NEW FACE, NEW BEGINNING
INSIDE THE MOST EXTENSIVE FACE TRANSPLANT IN HISTORY

THE SCIENCE OF SENSORY OVERLOAD
3D-PRINTED BODY PARTS
GUT BACTERIA & PANCREATIC CANCER
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Teamwork: the Cornerstone of Outstanding Medical Care

TIME AND TIME AGAIN, we see that hospital patients do best when the people caring for them share common goals and values, communicate effectively, and solve problems as a group rather than in isolation. Members of these teams have each mastered their own roles, know they can depend on each other, and thrive in environments conducive to collaboration and coordination. A dramatic example of this is the NYU Langone team that recently performed the most extensive face transplant in history.

In case you missed the headlines, Patrick Hardison, the recipient, is a 41-year-old father of five and former volunteer firefighter whose face was severely disfigured in the line of duty 14 years ago. Last August, he underwent a 26-hour marathon surgery, led by Eduardo D. Rodriguez, MD, DDS, the Helen L. Kimmel Professor of Reconstructive Plastic Surgery and chair of the Hansjörg Wyss Department of Plastic Surgery, to replace the skin and underlying tissue of his face, head, and neck. The operation was a success, thanks to Dr. Rodriguez's team of over 100 experts, drawn from a remarkably wide range of disciplines, from plastic surgery and transplant medicine to social work and psychology. Many of them trained together for over a year, rehearsing every step of the procedure over and over again until they could do it their sleep. You can read about their remarkable effort on page 10. I think you’ll agree that their story is a true testament to the power of collaboration.

Elsewhere in this issue, you’ll find other inspiring stories of medicine at its best: the neurologist and pediatric neurosurgeon who embarked on a daring surgery to save a young boy’s life, a psychiatrist whose basic research is elucidating the neurobiological roots of attention deficit hyperactivity disorder, and the physicians who are capitalizing on the power of 3D printing to improve surgical outcomes.

It’s endeavors like these that help put our institution at the forefront of academic medicine. I hope you enjoy reading about them.
The idea is not to improve the technology of imaging but to reconfigure how physicians interact with radiology services and radiologists.  REDESIGNING RADIOLOGY, PAGE 4 →
NEWS FROM MEDICINE

REDESIGNING RADIOLOGY

A $4 million federal grant funds an innovative project, led by NYU Langone, to rethink the day-to-day practicalities of radiological testing.

S

TEVE JOBS once said that design is “not just what it looks like and feels like. Design is how it works.” The visionary Apple CEO was talking about the iPod, the gadget that transformed the music industry, but his philosophy has struck a chord among researchers at NYU Langone.

Funded by a four-year, $4-million grant from the U.S. Agency for Healthcare Research and Quality, an innovative partnership between radiologists and population-health experts at the Medical Center aims to reimagine how radiology works in sprawling healthcare systems. The idea is not to improve the technology of imaging but to reconfigure how physicians interact with radiology services and radiologists, and vice versa. “Our goal is to determine how radiologists and non-radiologists can work together to improve patient safety and clinical outcomes,” says Soterios Gyftopoulos, MD, assistant professor in the department of radiology, who is among five NYU Langone researchers leading the project.

Radiology is not more error prone than any other aspect of medicine. The problem is that over the years, radiology has ingrained itself into virtually every medical specialty and every healthcare setting, with too little attention paid to the day-to-day practicalities of ordering tests, communicating findings, or managing follow-ups.

“If you need surgery, you go to the appropriate expert: a surgeon,” explains project co-leader Leora Horwitz, MD, associate professor of population health and medicine, and director of the Center for Healthcare Innovation and Delivery Science at NYU Langone. “But if you need a radiology test, it’s ordered by your primary care doctor, your orthopaedist, your oncologist, and so on. It’s not done by the radiologist, the one who really knows which type of scan is better to answer a given question.”

A second issue concerns how results are communicated. “A radiologist might report that there’s a 1-centimeter-wide cyst in the ovary, with the classic recommendation: ‘Clinical correlation advised,’” says Dr. Horwitz. “A more standardized report, with concrete guidance and a reference to supporting evidence would be much more helpful.”

Then there’s the issue of follow-up. “Let’s say an ER patient with a bad cough gets a CT scan that reveals a small lung nodule,” says Dr. Horwitz. “That scan should probably be repeated in a year to make sure it’s not cancer. But if I’m your primary care doctor, how do I know you’ve had a scan? How do I remember a year from now to follow up? I’m not pulling up charts of all my 5,000 patients every day.”

Considering that 400 million radiological tests are performed in the U.S. each year, the consequences of ignoring these issues are huge. If only a tiny fraction of those tests go awry, that puts a sizeable number of patients at risk for duplicative or inappropriate tests and delayed or missed diagnoses.

The team’s solution is the NYU Patient Imaging Quality and Safety Laboratory (PIQSL), which will connect an interdisciplinary group of clinicians and researchers at NYU Langone with experts at NYU’s Wagner School of Public Policy, its Stern School of Business and the award-winning design firm IDEO. This variegated group will work together on three complementary projects that will revamp the ambulatory radiology ordering process, reconfigure the inpatient interventional radiology consultation process, and create a new follow-up system.

“This is not just about having a good IT system,” says Dr. Horwitz. “This is about how people organize their work, and that involves culture, management, workflow, staffing—the kinds of things that people often take for granted but are fundamental to a well-functioning system.”

—GARY GOLDENBERG
HIJACKING THE IMMUNE SYSTEM

A rogue immune receptor conspires with gut microbes to fuel pancreatic cancer.

C

ENTRAL TO a healthy immune system is a family of proteins known as toll-like receptors, or TLRs, that acts like a pack of watchdogs trained to recognize and warn of dangerous microbes. “Their primary job is to bind by-products of infectious agents, such as bacteria and viruses and fungi, and mount an immune response,” says George Miller, MD, associate professor of surgery and cell biology at NYU Langone Medical Center. Other researchers have found that these receptors, discovered in the 1990s, can also bind the by-products of inflammation and cell death—the body’s own “inflammatory junk”—and turn on a potent immune response that, in select circumstances, can target cancerous cells for destruction.

In a new twist reported in *The Journal of Experimental Medicine*, Dr. Miller and colleagues recently found that at least one TLR protein can be co-opted by an aggressive pancreatic cancer. In susceptible mice, the researchers discovered that a TLR protein known as TLR9 can actually promote the equivalent of human pancreatic ductal adenocarcinoma. Deleting the receptor’s gene or blocking its function, conversely, protected the mice against tumor progression—an unexpected finding that points to a potential therapeutic target for a devastating disease.

More than 95 percent of patients succumb within five years of being diagnosed with pancreatic ductal adenocarcinoma, making it the fourth deadliest kind of cancer in the United States. Chronic inflammation of the pancreas can increase the risk of this cancer by 15-fold, and multiple studies have linked inflammation to the cancer’s progression. The mechanism behind the initial tumor formation, however, has remained unclear.

The new study’s key experiments used mice with a pancreatic cancer–linked genetic mutation. When the researchers activated TLR9 by adding the right mix of molecular bait for the protein to recognize and latch onto, tumor formation ensued, and the cancer accelerated. In these mice, additional experiments showed that the receptor gets turned on in a subset of pancreatic cells that mature and then pump out chemicals that promote tumor cell proliferation and keep the immune system suppressed within the tumor.

By genetically blocking or deleting the gene for TLR9, the researchers were able to protect the mice from tumor formation and improve their odds of survival. “The clinical implication is to potentially use this strategy in patients who are at high
risk for pancreas cancer, to block TLR9,” Dr. Miller says. Several research groups are already investigating small molecules that may block the receptor and work as anticancer agents.

Intriguingly, the research findings also implicate the microbiome, or the entire collection of microbes that naturally inhabit the gut, in pancreatic cancer. The study suggests that certain gut-dwelling bacteria can move into the pancreas. Once there, bacterial DNA sequences bind to TLR9, which then signals pancreatic cells to begin releasing the tumor-aiding chemicals.

This pancreatic cancer—boosting mechanism, it seems, may be hijacking a microbial system originally intended to ensure that the body’s immune system doesn’t attack naturally occurring microorganisms. “It’s a circumstantial thing. You’re not going to get pancreatic cancer just from the microbes,” Dr. Miller says. In someone with the right cancer-promoting genetic mutation, however, the microbes may help tip the scales toward tumor formation.

In other studies, Dr. Miller’s group has identified a shift in the microbial profile of patients with pancreatic ductal adenocarcinoma, when compared to healthy counterparts. More-detailed information about which microbes are setting those patients apart could be applied to follow-up studies in mice to zero in on the molecular factors that may be turning our natural watchdogs against us, causing them to dampen the immune system and abet the deadly cancer. • —BRYN NELSON

IN 2008, New York City became the first place in the country to require fast-food restaurants and coffee chains to post calorie counts for their food and drinks. The antiobesity measure, officials hoped, would allow consumers to be better informed about their food choices and respond by cutting back on their overall calories.

Research has shown that consumers fare poorly when estimating calories on their own, but that they read calorie displays in restaurants. A new study by researchers at NYU Langone Medical Center, however, reinforces the idea that the added information alone may not be enough to change consumers’ eating habits.

