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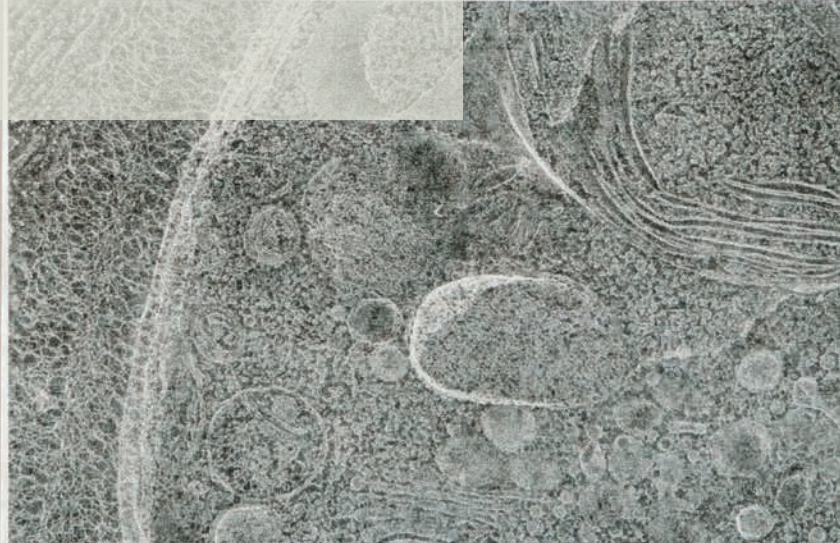
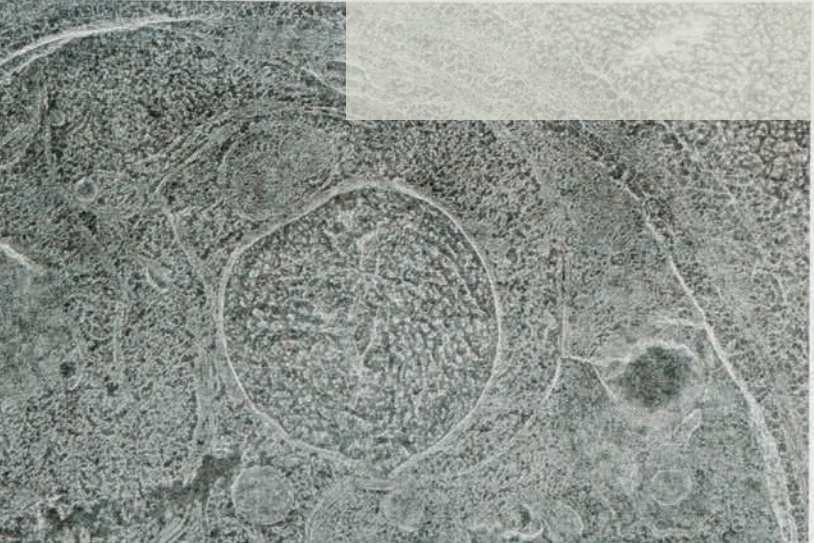
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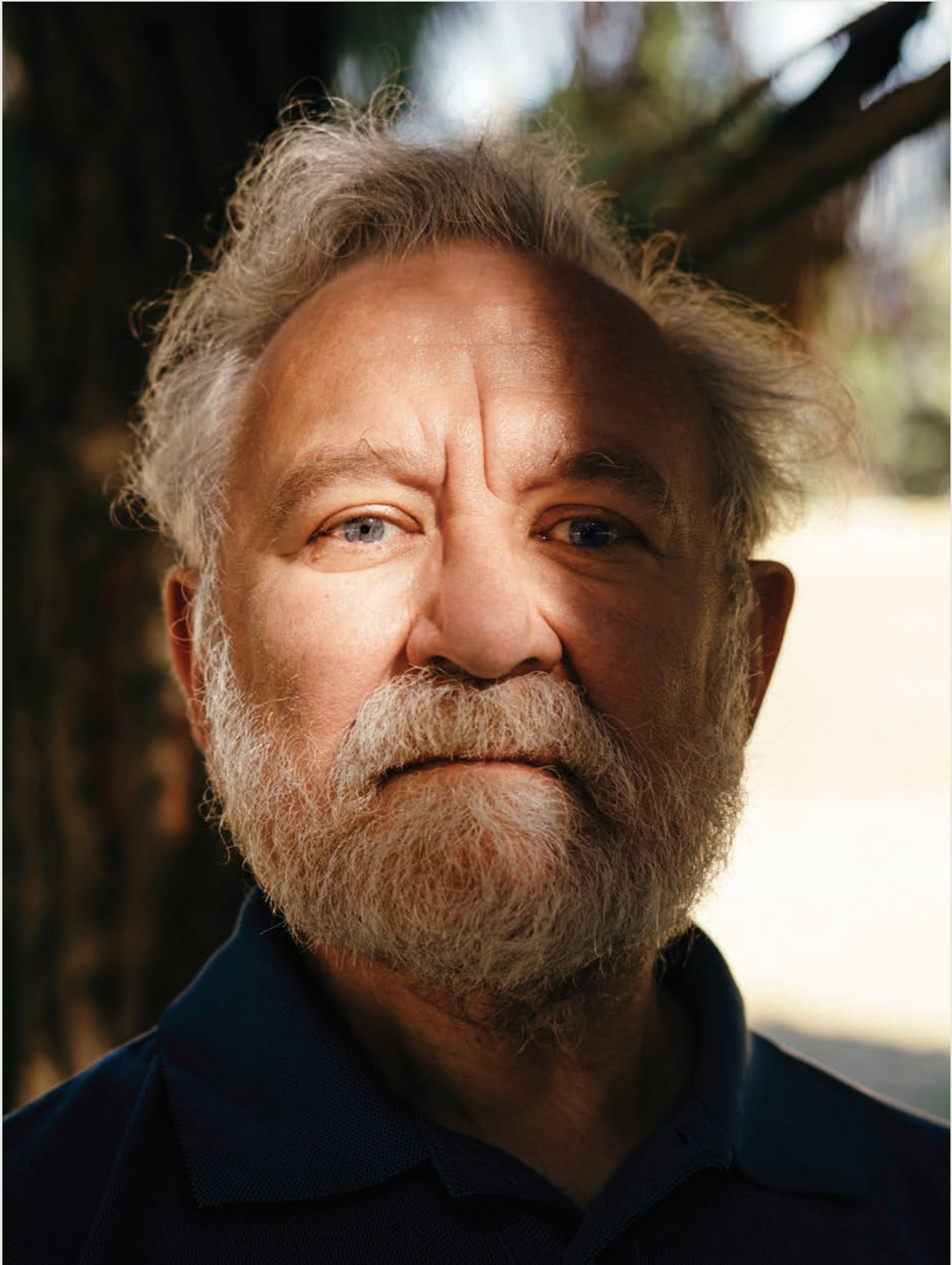
**Harnessing  
Serendipity  
Along  
unpredictable  
paths to discovery,  
Peter Walter has  
maintained a sure-  
footed approach –  
to the science as  
well as to the people  
he mentors.**

