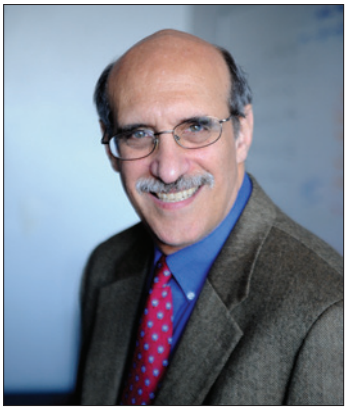
Martin Chalfie


Martin Chalfie

Future Nobel laureates, take note: You can bring 16 all-expenses-paid guests to watch you receive your prize in Sweden. Your spouse isn't counted among the 16, says Martin Chalfie, so his wife, Tulle Hazelrigg, had her own invitation. Their 16-year-old daughter, Sarah, took one guest slot, which left Chalfie with 15 seats to juggle. But he didn't have to use a seat for his Chicago high school friend and now fellow Nobel laureate, Bob Horvitz. Laureates have a permanent invitation to the December festivities.

Going to Stockholm

Chalfie proudly explains how he "fudged" his remaining invitations by rotating restricted tickets among colleagues from Columbia University, where he has been on the faculty since 1982, and friends, relations, and their spouses. Those who didn't get seats for the blow-out Nobel banquet took themselves out for a celebratory dinner on that night. By all accounts, they may have had a better time or at least a more relaxed evening, Chalfie reports. Personally, Chalfie declares that he had a ball throughout the many events of Nobel week: "It's a wonderful party. It's a great time."

There is no question though that Marty Chalfie deserved both the festivities and the 2008 Nobel Prize in Chemistry, say the colleagues and friends who made the trek. And like Chaucer's pilgrims bound for Canterbury, Chalfie and his guests all seemed to bring tales to tell.

Ghia Euskirchen, who is now a research scientist at Yale, arrived in Stockholm last December with her memories of the most fruitful one-month lab rotation in modern science. Euskirchen had just finished a master's degree in chemical engineering at Columbia in 1992 when she transferred into Columbia's biological sciences doctoral program. Noting that her engineering background included work with fluorescence, Chalfie asked Euskirchen if she would like to work on a project involving bioluminescent proteins. A literature search turned up a new report on the cDNA of a naturally fluorescent protein discovered in a Pacific jellyfish, *Aequorea victoria*, by Osamu Shimomura of the Marine Biological Laboratory.

Glowing Green

Euskirchen prepared the materials and inserted the gene into *Escherichia coli* as a preliminary test, only to discover that the Chalfie lab didn't have a microscope with the correct ultraviolet filters. Euskirchen took the sample back to her old engineering lab. Under blue light, she saw something glowing green. "There's no real contrast between organelles in bacteria and I was worried that it might just be pyrite," Euskirchen recalls. "I wasn't thinking about making a major discovery. I was just trying to demonstrate a basic competence as a new grad student. So I went and got friends to look at it." They saw something too.

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This was the first glimmer of green fluorescent protein (GFP) in an organism other than the jellyfish. Chalfie moved the work to his longtime primary lab model, *Caenorhabditis elegans,* and saw the GFP glowing inside six living neurons without any apparent disturbance to the animal. Further studies revealed GFP to be a small, inert, and relatively nontoxic molecule, easily diffused through living tissue. Properly inserted, the GFP gene is even inheritable.

GFP turned cell biology on its ear by making it possible for the first time to follow protein movements in a living cell. It led to the 2008 Nobel Prize for Chalfie, along with Shimomura and Roger Y. Tsien, the University of California, San Diego, biochemist who later developed GFP into a versatile rainbow of molecular tags.

That Chalfie took her along to the Nobel ceremonies was the height of graciousness, according to Euskirchen. After her one

momentous month in the Chalfie lab, she moved on to a thesis on yeast genetics with Teri Melese at Columbia.

It was no surprise to Euskirchen that Chalfie won a Nobel Prize for innovation. "Marty listens very intently and gets right to the bottom of whatever you're talking about," she explains. "He is very 'nonrigid' in his thinking, and he doesn't wait for new ideas to be sanctioned before adapting them."

