Harold Varmus

How Tumor Virology Evolved into Cancer Biology and Transformed Oncology

Harold Varmus

Meyer Cancer Center, Weill Cornell Medicine, New York, NY 10065;
email: varmus@med.cornell.edu

Annu. Rev. Cancer Biol. 2017. 1:1–18

First published online as a Review in Advance on September 28, 2016

The *Annual Review of Cancer Biology* is online at cancerbio.annualreviews.org

This article's doi:
10.1146/annurev-cancerbio-050216-034315

Keywords

retroviruses, oncogenes, genomics, targeted therapy, oncology

Abstract

The field of cancer biology has recently come of age, as witnessed by the initiation of this Annual Reviews journal this year. In this article, I argue that the major sources of cancer biology reside neither in cell biology nor in traditional cancer research, but instead in the domain once called "tumor virology." Speaking from the perspective of someone who "rode the wave" that uncovered cancer genes and their effects on cell behavior, I have tried to trace the influences, discoveries, and changing attitudes and practices that produced the vibrant scientific landscape that we now enjoy.

INTRODUCTION

A few months ago, while beginning to think about this retrospective, I was asked to guide one of the weekly discussions of interesting papers held by oncology fellows at Memorial Sloan-Kettering Cancer Center (MSKCC). I recommended one of the first reports of experiments in which inhibitory RNAs were used to seek genetic vulnerabilities in cancer cells driven by mutant alleles of the *KRAS* oncogene (Scholl et al. 2009). After the lively session concluded, it occurred to me that this event was not just intellectually stimulating and pleasurable. It was a sign of the remarkably different times in which we now do cancer research.

When I began working on cancer nearly 46 years ago (an admission startling even to me), this kind of session would have been unimaginable. This is not only because the methods and ideas underlying the paper—inhibitory RNAs, DNA sequencing, synthetic lethality, high-throughput screening, and more—had yet to be discovered. The very notion that oncologists, those in training or beyond, could gather to talk knowledgeably about sophisticated cell biology and genetics would have been unfathomable. But here were 15 clinical trainees, half of whom had already received PhD degrees in fundamental sciences, discussing some of the most complex questions in cancer research.

I mention this incident because it is emblematic of profound and welcome changes that have occurred over the past half-century and a reminder of how deeply linked cancer research has become to the central themes in the life sciences. In the past, cancers have been viewed as aberrations—the consequences of excessive exposures to mutagens, unfortunate infections by microbes, or unlucky by-products of aging. Although each of these is partially true, the critical element in contemporary thinking is that various causative factors produce alterations in cell genomes that distort the normal regulation of cell behavior. From this perspective, the study of cancers and the mechanisms by which they arise have become central to understanding the genetics, biochemistry, and physiology of normal animal cells and help to explain the dual passions of those MSKCC oncology fellows.

The story I will tell here is about the path that led to this new state of affairs. In that sense, this article differs from the kind of intellectual autobiography that commonly opens a volume of an Annual Reviews journal. Those articles, which I have read with pleasure over several decades, instructively track the development of new methods and the discovery of new facts within a single laboratory in the course of a senior scientist's long career. I intend to provide my perspective on how a field of biological research—represented by this first volume of the *Annual Review of Cancer Biology*—began, grew, evolved, and prospered: not an impersonal account, but one that discusses my views of changing tides in cancer research more than the ebb and flow of people, ideas, and findings in my own laboratory.

I was recently provoked to think about my early attitudes toward cancer research and cancer care by Vincent DeVita's new book, ambitiously entitled *The Death of Cancer*. Reflecting on his early days in oncology, which preceded my own training in medicine by only a few years, he noted that "the study of cancer was a stagnant field, a no-man's-land populated by only a handful of doctors and researchers regarded by most of their colleagues as nuts, losers, or both. That is what I thought, too. It was what most people in the medical field believed" (DeVita & DeVita-Raeburn 2015, p. 5).

As a student and then a house officer at the Columbia-Presbyterian Medical Center, I was at least semiconscious of the marginalization of oncology in our curriculum and clinical training: We rarely heard the word "cancer" after completing our pathology course; when we did, the message was not encouraging. (I vividly recall the renowned oncologist John Ultmann quoting *Hamlet* when teaching us about cancer therapy: "Diseases desperate grown/By desperate appliance are relieved/Or not at all" [act 4, scene 3, lines 9–11; Shakespeare 1623 (1997)].) Cancer patients

were treated not on the main wards of Presbyterian Hospital but instead in an adjacent facility, Delafield Hospital, that I rarely visited. Few if any research opportunities in the cancer domain were recommended.

A BRIEF PERSONAL HISTORY: HOW I ENTERED RESEARCH

Before discussing how this deplorable situation was reversed, I want to introduce a few features of my own history (Varmus 2009). My decision to become a scientist was protracted and far from preordained. Both my parents were health care professionals, and I took the courses necessary to apply to medical school while at Amherst College. But I avoided laboratory commitments, majored in English literature (writing a thesis about Charles Dickens), ran the college newspaper, and then headed to Harvard graduate school to continue literary studies.

A year later, however, I reasserted my medical ambitions. Some of my college classmates across the river at Harvard Medical School seemed to be enjoying themselves more than I was, and I was impressed by the idea that medical school would provide a greater palette of career options than did my immersion in seventeenth-century poetry. The spectrum of possibilities in fact seemed vast once I arrived at Columbia's College of Physicians and Surgeons. My interests evolved from psychiatry to tropical diseases to internal medicine—especially endocrinology and hematology, medical specialties showing some firm grounding in biochemistry and genetics. As I entered post-graduate training in medicine, my opposition to the Vietnam War and the obligation of physicians to serve drove me—and several of my more scientifically experienced contemporaries—to seek sanctuary in the US Public Health Service. Given my lack of any serious research experience and the feverish competition for what must have been about 100 positions, I was lucky to get an appointment as a National Institutes of Health (NIH) Clinical Fellow, assigned to an endocrinology research unit.

My research mentor was Ira Pastan, a young physician-scientist trained by the eminent NIH biochemist Earl Stadtman. Ira was then working on the role of adenyl cyclase in the release of thyroid hormone (Pastan & Macchia 1967). I knew something about endocrinology, enjoyed the logic of its clinical applications (i.e., replace molecules, such as thyroxine or insulin, that patients were known to lack), and saw it as a feasible path to an academic life for someone without strong laboratory credentials.

But before I arrived at the NIH in 1968 to take up my new duties, I learned that Ira and his colleague Bob Perlman had made a discovery that excited them but meant very little to me: Cyclic AMP could overcome catabolite repression of the *lac* operon in *Escherichia coli* (Pastan & Perlman 1968). Initially I was concerned that these findings would have little relevance to my interests in medical research and would be beyond my comprehension. Instead, working on this problem taught me some critical lessons: Molecular mechanisms (in this case, regulation of gene expression) are often universal; simple systems are valuable models for understanding complex biology; and new technologies (in my case, nucleic acid hybridization) allow answers to difficult questions. Using lambda transducing phage to obtain *lac* operon DNA, I also learned how to manipulate cell genomes, even before the recombinant DNA revolution (Varmus et al. 1970).

FINDING A FIELD OF MY OWN

Given my very limited exposure to oncology, the primitive state of cancer research, and my affiliations with endocrinology, it may seem surprising that I chose to work on cancer when I left the NIH in 1970. But there were some reasons. During medical school, a family friend working at the Rockefeller Institute pointed me to articles in the Institute's library about viruses that cause

cancers in animals. In that way, I learned that viruses with small DNA genomes appeared to have very few genes, at least one of which could turn a normal mammalian cell into a cancer cell (Vinograd & Lebowitz 1966). The idea left an impression. Then, during my first year at the NIH, my mother was diagnosed with breast cancer that had already spread to her lymph nodes. That brought me in touch with clinical oncology in a more significant way than could possibly have occurred at medical school. The crude therapeutic options that she endured—radical mastectomy, adrenalectomy, chemotherapy—appeared to reflect a poor understanding of the disease at a fundamental level. Finally, in an attempt to repair my deficiencies in modern biological research, I had enrolled (as did many of my medically trained contemporaries at the NIH) in a wide range of courses.

