SCIENCE & CENTS

Exploring the Economics of Biotechnology

Proceedings of the 2002 Conference on
Exploring the Economics of Biotechnology
Sponsored by the
Federal Reserve Bank of Dallas

Edited by John V. Duca and Mine K. Yücel

Science & Cents: Exploring the Economics of Biotechnology

Science & Cents: Exploring the Economics of Biotechnology

Proceedings of a Conference Sponsored by the Federal Reserve Bank of Dallas
April 19, 2002

Edited by
John V. Duca and Mine K. Yücel

Federal Reserve Bank of Dallas

The views expressed in this *Proceedings* are those of the authors and should not be attributed to the Federal Reserve Bank of Dallas or the Federal Reserve System. With the exception of the articles by Darby et al. and Zucker et al., articles in this *Proceedings* may be reprinted on the condition that the source is credited and a copy is provided to the Research Department, Federal Reserve Bank of Dallas, P.O. Box 655906, Dallas, TX 75265-5906. Additional copies of this publication can be obtained by calling 214-922-5254. It is also available on the Internet at www.dallasfed.org.

Published September 2003
Federal Reserve Bank of Dallas

Contents

Preface

The articles included in this *Proceedings* were presented at the Federal Reserve Bank of Dallas conference "Science & Cents: Exploring the Economics of Biotechnology" on April 19, 2002.

We wish to thank a number of people who helped make the conference possible. We especially thank Federal Reserve Bank of Dallas President Robert D. McTeer, Jr. for encouraging us to organize a conference on the economics of biotechnology. We are grateful to John Thompson of the Research Department for his help in hosting the conference. We also thank the conference speakers for sharing their insights and particularly Michael Lawlor for suggesting many of his fellow participants.

About the Contributors

C. Thomas Caskey is president and CEO of Cogene Biotech Ventures Ltd., a venture capital fund that supports early-stage biotechnology companies. He serves on several national research review panels, including the Intramural Human Genome Projects Special Review Committee at the National Institutes of Health, and on the editorial boards of the *Journal of the American Medical Association* and *Science*.

Michael R. Darby is Warren C. Cordner Professor of Money and Financial Markets at the University of California at Los Angeles. He is also director of UCLA's John M. Olin Center for Public Policy, chairman of The Dumbarton Group, a research associate with the National Bureau of Economic Research, and adjunct scholar with the American Enterprise Institute.

John V. Duca is a vice president and senior economist at the Federal Reserve Bank of Dallas, where he heads and conducts research in financial-side macroeconomics.

Rebecca S. Eisenberg is Robert and Barbara Luciano Professor of Law at the University of Michigan. Eisenberg, who teaches patent law, trademark law, and torts, is on the advisory committee to the director of the National Institutes of Health and on the Panel on Science, Technology, and Law at the National Academies.

Malcolm Gillis is president and Ervin Kenneth Zingler Professor of Economics at Rice University. He is on the National Academy of Sciences Board on Sustainable Development and a board member of the National Council for Science and the Environment, Houston Advanced Research Center, and Houston Technology Center.

Henry G. Grabowski is professor of economics and director of the Program in Pharmaceuticals and Health Economics at Duke University. He has acted as an adviser and consultant to the National Academy of Sciences, Institute of Medicine, Federal Trade Commission, Office of Technology Assessment, and General Accounting Office.

Timothy F. Howe is founding partner of Collinson, Howe & Lennox, a venture capital firm that provides management and advisory services to four closed-end investment pools representing more than $100 million in committed capital. He is also adjunct professor in the School of Business at Columbia University.

Michael S. Lawlor is a professor in the economics department and a research associate in the Social Science Section of the Department of Public Health Sciences at Wake Forest University. He also directs the interdisciplinary minor in health policy and administration. Lawlor is a financial economist and economic historian who specializes in the economic behavior of health organizations and the social influences on market behavior.

Frank R. Lichtenberg is Courtney C. Brown Professor of Business at Columbia University. He is also a research associate at the National Bureau of Economic Research. His research has examined how the introduction of new technology arising from research and development affects the productivity of companies, industries, and nations.

Dennis K. Stone is vice president for technology development at the University of Texas Southwestern Medical Center. He is also a professor of internal medicine, physiology, and biochemistry and holder of the NCH Corporation Chair in Molecular Transport. Stone was a Searle Scholar and has received the Established Investigator Award of the American Heart Association.

Mine K. Yücel is a vice president and senior economist at the Federal Reserve Bank of Dallas, where she heads and conducts regional economic research.

Lynne G. Zucker is professor of sociology and policy studies at the University of California at Los Angeles. She is also director of the Organizational Research Program at the Institute for Social Science Research and director of UCLA's Center for International Science, Technology, and Cultural Policy.

Introduction

Exploring the Economics of Biotechnology: An Overview

John V. Duca and Mine K. Yücel

Exploring the Economics of Biotechnology: An Overview

John V. Duca and Mine K. Yücel

The recent rapid pace of discovery in life sciences raises a host of economic issues. Advances in biotechnology will likely affect the well-being of people worldwide for years to come. While we can only speculate on the specific form those advances will take, we can address many of the economic questions raised by developments in the life sciences. What potential economic benefits does biotechnology offer? How is the industry's emergence similar to the infancy of now-established industries? What legal and regulatory issues does the industry face? How will biotechnology research be financed and what are the funding hurdles? Where do biotechnology firms locate?

To address these and other important questions on the subject, the Federal Reserve Bank of Dallas hosted "Science & Cents: Exploring the Economics of Biotechnology" on April 19, 2002. The conference brought together distinguished experts who discussed economic and scientific issues related to biotechnology.

