Crafting Science

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A Sociohistory of the Quest for the Genetics of Cancer

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For Kunio and Asae Fujimura, with love and respect;
and in memory of Anselm L. Strauss

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Introduction

Creating a New Realm

Harold Varmus, I and our numerous colleagues have been privileged to assist as a despised idea became the ruler over a new realm. The notion that genetic changes are important in the genesis of cancer has met strenuous resistance over the years. But now that notion has gained ascendancy.

—J. Michael Bishop, "Retroviruses and Oncogenes II"

In the late 1970s, researchers published articles linking genes in viruses that caused cancer in laboratory animals to normal genes in humans. Researchers proposed that these normal human genes, called "proto-oncogenes," could be triggered to cause cancer. By 1986 the proto-oncogene hypothesis was a "fact" asserted in basic biological textbooks, and in 1989 its principal proponents, J. Michael Bishop and Harold T. Varmus, won the Nobel Prize for their oncogene work.[1] Within a few years, thousands of researchers and laboratories and hundreds of millions of dollars became devoted to proto-oncogene research. "Cancer" had changed from a set of heterogeneous diseases marked by the common property of uncontrolled cell growth to a disease of human genes.

This book is a sociohistory of proto-oncogene research in the United States with an emphasis on the collective production of scientific facts. It recounts the explosive growth of a new field of research and the creation of a novel class of genes. I examine this case of scientific innovation in terms of the daily practices in laboratories and in the context of contemporary biological science.

I do not address the question of whether the proto-oncogene theory is a true or false explanation of the cause of human cancers. Instead, I consider the activities, tools, contexts, and processes through which scientific repre-

sentations are produced and accepted. This book explores the production of accepted knowledge.

My account of proto-oncogene research addresses certain technical aspects of oncogene research, but it differs from the accounts of oncogene scientists in several respects.[2] Their histories present experimental evidence to demonstrate that artificially altered proto-oncogenes transform normal cells into cancer cells. They also present evidence of altered proto-oncogenes retrieved from human tumor cells. While I give a history of this research employing selected accounts of technical achievements leading up to the proto-oncogene theory, I weave into my story an analysis of the representational, organizational, and rhetorical work done by researchers, students, sponsors, and audiences to create the "world" of proto-oncogene research.

I also consider some opposing voices. A few vocal dissenters have argued against the belief that normal genes are the roots of cancer. Proto-oncogene theorists call these scientists "heretics" and dismiss their criticisms as "sour grapes." I do not take sides or attempt to evaluate the truth of this claim. Instead, I use these alternative views as reminders that consensus, or at least common practice, is an achievement not to be taken for granted in scientific as well as in sociocultural and religious knowledge. These contrary views challenge, and thus make evident, the range of perspectives that otherwise would not be made public.

However, a critical role for proto-oncogenes in causing cancer has become fact for most biologists and many clinicians today. This development has not made available cures or therapies involving oncogenes. Although proto-oncogenes have moved into clinical practice to some degree in the form of diagnostic tools, cancer researchers caution that the path from their research to treatments for actual cancers is presently unclear.

Nevertheless, scientists, students, university administrations and departments, funding agencies, biological research supply and biotechnology companies, and Congress joined in the research effort on proto-oncogenes and their oncogenic processes. Participants from many different lines of work have come to practice a common approach in their studies of cancer. Especially in the United States the molecular biological approach, with proto-oncogene research at its center, gained an increasing proportion of cancer research support. Scientists began to use the term "oncogene bandwagon." Appropriating their term, I refer to this set of multiple cascading commitments to proto-oncogenes, and more generally to molecular genetic cancer research, as a *bandwagon*. Large numbers of people, laboratories, organizations, and resources became committed to one approach to a problem.

By 1984 the oncogene bandwagon was a distinct and entrenched phenomenon. As we will see, scientists acted on the basis of its existence, and

many researchers joined the bandwagon because it was just that. This snowball effect exemplifies how oncogene research had become a phenomenon sustained by its own infrastructure and momentum. Thus, the enthusiasm for a particular research problem, and for a particular technical approach, is a social phenomenon.

This book is also a study of change and continuity in science. I portray conceptual change in science as embedded in individual and collective changes in the organization of scientific work. More specifically, I describe a *process* within which theoretical or conceptual shifts are inseparable from both the local and broad-scale organization of work and the technical infrastructures of science and society. Through this process, cancer was represented as a disease of the cell nucleus and specified sequences of DNA.