The first, a virology lecture course taught in part by John Bader, one of the few people then working on Rous sarcoma virus (RSV), introduced me to the "provirus hypothesis," an idea advanced by Howard Temin at the University of Wisconsin. Temin had proposed that some RNA-containing, cancer-causing viruses, such as chicken viruses like RSV, were able to confer a permanent change in animal cells because their genes were converted from an RNA to a DNA form and then joined to host cell chromosomes (Temin 1975). Although an enzyme that could copy RNA to make DNA had never been observed, and the evidence for the proposed "provirus" was indirect and not compelling, the concept was appealing, and it seemed testable with the molecular hybridization methods I was then using. I could also dimly sense that the provirus concept could lead to many other interesting questions about virus replication, gene expression, and DNA synthesis and recombination—none directly cancer related but relevant to animal cell functions and studied with cancer-causing viruses.

Another idea arose from assigned readings in an evening seminar on carcinogenesis taught by Mike Potter, who was renown for inducing myelomas in mice with mineral oil injections (Potter & Boyce 1962). To consider etiological factors in carcinogenesis, Potter had introduced us to experimental systems for the induction of cancers—with chemicals, radiation, or viral infection—and to some of the epidemiological correlates in human beings—aging, family history, tobacco use, and occupational history. Although many of these studies were persuasive about contributing causes of cancer, they were generally uninformative about mechanisms. Animal viruses appeared to be the only feasible means to seek definitive evidence about whether cancers could be caused by genetic changes, in large part because they might reveal the specific kinds of genes that could drive cancerous changes in cells. As I learned later, the developmental biologist Theodor Boveri (1915) had made some remarkably prescient proposals about how changes in ploidy, both gains and losses, might provide an underlying mechanism. Still, the only reasonable opportunity to identify and isolate cancer genes, so that they could be studied directly, seemed to require cancer viruses. After all, there was then no technical approach to the isolation of an important animal gene from the untold thousands—or was it tens or hundreds of thousands?—of other genes.

Spurred on by these thoughts, I wanted to look for cancer genes by becoming a tumor virologist. There was also an implicit irony in this desire: I sought postdoctoral work on cancer knowing more about other medical subjects, such as infectious, cardiovascular, and endocrine diseases, than about oncology, and more about molecular biology, gene regulation, and bacterial genetics than about traditional cancer research. But I did not advertise an interest in cancer research per se (and certainly not in "cancer biology" as that term was rarely if ever used). "Tumor virology" was the term for the art I sought to acquire, with emphasis on the viruses—viral cancer genes and Temin's provirus hypothesis.

In fact, I was largely oblivious to what was more clearly "cancer research," such as the efforts being made by my contemporaries and their mentors at the National Cancer Institute (NCI) to treat childhood leukemias with chemical cocktails, or the experiments undertaken by various labs

to induce tumors in animals with chemicals, to transplant tumors from animal to animal, or to establish human cancer cell lines in culture. I also had little or nothing to say about how the studies I envisioned conducting with cancer-causing viruses of animals could help with the diagnosis, prevention, or treatment of human cancers—unless, of course, the viruses themselves proved to be closely related to viruses that caused human cancer. But, unlike some tumor virologists, I was not convinced that most human cancers had an infectious origin.

Initially, I faced a more pragmatic decision: whether to study the DNA- or the RNA-containing tumor viruses. Many factors influenced that decision, not the least of which were the place where and the people with whom I would work. In that sense, joining the small group of virologists at the University of California, San Francisco (UCSF)—composed of Mike Bishop, Leon Levintow, and Warren Levinson, who were beginning to work with RSV—was fate-determining. I had approached established figures in tumor virology. Renato Dulbecco, a DNA tumor virologist and later a Nobel Laureate at the Salk Institute, twice sent messages through his assistant that no space was available—in other words, "I am not interested in you!" Harry Rubin, an RNA tumor virologist at the University of California, Berkeley, who had helped to train Howard Temin, unnerved me with his contempt for molecular biology and the provirus concept—we were clearly incompatible. The team spirit and molecular approaches that I saw among the relative neophytes at UCSF were, in contrast, refreshing. And San Francisco appealed to me because of its cultural politics, architecture, and unstuffy urbanity.

The group I entered at UCSF was unusual. The faculty worked as a team, sharing ideas, resources, technicians, and trainees; all personnel met weekly under the rubric of "Rous Lunch" to discuss recent results. My long-term partnership with Mike Bishop began in the context of a larger team and was grounded in shared aspirations that he and I have described elsewhere (Bishop 2003, Varmus 2009).

CATCHING THE "ONCOGENE WAVE": A ROUTE TO CANCER BIOLOGY

During the next 15 years, when we coinhabited a rabbit warren of interconnected, windowless rooms on the fourth floor of the Health Science East tower at UCSF, I do not think any of us would have called ourselves cancer biologists. We were in a medical school department of microbiology and immunology, our primary research tools were retroviruses, and our methods were more molecular and virological than cellular. Indeed, there was neither a field nor a concept of "cancer biology"—as opposed to "oncology" (largely the diagnosis, treatment, and prevention of cancers), "tumor virology" (the field I had joined), or "cancer research" (a potpourri of weakly rationalized efforts to induce, propagate, or inhibit cancers, mostly in rodents or in cell culture, and to identify etiological factors such as tobacco).

Joining a scientific enterprise before its contours and dimensions become apparent is risky but potentially rewarding. At the beginning of his recent autobiographical article in the *Annual Review of Immunology*, my NIH colleague the late Bill Paul (2014, p. 2) noted the benefits of good timing: "I judge myself fortunate to have 'caught the immunology wave.' The field was just revving up when I entered it, and it has never looked back." We "caught" what might be called the "oncogene wave" at a very good time: the start of the 1970s. A sizeable number of RNA tumor viruses had been isolated (Vogt 1997); some convenient assays had been developed to measure oncogenic activity (Rosenberg & Jolicoeur 1997); and a few critical mutants affecting transformation had been derived. Peter Vogt's RSV deletion mutants had nonconditionally lost their cancer-causing ability but retained competence to multiply (Duesberg & Vogt 1970, Vogt 1971); Steve Martin's (1970) temperature-sensitive transformation mutant of RSV implied that a viral gene (later called

src, viral *src*, or v-*src*) made a protein required to initiate and maintain a cancerous state. But there was no understanding of how the gene worked, what kind of protein it encoded, or why it would be a persistent part of a viral genome, as it was dispensable for virus replication.

Our efforts to understand where v-*src* originated caused a visible swelling of the "oncogene wave," and that wave changed the landscape of cancer research. Some now famous experiments—carried out by trainees in our group, in collaboration with Peter Vogt and influenced by the supportive milieu of the West Coast Tumor Virus Cooperative (WCTVC)[1]—showed that the RSV oncogene was closely related to and presumably derived from a normal cellular gene. The experiments depended on the preparation of a radioactive complementary DNA probe for *src* by subtractive hybridization against the genome of Vogt's transformation-defective deletion mutant of RSV (Stehelin et al. 1976a). The "src probe" then detected homologous sequences in DNA from uninfected chicken cells and from a variety of other avian species (Stehelin et al. 1976b) and later in DNA from even more distant species, including mammals (Spector et al. 1978) and nonvertebrates.

Now that cloning of vertebrate DNA and even the sequencing of whole genomes have become commonplace, I am often asked why these experiments attracted so much attention and were so abundantly rewarded. Wouldn't the cellular *src* gene have been found eventually in the course of sequencing vertebrate genomes? Should the discovery of c-s*rc* have been applauded simply because it was made with relatively crude methods and perhaps as much as 25 years earlier than it would have been otherwise?

