

PRESIDENT'S REPORT

In his State of the Union address in 1971, President Richard Nixon called upon Congress “to launch an intensive campaign to find a cure for cancer.” Later that year, the National Cancer Act became law, the first salvo in what since has been referred to as “the war on cancer.”

After 40 years, where do we stand? This past year, cancers killed more than 550,000 Americans. More than three times that number were newly diagnosed. These figures make clear that a “cure” is nowhere in sight. Yet, four decades ago, it seemed plausible to imagine that we were on the trail of a single killer. Today, we possess the sobering knowledge that our quarry is actually hundreds of different illnesses and that it is unlikely that a single magic bullet will bring cancer’s carnage to a halt.

Cancer is so very much more complicated than we understood it to be in 1971. Over four decades, a major national investment in basic biological research—performed at Cold Spring Harbor Laboratory and academic and clinical centers of excellence across the nation and around the world—has yielded increasingly detailed knowledge of cancer at the genetic, cellular, and tissue levels. That knowledge has brought us the first effective targeted therapies for certain cancer subtypes. These point the way to a much more encouraging future.

I would like to recognize in this report a few of the landmark discoveries in which Cold Spring Harbor Laboratory scientists have had important roles, as prelude to describing a new Cancer Therapeutics Initiative. Grounded in such outstanding basic science, I am optimistic that the powerful approach we are taking at the Laboratory will contribute in the coming years to turning many major cancer types into manageable chronic illnesses or even cures.

Forty years is an eternity in biomedical science. It is important to remember that when a patient went to a clinic in 1971, there was very little that an oncologist could determine except for the fact that a cancer was present. Pathology on the tumor could help determine prognosis, but the ability to characterize tumors beyond gross pathology was rather limited. There were plenty of chemotherapies available, but responses to them were essentially hit or miss.

Forty years ago, we knew that the genetics of individual cancers was important. We knew that cancer cells had abnormal chromosomes compared to those of normal cells. But the concept that specific genes caused cancer had not yet been clearly formulated. Our initial focus, beginning in 1968 when Jim Watson became director of Cold Spring Harbor Laboratory and trained his sights on cancer, was on cancer-causing viruses because they carried genes that could promote cancer.

The notion that cancer could have a viral origin dates to the early 20th century and the work of Peyton Rous at The Rockefeller University, who discovered a virus in a type of chicken tumor that could be transferred via injection to baby chicks, which were subsequently observed to develop tumors. In the mid 1970s, J. Michael Bishop and Harold Varmus at UCSF found a gene in healthy chickens called *c-src* that was nearly identical to the cancer-causing gene in Rous sarcoma virus. They concluded that the oncogene in the virus did not represent a true virus gene but instead was a version of the normal cellular gene that the virus had acquired during replication in the host cell and thereafter carried along.

In 1981, Michael Wigler here at Cold Spring Harbor Laboratory was one of three researchers in the United States who independently discovered the first human oncogene, called *RAS*. It belongs to a family of genes critical in signaling networks that regulate cell growth and division. Soon thereafter, CSHL scientist Earl Ruley and MIT’s Robert Weinberg began to reveal some of the mechanisms through which oncogenes promote cancer. Their work shed light on the phenomenon of cooperating oncogenes, instances in which the progression of cancer depends on the products of two or more cancer-promoting genes, none of which is sufficient to cause cancer.



This notion dovetailed with the multiple-hit theory of oncogenesis, which led to the idea that cells in our body had to acquire mutations in multiple oncogenes. Following pioneering research by Alfred Knudsen at the Fox Chase Cancer Center, whose studies linked inherited cancer with spontaneous mutations in adult cells and predicted the existence of tumor suppressor genes, Ed Harlow at CSHL demonstrated that oncogenes could inactivate tumor suppressors, thereby providing another view of genetic cooperation to produce tumors. Thus, cancers could result not simply from the actions of cancer-promoting oncogenes—which encoded proteins that accelerated growth within the cell—but also from the simultaneous *absence* of action on the part of genes called tumor suppressors, whose normal function was to *prevent* cellular growth from running amok.

These early studies identified the kinds of malfunctioning or mutated genes that were at work in oncogenesis, and what mechanisms and pathways they undermined to permit uncontrolled cell proliferation and prevention of cell death, both of which were required for tumor progression. In parallel with the genetics of cancer was basic research on cell proliferation control in which many labs at CSHL had a major role and which proved important for understanding cancer. From the mid 1980s to early 1990s, CSHL scientists helped piece together an increasingly comprehensive molecular picture of replication of the genetic material in the cell nucleus and the workings of the cell division cycle that governed how cells proliferate. Defects in the control of cell proliferation are the main drivers of cancer progression, causing increasingly complex mutations in cancer cells that further promote tumor growth, loss of normal controls on cells within a tissue, and eventually metastasis.

