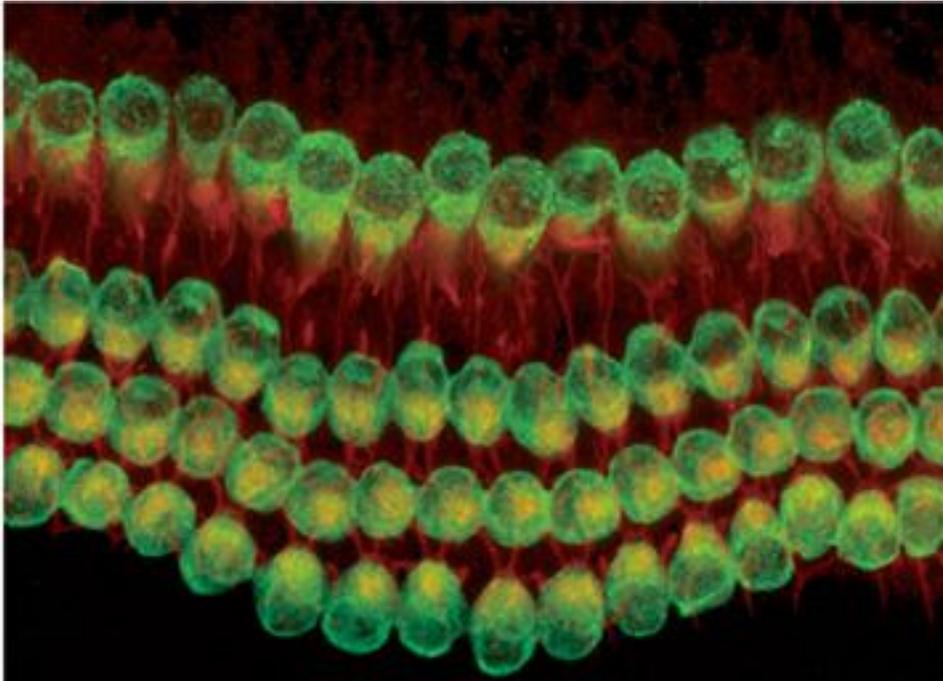
– Courtney Humphries

Hearing Restored after Noise Damage

In promising therapy for deafness, hair cells regrown in ears of mice

By MARY LEACH

January 9, 2013



In a normal cochlea, three outer rows of hair cells and one inner row can be seen. Image courtesy Albert Edge/Mass. Eye and Ear

Researchers at Massachusetts Eye and Ear and Harvard Medical School have demonstrated for the first time that hair cells can be regenerated in an adult mammalian ear by using a drug to stimulate resident cells to become new hair cells, resulting in partial recovery of hearing in mouse ears damaged by noise trauma. This finding, reported in the Jan. 10 issue of *Neuron*, holds great potential for future therapeutic application that may someday reverse deafness in humans.

“Hair cells are the primary receptor cells for sound and are responsible for the sense of hearing,” explains senior author, [Albert Edge](#), HMS associate professor of otology and laryngology at Mass. Eye and Ear. “We show that hair cells can be generated in a damaged cochlea and that hair cell replacement leads to an improvement in hearing.”

Hearing loss is a significant public health problem affecting close to 50 million people in the United States alone. [Sensorineural hearing loss](#) is the most common form and is caused by the loss of sensory hair cells in the cochlea. Hair cell loss results from a variety of factors including noise exposure, aging, toxins, infections, and certain antibiotics and anti-cancer drugs. Although hearing aids and cochlear implants can ameliorate the symptoms somewhat, there are no known treatments to restore hearing, because auditory hair cells in mammals, unlike

those in birds or fish, do not regenerate once lost. Auditory hair cell replacement holds great promise as a treatment that could restore hearing after loss of hair cells.

In the experiment, the researchers applied a drug to the cochlea of deaf mice. The drug had been selected for its ability to generate hair cells when added to stem cells isolated from the ear. It acted by inhibiting an enzyme called gamma-secretase that activates a number of cellular pathways. The drug applied to the cochlea inhibited a signal generated by a protein called Notch on the surface of cells that surround hair cells. These supporting cells turned into new hair cells upon treatment with the drug. Replacing hair cells improved hearing in the mice, and the improved hearing could be traced to the areas in which supporting cells had become new hair cells. “The missing hair cells had been replaced by new hair cells after the drug treatment,” Edge said, “and analysis of their location allowed us to correlate the improvement in hearing to the areas where the hair cells were replaced.”

This is the first demonstration of hair cell regeneration in an adult mammal. “We’re excited about these results because they are a step forward in the biology of regeneration and prove that mammalian hair cells have the capacity to regenerate,” Edge said. “With more research, we think that regeneration of hair cells opens the door to potential therapeutic applications in deafness.”

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A full list of authors and affiliations and full acknowledgement of all contributors is available in the pdf of the paper, [“Notch Inhibition Induces Cochlear Hair Cell Regeneration and Recovery of Hearing after Acoustic Trauma.”](#)

Mary Leach is director of public affairs for Massachusetts Eye and Ear.

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<http://neuro.med.harvard.edu/>

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<http://www.masseyeandear.org/>

Bertarelli Program in Translational Neuroscience and Neuroengineering

www.hms.harvard.edu/bertarelli/index.html

Joseph B. Martin, MD, PhD

Harvard Medical School Neurobiology Bio

<http://neuro.med.harvard.edu/faculty/martin.html>

Alfalfa to Ivy: Memoir of a Harvard Medical School Dean by Joseph B. Martin

<http://www.alfalfatoivy.com/>

Clifford Woolf, MD, PhD

Harvard Medical School Neurobiology Bio

<http://neuro.med.harvard.edu/faculty/woolf.html>

Boston Scientists Take Steps in Growing Cells for Hearing

The Boston Globe, January 9, 2013

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Featured Doctor: Clifford Woolf

Massachusetts General Hospital article

http://www2.massgeneral.org/anesthesia/index.aspx?page=news_media&subpage=121808_featured_doctor_woolf

Finding new ways to solve hearing problems

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Genes that fly in the face of pain

Boston Children's Hospital article

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