

Appropriations Subcommittee Statement on the Fiscal Year 2001 Budget

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February 29, 2000

Mr. Chairman and Members of the Committee, good morning. I am pleased to present the President's non-AIDS budget request for the National Institute of General Medical Sciences (NIGMS) for FY 2001, a sum of \$1.389 billion, which reflects an increase of \$73 million over the comparable Fiscal Year 2000 appropriation. Including the estimated allocation for AIDS, the total support requested for NIGMS is \$1.428 billion, an increase of \$74 million over the Fiscal Year 2000 appropriation. Funds for the NIGMS efforts in AIDS research are included within the Office of AIDS Research budget request.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's first performance report, which compares our FY 1999 results to the goals in our FY 1999 performance plan. As our performance measures mature and performance trends emerge, the GPRA data will serve as indicators to support the identification of strategies and objectives to continuously improve programs across the NIH and the Department.

The mission of the National Institute of General Medical Sciences is to support basic biomedical research that is not targeted to specific diseases. NIGMS funds studies on genes, proteins, and cells, as well as on fundamental processes like communication within and between cells, how our bodies use energy, and how we respond to medicines.

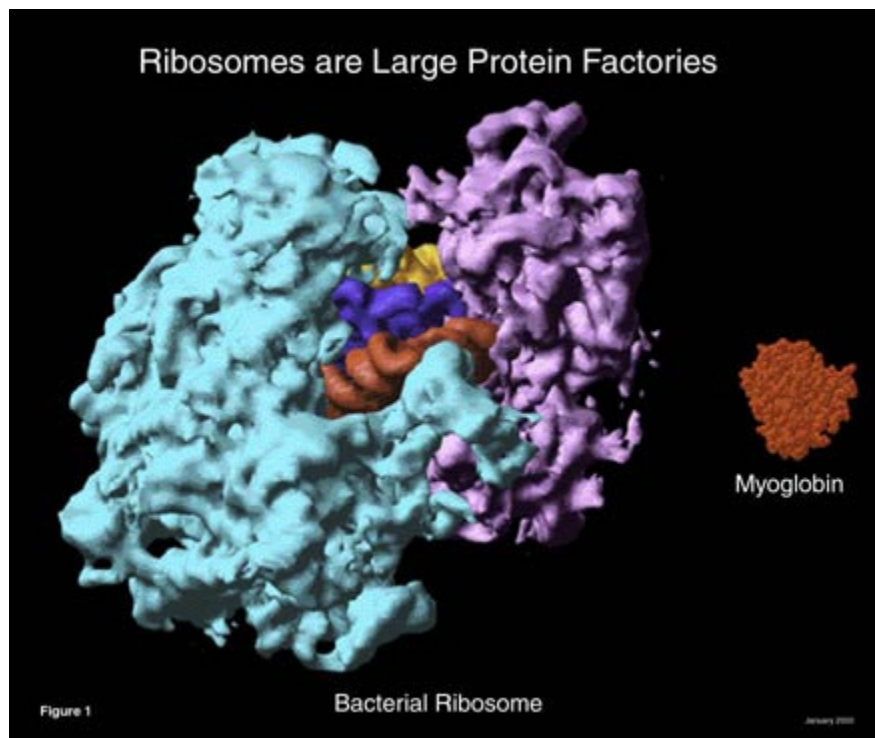
The results of this research increase our understanding of life and lay the foundation for advances in disease diagnosis, treatment, and prevention. NIGMS attempts to ensure the vitality and continued productivity of basic biomedical research, while producing the next generation of scientific breakthroughs and training the next generation of scientists. I am particularly pleased to announce that once again the current Nobel laureate in physiology or medicine, Dr. Gunter Blobel of Rockefeller University, was supported by NIGMS during the period when the work for which he was recognized was performed.

Snapshot of the Cell's Protein Factory

I would like to begin by describing a major advance of the past year, the determination of the detailed structure of the ribosome. This stunning accomplishment is the result of a broad body of research, largely supported by NIGMS, over a period of several decades. The ribosome is the particle in the cell where proteins are synthesized. It is a factory, made up of many molecules, which is small by our daily measures but is a giant compared to most other elements in the cell. It carries out a central activity for life--the accurate synthesis of

