Kobilka happily adjusts to post-Nobel life

By Tracie White

A week after being awarded the Nobel Prize in Chemistry, Brian Kobilka, MD, was back at work in his lab in the Beckman Center trying desperately to catch up. There are plenty more important scientific questions out there waiting to be answered.

“It’s gotten me further behind on every- thing than ever before,” he said, grinning. He was seated at his desk in his office just down the hall from the laboratories where his postdoctoral scholars and graduate students were busy conducting experiments on proteins. A poster of the image of the “molecular masterpiece” that helped him earn the Nobel hung on an office wall. The bike he rode to work from his Palo Alto home rested against another wall.

The tall, lanky biochemist was busy trying to respond to the 1,000 or so new emails in his inbox while keeping the ever-important lab work moving along. The Nobel is really nice. But for Kobilka, it’s all about the science.

“I’m trying to get back to working with my group, we need to keep going,” he said. “We have a lot of really exciting things happening. We’re working with Bob Lefkowitz (with whom he shares the prize) and his group on a receptor coupled to a different signaling protein. I just submitted another grant proposal for structu- rised-base approaches for drug discoveries.”

Despite the backlog of work, he had no complaints. Even with the overwhelming public attention that bombarded this shy son of a Midwestern baker who prefers to spend his time in his lab piec- ing together clues to life’s unsolved mysteries, winning the Nobel is a thrill.

“I still wake up in the morning and have to remind myself that it’s real.”

The Nobel committee awarded this year’s chemistry prize to Kobilka, 57, and his former mentor Robert Lefkowitz, 69, a professor at Duke University in Durham, N.C. The two will split the 8 million Swedish kronor, or about $1.2 million.

Kobilka plans to give the money to his two grown children.

The award was for work on G-protein-coupled receptors, or GPCRs, which serve as one of the main methods of communication within the body, conveying chemical messages for almost every normal bodily function. They are also the target for about 40 percent of all prescription drugs. The hope is that the work will lead to safer more effective medications.

The Royal Swedish Academy of Science in Stockholm, which awards the Nobel, is the new laureate in chemistry, Brian Kobilka speaks to a group of well-wishers at a reception Oct. 13 in the lobby of the Lokey building.

Freidenrich Center will help streamline clinical research

By Kris Newby

The Stanford University Medical Center officially opened the Jill and John Freidenrich Center for Translational Research on Oct. 17, advancing the capabilities of researchers across the university to conduct the vital clinical research that translates basic science discoveries into lifesaving treatments and diagnostics.

The three-story, 30,000-square-foot building at 800 Welch Road is a state-of-the-art facility See FREIDENRICHT, page 7

The Jill and John Freidenrich Center for Translational Research, which was dedicated Oct. 17, is the new hub for designing and conducting clinical trials involving human subjects at Stanford.

Natural process that activates brain’s immune cells could point way toward repairing damaged brain tissue

By Bruce Goldman

The brain’s key “breeder” cells, it turns out, do more than that. They secrete substances that boost the numbers and strength of critical brain-based immune cells believed to play a vital role in brain health. This finding adds a new dimen- sion to our understanding of how resi- dent stem cells and stem cell transplants may improve brain function.

Many researchers believe that these cells may be able to regenerate damaged brain tissue by integrating into circuits that have been eroded by neurodegenerative disease or destroyed by injury. But new findings by scientists at the School of Medicine suggest that another process, which has not been fully appreciated, could be a part of the equation as well.

The findings appear in a study published online Oct. 21 in Nature Neuroscience.

“Transplanting neural stem cells into experimental animals’ brains shows signs of being able to speed recovery from stroke and possibly neurodegenerative disease as well,” said Tony Wyss-Coray, PhD, professor of neurology and neuro- logical sciences in the medical school and senior research scientist at the Veterans Affairs Palo Alto Health Care System. “Why this technique works is far from clear, though, because actually neural stem cells don’t engrat well.”

Neural stem cells can endure essen- tionally unchanged for decades in two places in the mammalian brain, repli- cating just enough to meet the routine needs of those regions. In most parts of the brain, they aren’t found at all.

While of critical importance to maintaining healthy brain function, true neu- ral stem cells are rare. Far more common are their immediate progeny, which are called neural progenitor cells, or NPCs. These robust, rapidly dividing cells are poised to travel down a committed path of differentiation to yield new brain cells of several different types including neurons.

It’s known that treating humans with radiation or drugs that prevent NPC rep- lication causes memory deficits (“chemo brain”) and, in children, IQ losses of up to 20 points. Conversely, studies are being initiated to see whether infusing neural stem cells into brains affected by Alzheimer’s disease See BRAIN, page 3
1 What are the different kinds of stress responses?

**Dhabhar:** We define stress as a constellation of events that begins with a stimulus or challenge (stressor) that is detected by the brain (stress perception). The brain activates the fight-or-flight systems in the body (biological stress response). Acute or short-term stress results when the biological stress response is activated for minutes to hours. Repeated short-term stress is experienced during most day-to-day living situations when we encounter a series of stressors or challenges as we go through our lives. Although we need to conduct more studies to better understand this, it appears that most reasonably healthy people can deal with repeated short-term stressors (in fact most of us need to) as long as there are sufficiently long periods between stressors where stress-related biological factors are at very low levels, i.e. when the person is in a resting state.