In their previous research, scientists had conceptualized cancer in different, if still genetic, terms. These earlier studies developed tools that represented "genes" in experimental systems such as inbred mice and cell lines. Inbred mice from a particular line were considered to have identical genes. Nevertheless, these genes were imagined rather than materialized. Researchers could not point to a particular material entity and say, "This is the gene that created the cancer."

In the late 1970s and early 1980s, a few tumor virologists and molecular biologists announced that they had found a proto-oncogene that caused a cell to become cancerous. Their proto-oncogene, a material form of specific segments of DNA, was a novel representation of cancer, this time in terms of "normal" cellular genes. The multitude of previous representations of chemical carcinogenesis, radiation carcinogenesis, tumor progression, and metastasis then became (re)presented in terms of this new unit of analysis. I shall describe how this new unit of analysis, incorporating both theory and material, was developed in and from previous experimental systems. Moreover, this new representation formally linked the study of cancer to the study of normal development and evolutionary theory, as well as to other fields of research. Thus, researchers crafted and recrafted the proto-oncogene theory as well as links to problems of many different scientific worlds. Bridges were built between existing lines of research, which extended and transformed them into new lines of research.

Cancer Research as Collective Work

Like other scientific fields, biomedical cancer research is a collective and interactive process. It is conducted by people interacting with one another and with other elements through time. Many of these activities take place

within institutional frameworks.[3] Much biomedical research on cancer is organized along the lines of different traditions and disciplines. Shelves of books on cancer research, scores of journals and articles on cancer, and Index Medicus entries on cancer in the MedLine computerized data base indicate the expanse of contemporary biomedical cancer research fields and representations.[4] Histories of cancer research also describe a proliferation of lines of research, theories, and methods for understanding cancer causation, progression, epidemiology, and therapy. The problem of cancer is distributed among different worlds of practice, each with its own agenda, concerns, responsibilities, and conventions.[5]

Clinicians frame their problems in terms of individual cases, individual patients, and standard operating procedures: given present knowledge, how do we best treat the person? Medical researchers in the fields of radiology, epidemiology, oncology, endocrinology, neurology, and pathology work with both patients and theoretical abstractions that they construct using many cases distributed through time and space. How many patients respond to this treatment in which way? What can we say about initiation and progression of the disease when examining a number of patients over time? Basic researchers in the fields of genetics, virology, cell biology, organismal biology, molecular biology, immunology, and neuroscience work with theoretical abstractions and material models. How can we duplicate the cancer process in mice or cultured cells in order to use it as a tool for studying the disease? What are the origins of cancer? Among medical and basic researchers, the questions are broken down further. What is the role of the endocrine system in causing, promoting, or retarding the initiation or growth of the disease? What is the role of chemicals, of radiation, of viruses? What are the molecular mechanisms for the initiation and progression of the disease at the levels of genes and cells? Epidemiologists track the diseases as they appear in their different manifestations (breast, liver, colon, lung, brain, cervix, prostate) across families, "racial and ethnic" groups, occupations, countries, and regions. On the other end of the scale, pathologists examine cells in cultures taken from tumor tissues. These are just a few of the participants involved in constructing knowledge about cancer.

My ethnographic investigations concerned the interactions between participants in different worlds of cancer research. Scientists in different lines of research and treatment worked with different units of analysis, representations of data, research materials, scales of time and space, and audiences. However, many scientists had long presupposed the existence of some central "factor" linking multiple representations and types of cancers. They assumed that this central "common denominator" would eventually come to light, despite failed attempts to find it.[6]

In this context of specialized searches for the elusive "magic bullet" cure, oncogenes captured everyone's attention and imagination. Oncogene research quickly gained widespread acceptance and support across the different worlds in the early 1980s.

How did a conceptual model like the proto-oncogene theory become accepted so quickly across disparate situations, across many laboratories, and even across fields of research? I do not take consensus to be the norm in cutting-edge science. One lesson we have learned from ethnographic studies of science is that scientific practice is much more diverse and locally contingent than it was once assumed to be. Given this diversity and contingency, how did researchers from such diverse situations come to share many common practices and even agreements on proto-oncogenes?

Standardizing across Worlds

The phenomenal growth of proto-oncogene research occurred simultaneously with the production of a *package* of theory and methods. This new package consisted of the proto-oncogene theory of cancer along with standardized recombinant DNA and other molecular genetic technologies for realizing, materializing, testing, exploring, and adjusting the theory. Although these technologies included inbred mouse colonies, cell lines, and viral colonies created earlier in the century, the crafting of the proto-oncogene theory occurred in conjunction with the development of new molecular biological technologies in the early 1970s. This particular combination of theory and methods was then disseminated, adapted, and adopted across different research and clinical settings.