Brian Elbel, PhD, associate professor of population health and medicine, led earlier efforts that cast doubt on the impact of New York City’s calorie-labeling policy about a year after it went into effect. For a study published in a recent issue of the journal Health Affairs, the same group took a longer-term view of the policy. “Five to six years after labeling started, we still didn’t see any change in total calories purchased,” Dr. Elbel says.

The new study also suggested that the number of people who reported seeing and using the calorie labels was declining over time. “I think what that shows us is that while a subset of people are still seeing and using this information, we haven’t seen any population-level shift in the number of calories purchased as a result of labeling policies at fast-food restaurants,” Dr. Elbel says.

For the study, research assistants asked 7,699 people entering McDonald’s, Wendy’s, KFC, and Burger King restaurants to return their itemized receipts and answer a few follow-up questions in exchange for $2. The objective measure of calories purchased helped the researchers calculate what the consumers likely ate in all. The study compared calories consumed at the fast-food restaurants in New York City to the same restaurant chains in nearby New Jersey cities that lacked calorie displays. After tallying the numbers, the researchers found no significant difference between the two sets of consumers over time.

Dr. Elbel says the partial disconnect between people who still reported seeing and using the information but

IGNORING THE SIGNS
Federal law now requires calorie labeling on all menus in chain restaurants. But do the labels make a difference in how much we eat? A new study suggests not.

BRIAN ELBEL, PHD
ILLUSTRATION (FACING PAGE): ALEKSEI OSLOPOV / ISTOCK

NYU PHYSICIAN WINTER 2016
OR NEARLY half a century, scientists have known about the existence of a strange microbe that resembles spaghetti strands and dwells in the small intestines of mammals. Until only recently, no one could fully explain what these microorganisms—known as segmented filamentous bacteria, or SFB—were doing in the intestine or how they negotiated peace with the immune system. That mystery was partially solved in 2009 when a team of researchers led by Dan Littman, MD, PhD, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology at NYU School of Medicine, discovered in mice that SFB activate a subset of T cells known as T helper 17 cells. The immune system didn’t just tolerate the bacteria, the researchers found, but it seemed to rely on them as commensals, or beneficial microbes, to fight off pathogens.

DAN LITTMAN, MD, PHD

GUT INSTINCT

A new study reveals the mechanisms by which unusual bacteria in the small intestine bolster—or misdirect—the immune system.

F

“IT’S EXCITING because we’re finding really profound biological effects of these microbes,” says Dr. Littman.

Based on extensive molecular detective work, Dr. Littman and colleagues are now developing an even deeper understanding of this unusual partnership. In a recent paper published in Cell, the team partially mapped out the pathway by which SFB signal local patrols of these T helper 17 cells to quickly...
deploy and protect the intestinal wall from potential invaders. The new experiments add fresh evidence to support the hypothesis that other gut microbes might use similar tactics to activate specialized immune cells and trigger the release of infection-fighting molecules. The researchers’ work also suggests that friend could become foe if the signal sent by SFB or similarly acting microbes mistakenly switches the T helper 17 cells on in joints and other places where they aren’t needed. That faulty activation could turn the immune system against the body’s own tissue and trigger autoimmune diseases like rheumatoid arthritis.

“It’s exciting because we’re finding really profound biological effects of these microbes,” says Dr. Littman, a Howard Hughes Medical Institute investigator. “We’re beginning to get into the finer details, and this is critical to try to understand how different types of microbes can elicit different types of immune responses.”

Past research suggests that SFB can burrow into the mucosal lining of the outer wall of the intestinal tract and establish a physical communication link with cells by sticking to them. Some pathogenic bacteria, such as Salmonella, use this strategy to breach the intestinal barrier. Based on their recent study, Dr. Littman and his colleagues found that SFB take a friendlier approach, using the adhesion to boost the production of two proteins that activate T helper 17 cells in the wake of an injury.

In mice genetically engineered to lack these two proteins (known as serum amyloid A proteins 1 and 2), T helper 17 cells failed to produce the infection-fighting and inflammation-promoting molecules necessary for healing. When the team grew the cells in the lab and added the proteins back into the mix, the cells were once again able to produce the infection-fighting molecules. The results suggest a two-step activation process. In the first step, T helper 17 cells migrate throughout the gut and beyond, and prepare to fight. “The cells are poised,” says Dr. Littman. “They’re not going to do anything until they get some kind of an inflammatory signal.” In the second step, only those T cells that make it back to the ileum of the small intestine, where the SFB microbes dwell, receive the signal from the two proteins and begin churning out their infection-fighting molecules.

“There will probably be multiple types of bacteria that do what SFB does,” Dr. Littman says. “We need to identify bacteria that we can manipulate genetically, so we can really start taking apart the machinery to see what is it about those bacteria that elicits these very particular immune responses.”

● —BRYN NELSON
professor of cell biology, and neurology and neuroscience. “But we found a way to coax them and make them much better at it.”

The finding centers on sonic hedgehog, a well-studied gene whose encoded protein directs early brain development by sending signals that turn on other genes. Some scientists had suggested that boosting this protein’s signaling activity might aid myelin repair.

Instead, Dr. Salzer and colleagues have found just the opposite. “The big surprise from our study was that one of key endpoints in the hedgehog pathway actually turns out to be a brake on myelin repair,” says Dr. Salzer, whose team recently published its findings in the journal *Nature*.

In one set of experiments, the researchers effectively released that brake by genetically depleting the brain’s stem cells of GLI1, one of the genes normally turned on by sonic hedgehog. This disruption in hedgehog-directed signaling, they found, allowed the stem cells to be converted into a bigger crew of myelin-manufacturing specialists.

A second set of experiments yielded similar results. The scientists first inoculated mice with a protein that provoked the immune system to attack the neurons’ myelin covering, and then treated half of the afflicted animals with an experimental drug called GANT61, which has been previously shown to target GLI1. After a month on the drug, previously paralyzed mice regained most of their mobility, while their untreated counterparts remained severely disabled.

At the cellular level, the treated mice retained 50 percent more myelin, on average, and lost far fewer of the motor neurons that control movement in the lower extremities. By inhibiting the GLI1 protein, the GANT61 drug may free up the brain’s stem cells to orchestrate the necessary myelin repairs.

Translating these findings into an effective therapy will require a better understanding of how GLI1 proteins behave in humans, and Dr. Salzer believes a more potent drug will be needed. Even so, he says, the discovery of an “exciting target that hadn’t been explored” and his experimental results have earned his group a grant from the National Multiple Sclerosis Society and provided new momentum toward a badly needed clinical intervention.

—BRYN NELSON

### A KILLER GENE with a Not-So-Killer Name

Sonic hedgehog. It’s among the most memorable names in science. The hedgehog gene, discovered in fruit flies in the 1980s, plays a crucial role in early development. Researchers observed that fly embryos lacking it are covered in spiky, hedgehog-like projections, and the name stuck.

Since then, equivalent genes in humans, mice, and other animals have been discovered, including one named for Sonic the Hedgehog, the protagonist in a ‘90s video game. “It’s a whimsical name for a very serious molecule that has critical roles,” Dr. Salzer says. Sonic hedgehog mutations have been linked to cancer and a devastating disorder called holoprosencephaly, in which the brain fails to properly divide into its two halves.

Accordingly, some clinicians now prefer to use the gene’s more staid abbreviation: *SHH*.

—BR

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**NERVE FIBERS RENEWED**

A gene deletion restores mobility to rodents paralyzed by multiple sclerosis.
NEW FACE, NEW BEGINNING

Inside the 26-hour marathon surgery that gave firefighter Patrick Hardison a new face—and set a new standard for transplantation medicine

BY KENNETH MILLER
Eduardo D. Rodriguez, MD, announces the completion of the most extensive face transplant to date during a press conference held at NYU Langone Medical Center last November.
on August 14, 2015, surgeons lifted the skin from Patrick Hardison’s head as if pulling off a ski mask, exposing the underlying bone, muscles, ligaments, and blood vessels. With an electric saw, Eduardo D. Rodriguez, MD, DDS, removed the patient’s nasal and chin bones. The only features that remained recognizable were Hardison’s bright blue irises, staring out from naked eyeballs. “That’s when it became clear that there was no turning back,” recalls Leslie Bernstein, administrative director of NYU Langone Medical Center’s Hansjörg Wyss Department of Plastic Surgery and administrator of the Face Transplant Program. Watching from across the operating room, she remembered her long talks with Hardison, at the hospital and on a visit to his hometown, Senatobia, Mississippi.

The moment came approximately 12 hours after the start of the surgery—the most extensive face transplant ever performed—and 14 years after the catastrophe that upended Hardison’s life. The volunteer fireman ran into a burning house in September 2001, searching for a woman mistakenly believed to be trapped inside. When the ceiling collapsed, he managed to escape through a window, but his head and upper body were already on fire. Hardison was still in a medically induced coma when the 9/11 attacks occurred the following week. He lost his eyelids, ears, lips, and most of his nose, and was left with a mass of scar tissue from his scalp to his chest. Despite 71 reconstructive procedures, he remained unable to form normal facial expressions, to eat or laugh without pain, or to go out in public without attracting stares. He couldn’t blink or close his eyes. Although surgeons had sutured together flaps of skin to protect his vision, he was at risk of slowly going blind.