I think there are some reasonable justifications for its fame. First, an important scientific question was on the table; the result did not emerge unbidden from systematic genome sequencing. Further, the answer was strengthened by the tools we used: RSV is genetically unique among retroviruses in being fully competent for replication and transformation, so those functions could be independently examined; moreover, existing point and deletion mutants of RSV encouraged confidence that the "src probe" was mostly if not entirely derived from the v-*src* coding domain (Bernstein et al. 1976).

Happily for us, the sighting of the cellular *src* gene was not a "premature discovery" of the sort described by Gunther Stent (1972); experimental tools were available to extend our findings and connect them to current concepts of oncogenesis. More hybridization studies detected progenitors of several other viral oncogenes in normal cells (**Figure 1**; Rosenberg & Jolicoeur 1997), strengthening our conclusions. Our findings also excluded other hypotheses. By showing in these and later studies that cellular oncogenes (called "proto-oncogenes") were true cellular genes, conserved genes with introns and exons (e.g., Parker et al. 1981), we established that they are not components of endogenous proviruses, as posited by another widely discussed proposal (Huebner & Todaro 1969). Our conclusions also encouraged allegiance to a specific concept: that normal cellular genes might become cancer causing through mutations, changes in expression, or both. This concept could be broadly applied in cancer research, consolidating considerable epidemiological and experimental data about mutational agents as carcinogens (Varmus & Weinberg 1992).

Even the demonstration of evolutionary conservation of a vertebrate gene was novel and important at that time. So-called "single-copy" genes had rarely been convincingly detected in vertebrate genomes by hybridization methods; the cellular *src* gene was among the first to be molecularly

[1]The WCTVC was a collection of faculty and trainees from laboratories, largely in California, working on RSV and other retroviruses, who met every few months to discuss projects of common interest, often leading to collaborations. Among the participants were Peter Vogt (University of Southern California), Steve Martin (UC Berkeley), Peter Duesberg (UC Berkeley), Inder Verma (Salk Institute), Tony Hunter (Salk Institute), and Hung Fan (UC Irvine), as well as Mike Bishop and me, occasional others, and later virologists from the Fred Hutchison Cancer Research Center in Seattle.

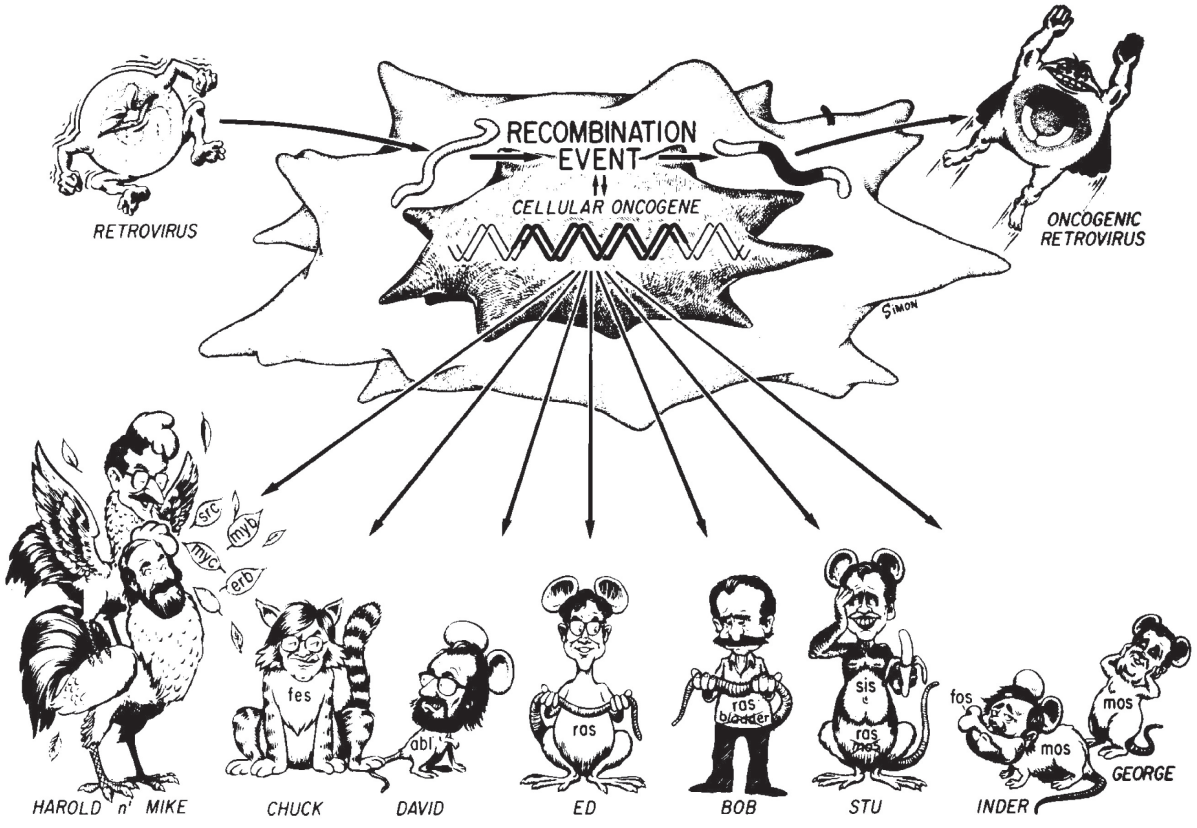

Figure 1

Retroviral transforming genes: Guides to cellular proto-oncogenes. This cartoon, which appeared on the cover of the annual Cold Spring Harbor RNA Tumor Virus Meeting abstract book in 1983, shows several of my retrovirologist colleagues who were involved in identifying the cellular progenitors of retroviral transforming genes. (*From left to right*) Mike Bishop and I with avian viral genes (*src*, *myc*, *myb*, and *erb*); Chuck Sherr with a feline viral gene *fes* (although he became more closely associated with another feline virus gene, *fms*); David Baltimore with the mouse leukemia virus gene *abl*; Ed Skolnick with *ras* genes from rat viruses; Bob Weinberg with a *ras* oncogene found in a human bladder cancer cell line; Stu Aronson with the *sis* gene from a monkey virus; Inder Verma with the *fos* and *mos* genes from mouse viruses; and George Vande Woude, also with the *mos* gene. Figure reprinted with permission from Jamie Simon, Salk Institute, here and in Varmus (2009).

detected without encoding an abundant protein such as globin. Further, measurements of the conservation of genes during evolution had been largely restricted to the use of surrogate assays, such as immune reactivity of proteins. Allan Wilson, the Berkeley geneticist who was our guide to avian evolution, had used the affinity of antibodies to various ovalbumins for such purposes, so he was delighted to learn that the melting temperatures for DNA-DNA duplexes formed between the viral *src* probe and DNA from chicken, duck, quail, and the exotic emu declined in accord with the evolutionary distances he had deduced (Prager et al. 1974).

As early as 1980, a mere five years after the discovery of c-*src*, enough cellular proto-oncogenes had been discovered by tracking retroviral oncogenes to their sources to require a new nomenclature that might bring clarity to a rapidly expanding field. After a long evening program during the annual Cold Spring Harbor (CSH) RNA Tumor Virus meeting that year, John Coffin and I assembled an informal group, including many retrovirologists responsible for detecting the new

genes, to assign new names to these genes. Over several hours and beers in a room in historic Blackford Hall, we came up with most of distinctive names those genes still bear today—*myc*, *ras*, *abl*, *erbA* and *erbB*, *mos*, and several others—different names to emphasize the different sequences and characteristics of viral oncogenes, and evocative names that usually reflected the name of the virus in which it was found (as in *ras* for rat sarcoma virus or *myc* for myelocytomatosis virus; Coffin et al. 1981).[2] We agreed at the outset that these genes should not all be called "*src*" genes—a common but confusing practice—because the various *onc* genes did not generally cross-hybridize and did not appear to make the same types of protein.