**Chronic or long-term stress results when the biological stress response is activated for months to years.** This can have protective and beneficial effects. We have found that when short-term stress is coupled with immune activation, for example during surgery or vaccination, the ensuing immune response is enhanced. The beneficial effects of short-term stress make sense because the fight-or-flight stress response is an important fundamental survival mechanism. Without this response a lion has no chance of catching a gazelle (and hence eating to live another day). Importantly, without this response the gazelle has no chance of escape. During a fight-or-flight stress response, organs like the skin and underlying tissue are likely to be damaged (e.g. an attack results in wounding and infection) by a stressor (e.g. predator or aggressor) and therefore enhancing immune function in these organs during these times would ensure better protection. Our research aims to harness this natural stress response to boost protective immune function during wound healing, cancer, infection, and cancer. Such benefits of short-term stress might also translate to better mental or physical performance under conditions where chronic stress is low and the individual is trained or practiced in the task at hand.

**We have been trained to think that all stress is bad, but tell us how there might be benefits to stress.**

**Dhabhar:** You’re right in that the overwhelming focus of stress-related research has been on the BAD effects of stress. This is with good reason because it is known that stress can have significant deleterious effects on health. In general, chronic or long-term stress can have harmful effects. In contrast, acute or short-term stress can have protective and beneficial effects. We have shown that when short-term stress is coupled with immune activation, for example during stress or vaccination, the ensuing immune response is enhanced. The beneficial effects of short-term stress make sense because the fight-or-flight stress response is an important fundamental survival mechanism. Without this response a lion has no chance of catching a gazelle (and hence eating to live another day). Importantly, without this response the gazelle has no chance of escape. During a fight-or-flight stress response, organs like the skin and underlying tissue are likely to be damaged (e.g. an attack results in wounding and infection) by a stressor (e.g. predator or aggressor) and therefore enhancing immune function in these organs during these times would ensure better protection. Our research aims to harness this natural stress response to boost protective immune function during wound healing, cancer, infection, and cancer. Such benefits of short-term stress might also translate to better mental or physical performance under conditions where chronic stress is low and the individual is trained or practiced in the task at hand.

**While acute stress may be beneficial in the right circumstances, what about chronic stress?**

**Dhabhar:** Chronic stress generally has harmful effects. Chronic stress has been associated with increased biological aging, suppression or abnormal regulation of immune function, increased susceptibility to some types of infection, and worsening of diseases like depression, heart disease, and some types of cancer.

However, it is important to appreciate that Mother Nature has given all living beings, including humans, resilience mechanisms so we don’t just give up and where we need to start experiencing chronic stress. The bad thing is that as humans we can put ourselves (or others) under so much chronic stress that even the powerful resilience mechanisms that nature has given us can break down.

Interestingly, there exist remarkable differences among individuals in their degree of stress resilience. Some individuals can continue to function normally or even well under significant amounts of chronic stress, while others may be less able to do this. Another key area of research in our lab is to investigate the mechanisms and resilience of health. Our long-term goal is to enable the development of interventions that would increase stress resilience especially in individuals who find themselves in chronically stressful situations.

2 How can stress impact the development and progression of cancer as well as its role in other medical conditions?

**Dhabhar:** Chronic stress has been shown to accelerate biological aging, suppress immune responses, enhancing harmful immune responses and by increasing factors like blood vessel growth factors and pro-inflammatory responses that enable tumors to grow, spread, and metastasize. It also appears that chronic stress can produce long-term increases in inflammatory and oxidative damage. These may be ways, although there could be more, in which chronic stress can affect other medical conditions. This needs to be investigated further.

3 What are some techniques for reducing chronic stress?

**Dhabhar:** The key is to prevent long-term elevation or abnormal regulation of stress-related biological factors at the time spent in the resting state. My lab and others are working on identifying new strategies, though from what we know so far, it’s pretty much grandma’s advice: Sleep well, eat and exercise in moderation, and engage in activities that reduce your chronic stress and ultimately help you feel relaxed and rested. Ultimately you might need to retrain your stress response. Such an activity could involve yoga or meditation but it could also be walking, running, fishing, beating up skeletons, drumming, singing, etc., and is likely to involve different strokes for different folks.

This is important to find what works for you and then to do it consistently. Consistency may be more important than intensity, so, for example, going on a brisk walk on a frequent and regular basis for reasonable time each week is likely to be more beneficial as fast as you can once every few weeks. Genuine support from friends and family, having someone you can truly talk to, can also be an effective chronic stress buffer.

Troubled teens may benefit from online access to health records

By Erin Digita

Online health records could be surprisingly useful for at-risk teenagers who cycle through the juvenile justice system. A new study from the School of Medicine and the Santa Clara Valley Medical Center found that these young people have high rates of Internet use and an unexpectedly favorable attitude toward accessing their health records online.

Teens who get in trouble with the law could particularly benefit from online health records because they generally have worse health than other adolescents. Anoshiravani, MD. “They’re often not considered when it comes to new ways of engaging patients.” Anoshiravani is an adolescent medicine specialist at Lucile Packard Children’s Hospital, a clinical assistant professor of adolescent medicine at Stanford and the medical director of the Santa Clara County Juvenile Custody Institutions.

