DIRECTOR’S REPORT

The horrible events in September of 2001 in New York, Washington, and Pennsylvania changed our nation forever. No longer can we assume that those who are ignorant of decency and what America stands for will not interrupt our way of life. For those of us who work on research to improve the lives of people, it is difficult to understand how anyone could get to the point of needlessly killing so many. Immediately following September 11, our research goals seemed pale compared to the efforts of those who stood in the face of terrorism and who worked in the rescue efforts. But it did not take long to realize that our mission to fight cancer and other diseases is equally important. The paradox is that the nation which provides the most benefits to mankind through biomedical research is the one that is attacked because of what it stands for. But giving in to tyranny is not in the ethos of this nation. The best way to answer terrorism is to continue to do what we do best, and that is to help those who cannot help themselves. This is particularly true for those with cancer.

The modern era of our nation’s effort to understand and treat cancer, which began with the signing of a new National Cancer Institute Act by President Nixon in December of 1971, is now 30 years old. Although the National Cancer Institute first came into existence in 1937 with the signing of an act by President Franklin D. Roosevelt, only a revolution in biological research in the latter half of the twentieth century enabled cancer to be studied in a rational way and with confidence that success might be possible. During the past 20 years, basic research into the causes that underlie cancer has opened the door to opportunities for diagnosis and treatment such that now, as we enter a new era in cancer research, meaningful progress is possible. To fully exploit these opportunities, however, academic research institutions and the private sector must approach the cancer problem in a fundamentally new way. Although investigator-initiated research should remain the backbone of publicly funded research, large projects that move basic research results into the clinic, commonly called “translational research,” require close cooperation between academia and the private sector. Interdisciplinary approaches are the future for research that will make a real difference to patients, but achieving ambitious goals solely with public funds may not be possible. It is now time to re-think how translational cancer research should be assessed, supported, and performed.

The roots of the modern understanding of cancer came from a number of sources. Prominent among these was the study of viruses that caused tumors at the site of inoculation in experimental animals. These viruses carried genes that could change a normal cell into a cancer cell. Research using both RNA and DNA tumor viruses, with Cold Spring Harbor Laboratory preeminent among institutes studying DNA tumor viruses, showed that a small set of genes could transform otherwise healthy cells into cells that grew into a lethal tumor, eventually metastasizing and killing the animal. But relatively few virus genes proved to have any part in inducing human cancers. Notable exceptions were the transforming genes present in the DNA-containing papillomaviruses that, when carried into the epithelial or glandular cells of the cervix, initiate cervical cancer in women.

A few cancer-causing genes were found in RNA tumor viruses that had direct orthologs in human cells. These virus-related human genes, when altered by mutation or
when overexpressed, contributed to human cancer. Michael Wigler codiscovered here at CSHL, at the same time as Robert Weinberg at the Massachusetts Institute of Technology, one such gene in 1981, the so-called ras oncogene. Another notable example was the v-myc gene that was first defined in an avian retrovirus that caused myelocytic leukemia in chickens. Later, a related human gene called c-myc was found to be overexpressed in a variety of tumors, including lymphomas, leukemias, and lung, cervical, ovarian, breast, and gastric cancers. The c-myc gene was converted into an oncogene either as a result of chromosome translocation (the aberrant exchange between two unrelated chromosomes), by gene amplification, or by mutation directly in the gene itself.

Cancer progression can occur when another type of human cancer gene, called a tumor suppressor gene, is deleted in the cancer tissue, again contributing to the tumor cell’s ability to proliferate uncontrollably. This type of cancer gene was first appreciated by studying the inherited predisposition of cancer in families that had a high incidence of rare cancers. Later, in the late 1980s and early 1990s, familial cancer genetics identified a series of important oncogenes and tumor suppressor genes, including the now well-studied BRCA1 breast cancer susceptibility gene. Recent research, however, has shown that the number of people who have a higher probability of succumbing to a particular type of cancer by inheriting a defective gene from their parents is relatively small compared to those who have no obvious inherited predisposition, but nonetheless get the disease. It is therefore more likely that the main burden of cancer in our population occurs because of the accumulation of genetic changes that occur within a person’s lifetime. Some of these changes may be promoted by environmental factors such as cigarette smoking, but others are a result of normal damage to the genome over time. Our longevity plays in favor of acquiring the necessary genetic changes that can result in cancer. In a quirk of fate, some cancer-promoting mutations actually cause further genome instability, thereby accelerating the process of acquiring more genetic changes and, ultimately, cancer.

During the past few years, a new view of cancer has emerged which suggests that the cancer cell itself, with all its genetic changes, is not the only culprit in the progression to metastatic tumor growth. This view of cancer has been best put forward in a review by Cold Spring Harbor Laboratory alumnus Douglas Hanahan and Robert Weinberg. They pointed out that for a tumor to develop to the stage where it is a clinical problem, the tumor must have a number of acquired characteristics. These include changes that allow the cancer cells themselves to produce and receive growth signals, to avoid being killed by a process called apoptosis, to proliferate with limitless potential, to attract a blood supply to sustain the increase in cell mass, and to invade and escape from the surrounding tissue. I would add another acquired characteristic—that of escaping from the body’s immune surveillance that almost certainly helps in suppressing tumor growth, but of which little is known.