Within just a few more years, it was apparent that these proto-oncogenes encoded a wide variety of proteins essential for normal cell physiology. Some of the proteins were largely cytosolic and had novel biochemical functions, such as the protein-tyrosine kinase activity of the products of *src* and several other proto-oncogenes (Hunter 2009) or the GTP-binding and GTPase activity of *ras* gene products (Bourne et al. 1990). Others were secreted growth factors, transmembrane receptors, other cytoplasmic signaling molecules such as protein-serine/threonine kinases, or transcription factors and cofactors. Over time, it became apparent that these proteins were central to cell signaling and gene regulation, governing cell growth, death, and development (Rosenberg & Jolicoeur 1997).

The cellular homologs of retroviral oncogenes had been sought, in part, because of the possibility that mutant or dysregulated versions of such proto-oncogenes might be involved in human cancers. By the mid-1980s, point mutations or larger derangements of proto-oncogenes were identified in several human tumors (Varmus 1984). Point mutations in the proto-oncogenes belonging to the *ras* gene family were perhaps most telling and dramatic because they were discovered by a functional assay for transformation and because the mutations were identical to those first observed in viral *ras* genes (Der et al. 1982, Parada et al. 1982, Shimizu et al. 1983, Taparowsky et al. 1982).

Today, the "oncogene wave" is a virtual tsunami. Literally hundreds of genes, most of which have never appeared in retroviral genomes, are associated with human tumorigenesis because new genomic methods can rapidly compare tumor DNAs with germ line DNA from the same individual to identify recurrent somatic changes [Catalogue of Somatic Mutations in Cancer (**http://cancer.sanger.ac.uk/cosmic**) and The Cancer Genome Atlas (**http://cancergenome.nih.gov**)]. The repetitive sighting of such mutations implies that the changes confer a selective advantage on the cells in which they occur. But studies to ascertain the biological consequence of most of these alterations—are they "drivers" of neoplasia or merely coincidental "passengers"?—are required before pursuing them in greater scientific depth or before using them for therapeutic or diagnostic purposes. In a sense, retroviruses had already performed such experiments; the v-*onc*'s that brought to light the first wave of cellular proto-oncogenes were known from the start to have oncogenic potential: They made the viruses that carried them oncogenic!

Animal Cells and Viruses

To understand more fully the important part that tumor virology played in the unveiling of cancer genes, I need to return to 1970. Early that year, as I was preparing to cross the country from the NIH to UCSF, Howard Temin and Satoshi Mizutani (1970) and David Baltimore (1970)

[2]The authors of this paper recommended placing a "c" in front of the name of the gene when it denotes the cellular form, with a "v" to be used for the viral form only when needed for clarity. It is another measure of the changing tides of cancer research that the "c" is now used rarely and mainly to distinguish among related cellular genes (e.g., *BRAF* and *CRAF* or *NMYC* and *CMYC*). Ironically, one gene whose name is frequently preceded by a "c"—*MET*—has never been found in a naturally occurring retrovirus.

announced their detection of an RNA-dependent DNA polymerase activity, reverse transcriptase (RT), in RNA tumor virus particles. This revolutionary discovery put to rest the general skepticism about the provirus hypothesis, countered the major specific objection to it (the lack of an enzyme known to synthesize DNA from an RNA template), and led eventually to the adoption of the term "retroviruses" for the RNA tumor viruses.

The discovery did not quell my interest in the replication cycle of RNA tumor viruses. Many important questions remained unanswered, and RT could be used to answer them by making virus-specific radioactive DNA to use as hybridization probes for retroviral sequences, DNA or RNA, in infected cells. In this way, experiments that would have otherwise been difficult if not impossible in an era that preceded molecular cloning were made feasible: tests for viral DNA intermediates in newly infected cells; for the existence, location, and organization of integrated viral DNA; and for synthesis and processing of viral messenger RNA. Most significantly for the story here, RT permitted the search for cellular versions of viral genes, especially viral oncogenes, in uninfected cells.

At that time, all kinds of animal viruses, oncogenic or lytic, were considered essential instruments for understanding features of eukaryotic cell biology. A prominent Gordon Conference, the only one that I regularly attended, named "Animal Cells and Viruses," symbolized this credo. The coupling reflected the intimate and revelatory relationships between many kinds of animal viruses and their host cells. DNA replication was intensively studied in animal cells by using DNA viruses, such as SV40 and the adenoviruses (Brush et al. 1995). RNA splicing was discovered by examining the adenovirus transcriptional program (Berget et al. 1977). And many principles of protein synthesis, such as the mechanism of initiation, were established using enteroviruses, reoviruses, and influenza viruses (Kozak & Shatkin 1979). Similarly, the molecular probes made available by RT enhanced the opportunities for studying animal cell biology by following the replication and expression of RNA tumor virus genomes.

RNA tumor viruses were already viewed as especially powerful tools for probing cell functions because they usually multiplied in a harmonious relationship with their host cells, not by usurping essential functions and destroying cells. Although reverse transcription seemed idiosyncratic [only later would cellular enzymes, such as telomerase (Blackburn 2010), be recognized as RTs], many steps in the retrovirus multiplication cycle became vantage points for probing animal cell biology: virus entry through cell surface receptors (Hunter 1997); integration of viral DNA into host chromosomes by DNA recombination and repair (Brown 1997); control of viral RNA synthesis by host RNA polymerase in response to transcriptional signals in the provirus (Rabson & Graves 1997); splicing and translation of viral RNA by cellular machinery, with unusual features such as ribosomal frameshifting and nonsense suppression (Jacks 1990); and modification and assembly of proteins to make viral particles, a proxy for other kinds of protein assemblies (Swanstrom & Wills 1997). Furthermore, hereditary transmission of proviral DNA ("endogenous proviruses") and other so-called "retrotransposons" in many species—culminating much later in the finding of large quantities of "retro elements" even in human genomes (Lander et al. 2001)—implied roles for retroviruses and related "mobile DNA" in evolution. The quasi-random integration of proviral DNA during infection suggested that proviruses could serve as insertional mutagens, inactivating or activating host genes during carcinogenesis by retroviruses that do not carry viral oncogenes. Indeed numerous proto-oncogenes were discovered [e.g., *Wnt-1* (Nusse & Varmus 1982)] or validated [e.g., c-*myc* (Hayward et al. 1981, Payne et al. 1982) and c-*erbB* (Miles & Robinson 1985)] as a consequence of proviral insertion mutations by such viruses.

For all these reasons, retrovirologists have tended to consider ourselves cell biologists too. But however much the retrovirus life cycle taught us about cell biology, its significance paled in comparison with the influence of retroviral oncogenes and their precursors on cell biology.

Even the relatively small menagerie of cellular genes found by tracing retroviral oncogenes to their cellular origins fairly quickly reset the sights of tumor virologists. Over the course of just a few years, the functions of c-*onc*'s and v-*onc*'s, of normal and mutated proto-oncogenes, assumed a more central position in the laboratories of most tumor virologists than did the viruses themselves. This trend became only more pronounced with the advent of technologies that no longer required the simplicity of animal viruses to penetrate the complexities of animal cells—methods for cloning and sequencing individual host genes; for introducing and regulating genetic information in cells or animals; and for characterizing the protein products of those genes, their locations, and their biochemical properties. In other words, it became less important to use viruses to probe normal and neoplastic cell behavior.

I have emphasized how retroviruses have enriched biology in many ways, most obviously by leading us to proto-oncogenes. But it goes almost without saying that tumor virology, similar to all fields, has benefited from advances in many other disciplines. I have already mentioned "imported" methods—such as molecular hybridization, recombinant DNA technology, and DNA sequencing—that allowed progress in tumor virology; cancer biology is now dependent on many others, including genetically engineered mice, inhibitory RNAs, and (most recently) efficient DNA editing. The routes to discovery in all fields of science are two-way streets.