Jellyfish cDNA

Another member of the Chalfie party was the scientist who created the jellyfish cDNA used by Euskirchen. That was Douglas Prasher, who first cloned the gene in 1992 at the Woods Hole Oceanographic Institution. He too traveled to Stockholm on Chalfie's guest list. (By agreement, Prasher's wife was on the Tsien guest list.)

Ironically, when the 2008 Nobel Prize was announced, Prasher was out of science, working as a van driver in Huntsville, AL. His National Aeronautics and Space Administration–funded biology-in-space lab there had been eliminated by budget cuts. "It is unfortunate that somebody as talented as Douglas is not in a science job now," says Chalfie of his one-time collaborator. He adds that he hopes that the Nobel publicity and new U.S. priorities for research funding will change that.

Also in the party was Jonathan Hodgkin of Oxford University. It was Hodgkin's third trip to Stockholm with a laureate. He went as a child when his father, Alan Lloyd Hodgkin, won the 1963 Nobel Prize in Physiology or Medicine. Hodgkin took his second trip with his former Cambridge colleagues John Sulston and Sydney Brenner, who along with Bob Horvitz won the first "worm" Nobel Prize in 2002. His third Nobel guest trip—and probably his last, Hodgkin predicts—grew out of his friendship with Chalfie that started in 1977. That's when Chalfie arrived in Cambridge, UK, for a postdoc in Sulston's *C. elegans* lab.

"Marty and I have been more or less permanent friends ever since," says Hodgkin. Although, he adds, this is not the same as being Chalfie's best friend. "There's too much competition for that title," Hodgkin dryly notes.

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A Smarter Protein

Hodgkin was not the least bit surprised that a Nobel Prize was awarded for the discovery of GFP and that his friend was one of the winners. "GFP is much smarter than anything we ever imagined," he declares, recalling the frustrations of using earlier protein reporter methods such as antibody staining or glactosidase enzymes.

If Hodgkin wasn't surprised, Chalfie still is. As a Harvard undergraduate, Chalfie all but gave up on a science research career after a disastrous summer lab experience. He graduated with a degree in biochemistry but was convinced he had no talent at the bench. Chalfie sold dresses for the family business and taught high school chemistry for a year before a second summer in the Yale lab of Jose Zadunaisky restored his confidence. He returned to Harvard University for his Ph.D. in neurobiology with Robert Perlman. Twenty-two years later, Chalfie put his mentor on his Nobel guest list.

Ironically, Chalfie's role was central to the discovery of GFP, but GFP is not all that central to Chalfie's career interest in the molecular basis of touch, according to Hodgkin. "The whole GFP thing was not the main thrust of his work," Hodgkin says, "but then Marty has always been generous with his materials and interested in new methods. He's gone on to develop many other useful methods."

GFP was a game changer, says another Chalfie pilgrim to Sweden, Phil Anderson of the University of Wisconsin–Madison. For the Nobel Prize, that's as it should be, says Anderson, because the scientific prizes are not given for lifetime achievement but for breakthroughs. Clearly GFP was such a discovery, even if the initial breakthrough required only a month's work. "It's hard to imagine science today without GFP," says Anderson. Another longtime friend, he reports that he was absolutely "giddy" when he heard that Chalfie had won the prize.

A Victory for Small Science

Chalfie and Anderson go back to 1978, when Anderson was an American postdoc fresh off the plane in Cambridge. Anderson was a complete neophyte when it came to *C. elegans*. Chalfie took him under his wing for a crash course in