AN ECONOMIC PERSPECTIVE ON THE BIOTECH REVOLUTION

Professor **Michael Darby** of the University of California at Los Angeles opened the conference with an economic perspective on whether biotech advances will kindle a new industrial revolution. He emphasized that biotech research appears to be a major, metamorphic revolution that is creating new industries, rather than incremental progress that perfects existing products.

As with earlier metamorphic revolutions, a lack of data and history hampers our ability to gauge biotech's importance. Another characteristic of such revolutions is that many new firms enter an emerging industry that has few or no incumbents, but just a fraction of these new firms succeed and thrive. The biotech sector is still in its formative stage, so the number of firms will proba-

bly expand before declining during the shakeout phase that often occurs in an industry's development. Nevertheless, as Darby stressed, many of the economic benefits to society accrue during the consolidation and maturation stages of an industry's life cycle.

Darby also noted that biotech research is hard to imitate and has a natural excludability in that innovators have a profound advantage over imitators in creating successful applications from the research. In particular, success in biotech is highly correlated with links to star scientists at universities, and these links are empirically the most important factors affecting the probability of success. For this reason, Darby stressed that drawing top scientific talent and expanding university research are critical to increasing biotech activity in areas like Texas.

Columbia University Professor **Frank Lichtenberg** reviewed some of the limited evidence on biotech's promise from studies of the economic benefits of drugs, the most established biotech-related industry. These benefits include lower overall medical costs, higher productivity, and increased longevity. Lichtenberg said that combined, these savings imply that $34 spent on prescriptions boosts output by roughly $152.

Of course, these findings are based on past experience, and there is no guarantee that future advances will pay off as handsomely. Nevertheless, the track record for new pharmaceuticals is impressive and should be considered when evaluating policy proposals that affect incentives for innovation. This caution also applies to other biotech industries, especially in light of the key role highly risky research plays in biotech advances, a point stressed by other conference speakers.

THE INTERDISCIPLINARY NATURE OF BIOTECH RESEARCH

Two conference presentations spotlighted the complex, interdisciplinary nature of biotechnology research. In his keynote address, Rice University President **Malcolm Gillis** focused on the critical roles nanotechnology and bioinformatics will likely play in biotech advances.

Gillis noted that the development of biotech will help accelerate growth in dozens of other industries, thereby fostering overall economic growth. Biotech innovations are generally the outcome of the interplay of a collection of discoveries in different fields over a long period. In particular, Gillis stressed how biotech progress is propelled by a synthesis of new technologies, not only from the biosciences but also from other sciences, such as information technology and nanotechnology.

Gillis noted that mathematical, statistical, and computer methods are indispensable to analyzing biological, biochemical, and biophysical data. For example, computational cancer research deals with an overwhelming number of possible combinations and permutations of cancer-causing mutations, a problem bioinfor-

matics is well suited to handle. Another subfield is pharmacogenomics, which combines computational sciences with biochemistry and pharmacology and offers the potential for customizing drugs to the genetic makeup of individuals and developing new insights into disease prevention.

Gillis also described the growing research in the interface between biotechnology and nanotechnology, such as developments in the design and use of nanomaterials for biomedical engineering. He sees biotech as the principal arena for an ongoing, far-reaching synthesis of science and engineering. Gillis noted that the interplay between bio-, nano-, and information technology will have a striking impact on health maintenance, diagnosis, and treatment. He also predicted that biotechnology will provide an array of products and services to fuel sharp increases in living standards.

Tom Caskey, head of Cogene BioTech Ventures Ltd., a biotechnology venture capital fund, stressed how technical innovations from several areas of science are being used in the new field of proteomics. Caskey discussed the convergence of new technologies that enable a new industrial approach to health products. He noted that many different technologies in chemistry and biology are being combined to develop new therapeutics. For example, recombinant DNA technology and genome sequencing have helped researchers understand the structure of HIV and aided work on developing HIV vaccines and treatments. More broadly, advances in recombinant DNA technology, the study of cell growth, proteomics, and bioinformatics contribute to the development of proteins that can be used to prevent and treat diseases.

Caskey also briefly discussed the financial drivers of the biotech industry, pointing out that the National Institutes of Health (NIH) and large pharmaceutical firms are the main source of funds, with a small amount coming from venture capital. He then spoke of some developments in Texas and shared his ideas about what is needed to foster biotech in the state. These include increasing the number of new firms, improving the recruitment of pharmaceutical and large biotech firms to the region, and enabling in-state and out-of-state firms to consolidate. Caskey concluded that achieving these goals requires upgrading business plans and management, recruiting biotech talent, bolstering venture capital funding, and improving state and regional incentives.

LEGAL AND REGULATORY ISSUES FACING BIOTECHNOLOGY

Two speakers addressed the legal and regulatory issues surrounding biotechnology. Duke University Professor **Henry Grabowski** emphasized that two of the biggest hurdles for drug research are high risk and high costs. Only 22 percent of drugs that enter clinical trials eventually receive Food and Drug Administration approval, he noted. Furthermore, even among approved drugs there are few winners. Plus, R&D costs are high and are rising sharply. Adjust-

ing out-of-pocket costs for risk and time, Grabowski and his research colleagues estimate that developing a new drug costs roughly $800 million.

Obviously, inventors need to capture enough of the economic returns to make their investment worthwhile. In general, biotech firms defend their intellectual property through patents and an evolving set of legal strategies. Because R&D costs and risks are high, patents need to last long enough for firms to recoup their risk-adjusted R&D costs without unduly dissuading patent holders or their potential competitors from conducting more research. Grabowski pointed out that patents provide outsiders with information about new discoveries, which, in turn, spurs more research. He said that surveys of biotech firms have shown that considerations surrounding patent protection are the most important factor affecting R&D decisions.