The Transformation of Tumor Virology

Looking back on the 1980s, I now recognize some subtle signs that the field I had entered, tumor virology, was being gradually transformed into the field that many of us now say that we inhabit: cancer biology. An inner logic has prevailed: Our reliance on tumor viruses for the investigation of oncogenes and (to a lesser extent) tumor suppressor genes was bound to yield to greater experimental freedom—based on new capacities to manipulate genes as molecularly cloned DNA and, later, to edit or perturb them in living cells and organisms. During this transition, symbols of change began to appear—the choice of journals in which we published, the meetings we attended, the textbooks we used. Further, the turning away from tumor virology was followed in the 1990s by a transition even more momentous: the partial unification of laboratory and clinical sciences in cancer research, as discussed below.

By 1980, retroviruses had delivered a very substantial down payment on their promise, offering up a variety of cancer-causing genes with interesting properties that implied diverse roles in the governance of cell functions. A broad array of questions about those functions suddenly seemed answerable. Indeed, some initial answers for proteins encoded by *src* and a few other oncogenes were already in hand (Bishop & Varmus 1982). This shift toward oncogenes by many retrovirologists did not mean that retroviruses were no longer worth studying for other reasons. Indeed, once HIV was identified as the infectious cause of AIDS, retroviruses seemed even more interesting, medically important, and in desperate need of study (Gallo & Montagnier 1988). Moreover, numerous fundamental issues remained unresolved: the mechanisms of viral attachment and entry; the host factors required for infection, including surface receptors and auxiliary factors for the synthesis and integration of viral DNA; the susceptibility of viral enzymes (RT, protease, integrase) to inhibition by drugs; explanations for drug resistance; and pathogenic factors, especially those that HIV exercised in T cells. But the utility of retroviruses for the study of cancer was palpably diminishing.

One telling sign of this shift was a change in the place where basic scientists went to learn about dramatic new findings in cancer research. When I entered tumor virology in 1970, that place was (indisputably, I think) the CSH Tumor Virus meeting. As the fields of RNA and DNA tumor virology expanded in the early 1970s and their approaches began to diverge, the meeting was divided into separate gatherings of RNA and DNA tumor virologists. But in the mid-1980s,

the CSH RNA Tumor Virus meeting became increasingly about HIV, with more attendees drawn from the worlds of immunology and clinical virology than from cancer research.

At the same time, many of those who worked with the oncogenic retroviruses of birds and rodents gravitated to a new annual meeting, started in Frederick, Maryland, in 1985 by George Vande Woude (Hunter & Simon 2007). The Oncogene Meeting brought DNA tumor virologists back into contact with RNA tumor virologists—in part because, by the late 1980s, it was becoming clear that the mechanisms used by RNA and DNA tumor viruses to transform cells are not, after all, so far apart. For both classes of viruses, transformation is dependent on instructive relationships between host and viral genes. While retroviruses commandeer certain cellular genes that drive carcinogenesis when mutations or changes in expression confer a gain of function, most DNA tumor viruses are oncogenic because viral proteins required for virus replication interfere with the function of cellular genes, such as the retinoblastoma susceptibility gene (Whyte et al. 1988) or the gene encoding the p53 protein (Crawford et al. 1980), now widely known as tumor suppressor genes (Weinberg 2007b)—the yin to the yang of proto-oncogenes.

Another measure of the shift from tumor virology to cancer biology is reflected in the books that served as "bibles" for cancer research. In the 1970s and 1980s, for instance, the CSHL Press volumes on the molecular biology of tumor viruses were on everyone's shelf, considered essential reading, and supplemented with new data even before new chapters were written (Tooze 1980, 1981; Weiss et al. 1982, 1985). Since 1981, however, there has not been a new edition of *DNA Tumor Viruses*, and *Retroviruses* (which initially followed the seemingly definitive *RNA Tumor Viruses* by only about a dozen years) was published nearly 20 years ago and has not been revised (Coffin et al. 1997). Those who now study the genes once sought by tumor virologists have shifted their loyalties to Bob Weinberg's (2007a) comprehensive text, *The Biology of Cancer*, the "bible" of cancer biology.

Similar trends are evident in the choice of specialty journals for publication and in references to review articles in conversation and print. The allegiance many tumor virologists felt toward journals such as the *Journal of Virology* or *Virology* has long ago passed to *Cancer Cell*, *Genes and Development*, or *Cancer Discovery*, journals more attentive to the biology of cancer cells than to oncogenic viruses. [Of course, the general and highly cited journals such as *Nature*, *Science*, and *Cell* have retained their appeal for a variety of reasons, including the possibility of career enhancement (Alberts et al. 2014).] Among the many review articles published in our field, the ones I now hear most often discussed are Hanahan & Weinberg's (2000, 2011) two highly cited essays on the "hallmarks of cancer," certainly not anything from tumor virology.

At the same time, landmark original work on tumor viruses has become less frequent. A compendium of over 120 foundational papers, *Selected Readings in Tumor Virology*, which Arnie Levine and I selected and assembled over 30 years ago (Varmus & Levine 1983), now looks battered by age, but would there be many more articles if we were to update this collection today? Certainly we would add a few papers on the identification of new human tumor viruses, such as Kaposi sarcoma herpesvirus (Chang et al. 1994) and Merkel cell polyomavirus (Feng et al. 2008). We would choose some papers on the success of vaccines against cancer causing viruses, hepatitis B virus (Blumberg & London 1982) and human papillomavirus (Kirnbauer et al. 1992), and perhaps on the beginnings of a vaccine against another cancer-causing virus, Epstein-Barr virus (Kanekiyo et al. 2015). We might also include the characterization of the 9% of human gastric cancers that carry Epstein-Barr virus DNA (Cancer Genome Atlas Res. Netw. 2014), a paper or two about hepatitis C virus (HCV)-associated cancers and the drugs that eliminate HCV from infected patients (Lamarre et al. 2003, Lohmann et al. 1999), or an overview of antiviral measures that should be used to introduce cancer control into global health programs (Varmus & Trimble 2011).

But these works, however important, are few compared to the outpouring of papers providing new information about the biology of cancer: the means by which cancer cells invade and metastasize; their metabolic features; their angiogenic properties; the vulnerabilities conferred by loss of DNA repair mechanisms; the complex regulation of immune responses to cancer cell antigens; the components of the tumor microenvironment; the control of gene expression by epigenetic as well as more traditional mechanisms; the similarities of some cancer cells to renewable stem cells in tissue lineages; and the susceptibilities of cancer cells to pharmacological inhibitors, inhibitory RNAs, and secondary mutations that confer synthetic lethality. These topics and many more will doubtlessly be subjects of articles in this and subsequent volumes of the *Annual Review of Cancer Biology*.

ANOTHER TRANSFORMATION: FUSION OF LABORATORY AND CLINICAL DOMAINS

The changes that slowly converted tumor virology to cancer biology in the 1980s occurred just before another major transformation: the gradual and still partial convergence of what had traditionally been two separate spheres of influence—the molecular biology of cancer and the clinical practice of oncology—to form a world in which laboratory scientists and clinicians talk to and work with each other in meaningful ways (**Figure 2**).