Now, the 41-year-old father of five lay anesthetized and utterly vulnerable, awaiting a new face from a young man who’d been fatally injured two days earlier. If all went well, Hardison would regain much of what had been taken from him. If things went badly, the likely scenarios were either death or a disfigurement more severe than before.

Dr. Rodriguez, the Helen L. Kimmel Professor of Reconstructive Plastic Surgery, chair of the Hansjörg Wyss Department of Plastic Surgery, and one of the leading surgeons in this field, had spent more than a year preparing the clinicians in this room—along with dozens of others—for the groundbreaking operation. Yet even he had put the odds of success at just 50-50.

Few other surgical procedures are as medically daunting
As a face transplant, and few raise as many complex ethical, philosophical, and psychological issues. “It’s at the far end of what we call the vascularized composite allografts,” observes Arthur Caplan, PhD, the Drs. William F. and Virginia Connolly Mitty Professor of Bioethics. “You’re transplanting skin, nerves, muscles, blood vessels, and other tissues all at once. The new face has to feel, taste, smell, communicate verbally and visually, and fit certain aesthetic criteria. And unlike a heart or liver, whose function is basically mechanical, a face is central to a person’s identity. Emotionally, it stands alone.”

Wanting a new face is generally not a matter of life and death. It can, however, profoundly improve a patient’s quality of life, complicating the risk-benefit calculations that must be made before any major surgery—especially a transplant, which requires the patient to take immunosuppressant medications indefinitely to prevent rejection.

The expense is another factor. A procedure that can cost nearly $1 million, including pre- and postoperative care, cannot be undertaken lightly, but the potential gains for other patients must also be considered. Although face transplantation is still in its infancy, it has already spawned technical innovations that may prove useful elsewhere in plastic surgery, transplant medicine, regenerative medicine, and beyond. The possible payoffs have attracted growing interest from some of the world’s leading academic medical centers, as well as the U.S. Department of Defense. The logistical challenges, meanwhile, have kept the pace of research slow.

The first face transplant was performed in 2005, on a French woman who’d been mauled by a dog; surgeons in Paris successfully replaced her nose, cheeks, lips, and chin. Since then, there have been 37 such procedures, but only a dozen have encompassed an entire face. Hardison’s would be the first to involve the scalp, as well, and to include functional eyelids. (In other cases, the recipients were blind, with no need to blink, or skin was simply grafted to existing eyelid muscles.) “No one had ever replaced this quantity of tissue before,” says Dr. Rodriguez. “There was no medical experience to show it was possible.”

As a boy, David Rodebaugh, the donor (left), dreamed of becoming a firefighter, like Patrick Hardison (right).

Dr. Rodriguez was determined to prove it could be done. The son of Cuban immigrants, he’d initially set out to become a dentist (he even graduated from NYU College of Dentistry) but found his vocation after a mentor recognized his talent with a scalpel. A prolific researcher as well as a sought-after surgeon, he has published extensively in peer-reviewed scientific journals. In 2012, while at the University of Maryland, he performed what was then the most ambitious face transplant ever, on a man who’d lost his lips, nose, and jaws in a shotgun accident; tissue from the hairline to the neck was replaced, including both jawbones and part of the tongue.

That surgery led to the recruitment of Dr. Rodriguez the following year by NYU Langone, which sought to build its own and expand its existing transplant program. “There’s a tremendous amount to learn from face transplants,” says Robert I. Grossman, MD, the Saul J. Farber Dean and CEO of NYU Langone. “How do we advance our microsurgical techniques? How do we improve interdisciplinary teamwork in the operating room? What are the psychiatric consequences? The surgery is a tour de force.”

So much so that it required assembling a team of over 100 physicians, nurses, technicians, and support staff, drawn from multiple disciplines, including plastic surgery, anesthesiology, radiology, ophthalmology, critical care, physical medicine and rehabilitation, psychology, psychiatry, and social work. It also required finding an inaugural patient. The ideal candidate would be someone capable of handling
the emotional stresses surrounding the procedure, of understanding the potential pitfalls, and of following the regimen necessary for a successful long-term outcome—not only taking an array of medications, but avoiding activities that could compromise the health of the graft, such as cigarette smoking or excessive sun exposure.

Hardison, who had approached Dr. Rodriguez before the surgeon’s move to New York, was already in the running, but before he could be selected, he had to undergo a battery of physical, psychological, and other evaluations. Dr. Rodriguez traveled to Senatobia (pop. 8,165) with several team members—administrator Bernstein; plastic surgeon Alexes Hazen, MD; psychologist Aileen Blitz, PhD; and senior social worker Sally Klein—to assess Hardison’s social and physical environment. They met with his friends, family members, primary care physician, pharmacist, and pastor. In the end, Hardison prevailed over two other candidates. “Patrick had proven his resilience over many years and many surgeries,” Dr. Blitz explains. “Although he was divorced, he was very involved with his kids and his community. He had lots of people behind him, including his old firefighting buddies and a brother who was willing to sign on as his designated caregiver. He was bright and motivated. All his ducks were in a row.”

And he fully grasped the possibility of failure. “There are things in life that are worse

**MAKING THE CUT**

**A Race against Time to Print the Perfect Surgical Tool**

Of the hundreds of surgical tools prepared for Patrick Hardison’s historic face transplant, perhaps none was more innovative than a set of plastic cutting guides custom built in Golden, Colorado, and express-delivered to NYU Langone on the day of the surgery. The guides, intended to steer the surgical blades as they sawed through bone, would ensure that the donor’s chin, nose, and cheekbones fit seamlessly on Hardison’s face.

The jigs could not be completed until a donor became available, but the manufacturer—3D Systems, a leader in the field of three-dimensional printing—spent a year planning for the actual surgery with NYU Langone. The teams in Golden and New York staged rehearsals with cadavers, honing the complex process so that the guides could be completed and delivered to the operating room during the early stages of the procedure. By the time David Rodebaugh’s body arrived at NYU Langone last August, says Katie Weimer, vice president, Medical Devices, 3D Systems Healthcare, “we knew down to the minute how long it would take”—just over 10 hours, from start to finish.

First, the company converted CT scans of both men’s heads into three-dimensional digital models. In online consultation with the surgeons, the Colorado team used the models to design templates enabling the donor’s bones to be snapped into place like puzzle pieces. The guides were then printed using a biocompatible resin, with each 0.15-millimeter layer cured by laser light before the next was added, a process that by itself took several hours.

When the donor arrived at the Medical Center, the modeling company began work on the guides. Three sets were printed, in case backups were needed, and the next morning, to allow for transportation mishaps, staffers hand-carried the sets from Colorado on three separate flights. The guides were in the surgeons’ hands by 11:00 a.m., ready to be sterilized and clamped into place on the donor’s and recipient’s faces.

“This case went flawlessly,” says Dr. Rodriguez, MD, DDS, the Helen L. Kimmel Professor of Reconstructive Plastic Surgery and chair of the Hansjörg Wyss Department of Plastic Surgery, who led the effort. “All of our pregame preparation really paid off.”

A computer model of the surgical cutting guides custom-printed for Patrick Hardison’s face transplant
“IF ANYONE WANTED TO TRAVEL, THEY’D LET ME KNOW FIRST,” BERNSTEIN RECALLS.

than dying,” Hardison said, whenever the topic came up. “I’ve known that for 14 years.”

He was placed on the transplant list in August 2014, and the team began rehearsing for his surgery. There were numerous dry runs, using paired cadavers. Team members drew up patient flow charts and organized surgical instruments into dozens of trays. Other members crafted a business plan in which a grant from NYU Langone would cover the first 90 days of medical costs, and Mississippi Worker’s Comp would then take over.

Hardison, meanwhile, journeyed northward for monthly consultations. His health and medications were closely monitored. He received psychological and pain-management counseling (including instruction in techniques such as self-hypnosis and mindfulness training, aimed at reducing his need for prescription analgesics). Then he flew back home and waited.

The transplant team waited, too, perpetually on call. “If anyone wanted to travel, they’d let me know first,” Bernstein recalls. “I’d say, ‘You can go, but where can I reach you? And if we need you, how will you get back?’ ”

Because face transplants are so rare, would-be recipients don’t have to line up for an organ. But a shortage of donors plagues every area of transplant medicine, and a patient seeking a new face draws from a particularly narrow pool. Besides the usual requirements of tissue matching, the graft must be appropriate in appearance. For Hardison, that ideally meant finding a fair-skinned male donor—no easy task in New York City, whose population is just 33 percent non-Hispanic white. A further obstacle was a New York State regulation barring the transport of a dead or brain-dead body across more than one county line.

Although NYU Langone representatives eventually persuaded state officials to alter the rule, the change made little difference. By the one-year anniversary of Hardison’s search, only two potential donors had appeared—one whose complexion was a good match but whose tissue profile wasn’t, and another a darker complexion. Hardison was willing to accept the second candidate, but the man’s family withdrew him from consideration.