BY ESTHER LANDHUIS

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PHOTOGRAPHY BY JAKE STANGEL



For a video about Peter Walter – and a glimpse of his lab’s mascot – go to [hhmi.org/bulletin/fall-2015](http://hhmi.org/bulletin/fall-2015).

IT’S A CREATURE OF LEGEND, a rare symbol of the inscrutable and unattainable. Yet in Peter Walter’s large, third-floor office at the University of California, San Francisco (UCSF), a dazzling white specimen sits in plain view. “She’s our lab mascot,” says the German-born scientist, gesturing at the stuffed unicorn perched on a swivel chair beside bulging bookcases. “She represents the mystical things we discover.”

The unicorn – a BigPlush.com purchase – stands three feet tall and has ink sketches of the group’s most beloved molecules taped to her chest and brow. The lab presented Walter with the endearing monstrosity last fall, at a boat party celebrating his most recent awards. Walter’s prize-worthy research has unveiled fundamental pathways in the cell that control how proteins are made and where they go. Imbalances in these systems can lead to a variety of diseases.

Why a unicorn? The one-horned icon harkens back to an article Walter shared with the lab, as he often does, to spur dialogue about topics of interest beyond his Genentech Hall quarters. This article’s author was taking a jab at big-data science – likening the hunt for discoveries within huge data sets to the arcade game where you try to grasp small toys by maneuvering an electronic “claw,” usually to no avail. The story had an amusing photo of a claw machine loaded with plush unicorns – prizes “most people can never grab,” notes postdoctoral fellow Margaret Elvekrog. “But Peter did.”

Walter doesn’t come across as a go-getter. At a recent lab meeting, the white-bearded biochemist greeted group members with smiles and an occasional hug. His outfit that July morning consisted of a loose, blue button-down with khakis and Birkenstocks. During brief interjections, the professor’s tone conveyed confidence and light-heartedness. But his interruptions were few. For most of the presentation, Walter peeled an orange and listened intently, brow furrowed.

