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.

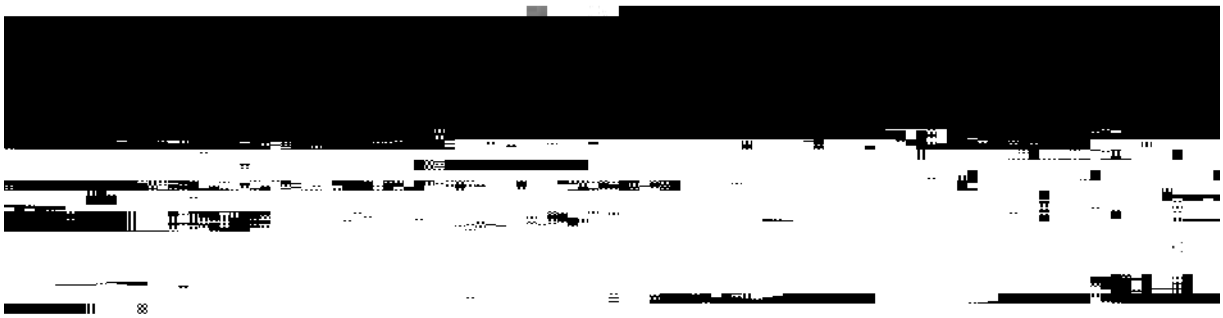
I would like to recognize in this report a few of the landmark discoveries in which Cold Spring Harbor Laboratory scientists have had important roles, as prelude to describing a new Cancer Therapeutics Initiative. Grounded in such outstanding basic science, I am optimistic that the powerful approach 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 overexpressed 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 ar Dc:lmf 59d""aio(f 5:lmpoc:lmf 59aiolDtfaio(f ,:lmf 595ef[c5)fGf"5l(fe551f"5os51fn5lkfeknm5(frs51fn5
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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

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