By midsummer 2015, Hardison was nearing despair. Then, on August 12, LiveOnNY—the nonprofit that coordinates organ donations in the New York metropolitan area—notified Dr. Rodriguez that another face had become available. It belonged to David Rodebaugh, a 26-year-old bike mechanic who’d sustained a massive head injury in a cycling accident and was now brain dead. Rodebaugh was tall and fair, like Hardison, and according to his grieving mother, he’d always dreamed of becoming a firefighter. Instead, his own tragedy had given him the chance to relieve a former firefighter’s suffering.

The next morning, when the initial lab work came back looking promising, Dr. Rodriguez asked Hardison to get on a plane to New York. By the time it landed, the results were in: Rodebaugh was an excellent cross-match.

By 7:00 a.m. on August 14, Dr. Rodriguez and three surgical assistants began the dissection of Rodebaugh’s face, meticulously identifying and preserving nerves and blood vessels. Meanwhile, surgeons allocated by LiveOnNY prepared to harvest Rodebaugh’s heart, kidneys, and liver for transplant in four other patients. Soon afterward, Hardison arrived in the adjoining OR. As IV lines delivered anesthesia, the surgical team set to
work removing his mask of scar tissue. Around 11:00 a.m., 3-D–printed cutting guides based on CT scans of Rodebaugh’s head arrived from Colorado (see “Making the Cut”). In the donor room, Dr. Rodriguez began sawing portions of bone from Rodebaugh’s facial skeleton (the chin, nasal structure, and a sliver of the cheekbones), leaving them attached to the inner skin. This technique, which had never been used before, would help ensure that the face was properly secured to fit its new owner.

Shortly before 7:00 p.m., the surgeon went next door to finish the tailoring of Hardison’s facial skeleton. Then, he returned to the donor room and completed the operation on Rodebaugh. Dr. Rodriguez placed the donor’s face in a basin of preservative solution and wheeled it to the recipient room on a rolling stand. He draped the hood of flesh over Hardison’s head, snapped the bones into place, and secured them with plates and screws. Peering through a microscope, he stitched the major sensory nerves together—others were expected to grow back over time—and began connecting the major blood vessels.

Hardison’s internal jugular vein was larger than Rodebaugh’s, and a suture failed; the patient quickly lost two pints of blood. Dr. Rodriguez stopped the flow by clamping the external carotid artery. After creating a new junction, he loosened the clamp, and the face turned a reassuring pink. It also began to swell, as expected, ballooning to 50 percent larger than its normal size.

The team continued to work through the night, redraping the eyelids and joining nostrils and outer lips to their respective mucosa. At 9:30 a.m., on August 15, more than 26 hours after making his initial incision, Dr. Rodriguez finished sewing up the scalp. “Congratulations, everyone,” he said, and there were hugs and high-fives all around.

“After the surgery is when the real work begins,” says Nicole Sweeney, NP, who coordinates patient care for the Face Transplant Program. During the first week, there were late-night scares involving fluctuations in blood pressure and an unstable airway. Hardison needed therapy to relearn how to speak and swallow; he had bouts of frustration and anxiety. On day nine, when Dr. Rodriguez handed him a mirror for the first time, his face was still...
so swollen that his mouth wouldn’t close. He gazed silently at the reflection, his expression impossible to read.

But Hardison was able to blink for the first time since 2001, and his progress in other areas proved rapid. By early October, he was holding conversations and eating solid food. When his kids came for their first visit, tears were shed, but then the whole gang went out for barbecue. Two weeks later, Hardison was discharged to outpatient status; he moved to an apartment across the street from the hospital, returning daily for ongoing rehabilitation. He took a shopping trip to Macy’s and was overjoyed when no one stared.

In November, he returned to Senatobia, where a parade was held in his honor. Hardison rode in an open limousine and was serenaded by honking fire trucks. He enjoyed a Thanksgiving feast with his family. He appeared on Nightline, where he spoke passionately of his gratitude to Rodebaugh and his loved ones. He showed the first inklings of a smile.

That didn’t mean he was out of the woods. Although no face transplant patient has died during surgery, three have perished within the first year, either from infections or complications related to rejection. Indeed, almost every patient has had an episode of acute rejection within the first 90 days. But by February, when this article went to press, Hardison had not. Bruce Gelb, MD, assistant professor of surgery, and director of renal transplantation at NYU Langone, who designed his immunosuppressant regimen, credits a postoperative dose of rituximab, a monoclonal antibody used to treat blood cancers and autoimmune disorders that has also shown efficacy in preventing rejection in kidney transplants. Hardison is the first face-transplant patient to receive rituximab (in addition to the standard combination of thymoglobulin, tacrolimus, and low-dose prednisone, and his continued health may encourage the use of this medication for those who follow.

Dr. Rodriguez was recently awarded $2.5 million by the Defense Department to aid in continued face-transplant research. He’s already looking for his next patient. But Hardison will remain in his care for years to come, returning for regular checkups as well as occasional surgeries to adjust his new features, and consulting as needed with the rest of the team. “This is not an operation for everyone,” Dr. Rodriguez says. “It’s for very courageous people. We’re in awe of Patrick, and we’ll be here for him as long as he needs us.”
**F A PICTURE** is worth a thousand words, a 3D model tells the whole story, and that advantage can make all the difference in the operating room. As 3D printers become more sophisticated, accessible, and affordable, a growing number of surgeons at NYU Langone Medical Center are employing them to transform two-dimensional CT and MRI scans into lifelike three-dimensional models. Anatomical replicas of patient body parts can help surgeons to better prep for and execute complex operations. In some cases, they can even reveal previously unseen defects or obstructions, prompting surgeons to radically rethink their approach to an operation or guiding them during the procedure.

"Looking at a screen, you can't always see around the corner," says pediatric neurosurgeon Donato Pacione, MD, assistant professor of neurosurgery, who recently published a case study on 3D modeling in the *Journal of Neurosurgery*. "Now we're actually bringing the 3D models with us into the operating room to help guide our surgical approaches."

Surgical planning is just one way doctors are capitalizing on the fast-moving field of 3D printing. The technology is also being used to print patient-specific surgical cutting guides (see page 14, "Making the Cut"), to model rare anatomical pathologies for medical education (a welcome alternative to fragile samples jarred in odorous formaldehyde), and even to print custom prosthetics.

Hurdles remain, to be sure. Insurance companies do not yet reimburse for the expense, and physicians must often invest their own time and resources into mastering the design software. But for the surgeons who created the five anatomical models showcased here, those challenges were trivial when weighed against the potential benefit: better patient outcomes.
**Compressed Spine**

**THE CASE:** An 11-year-old child required follow-up surgery after an operation conducted six years earlier to correct a congenital defect that compressed his spine into the base of his brain. When the best surgical approach could not be discerned from MRI and CT scans, the surgical team ordered a 3D–printed model of the patient’s skull base, cervical spine, carotid arteries, and preexisting spinal hardware (top photo). With the ability to examine the model from all angles, the key surgical maneuvers became clear. “We saw that if we changed the position of the spine, we’d be in a much better situation,” says Dr. Pacione, who performed the surgery with David Harter, MD. “It turned out to be very effective, and it was the model that guided our thinking.” The two surgeons, both assistant professors of neurosurgery at NYU Langone, ordered a postoperative model (bottom photo) to confirm the patient’s improved spinal alignment.

**THE 3D PRINTER:** Replicated bone, metal, and blood vessel tissues were fashioned from three different materials on Stratasys 3D printers in Israel and New York.
**The Case:** A seven-year-old child with multiple holes in the septum wall separating the left and right sides of her heart had undergone several procedures, only partially successful, to repair the condition. Unfortunately, an implanted closure-device made the remaining holes impossible to see on CT scans, and as a result, two recent attempts to repair the defects via catheter had failed. This 3D model showing a cross-sectional view of the patient’s heart solved the problem by revealing the location and structure of the holes, and the safest path to reach them. “Being able to view the model is what made the transcatheter closure possible,” says Puneet Bhatla, MD, assistant professor of pediatrics and radiology, and Director of Congenital Cardiovascular Imaging at NYU Langone, who helped create the 3D replica. “We went in informed. No surprises.” The team consulted the model several times while implanting five new closure devices in the patient’s heart. The procedure was a success, and today the patient is doing fine.

**The 3D Printer:** The model was created from CT-angiography data using a Connex3 3D printer in Toronto, Canada.
**THE CASE:** A 66-year-old patient required surgery to destroy a tumor in his prostate the size of a gumball. Lead surgeon Samir S. Taneja, MD, determined that the best course of treatment was to ablate the cancerous tissue with targeted radio-frequency energy. In order to be successful, this type of minimally invasive therapy required a detailed understanding of the tumor’s position in relation to the urethra, surrounding nerve tissue, and other structures. Dr. Taneja and his team used this relatively simple 3D model of the patient’s prostate to guide them before and during the procedure. “We found the model to be extremely helpful in fully destroying the tumor while sparing healthy, adjacent tissue,” says Dr. Taneja, the James M. Neissa and Janet Riha Neissa Professor of Urologic Oncology, and codirector of the Smilow Comprehensive Prostate Cancer Center.