An HHMI investigator since 1997, Walter has a tried-and-true approach: pose a single, simple question and probe it painstakingly. As a graduate student, Walter explored how a cell’s proteins know where to go. What he found – the molecular machinery that brings nascent linear peptides to the intracellular factory that fashions them into three-dimensional proteins – helped propel his advisor, Günter Blobel, to the 1999 Nobel Prize in Physiology or Medicine.

The discovery also landed Walter his own lab at UCSF. There, the young scientist continued to study protein trafficking but shifted his gaze.

His new focus: the signals that tell the nucleus when the cell’s protein-folding factory – a maze-like structure called the endoplasmic reticulum (ER) – is overloaded. By the early 1990s, Walter’s team uncovered the set of molecules that transmits this information. Called the “unfolded protein response” (UPR), this quality-control system senses when misfolded proteins accumulate and spurs the cell to make more ER. The UPR “makes life-or-death decisions for cells,” says Walter. But if things go awry, it can prompt neurons to die inappropriately, leading to neurodegenerative disease, or keep alive menacing cells, causing cancer.

Through a 2008 Hughes Collaborative Innovation Award – a program designed to support team projects of ambitious scope – Walter and colleagues synthesized small molecules that can regulate the UPR. Now the researchers are probing how the UPR functions in various disease models in the hope of one day tweaking the system to help patients. One compound made recent headlines because it enhances cognition in mice. This molecule is undergoing further development at Calico, a Bay Area biotech firm devoted to fighting age-related diseases.

Walter’s pioneering research on the unfolded protein response has earned him a growing list of accolades – including a Shaw Prize and a Lasker Award in 2014, and this year’s Vilcek Prize in Biomedical Science, which recognizes creative contributions of immigrants.

## Chasing Freedom

Walter’s path toward success began in the 1960s, when he was a curious lad tinkering with chemicals at his parents’ *Drogerie* (a store that sells nonprescription medicines and household products) in West Berlin. Those playful experiments produced a few explosions, admits Walter, “some of which my parents never knew about.”

The “ignorance is bliss” mantra likely applies. His explorations in the family shop led Walter to decide by age 12 that he would major in chemistry. However, the science training he got as an undergraduate at Free University in Berlin was unsatisfying. The lab experiments were too prescribed, Walter recalls.

Determined to improve his English so he could read important biochemistry papers, Walter applied for a Fulbright scholarship to study abroad. He was rejected. But thanks to a different fellowship, Walter was able to pack his bags and fly to Nashville, Tennessee, where he spent nine months working on the biosynthesis of a fungal alkaloid in Tom Harris’s lab at Vanderbilt University. “I got two papers out of that,” says Walter. “And I picked up some English.”

But most of all, he relished the independence. “As a lowly student, I was given tremendous freedom to play and use sophisticated instruments,” says Walter in his lilting German accent. “I was immersed in real research rather than having to follow a curriculum and do experiments that zillions of students had done before.”

That appreciation for unbridled freedom carries through to this day, as Walter manages two dozen technicians, students, and scientists in his lab at UCSF. “He gave us freedom to follow our passions,” says Carmela Sidrauski, a former PhD student and postdoc in the Walter lab. “He’s not scared to go into areas he hasn’t yet explored. He will take the journey with you.”

Walter compares the journey of a scientist to that of an artist. “It’s not enough to do the same thing over and over and do it perfectly,” he explains

Given his travel schedule, Walter appreciates the fact that the succulents on his office windowsill tolerate erratic watering.



during a drive across town to his two-story brick home, whose garage he's converted into a woodshop. "In science and art, the essence is doing something no one has done before."

That principle permeates gatherings of his lab team. Years ago, at one of the group's annual retreats, Walter brought canvases and acrylics and had everyone paint their own project. "I wasn't sure if that would go down like a lead balloon," he says. "But everyone got into it." Holiday parties at the Walter home include a "Secret Santa" gift exchange where lab members give each other homemade books, board games, and such. One travel-heavy year, Walter received a Waldo-style "Where's Peter?" map.

Now that grant writing and traveling leave the senior scientist little time to tinker in the lab, Walter tools around in his home woodshop. Some creations are whimsical – for example, a garden sculpture of cubes giving birth, or a six-foot-long twisted copper fountain. Others are highly practical – like the clock he plans to give his younger daughter for her October wedding. "I like creating things with my hands," Walter says. "I'm constantly inventing little tricks and solving problems."

