Written Testimony of Gerald M. Rubin, Ph.D.,
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Mr. Chairman and Members of the Committee:

Thank you for the opportunity to speak before you today. I am Gerald Rubin, a Vice President at the Howard Hughes Medical Institute (HHMI) and Director of the Janelia Farm Research Campus in Ashburn, Virginia. I am honored to testify before the committee as it begins to examine the mechanisms for funding high-risk, high-reward research, and the appropriate role of the federal government in supporting such research in the United States.

My testimony will cover three broad areas: HHMI's approach to biomedical research; HHMI's motivation for creating a new kind of research center at Janelia Farm; and a summary statement that reflects my perspective on how the federal government could improve its support of high-risk, high-reward research.

The Howard Hughes Medical Institute Invests in People, Not Projects

Nearly 25 years ago, as the HHMI Trustees prepared to sell the Hughes Aircraft Company to General Motors Corp., in order to establish the first permanent endowment for the Howard Hughes Medical Institute, *The New York Times* issued an emphatic challenge to the leadership of the newly reorganized entity. In an editorial that was published on June 15, 1985, the newspaper urged the Institute to avoid the temptation to plug gaps in federal spending and instead to "be more venturesome and fund high-risk research, and by methods as different as possible from the Government's."

As a science philanthropy whose explicit goal is the discovery of new knowledge, HHMI seeks to use its investments of intellectual and financial capital to seed growth and change, to foster fresh thinking.

HHMI's biomedical research philosophy 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.

The Institute takes the "long view," preferring to nurture 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 distinguishing characteristics of HHMI's scientists are qualities such as creativity, a high tolerance for risk-taking, and a commitment to discovery, productivity, and perseverance.

HHMI's unique research model is an imaginative and powerful alternative to project-based research support or funding biomedical research through grants. The Institute's flagship research program, the HHMI Investigator Program, currently employs 346 researchers who direct Institute laboratories on the campuses of 72 universities and other research organizations throughout the United States. HHMI scientists represent a wide range of biomedical research disciplines—from chemistry, neuroscience, and

bioinformatics to structural biology, immunology, and clinical genetics. They include mathematicians, physicists, engineers, physicians, chemists, and classically trained molecular and cellular biologists.

The success of HHMI's "people, not projects" philosophy can be seen in the high productivity and breakthrough insights generated by HHMI investigators. In recent years, HHMI researchers have made many major research advances, including:

- Identifying a new drug that is now approved by the FDA to treat patients whose chronic myeloid leukemia failed to respond to standard treatment with Gleevec
- New microscopes and imaging techniques that let researchers visualize cells and proteins with unprecedented resolution
- A non-invasive test for genetic mutations associated with colon cancer
- Gene microarrays and "protein chips," enabling researchers to simultaneously measure the function of thousands of genes or proteins

HHMI investigators have been awarded Nobel Prizes in eight of the last 10 years, and 12 investigators overall have received the Nobel Prize. Currently, there are 131 HHMI investigators who are members of the National Academy of Sciences. Election to the Academy – one of the highest honors a scientist can receive -- is based on distinguished and continuing achievement in original research. HHMI investigators presently compose about six percent of the Academy's 2,100 current members (this does not include foreign associates).

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.

After they have been 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 HHMI 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.

In reviewing its scientists, HHMI expects not only that its investigators be talented and productive scientists, but also that they demonstrate some combination of the following attributes to an extent that clearly distinguishes them from other highly competent researchers in their field:

- They identify and pursue significant biological questions in a rigorous and deep manner.
- They push their chosen research field into new areas of inquiry, being consistently at its forefront.

- They develop new tools and methods that enable creative experimental approaches to biological questions, bringing to bear, when necessary, concepts or techniques from other disciplines.
- They forge links between basic biology and medicine.
- They demonstrate great promise of future original and innovative contributions.

HHMI's annual research budget, though substantial, is dwarfed by the nation's investment in research through the National Institutes of Health and the National Science Foundation. 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.

Examples of HHMI's Approach to Science

HHMI scientists work avidly and passionately toward tomorrow's discoveries. Sometimes inventing wholly new areas of study, HHMI researchers are pioneers in such areas as neuroscience, genomics, and computational biology. The examples below are just a few of many that illustrate HHMI's approach to science.

Richard Axel and Linda Buck

The olfactory mechanics that make possible the 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 process of smelling an odor begins with odorant receptors that are located on the surface of nerve cells inside the nose. Researchers now know that when an odorant receptor detects an odor molecule, it triggers a nerve signal that travels to a way station in the brain called the olfactory bulb. Signals from the olfactory bulb, in turn, travel to the brain's olfactory cortex. Information from the olfactory cortex is then sent to many regions of the brain, ultimately leading to the perceptions of odors and their emotional and physiological effects.

The trail to the Nobel began many years earlier as an 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. She 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. Buck became obsessed with finding the odorant receptors and stayed on in Axel'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 decided to conduct an exhaustive search for GPCRs in the olfactory epithelium by taking a novel approach.