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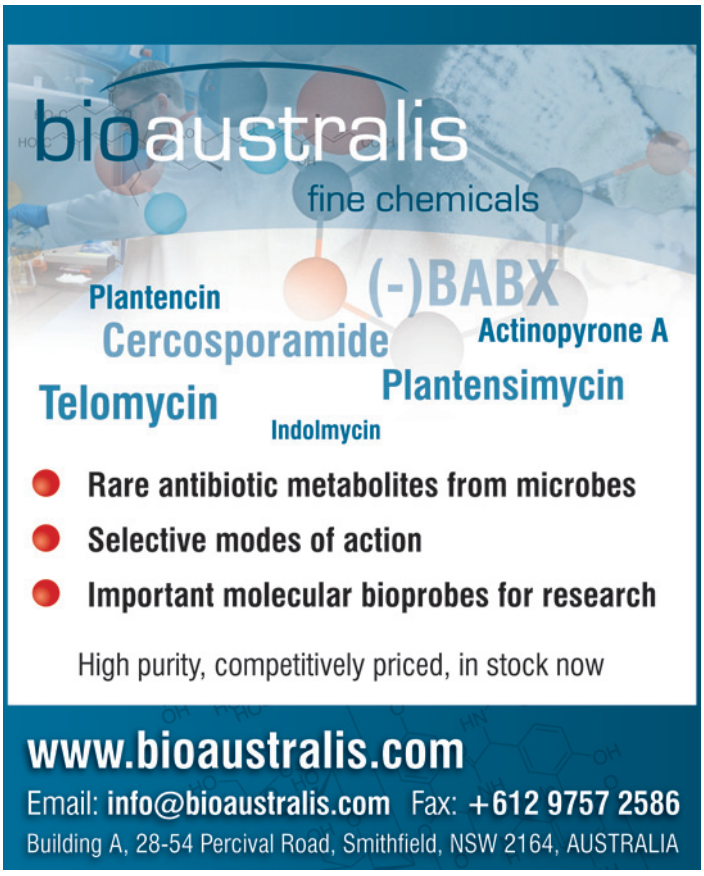

worm breeding and much else, Anderson recalls. Chalfie was the great organizer for American postdocs and their families. He set up pub outings, restaurant parties, and a job-talk critique club. (Chalfie also "organized" the 1979 birth of Anderson's son, Joe. Anderson confesses that despite his own nonchalant belief that there was no hurry, Chalfie insisted that Anderson and his heavily pregnant wife, Donna, go to the Mill Road Maternity Hospital. Joe was born less than an hour later.) Nobel week in Stockholm was the ultimate Chalfie-organized outing, according to Anderson.

Back in Wisconsin, a colleague of Anderson's pointed out the small scale of Chalfie's big discovery. "He said, 'This is a victory for the little guy, a victory for small science.' And I think that this is a perfect example of a really clever idea that proves to have a huge impact on science," says Anderson. "It also proves that we all could be just a month away from a Nobel Prize."

Chalfie has a third take on his Nobel Prize. The award ceremony, the Nobel lecture, and the gathering of old friends for a weeklong party were delightful. But whether or not discovering GFP was a sideline, Chalfie says that his own work on mechanosensation was the first beneficiary. The first multicelled animal to glow with GFP was *C. elegans*. And if he had not been working on a transparent animal like *C. elegans*, Chalfie believes that he would not have seen the point of a glowing jellyfish protein.

Back in Touch

The white tie and long tails Chalfie wore to the Nobel ceremony have gone back to the formalwear rental company in Stockholm. The amazing publicity is dying down, and Chalfie has gone back to the problem he has relentlessly pursued since his Cambridge days. Chalfie explains, "[There is] a vast array of mechanical senses in us and in other organisms. These include touch, hearing, balance, stretch, detection of blood pressure, and perhaps the detection of changes to bone in terms of stress. There's the sense of position—proprioception—and any number of other senses that detect mechanical force within our cells. One thing about the nerve cells that sense mechanical stimuli is that for the most part, we have no clue as to how they work. So that's a wonderful problem."

To solve this wonderful problem, Chalfie has built up a large library of *C. elegans* "touch" mutants at Columbia. One initial clue to the nature of mechanical sensation, Chalfie explains, was the sheer speed of the response—typically less than a millisecond. This steered his attention toward super-fast ion channels and through his numb-to-touch mutant worms to a family of channel proteins called DEG/ENaC. Chalfie believes that DEG/ENaC proteins are the first neuronal mechanosensory transducers to be identified.

The search for mammalian homologs, though, has not been easy. So far, no one has produced a mouse mutant null to touch. Chalfie says that this is probably because touch is so fundamental to survival that there must be redundant genes. But he reports that there are labs working on mouse double and triple mutants that might provide a mammalian homolog to his channel-defective worms. Twenty-five years into the problem, Chalfie believes that things are just getting interesting in the neuroscience of touch. That tale and that scientific journey are still unfolding. ■

—John Fleischman