Professor **Rebecca Eisenberg** of the University of Michigan also stressed the importance of patent strategies for inventors to capture the returns to R&D in biotech. An impediment to this is that existing patent practices may be unsuitable for the fast-changing biotech landscape because it takes time for the law to catch up with science. Today, the value of an innovation is not in the direct production of therapeutic or diagnostic products but in the use of that innovation in research and product development. For this reason, many innovators pursue reach-through strategies to claim a share of the value of future products. These strategies include licensing agreements that allow others to use an invention in exchange for a share of future products and pursuing damages for the unlicensed use of an invention that has led to the development of a profitable product.

Eisenberg argued that these reach-through strategies help with the valuation and financing of biotech research and tools. After discussing the pros and cons of the different strategies, she concluded by observing that patent law has traditionally limited patent protection to actual accomplishments and future variations that arise from work that is routine and predictable. She considers this a sensible limitation that guides patent examiners away from granting patent rights that would unreasonably cover future research. Eisenberg believes there are good reasons for permitting prior innovators to capture a fair share of the value their discoveries contribute to subsequent downstream innovation. Nevertheless, she is generally more comfortable with strategies in which licenses are negotiated in the marketplace than with strategies that require negotiation in the course of patent prosecution.

FINANCING BIOTECH RESEARCH

Funding expensive research that has highly risky returns is another hurdle for biotech. Aside from pharmaceutical research, which is often done by established companies, much biotech research is conducted by new firms that are partly funded by venture capitalists and other private equity investors. Much of

their applied research is based on basic or generic research that is either publicly funded or conducted at publicly funded universities and other institutions. Given that future biotech research is likely to branch out beyond old-style pharmaceutical R&D, the session on funding biotech research focused on the roles played by venture capital and the public sector.

Timothy Howe, a founding partner of the venture capital firm Collinson, Howe & Lennox, emphasized several points about the role of venture capitalists. First, biotech venture capital firms combine managerial with scientific talent in picking, funding, advising, and even managing biotech start-ups. This enables scientists at start-up firms to focus on inventing. A second point is that most venture firms directly invest in young companies, without intermediaries. The distribution of returns is highly skewed, with few big winners. Venture capital firms also have an incentive to diversify their investments across different solutions to medical problems, which can be found not only in biotechnology but also in medical devices and health service firms.

Howe sees a shift in the type of science funded by venture firms, from conventional drug development in the 1980s and genomics in the 1990s to projects in proteomics, the study of how human genes produce proteins that act on the body. Howe sees the pharmaceutical industry moving from being vertically integrated to horizontally organized and dominated by a few major players in distinct horizontal segments, such as research and target discovery, clinical testing, and distribution. Finally, Howe believes the rising share of gross domestic product devoted to health and the related aging of the baby-boom generation are big incentives for venture capital firms to enter the medical arena.

Another important source of funding for biotech research is government. Wake Forest University Professor **Michael Lawlor** emphasized that the benefits arising from certain types of research warrant some form of public subsidy. Lawlor asks why returns to R&D have historically exceeded those on other investments and have not been driven down to normal by increased investment. One reason is that there are high-risk premiums on biotechnology investments because there are few winners. Another is that the economic value generated by inventors' discoveries spills over to others, and inventors recoup only a part of the economic value of their research.

Lawlor discussed three public policy options for addressing underinvestment, along with the drawbacks of each: an industrial policy (which invests directly in the research and production of goods), tax incentives, and direct funding of R&D. Because of the drawbacks to the industrial policy and tax approaches, the United States has mainly pursued a strategy of directly funding basic research through the National Institutes of Health, coupled with developing a system of patent and copyright protections for applied research. From Lawlor's perspective, NIH's approach yields many public benefits, while limiting some of the pitfalls of government intervention. In particular, he noted that Congress sets the

overall budget of the NIH, but panels of scientists select the research projects to fund.

Lawlor stressed that in recent decades public R&D funding has changed in response to the increased complexity of research, which is more interdisciplinary and has blurred the lines between basic and applied research. Recognizing this and seeking to encourage the transfer of federally funded research to the private sector, Congress passed legislation in the mid-1980s creating cooperative research agreements that allow federally funded laboratories to establish profitable links with commercial firms. Lawlor noted that the complex, direct-funding approach that has evolved in this country has helped make the United States the world leader in biotech research.

LOCAL DETERMINANTS OF BIOTECH RESEARCH

Dennis Stone, vice president for technology development at the University of Texas Southwestern Medical Center in Dallas (UTSW), focused on biotech activity in the Dallas/Fort Worth metro area and emphasized the role of the university. Unlike the information technology industries, biotech depends on the university as a technology source. Stone illustrated the scope of the University of Texas' biotech presence, using life science research expenditures and patent data.

Stone noted that Dallas has few biotech companies because of barriers to entry facing start-ups. In his opinion, the main barriers include the lack of biotech entrepreneurs, the lack of local venture capitalists, the academic culture of local faculty, and the fact that UTSW cannot form companies. Stone said that fostering the growth of seed capital, venture capital, and biotech space is needed for biotech to flourish in Dallas. In addition, he sees a need to increase the flexibility of firms to operate with public institutions such as UTSW and to bolster cooperation among North Dallas stakeholders.*

The last conference speaker, UCLA Professor **Lynne Zucker**, discussed broader patterns across the country. Zucker began with a glimpse of Texas' science base. Using several gauges, she showed that Texas was below the high-tech-state average for a variety of measures of scientific prowess.