Further analysis of the PCR products narrowed the search to one candidate. Buck cloned this PCR product, sequenced five of the clones, and found precisely what she had been looking for. When Buck finally found the genes in 1991, she could not believe her search was over. Furthermore, none of the genes she found had ever been seen before. They were all different, but all related to each other.

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, the journal *Science* published two elegant articles by MacKinnon. In the first article, 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.

Huda Zoghbi

Using some of the most advanced techniques in genetics and cell biology, HHMI investigator Huda Zoghbi and her collaborators unraveled the genetic underpinnings of a number of devastating neurological disorders, including Rett syndrome and spinocerebellar ataxia type 1. Their discoveries may one day lead to better methods for treating these diseases and provide new ways of thinking about more common neurological disorders, including autism, mental retardation, and Parkinson's disease.

Zoghbi’s interest in Rett syndrome began long before she established her own research laboratory at Baylor College of Medicine. While in the second year of medical residency, Zoghbi encountered a very puzzling patient. The girl had been a perfectly healthy child, playing and singing and otherwise acting like a typical toddler. Around the age of two, she stopped making eye contact, shied away from social interactions, ceased to communicate, and started obsessively wringing her hands. The girl made a huge impression on Zoghbi, who set out to determine what could have caused this sudden neurological deterioration.

Sixteen years after she saw that first patient, Zoghbi and her collaborators identified *MECP2*, the gene responsible for Rett syndrome. Children afflicted with this rare neurodevelopmental disorder develop normally for about six to 18 months and then start to regress, losing the ability to speak, walk, and use their hands to hold, lift, or even point at things. *MECP2*, it turns out, encodes a protein whose activity is critical for the normal functioning of mature neurons in the brain; it is produced when nerve cells are forming connections as a child interacts with the world. The disease occurs primarily in females, because boys who inherit an inactive form of *MECP2*—which lies on the X chromosome—usually die shortly after birth. Girls survive because, with two X chromosomes, they stand a good chance of inheriting a healthy copy of the gene.

For the first 15 years of her career, Zoghbi spent 20 percent of her time seeing patients with childhood neurological disorders. Driven by a desire to improve the clinical outcome of her patients, she became convinced that more basic research was needed.

Zoghbi and her colleagues have also identified the mutation responsible for spinocerebellar ataxia type 1 (SCA1), a neurodegenerative disorder that renders its victims unable to walk or talk clearly, or eventually to even swallow or breathe. The culprit is a sort of genetic stutter that increases the size of the SCA1 gene. The normal gene harbors a stretch of nucleotides in which the sequence CAG is repeated about 30 times. In individuals with the disease, the tract expands to include 40 to 100 iterations. As a result, the product of the mutant gene—a protein called ataxin-1—grows large and

sticky, forming clumps throughout the cell. These ataxin-1 aggregates overwhelm the molecular machinery that cells use to recycle damaged proteins and eventually disable the neurons involved in controlling movement. Using mice and flies that produce the mutant protein, Zoghbi is now searching for compounds that enhance the clearance of ataxin-1 tangles. Such drugs could slow the progression of the disease or prevent it altogether.

Creating a New Scientific Culture at Janelia Farm

Although the Institute already had the highly successful HHMI Investigator Program, the scientific leadership continued to explore new ways to support the research of some of this nation's most creative scientists. The genesis of the Janelia Farm Research Campus occurred in 1999 in a series of informal conversations at HHMI about ways to expand the boundaries of biomedical research.

The blueprint for Janelia Farm grew out of an acknowledgment by HHMI leadership that while most biomedical problems are handled well in a university setting, there are some that are better addressed in a place where small groups of researchers with different skills can work together without the barriers typically encountered at a university. Development of new tools to facilitate biological discovery, for example, can require diverse expertise. But at universities, scientists from different fields are often compartmentalized, and demands placed on researchers by their departments may restrict collaboration outside those walls. To avoid these constraints, HHMI decided to bring together researchers from disparate disciplines in a free-standing campus.

Scientists at the Janelia Farm Research Campus, which opened in 2006, are working in two synergistic areas: discovering the basic rules and mechanisms of the brain's information-processing system, and developing biological and computational technologies for creating and interpreting biological images. These two areas were chosen because they are truly large, unsolved problems in biology and because there is a very good chance that they will not be solved by one laboratory or by scientists in one discipline.

In planning Janelia Farm, HHMI carefully studied the structure and scientific culture of other important research models at both academic and for-profit biomedical laboratories, including the Medical Research Council Laboratory of Molecular Biology (MRC LMB) in England and the former AT&T Bell Laboratories in the United States. The MRC LMB and AT&T's Bell Labs are generally considered to have been the most successful research institutions in biology and electronics, respectively.

Though the MRC LMB and Bell Labs were different in many ways, they did have several things in common. Both institutions kept research groups small, and principal investigators worked at the lab bench. The single sponsor provided all funding—applying for outside grants was not allowed—and good support services and infrastructure were in place. Notably, both institutions evaluated their own people rather than rely on expert opinions from outsiders. HHMI decided to incorporate these core concepts into Janelia Farm.

