DIRECTOR'S REPORT

Throughout its history, research in the biological and biomedical sciences has been driven by the passion, intellect, and vision of individual scientists. Even when collaboration produced a great discovery or advance, the investigators concerned brought their unique perspective to the team effort. A large proportion of the research funds provided by the National Institutes of Health (NIH) supports investigator-initiated research. The extent of this support and the pool of available scientific talent are among the chief reasons that the United States has led international biomedical research for many decades. But there are disturbing signs that this lead is being undermined.

Breakthroughs in science are unpredictable. Little did we know that research on flower pigments in the early 1 990s or investigation of gene expression in soil worms in 1998 would make possible one of the most surprising biological discoveries in recent times: the ability of small RNA molecules to control gene expression by interfering with either gene transcription or protein synthesis. Now RNA interference (RNAi) is being studied in many laboratories. Greg Hannon and his Cold Spring Harbor colleagues have made important insights into its biochemistry by identifying many of the key enzymes involved in producing small RNAs in the cells which guide destruction of the mANA that is translated into protein. Recent collaborative studies with Leemor Joshua-Tor on the structure of one of these enzymes have indicated how RNAi-directed suppression of mANA works.

Understanding the biochemistry of RNAi has allowed Greg to develop libraries of RNAi-based molecules that can selectively turn off the expression of any human, mouse, or rat gene. These libraries are powerful tools for biomedical research and have attracted the interest of biotech and pharmaceutical companies. A collaboration between teams of Cold Spring Harbor scientists led by Greg Hannon and Scott Lowe has shown that the small RNAi molecules can be expressed in animal cells to control gene expression in specific tissues or produce genetically defined tumors for identifying and validating cancer therapy targets. RNAi technology has made possible a new era of genetic analysis in mammalian cells and has stimulated the formation of biotechnology companies using RNAi to screen for new therapies and even the application of RNAi molecules as drugs. Their success would be yet another example of the importance of basic research to medical and industrial development.

Sometimes, the execution of investigator-initiated ideas requires large numbers of scientists to work in a coordinated manner. The development of radar during World War II by a team of scientists assembled at the Massachusetts Institute of Technology and led by Alfred Loomis, as chronicled in Jennet Conant's book Tuxedo Park, is an excellent example. This successful, team-driven science followed the breakthrough British discovery of the resonant cavity magnetron, but the team approach was essential to moving the science from basic discovery to important application. Team science has emerged in biological research, most notably in the Human Genome Project where, first, many scientists reached a consensus that obtaining the complete sequence of human DNA would be good for all of research and, second, international teams of scientists worked collectively from 1 990 to 2003 to achieve a goal that has transformed how we do biology.

During the past year, I have been engaged in planning such an approach to the im-

provement of cancer diagnosis and treatment. Asked by the director of the National Cancer Institute, Andrew von Eschenbach, to advise on the best application of new technologies, a small committee chaired by Lee Hartwell and Eric Lander has produced a report that was presented in draft form to the National Cancer Advisory Board in September 2004 and in final form in February 2005. The committee, and many of its advisors, strongly favors the establishment of a national, team-based effort to identify all of the major cancer-causing genes in the approximately 50 major types of human cancer. The approach taken in this Human Cancer Genome Project is the collection of tumor samples from patients who have undergone treatment and identify in their cancer genome the genetic alterations. Such alterations include point mutations in the DNA-coding and -noncoding regions of genes, or amplifications and deletions of genes or segments of chromosomes. We even envisioned identifying the epigenetic changes in cancer genomes that might lead to the lack of expression of a particular tumor suppressor gene. All of this information, if collected from enough patients, compared with data from conventional pathology, and correlated with clinical outcomes, could be used for the diagnosis and prognosis of tumors, helping to guide oncologists to the best available current treatment. Such DNA-based diagnosis and prognosis relies on the too few therapeutic approaches now available for treating cancer. Importantly, the identification of genes that are overactive in human tumors may suggest new targets for cancer therapy that could be validated using the new RNAi technology. Within a few years, DNA-based diagnosis of human cancer could be in routine clinical use. But will there be enough research funds to make this happen?

Research is supported by the NIH from discretionary funds voted by Congress. Because of the large current federal budget deficits, discretionary spending is now more limited than in recent years, and the latest NIH budget did not keep pace with inflation. Because of existing commitments to 4- year grants, funding for new work is being progressively reduced. Already only one in six applications to the National Cancer Institute (NCI) will be funded, and this proportion may drop to the historic lows of 1 0% that were experienced in the late 1980s. If a career in science comes to be seen as worrying about obtaining necessary resources, more than accomplishing goals, fewer talented young Americans will apply to science graduate schools. It is already the case that many foreign graduate students are reluctant to study in the United States at the present time because of restrictions on visas and travel. The effect of these trends on all of biomedical research in this country may be challenging and long-lasting. At a minimum, we will be unable to move forward with sufficient speed on high priorities such as in the use of genome information to diagnose and treat cancer.

Restrictions on funding are coinciding with attacks on some kinds of research, particularly in the high-profile area of embryonic stem cell research. Federal support for human embryonic stem cell research is not possible, prompting individual states to fund independent research initiatives. However, specialists in developmental and regenerative biology who live and work in states that lack such support will not easily be able to contribute to this complex area of research, despite their expertise and their potential to improve stem cell science. Even more troublesome are restrictions placed on universities. Because research on human embryonic stem cells cannot be performed in a building where federal research funds are being used, universities and research institutions must build isolated research facilities for embryonic stem cell research, at a cost of many tens of millions of dollars that more logically could support the research itself.

The pressures of limited funding and the political debate about some aspects of biology have led some advocates of biomedical research, often people without training in sci-

ence, to overstate their case, making claims that research is ripe for major advances in regenerative therapy or hinting that cures are just around the corner. This is almost certainly not true for human embryonic stem cell research. Such blind advocacy is dangerous for the research enterprise, raising false expectations for those afflicted with a disease or disability. But support for this type of research is absolutely necessary because if it is not done, we will never realize the potential that exists.

A widely anticipated report from the National Academy of Sciences is expected in early 2005 to establish guidelines for the advancement of human embryonic stem cell research and I hope that it will be the basis for more rational thinking in this overheated debate. We will only find out if truly valuable treatments will emerge from this or any other promising area of biomedical research if in the future, research is allowed to move forward with adequate funds, we have sufficient ability to attract talent, and there is a reduction in political interference.

Some areas of research, however, are ripe for major inroads in diagnosis and perhaps therapy. Certain types of cancer fall into this category. The success in targeting therapy to molecularly characterized tumors is the wave of the future and now requires coordination and funds. If academia can pull together to approach complex medical problems as a coordinated community, like it did with sequencing the human genome, then we will have made a significant advance in the sociology of science. Such an approach to science, however, should still respect the unique talents of those involved because even in large-scale and coordinated research efforts, individual scientists will generate the ideas to get the job done.