

The Long Road To Renown: The 2015 Vilcek Foundation Prizes

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*“Sometimes the eye sees what the mind mistrusts,
Sometimes there is a green too green for belief.”*

—Shara McCallum (American poet, born in Jamaica)

IN THE FIRST DECADES of the 20th century, American scientists studying and working overseas outnumbered foreign scientists working in the United States. But after World War II, the United States began its rise toward global scientific leadership, partly because of an influx of scientists fleeing Nazism or Communism and partly because the country largely escaped the ravages of war. The United States soon became a magnet for foreign students and trainees; many who arrived stayed, strengthening the country's scientific establishment.

The goal set forth by the founders of the Vilcek Prize is to recognize contributions of immigrant biomedical scientists in the United States. The year 2015 marks the prize's 10th anniversary. Over the last decade, 11 researchers have received the Vilcek Prize in Biomedical Science. Of these, 7 were born in Europe, 3 were born in Asia, and 1 was born in South America.

To recognize a younger generation of outstanding foreign-born scientists, the Vilcek Foundation began awarding Annual Prizes for Creative Promise in Biomedical Science in 2009; applicants for these prizes must be no more than 38 years of age. Since 2013, 3 winners are chosen every year. Among a total of 13 young recipients of these prizes, 7 were born in Asia, 5 were from Europe, and 1 was born in New Zealand. Although the average age at which biomedical scientists begin an independent career has steadily drifted upward, the accomplishments of the young prize winners are striking (1–5).

The Vilcek Foundation Prizes are the only major prizes earmarked for foreign-born scientists. Concomitantly, the Foundation honors an equal number of exceptional foreign-born artists active in the United States in a range of fields of endeavor, including literature, visual arts, culinary arts, and fashion. This year, the Vilcek Prizes once again bear witness to the wealth of immigrant talent this country is fortunate to possess: The 2015 awardees in biomedical science are Peter Walter, recipient of the Vilcek Prize, and Sun Hur, Franziska Michor, and Rob Knight, recipients of the Creative Promise Prizes.



Peter Walter. Photo credit: Elisabeth Fall.

Deciphering Cellular Quality Control: Peter Walter, Winner of the 2015 Vilcek Prize in Biomedical Science

“Eternal duration is promised no more to works of men than to men.” So declares the narrator of *Time Regained*, the final volume of Marcel Proust's magnum opus *In Search of Lost Time*, a novel whose abiding influence places it squarely among the supreme literary works of the 20th century. The wooden sculpture that once occupied pride of place in cell biologist Peter Walter's well-appointed living room in the San Francisco Bay Area seems to subtly mock the logic of Proust's observation on impermanence. Wedged between a pair of vertical bars set on a steel-gray pedestal, a circular mechanical clock documents the passage of time. In a bid to counter time's inexorable march, a rope and pulley weighted with a stone and rigged to the bars relentlessly squeeze the clock and funnel salvaged time into a clear glass vial—a metaphorical repository of regained time.

Walter's time-restoring device is just one example of the dozens of wood and metal curios that he has handcrafted over the years. Adept at art and science, Walter, a professor of cell biology at the University of California, San Francisco and winner of the 2015 Vilcek Prize for Biomedical

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Science, has combined his creative gift and scientific curiosity to proffer exquisitely detailed accounts of the movements of proteins within cells. Historicized in the *Annals of Cell Biology* for enabling a fundamental understanding of how cells work, Walter's findings on the mechanisms that control the abundance of compartments within cells and the shuttling of proteins between them span nearly 4 decades and bear a host of implications for treating human diseases, including type 2 diabetes, inflammatory bowel disease, and cancer.

When he enrolled at the Free University in his native West Berlin to study chemistry in 1973, the 19-year-old Walter was eager to channel years of enthusiasm for the subject into systematic apprenticeship. His eagerness was in part the result of childhood adventures with chemicals in his father's drugstore—a veritable workshop for a boy enamored with chemical reactions and their sometimes scintillating results. Walter's mechanical turn also influenced his choice of chemistry at university; his homebrew paper chromatography machine earned him third prize in a high-school contest hosted by a local periodical to spot promising young researchers. However, soon after he entered the university, he realized that fluency in English was crucial to success in science. Undeterred by a failed attempt to secure a Fulbright fellowship to study in the United States, Walter applied for an academic exchange fellowship, which allowed him to attend Vanderbilt University in Nashville, Tennessee in 1976.