In the mid 1970s, CSHL alumni Philip Sharp at MIT, Richard Roberts and Louise Chow at CSHL, and their colleagues made the brilliant discovery of “split genes,” Nobel Prize-winning research that enabled us to see how the RNA messages of genes could be spliced together in multiple ways, to generate different proteins from a single gene. As Adrian Krainer has shown in recent years,

this alternate splicing contributes to the emergence of cancer in humans. Most interestingly, Adrian has shown, together with Harvard's Lew Cantley, that the switching by RNA splicing from one form of a gene to another form can endow cells with completely different metabolic outcomes, making cancer cells very different from normal cells. These metabolic changes will likely provide new therapeutic opportunities that exploit basic differences between cancer and normal cells.

With the realization that cancer is fundamentally a genetic disease, it became imperative that we understand the entire human genome. The 1990s marked the beginning of the effort to sequence the human genome and the genomic era in cancer research, and CSHL was among the leaders and innovators. The essence of genomics is captured beautifully in work first performed by Mike Wigler and colleagues around this time. They devised ingenious technical means with which to compare thousands of genes at a time in tumor samples and a patient's corresponding healthy tissue. This immediately led to the discovery of the *PTEN* tumor suppressor gene, mutated in many human cancers. Since 2003, Mike and his collaborators have also called our attention to areas of deletion and amplification across entire genomes, revealing, respectively, a vast array of tumor suppressor genes and oncogenes. This research has introduced a new dimension to the search for the genetic culprits of cancer—phenomena such as gene copy-number variations—not known to exist at this scale before the advent of technologies that study the entire genome.

Amplified and deleted genomic segments in our genome are commonplace. We all have them, and they are often harmless. But when they occur in certain parts of our DNA, the impact can be devastating. Alea Mills of our faculty has provided an excellent example in the context of cancer. Following up on knowledge that a large region of human chromosome 1 was very often deleted in human cancers, Alea was able to determine that the region contained a novel tumor suppressor gene, *CHD5*, that proves to be a master control switch regulating other tumor suppressor genes.

The pace of our insights has grown along with our technological capabilities. It has proven possible to “mine” comparative genomic data obtained from tumor samples to identify, for instance, all over-expressed genes in a particular cancer and then to overexpress the corresponding genes in laboratory mice. It has also been possible to use designer short hairpin RNAs, members of a class of naturally occurring small RNA molecules studied in Greg Hannon's laboratory, to identify many new tumor suppressor genes or to screen for new therapeutic targets in human cancers.

Building upon human genetics research from Mike Wigler, Jim Hicks, and their clinical colleagues Scott Powers and quantitative biologist Alex Krasnitz have identified many genomic regions in human cancer tissue that are either amplified or deleted, enabling insights gleaned from patients to be incorporated into the development of animal models of many cancer types, including liver, colon, prostate, pancreas, and breast cancers, as well as various types of leukemia. In recent years, Scott Lowe and others have made great strides with “mosaic” mouse models, genetic hybrids that use tissue-specific stem cells to introduce quickly into mouse cells the same genetic mutations found in human tumors. These mosaic mice have tumors that mimic the course of human cancers, enabling assessment of why chemotherapy works in some patients and not in others, and validation of whether new therapeutic targets will work on cancers that are resistant to current treatment.

We have learned that the underlying genetics of a tumor determines its response to therapy and can therefore be exploited for both diagnosis and prognosis of tumor subtypes. Carrying this analysis further, Mike Wigler and Jim Hicks developed a method to study genomic heterogeneity *within* a patient's breast tumor, allowing them to identify cellular subpopulations as well as map their spatial organization. This analysis was used to advance our understanding of how a tumor evolves over time, driven by genetic changes that are not visible if the entire tumor is considered to be uniform.

Using powerful RNA-based tools developed at CSHL, we are learning how to identify new targets for cancer therapy and to probe why an existing targeted drug works brilliantly for one patient and fails utterly with another. Previously, both might superficially have appeared to have the same kind of cancer, but now genetic analysis can separate tumor responses into subgroups, even within a particular tumor tissue type. RNA-based technology and cancer genetic techniques are also enabling

CSHL scientists to study closely the perplexing phenomenon of resistance to existing drugs. It is now very clear that new, targeted therapies have to be developed for each genetic subtype of tumor.

Targeted therapies made a huge impact with the development of Gleevec, designed specifically to block an oncoprotein produced by a mutant gene in the so-called Philadelphia chromosome, a misshapen chromosome discovered at the University of Pennsylvania and Fox Chase Cancer Center in 1960 and now understood to be the result of a translocation—a fragment of chromosome 9 fused to a fragment of chromosome 22. Gleevec helps only those patients who have this uncommon mutation, which is the cause of most cases of an acute blood cancer called chronic myelogenous leukemia, or CML.

Similarly, Tarceva is a drug that very specifically blocks the product of a mutant version of a gene called *EGFR* (epidermal growth factor receptor), present in a subset of lung cancer cases. Like Gleevec, Tarceva is not an indiscriminate killer of cells, both cancerous and healthy, like old-line chemotherapies. Rather, it works well in many patients who have a specific EGFR mutation, but it does not help those whose lung cancers have other genetic drivers. However, Tarceva, when effective, typically holds the cancer at bay only for a year or two and then drug resistance emerges. Raffaella Sordella's lab at CSHL recently has found a new mechanism by which responsive lung cancers develop resistance to the drug.