### The Detergent Trick

Of course, persistence and ingenuity also pay off at the lab bench. Six years before Walter started his PhD at Rockefeller University in New York in 1977, his advisor, Blobel, had proposed a controversial theory. He hypothesized that proteins destined for the ER carry a signature sequence – an address tag that lets the cell know where that protein needs to go. The idea was intriguing, but without direct evidence many scientists dismissed it. They figured proteins simply drifted to the ER by thermodynamic forces, not through a specific targeting mechanism. To prove the latter, Blobel, an HHMI investigator since 1986, would need to isolate this targeting machinery.

As a first step, Blobel worked out a system for studying protein assembly in a test tube. That was quite a feat in and of itself. But there was a nagging problem: when Walter, as a new graduate student, tried to purify an agent responsible for transporting new peptides to the ER, its activity seemed to fizzle out in one of the wash steps.

Puzzled but captivated, Walter repeated the experiment again and again, adjusting the conditions meticulously. Instead of discarding "dead" wash fractions, he stashed them in the fridge. He was "waiting for the day they would wake up," Blobel says.

Sure enough, Walter discovered he could revive the samples with a dash of nonionic detergent. Now he could use conventional procedures to purify the molecular assembly that brings fledgling proteins to the ER. Dubbed the signal recognition particle (SRP), this complex gloms onto a sequence of amino acids on some newly forming peptides. The SRP then ferries the peptides to the ER by docking at a specific surface receptor.

### Fast Fame

Walter described the purification of SRP in a landmark 1980 paper. His findings provided the first evidence that proteins reach the ER not by chance but through a controlled process governed by dedicated

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—CARMELA SIDRAUSKI

**Peter Walter, who's won both the Shaw Prize and a Lasker Award, has been on the UCSF faculty since 1983.**



targeting machinery. He became “instantly famous,” Blobel says. Walter soon made an even bigger splash – and reeled in job offers – after a serendipitous mishap lifted the veil on one of SRP’s most intriguing features.

Walter routinely measured the concentration of his samples of purified SRP on the lab’s spectrophotometer. This machine shines ultraviolet light through a solution and calculates how much gets absorbed. Assuming SRP to be a protein complex, Walter set the spectrophotometer to read at 280 nanometers – the wavelength for detecting proteins. However, one day a lab member doing a different experiment had calibrated the device to 260 nanometers instead of 280. When Walter came along later with his SRP sample, the signal was twice as high as he was used to seeing.

“He could have said, ‘Oh well, this was an accident,’” Blobel says. Instead, Walter pondered the data and realized something else was going on. The SRP is no ordinary protein complex – it contains a previously undetected RNA. (Unlike protein-containing samples, which are read at 280 nanometers, nucleic acid solutions are

measured with the spectrophotometer set to 260 nanometers.)

Happenstance might have nudged the SRP-RNA discovery. However, “luck is only recognized by those who are prepared,” notes Blobel. Walter “is an incredible detective,” he says. “From the tiniest bit of evidence, he pursues and eventually finds what is beautifully hidden.”

One of Walter’s current graduate students, Aaron Mendez, is glad nothing escapes his mentor’s scrutiny. “Often you get blinded when you see a negative result,” Mendez says, recalling a perplexing experiment where a manipulation that was supposed to help his cells live longer instead made them drop like flies. “It was demoralizing,” he says. “Peter helped me get out of my tunnel vision. Sometimes it’s the things that don’t work that end up opening new avenues.”

In that case, Walter guided his student through a rough patch by reminding him of the bigger picture. Other times, Walter brings focus to students’ work.

## “Peterizing”

When Sidrauski wrote her first paper as a graduate student in the lab two decades ago, she appreciated Walter’s steel-trap mind. Scrolling through the manuscript line by line, “he would ‘Peterize’ the text – *What does this mean? Why did you do the experiment?* – translating it so someone without the background could understand,” recalls Sidrauski, who now works at Calico. “You could always tell when Peter had revised a manuscript.”

Though long and arduous, writing papers together was one of the things Sidrauski loved most about working with Walter. She brought papers to his home on weekends – the only time he wasn’t booked – and they would pore through them over a glass of wine. “Sometimes it got so late I’d stay for dinner with his wife and family,” says Sidrauski.

Walter met his wife, Patricia Caldera, at a party while both were working on their PhDs in New York. A native of Mexico, Caldera helped coordinate UCSF’s outreach to local science teachers until retiring a few years ago. The couple raised two daughters; Gabriela is an architect in San Francisco, and Sylvia is a schoolteacher in Portland, Oregon.