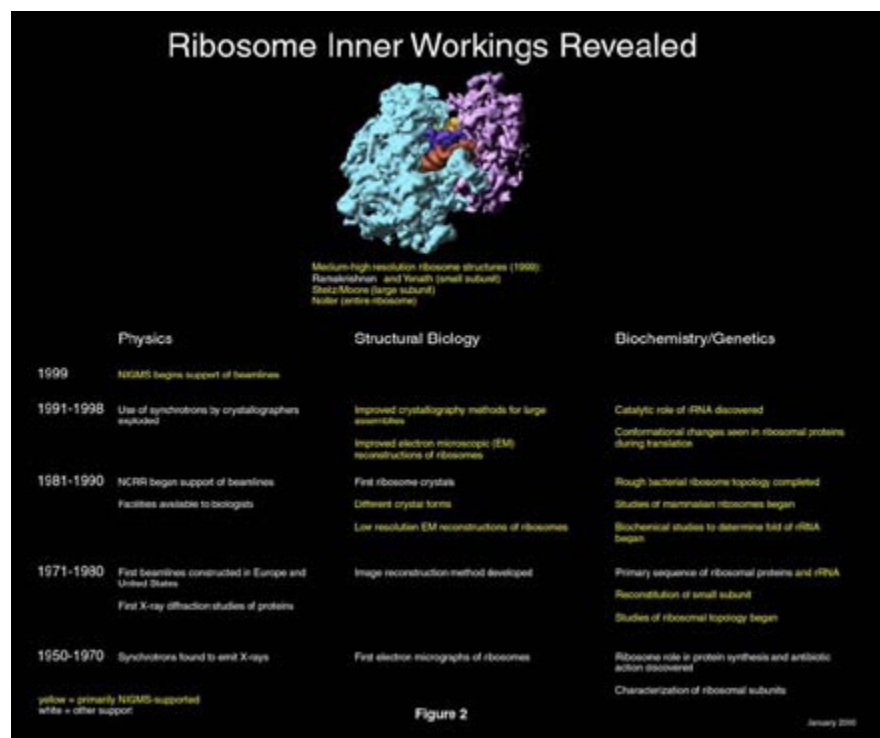
the proteins that form the body's structures, such as muscle and collagen, and that catalyze the chemical reactions in living systems. Consequently, ribosomes are found everywhere in nature, and they don't appear to differ much between species. It's as if nature got it right the first time and didn't want to make many changes.

A major goal of modern biology has been to lay bare the mechanism by which the protein synthesis factory functions. To do so, it was ultimately necessary to identify, in great detail, the three-dimensional structure of the particle, using X-ray crystallography as a primary tool. The difficulties of this undertaking can be appreciated when it is understood that the ribosome is made up of two subunits of unequal size, comprised of a total of 54 individual proteins as well as three RNA strands (**Figure 1**). The determination of a single protein structure can still be a difficult process, so attempting to understand such a complex entity was an intimidating prospect.



The astonishing breakthroughs of the past year are the result of dogged effort, with contributions over many years from many sectors of science. The next figure (**Figure 2**) shows the different avenues of research leading to the current achievements. It represents selected highlights, with the NIGMS-supported efforts shown in yellow. What is clear is that contributions were required from chemistry and physics, as well as genetics, biochemistry, and structural biology, to arrive at our current understanding. We are particularly pleased to have supported Dr. Ada Yonath, from the Weizmann Institute of Science in Israel, at a time when there was still great doubt that it would be possible to achieve the structure.

This investment, and our subsequent support over 15 years, demonstrates the value of funding high-risk, high-payoff approaches.



Although the detail currently visible is not yet at a level sufficient to identify individual atoms, we are confident that the research teams we are supporting will arrive at this goal. This should provide unique insights into antibiotic action and resistance, since many antibiotics—including erythromycin and tetracycline—work by blocking bacterial ribosome function. Even this will only mark a new beginning, since, as with any factory, the various machines operate to absorb raw material, process it, and then release it in a form that can be used. To follow this process, it will be necessary to capture and visualize the machine at different points in the manufacturing cycle. But this is yet to come, and where we are today is exciting enough, for the new knowledge will greatly improve our understanding of a fundamental component of living systems.

Major Initiatives

I would like to spend the rest of my time describing some of the opportunities that are being addressed with the increased funds that Congress appropriated to NIGMS. In particular, I would like to focus on three new initiatives--pharmacogenetics, structural genomics, and large-scale collaborative research--and then close with a description of the expansion in our support for minorities in research.

Pharmacogenetics is the effect of inheritance on drug action. In 1998, it was reported that adverse drug effects account for 100,000 deaths per year, as well as 5-10 percent of hospital admissions. The old joke of "take two pills and call me in the morning" may be appropriate for many people, but what works for the majority of the population may not be effective, and could even be dangerous, for some. The program we have initiated plans to systematically collect and interpret information about the inherited variations in humans that result in poor responses to drugs. The scientists we will support will coordinate their activities in a research network so that the results obtained can be maximally useful, and all will deposit their results in a shared repository. This effort will be conducted in collaboration with the [National Heart, Lung, and Blood Institute](#); the National Human Genome Research Institute; the [National Institute of Environmental Health Sciences](#); the [National Institute of Mental Health](#); and the [National Institute on Alcohol Abuse and Alcoholism](#).