The problem of resistance suggests the difficulty of the task before us and leads me to caution against undue optimism that “a cure” is just around the bend. There are 50-odd major types of human cancers based on tissue type alone, and there are probably six or seven important subtypes within each tissue type (and maybe more), each one of which needs to be treated with what I anticipate will be a cocktail of targeted drugs rather than a single one. Only then will the resistance that cancers naturally develop be avoided. In the not-distant future, therefore, major cancers will be treated in the manner that we now treat HIV infections, with multiple drugs that minimize the development of resistance. For now, therefore, chronic management of cancer is a more realistic prospect than its eradication, and this will be a major advance if the targeted drugs do not cause major side effects, as in the case of Gleevec.

Our Cancer Therapeutics Initiative brings together many of the innovative elements I have discussed here. Beginning, importantly, from human tumor samples—which we obtain through our collaborations with leading clinical centers—we use our state-of-the-art sequencing and genome analysis capabilities to generate tumor profiles. Working with subsets of genes that emerge for genetic analysis of human tumors, RNA interference (RNAi) technologies can rapidly identify the Achilles' heel of the cancers and suggest new therapeutic targets. Validation of these targets in mouse models of human cancer will most likely increase the success rate of drugs that eventually enter into the clinic. We have learned the hard way that there is no substitute for observing the molecular mechanisms of cancer and their response to therapies within the incredibly complex living environment in which actual cancers emerge, grow, and spread.

The net impact of our initiative—which I estimate will cost \$100 million over a period of years—will be the ability to systematically discover and rapidly validate new targets for cancer drugs. Such an initiative will require constant interactions with the pharmaceutical industry to bring the validated targets to human clinical studies. This will require seamless interactions among scientists in industry and academia. Academic scientists lack the resources to develop drugs, and given well-validated targets, industry has proven to be very effective at developing drugs that work. The problem is that industry has not been good at discovery of targets with a high probability of clinical success. This is where I expect academia will excel.

While the Cancer Therapeutics Initiative is needed, CSHL will continue vigorously to pursue basic research on small RNAs, genome structure and organization, cellular signaling pathways and networks, and other aspects of fundamental biology, work that will lead us to other new technical capabilities and understanding. It is possible that research performed on our campus will help solve the technical problems that currently prevent us from using RNAi to directly shut down cancer genes

in human patients. Other areas of basic research, notably on the immune system, tumor metabolism, and tumor microenvironment, are likely to be of increasing importance in the years just ahead.

There is one additional element in our fight against cancer that I would like to mention, and it concerns the current state of our clinical trials system. If we and others are successful in identifying novel, very specific drug targets in subtypes of the major cancer killers, it is vitally important that drugs developed against these targets not get bogged down in regulatory delays. A drug recently developed against a comparatively rare genetic mutation in lung cancer gene called *ALK* provides a case in point. A recent early-stage clinical trial of an experimental drug called crizotinib was notably successful in patients with non-small-cell-lung cancer (NSCLC) who harbored the *ALK* mutation, with tumor shrinkage and stabilization in the range of 85%. Strikingly, about three-quarters of the patients remained on the drug after the clinical trial met its endpoint. Under the current system, the FDA will require the drug developer to randomize treatment in a phase III trial, splitting a group of *ALK*-positive patients into two groups, only one of which will receive the drug. The desired endpoint would be to demonstrate a survival advantage, a process that takes years to play out.

Proceeding in this manner I would argue is unethical and costly. In some cases, such as this one, phase III trials could be bypassed. A drug showing overwhelming responses in multicenter, early-stage trials in a cancer type with poor prognosis should promptly be granted temporary approval. It should be placed directly into broad clinical use in appropriate genetically screened patients who wish to be treated with it, including early-stage cancer patients. The drug's developer, meantime, should be required to report the full course of all patients, irrespective of outcome. Hospitals and clinics performing these trials should be protected from patient litigation if the therapies do not work, allowing multicenter trials to proceed unhindered by legal complications. For a period of years, all adverse side effects and outcomes should be reported and the drug's temporary approval rescinded if previously unnoticed safety issues emerge or if the drug proves not to have the desired effect when a larger group of patients have been treated. Short of this, however, I believe humanitarian and cost considerations demand that a new drug found to have overwhelming initial success in a genetically defined subpopulation of patients with otherwise poor prognosis should be made available while further data on efficacy and side effects are being collected.

If we are serious as a society about advancing the state of cancer treatment, we should rethink the clinical trials process, particularly as we use new methods of discovery made possible by decades of remarkable basic scientific and clinical research to find the next generation of targeted therapies. These, if used in combination treatments, promise to make cancer a disease that millions of Americans will be able to live with, while enjoying a decent quality of life. It is not an easy goal, but one that should be among the nation's highest priorities.

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President