Researchers at Janelia Farm are freed from most of the administrative, grant writing, and teaching duties that consume time at a university. Traditional academic environments are suitable for a large proportion of research projects, but they can be too conservative and restrictive, stifling the kinds of creative, long-term projects that can lead

to true breakthroughs. This is true, in part, because the reliance on external funding sources forces scientists to define their research programs in advance when they apply for grants.

By setting the course of the research plan up front, scientists are restricted in their ability to pursue questions and opportunities that arise during their studies. The bulk of the scientific community is limited to projects that can be funded by peer-review committees, which tend to be very conservative. These grants have to be reviewed every three to five years, making it very difficult for people to take on high-risk, high-reward projects.

It is important to remember that we think of Janelia Farm as an experiment. We don't have all the answers. We have a working hypothesis. We formulated the hypothesis by studying previously successful research institutions and analyzing what made them successful. We may not get it exactly right at first, but we'll adapt. We will revise the hypothesis, like any good scientist would do.

Ultimately, we believe the success of our approach might be measured by a "deletion test." Twenty years from now, would the scientific landscape look substantially different if Janelia Farm's contributions were to be deleted? Of course, since Janelia Farm is only three years old, we do not know the answer yet.

Summary Statement and Perspective on Federal Support for Scientific Research

The central question that I have been asked to address is what is the best mechanism that federal funding agencies can use to support high-risk, high-reward research. I have outlined HHMI's approaches, which focus on people, not projects. It is worth noting here that although there are numerous organizational cultures in which scientific research is conducted, from HHMI's perspective, no single culture has emerged as "the best."

But with regard to funding, my own personal bias, backed up by HHMI's nearly 30-year "experiment," is that in the long run, high-reward research comes from focusing on people, not projects. And I believe that federal funding agencies, such as the National Institutes of Health and the National Science Foundation, should allocate a greater portion of their research portfolios to supporting truly innovative scientists (identified as such by their track record) and not make funding decisions based on the projects those researchers propose to study.

In today's funding environment, researchers are compelled to define in advance the goals, methods and likely outcomes of their research project in a detailed grant application. While this "funding model" may be appropriate for some types of biomedical research, it has two major limitations. First, proposals for higher-risk projects – even those that may have enormous impact if successful – have traditionally fared poorly. Second, the ability to move quickly to take advantage of unforeseen targets of opportunity is severely constrained.

As I like to say, how can a scientist capitalize on a flash of insight that occurs at 3 AM, if he or she must first write a grant proposal and then wait a year—even if their grant application is successful—for funding to test the idea? Federal funding agencies need to do a better job of providing research support under terms that permit rapid

changes in research direction and encourage taking on challenging research problems, even if the chance of short-term success is low.

I think these changes will bring "more innovation per dollar spent" without adding more money into the research budgets of these agencies. In 2003, I was asked to join a task force convened by Dr. Elias Zerhouni, NIH Director at that time. The group was charged with recommending new ways to fund high-risk, high-impact research. Our panel made three main recommendations, but I will focus on just one of those: establishing a new set of awards to researchers based on their track record. In fact, the journal *Science* covered our panel's recommendations in a news story headlined, "NIH to Award People, Not Projects." That headline nicely summed up our recommendations. But in practice, the NIH came up short in carrying out this initiative.

Take the NIH Director's Pioneer Awards, for example, which were aimed specifically at stimulating highly innovative research and supporting promising new investigators. Our task force recommended that the NIH award 10 percent of its R01 grants – which would equate to roughly 700 grants – on a "people, not project" basis. In 2004, the first year the awards were made, the NIH selected only nine Pioneer Award recipients from among approximately 1,000 nominations.

It is somewhat more encouraging to see that this year NIH has awarded a total of 115 grants for high-risk, high-reward research through its Pioneer Awards, New Innovator Awards, and the NIH Director's Transformative R01 Awards. The total number of these types of awards, however, still falls far short of our 2003 recommendations.

Even with these new awards, the NIH research budget is still heavily weighted toward project-oriented research, with 98 percent of grants going to projects. As I stated earlier, I strongly believe that giving money to scientists of exceptional and demonstrated creativity is a better way to promote innovation. In my opinion, even a modest shift in the federal research funding portfolio – going from 98 percent to 90 percent project-oriented – could make a big difference in producing innovative and potentially transformative research results.

I would like to end with a quotation from the Nobel Prize winner Max Perutz, who directed the Medical Research Council Laboratory of Molecular Biology in England for more than 20 years: "…(C)reativity in science, as in the arts, cannot be organized. It arises spontaneously from individual talent. Well-run laboratories can foster it, but hierarchical organization, inflexible, bureaucratic rules, and mounds of futile paperwork can kill it. Discoveries cannot be planned; they pop up, like Puck, in unexpected corners."

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee might have.