Anoshiravani’s team conducted in-person interviews with 77 incarcerated teens who received treatment at the Santa Clara Valley Medical Center. The teenagers were asked whether these youth had the resources and inclination to use online health records out of the juvenile justice center (they do not have Internet access while detained.)

The teens had similar rates of Internet use in general, adolescent populations, with 87 percent saying they used the Internet at least once per week when not detained. Home computers and cell phones were their most common tools for accessing the Internet, the study found. The finding contradicts older research suggesting a lack of Internet use in poorly educated and impoverished groups. “Things have shifted; the digital divide still exists between older individuals of different backgrounds, but among adolescents there is a generation of tech access, even for the most underserved,” said Gregory Gaskin, a Stanford medical student who is the first author of the paper. The U.S. health-care system is gradually replacing paper charts with computerized electronic medical records, and some providers are beginning to allow patients to access portions of the records online. The researchers wondered whether this target group of teenagers would be interested in seeing their health information on the Web.

The teens were enthusiastic about the option, with 90 percent saying it would be useful to have their health information automatically put online so they could access it later.

“I didn’t expect this level of interest,” said Jennifer Packard Children’s Hospital, a clinical assistant professor of adolescent medicine at Stanford and the medical director of the Santa Clara County Juvenile Custody Institutions.

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About face: Study shows long-ignored segments of DNA play role in coordinating early stages of face development

By Christopher Vaughan

The human face is a fantastically intricate thing. The billions of people on the planet have faces that are individually recognizable because there are subtle differences in its folds and curves. How is the face put together during development so that, out of billions of people, no two faces are exactly the same? School of Medicine researcher Joanna Wysocka, PhD, and her colleagues have discovered genetic elements that guide the earliest stages of the process. Their research, published in the Sept. 13 issue of Cell, Stem Cell, provides a resource for others studying facial development and could give insights to the cause of some facial birth defects. Because there is not enough genetic information in the body to define exactly where each cell will go, development of the face proceeds much like origami—where each cell will go, development of disorders of facial development, such as cleft lip or cleft palate. In these disorders, sheets of cells from opposite sides of the embryo, leaving a cleft or gap. "By identifying neural crest enhancers, our study will help researchers better understand where and when cells are needed," said Wysocka. What’s useful about their discoveries is that researchers will now know much better where to look for genetic variants that can explain these facial abnormalities or even why each human being has a unique face," said Alvaro Rada Iglesias, PhD, who is the first author on the paper and a member of the Wysocka laboratory. Although only a handful of enhancers were already shown to be important in regulating early neural crest development, research by Wysocka and her colleagues has produced thousands of such enhancers that are active in determining the behavior of these cells. Moreover, this research showed that the information contained within those enhancers can be used to identify novel genes controlling neural crest and face formation. "Our results will serve as a resource for other investigators," she said. Wysocka expects that the usefulness of the data will extend far beyond facial development. By having the sequences of thousands of these enhancers, scientists can look at the kind of DNA patterns or “motifs” that are common in these enhancers and use that information to look for enhancers that regulate genes throughout development. Other Stanford co-authors include former postdoctoral scholars Ruchi Bajpai, PhD, and Samantha Bruggman, PhD; graduate student Sara Prescott; and senior research scientist Tomet Swig, PhD. The research was funded by the National Institutes of Health, the Searle Scholars Program, the W.M. Keck Foundation, EMBO and the Siebel Scholars Program.

Brain

Brain continue from page 1

can enhance patients’ memory function. One category of brain cells, microglia, descends not from neural stem cells but from an immune lineage and retains several features of immune cells. "Microglia are the brain’s resident immune cells," Wysocka said. Unlike other much larger mature brain cells, microglia can proliferate throughout adulthood, especially in response to brain injury. They can, moreover, migrate toward various "chemical signaling" substances, and gobble up bits of debris, microbial invaders or entire dead or dying neurons.

Microglia normally are distributed throughout the brain — rather small, quiescent cells sprouting long, skinny projections that meekly but efficiently survey large areas that, taken together, cover the entire brain. But if this surveillance reveals signs of a disturbance, such as injury or infection, the microglia whir into action. They begin proliferating and their puny bodies puff up, metamorphosing from mild-mannered "Clark Kent-like reporters to buffed Supermen who fly to the scene of trouble, where they secrete substances that can throttle bad actors or call in reinforcements. Within these activated cells, internal garbage dispositions called lysosomes form in large numbers and start whirring, ready to make micromeat out of pathogens or cellular debris.

In addition to their part patrol-officer, part cleanupcrew role, microglia can also secrete substances that help neurons thrive. They also contribute to the ongoing pruning of unneeded connections between neurons that rewire our lives throughout development.

But like immune cells elsewhere, said Wyss-Coray, microglia can be a force for evil if they engage in too much or inappropriate activity. They might, for instance, try to remove healthy cells (as occurs in Parkinson’s) or stop clearing up garbage strewn about the brain (for example, Alzheimer’s plaque).