Zucker stressed that biotech has had few big winners and many losers, as only 10 percent of biotech start-ups grow into reasonably large firms. Her research shows that basic university science is integral to successful commercialization of scientific discoveries. Firms working with star scientists are much more likely to be successful, controlling for other factors. Her findings also show that local venture capital has been key to the industry's growth, increasing the productivity of R&D and fueling firms' expansion. Zucker concluded by noting that Texas' biotech success will be driven by the number and quality of

* Dr. Stone's presentation is not included in this proceedings.

top research university bioscientists, especially those with ties to firms, and stressed the need for more investment in the state's scientific base.

ECONOMIC IMPLICATIONS OF BIOTECHNOLOGY

Several broad implications arise from the conference. One is that if past technological revolutions are any guide, more research is needed to develop gauges of biotech activity. Also, the benefits of biotech advances are likely to be felt long after the inevitable shakeouts that will cull firms' ranks. In addition, although health care premiums are growing rapidly and drug cost increases are getting a lot of press, we should remember that the benefits of new drugs have historically outweighed their higher cost.

Another broad implication is that while policymakers should spur basic and generic research, they must ensure that incentives are appropriate for markets to perform efficiently. Intervention in the form of price controls or forcing biotech firms to relinquish property rights could discourage innovation. Given the high cost and risks of biotech research, emerging industries need a few big winners to justify investing in many new ideas. In addition, patent and royalty laws need to catch up with technological innovations so markets can perform better.

Other implications concern the interdisciplinary nature of biotech research, which encompasses a broad scientific base and may greatly affect other areas and industries. Current biotech science draws on advances in chemistry, biology, computational methods, and medicine to develop new therapeutics. Looking ahead, the interplay of advances in biotechnology, informatics, and nanotechnology could extend biotech applications to an array of products and services inconceivable only a short time ago, greatly improving quality of life and boosting economic growth. But to succeed, biotechnology firms must draw on specialists from different areas, foster technical collaboration among these scientists, and credibly communicate their findings to regulatory agencies, customers, and investors.

The conference presentations also have implications for investors. Direct implications include recognizing the high risks in holding large stakes in individual biotech firms. Given the difficulties in capturing the value of inventions, investors should consider the risk that innovations could benefit end users more than inventors.

Perhaps the biggest implications for investors arise from the indirect effects of biotech research on benefit costs and customer bases for all sorts of companies. In particular, biotech could increase longevity beyond most projections, raising the risk to firms with large defined-benefit pension obligations and the Social Security retirement system. On the other hand, medical advances might help control the projected jump in Medicare benefits, which are expected to produce bigger budget shortfalls than the looming Social Security problem. Another demographic implication is that spending patterns could shift more

than expected if longevity increases more rapidly than projected, particularly if medical advances reduce disabilities and improve the quality—as well as the quantity—of life.

The conference presentations also have implications for local government policies aimed at fostering biotech activity. The recipe for success in biotech seems to be a strong scientific base built around top-rated academic institutions, which provide groundbreaking research and draw star scientists to the region. The second important element is the ability to commercially develop the innovations coming out of research institutions. To become a major player in the biotech arena, Texas needs to not only continue to develop its strong research base but also foster the venture capital investment needed to commercialize the innovations from the state's research institutions.

PART ONE

An Economic Perspective on the Biotech Revolution

Growing by Leaps and Inches: Creative Destruction, Real Cost Reduction, and Inching Up

Michael R. Darby and Lynne G. Zucker

The Benefits to Society of New Drugs: A Survey of the Econometric Evidence

Frank R. Lichtenberg

Growing by Leaps and Inches: Creative Destruction, Real Cost Reduction, and Inching Up

Michael R. Darby and Lynne G. Zucker

Drunk: Can you help me find my keys?
Passerby: Sure, where exactly did you drop them?
Drunk: Way over there by the trash can.
Passerby: Then why are you searching over here?
Drunk: The light's much better under the lamppost.
—Milton Friedman (Economics 331, 1967)

The class laughed after hearing this joke, not yet realizing how well it described the profession for which they were preparing. Even those present who cannot carry memory of a joke home from the barbershop still remember the day they first heard that little joke. The thesis of this article is that the economics profession has spent years looking for technological progress under the familiar lamppost of research and development (R&D) by incumbent firms aimed at improvement in existing commodities or productive methods. Such *perfective progress* (as we call it) is amenable to hedonic measurement and analysis of firm behavior and market equilibrium in terms of return on investment, public goods, and positive externalities. We show here that *metamorphic progress*, associated with creation of new industries or technological transformation of existing industries, is of the same or higher order of magnitude as a source of technological progress.

We believe that our approach complements Arnold C. Harberger's recent emphasis on the concentration of growth in a few companies in a few industries that are achieving dramatic real cost reductions. He began to formulate his own schema in his 1990 Western Economic Association presidential address and by his 1998 American Economic Association presidential address could report

This article first appeared in *Economic Inquiry* Vol. 40, no. 3.
Reprinted by permission of the publisher, Western Economic Association International.

considerable empirical evidence in support of this concentration (Harberger, 1998). Harberger distinguishes between yeast, which makes bread rise evenly, and mushrooms, which pop up unexpectedly in the back yard. In titling this article, we had in mind the Japanese picture of progress by inching up—or Frank Knight's (1944) Crusonia plant, which grows proportionately except as parts are cut off and eaten.[1] In contrast, we emphasize the process of this or that industry leaping forward at any given time—a process that may have prompted Schumpeter's (1934) model of creative destruction.

Breakthrough discoveries in science and engineering—particularly invention of a new way of inventing, such as corn hybridization, integrated circuits, and recombinant DNA—typically drive metamorphic progress. These discoveries are rarely well understood in the early years following them. As a result, natural excludability is characteristic of these radical technologies due to the extensive tacit knowledge required to practice them and the lengthy period of learning-by-doing-with at the lab bench required to transfer them. Thus, metamorphic progress cannot be analyzed following Arrow's information as a public good paradigm.