There are many ways of collecting the set of acquired tumor characteristics, and clearly accumulating genetic changes in the cancer cell is the primary driving force. But as Hanahan and Weinberg point out, cells that surround the cancer, such as invading immune system cells and the surrounding “normal” tissue, can provide many of the factors necessary to sustain and even change a cancer cell. Importantly, this new view of cancer progression offers a new way of thinking about cancer therapy. If the acquired characteristics are necessary to create a clinically dangerous tumor, then attacking one of them should provide new hope for cancer treatment. Attacking two different acquired characteristics might provide a benefit greater than the sum of the two alone, and so on. We are just entering an era where this thinking is being tested in the development of new cancer therapies.
The most common method of treating cancers now is to treat the tumor with agents that cause catastrophic damage to cells, such as chemotherapy with DNA intercalating drugs, with drugs that damage the apparatus that ensures accurate segregation of chromosomes, or with radiation that both damages DNA and causes chromosome mis-segregation. These methods take advantage of the loss in cancer cells of the normal response to such external stresses, allowing the cancer cell to proliferate and eventually die due to the catastrophic accumulation of damage. But as we well know, such therapies are toxic to normal cells as well, and the window between killing cancer cells and normal proliferating cells is often all too small. Moreover, as clearly shown by Scott Lowe and his colleagues here at CSHL, cancer mutations such as those in the p53 tumor suppressor pathway can cause resistance to such treatments. This is why cancer therapies must be multidimensional, attacking the tumor from different angles. These new approaches include targeting the proteins in a cancer cell that initiate the tumor to proliferate in the first place, inhibiting the blood supply by anti-angiogenesis therapy, and inducing an immune reaction to the tumor cells.

A priori, it might seem that the protein products of the genetic changes that occur in a cancer cell might not be good targets for cancer therapy because they usually occur early in the life of the cancer cell. Since many genetic changes occur during the life of cancer cells, there is no guarantee that inhibiting one oncogene product will be sufficient to inhibit growth of the cancer cell and even shrink the tumor. But recent results from both basic and clinical research suggest that there is hope for this approach.

Recent research from Michael Bishop, one of the pioneers of cancer genetics, and his colleagues suggests that the primary changes in a cancer cell may well be an Achilles’ heel. They created tumor cells that overexpressed the c-myc gene under conditions where it could be turned off at will. In experimental animals, c-myc-dependent tumors arose with predictable frequencies, but interestingly, and for many people unexpectedly, when the c-myc gene was turned off, not only did the tumors stop growing, but the cancer cells died and the tumor regressed. Thus, although a cancer might require multiple genetic changes, targeting a single oncogene product might be sufficient for therapy.

Concomitant with this basic research, a new, targeted therapy for chronic myeloid leukemia (CML) emerged with the advent of the Novartis drug Gleevec™, producing remarkable clinical effects. This small-molecule drug inhibits an enzyme produced by the BCR-ABL oncogene that is the principal cause of CML. Early in the clinical studies, patients responded dramatically, demonstrating that a therapy against a single oncogene product can be most effective. Later, however, some patients developed resistance to the drug and their tumors relapsed. When examined at the molecular level, the BCR-ABL oncogene either had further mutated or was now overexpressed at higher than initial levels. Although this was not good for the patients concerned, it proved a very important scientific point—that the drug was really making a difference by targeting the BCR-ABL oncogene that caused the tumor, rather than a combination of unknown targets that might be related to BCR-ABL. These clinical results validated the concept of single-target, specific anticancer cell therapy and rightly caused much excitement.

As I described in last year’s Annual Report, Michael Wigler, Robert Lucito, and their colleagues here at CSHL, in collaboration with Scott Power’s group at a nearby biotechnology company, have undertaken a large project to identify many of the genetic changes that occur in primary human tumors. Initially focusing on breast cancer in collaboration with clinical colleagues at Memorial Sloan-Kettering and Duke University School of Medicine, they developed techniques that are applicable to all cancers, given sufficient re-
sources. The overrepresented or amplified oncogenes in cancer cells, like c-myc, are readily detected in cancer DNA derived from primary cancer biopsies. During the past year, this joint program between an academic research institution and the private sector has been enormously successful, with the identification of many new human oncogenes that have the potential to become targets for anticancer therapy. Indeed, some of the gene products are already under preclinical investigation. Paradoxically, the success of the project points to a fundamental problem of how to fund such large cancer research projects.

In the not-too-distant past, basic research emerging from academic research laboratories would be published in the scientific literature. Only much later would private industry incorporate the published results into their disease programs. With the advent of the biotechnology industry, biotech companies more rapidly acquired the results from basic research laboratories and, with the help of the significant financial resources from venture capital, they could add commercial value and, in a very few cases, take products into the clinic. But very few basic research results are immediately applicable to clinical advances, and it often takes years of additional research to reach the stage where large pharmaceutical companies would invest the considerable sums needed to develop a drug. In the vast majority of cases, translational research is conducted, further developing the initial research so that it can be applicable in the clinic. The problem that arises, however, is that translational research is expensive and involves scale-up of the basic research capabilities that is beyond the resources of public funding mechanisms such as grants from the National Institutes of Health (NIH). A typical, investigator-initiated research grant from the NIH could not support such translational research, since it often involves the use of chemistry and other resources only available to large pharmaceutical companies. Bridging this large gap must be a high priority in disease-based research.