In a series of experiments, Wyss-Coray and his colleagues have shown that NPCs secrete substances that activate microglia. First, the researchers observed that microglia were characteristically abundant and active in the two regions in the mammalian brain where NPCs reside and new neurons are formed. Wondering whether the NPCs might be causing this increased microglial activity, the scientists infected a culture of human cortical microglia in a culture medium in which NPCs had previously been steeped. Two days later, they saw that the microglia had multiplied more, expressed different amounts of various signal molecules and featured more lysosomes. "The microglia were ready for action," said Wyss-Coray.

So they injected NPCs into an area of mice’s brains that — remarkably — were actually not found. In the same area in the opposing brain hemisphere, they injected a control solution. Again they found significant differences in microglial function and activity, and more microglia in the NPC-injected side had assumed a "Superman" as opposed to a "Clark Kent" body shape. When they repeated this experiment using only the NPC-derived discs instead of NPCs themselves, they also got similar results. Clearly NPCs were secreting something, or some things, that were spurring microglia to action.

Using sophisticated lab techniques, the team monitored purified NPCs plus several other cell types found in the brain and assessed nearly 60 different substances known to have powerful cell-to-cell signaling properties. Several such substances, it turned out, were secreted in much larger amounts by NPCs than by the other cell types: most notably, vascular endothelial growth factor, or VEGF — a well-known molecule produced by many cell types throughout the body. VEGF stimulates the formation of blood vessels and can therefore help heal wounds or "motifs" that are common in these enhancers and use that information to look for enhancers that regulate genes throughout development.

Other Brain Cell Types

Neural progenitor cells can differentiate into most types of cells that inhabit the brain. But they also secrete substances that stimulate the brain’s resident immune cells, or microglia.
Kobilka continued from page 1

Nobels, also single out Kobilka’s achievement in his 3-D imaging of one of the receptors bound to its signal-generating machinery. The Nobel committee’s choice of Kobilka’s three-dimensional atomic structure displayed on the poster in his office.

“I think it’s the work represented by this image that earned me the award,” he said, during the first of many interviews to come that day, holding up the poster, which is a copy of the Sept. 29, 2011, cover of Nature in which he published the work. The image, which looks like a bunch of multi-colored spiraling ribbons used to decorate a birthday present, is a representation of the trio of the molecular and cellular physiology.

Kobilka’s family reflected the painstaking 20-year journey driven by Kobilka’s determination, unbelievable patience, collaboration skills and unquenchable scientific curiosity.

“I came into the lab one morning and in the cor

Kobilka was recruited by Richard (Dick) Tsien, PhD, professor and chair of the then-nascent Department of Molecular and Cellular Physiology. We loved this area, but never thought we could afford it,” Tong Sun said. The couple had purchased a house, and Tong Sun enrolled in medical school. For a time, Kobilka supported his family by “moonlighting” at the lab to work.

Kobilka was at home asleep on Oct. 10 when he got the early morning call from the Nobel committee. The first phone call went unanswered. He and his wife assumed it was the wrong number. But they picked up on the second try.

Kobilka, who had confessed in earlier interviews when rumors of a possible Nobel began to surface that he was “desperately fearful” of talking to the press, now faced the first day of a new life as a science celebrity — a day filled with scores of interviews with reporters from around the world, a televised press conference, an onslaught of attention from people beyond movie stars and politicians ever experience.

In the interviews, he described growing up in Lincoln Falls, Minn., a town of 7,000, where his father, Franklyn, owned a bakery.

Many of the skills Kobilka uses in running his science lab he learned growing up in the bakery, watching his dad manage about 20 employees, and his mom, Betty, ice the cakes. He learned hard work, starting the day early before sunrise — and a love of pastry.

“A lot of the ways that I work in my lab come from my experience watching my father,” he said. “You have to advise people, organize people, motivate people. My dad had to do that to do everything. If someone called in sick, my dad would be the baker or run the fryer. He probably even washed pans. It was a fantastic bakery.”

Andrew Kruse, a 27-year-old graduate student in Kobilka’s lab since 2009, who took a break from reconstituting lipids to join in the celebrations.

“I'm heading back to the lab,” he said yawning. “We were just talking about how much we care about science.”

Firling also remembered Kobilka’s knack for technological innovation, a skill which helped push over the next few decades. He and his future wife working together in the developmental biology lab built a tissue-culture hood using scrap heavy plastic from his father’s bakery. “I came into the lab one morning and in the corner was the ugliest thing you could imagine,” Brian said. “He had gone to the lumberyard, and gotten plastic from his father’s bakery, and constructed the sterile hood that we needed to do our experiments,” Firling said.

Kobilka’s interest in research continued to grow as a medical student at Yale University, Medical School, where he first learned to juggle the responsibilities of clinical care and lab work.

He and Tong Sun married in 1978, and soon after Kobilka became a postdoctoral scholar at Duke in Lefkowitz’s lab, the premier lab studying receptors for adrenaline. T ong Sun worked alongside him as they raised their two young children. Today, their son, Jason, 31, and daughter, Megan, 28, live nearby in the San Francisco Bay Area.

Kobilka became a licensed internist, a skill that would come in handy when he needed extra cash during lean years.