The importance of metamorphic progress based on naturally excludable technologies motivates a challenging and exciting research agenda to remove the black box covering the linkages among scientific breakthroughs, high technologies, entry and success in nascent industries, and the movement toward industrial maturity where government statistics and economic research are most likely (coincidentally) to begin. There are real data problems in studying hundreds of private start-up companies in industries still lumped into one or another classification ending in "n.e.c." (not elsewhere classified). They are manageable, however, if economists are willing to exploit unconventional sources and methods more familiar to organizational theorists, such as industry directories, financial practitioners' online services, the ISI and other scientific literature databases, and sophisticated matching methods for linking firms and individuals across databases.

Before addressing these central issues, we make a necessary digression in the next section to clarify the relationship between metamorphic progress and the supposed acceleration of secular productivity growth post-1995 labeled the new economy by Federal Reserve Chairman Alan Greenspan (2000a, 2000b, 2001) and others.[2] In section II, we review a large and important sociology of organizations and management literature that has identified recurrent patterns of industry formation. These patterns clearly indicate that the formation process involves decades of change in numbers and average size of firms inconsistent with standard microeconomic analyses of entry and exit for industries in and around equilibrium. We also review equilibrium models of industrial organization, highlighting key points of difference and congruence. In the third section we report in some detail on research on biotechnology by us and others, emphasizing theoretically and empirically interesting results that appear to be

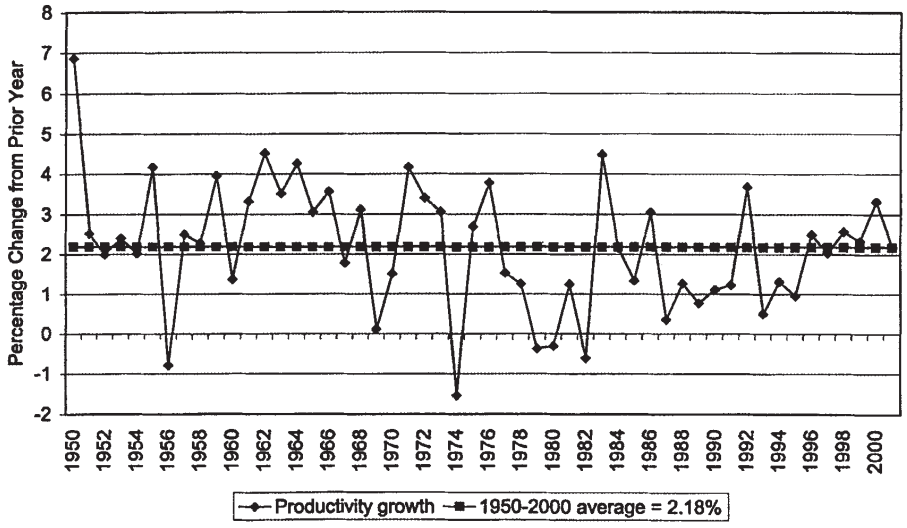
generalizable to other industries during their formative and transformative phases. The fourth section focuses on natural excludability, which is central to understanding the slow diffusion of very profitable innovations. We then point out the implications of these results for important issues in policy analysis and welfare economics. In the concluding section we attempt to draft a collective research agenda that suggests some next steps for economics and its sister disciplines in understanding growth and the wealth of nations.

I. METAMORPHIC PROGRESS AND THE NEW ECONOMY

Experience suggests that our arguments on the importance of metamorphic progress can be misread—and perhaps dismissed—as supporting or even implying the new economy ideas discussed most significantly by Greenspan (2000a, 2000b, 2001). We have no reason to believe that the processes driving metamorphic progress have either accelerated or decelerated in the last half of the 1990s and thus have no expectation of change in either direction of overall technical progress.

Little support for any extraordinary productivity growth in 1996–2000 is found in the 1950–2001 record of U.S. nonfarm-business labor productivity growth reported in Figure 1.[3] We believe that the years 1996–2000 are better

Figure 1
U.S. Nonfarm-Business Labor Productivity Growth, 1950–2001



SOURCE: U.S. Department of Labor, Bureau of Labor Statistics.
NOTE: Nonfarm business sector: output per hour of all persons.

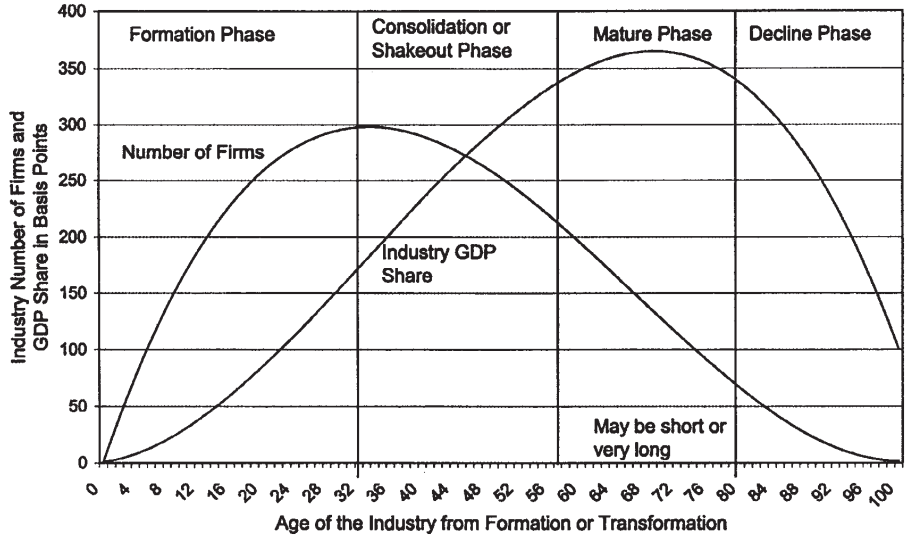
characterized as years of average productivity growth with one year moderately above average. Despite his best efforts, Rudebusch (2000) was unable to find any statistically significant increase in potential output (corrected for cyclical movements using the demographics-adjusted unemployment rate).[4] This sort of new economy looks very much like the same old economy. Indeed, 1995–2000 productivity growth was considerably below that experienced in the period 1960–68 just preceding the great inflation. We believe that the evidence is fully consistent with normal procyclical patterns.