As part of the pharmacogenetics initiative, we assembled an advisory group in May of 1999 to consider possible areas of misunderstanding and the ramifications of future research in pharmacogenetics. Since many identifiable differences in the response to drugs have emerged from studies of populations, it is necessary to consider issues of stereotyping and stigmatization of communities, and the possible resulting harm to individuals, such as discrimination in access to various social benefits, that might arise from membership in an identified group. The members of the advisory group, as well as participants in several follow-up focus groups, felt that the possible benefits of the pharmacogenetic research efforts outweighed the risks. However, they recommended that we provide a clear statement to the public of the goals of the research and the issues involved, and that we ensure that we have appropriate mechanisms in place to maintain privacy and confidentiality.

A second major effort is the Protein Structure Initiative, which attempts to use the information developed by the [Human Genome Project](#) and other genomic programs to identify the structures of all the proteins in nature. The benefits of understanding three-dimensional protein structure have been demonstrated many times. Applications include drug design and understanding of the molecular basis of disease. It is certain that a complete catalog of structures and their relation to function would provide insights into the operation and integration of biological systems that we cannot now fully comprehend. However, such an experimental effort directed at solving the structure of every protein in nature is not feasible. It would take decades and be extremely expensive. Fortunately, there is a shorter route to this goal. Proteins appear to fall into "families" of related structures. If the detailed structure of one or a few members of each family is known, it is possible to infer the structures of the other family members.

We have mounted a program, beginning in FY 2000, to test approaches to identifying appropriate protein family targets, as well as to develop high-speed procedures to determine structures. Grant recipients will be asked to operate as an interactive team, sharing information about progress on a regular basis and depositing data in a shared repository to ensure there is no duplication of effort. This will be integrated with other such programs around the world. To this end, an international meeting to ensure coordination and collaboration is planned for the spring of 2000.

The last initiative I would like to describe attempts to address major problems in biomedical research by facilitating the collaboration of large groups of investigators. Although awards to individual investigators are the mainstay of our support for research, it has become clear that to put all the information together to understand how biological systems operate, something more may be required. We are attempting to provide that additional support through an approach which we term "glue grants." This is because we will supply the "glue" that will catalyze the interactions between already funded investigators to aim at problems that they could not pursue individually. In general, the glue grants will support large-scale, interdisciplinary approaches to significant biological problems by providing the resources for such items as core facilities, database development, and electronic media for effective collaboration. This approach is itself an experiment in the organization of scientific effort. It should provide one opportunity to see how the flood of information coming from individual laboratories can be integrated and amplified to address important problems of biology.

Finally, a major goal of the NIGMS is to establish programs that will result in a cadre of highly qualified researchers. This requires developing flexible training mechanisms that reflect the rapidly changing needs of science, as well as providing cross-disciplinary training. The NIGMS predoctoral training programs remain a benchmark for graduate training, and have evolved to incorporate new areas as science developed. Most recently, we have initiated a training program in bioinformatics--the field at the interface of biology and computer science--to address this emerging area. Bioinformatics is increasingly needed to manage and mine the vast quantities of data that biomedical scientists are generating.

Similarly, we have expanded our programs targeting underrepresented minorities to ensure that future demands for scientific personnel will be met. We have developed new programs to enhance the research environment at minority-serving institutions; to support computer infrastructure via supplements to existing grants; to provide technical assistance in grant writing; and to combine a traditional postdoctoral experience with an opportunity to develop teaching skills through mentored assignments at minority-serving institutions. At

the same time, the average size of individual research budgets in our Minority Biomedical Research Support (MBRS) programs has doubled over the last 3 years, while the number of students supported in these programs has increased by 60 percent. We anticipate our increased investments to show real benefits in an increasing number of minority students going into biomedical research, and we are developing evaluation procedures to track the outcomes of our efforts.

We are particularly pleased with the results of the Bridges to the Future Program, which is cofunded by NIGMS and the NIH Office of Research on Minority Health. The results indicate that students in the program make the transition from 2-year to 4-year institutions and receive bachelor's degrees at a rate of about twice the national average. Although the part of the program that supports the transition from a master's degree to a Ph.D. has as yet only small numbers, the data available also suggest that the transfer rate of these students to Ph.D.-granting programs is also about twice the national average.

In conclusion, NIGMS remains dedicated to developing approaches to ensure that biomedical research continues to progress. The resources that we have received will permit us to take advantage of the rapidly expanding opportunities in science.

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