NIH must support broadly focused basic research

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> NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability (from the NIH Mission Statement*).

The NIH undertook a daring and radical research strategy after World War II. Previously, the Institute had mostly supported medical research with a disease or public health focus. Heeding the call of visionary leaders, such as Vannevar Bush, and with the support of the US Congress, the scope of NIH-funded basic research was expanded to encompass any organism that could be used to address fundamental questions about how cells work and how organisms develop and operate. This visionary program was based on the belief that there was an underlying unity to life, and that something learned about living cells in one organism, where studies were relatively easy, would inform our understanding of life in mammals and humans, where studies were harder. As a result, the NIH greatly increased its support for work at universities and by doctorates (PhDs) as well as doctors (MDs). A hallmark of this style was that the topics of basic research R01 grants were not solicited, but rather were investigator-initiated. In recent years, however, this strategy has increasingly come under question.

The NIH's broad and species-diverse program of basic research during the last 60 years generated a revolution in our understanding of biology and medicine. From bacteria, we learned what genes were, how they worked, and how they could be sequenced; from yeast, we learned how cells control their own proliferation via the cell cycle; from the fruit fly *Drosophila*, we learned how genes control an embryo's development; from the nematode *Caenorhabditis elegans* and from plants, we learned how the genome controls internal parasites using RNA interference; from animals throughout the phylogenetic tree, we vastly deepened our understanding of evolutionary relationships; and again from bacteria, we learned how to correct mistakes in our genomes using clustered regularly interspaced short palindromic repeats (CRISPR). Technologies developed from diverse organisms spawned molecular biology, recombinant DNA, genomics, and bioinformatics. During this period, the NIH basic research portfolio, led by its basic science institute, the National Institute of General Medical Sciences, achieved the greatest record of biological accomplishment by any institution at any time in human history.

The payoffs for human medicine and human culture have been incalculable. Among countless breakthroughs, we have identified the genes underlying many genetic diseases, transformed our understanding of many common diseases, greatly improved patient care, and stopped the spread of a deadly viral disease.

The National Institutes of Health, to its detriment and that of society at large, appears to be veering away from its traditional mission of broad, species-diverse research. Image courtesy of Carnegie Institution for Science.

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*https://www.nih.gov/about-nih/what-we-do/mission-goals.

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As a population we are living longer than ever before. The methods used by the traditional pharmaceutical industry have been revolutionized and an entire new industry, biotech, was founded. We can contemplate our own genomes and begin to benefit from therapies that are tailored to individuals, rather than a population average. We can reconstruct our origins as a species and how we are related to myriad human subgroups that interest us.

Investing broadly in the basic knowledge of life processes paid off for the NIH, for medicine, and for society in ways that could scarcely have been imagined or justified when they were begun. These rewards came by pursuing fundamental biological discoveries wherever that might lead, and by recognizing that creative individual researchers can best anticipate where research needs to go to achieve the basic research breakthroughs of the future. The gamble that the NIH took that life was unified and could be studied in bacteria, yeast, insects, worms, and plants, as well as fish, frogs, mice, and humans, turned out to be a winning ticket that generated lottery-like returns. It made the United States the world leader in biological science, medicine, and biotechnology.

A New Course for Basic Research?

Given this record, why is the NIH now narrowing its vision for basic research to favor subject matter preselected in-house and emphasizing primarily mammalian models? The critical role played by basic research continues to be recognized, as recently noted by NIH director Francis Collins (1). What seems to be taking hold, however, is a view that in the postgenomic world, the NIH can direct basic research to the most important areas, and should favor research on mammalian systems and reduce or eliminate studies of diverse and more distant species. Reflecting this trend, proposals submitted to "basic science" study sections increasingly lose favor if they are judged "irrelevant" to a human medical condition. Basic research using invertebrates that are not disease vectors or pathogens, including novel organisms whose study has only recently become feasible, risks simply being dismissed as unrelated to this new concept of the NIH basic research mission.