In summary, although changes in the rate of metamorphic progress might explain a new economy increase in potential-output growth, we do not believe that has occurred in recent years. Landefeld and Fraumeni (2001) provide a nice review of the debate and measurement issues in regard to the new economy hypothesis.

II. PATTERNS OF INDUSTRIAL FORMATION

The typical pattern of formation of new industries involves a few firms initially entering, growing to many, and ultimately consolidating, producing the curve shown in Figure 2 for number of firms. When the number of firms stabilizes or begins to decline, that does not necessarily imply that the overall industry size also declines. What typically happens instead is that the remaining suc-

Figure 2
The Four Stages of an Industry's Life Cycle



cessful entrants grow fast enough that the overall size of the industry continues to increase (as does the average size of the remaining firms), as shown in the industry gross domestic product share curve in Figure 2. Costs of adjustment in size are generally nonlinear, with fixed costs of adjustment rather than the standard assumption of convex adjustment costs, as the review of evidence in Haltiwanger (1997) shows.[5] Thus the peak number of firms is reached at a time when industry output is still growing. The general form of the industry life cycle shown in Figure 2 has been strongly supported in empirical research.

We first review the findings relevant to our main line of argument in the population or organizational ecology approach in the sociology/management literature. We then do the same for the more familiar (to economists) industrial organization literature concerned with learning by firms under competition. We aim to place our own approach in a broader context, not to attempt a global review.

Organizational Ecology

Populations of organizations emerge sharing the same organizational form, meaning central or core design. Reviews by Baum (1996) and Singh and Lumsden (1990) identify a wide range of organizational forms, including savings and loan associations, hotels, life insurance companies, day care centers, semiconductor firms, and California wineries. The mixture of private and public organizations is typical of ecological research and represents exploitation of available data resources rather than systematic comparison across these two sectors.

Most ecological research gathers data on the initial or at least early growth of each organizational form and sometimes captures the full life cycle of a population as shown in Figure 2. Organizational ecology focuses attention on the founding/birth of firms and on the population dynamics that support moving from the initial founding of a single firm to emergence of a new industry. Clearly, a population is generally a significantly narrower group of firms than an industry and has the advantage of studying proto-industries during the process of their development.

The hypothesized shape of the number of firms curve shown in Figure 2 has been broadly supported across strikingly different empirical settings, as shown for trade associations by Aldrich and Staber (1988, Figures 7-2 to 7-5), local units of Mothers Against Drunk Driving by McCarthy et al. (1988, Figures 5-1 and 5-2), labor unions by Carroll and Hannan (1989, Figure 1), telephone companies by Barnett and Amburgey (1990, Figures 4.1 and 4.3), and Finnish newspapers by Miner et al. (1990, Figures 1, 2, 3). But theory development has not kept pace with empirical work, and the framework within which results can or should be interpreted is often unclear, contradictory, or disconfirmed. Variables proliferate with few validity tests and tenuous relationships to theoretical

dimensions of central interest; central theoretical constructs often have no clear empirical referents.[6]

Probably the most robust thread in ecological theory is organizational form, introduced explicitly and developed in McKelvey (1982), McKelvey and Aldrich (1983), and Romanelli (1991). Processes by which new forms are developed include imprinting at the period of emergence in Stinchcombe (1965), and the source and emergence of varieties of forms in Brittain and Freeman (1986), Marrett (1980), and Aldrich and Waldinger (1990).

What underlies the initial emergence and early growth of a new organizational population? Ecological research has only recently gone beyond measuring the effects of the number of prior births on the number of births in the next period, called population dynamics, and the number of organizations in a population in the prior period, called population density. Zucker et al. (1998c) show that fundamentals of resource reallocation and mobilization, coupled with resource quality, provide significantly stronger predictive power, especially in predicting location of growth than population dynamics or density. We report repeated dynamic simulations demonstrating that population ecology model predictions are essentially uncorrelated with the panel data on biotechnology entry by year and region, whereas our alternative model has correlation coefficients averaging above 0.8.

Industrial Organization

Most theory and research in industrial organization (hereafter, I/O) begins where organizational ecology leaves off. Ecology-based research focuses on the history of development of an organizational population—the process of industry emergence. I/O research has been primarily concerned with firms in mature industries and processes central to mature industries life cycles, including growth and turnover, as Caves's (1998) recent review indicates. In mature industries, observed differences in profitability, productivity, industry output shares, investment, and similar variables provide the basis for entry by the firm as well as the basis for later changes in firm strategy, predicting growth and turnover in industries.

Studies in industrial organization broadly support the pattern of change shown in Figure 2 but only for a subset of companies operating in mature industries, as Caves summarizes (1998, 1958–59): "Hazard rates for incumbents are lower than for entrants through all stages of the cycle in 'non-technical' products (where experience advantages might be great)," but "higher for 'technical' products, where entrants bring the continuing flow of innovations." The latter results come from Audretsch (1991). Klepper and Miller (1995) and Klepper (1996) show that the number of firms offering a product reaches a long-run stable equilibrium after declining from an early peak through a prolonged, steady

shakeout phase that suggests continuing competition among firms to reduce costs rather than initial entry that overshoots the potential market.