Walter considers the lab his “second family.” Its members are close-knit and supportive. In between experiments, many bustle around the lounge that joins the lab to Walter’s office, gulping coffee or chatting over lunch. The group includes musicians, artists, and athletes from all corners of the world. Yet the diverse crew carries on like a well-oiled machine, even when Walter travels for weeks at a time. Some think the secret is Walter’s knack for attracting highly motivated free spirits like himself. (Walter himself says he looks for “endless curiosity and independence” in prospective lab members.)

“Each person has a strong personality,” says postdoc Diego Acosta-Alvear. “A lot of us have creative passions.” Acosta-Alvear, for example, plays the electric bass. He’s also building one. On sporadic weekends Acosta-Alvear carefully cuts, sands, and laminates wood pieces in Walter’s garage woodshop. Construction of the five-string fretless “baby” began about two years ago, before Acosta-Alvear’s wife gave birth to a real one – their daughter Ana Sofia.

The bass project grew out of conversations with Walter during a painful turning point in Acosta-Alvear’s research. “I had to leave a main project I’d been working on for a couple of years. It was a hard time for me,” recalls Acosta-Alvear. “Peter offered his home, his shop, and his help so I could have something to do outside of lab, to help me regroup and refocus.”

## UPR and Beyond

When Walter arrived at UCSF in 1983 to set up his own lab, he, too, made a deliberate shift from the research he had previously pursued at Rockefeller. “I wanted to start something new,” recalls Walter, gazing out his office window. On a knoll below stands *Dreamcatcher*, a 50-foot-tall steel sculpture by Mark di Suvero installed by the university to inspire innovation.

Back in the 1980s, scientists knew that when misfolded proteins accumulate, the cell makes more ER. It was also clear that this compensatory activity is triggered by changes in the expression of genes in the cell’s nucleus. But how does the nucleus know what’s going on in the ER? “We wondered how that information travels between different compartments,” Walter says.

To find out, two of his graduate students, Jeff Cox and Caroline Shamu, set up a yeast genetic screen. They wanted to identify molecules responsible for ER-to-nucleus communication – a pathway now known as the unfolded protein response. They discovered Ire1, a sensor molecule embedded in the ER membrane. However, unlike a typical membrane receptor – which activates a cascade by transmitting a signal to another protein, which in turn hands it off to another protein, and so forth, until the signal reaches the nucleus – Ire1 behaves like a bunch of different proteins bundled into one package. Its sequence of actions triggers a splicing event that signals the nucleus to turn on genes that will boost the cell’s ER resources. “As the story progressed, it became super exciting,” says Walter. “Every bit of this pathway is bizarre.”

But here’s the clincher – the essential UPR features that were discovered in yeast are also found in mammals. The mammalian UPR is more complicated, though: it has three branches, each controlled by a different sensor (Ire1, ATF6, or PERK), whereas yeast just have Ire1.

Collaborating with several groups, Sidrauski and others in the Walter lab identified small molecules that modulate the activity of each UPR branch in mammals. One of these modulators, ISRIB, makes cells

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—PETER WALTER

insensitive to a particular chemical change – phosphorylation of the eIF2 molecule. Normally, this phosphorylation event puts a brake on memory consolidation.

Nahum Sonenberg, a biochemist at McGill University in Montreal and an HHMI senior international research scholar, had a mutant mouse in which this phosphorylation event is partially blocked. Those mutants outperformed normal mice in tests of cognition. Walter surmised that giving mice ISRIB would be the pharmacological equivalent of the genetic tampering that made Sonenberg’s mutants smarter. Indeed, when the team injected ISRIB into ordinary mice, the animals learned better.

ISRIB activates a complex of proteins that, if mutated in people, can cause a rare and often fatal neurodegenerative disorder.

At Calico, Sidrauski and her colleagues are conducting preclinical studies to explore whether it may be possible to prevent neurological deterioration in patients with this disorder by using ISRIB to revive activity in the flawed proteins.

Walter stresses that they did not begin by focusing on a particular disease. “We are trying to understand the basic ways by which cells operate,” he says. That knowledge can then guide the research along paths that lead to an exploration of what goes wrong in disease and whether it’s possible to intervene clinically.

The unpredictable nature of this journey led Walter, in a 2010 commentary, to describe the path to discovery as “serendipity.” It’s thus no surprise that when he and his labmates began discussing names for their unicorn mascot, Serendipity was Walter’s own suggestion. After all, “she represents the mystical things we discover,” he has pointed out. Just as many scientific questions remain unanswered, the unicorn’s name was still unsettled. But she’s due to be christened at the lab’s annual retreat this fall. ■