At Vanderbilt, the culture shock was palpable. By the mid-1970s, Berlin boasted a profusion of artists and intellectuals whose iconic legacy included, for example, the novels of the writer Christopher Isherwood, the trilogy of albums by the rock musician David Bowie, and the New German Cinema of the filmmaker Werner Herzog, bespeaking the cultural riches that lent the city its cosmopolitan allure. By comparison, 1970s Nashville seemed something of a backwater, largely untouched by the zeitgeist. Yet, for all its cultural sophistication, says Walter, Germany lagged behind the United States in its approach

to science education, favoring knowledge over inquiry. So it was a welcome change when Walter embarked on an independent research project in the laboratory of Vanderbilt biochemist Thomas Harris, who put Walter through his paces, nurturing his scientific temperament and shaping his skills in organic synthesis.

During the year at Vanderbilt, Walter helped unravel how a fungal pathogen that afflicts red clover trees in Tennessee makes an alkaloid that causes clover-grazing cattle to slobber, posing an unsightly challenge to farmers. The experiments may have been esoteric, but they familiarized Walter with the scientific method and led to a 1979 report in *Biochemistry* (6). "In the end, I questioned whether anybody really would care where every carbon [atom in the compound] came from. That, to a large degree, determined my move towards more biological questions," recalls Walter.

The move came about in 1977 when, upon the urging of Rockefeller University biochemist Stanford Moore, whom he had met during a chance encounter at Vanderbilt, Walter applied to the graduate program at Rockefeller. Facing initial rejection, Walter had all but decided to return to Germany, but when he advanced on the waiting list and was offered a position to pursue a Ph.D., his career took a decisive turn—one that shaped his decades-long research interest and cemented his position in cell biology.

When he began his Ph.D. in the laboratory of Rockefeller cell biologist Günter Blobel, Walter understood the importance of the work he undertook, but he had nary a clue that it would garner Blobel a Nobel Prize 2 decades later. By the late 1970s, much of the ground for Walter's now-famous contributions to protein transport had been laid. Working with his colleague David Sabatini, Blobel had addressed a fundamental question that had long flummoxed cell biologists: How do proteins, which are made in cellular factories called ribosomes, reach their proper locations inside cells? Through experiments that dismantled and reassembled in test tubes the machinery required for the cellular wanderings of proteins, Blobel had proposed that nascent proteins carry address tags that enable their routing within cells. Before long, biochemist Cesar Milstein found experimental evidence for just such a tag in a secreted protein.

Building a theory on mounting evidence, Blobel and cell biologist Bernhard Dobberstein laid down a notion fittingly named "the signal hypothesis." The hypothesis held that as freshly minted proteins enter the cellular compartment called the endoplasmic reticulum (ER), a labyrinthine network of tubes studded with ribosomes, signal sequences direct their passage through a channel in the ER membrane, jumpstarting their journey toward their final destinations in cells. This passage, known to cell biologists as protein translocation, became the focus of Walter's doctoral work. "The [goal] was to determine how protein translocation happens. I thought the question was open-ended and exciting. We tried to set up assays that would characterize the translocation capacity of the endoplasmic reticulum," recalls Walter.

The assays involved nimble enzymatic disassembly and reconstitution of the essential ingredients for protein translocation and resulted in a 1979 report (7). "We can shave the [membrane] with proteases, and translocation



Time Machine. Sculpture and photo credit: Peter Walter.

activity was lost, and we can add an extract back from a mildly proteolyzed membrane fraction and restore the translocation activity. That gave us positive evidence that there indeed must be some sort of machinery that promotes protein translocation,” recalls Walter. Years later, cell biologists Randy Schekman and Tom Rapoport discovered the protein translocation channel, but Walter purified the 6 polypeptide constituents of a related apparatus and described them in a 1980 *Proceedings of the National Academy of Sciences* article, setting the stage for a triad of papers in the *Journal of Cell Biology* that recounted in stunning detail the mechanics of signal sequence recognition and protein targeting to the ER membrane (8–11).