I/O research is based directly on economic theories of competition. From the I/O perspective (Caves, 1998, 1947, note 2), organizational ecology "suffers from eschewing simple priors about business behavior: intended profit-maximization and the need to cover costs to keep a firm's coalition together." Hence, the orienting theories underlying population ecology and I/O are sufficiently different that there has been little cross-fertilization, despite empirical research on the same or very similar underlying processes.[7]

Our research program seeks to build a bridge between these two related approaches by bringing organizational ecology's focus on industry emergence into a model that includes wealth maximization and measures of resources (e.g., intellectual human capital of the stars, venture capital), competencies (e.g., main technology employed), and external environment (beyond other firms to include top-quality universities and other local characteristics, as well as quality of the local labor force and national cost of capital).

In standard I/O studies, two major theoretical approaches have developed over the past two decades to deal with empirical inconsistencies with earlier models, such as the law of proportionate growth. Central to both are the processes of learning by and the characteristics of the information available to firms in an industry. Learning about the decisions and success of other firms, as well as your own firm through its experience, improves the firm's efficiency and hence growth and survival.

Most models of competition and growth are more suited to manufacturing and other routinized production contexts where the main source of uncertainty is arguably how an entering firm will perform relative to existing firms in that same industry. In Jovanovic (1982) and Lippman and Rumelt (1982), firms learn about their competitiveness only after entry through experience relative to that of other firms. Because costs are random and different between firms, a potential entering firm does not know its own expectation but knows the distribution of all firms' costs in that industry. Firms differ in size because some discover that they are more efficient than others, not because of fixity of capital. These models have proven themselves in numerous empirical studies of mature industries as reviewed by Caves (1998).

Recent large-scale research in I/O has documented the variability of the performance path of individual firms, as shown especially in panel studies by Davis and Haltiwanger (1992) and Pakes and Ericson (1998). A recent model developed by Ericson and Pakes (1995) explicitly incorporates firm-specific changes in investment in response to changes in uncertainty and to evolution of competing firms and other industries. The success of the firm in terms of profitability and value is determined by the stochastic outcome of its investment, within the context of success by other firms in the same industry and the con-

text of competitive pressures from new entry and other industries.

This model endogenizes the processes of selection in industry evolution and thus both entry and exit. Industry-level dynamics are predicted to develop over time in an increasingly regular way, spending more time in natural states, including number of incumbents and entrants and exits, but failing to reach a limit. The Ericson-Pakes approach provides a more complete model of firm behavior in industries where production is not routine but where central tasks are invented and reinvented as the frontiers of knowledge develop, whether due to technological breakthrough or other kinds of invention, from quality circles to new financial instruments.

III. FINDINGS FOR BIOTECHNOLOGY AND OTHER SCIENCE-DRIVEN TECHNOLOGICAL REVOLUTIONS

The process underlying metamorphic progress is defined by the introduction of a new breakthrough technology that either eliminates the ability of firms practicing the old technology to survive or creates an entirely new industry.[8] If the technological breakthrough relies on the same scientific and engineering base as the previous technology, incumbent firms are generally strengthened as they readily convert to the new technology. Focusing on what happens to incumbent firms, Tushman and Anderson (1986) refer to these changes as competence-enhancing. If the science and engineering base of the new technology is disjoint from that of the existing technology, existing firms tend to shrink and exit and many new entrants arise practicing the new (incumbent's) competence-destroying technology (Tushman and Anderson, 1986; Henderson, 1993).

We emphasize whether the breakthrough technology is *incumbent-enhancing* or *entry-generating*. Incumbent-enhancing breakthroughs are the same as Tushman and Anderson's competence-enhancing breakthroughs. Entry-generating breakthroughs include both their competence-destroying technologies and breakthroughs that create whole new industries. The key example of entry-generating breakthroughs is the entrepreneurial start-up phase in high-technology industries characterized by a high valuation on ability to practice the new technology while any incumbent firms' expertise in a previous technology becomes obsolete and, often, a barrier to adoption of the new technology.

Much recent research—including ours—has concentrated on industries being formed or transformed in response to entry-generating technological breakthroughs. Nonetheless, Tushman and Anderson (1986) provide an impressive list of incumbent-enhancing breakthroughs, and the recent work by Harberger (1998) and his associates suggests that metamorphic progress of this type is also a relatively frequent feature of a growing economy. In contrast, we (Darby and Zucker, 2001; Zucker and Darby, 2001) found in Japan that the technological breakthroughs that led to a wave of entrepreneurial start-ups in the

United States were adopted more or less successfully either by established firms with congruent scientific bases that took advantage of the opportunity to enter new industries or by technological transformation of incumbent firms. The key institutional difference that appears to have led to different metamorphic processes in the two countries was the (recently relaxed) Japanese prohibition on public offerings of stock in firms without an established record of substantial profitability. The extraordinary length of private financing implied by this prohibition effectively eliminated the possibility of Japanese startup firms financed by venture capitalists.

Research on the formation/transformation entrepreneurial phase in high-technology industries has proceeded far enough that we can begin to define and (in some cases) tentatively answer key questions about processes that shape metamorphic change and ultimately the total rate of technological progress in the economy. We focus here on entry-generating breakthroughs, but incumbent-enhancing metamorphic change also may be important for technological progress.[9]

Many Are Called, but Few Are Chosen

Entry-generating breakthroughs are characterized by a formation phase of perhaps 10 to 20 years (see Figure 2) during which many more firms enter the industry than will survive in the long run. In the following consolidation or shakeout phase of perhaps 10 to 30 years, most of these firms are either absorbed by the industry's winners or leave the industry at their owners' initiative or that of their creditors.[10] This occurs even as industry output continues to grow dramatically; average (surviving) firm size grows even more rapidly. The consolidation phase may be followed by an extended period of stability corresponding to the standard price-theory model of entry and exit maintaining zero-economic profits and optimal firm size. A final phase of decline is not necessary but often observed. Alternatively, the entire process may be interrupted in any phase by another metamorphic breakthrough.