**THE 3D PRINTER:** The prostate and tumor were manufactured using a combination of two different rigid opaque materials on a Connex2 3D printer at New York University’s LaGuardia Studio.
**THE CASE:** A 55-year-old woman was diagnosed with a complex brain aneurysm. This model of the ballooning artery in her brain was created on a relatively inexpensive 3D desktop printer, using just a few dollars’ worth of resin. Purchased with an educational grant by the Resident Education Fund, the printer is located on the Medical Center’s campus and is available for use by neurosurgery residents. Models like this are increasingly used to test the fit of a variety of surgical clips that block blood flow to an aneurysm—thus minimizing the need to experiment with different clips during an operation, which can increase the risk of a rupture. The model was also used as a guide during the procedure itself. “The orientation of the aneurysm model perfectly matched the actual aneurysm,” says neurosurgery resident Omar Tanweer, MD, who taught himself the software needed to design the model, and assisted on the procedure.

**THE 3D PRINTER:** The model was printed at NYU Langone Medical Center using white methacrylate photopolymer resin on a Form 2 desktop stereolithography 3D printer.
**THE CASE:** A 59-year-old patient required surgery to remove a tumor the size of a golf ball on his right kidney. When urologic oncologist William Huang, MD, was not satisfied with the preoperative planning using conventional imaging, he ordered this 3D model. With a 360-degree view of the tumor and its location with respect to the rest of the kidney and other organs in the body, Dr. Huang chose to approach the tumor from behind the abdominal cavity instead of in front of it. The model also allowed him to better explain the surgery to the patient and to navigate more easily during the procedure than with an intraoperative ultrasound probe. “As a kidney surgeon, I find 3D models extremely useful,” says Dr. Huang, associate professor of urology at NYU Langone. “Two-dimensional imaging studies cannot demonstrate the spatial relations between tumor and nearby structures nearly as well as the model can.”

**3D PRINTER:** This model was printed for NYU Langone by Materialise, a 3D–printing company based in Belgium, using a combination of three rigid opaque materials on a Connex3 3D printer.
Inspired by the mystery of consciousness, MICHAEL HALASSA, MD, PhD, a psychiatrist and neuroscientist at NYU Langone, is piecing together the neurobiological puzzle of how we pay attention in a world of distractions.

BY ADAM PIORE
Since Dr. Michael Halassa joined NYU Langone in 2014, his experiments have revealed—in unprecedented detail—the neural circuits that filter incoming sensory stimuli and focus attention.
At first, Michael Halassa, MD, PhD, thought there might be a mistake. It was 2009, and Dr. Halassa, then a doctoral student at the Massachusetts Institute of Technology, was learning how to use electrodes to record brain activity in sleeping mice. A few days before, he’d stuck scores of electrodes into a thin sheet of neural tissue called the thalamic reticular nucleus, or TRN, a structure that any medical textbook would have told you consisted of brain cells that fired only in unison.

Yet the neurons were behaving oddly. Dr. Halassa, now assistant professor of psychiatry, and neuroscience and physiology at NYU Langone Medical Center and a member of its Neuroscience Institute, noticed some were far more active than others. What could these brain cells, thought to constitute a monolithic relay station for sensory information, possibly be up to? Dr. Halassa’s effort to answer that question is revealing new insights into what’s known as selective attention, the all-important ability to block out distractions and concentrate on a single task.

It’s a timely inquiry in this era of sensory overload. It also gets at questions that have flummoxed neuroscientists for decades. How is it, for instance, that a soldier defusing a bomb in the middle of a battle can focus as grenades explode all around? How can a driver pay attention to the road when his children are fighting in the backseat? “After you’ve learned the value of things in the world, how does your brain bias your senses to augment certain things and suppress others?” Dr. Halassa says.

Dr. Halassa, who completed a residency in psychiatry at Massachusetts General Hospital in 2013, takes inspiration from his patients. Some of them suffer from attention deficit hyperactivity disorder, or ADHD, America’s most prevalent mental-health issue among young people, and one that also affects up to 5 percent of adults. The underlying causes of ADHD, like so many conditions rooted in the brain, remain mysterious—a longstanding fog that has limited treatment options to a handful of stimulants like amphetamines and methylphenidate. Dr. Halassa, as a clinician-researcher, is in a unique position to help. In deciphering the neural underpinnings of selective attention, he’s been able to offer his patients smarter coping strategies rooted in biology and informed by research, and in the long run, he’s laying the groundwork for entirely new classes of medication.

“The underlying circuitry in mental disorders like ADHD, autism, and schizophrenia has not been worked out,” says Charles R. Marmar, MD, the Lucius N. Littauer Professor of Psychiatry and chair of the Department of Psychiatry at NYU Langone. “Mike is poised to change that.”

In the 19th century, the American philosopher and psychologist William James described attention as something like a spotlight whose beam casts irrelevant details into the mental shadows. Almost 100 years later, molecular biologist Francis Crick picked up on that theme. The Nobel laureate spent the last decades of his life studying the brain. In a 1984 paper published in the Proceedings of the National Academy of Sciences, Crick offered what he termed a “speculative hypothesis” on how the brain might actively direct “the searchlight” of attention.

At the time, conventional thought held that the thalamus, comprising a pair of walnut-size structures located just above the brain stem, served as a passive relay for sensory and motor signals zipping to and from the cerebral cortex, the outermost folds of the brain that are central to conscious thought. But Crick was skeptical. “Its size and its strategic position make it very probable that it has some more important function,” he wrote.

A thin layer of nerve cells covering the thalamus, the TRN—the same structure Dr. Halassa stuck with electrodes—particularly intrigued Crick. He had no proof, but he suspected that this long-overlooked brain structure might house the neural circuitry responsible for directing our attention, green-lighting some senses while blocking others.

Though Crick’s name ensured that his unproven hypothesis received widespread attention, by the time he passed away in 2004, most neuroscientists were convinced that the prefrontal cortex, an area of the brain widely believed to govern behavior, in fact controlled selective attention. In 2001, MIT neuroscientist Earl Miller, PhD, published an influential paper explaining how this might work. Miller trained monkeys to remember a picture and to respond whenever they saw the picture again. But by presenting different cues before each trial, he also taught them to vary their responses. To his surprise, Miller discovered far more neurons fired in the prefrontal cortex each time he changed the rules than when he simply prompted the monkey to momentarily remember a photo.

“This told us something,” Miller says. “The job of the prefrontal cortex is to learn the rules of the game.” Miller compared the prefrontal cortex to “a railroad switch operator,” and the rest of the brain to an elaborate network of railroad tracks. It was the job of the switch operator to
DIVIDED ATTENTION

New research shows that a network of “inhibitory” cells within a sliver of brain tissue called the thalamus reticular nucleus, or TRN, functions much like a gatekeeper, opening and closing cellular gates to modulate the flow of sensory information to the cortex. In one experiment, NYU Langone researcher Dr. Michael Halassa showed that when a mouse concentrates on visual stimuli, its TRN cells activate and “close the gate” on competing auditory information, allowing visual information to flow uninterrupted to the cortex.

activate some parts of the track and take others off line. “The prefrontal cortex,” he explains, “sends top-down signals to the rest of the brain, essentially activating the pathways you need to engage in goal-directed behavior.”

It was brilliant science—but something was missing.

In 2009, Dr. Halassa wasn’t thinking about the neural circuits governing attention, or high-level cognition when he stumbled upon his strangely behaving neurons in the TRN. He simply wanted to know more about how the thalamus worked.

Dr. Halassa got an early start in science. He began medical school in his native country of Jordan in 1997, at age 16. Back then the writings of distant Western scientists like Francis Crick were a lifeline to the outside world. Dr. Halassa had always felt like somewhat of an outsider in the insular, deeply religious Muslim culture of his homeland. His family was Christian, which placed them squarely in the minority, and though Dr. Halassa was somewhat sheltered from radical anti-Christian sentiment because he attended private Christian schools, he felt threatened enough to take up boxing so he could defend himself. (He would eventually star on the Jordanian national boxing team and win a silver medal in the Pan-Arab games.)

In medical school, removed from the bubble of Christian schools, Dr. Halassa often found himself at odds with his classmates and instructors, many of whom had become radicalized and viewed Western scientific doctrines with
“After you’ve learned the value of things in the world, how does your brain bias your senses to augment certain things and suppress others?”

suspicion. Evolution was grudgingly taught, for instance, but dismissed as nonsense. So during his second year of college, he accepted an internship opportunity at Johns Hopkins University. It was the first of many trips abroad, and by the time Dr. Halassa graduated, he was admitted to a doctoral program in neuroscience at the University of Pennsylvania.

In graduate school, Dr. Halassa’s fascination with consciousness deepened. He discovered a role for supportive brain structures known as glia cells in the regulation of sleep and published a number of influential papers. After all, what is sleep but a different state of consciousness? He then turned his attention to the TRN, inspired by long conversations with Giulio Tononi, MD, PhD, an accomplished neuroscientist and psychiatrist widely recognized for his scientific investigations of consciousness. Like Crick and Tononi, Dr. Halassa soon became convinced that the TRN, serving as the gateway between the thalamus and the cortex, was somehow involved in consciousness. But very little was known about the connection.