The apparatus made up of the 6 polypeptide subunits was christened the signal recognition protein (SRP), which recruits protein-making ribosomes to the ER membrane and latches onto the signal sequences on nascent polypeptides emerging from the ribosomes to help ferry them into the ER. But it was not until 1982 that Walter discovered through happenstance that the SRP also contained a nucleic acid component: an RNA molecule that turned out to be an integral part of the SRP. The RNA molecule, reported in *Nature*, added to a growing appreciation of previously unrecognized roles for RNA, thought to be mostly dedicated to the flow of genetic information for protein synthesis (12). The finding also led to the renaming of the SRP as signal recognition particle, now that the apparatus was revealed to be a mix of protein and nucleic acid.

His reputation in the field firmly established, Walter accepted an assistant professorship at Rockefeller University in 1982 but was lured a year later to the University of California, San Francisco (UCSF). Although he had long meant to return home to Germany, the decision to settle in the United States had been stealing toward him over the years and was solidified when cell biologists Bruce Alberts, Marc Kirschner, and Regis Kelly encouraged him to accept a faculty position at USCF.

Walter’s labors on the SRP betoken a person of career-defining passion, as he relentlessly pursued the subject in his adopted home. The culmination of nearly 2 decades of Walter’s sustained research on the intricacies of protein translocation is evident in the electron microscopic and crystallographic structure of the SRP, in the discovery of its receptor, and in the realization that the particle is conserved across all forms of life. Such gimlet-eyed studies of protein peregrinations garnered Walter a 1988 Eli Lilly Award and a 1989 Alfred P. Sloan Award.

It is a sign of Walter’s intrepidity as a scientist that when a pair of graduate students—Caroline Shamu and Jeffery Cox—suggested an avenue of research that represented a departure from the SRP in the early 1990s, he readily embraced the challenge. The new venture led to insights into how cells deal with stress triggered by the buildup of misfolded proteins in the ER. Previous studies had found that the ER responds to stress by titrating its own contents, in particular, by altering the amounts of enzymes that help newly formed proteins fold into their correct shapes. By triggering gene switches that act in the cell’s nucleus to ratchet the levels of ER enzymes involved in protein folding, the ER enables cells to adjust their protein-folding capacity. That finding, now nearly a quarter-century old, resulted from the cumulative efforts of a small army of



The drugstore Peter Walter’s family owned in Kreuzberg, Berlin, circa 1954. Photo courtesy of Peter Walter.

researchers, including Amy Lee of the University of Southern California; Mary-Jane Gething and Joseph Sambrook of the University of Texas Southwestern Medical Center; Linda Hendershot of the University of Alabama, Birmingham; and Hugh Pelham of the Medical Research Council Laboratories in the United Kingdom. But the line of communication between the ER and the nucleus remained largely unknown.

Like archaeologists collating fragments of evidence into a coherent find, Walter’s team set out to identify parts of the communication line called the “unfolded protein response.” The first node in the line to emerge from a series of yeast genetic screens perfected in the laboratory was a membrane-spanning enzyme called Ire1, which, by virtue of being a kinase, can turn cellular signaling on and off (13). (Meanwhile, Japanese molecular biologist Kazutoshi Mori, then a postdoctoral fellow in the Sambrook/Gething laboratory in Texas, had uncovered the role of Ire1 around the same time.) Not long after this discovery, the team identified a gene switch called Hac1, which controls the production of ER resident enzymes that foster protein folding (14). But it was not until graduate student Carmela Sidrauski discovered a third node in the line—an enzyme known as tRNA ligase—that the pieces could be assembled to unravel the regulatory response (15).

When the assemblage was unveiled, it proved to be one of bedeviling ingenuity: The team found that when the Ire1 kinase, which straddles the ER membrane, senses a surfeit of unfolded proteins in the ER, it clusters on the membrane, activating the portion of the kinase that lies in the cytoplasm. It turned out that the kinase is attached to a nuclease module, which upon activation cleaves the RNA message of the Hac1 gene switch. Next, the tRNA ligase splices together two fragments of the Hac1 RNA message, enabling the cell to make Hac1 protein, which then promptly turns on the unfolded protein response. “It was one of those completely unexpected, serendipitous observations where following up on something that didn’t make sense led to a major discovery,” says Walter, characterizing the cellular response as a scheme worthy of Rube Goldberg, the American sculptor renowned for gadgets of Gordian

design. For solving such a daunting puzzle, Walter was duly rewarded with the 2009 Gairdner International Award, the 2014 Shaw Prize, and the 2014 Lasker Basic Medical Research Award, all shared with Mori, now at Kyoto University.