The family moved to Stanford in 1989 when Kobilka was recruited by Richard (Dick) Tsien, PhD, founder and chair of the then-nascent Department of Molecular and Cellular Physiology. We loved this area, but never thought we could afford it,” Tong Sun said. The couple had purchased a house, and Tong Sun enrolled in medical school. For a time, Kobilka supported his family by “moonlighting” on weekends as an emergency room physician to pay his mortgage and his wife’s medical school tuition.

“I held onto medicine. I was afraid I might fail in research,” he told the crowd of about 100 at the press conference the morning of the announcement. Thus began years of dogged research, marked by significant funding setbacks [see story on page 5], as he continued his quest to uncover the structure and function of GPCRs.

He explained his quest as something a friend of his called “irrational optimism.”

“You can have ideas that other people might think are crazy,” Kobilka said at the press conference. “People at Stanford will help.”

The mentor

Kobilka’s lab is on the first floor of the Beckman Center. On the morning of the Nobel announcement, his lab of about 10 postdoctoral scholars and graduate students began to hear the news — through Facebook posts, text messages, friends calling from the East Coast. They trickled into the lab at about 8:30 a.m. as if it were a normal workday and started congratulating each other. They have some funny jokes, back clapping, and gathering in the hallways to gossip. Other postdocs came out of nearby labs to offer congratulations.

“When you meet Brian, you see his intensity,” said Aashish Manglik, an MD/PhD student. “For Brian, it’s perseverance and creativity. I’m pretty inspired by Brian. It’s obvious how much he cares about science.”

“He’s very hands-on,” said Andrew Kruse, a 27-year-old graduate student. “He still works in the lab.

At just before 10 a.m., Kobilka arrived at the lab, hugged his wife, glanced at his postdocs and students, then led them to the press conference in the building next door. No one said anything, but he continued to glance over his shoulder, like a mother duck making sure her ducklings were following along.

Everyone says Kobilka always takes care of his lab.

“He’s a great teacher, very patient — the students and postdocs will tell you,” Tong Sun said. “He has an open door for students and is on a first-name basis with them. He still does bench work, even the mundane stuff. That way, he’s familiar with the protocols, and when postdocs have problems they can help him trouble shoot at the press conference, Kobilka talked about his deep respect for his ‘brilliant’ Stanford students.

“How many times I’ve thought, ‘How am I going to hate that this kid is way smarter than I am’?”

His lab stuck together, sitting in the front of the crowd. After the press conference, they went back to the lab to work.

Back to work

The department finally held a “post-celebration” party later that day. In the afternoon a crowd of 100 or so scientists and students packed into the lobby of the Beckman Center, eating chocolate cake and drinking champagne. The words spoken at the press conference by Philip Pizzo, MD, dean of the medical school, still hung in the air: “In a day when big teams and massive labs have become the common mediator of modern science, Brian Kobilka stands as a model of how a small group of committed scientists can illuminate deep mysteries and open doors to new solutions that will ultimately improve human life.

By the time of the party, Kobilka was looking tired but content — an empty champagne glass hung from one hand. A giant copy of the Nature poster along with bunches of red and white balloons decorated the gathering.

“It’s really great to see him win this,” said Kruse, a student in Kobilka’s lab since 2009, who took a break from reconstituting lipids to join in the celebrations. “I’m heading back to the lab,” he said yawning. “We can still get a couple more hours of work in.”

1. Colleagues, staff and students line up to take Kobilka’s photo during an Oct. 13 reception in the Leiby building. 2. The shy Kobilka talks to reporters at his Palo Alto home, hours after the Nobel Prize announcement. 3. Kobilka with son Jason, wife Tong Sun and daughter Megan at the Oct. 13 reception. 4. Kobilka speaks at the Oct. 10 press conference, along with Stanford President John Hennessy (left) and medical school Dean Philip Pizzo. 5. At a departmental party the afternoon of Oct. 10, professor William Weis leads the group in toasting Kobilka’s accomplishments.
cascades of hundreds of reactions inside the cell. These reactions lead to countless responses, from a heightened heart rate after a shock, to an awareness of lightning during a storm or the memory of your favorite song’s lyrics. Although the scientific and technical challenges of crystallization are daunting, Kobilka also struggled to obtain the funding necessary to keep his lab aloft [see "Funding the dream," page 257].

"The Nobel award speaks to several things: endurance, brilliance, dedication and commitment," said Philip Pizzo, MD, dean of the School of Medicine at a press conference the morning the prize was announced. "To assembling the whole molecule, to crystallization, is possibly the most personally passionate belief in something." Kobilka’s research focuses on deducing the three-dimensional structure of a complex, vital cog in the cellular machinery — that of a family of receptor molecules that convey a dazzling array of chemical messages such as hormones from the surface of the cell into the cell’s interior.

To do so, he relied on a technique called X-ray crystallography, which involves creating an image that the Nobel committee called “a molecular masterpiece.” A protein, when stuck on the top, represents a hormone, and it’s activating a very large molecule inside the cell, said Kobilka during the press conference. "I knew that money was funneled to Kobilka’s lab during those times, ending with one end outside the face of the cell into the cell’s interior."