As a postdoctoral student at MIT, Dr. Halassa set out to map the path of each neuron in the TRN and its connections to the thalamus. Here, Dr. Halassa employed the technology of optogenetics to genetically engineer mice to express light-sensitive proteins within different regions of the thalamus. Then, he used light to activate the proteins and illuminate cells one by one while tracing their connections. In so doing, he demonstrated conclusively that the cells of the TRN branched out to distinctly different regions of the thalamus.

Cells within the TRN were known to inhibit or suppress other neurons. Interestingly, in studying slumbering mice, Dr. Halassa noticed a cluster of chatty TRN cells firing into sensory regions of the thalamus. If the TRN was a gate, as Crick had suspected, then these active cells might well be suppressing sensory information that would otherwise flood into the prefrontal cortex and disrupt sleep.

Dr. Halassa offered this and other conclusions in a landmark paper published in the journal Cell in 2014. His contributions drew national attention and helped the young researcher win a variety of awards, including most recently, a prestigious 2015 Alfred P. Sloan Research Fellowship, awarded to early-career scientists with outstanding promise.

It also attracted the attention of NYU Langone’s rapidly expanding team of top-tier neuroscientists, who persuaded Dr. Halassa to join them.

“Mike represents a new breed of scientist who has both clinical training and a very strong basic science background,” says neuroscientist Richard Tsien, PhD, the Druckenmiller Professor of Neuroscience, chair of the Department of Neuroscience and Physiology, and director of the Neuroscience Institute. “His ability to bridge both worlds is unusual.”

In his new laboratory at the Neuroscience Institute, Dr. Halassa sought to translate Earl Miller’s work on the prefrontal cortex to mice. Unlike monkeys, mice would give him pinpoint control over brain-cell activity. “Using mice would allow us to understand exactly how the prefrontal cortex directs the spotlight of attention,” Dr. Halassa says.

Most neuroscientists had assumed that the process was largely confined to the top part of the brain, the cerebral cortex, with the prefrontal cortex at the center of it all. Miller’s “switch operator” in the prefrontal cortex, the theory went, interfaced directly with the sensory areas at the back of the cortex. The evidence offered to support this theory, however, was circumstantial, and the literature made no mention of the TRN in this process. Dr. Halassa had already demonstrated a surprising role for the TRN in gating incoming sensory information in sleeping mice. Was there some role for this structure in gating different types of senses when mice were awake?

In one experiment, Dr. Halassa trained mice to either respond to light and ignore sound, or ignore light and respond to sound. As a context for the choice, he paired each option with a unique pattern of white noise. “This allowed us to study both how the brain can tell these contexts apart,” he says, “and how it allows the sensory systems to augment certain inputs and suppress others.”

After identifying which cells within the TRN activated while the mice concentrated on each task—attending to sound or attending to light—Dr. Halassa again traced their connections. As he found with sleeping mice, the act of choosing sound over visual cues—or vice versa—lit up unique pathways of cells stretching into different areas of the thalamus. But then Dr. Halassa noticed something he didn’t expect: the neurons in the TRN appeared to fire as soon as the mouse heard the white noise. In other words, the TRN seemed to be firing in anticipation of incoming stimuli. As Halassa contemplated the possibilities, he had an epiphany—perhaps Earl Miller’s switch operator at the front of the brain wasn’t modulating the brain’s sensitivity to sensory information through other regions of the cerebral cortex, as commonly
assumed. Perhaps it was doing so through the thalamus—
with the TRN central to the routing process.

Methodically, Dr. Halassa used optogenetics to disable
different parts of the brain, and then watched to see what
impact it had on the ability of the mice to appropriately respond to different sensory information. When he knocked
the prefrontal cortex off line, changes in the cells of the
TRN disappeared, and the mice were unable to properly concentrate most of the time. Similarly, when he knocked the
TRN off line, the prefrontal cortex went dark, and the mice
were similarly distracted. The two brain regions were clearly connected.

It was a truly game-changing discovery. When he
published the findings in the journal Nature this past fall,
colleagues quickly grasped the implications. MIT's Miller,
for one, noted that he, and the rest of the field, had long
discounted the role of the TRN in attention. "We didn't talk much about the thalamus," Miller says. "We thought
selective attention was mainly a cortical phenomenon. You have cascading top-down activity from higher cortical areas
directly influencing low cortical areas." Dr. Halassa's paper,
he notes, "very elegantly shows" that the prefrontal cortex's
"track switching" influence was "mediated through the
thalamus," an idea that had never before been proven.

NYU Langone neuroscientist Gordon Fishell, PhD, believes
Dr. Halassa's paper finally proves Crick's big picture theory
about the role of the TRN. "Crick suggested it, but it was an idea without a lot of data," says Dr. Fishell, the Julius Raynes Professor of Neuroscience and Physiology, and associate director of the Neuroscience Institute. "Mike is just this young scientist fresh out of a postdoc; and he does this incredible study. It's just amazing. He has the proof!"

But the largest potential impact of these findings may come in the clinic. Already Dr. Halassa's findings have changed the way he thinks about his ADHD patients. "We have learned from the lab that where you allocate your attention is an executive function, controlled by the prefrontal cortex," Dr. Halassa says. But how you allocate your attention happens in sensory circuits. Attention requires two different players. You can imagine that ADHD could be either an executive dysfunction or a sensory-processing deficit. Both would be labeled as ADHD right now, because we don't have better tools."

In one clinical technique, Dr. Halassa attempts to determine if a patient is better able to focus when placed in a dark room without other sensory distractions. Those patients that say they can concentrate better in the dark may have problems rooted in their sensory circuits, Dr. Halassa believes. Those who still can't focus, meanwhile, likely have deficits stemming from executive dysfunction.

"This is something my patients actually taught me," Dr.
Halassa says. "It is something that is not very obvious if you don't deal with human beings."

Dr. Halassa has several other studies in the works, looking at mice models of other psychiatric diseases, among them autism, and is uncovering compelling evidence that in fact, at least some of the symptoms can be traced to dysfunction in the TRN.

That Dr. Halassa has managed to upend conventional thinking about selective attention and rewrite the textbook on a largely dismissed brain region—all at the age of 34—strikes many of his colleagues as remarkable. "Mike has never been put off by tough questions," says Philip Haydon, PhD, Dr. Halassa's doctoral advisor at UPenn and an expert on glial cells. "He sets his eyes on a problem and then figures out how to address it, and it's really quite remarkable. He's unafraid to challenge the greatest mysteries."
Knowing When to Push
How defying surgical dogma and heeding a mother’s wishes saved a young boy’s life

IN 1997, when Riccardo Maffii was only two weeks old, his mother, Alessandra Smeraldi, noticed that his right foot moved oddly. By three months of age, the infant was experiencing several seizures a day. Doctors at a local hospital in Florence, Italy, diagnosed Riccardo with tuberous sclerosis, a genetic disorder that causes benign growths (called tubers for their potato-like appearance) inside various organs. A leading cause of epilepsy and autism, the disease afflicts 1 million people worldwide and usually strikes during the first year of life, just when the brain is trying to reach important milestones. In Riccardo’s case, multiple tubers the size of an egg had sprouted within his brain. Medications did nothing to quell the seizures, and surgery would be difficult, if not impossible, doctors insisted, owing to the large number of tubers.

When Riccardo was four months old, Smeraldi found her way to Orrin Devinsky, MD, professor of neurology, neurosurgery, and psychiatry, and director of NYU Langone Medical Center’s Comprehensive Epilepsy Center. By monitoring Riccardo’s brain activity, Dr. Devinsky and his team were able to pinpoint the sources of Riccardo’s seizures. “There were two foci, one in each hemisphere of the brain,” notes Dr. Devinsky. He told Smeraldi that he agreed with the doctors in Italy: surgery was not an option. If any tissue were inadvertently damaged—a rare but potential consequence of brain surgery—corresponding structures in the opposite hemisphere might not be able to take over any lost functions.

Smeraldi and her son returned home with a new regimen of medications, but Riccardo’s seizures worsened in
frequency and intensity. By the time he was two years old, his language skills and both his fine and gross motor skills were all delayed. Returning to NYU Langone, Smeraldi pushed Dr. Devinsky for a solution. “Instead of pushing back, we reexamined the rules,” says Dr. Devinsky.

Dr. Devinsky called in Howard Weiner, MD, professor of neurosurgery and pediatrics, a specialist in the surgical treatment of epilepsy. Meeting with Smeraldi, Dr. Weiner, then two years out of fellowship training, was honest about his apprehensions: “I explained to Alessandra that this was a conceptual leap, that the accepted dogma was not to operate on both sides of the brain, and that bilateral surgery doubles the risks.”

Smeraldi was undeterred. “Riccardo lived in a fog,” she recalls. “He couldn’t laugh or experience any joy. He had no life at all.” She told Dr. Weiner that she trusted him to help her son and politely insisted, “We are not going back home until something is done.”

Dr. Weiner was moved by Smeraldi’s determination. “There was risk in doing the surgery,” he acknowledges, “but there was also risk in doing nothing. Attacked by constant seizures, Riccardo would have continued to deteriorate and most probably would have been institutionalized.”