In my early days as a tumor virologist at UCSF, encounters with my oncological colleagues were usually socially awkward; we simply had very little to say to each other and did not know each other's vocabularies or viewpoints well enough to launch a productive conversation. When it became apparent in the 1980s that oncogenes and tumor suppressor genes were central to neoplasia and would eventually have some role in diagnosis, treatment, and prevention, we made some tentative efforts to get to know each other. For instance, several UCSF faculty, ranging from yeast geneticists to full-time clinicians, gathered monthly, lured by free pizza, to hear how oncologists conduct clinical trials and how molecular biologists implicate cellular genes and proteins in human

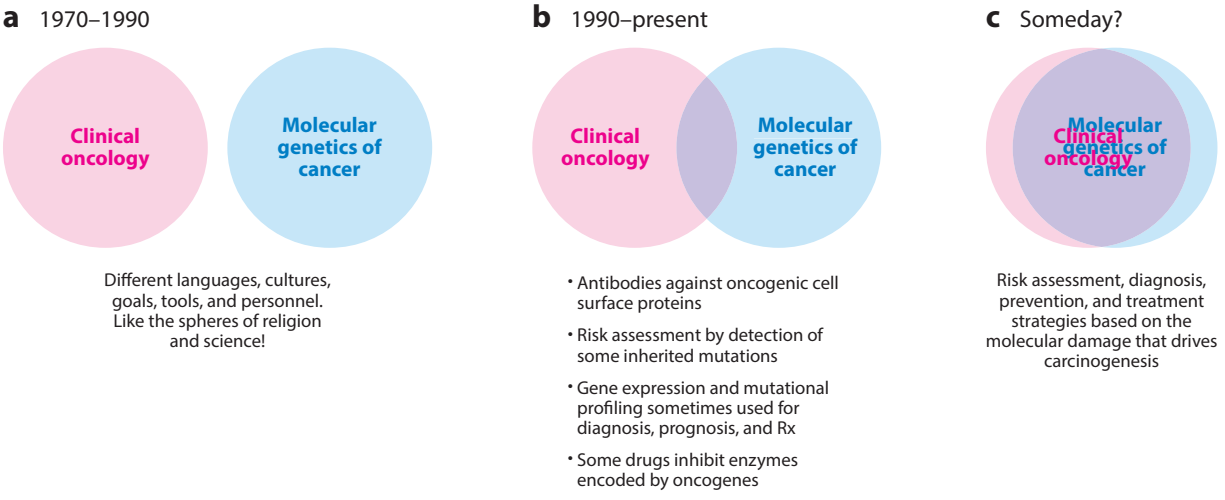

Figure 2

Venn diagrams of the approximate relationships of "two worlds," cancer genetics and clinical oncology, as they change over time, as discussed in the article.

cancers. Still, the cultures remained quite far apart, and the discussions were halting, requiring translations.

More than new diagnostic labels and promises of new therapeutics were needed to make a significant cultural fusion of these worlds. A strong push came from two landmark achievements in the treatment of specific human cancers. The first was the effective use of a monoclonal antibody (trastuzimab) to treat breast cancers bearing more than the usual amounts of a transmembrane tyrosine kinase encoded by an occasionally amplified gene (*HER2*, *ERBB2*) closely related to a previously identified proto-oncogene (c-*ERBB*) (Slamon et al. 2001). The second and even more compelling event was the extraordinary response of early stage chronic myeloid leukemia (CML) to imantinib (Druker et al. 2001), a small molecule inhibitor of the exaggerated kinase activity in the fusion protein encoded by the proto-oncogene c-*ABL*, part of the long arm of chromosome 9 that is transposed to chromosome 22 in nearly all cases of CML to form the Philadelphia chromosome (Nowell & Hungerford 1961, Rowley 1973).

These monumental events were the products of some powerful new elements in the worlds of cancer research: trained oncologists who were also schooled in molecular biology—the generational predecessors to the oncology fellows I described at the start of this article, a biotechnology industry that was poised to use recombinant DNA and hybridoma technology to make new products for cancer treatment, and a community of enlightened disease advocates and patients attuned to the hypothetical possibilities of using rational molecular therapies. The technical advances that made these two achievements (and a few less well-known others) possible in the 1990s—especially DNA cloning and sequencing, antibody engineering, and efficient drug screening—have fueled further efforts, too numerous to describe here, to develop and test more targeted drugs, to devise novel immunotherapies, and to shift the practice of oncology to an evidence-based model called "precision medicine" (Natl. Acad. Med. 2011).

Such changes in medicine, of course, do not proceed in a social vacuum, so any full account of what is happening now would need to take greater notice of economic, political, educational, and cultural conditions. Further, the changes I have tracked do not explain other developments in oncology: new approaches to cancer prevention and assessment of cancer risk, both environmental and genetic; improvements in screening and early detection of certain cancers; the recent successes with immunotherapies (which owe a lot to fundamental immunology and much less to tumor virology); symptom control in cancer patients; and the emerging role of oncology in global health.

A FINAL WORD

I have tried to outline the pathway by which tumor virology, one of a diversity of experimental approaches to cancer half a century ago, led to the discovery of the first vertebrate genes implicated in carcinogenesis. Unveiling the functions of those genes helped to create the field of cancer biology, whose successes catalyzed the ongoing fusion of molecularly based research and clinical oncology and are being celebrated by the launch of this new Annual Reviews journal.

The former tumor virologists who now call themselves cancer biologists have had to reconceive our place in the scientific ecosystem. I view my own group, for example, working somewhere between genomics (where mutations are discovered in human cancers) and therapeutics (where new drugs and immunotherapies are developed and tested). This domain, shown schematically in **Figure 3**, encompasses our three current research projects—on the functions of mutant splicing factors (Fei et al. 2016), the synthetic lethal effects of certain pairs of mutant oncogenes (Unni et al. 2015), and the determinants of different genotypes found in lung cancers arising in different cell lineages. Such projects also reveal how far cancer research has come since the early days of

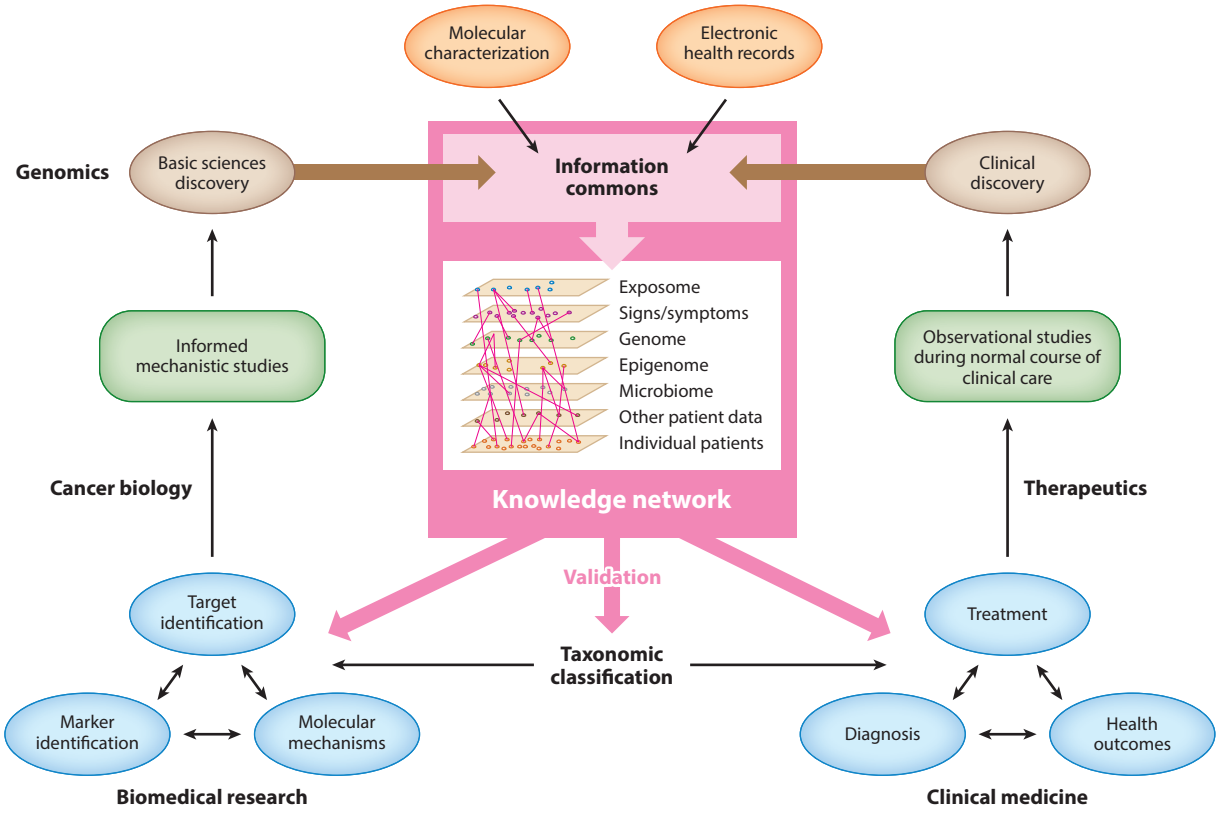

Figure 3

An annotated version of a figure reproduced from a 2011 report from the Institute of Medicine (*Towards Precision Medicine*), showing the relationships among various activities on the current landscape of cancer research and practice. As mentioned in the text, I envision the field of cancer biology, at least as practiced in my own laboratory, to lie between cancer genomics and cancer therapeutics. Figure adapted with permission from Natl. Acad. Med. (2011).

tumor virology, engaging us with cell biology in ways that would have been inconceivable when my contemporaries and I called ourselves tumor virologists.