The proto-oncogene theory was initially constructed as an abstract notion, using a new unit of analysis, the proto-oncogene, for studying and conceptualizing cancer. The theory's conjunction of general and specific aspects was used by researchers in many extant lines of research to interpret the theory to fit their separate concerns. Scientists liberally translated the abstract notion to change and add to their laboratories and problem structures without generating major conflicts with preexisting frameworks, yet they simultaneously transmuted their previous notions and technologies.

The general aspect of the package was embodied in concepts and objects—such as genes, cancer, cancer genes, viral genes, cells, tumors, normal growth and development, and evolution—that often had different meanings and uses and were represented by different practices in diverse lines of work on cancer. These concepts and objects linked proto-oncogene research to work in evolutionary biology, population genetics, medical genetics, tumor

virology, molecular biology, cell biology, developmental biology, and carcinogenesis. They were interpreted and treated differently to allow for both variability in practices and specificity within work sites. In other words, researchers in several fields of biology manipulated these concepts and objects to draw on one another's work to support, extend, and maintain the integrity of their lines of research. For instance, studies of genes and tumors were transformed by molecular biologists into studies of DNA sequences in tumor cells in vitro *and* by hormonal carcinogenicists into studies of tumor breast tissue samples taken from laboratory mice. The same genes could be studied by molecular biologists interested in cancer and by *Drosophila* geneticists interested in genes involved in normal growth and differentiation. One could say that proto-oncogenes have become a lingua franca for biologists!

These genetic studies employed recombinant DNA and other molecular biology technologies. At the time that Bishop and Varmus and their colleagues were framing the proto-oncogene concept, molecular biologists were creating new molecular genetic technologies, especially recombinant DNA techniques. The idea that cells could be transformed from normal states to cancerous states by genetic switches involving DNA sequences might have remained an idea—might never have been transformed into practice—without the development of molecular biological technologies. Bishop (1989:15) stated that "the contemporary image of the cancer cell . . . was forged from the vantage point of molecular genetics and with the tools of that discipline." According to scientists, recombinant DNA and other molecular genetic techniques provided a means by which they could enter the human cell nucleus and intervene and manipulate the nucleic acids of genes to study their activities in ways never before possible. By the mid-1980s, the researchers I interviewed had come to see these technologies, not as objects of research, but as tools for asking and answering new questions and for stimulating a flurry of work at the molecular level on questions previously approached at the cellular and organismal levels.

"Technical" standardization proved even more important for understanding the extraordinary growth of this line of research.[7] It provided a means through which techniques could be transported between labs. Even previously "low-tech" laboratories began to incorporate high-tech equipment and skills. An example of technical standardization was the dissemination of particular research materials such as molecular probes for certain oncogene sequences. After their experimental creation in research laboratories, the (re)production and distribution of probes were farmed out to nonprofit biological materials distributors (such as the American Type Culture Collection) and biological supply companies. By providing the same probes to many different laboratories, these distributors contributed to the standardization of

oncogene research practices and the reproduction of practices, results, protocols, and representations across laboratories. Chapters 4 and 5 discuss the *reproductive* and *regulatory* role of recombinant DNA technologies and other molecular genetic techniques in oncogene research.

Proto-oncogene research was "standardized" even further by the introduction of experimental protocols that associated proto-oncogene theory with molecular genetic technologies. Because the proto-oncogene theory was framed in "molecular genetic language," new molecular genetic methods were required to probe questions originally framed in the "language game" of other methods.[8] Researchers untrained in molecular biology or retrovirology began to incorporate the combination of the abstract, general proto-oncogene theory and the specific, standardized technologies into their research enterprises. By reconstructing oncogene research in these new sites, a variety of research laboratories locally *concretized* the abstract proto-oncogene theory in different practices to construct new problems and new laboratory artifacts. Suddenly, novel entities such as *myc, abl, fos,* and other (onco)genes were named and defined, and novel organisms were created through gene transfer techniques. By 1989, Du Pont Corporation was advertising in science journals its transgenic OncoMouse™ (see Figure 1.1), a "technology" that physically incorporated a specific oncogene in the laboratory animal itself.

> The OncoMouse™/*ras* transgenic animal is the first *in vivo* model to contain an activated oncogene. Each OncoMouse carries the *ras* oncogene in all germ and somatic cells. This transgenic model, available commercially for the first time, predictably undergoes carcinogenesis. OncoMouse reliably develops neoplasms within months . . . and offers you a shorter path to new answers about cancer. Available to researchers only from Du Pont, where better things for better living come to life.

