

**Testimony
Before the
Subcommittee on Research and Technology
Committee on Science, Space, and Technology
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**Statement of
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Chairman Bucshon, Mr. Lipinski, and other Committee members:

Thank you for conducting this important hearing that addresses critical issues about the state of the American scientific enterprise.

This is a pivotal moment for our enterprise. On the one hand, the United States continues to lead the world in its investments, both public and private, in most fields of science and technology; and its discoveries and applications of scientific knowledge have enriched the country, improved the world, and expanded opportunities for further discovery and application. But, over the past few years, our financial commitments to the pursuit of science have contracted in most fields, while other countries have quickened the pace of their investments, threatening our reputation as the world's leader in research and development (1).

Under these circumstances, it is important for the nation to evaluate its scientific enterprise---and not just to determine how much we are prepared to invest. We must also understand the operation of our enterprise well enough to know how the basic and applied sciences can most effectively work together to create knowledge and to use that knowledge for the benefit of society through the applied sciences. I take that to be the ultimate goal of this hearing.

Such an evaluation of the scientific landscape is difficult because the terrain is complex and can be viewed in at least four dimensions. First, many approaches to science exist

as defined disciplines, and a confluence of disciplines is often required for important discoveries (2); second, within many fields of inquiry, there is a spectrum of activities, ranging from basic studies of the fundamental principles of nature to more pragmatic efforts to use basic knowledge to solve a wide range of societal problems, as originally described by Vannevar Bush (3); third, these many activities are supported by a variety of sources, including many governmental agencies, small and large companies, academic institutions, and private philanthropies; and, finally, financial support, especially from federal science agencies, is provided through several kinds of mechanisms, including small and large grants to individuals, teams, and institutions for open-ended or targeted research or for training.

Balancing the elements in the landscape of science

Achieving an appropriate balance among these elements of the scientific enterprise is of obvious interest to this Subcommittee and to those, like today's panel members, who direct or have directed research on behalf of U.S. government agencies, academic institutions, or private companies. Based on my own experience and observations as a leader of biomedical research in both the governmental and academic sectors, I would like to make four main points to help guide our discussion of the current dilemma:

- 1) For most major advances in medicine, several scientific disciplines have been essential. (I will provide old, recent, and prospective examples below.) Thus the likelihood of more progress in the decades ahead requires diversified support and the encouragement of multi-disciplinary work.
- 2) When financial support is highly competitive, the choice of research projects veers towards the development of deliverable applications of existing knowledge and away from basic science, posing a serious risk to future productivity. This demands informed guidance from leaders in government and industry to ensure the maintenance of a healthy environment for fundamental research.
- 3) Coordinated efforts among funding sources are desirable and possible but require the cooperation and attention of institutional leaders.
- 4) In my own domain of cancer research---and generally in medical research---several promising efforts are being made by the NCI and rest of the NIH to encourage interdisciplinary "team" science, protect investigators pursuing fundamental studies, and work with funding partners. (Again, some specific examples will be mentioned below.)

The importance of multiple disciplines to solve problems in medicine

From its earliest days, medical science has been dependent on the disciplines of physics and chemistry. The truth of this assertion is evident from any list of major developments in medicine (4): microscopes (to identify infectious agents and cellular structures), X-ray machines (to reveal the living skeleton and delivery cancer therapy), radioisotopes (to track biological molecules and treat certain cancers), pharmacology (to determine the composition and fate of therapeutic drugs) and the EKG and EEG (to monitor the functional status of the heart and the brain through electrical activity).

More recently, major advances in the study of genes, proteins, and cells---from human beings and many other organisms---have revolutionized the study of normal and diseased human beings. This has been possible only because of crucial discoveries (e.g., crystallography, mass spectroscopy, nuclear magnetic resonance, DNA sequencing methods and machines) that require physics, mathematics, engineering, and chemistry. Furthermore, the massive data sets now available from the use of these methods would neither exist nor be useful without the powerful tools provided by computational science. New devices for characterizing at one time many genes, many proteins or even many individual cells are the products of advances in physics and engineering---such as microfluidics, cryolithography, materials sciences, and nanotechnology.

Similarly, the ambitions of newly launched initiatives, such as the President's BRAIN project or therapeutics based on genetic signatures ("precision medicine"), will depend on principles of electrical circuitry, optogenetics, computation, mathematical modeling, and chemi-luminescence. In other words, the future of medicine, just like the past and present, will depend on the vibrancy of allied fields of science and technology and on the alertness of leaders of those fields to the possibilities for productive interaction.

Basic research is endangered but essential for future discoveries that will be applied to medicine

Most facets of medical research have been transformed over the past decade or two by the unveiling of genetic blueprints and the identification of the specific genetic and biochemical lesions that cause most human diseases. This means that even basic biomedical scientists without direct medical experience can now study human diseases and the means to prevent and treat them more effectively. Because the benefits of such work are immediately obvious and highly valued, the tendency to shift away from fundamental studies to such disease-targeted (or so-called "translational") sciences is

understandable, especially at a time when the success rates for applicants for NIH grants have fallen to unprecedented lows (in the mid-teens).

However, despite enormous increases in knowledge about mammalian biology, it is also clear that fundamental features of biological systems have yet to be discovered---sometimes because we have yet to develop the necessary experimental tools, sometimes because the right questions have yet to be asked and the right experiments have yet to be done.

This has been demonstrated dramatically over the past few years by the discovery of several unanticipated forms of RNA molecules that perform functions other than their well-known roles in the synthesis of proteins. Some very small RNA's interfere with the expression of one or more genes---functions that are biologically critical and experimentally transforming---and other longer RNA's have yet to be assigned a clear function. The need to study unusual organisms to probe the depth of biological complexity has also been illustrated by recent findings of enzymes that can permit rapid and efficient re-engineering of genes (e.g., the TALEN and CRISPR systems) and of proteins that allow monitoring of gene expression and function with light of defined wave-lengths (fluorescent proteins).