I see another trend that will be increasingly important to cancer biologists over the next decade or more: an effort to go beyond the complex differences that genomics, in particular, has revealed about individual cancers, and toward the commonalities that unite large numbers of cancers. At the simplest level, this means placing more emphasis on the most common oncogenic lesions, especially mutant *RAS* oncogenes, and loss of some tumor suppressor genes, such as *TP53*, *PTEN*, and *RB*. Such genes have certainly not been neglected; there are tens of thousands of papers about each of them listed in PubMed. But persistence, new resources, and new technologies should be focused on the control of cancers driven by such common mutations. The NCI's RAS Initiative at the Frederick National Laboratory for Cancer Research is one recent example of what might be done (**http://www.cancer.gov/research/key-initiatives/ras**). The application of advances in structural biology to the correction of *TP53* mutants is another (Soragni et al. 2016). A better understanding of the signaling networks in which oncogenic mutations do their mischief may ultimately allow cancer treatments to be targeted not just at the mutated components but at critical wild-type elements of the perturbed networks.

A less obvious and less mutant-centric approach is through the phenotypic commonalities summarized in the review articles by Hanahan & Weinberg (2000, 2011). Understanding the "hallmarks of cancer" should reveal—and in some cases already has produced—new ways to think about cancer therapies, directing them not only against miscreant oncoproteins and the networks in which they act, but also toward exploitation of the physiological abnormalities found in cancers with a wide variety of genotypes: impaired repair of DNA, dysregulation of genes, abnormal cell metabolism, neoangiogenesis, and aberrant RNA processing. Such approaches might evade some of the problems encountered with current targeted therapies—consequences of the heterogeneity of primary and metastatic tumors, the evolution of cancer cells, and the emergence of drug resistance (Jamal-Hanjani et al. 2015).

In taking on challenges of this magnitude, cancer biology needs to attract the kinds of brilliant trainees with whom I opened this article and bring cancer research even more squarely into the center of action in the life sciences—a long way from where cancer research stood when I entered medical school over a half century ago.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

Alberts B, Kirschner MW, Tilghman S, Varmus H. 2014. Rescuing US biomedical research from its systemic flaws. *PNAS* 111:5773–77

Baltimore D. 1970. RNA-dependent DNA polymerase in virions of RNA tumour viruses. *Nature* 226:1209–11

Berget SM, Moore C, Sharp PA. 1977. Spliced segments at the 5′ terminus of adenovirus 2 late mRNA. *PNAS* 74:3171–75

Bernstein A, MacCormick R, Martin GS. 1976. Transformation-defective mutants of avian sarcoma viruses: the genetic relationship between conditional and nonconditional mutants. *Virology* 70:206–9

Bishop JM. 2003. *How to Win the Nobel Prize: An Unexpected Life in Science*. Cambridge, MA: Harvard Univ. Press

Bishop M, Varmus H. 1982. Functions and origins of retroviral transforming genes. See Weiss et al. 1982, pp. 999–1108

Blackburn EH. 2010. Telomeres and telomerase: the means to the end (Nobel lecture). *Angew. Chem. Int. Ed. Engl.* 49:7405–21

Blumberg BS, London WT. 1982. Hepatitis B virus: pathogenesis and prevention of primary cancer of the liver. *Cancer* 50:2657–65

Bourne HR, Sanders DA, McCormick F. 1990. The GTPase superfamily: a conserved switch for diverse cell functions. *Nature* 348:125–32

Boveri T. 1915. Concerning the origin of malignant tumours by Theodor Boveri, transl. annot. H Harris, 2008, in *J. Cell Sci.* 121:1–84

Brown PO. 1997. Integration. See Coffin et al. 1997, pp. 161–203

Brush GS, Kelly TJ, Stillman B. 1995. Identification of eukaryotic DNA replication proteins using simian virus 40 in vitro replication system. *Methods Enzymol.* 262:522–48

Cancer Genome Atlas Res. Netw. 2014. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 513:202–9

Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, et al. 1994. Identification of herpes virus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 266:1865–69

Coffin JM, Hughes SH, Varmus H, eds. 1997. *Retroviruses*. Woodbury, NY: Cold Spring Harb. Lab. Press

Coffin JM, Varmus HE, Bishop JM, Essex M, Hardy WD Jr., et al. 1981. Proposal for naming host cell-derived inserts in retrovirus genomes. *J. Virol.* 40:953–57

Crawford LV, Lane DP, Denhardt DT, Harlow EE, Nicklin PM, et al. 1980. Characterization of the complex between SV40 large T antigen and the 53K host protein in transformed mouse cells. *Cold Spring Harb. Symp. Quant. Biol.* 44(Pt. 1):179–87

Der CJ, Krontiris TG, Cooper GM. 1982. Transforming genes of human bladder and lung carcinoma cell lines are homologous to the *ras* genes of Harvey and Kirsten sarcoma viruses. *PNAS* 79:3637–40

DeVita VT Jr., DeVita-Raeburn E. 2015. *The Death of Cancer: After Fifty Years on the Front Lines of Medicine, A Pioneering Oncologist Reveals Why the War on Cancer Is Winnable—And How We Can Get There*. New York, NY: Sarah Crichton

Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, et al. 2001. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N. Engl. J. Med.* 344:1031–37

Duesberg PH, Vogt PK. 1970. Differences between the ribonucleic acids of transforming and nontransforming avian tumor viruses. *PNAS* 67:1673–80

Fei DL, Motowski H, Chatrikhi R, Prasad S, Yu J, et al. 2016. Wild-type U2AF1 antagonizes the splicing program characteristic of U2AF1-mutant tumors and is required for cell survival. *PLOS Genet.* 12:e1006384

Feng H, Shuda M, Chang Y, Moore PS. 2008. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 319:1096–100

Gallo RC, Montagnier L. 1988. AIDS in 1988. *Sci. Am.* 259:41–48

Hanahan D, Weinberg RA. 2000. The hallmarks of cancer. *Cell* 100:57–70

Hanahan D, Weinberg RA. 2011. Hallmarks of cancer: the next generation. *Cell* 144:646–74

Hayward WS, Neel BG, Astrin SM. 1981. Activation of a cellular *onc* gene by promoter insertion in ALV-induced lymphoid leukosis. *Nature* 290:475–80

Huebner RJ, Todaro GJ. 1969. Oncogenes of RNA tumor viruses as determinants of cancer. *PNAS* 64:1087–94

Hunter E. 1997. Viral entry and receptors. See Coffin et al. 1997, pp. 71–119

Hunter T. 2009. Tyrosine phosphorylation: thirty years and counting. *Curr. Opin. Cell Biol.* 21:140–46

Hunter T, Simon J. 2007. A not so brief history of the Oncogene Meeting and its cartoons. *Oncogene* 26:1260–67

Jacks T. 1990. Translational suppression in gene expression in retroviruses and retrotransposons. *Curr. Top. Microbiol. Immunol.* 157:93–124

Jamal-Hanjani M, Quezada SA, Larkin J, Swanton C. 2015. Translational implications of tumor heterogeneity. *Clin. Cancer Res.* 21:1258–66

Kanekiyo M, Bu W, Joyce MG, Meng G, Whittle JR, et al. 2015. Rational design of an Epstein-Barr virus vaccine targeting the receptor-binding site. *Cell* 162:1090–100

Kirnbauer R, Booy F, Cheng N, Lowy DR, Schiller JT. 1992. Papillomavirus L1 major capsid protein self-assembles into virus-like particles that are highly immunogenic. *PNAS* 89:12180–84

Kozak M, Shatkin AJ. 1979. Characterization of translational initiation regions from eukaryotic messenger RNAs. *Methods Enzymol.* 60:360–75

Lamarre D, Anderson PC, Bailey M, Beaulieu P, Bolger G, et al. 2003. An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. *Nature* 426:186–89

Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, et al. 2001. Initial sequencing and analysis of the human genome. *Nature* 409:860–921

Lohmann V, Korner F, Koch J, Herian U, Theilmann L, Bartenschlager R. 1999. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 285:110–13

Martin GS. 1970. Rous sarcoma virus: a function required for the maintenance of the transformed state. *Nature* 227:1021–23

Miles BD, Robinson HL. 1985. High-frequency transduction of c-*erb*B in avian leukosis virus-induced erythroblastosis. *J. Virol.* 54:295–303

Natl. Acad. Med. 2011. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Washington, DC: Natl. Acad. Sci. Eng. Med.