While the new proto-oncogene conceptual framework provided a *metaphoric* and *discursive* alliance between different lines of research, the *material* linkages were established through standardized technologies like molecular probes and the OncoMouse™. The commercial strings attached to these practical linkages contributed to the development of oncogene research. Researchers framed their problems and questions in terms of proto-oncogenes and their laboratory practices in terms of standard research protocols, recombinant DNA and other molecular genetic technologies (molecular hybridization, molecular cloning, nucleotide sequencing, and gene transfer), instruments (nucleotide sequencers, computer software and data bases), and materials (molecular probes, reagents, long-passaged cell lines,

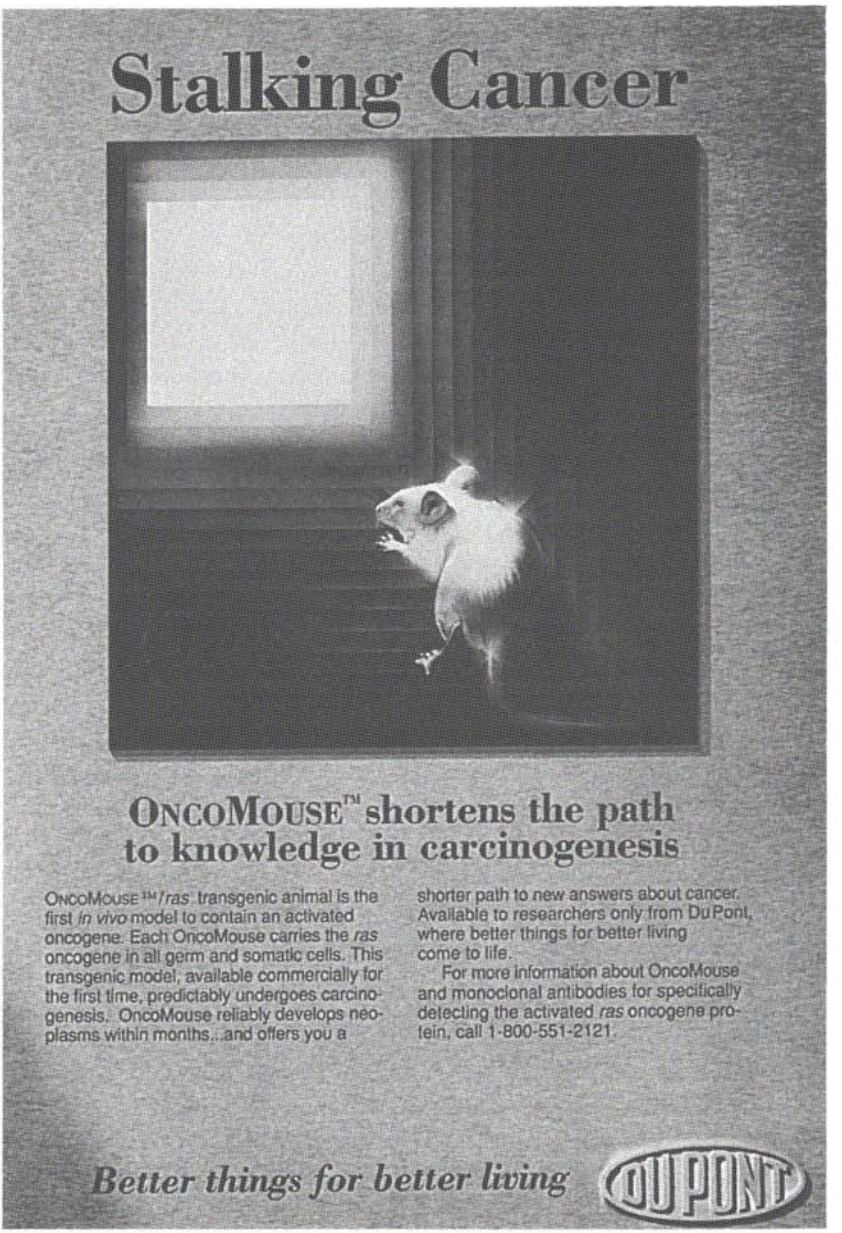

Figure 1.1 Du Pont Corporation's advertisement for a transgenic OncoMouse™, a "technology" that physically incorporated a specific oncogene in the laboratory animal itself, was published in science journals during 1989–1990. It is an example of the normal production of standardized pathological animals.