Having uncovered the tortuous sequence of events that allow the trio of proteins to respond to ER stress, the team puzzled over a simple question: How does Ire1 tell apart folded and unfolded proteins in the ER? A fine sense of pattern recognition is a frequent hallmark of a superior scientific intellect, and it was precisely such a sense that enabled Walter to divine the nature of the interaction between Ire1 and unfolded proteins in the ER. Just as immune sentinel proteins recognize invading pathogens by binding to protein fragments derived from the invaders, Walter and his team surmised, Ire1 might sense its targets by directly binding to them.

Working with UCSF structural biologist Robert Stroud, Walter unraveled the crystal structure of the portion of Ire1 that lies in the ER of yeast cells. The structure revealed that Ire1 contains a canyon-like groove, and mutating certain amino acids that line the groove diminished the enzyme's ability to bind to unfolded proteins. Following a series of structural studies, Walter and his team reported in *Science* in 2011 that unfolded proteins directly bind to Ire1 (16). "Pretty much everything we learned about this pathway in yeast directly translated to mammals, although things are a little more complicated in mammalian cells where three parallel pathways act in concert during ER stress. They divide the work to deliver a more nuanced response," says Walter.

The signaling pathways together help mammalian cells deal with stress, but if the buildup of unfolded proteins overwhelms cells, the pathways conspire to turn on a program of cell death for the benefit of the organism, sacrificing overburdened cells heaving with the heft of misshapen proteins. Because it is involved in such a vital decision in the lives of cells facing stress, the response is implicated in a range of diseases, including cancer, an outcome of runaway cell division, and type 2 diabetes, a condition marked by the death of insulin-secreting pancreatic cells. Thanks to a grant from the Howard Hughes Medical Institute for collaborative research, Walter and his co-workers are trying to identify chokepoints in the byzantine signaling network that could be targeted by candidate drugs to safely prod stressed cells toward either recuperation or death.

To that end, Walter struck up a partnership with researchers at McGill University in Montreal, Canada and the San Francisco-based biotech firm Genentech to scour a collection of more than 100,000 chemical compounds for those that selectively hobble the signaling pathways implicated in cell stress. One such compound, dubbed ISRIB or integrated stress response inhibitor, counters the effects of an enzyme called PERK, a pivotal component of 1 of the signaling pathways. When triggered by ER stress, PERK modifies a protein called eIF2 α , tamping down protein synthesis in brain cells and hampering the brain's ability to form long-lasting memories. Mutations in eIF2 α and its partners have been linked to human brain diseases such as vanishing white matter disease and familial intellectual disability syndrome. A

compound that blocks the PERK pathway, the team reasoned, would lift the brake on protein synthesis in brain cells, allowing memory consolidation to proceed unimpeded.

In experiments with mice, the compound lived up to expectations; mice injected with ISRIB learned to locate a submerged platform in a water maze much faster than those that did not receive the compound, as the team reported in a 2013 *eLife* article (17). ISRIB appeared to enhance the ability of mice to remember spatial cues and context-based fears, raising the possibility of a drug that might prove similarly effective in enhancing long-term memory in people with cognitive deficits. At the very least, says Walter, the compound may prove a powerful tool to plumb brain functions currently beyond experimental reach.

Another collaboration with Genentech is a hunt for compounds to combat multiple myeloma, a cancer of antibody-secreting white blood cells in the bone marrow that has largely eluded a cure. Typically afflicting people over the age of 50 years, the disease affects the immune system, kidneys, nerves, and bones. Although the precise triggers of the disease remain unclear, it is thought to occur when the unfolded protein response fails to induce cell death, leading to the unchecked division of white blood cells. Together with UCSF cancer biologists Kevan Shokat and James Wells, Walter's team hopes to identify compounds that can kill cancerous white blood cells. Ire1, a lynchpin enzyme in ER stress, lies at the heart of these efforts. "We have two compounds in hand, and multiple myeloma cells stop growing in the presence of these Ire1 inhibitors. We are now looking at combinatorial effects with other known treatments," says Walter. But these are early days, he adds, noting that the spadework to determine the suitability of the inhibitors for preclinical trials is under way.

