

The HHMI Investigator Program

The Howard Hughes Medical Institute's approach to biomedical research can be summarized in three words: people, not projects. By appointing scientists as HHMI investigators — rather than awarding research grants — the Institute provides long-term, flexible funding that enables its researchers to pursue their scientific interests wherever they lead.

HHMI believes that scientists of exceptional talent and imagination will make fundamental discoveries of lasting scientific value and benefit to humanity if they are given the resources, time, and freedom to pursue challenging questions.

The Institute nurtures the creativity and intellectual daring of scientists who are willing to set aside conventional wisdom or the “easy” question for a fundamental problem that may take many years to solve. Among the characteristics that distinguish this group of scientists are qualities such as creativity, a penchant for risk-taking, and a commitment to discovery, productivity, and perseverance. This unique research model is an imaginative and powerful alternative to funding biomedical research through grants.

The flagship HHMI Investigator Program employs approximately 300 HHMI researchers, among them 12 Nobel laureates and 124 members of the National Academy of Sciences. In the last decade, HHMI investigators have won eight Nobel Prizes. These exceptional scientists direct Institute research laboratories on the campuses of 64 universities and other research organizations throughout the United States.

Since the early 1990s, investigators have been selected through rigorous national competitions. The Institute solicits applications directly from scientists at medical schools and other research institutions in the United States, with the aim of identifying those who have the potential to make significant contributions to science. HHMI employs an open application process to ensure that it is selecting its researchers from a broad and deep pool of scientific talent.

Once selected, HHMI investigators continue to be based at their home institutions, typically leading a research group of 10-25 students, postdoctoral associates and technicians, but they become Institute employees and are supported by field staff throughout the country.

With freedom and flexibility come high expectations for intellectual output. HHMI demands creativity and innovation. Investigators are expected to work at the frontiers of their chosen field, to ask fundamental questions, and to take risks. HHMI prizes impact over publication volume in its merit-based renewal of investigator appointments and recognizes that some areas of research will proceed more slowly than others.

Those same principles apply to the HHMI researchers at the Janelia Farm Research Campus, where leading scientists pursue long-term, high-risk, high-reward research in a campus specially designed to bring together researchers from disparate disciplines.

Through its model for supporting basic biomedical research, the discoveries made in HHMI laboratories across the country, its commitment to sharing new knowledge and research tools, HHMI nourishes the broader science and education community.

HHMI's annual budget, though substantial, is dwarfed by the nation's investment in research through the National Institutes of Health. Yet in holding fast to a distinctive

model for supporting scientific research, HHMI uniquely serves science, creating a culture of inquiry that encourages the free and unfettered pursuit of knowledge.

HHMI Research

Every day in laboratories around the country, HHMI scientists work avidly and passionately toward tomorrow's discoveries. Each day they get closer to findings that may have a significant impact on the diagnosis and treatment of many human diseases, from cancer and AIDS to heart disease and arthritis. HHMI investigators are learning to outwit the shifty bacteria, viruses, and parasites that cause infectious diseases. They're paving pathways to deeper understanding of aging, memory, the immune system, and the brain.

Plumbing the depths of plant and animal genomes, HHMI investigators are continually finding new understandings of the ways genes work. Sometimes inventing wholly new areas of study, HHMI researchers are pioneers in such areas as biological regeneration, DNA microarray technology, and computational biology. Through the challenging work of basic science, they bring us closer every day to the next stunning discovery.

The stories below are just two of many that exemplify HHMI's approach to science.

Richard Axel and Linda Buck

The olfactory mechanics that make possible this exquisite ability to discern smells from the most subtle to the blatant have been the subject of study for HHMI investigators Richard Axel and Linda B. Buck for much of their research careers. Axel and Buck, who joined HHMI in 1984 and 1994, respectively, were awarded the 2004 Nobel Prize in Physiology or Medicine for their discoveries of "odorant receptors and the organization of the olfactory system."

The trail to the Nobel began many years ago as a bold attempt to understand how the brain creates an internal representation of the external sensory world. Little was known about the mechanics of smell before Axel and Buck published their seminal discovery of odorant receptors.