With Dr. Devinsky’s blessing, Dr. Weiner agreed to operate. He has since operated on some 100 patients with multiple tubers—more than any other neurosurgeon in the country—but Riccardo would be his first. His decision was influenced, in large part, by his residency and fellowship training at NYU Langone and the philosophy he absorbed as a member of the Division of Pediatric Neurosurgery within the Department of Neurosurgery. The internationally renowned division, part of NYU Langone’s Hassenfeld Children’s Hospital, was the first pediatric neurosurgical service in New York City and is now the largest in the tri-state area. Its founding director, the late Fred Epstein, MD, was a trailblazing neurosurgeon who devised techniques to operate on slow-growing tumors intertwined with the brain stem and spinal cord, and who used lasers and ultrasound to remove benign tumors long thought to be inoperable because of their location.

Jeffrey Wisoff, MD, professor of neurosurgery and pediatrics, and director of the Division of Pediatric Neurosurgery, who trained under Dr. Epstein, says that his mentor taught him to be “appropriately aggressive” when the stakes are high. A surgical innovator himself, he pioneered techniques for removing deep-seated brain tumors. “Because children have such a long life span,” Dr. Wisoff explains, “we want to extend their lives for decades, not months. We look to win the war, not the battle. That gives us a mandate to push the envelope.”

Dr. Wisoff, MD, director of NYU Langone’s Division of Pediatric Neurosurgery. “We want to extend their lives for decades, not months. We look to win the war, not the battle. That gives us a mandate to push the envelope.”

“Children have such a long life span,” explains Jeffrey Wisoff, MD, director of NYU Langone’s Division of Pediatric Neurosurgery. “We want to extend their lives for decades, not months. We look to win the war, not the battle. That gives us a mandate to push the envelope.”

devised a novel three-stage approach to reduce the risk of complications. First, he would place electrodes on the surface of the brain to precisely map the seizure foci. Then, he would perform two successive surgeries, one on each hemisphere, to remove the troublesome tissues. In theory, staging the surgeries would provide a measure of safety. If Riccardo didn’t respond well to the first procedure, the second could be postponed or skipped entirely. There was no way to predict how the young boy would react to three invasive procedures, but each step went as planned.

Within days of the operation, Smeraldi noticed a difference. “Riccardo was more serene, more attentive,” she says, “and he started to smile again.” The boy was discharged after a week, never to suffer another seizure. Today, 16 years later, Riccardo is enrolled in high school, though he does have some cognitive deficits. “He’s a cheerful boy,” says his mother, “and he’s doing well within his own limits.”

In pediatric neurosurgery, one of the rules we live by is to listen to the mothers,” says Dr. Weiner. “Here was a case where the mother was driving us to operate, and despite our own bold philosophy, we were being conservative. Perhaps too conservative.”
BENJAMIN NEEL, a renowned physician, researcher, and administrator, joined the NYU Langone Medical Center community in early 2015 to lead its National Cancer Institute–designated cancer center. Before returning to New York, where he earned his MD and PhD degrees, he most recently served as director of the Ontario Cancer Institute at Princess Margaret Cancer Center, Canada’s largest cancer research center.

We’re almost 45 years into the “war on cancer.” Why haven’t we seen more progress?

In President Nixon’s famous “war on cancer” speech, he used the analogy that if we could put a man on the moon in 10 years, we ought to be able to end cancer in our lifetime. That was a false analogy. The science behind putting a man on the moon was pretty much settled during Newton’s time, and the basic principles of rocketry were elucidated by Robert Goddard in the early 20th century. Going to the moon was “just” an engineering feat—an amazing engineering feat—but it didn’t require that much new science.

It was a completely different situation for cancer back in 1971. We didn’t have a fundamental understanding of gene regulation. Since cancer is a disease of our genes, there was no rational way to approach cancer. Now, we have identified between 500 and 1,000 genes that, in various combinations, can cause different cancers, and we have a whole new set of weapons to turn against cancer cells.

I understand the public’s frustration. It seems like everybody knows somebody who has cancer and that we’re not making any progress. But, actually, we’ve made a lot of progress. But much less so compared to heart disease. Is that a fair comparison? And isn’t the incidence of cancer actually increasing?

It’s true that we are seeing an increase in absolute cancer incidence, but that’s because people are living longer—thanks largely to the success in treating heart disease. There’s actually been no increase in the age-adjusted incidence of cancer.

Now, why are we so successful against heart disease? I don’t want to denigrate my cardiologist friends, but heart disease is not really as sophisticated a
“It seems like everybody knows somebody who has cancer and that we’re not making any progress. But, actually, we’ve made a lot of progress.”

biological problem as cancer. Much of the fundamental biology was established in the mid to late ’70s. Decades later, we’re seeing the clinical applications of those insights. I think we’ll have the same lag between new discoveries in cancer and starting to see dramatic improvements in cancer therapy. That’s why we are now seeing the impact of major advances over the last 10 to 15 years, and these will accelerate over the next 10 to 20 years.

Prevention has had a major impact on heart disease. Does prevention play a similar role in cancer? The same measures that help prevent heart disease could also have a huge impact on cancer. People shouldn’t smoke, they should exercise, and most important of all, they should maintain an appropriate weight. Obesity is now passing smoking as the number one risk factor for cancer. We could prevent probably up to 60 percent of all cancers today if people just applied what we already know about prevention.

As a cancer researcher, are you more or less fearful of cancer than the average person? I’m neurotic, so maybe more! But I probably have more confidence in how preventive steps can mitigate cancer and other diseases. I try to practice what I preach, although I’ve been very bad at going to the gym recently.

What are the most promising cancer therapies? One is immunotherapy. The results can be so impressive because you’re pitting one evolutionary system, the immune system, against another, the tumor. Another promising area is epigenetic therapy. If we can figure out how to tweak the epigenetic, or regulatory, state of a cell, we should be able to convert the cell into a state that will not be susceptible to the underlying genetic mutations that are driving the cancer.

What’s your vision for the Perlmutter Cancer Center? My vision is to create a world-class academic cancer center. That includes offering a wide range of state-of-the-art clinical trials, where we get drugs to patients earlier than they would be available through the regular approval process. For many of our patients—namely, those who have few therapeutic options—the best medicine is a clinical trial. If any of my family members or friends had cancer, I would insist that they were treated at an academic medical center, with access to the latest therapies, including experimental treatments. That means bolstering our basic research, our clinical trials capability, and the number of high-level clinical investigators.

How are you promoting more interaction between scientists and clinicians? One of my roles is to be the Cancer Center matchmaker. We’ve started a weekly faculty lunch that has either a basic scientist or a clinician talking about a research problem or a disease of interest. Second, we’ve started an off-site retreat, a more formal place where people can interact. Some collaborations have already come out of this. For example, at a recent faculty lunch, one of our best immunologists, Dan Littman [the Helen L. and Martin S. Kimmel Professor of Molecular Immunology, a professor of pathology and microbiology, and a faculty member in the Molecular Pathogenesis Program in the Skirball Institute of Biomolecular Medicine], mentioned his research into mycobacteria, which cause tuberculosis, and the type of immune response they provoke. Later, I realized that this could be how a vaccine for TB, called BCG, works as a therapy for noninvasive bladder cancer. Nobody really understands this. But it’s important to know, because if we can determine what antigen is provoking the response and the cells that are responding, we might be able to develop a new treatment for invasive bladder cancer. One of our urologists is now exploring this idea with Dr. Littman.

For a number of cancers, especially early prostate cancer, there’s confusion among patients as to the best clinical approach. Any words of wisdom? This is a very difficult area, obviously. It comes down to undertreating versus overtreating. For low-grade prostate cancer, there’s a lot of evidence that watchful waiting is better than interventional strategies because of the risk of impotence and incontinence. That said, many men can’t stay on a watchful-waiting protocol, knowing they have a cancer growing inside them. This is actually our problem, a scientific problem. We should be able to define which tumors are the bad actors and which ones aren’t in a more sophisticated way. Meanwhile, the best advice I can give is to get a couple of opinions, find a doctor you have confidence in, and then decide.

Did cancer have anything to do with your choice of profession? There are very few people who haven’t been affected by cancer. For me, it was my grandmother. I was very close to her. She died, most probably, of primary lung cancer. At the time, there were no treatments for her disease. Yet we now know that as a nonsmoker, she probably had one of the forms of lung cancer caused by specific mutations that can be targeted with some of our new anticancer drugs. I decided to do cancer research based on her experience. ✿
Michele Pagano, MD
NEW CHAIR OF THE DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Michele Pagano, MD, the May Ellen and Gerald Jay Ritter Professor of Oncology and professor of pathology, was appointed chair of the Department of Biochemistry and Molecular Pharmacology last October. Dr. Pagano is a leading authority on the cellular recycling of proteins, known as the ubiquitin system. His identification of F-box proteins, which label waste within cells for recycling, opens a window onto cellular growth, proliferation, and DNA repair, and helps explain how defects in the cell’s waste-removal processes lead to disease. One F-box protein, for example, may provide a key to treating certain aggressive cancers.