Whatever the medical gains from his work, Walter's contributions to cell biology spring from a well of seemingly insatiable curiosity with which he has winkled out of cells fundamental truths about their workings. Among the findings that bear witness to his commitment to basic research, Walter and his postdoctoral fellow, Benoît Kornmann, brought to light a surprising mode of contact between the ER and mitochondria, the energy factories of cells. Mitochondria are mostly excluded from the intricate cellular shipping network based on packages called vesicles, but Walter's team found that yeast mitochondria rely on an elegantly simple workaround to get their consignment of membrane lipids. A complex made of 4 proteins bridges the space between the ER and mitochondria, yoking the compartments together and enabling the exchange of lipids between them. Aptly named ERMES (ER-mitochondria encounter structures) after the mythological go-between of the Greek gods, the complex may also serve to shuttle calcium ions, which enable mitochondria to generate energy and control cell death. Resoundingly clear from most of his publications, the findings underscore Walter's interest in basic research (18).

If Walter's centripetal influence in cell biology is not evident in the laurels lavished on him over the years—memberships in the U.S. National Academy of Sciences, the European Molecular Biology Organization, and the



Franziska Michor. Photo Kathryn Costello/Vilcek Foundation.

American Academy of Arts and Sciences—his coauthorship of recent editions of *Molecular Biology of the Cell*, arguably the discipline’s definitive textbook, is a sure sign of his command in the field. “One very laudatory reviewer said that the book is as hard to pick up as it is to put down,” he says, amid titters. “It’s difficult work, and it takes years to put together each edition, but in the end, it’s incredibly rewarding. It has been very impactful.”

Asked what spurs his creative instincts, whether in the laboratory or workshop, Walter says, “In the most abstract sense, there are many connections between science and art. Both are curiosity-driven, and you always want to do something new.” Yet curiosity may not be the only animating spirit behind Walter’s accomplishments. At the root of his seemingly divergent pursuits, aglow with mutual inspiration, might lie a unifying desire to glean the essence of things by observation, tinkering, and interpretation.

Stacking the Deck Against Cancer: Franziska Michor, Winner of the 2015 Creative Promise Prize in Biomedical Science

What sets apart Franziska Michor from many of her mathematician colleagues is the pace at which her findings, deeply rooted in theory as they are, have been put to practical use. Poised to influence the landscape of cancer treatment, Michor’s modeling efforts might yield palpable benefits for patients. Michor, a professor at Dana-Farber Cancer Institute and Harvard University, has combined the predictive power of mathematics and the experimental insights of biological research to improve treatment outcomes for cancer patients.

Born in Vienna, Austria to a mathematician father and a nurse mother, Michor resolved to use her quantitative skills to solve problems of relevance to people. After completing studies of mathematics and molecular biology at the University of Vienna, she enrolled in a graduate program at Harvard University, earning her Ph.D. degree 3 years later. At Harvard, she used modeling to unravel the evolution of cancer cells. She struck up a partnership with oncologist Charles Sawyers, who was then at the University of California, Los Angeles, to predict how tumors respond to Gleevec, long hailed as a miracle drug for chronic myeloid leukemia. One outcome of the work demonstrated the

role of cancer stem cells, a group of self-renewing cells that are thought to evade drugs and sustain cancer. The discovery furnished a likely explanation for the drug resistance seen in some patients. Michor has since pursued translational research with unwavering focus—first at Memorial-Sloan Kettering Cancer Center in New York, where she moved in 2007 and later at Dana-Farber, where she returned in 2010 for an associate professorship.

Over the years, Michor’s modeling efforts have led to a wealth of insights on cancer biology and treatment. To wit, she has used clinical data to model the rate at which pancreatic cancers spread, launched a clinical trial of a novel dosing regimen to delay the onset of resistance to the targeted lung cancer drug Tarceva, and most recently, prolonged the survival of mice with a form of brain tumor called proneural glioblastoma using an unconventional radiation therapy schedule. Preparations for a clinical trial of the modified radiation schedule are under way.

Michor’s intellectual precocity is evident in the leading role she plays in oncology; in 2009 she became the only junior faculty member to direct one of the 12 National Cancer Institute-sponsored research centers in the United States for bridging cancer biology and the physical sciences. At the age of 32, she is the youngest scientist to win the Creative Promise Prize in Biomedical Science.