In 1991, Axel and Buck (who was working on her second postdoctoral fellowship in Axel's lab), were three years into their search for odorant receptors. Approaching the problem with her training in immunology, Buck had been trying to identify rearranged genes in the mammalian nervous system. "I was intrigued by the possibility that gene rearrangement or gene conversion might be involved in the generation of a varied set of odorant receptors or regulate their expression, as with antigen receptors in the immune system," she says. "I became obsessed with finding the odorant receptors and stayed on in Richard's lab to look for them."

Buck and Axel, who is at Columbia University, initially adopted an "unbiased approach" with regard to the structure of odorant receptors, choosing to focus on two assumptions: that the receptor proteins would be selectively expressed by olfactory sensory neurons

and, given the structural diversity of odorants, there would be a family of related, but varied, odorant receptors that would be encoded by a family of related genes.

Their efforts produced nothing at first. The tide turned when, using scattered evidence from other labs, Buck decided to narrow her search to G protein-coupled receptors (GPCRs), many of which were known to be involved in cell signaling. Making use of the recently developed gene amplification technology called PCR, or polymerase chain reaction, Buck says, she “decided to conduct an exhaustive search for GPCRs in the olfactory epithelium by taking a novel.”

Further analysis of the PCR products narrowed the search to one candidate. “When I cloned this PCR product and sequenced five of the clones, I found precisely what we had been looking for,” says Buck, who is now at the Fred Hutchinson Cancer Research Center.

“I had tried so many things and had been working so hard for years, with nothing to show for it,” says Buck. “So when I finally found the genes in 1991, I couldn’t believe it. None of them had ever been seen before. They were all different, but all related to each other. That was very satisfying.”

Roderick MacKinnon

Roderick MacKinnon of The Rockefeller University joined the Howard Hughes Medical Institute in 1997 as a self-taught structural biologist. Already an accomplished scientist, MacKinnon considered his HHMI appointment a special opportunity to take an entirely new research direction in order to further his work.

Prior to coming to Rockefeller, MacKinnon was a successful scientist at Harvard Medical School, where he ran a laboratory that studied ion channels, tiny doughnut-shaped pores that penetrate the membrane that surrounds living cells. They permit ions—charged atoms of potassium, sodium, chloride, and calcium—to flow across cell membranes, thereby generating electrical signals. Ion channels are fundamental to health and to the normal function of the human body; their impulses create the sparks of the brain and nervous system, allowing us to walk, talk, fall in love, and, for example, cast a fishing line with accuracy.

Building on decades of clever observations by their predecessors, MacKinnon and others had been inching toward a deeper understanding of how the pores performed their feats of exquisite discrimination among ions and responsiveness to minute changes in their environment—enabling the cell membrane to suddenly become permeable, but only to highly specific types of ions.

But though the genes behind the channel proteins had been cloned, which gave scientists new traction on the problem, channel aficionados were still struggling.

Trained as a physician, MacKinnon decided to teach himself the rudiments of x-ray

crystallography because he wanted to find a way to solve a specific problem: defining the structure and mechanism of the channel that controls the flow of potassium into the cell. To devote himself to this pursuit, he moved his laboratory from Harvard to Rockefeller University, where he was named an HHMI investigator shortly after joining the faculty. His creativity, ability to approach his research from a new perspective, and single-minded pursuit of a significant scientific problem exemplify many of the attributes HHMI seeks in its investigators.

In April 1998, *Science* published two elegant articles by MacKinnon. In the first, he defined the “inverted teepee” structure of the potassium channel in a strain of bacteria and in the second he confirmed that the human potassium channel was structurally similar. MacKinnon continues to generate new insights that illuminate the structure and function of ion channels. These insights are critical to understanding new approaches for treating human diseases as varied as hypertension and epilepsy. Like many other HHMI investigators, MacKinnon has focused on fundamental biological questions that have significant implications for the understanding and treatment of human disease.

Five years after those *Science* articles were published, MacKinnon received the ultimate vindication of his out-of-the-box creativity and persistence in the face of high risk: He shared the 2003 Nobel Prize for Chemistry with Johns Hopkins researcher Peter C. Agre who discovered water channels in cells. Agre was a member of HHMI's Scientific Review Board at the time he received the Nobel Prize.