Mechanisms are needed that radically change the way such projects are viewed and supported. Clearly, public funds from granting agencies are not going to keep pace with the rising costs of research. Even though venture capital resources have grown significantly in the past decade, they will not carry the entire burden of the rapidly expanding biomedical research enterprise. The pharmaceutical industry is already inundated with drug targets, and they will only occasionally invest in the earliest stages of research outside of their internal programs. It seems that the most efficient method for translating interesting new research ideas into the preclinical stage is an intimate interaction between the biotechnology industry and academia.

Although interactions between academia and the biotech industry are going on all the time, and in many ways changing the research landscape, there are inadequate funding mechanisms to allow seamless cooperation. Individuals obtaining relatively small research grants for specific projects support the vast majority of traditional academic cancer research. This should continue, but the NIH should introduce new mechanisms that allow rapid scale-up of research when it is appropriate and at the same time allow seamless integration of funds from private sources, be they from private foundations or industry. Currently, it is very difficult to present a large translational research program to the panels that review smaller, investigator-initiated research grants. Large, multifaceted projects that need resources from the NIH and industry should be presented and reviewed as a single project, with the NIH grant funds supporting some of the research. The NIH already has the capacity to support clinical trials in collaboration with industry, but it is translational research, which links basic and clinical research and advances new ideas, that is not now planned and reviewed in the most efficient way. Many opportunities are being missed because of the lack of suitable funding mechanisms and flexibility.
There also needs to be a change in the way such projects are viewed by the NIH. Most cancer research in the United States occurs in Cancer Centers. These Centers receive core support based primarily on the grant funds that derive from the National Cancer Institute (NCI) and other peer-reviewed cancer research from public sources. But under current NCI guidelines, research supported by funds from private sources is not considered relevant for core funding when a Cancer Center is periodically assessed for what it is doing in translating basic research into the clinic. As private-public cooperation in research funding increases, and it must in this new era, such impediments to translational research should not deter what Cancer Centers might do in the future.

Thirty years after initiating the modern era of cancer research, the NCI is in excellent shape and has the capability to rapidly respond to the opportunities made possible by the huge advances in basic research. I had the privilege of serving on an oversight board at the NCI for the past 6 years, the last 2 years as chairman, and seeing firsthand how large projects could work. Under the direction of Rick Klausner, the NCI was revitalized. Many opportunities were advanced with great success, particularly those that took advantage of the concomitant sequencing of the human genome. Now is the time to apply some of the same strategies to translational research, such as discovering new technologies for early diagnosis and, most importantly, for cancer treatment.

There has been a call for a complete rewriting of the National Cancer Institute Act to revitalize the nation’s effort on cancer. The stated goals are to expand the number of researchers studying cancer, particularly those in translational research; to encourage the private sector to focus on cancers that as yet do not have standard therapies; to improve the number and efficiency of cancer trials; to increase research on cancer prevention; and to improve patient care. These are all laudable goals, but in achieving them, the mission of the NCI must be underpinned by strong basic research. As basic research provides opportunities for many new treatments, no amount of public funds will support the infrastructure to test all of the potentially beneficial approaches. A better mechanism for public-private cooperation is needed.

The new proposed legislation calls for an expansion of the Cancer Centers program to establish translational cancer centers to help move drugs and technologies into clinical trials. Again, this seems to be a valuable goal, but it is already the mission of existing Comprehensive Cancer Centers who are required to combine basic and clinical research. Effective translational research should be accomplished by the nation’s best Comprehensive Cancer Centers. It is far from clear whether a new and potentially expensive physical infrastructure is needed. Furthermore, there is no guarantee that the most promising research applications will emerge from within the proposed new translational centers. Equally likely is that centers such as our own will contribute valuable new approaches that will have a large impact on translational cancer research.

More effective ways are needed to integrate vast private resources into partnerships with academic cancer research centers, and in a manner that will not penalize the core support for the Cancer Center. The existing peer-review mechanism for small, investigator-initiated research, which can take up to 1 year or more before a new proposal may be supported, is not adequate. Since academic institutions do not by themselves have the resources to establish such large translational programs in the hope that a proposal might be supported in 1 year's time, many opportunities are lost. One simple and effective way for such cooperative programs to be implemented is to institute a separate peer-review mechanism that can appreciate and assess translational research, particularly research that involves private and academic interactions. Precedents have been set at the National
Institute of Human Genome Research, where very large, goal-oriented, peer-reviewed research involves industry and academic laboratories, with industry often assuming a large portion of the costs. Other institutes such as the NCI should rapidly move in this direction, establishing new mechanisms that could easily handle issues such as conflicts of interest and the expected large multicomponent budgets, and yet still move with a pace that is expected by a public calling out for meaningful action against cancer.