Dr. Pagano joined NYU Langone Medical Center in 1996 and has served as director of the Growth Control Program at the Laura and Isaac Perlmutter Cancer Center since 2000. Dr. Pagano earned his undergraduate, medical, and research degrees in molecular endocrinology from the Federico II University in his hometown of Naples, Italy. He then completed a postdoctoral fellowship at the European Molecular Biology Laboratory in Heidelberg, Germany, and later cofounded the biotechnology company Mitotix, in Cambridge, Massachusetts.

He has received many prestigious grants, including a MERIT Award from the National Cancer Institute in recognition of his outstanding achievements in cancer biology. In 2008, he was appointed a Howard Hughes Medical Institute investigator.

Joel Schuman, MD
NEW CHAIR OF THE DEPARTMENT OF OPHTHALMOLOGY

Joel Schuman, MD
NEW CHAIR OF THE DEPARTMENT OF OPHTHALMOLOGY

Clinician-scientist Joel S. Schuman, MD, has been appointed chair of NYU Langone Medical Center’s Department of Ophthalmology. Dr. Schuman’s pioneering work has led to significant advances in the detection and treatment of glaucoma, a disease that damages the eye’s optic nerve and can result in irreversible vision loss.

Dr. Schuman joins NYU Langone following a distinguished career at the University of Pittsburgh School of Medicine, where he was professor of ophthalmology, chair of the Department of Ophthalmology, and director of the University of Pittsburgh Medical Center Eye Center. Dr. Schuman also held appointments at the university’s McGowan Institute for Regenerative Medicine, the Center for the Neural Basis of Cognition, and as professor of bioengineering at the Swanson School of Engineering.

A National Institutes of Health–funded researcher, Dr. Schuman and his colleagues were the first to discover a molecular marker for glaucoma. The discovery has paved the way for advances in the detection and treatment of the disease, which often causes no symptoms in its beginning stages.

To aid in its early detection, Dr. Schuman and his colleagues developed a groundbreaking medical imaging procedure that creates a 3-D map of the eye, called optical coherence tomography (OCT). This quick and noninvasive procedure allows ophthalmologists to measure the thickness of the retina and better diagnose retinal diseases. Dr. Schuman will continue to advance OCT technology at NYU Langone.

Dr. Schuman received his medical degree from Mount Sinai School of Medicine. He completed his residency in ophthalmology at the Medical College of Virginia, and clinical and research fellowships in glaucoma at the Howe Laboratory of Ophthalmology, part of Harvard Medical School’s Massachusetts Eye and Ear Infirmary.

Dr. Schuman is the recipient of numerous honors and awards. In 2002, he received the New York Academy of Medicine’s prestigious Lewis Rudin Glaucoma Prize for the most outstanding scholarly article on glaucoma published in a peer-reviewed journal. In 2013, he received the American Academy of Ophthalmology Life Achievement Honor Award; and he was named a Gold Fellow of the Association for Research in Vision and Ophthalmology Fellows Class of 2014. He has published more than 300 peer-reviewed articles, and authored or edited eight books.
LAST OCTOBER, Swiss philanthropist and businessman Hansjörg Wyss donated $20 million to establish a named department of plastic surgery at NYU School of Medicine. “It’s a truly transformational gift that will propel the department into its next phase of growth,” says Eduardo D. Rodriguez, MD, DDS, the Helen L. Kimmel Professor of Reconstructive Plastic Surgery and chair of the newly named Hansjörg Wyss Department of Plastic Surgery.

Wyss’s gift builds on the department’s strong reputation. Founded in 1955, it’s one of the few fully accredited academic plastic surgery departments in the country. It has the largest academic group of board-certified plastic surgeons, one of the largest residency and fellowship programs, and a highly regarded research program that has made major contributions to medicine.

Wyss, the founder of Synthes, Inc., a global medical-device manufacturer, has been a strong supporter of Dr. Rodriguez. His philanthropic gifts to the surgeon’s research efforts and educational initiatives during Dr. Rodriguez’s tenure at Johns Hopkins University and the University of Maryland Shock Trauma Center helped lay the groundwork for Dr. Rodriguez’s landmark face transplant at the University of Maryland Medical Center in 2012.

Wyss’s contribution to NYU Langone will help its plastic surgery department establish new clinical trials, bolster existing programs, invest in new technology, and develop novel procedures. “I feel I have a duty to repay my good fortune through philanthropic endeavors that expand the reach of human possibility and compassion,” says Wyss.

AROUND CAMPUS

Philanthropist Hansjörg Wyss
DONATES $20 MILLION TO ADVANCE NYU LANGONE’S HISTORIC DEPARTMENT OF PLASTIC SURGERY

NYU PHYSICIAN WINTER 2016 35
Bernard A. Birnbaum, MD

In 2007, not long after Bernard A. Birnbaum, MD, was appointed senior vice president, vice dean, and chief of hospital operations, he was informed that NYU Langone Medical Center’s performance on several quality and safety measures had much room for improvement. An evaluation showed that only 60 percent of patients at NYU Langone were receiving optimal care. “When I told Bernie that I didn’t think our performance was good enough, he said, ‘You’re absolutely right. What do you need?’” recalls Martha Radford, MD, chief quality officer. Before long, he created a multidisciplinary executive group to identify quality and safety issues and help implement reforms. Within one year, NYU Langone’s score rocketed to 90 percent. Today that figure stands at greater than 99 percent.

Dr. Birnbaum died on September 14, 2015, at the age of 58, after battling pancreatic cancer.

Cancer had also claimed the life of Dr. Birnbaum’s mother, and the inadequate care she received during her illness played a big role in his decision to become a physician. An alumnus of NYU School of Medicine, Dr. Birnbaum completed his radiology residency and abdominal imaging fellowship at NYU Langone. “Bernie had an eye, as we say in radiology,” explains Hildegard Toth, MD, associate professor of radiology, who trained with him. “He had a visual gift for noticing things others might overlook.”

Andrew Brotman, MD, senior vice president and vice dean for clinical affairs and strategy and chief clinical officer, believes that Dr. Birnbaum’s meticulous attention to detail served him well. “Operations is all about details—getting down to the granular level of how things work,” says Dr. Brotman. “Bernie’s dedication to quality and safety was unparalleled among anyone I’ve ever worked with. He had a mission-driven personality that made him ideally suited to his job."

Dr. Birnbaum’s early experience with inadequate healthcare inspired a career-long quest to ensure that patients receive the best care possible. “Bernie liked to say that hope is not a strategy,” recalls Robert Press, MD, PhD, his successor as chief of hospital operations. “He insisted that to improve performance, you need a plan.” In his nine-year tenure as chief of hospital operations, Dr. Birnbaum set the strategic direction, as well as the goals, for widespread reforms to enhance quality and safety. His primary tools in this effort were the Lean Management initiative, a highly collaborative program designed to improve efficiency and eliminate waste, and Epic, an integrated electronic health records system, which provides a platform for measuring quality and safety standards.

“Bernie had a mission, not an agenda,” notes Martin Costa, director of the Lean Management Office. “Ever the radiologist, he sought out the root cause of the problem, and his insatiable curiosity led him to solutions.” Dr. Birnbaum’s passion for problem solving served him well during Hurricane Sandy, when he led the Incident Command Team, a group of administrators charged with hospital-wide crisis management. His calm, steady leadership enabled hundreds of members of the NYU Langone community to safely evacuate 322 patients within 13 hours.

Remarkably, only one year after suffering over $1 billion in damages during the storm, NYU Langone was ranked number one among the nation’s leading academic medical centers by the University HealthSystem Consortium (UHC) Quality and Accountability Performance Scorecard—a distinction it has now earned for three consecutive years.

In honor of Dr. Birnbaum, UHC renamed the award for its annual quality and accountability study the Bernard A. Birnbaum, MD, Quality Leadership Award. “Of everything we achieved together, the UHC award was what Bernie took the most pride in,” notes Robert I. Grossman, MD, the Saul J. Farber Dean and CEO of NYU Langone. “It’s an amazing tribute to Bernie and his entire team.”

Dr. Birnbaum is survived by his wife, Maj Wickstrom, MD; their children, Sarah and Noah; his sister, Mindy; his brothers and sisters-in-law, Robert and Susan Birnbaum, and John and Heidi Birnbaum; his mother-in-law, Margaret Wickstrom; and his brother-in-law and sister-in-law, Dan and Cindy Wickstrom.
EVERY ASPIRING PHYSICIAN DREAMS OF THE DAY SOMEONE WILL CALL HIM OR HER "DOCTOR" FOR THE FIRST TIME. But getting there takes a lot more than hard work and dedication—it takes resources. By contributing to the NYU School of Medicine Alumni Campaign, you help ensure that our next generation of physicians will have access to the best teaching and research, along with a competitive financial assistance package. When you make a gift, you help us guarantee that all of our students will have the means to complete our rigorous education. One day, you may even have the privilege of addressing them yourself as "Doctor."

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To learn more about making your planned gift to NYU Langone, please contact Marilyn Van Houten at 212.404.3653 or marilyn.vanhouten@nyumc.org.

Moses V. Chao, PhD, professor of cell biology, neuroscience and physiology, and psychiatry, is a distinguished researcher at NYU Langone, and former president of The Society for Neuroscience.