Hostility to the broad vision of the NIH's basic research mission is not limited to study sections, but is also to be found within the NIH itself. A major NIH initiative to learn how the nucleus controls gene expression, the 4D-Nucleome project (https://commonfund.nih.gov/4Dnucleome/index), was administratively restricted almost entirely to mammalian models; for example: "The applicant should articulate how the Specific Aims will contribute to a greater understanding of the fundamental principles of the nuclear organization of mammalian genomes" (grants.nih.gov/grants/guide/rfa-files/RFA-RM-14-030.html). This restriction ignores the fact that gene-expression mechanisms are highly conserved in all metazoan organisms. Indeed, much of what we currently know about nuclear structure and function has come from analyzing more tractable single-celled, invertebrate, and nonmammalian creatures. Likewise, one primary aim of President Obama's BRAIN Initiative was to improve basic understanding of nervous systems (www.braininitiative.nih.gov). The NIH's own advisory committee recommended that a broad-based initiative be launched involving a range of organisms, and Congress voted its support. However, by the time the NIH issued calls for grant applications, restrictions on nonmammalian systems had appeared. Limiting basic research support to mammalian systems is logically equivalent to returning to the days before World War II, when the NIH had little impact on biology or medicine compared with today.

Some believe that an increased emphasis on mammalian systems is now justified because lower organisms, and even mammals such as mice, differ critically from humans in biological mechanisms related to disease. However, this conclusion is not scientifically justified, as there are many plausible reasons other than intrinsic species differences that may explain why disease models have often failed in the past. The reality is that over recent decades we have learned that the genes, cells, pathways, tissues, and organs of mammals are actually far less special than had been expected. Most diseases are affected by changes in common pathways and mechanisms that were inherited from a common ancestor of invertebrates and vertebrates and that can be studied in a wide range of systems.

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Another oft-heard motivation for emphasizing mammalian systems is that scientific advances, such as CRISPR-mediated gene editing, have made them technically equivalent to simpler models. Although all systems have enjoyed technological advances, it is not clear that mammalian systems have actually gained any ground in relative terms. Organisms generated with a desired genetic alteration do not yield insight by their mere existence. Mutant alleles must be combined in complex combinations, analyzed in precise cellular subsets, and used to identify interacting genes in unbiased screens, to provide maximal biological understanding. The ability to carry out such studies is heavily influenced by the availability and cost of strains from sophisticated stock collections, and by the organism's generation time, factors that have changed little.

In the expansive view of NIH research, all biological systems whose properties make them worthy of current study are synergistic partners with mammalian and human systems, not competitors. Work that discovers new pathways and mechanisms frequently benefits from the speed, flexibility, and technical power of nonmammalian models. Such discoveries subsequently inspire or aid in the interpretation of mammalian research that becomes more informative and successful as a result. Indeed, progress on

mammalian and human systems will dramatically decrease if diverse, nonmammalian studies are significantly curtailed, because studies with a broad range of models advance our understanding of conserved biological mechanisms and cannot be replaced by increasing the number of narrowly focused studies.

Yes, it can be difficult to explain to vocal members of Congress and the public why investing in strange-sounding systems and research projects is the right thing for the NIH to do. It should not be the duty of the NIH alone—or of researchers using these systems—to make this important case. Everyone in the scientific community should be helping to accomplish this job. A predominantly mammalian/human basic research portfolio with high "disease relevance" will not be a winning research ticket in the years to come. If broadly focused, investigator-initiated research continues to be supported anywhere else in the world, that country might well overtake the United States research enterprise, no matter how much money is spent here on a narrow, managed vision. That country would do so using the same proven strategy that we used to achieve prominence during the last 60 years.

Losing world leadership in basic medical knowledge that was created by so many years of inspired NIH investment would be a real tragedy for American science and medicine. We must stop the NIH's current slide back toward a narrowly focused institution before irreversible damage is done to our country's health and economic well-being.

1 Collins FS, et al. (2016) Basic science: Bedrock of progress. *Science* 351(6280):1405.