About 40 percent of medications available today target these G-protein-coupled receptors, of which there are about 800 family members. "Many in the scientific community thought that his work might be an unattainable goal," said Stanford University president John Hennessy, PhD. "But Brian managed to achieve it through hard work, diligence and many years.” Proteins are linear strings of amino acids that fold into complex and dynamic shapes. G-protein-coupled receptors, or GPCRs, are also known as seven-transmembrane receptors because they snake in and out of the cell membrane many times, ending with one end outside the cell and the other inside. As such, they sit like a rubber band with a portion sticking out on each side. On the exterior, the receptor awaits binding by a specific signal, such as a hormone or neurotransmitter. When a signaling molecule binds the outside of the receptor, the whole receptor changes shape and activates a class of molecules called G proteins in the interior of the cell. The G proteins activate many other molecules within the cell to amplify the original signal, beginning a complex biological cascade.

"When I started there was a lot of skepticism about whether such receptors even existed, and there was no way to study them," said Lefkowitz during a Duke press conference on Oct. 10. Lefkowitz’s research dispelled such skepticism, and he has been advancing the understanding to a new level. "What Kobilka has done is to convert this to an atomic level," said Kobilka, explaining that it was now possible to see the protein “literally at atom by atom.”

When I joined the Lefkowitz lab, we didn’t really have any idea what these proteins looked like,” said Kobilka. "We didn’t have DNA or an amino acid sequence.” Lefkowitz and Kobilka focused their attention on the epinephrine receptor, also known as the beta-adrenergic receptor. (Kobilka wanted to learn more about how the receptor functions because he’d discovered the dramatic effect that epinephrine, or adrenaline, had on patients in cardiac arrest.)

Prior to 1984, Jeff Benovic, PhD, in the Lefkowitz lab, had been trying to crystallize significant amounts of beta-adrenergic receptor protein from hamster lung tissue. "We didn’t have any amino acid sequences. With colleagues in the lab and at Merck Laboratories, Kobilka used these amino acid sequences to deduce nucleotide sequences for a few fragments of these proteins. The resulting nucleotide sequences were used to isolate a fragment of the mammalian genome that encoded the entire protein sequence of the beta-adrenergic receptor — much like a literary historian might use a unique string of words to identify an ancient manuscript.

When Kobilka and Lefkowitz studied the resulting full-length sequence of the beta-adrenergic receptor, they were surprised to realize that it was similar to that of another, seemingly unrelated receptor called rhodopsin that detects light in the retina of the eye. This research helped the scientists realize that GPCRs are a large family, with many different examples throughout the body.

"In retrospect, we should have expected this," said Kobilka. "But at the time it was very novel.” In 1989, Kobilka left Duke to come to Stanford, where he devoted himself to learning more about the GPCRs, and to finding some way to visualize the three-dimensional structural model of the molecule — an extremely difficult technical endeavor due to the protein’s size and complexity and the way it’s embedded tightly inside the cell membrane. Knowing the structure, however, is important to be able to design Drugs to activate or inhibit the receptors.

The research required producing copious amounts of the large, intricately folded molecule, and then coothing it to form pure crystals that could be analyzed with X-rays. Observing how the X-rays change paths, or diffract, as they pass through the crystals gives scientists clues about the molecule’s structure. The technique is the same as that used by James Watson and Francis Crick to determine the double-helical structure of DNA, but the process had to be new to Kobilka.

"One of my early collaborators was Bill Wei,” said Kobilka. (Wei, PhD, is the William M. Hanna Professor and professor of structural biology at the medical school.) “I remember, in the early days, I would get my crystals of salt or detergent rather than protein, and he would come look at them and try to let me down gently.” Getting the beta-adrenergic receptor to crystallize required the concerted effort of not just Kobilka, but many other researchers and collaborators. It was difficult not only because the researchers had small amounts of the protein, but also because it depends on its interaction with a sugar molecule for stabilization. In particular, the seven trans-membrane regions of the protein — it’s somewhat hydrophobic, meaning they avoid water-based solutions. "The researchers finally overcame these difficulties with special detergents that money was funneled to Kobilka’s lab during those times, ending with one end outside the face of the cell into the cell’s interior."

About 40 percent of medications available today target these G-protein-coupled receptors, of which there are about 800 family members. "Many in the scientific community thought that his work might be an unattainable goal," said Stanford University president John Hennessy, PhD. "But Brian managed to achieve it through hard work, diligence and many years.” Proteins are linear strings of amino acids that fold into complex and dynamic shapes. G-protein-coupled receptors, or GPCRs, are also known as seven-transmembrane receptors because they snake in and out of the cell membrane many times, ending with one end outside the cell and the other inside. As such, they sit like a rubber band with a portion sticking out on each side. On the exterior, the receptor awaits binding by a specific signal, such as a hormone or neurotransmitter. When a signaling molecule binds the outside of the receptor, the whole receptor changes shape and activates a class of molecules called G proteins in the interior of the cell. The G proteins activate many other molecules within the cell to amplify the original signal, beginning a complex biological cascade.

By Krista Conger
Bully pulpit, meet Brian Kobilka. Only a week after winning a Nobel Prize, Kobilka was hit with one from his new colleagues about possible cuts to research funding should Republicans win the White House next month. His name’s added to the list of other Nobel laureates in support of President Obama.