Nowell PC, Hungerford DA. 1961. Chromosome studies in human leukemia. II. Chronic granulocytic leukemia. *J. Natl. Cancer Inst.* 27:1013–35

Nusse R, Varmus HE. 1982. Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome. *Cell* 31:99–109

Parada LF, Tabin CJ, Shih C, Weinberg RA. 1982. Human EJ bladder carcinoma oncogene is homologue of Harvey sarcoma virus *ras* gene. *Nature* 297:474–78
Parker RC, Varmus HE, Bishop JM. 1981. Cellular homologue (c-*src*) of the transforming gene of Rous sarcoma virus: isolation, mapping, and transcriptional analysis of c-*src* and flanking regions. *PNAS* 78:5842–46
Pastan I, Macchia V. 1967. Mechanism of thyroid-stimulating hormone action. Studies with dibutyl 3′,5′-adenosine monophosphate and lecithinase C. *J. Biol. Chem.* 242:5757–61
Pastan I, Perlman RL. 1968. The role of the lac promotor locus in the regulation of β-galactosidase synthesis by cyclic 3′,5′-adenosine monophosphate. *PNAS* 61:1336–42
Paul WE. 2014. Endless fascination. *Annu. Rev. Immunol.* 32:1–24
Payne GS, Bishop JM, Varmus HE. 1982. Multiple arrangements of viral DNA and an activated host oncogene in bursal lymphomas. *Nature* 295:209–14
Potter M, Boyce CR. 1962. Induction of plasma-cell neoplasms in strain *BALB/c* mice with mineral oil and mineral oil adjuvants. *Nature* 193:1086–87
Prager EM, Brush AH, Nolan RA, Nakanishi M, Wilson AC. 1974. Slow evolution of transferrin and albumin in birds according to micro-complement fixation analysis. *J. Mol. Evol.* 3:243–62
Rabson AB, Graves BJ. 1997. Synthesis and processing of viral RNA. See Coffin et al. 1997, pp. 205–61
Rosenberg N, Jolicoeur P. 1997. Retroviral pathogenesis. See Coffin et al. 1997, pp. 475–585
Rowley JD. 1973. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature* 243:290–93
Scholl C, Frohling S, Dunn IF, Schinzel AC, Barbie DA, et al. 2009. Synthetic lethal interaction between oncogenic *KRAS* dependency and *STK33* suppression in human cancer cells. *Cell* 137:821–34
Shakespeare W. 1623 (1997). *Hamlet*. In *The Norton Shakespeare*, ed. S Greenblatt, W Cohen, JE Howard, KE Mauss. New York: Norton
Shimizu K, Goldfarb M, Suard Y, Perucho M, Li Y, et al. 1983. Three human transforming genes are related to the viral *ras* oncogenes. *PNAS* 80:2112–16
Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, et al. 2001. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med.* 344:783–92
Soragni A, Janzen DM, Johnson LM, Lindgren AG, Thai-Quynh Nguyen A, et al. 2016. A designed inhibitor of p53 aggregation rescues p53 tumor suppression in ovarian carcinomas. *Cancer Cell* 29:90–103
Spector DH, Varmus HE, Bishop JM. 1978. Nucleotide sequences related to the transforming gene of avian sarcoma virus are present in DNA of uninfected vertebrates. *PNAS* 75:4102–6
Stehelin D, Guntaka RV, Varmus HE, Bishop JM. 1976a. Purification of DNA complementary to nucleotide sequences required for neoplastic transformation of fibroblasts by avian sarcoma viruses. *J. Mol. Biol.* 101:349–65
Stehelin D, Varmus HE, Bishop JM, Vogt PK. 1976b. DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. *Nature* 260:170–73
Stent GS. 1972. Prematurity and uniqueness in scientific discovery. *Sci. Am.* 227:84–93
Swanstrom R, Wills JW. 1997. Synthesis, assembly, and processing of viral proteins. See Coffin et al. 1997, pp. 263–334
Taparowsky E, Suard Y, Fasano O, Shimizu K, Goldfarb M, Wigler M. 1982. Activation of the T24 bladder carcinoma transforming gene is linked to a single amino acid change. *Nature* 300:762–65
Temin H. 1975. *Nobel Lecture: The DNA Provirus Hypothesis*. Stockholm: Nobel Media
Temin HM, Mizutani S. 1970. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. *Nature* 226:1211–13
Tooze J, ed. 1980. *DNA Tumor Viruses*. Woodbury, NY: Cold Spring Harb. Lab. Press
Tooze J, ed. 1981. *DNA Tumor Viruses*. Woodbury, NY: Cold Spring Harb. Lab. Press. 2nd ed.
Unni AM, Lockwood WW, Zejnullahu K, Lee-Lin SQ, Varmus H. 2015. Evidence that synthetic lethality underlies the mutual exclusivity of oncogenic KRAS and EGFR mutations in lung adenocarcinoma. *eLife* 4:e06907
Varmus H. 1984. The molecular genetics of cellular oncogenes. *Annu. Rev. Genet.* 18:553–612
Varmus H. 2009. *The Art and Politics of Science*. New York: Norton

Varmus H, Levine AJ, eds. 1983. *Selected Readings in Tumor Virology*. Woodbury, NY: Cold Spring Harb. Lab. Press

Varmus HE, Perlman RL, Pastan I. 1970. Regulation of *lac* messenger ribonucleic acid synthesis by cyclic adenosine 3′-5′ monophosphate and glucose. *J. Biol. Chem.* 245:2259–68

Varmus H, Trimble EL. 2011. Integrating cancer control into global health. *Sci. Transl. Med.* 3:34–36

Varmus H, Weinberg RA. 1992. *Genes and the Biology of Cancer*. New York: Sci. Am. Libr.

Vinograd J, Lebowitz J. 1966. Physical and topological properties of circular DNA. *J. Gen. Physiol.* 49:103–25

Vogt PK. 1971. Spontaneous segregation of nontransforming viruses from cloned sarcoma viruses. *Virology* 46:939–46

Vogt PK. 1997. Historical introduction to the general properties of retroviruses. See Coffin et al. 1997, pp. 1–25

Weinberg RA. 2007a. *The Biology of Cancer*. New York: Garland Sci.

Weinberg RA. 2007b. Tumor suppressor genes. In *The Biology of Cancer*, pp. 231–74. New York: Garland Sci.

Weiss R, Teich N, Varmus H, Coffin J, eds. 1982. *RNA Tumor Viruses*. Woodbury, NY: Cold Spring Harb. Lab. Press

Weiss R, Teich N, Varmus H, Coffin J, eds. 1985. *RNA Tumor Viruses*. Woodbury, NY: Cold Spring Harbor Lab. Press. 2nd ed.

Whyte P, Buchkovich KJ, Horowitz JM, Friend SH, Raybuck M, et al. 1988. Association between an oncogene and an anti-oncogene: The adenovirus E1A proteins bind to the retinoblastoma gene product. *Nature* 334:124–29