Furthermore, our understanding of the circuitry of biochemical signals that govern cell functions (such as cell growth, death, aging, metabolism, migration, information processing, and immune responses) are still in a primitive state. Unanticipated results and methods that can come only from unfettered basic research---involving biology, chemistry, physics, math, computational sciences and other disciplines---will be required to solve these problems and generate a new and completely unanticipated set of ideas from which practical applications can be developed.

Funders of research should aim for a balanced and synergistic portfolio

Many kinds of organizations support a wide array of research and development, so it is unrealistic to expect all components to attend to the needs of all disciplines or to the full spectrum of basic to applied research. For example, the financial demands placed on commercial entities prevent any extensive commitment to unfettered basic research, but those demands do intensify their interest in using new discoveries for development of useful products. Conversely, governmental science agencies, academic institutions, and some charities that support research have a mandate to invest in fundamental science with a long view---a long view that some unanticipated discoveries will be revolutionary in concept, establish positions of national and institutional leadership, and provide new foundations for product development by industry. Indeed, these are the

ideas, articulated by Vannevar Bush nearly seventy years ago (3), that have been the basis for the past successes of American science.

Because the boundaries of research are more difficult to define than the extremes, there will inevitably be overlap in the ambitions of the entities that fund research, just as there are in the ambitions of those who perform it. But, when research appears to be tilting towards the applied, it is incumbent on those responsible for basic research---especially the major funders, such as the U.S. government---to rise to its defense. At the same time, those government agencies, along with universities, private funders, and commercial entities, should be seeking ways to collaborate for at least three purposes: to learn where and how scarce resources are being committed; to seek opportunities to engage in collaborative work; and to exchange information that may accelerate progress along the full spectrum of research and development.

NCI uses a variety of mechanisms to promote effective, multi-disciplinary research

Especially in times of fiscal duress, it is essential that the government's science agencies maintain the public's trust by deploying their funds in accord with practices that have been productive in the past. The NCI, a component of the NIH, has benefited historically from a portfolio of funding mechanisms. These include the award of various kinds of grants and contracts to individuals, groups, and institutions to perform studies that range from investigator-initiated to agency-determined; the development of an intramural research program conducted by government scientists in NCI laboratories; and the use of a government-owned, contractor-operated cancer research laboratory in Frederick, Maryland.

We use these mechanisms to support basic, translational, and clinical work on a wide variety of cancer-related problems and to train scientists in several disciplines. Over the past few years, we have taken advantage of the flexible nature of the mechanisms to establish new programs that we believe are suited to the opportunities and stresses of our times. Some of these efforts are especially noteworthy in the context of today's discussion because of their inter-disciplinary or collaborative nature:

- The Cancer Genome Atlas (TCGA) project, now drawing to a close, has supported many hundreds of DNA sequencers, geneticists, bioinformatics experts, oncologists, and others to identify and compile an extensive set of characteristics about over twenty of the most common forms of human cancer. Now this information is being mined for general patterns, used for the pursuit of new diagnostics and therapeutics, and employed as a basis for more detailed studies of certain cancers.

- The Frederick National Laboratory for Cancer Research (FNLCR), itself modeled in part on the Department of Energy's national laboratories, has developed important core laboratories that serve the nation's efforts in nanotechnology (the Nanotechnology Characterization Laboratory [NCL]), imaging, and other complex multi-disciplinary fields. (The NCL is also part of the National Nanotechnology Initiative, collaborating with other NIH Institutes, DOD, NSF, and DOE.)
- The FNLCR recently initiated a nation-wide project to identify new strategies for attacking cancers driven by one of the three major genes in the RAS family. (Such cancers constitute about a third of all human tumors.) The RAS project has engaged a wide range of scientific expertise---in structural biology, protein chemistry, DOE-derived cell imaging methods, and computation--- and investigators at many institutions.
- Both the intramural and the grant-making programs at the NCI have promoted the engagement of engineers, mathematicians, and physicists in cancer research. The intramural program has developed a partnership with physicists at the University of Maryland for collaborative projects. The extramural program has issued a request for applications to continue or create centers for the use of physical sciences in cancer research, and it issues grants and contracts for mathematicians to model cancerous cell behavior and for computational scientists to build cloud-based systems to store and analyze large data sets.
- To provide greater stability for NCI-funded investigators who have a record of high achievement and wish to engage in ambitious, long-term studies, the NCI has recently announced an Outstanding Investigator Award. We believe that these awards will encourage our best investigators to undertake risky work, particularly in the vulnerable fundamental sciences.
- To make "precision medicine" a reality in cancer treatment, the NCI is reorganizing the conduct of its clinical trials to include genetic characterization of each patient's tumor and reference to large databases of clinical information to guide the choice of drugs to be tested. This requires extensive interaction with the FDA, the pharmaceutical industry, and patient advocacy groups, as well as collaboration among scientists and clinicians from several disciplines.
- The NCI's Provocative Questions initiative was created a few years ago to bring imaginative scientists from several disciplines together to identify important questions about cancer that have yet to be adequately addressed. The most interesting

questions are advertised by the NCI as topics for individual research projects and many grants have been awarded.

Reprise

Our complex and traditionally successful scientific enterprise now confronts expanded opportunities at a time of fiscal constraints and foreign challenges to its past dominance. Nurturing the health of many disciplines, preserving the nation's commitment to fundamental research, and coordinating the support of research from many funding sources will be essential to realize the potential of the nation's enterprise. The NCI is committed to those goals and has taken several steps to honor those commitments.

References

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