The importance of funding for basic research — and the struggle that many scientists face — is deeply personal to Kobilka. His funding from the National Institute of Neurologic Diseases and Stroke and the National Institute for General Medical Sciences for the past 25 years. But according to another Stanford laureate, Andrew Fire, it’s one thing to win the Nobel Prize but quite another to make more people want to do research like this ultimately leads to pharmaceutical products and other innovations from which we all benefit,” he said.}

Advocating for U.S. science funding tops Kobilka’s agenda

His work is a good example of how basic research can, over decades, lead to significant improvements in human health. Roughly 800 different GPCRs have been identified to date, making them one of the largest families of human proteins and are involved in a variety of the body’s functions.

"Winning the Nobel doesn't mean every grant is going to get approved," said Fire, who shared the 2006 Nobel Prize in Physiology or Medicine last year. "But according to another Stanford laureate, Andrew Fire, it’s one thing to win the Nobel Prize but quite another to make more people want to do research like this ultimately leads to pharmaceutical products and other innovations from which we all benefit,” he said.}

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Inside stanford Medicine            october 22, 2012

Kobilka (center) shares a happy moment with his lab before heading to the Oct. 10 press conference.
Four members of the School of Medicine faculty have been elected to the Institute of Medicine. They are: Stephen Quake, MD, professor of genetics and bioengineering, and director of the Stanford Energy Systems Lab; David Spiegel, MD; and David Stevenson, MD. With their selection, the medical school now has a total of 69 IOM members.

Minor joined Stanford on Sept. 1 and will become the dean of the School of Medicine on Dec. 1. He was previously the provost at Johns Hopkins University. An oncologist specializing in the diseases and disorders of the inner ear, he discovered a disorder called superior canal dehiscence syndrome, which is characterized by intense, pressure-like dizziness, and developed a surgical procedure to correct it.

Quake is the Lee Otterstrom Professor in the School of Engineering and professor of bioengineering and of applied physics and an investigator for the Howard Hughes Medical Institute. A pioneer in the relatively young discipline of bioengineering, his innovations include a rapid DNA sequence, a non-invasive prenatal test for Down syndrome and the biological equivalent of the integrated circuit.

Spiegel is the Jack, Samuel and Lulu Willson equivalent of the integrated circuit.

Stevenson, the Harold K. Faber Professor of Pediatrics, is vice dean of the School of Medicine and director of the Johnson Center for Pregnancy and Newborn Services at Lucile Packard Children's Hospital. Much of his research focuses on neonatal outcomes and how develops to prevent preterm birth. He also serves as senior associate dean for academic affairs and co-director of the Stanford Center for Clinical and Translational Education and Research.

Established in 1970 by the National Academy of Sciences, the Institute of Medicine is recognized as a national resource for independent, scientifically informed analysis and recommendations on health issues. Its active membership consists of 1,732 highly accomplished professionals. The elections were announced Oct. 15.
Meet the heroes behind ‘Rare’ film at Bay Area Science Festival on Nov. 1

It takes a cast of heroes to find cures to rare diseases, and viewers of a free San Francisco screening of the award-winning documentary, Rare, will be able to join the cast of heroes, the film subjects. A recent post-film discussion on what it takes to transform medical discoveries into life-saving treatments.

Discussion panelists will include Heather Kirkwood, one of the clinical trial participants in the film; Stanford filmmakers Maren Gräning-Monsen, MD, and Nicole Newham; and a Stanford rare disease researcher Heshan Anoshiravani. By it, will help us address one of medicine’s great challenges — how to swiftly and safely bring laboratory breakthroughs to the bedside of patients.

“The Freidenrich Center will be Stanford’s hub for the medical studies, also known as clinical trials, that involve testing new drugs and other therapies with human participants. While previously clinical research had been distributed across seven buildings on and off campus, the opening of the Freidenrich Center allows much of that work to be consolidated at one site.

“Now both adult and pediatric patients can participate in studies without having to visit multiple buildings and hassle with parking,” said Branimir Sikic, professor of medicine and program director of Stanford’s Clinical and Translational Research Unit. “This centralized unit is making a world of difference for both research teams and patients, by providing a comfortable and beautiful facility to increase efficiency, manage study activities, and enhance sample collection and processing.

Funded by longtime Stanford supporters Jill and John Freidenrich, the concept for the center was inspired by Jill Freidenrich’s own experience facing breast cancer. “We are so pleased that the Center For Translational Research at Stanford has become a reality, allowing scientific discoveries to be translated into clinical treatments in a much more efficient way,” said John Freidenrich.

The ground floor is the patient intake area, which has 16 patient beds, three pediatric study rooms, a sample-collection area, two physician rooms, and an outdoor play area with a separate entrance for pediatric subjects. There are also specialized rooms for informed-consent discussions, remote observation, sleep studies and exercise physiology testing.

Floors two and three provide office space for Spectrum, directed by Beverly Mitchell, MD, chair of the School of Medicine, and the clinical trials office for Stanford Cancer Institute, directed by Beverly Mitchell, MD, and the George E. Becker Professor of Medicine. “It is great to have the Cancer Clinical Trials Office and the majority of the cancer institute clinical research staff under one roof,” said Miriam Bischoff, executive administrative director of clinical research for the Stanford Cancer Institute. “Previously, staff were in separate locations all over campus. Now that we are together, collaboration has increased.”