Solving a Riddle of Self-Identity: Sun Hur, Winner of the 2015 Creative Promise Prize in Biomedical Science

If scientific promise can be measured by the knack for uncovering nature’s ingenious ways, molecular biologist Sun Hur has proven her mettle beyond reasonable doubt. Hur, an associate professor at Harvard Medical School with a joint appointment at Boston’s Children’s Hospital, has determined how the immune system takes the measure of disease-causing viruses and targets them for destruction. She has found that innate immune cells, endowed with proteins called pattern recognition receptors, use a molecular yardstick to distinguish viral genetic material from their own.

Hur was born in Seoul, South Korea. From a young age, she was smitten with physics, which she pursued at Seoul’s Ehwa Womans University. But during her college years, complex biological systems claimed her interest. So she



Sun Hur. Photo credit: Kathryn Costello/Vilcek Foundation.



Rob Knight. Photo credit: John Anderson/Vilcek Foundation.

attended a summer internship at Woods Hole Oceanographic Institute in Massachusetts and enrolled in an exchange program at the University of California, Santa Barbara in 2000. Coveting the academic freedom enjoyed by scientists in the United States, Hur stayed in Santa Barbara for graduate studies with chemist Thomas Bruice. During a Ph.D. program completed in just 2 years, Hur published influential reports on the computational analysis of enzyme reactions. In her postdoctoral apprenticeship with University of California, San Francisco structural biologist Robert Stroud, she uncovered the molecular secret behind the specificity of an RNA-modifying enzyme involved in protein synthesis.

Hur's interest in the immune recognition of viruses with RNA genomes owes a clear debt to her work in Stroud's laboratory but has since come a long way. One class of pattern recognition receptors distinguishes cellular RNA from double-stranded RNA derived from viruses. Hur's team found that one such receptor, MDA5, assembles into a filament along double-stranded RNA molecules to measure their length and gauge their provenance, thus helping to spot invading RNA viruses. Once the viral identity of the RNA is established, the receptor mobilizes immune molecules to dispatch the virus. She found that mutations in MDA5 can lock the molecule in a filamentous state, leading to an inflammatory disease called Aicardi-Goutieres Syndrome. For her varied contributions, Hur has earned several accolades, including a Pew scholarship and a Massachusetts Life Science Center Award.

Curating a World of Microbes: Rob Knight, Winner of the 2015 Creative Promise Prize in Biomedical Science

To bill Rob Knight as a toolmaker might be to downplay the impact of his computational efforts on human and environmental well-being. In little more than a decade, Knight has cataloged microbial communities across environments, mapped the microbial denizens of different parts of the human body, and demonstrated that microbes can influence metabolic health. Applying the tools of sequencing and data analysis to an eclectic range of issues, Knight, now a professor at the University of California, San Diego, has earned a place among today's leaders in microbiome research.

Born in Dunedin, New Zealand, Knight earned a Bachelor's of Science degree in biochemistry from the University of Otago. In 1996, he set off for the United States, where he eventually began graduate studies. After a false start working on genetic engineering to control mammalian pests, Knight joined molecular biologist Laura Landweber at Princeton University to study the evolution of the genetic code.

After receiving a Ph.D., Knight pursued a postdoctoral position with molecular biologist Michael Yarus at the University of Colorado, Boulder (USA) where he met microbial ecologist Norman Pace, renowned for his techniques for the wholesale cataloging of microbial communities using 16S ribosomal RNA as a molecular yardstick. Recruited to a faculty position at Boulder in 2004, Knight fashioned a range of bioinformatics tools, including a gene sequencing technique called barcoded pyrosequencing, which reduced the cost and increased the efficiency of microbial community sequencing, a data-clustering tool called UniFrac, which uses evolutionary relationships to compare microbial communities across environments, and an open-source toolbox called QIIME for the taxonomic classification of microbes through the analysis of large sequencing datasets.

Whether it is documenting differences in the microbes that inhabit the guts of lean and obese people, surveying the microbial milieu of our homes and workplaces, or building an atlas of Earth's microbes, Knight has helped launch projects with clear societal implications. Knight's swift rise to the top of his field is evident in his accolades. He has earned a Howard Hughes Medical Institute Early Career Scientist award and a Kavli Fellow award, and was elected as a fellow to the American Association for the Advancement of Science. FJ

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