The architecture of the Freidenrich Center borrows design elements from the Le Ka Shing Center for Learning and Knowledge, located at the heart of the medical school campus, with its sweeping roofline, limestone exterior and Stanford-red clay façade. Glass walls open to gardens, a pediatric play area and a sunny patio — a radical departure from the sterile clinical environments of old. Interior colors and finishes are drawn from nature, further dissolving the visual barriers between the inside and outside.

“The Freidenrich Center provides a much-needed permanent home for clinical and translational research in child health,” said Mary Chen, manager of Spectrum Child Health. “The center brings together research stakeholders in a highly collaborative environment, allowing us to address issues important to child health much faster and more efficiently than ever before.”

The construction of the Freidenrich Center marks the beginning of the transformation of Welch Road, which is being redeveloped, along with the new hospital, to be more pedestrian friendly, more integrated with the main campus and more connected to child health.
It was around Christmas last year when William Wykle-Madro and his family realized something wasn’t right. The 17-year-old high school senior had been born with a heart abnormality that left him with two chambers, rather than four, and his health had begun a precipitous decline that winter.

“When a physician at Lucile Packard Children’s Hospital informed his family that a heart transplant was their only option, they were stunned — and utterly unprepared for the realities such a decision involved. Luckily they had someone in their corner from day one. She's just a walking angel,” said Sheron Wylie-Madro, William’s mother.

She was referring to Mary Burge, LCSW, Packard Children’s Hospital’s pediatric heart transplant social worker. For more than 30 years Burge has attended to just about every non-medical issue that comes up while preparing for and recovering from the procedure. For patients and their families, she’s something of an all-purpose fixer.

“She sorted out our insurance situation. She worked out my accommodations. She wrote a letter to my husband’s workplace, explaining that he needed to be away for a period,” Wylie-Madro said. “She even worked with William’s school to make sure he’d be getting credit for certain classes.”

Here she stopped not because she ran out of examples but because William started intersecting his own.

“I play a little guitar, and while I was out, she found out she arranged for the hospital’s guitar teacher, Jeff Buenz, to play at my bedside,” the teen said. “When he offered to do things they couldn’t or shouldn’t still make me get teary,” she said. “They start out weak, frail, slumped over. Then, after the transplant, there’s the ventilator, the scar, the chest tubes. But then you see them shedding all those things, and sitting up straighter, and then walking and eventually going to school, riding a bike, on a skateboard, doing ballet. It’s incredible. And I can tell these stories to new families, and it’s comforting to them. So it was with William and his family. On May 4, in a 10-hour procedure, he received his replacement heart. Today his recovery is going extremely well. William has become a vocal advocate for organ donation and has been accepted at UC San Diego to study engineering in the fall of 2013. A month after his transplant, Burge celebrated William’s graduation from high school, held in the hospital school. “She brought me a stethoscope,” William said with a laugh. “It said, ‘I graduated. I accept cash.’”

Stanford Hospital receives gold medal for leadership in organ donation

The United States Department of Health and Human Services has awarded Stanford Hospital & Clinics its 2012 Gold Medal of Honor for its lifesaving work to increase the number of organs available for transplantation.

One of 22 hospitals in the country and one of four hospitals in California that earned a gold medal, Stanford Hospital surpassed national goals by improving donation rates, and expanding clinical processes for recovering organs.

The hospital was recognized at a ceremony Oct. 4 at the seventh National Learning Congress for Organ Donation and Transplantation Community of Practice held in Grapevine, Texas. Stanford Hospital social worker Timothy Chamberlain accepted the award with colleague and assistant patient care manager Maureen Fay, RN.

“This award is a testimony of Stanford’s commitment to honoring patients’ wishes and rights to help save the lives of others,” said Chamberlain, who assists patients’ families with end-of-life issues. “It speaks to the tireless work our bedside nurses, operating room staff and doctors do to help in this important process. But, most of all, this award honors the incredible people who volunteered to be organ and tissue donors and the families who agreed — even in the midst of grief and loss — to give the gift of life to total strangers.”

Mastro Violetta Jennifer Julian, 54, who received a double lung transplant at Stanford Hospital in 2006 and a second chance at life thanks to an anonymous donor, echoed Chamberlain’s sentiments. “The donor family made that very difficult choice to turn their loss into life for others — for people like me,” Julian said. “If not for their selflessness, I wouldn’t be able to breathe on my own today. They are true heroes.”

Today there are more than 110,000 people on the UNOS National Organ Transplant Waiting List. “Of those waiting, one in three will die due to the organ shortage,” said Carlos Esquivel, MD, PhD, chief of Stanford’s transplantation division. “So, the work that we at Stanford and others involved in organ donation are doing to reduce the number of people on this list is crucial.”

Cindy Siljestrom, chief executive officer of the California Transplant Donor Network, which works with Stanford and other hospitals in Northern and Central California and Northern Nevada counties on facilitating organ and tissue donation for tissue plantation, said “CTDN is pleased to share in recognizing Stanford. What we see each day in working with them is a commitment to the idea that lives are saved and improved through organ and tissue donation.”

About 10,000 people are waiting for organs in the area served by CTDN alone. Eight people potentially can be saved because of organs from a single deceased donor, and that same donor can improve the lives of more than 50 people through tissue donation. People can register as a donor by going to ctdn.org.