Why are so many more new firms or new operations of existing firms created than are really needed? Is their creation and destruction a case of organizational waste and entrepreneurial misjudgment or is firm-number overshooting valuable and entry *ex ante* justified? Uncertainty about which entrants will be most successful in implementing the new technology is sufficient for the observed pattern to be efficient, as shown by Jovanovic and MacDonald (1994) and Ericson and Pakes (1995), and recently elaborated by Bernardo and Chowdhry (2002).

For incumbent-enhancing breakthroughs it is obvious that the most successful implementers will be among the incumbent firms where much expertise relative to the technology and cooperative technologies is present. Indeed, one or more of these firms is likely to be the source of the breakthrough. Though inventing and early adopting incumbent firms are likely to improve their stand-

ing in the industry (Tushman and Anderson, 1986), there is no reason for any outsiders to enter in the expectation that they will outcompete the incumbents. Thus the overshooting of firm numbers is characteristic of only entry-generating metamorphic progress.

Although there are many hopeful entrants in the latter case, few of them typically survive. For example, Table 1 presents some data on new U.S. biotechnology firms in 1989 drawn from a study we did with Jeff Armstrong (Zucker et al., 2002). The first of these firms was founded in 1976 to exploit the string of technological breakthroughs in the life sciences, most of which followed directly or indirectly from the invention of genetic engineering as reported by Cohen et al. (1973). Firm formation accelerated after the 1980 U.S. Supreme Court decision that upheld the patenting of engineered cells and cell parts and the underlying recombinant-DNA technology covered by the Cohen-Boyer patent (1980). By 1990 over half of the employees in the industry were concentrated in the top 10% of the firms, and over two-thirds of the industry were in the top 20% of the firms. Figure 3 illustrates these data and shows that the same top 21 firms (out of 211) also accounted for 54% of the growth in employment from 1989 to 1994.[11] More generally, Lamoreaux and Sokoloff (2002, Table 6) show that U.S. patents have been concentrated in a relatively few career inventors since the 1870s.

Academic Science Matters a Lot

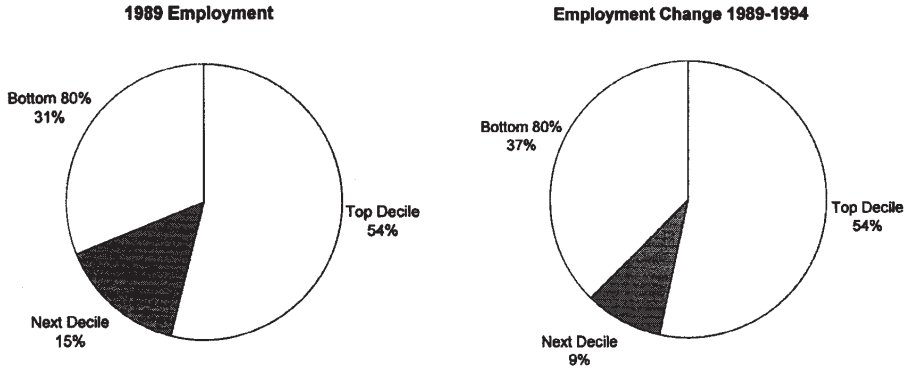
Entry-generating metamorphic progress almost always arises from outside the industry(ies) to which it will be applied. Many observers have pointed to anecdotal evidence of the importance of research universities as a source of breakthroughs that have created such regions as the Silicon Valley around Stanford; Route 128 around MIT and Harvard; and the Research Triangle Park around Duke, the University of North Carolina–Chapel Hill, and North Carolina State University.[12] Mansfield (1995) documents the important role played by academic research in even incremental industrial R&D, that is, in perfective progress.

Table 1
Concentration of Employment in New Biotech Firms, 1989

	Number of firms	Employment in 1989 (%)
Top decile	21	53.8
Next decile	21	15.0
Bottom 80%	169	31.2
Totals	211	100.0

SOURCE: Calculations of the authors for the biotech-using firms that disclosed employment for 1989 and 1994 and were formed after 1975 in the Zucker et al. (2002) database.

Figure 3
Concentration of U.S. New Biotechnology Firms' 1989 Employment and Employment Change 1989–94



A stream of recent research on innovation in the United States has found evidence of "geographically localized knowledge spillovers" occurring in areas around major universities: Jaffe (1986, 1989), Jaffe et al. (1993), Audretsch and Feldman (1996), and Henderson et al. (1998). The underlying assumption is that proximity to a major university itself provides technological opportunity; the localization is assumed to be due to the social ties between university and firm employees or to firm employees' access to seminars at the university. The importance of distance is strengthened by Adams and Jaffe's (1996) finding that geographic distance is an important impediment to flow of technology even within the firm.

Zucker et al. (1998b) and Darby and Zucker (2001) find that firms are more likely to begin using biotechnology near where and when "star" bioscientists are actively publishing in the United States and Japan, respectively. Although these findings have been cited as evidence of geographically localized knowledge spillovers, we read our results—and those of the other authors cited—as only demonstrating geographical localization of knowledge. Zucker et al. (1998a, 2002) and Zucker and Darby (2001) show for California, the United States, and Japan, respectively, that university effects on nearby firm R&D productivity are highly concentrated in the particular firms with bench-science working relationships with top academic scientists and practically absent otherwise. We identify these academic-firm *links* by the academic scientist publishing a journal article that also has one or more firm-affiliated authors.[13] Table 2 and Figure 4 indicate the close connection between links to top research university faculty and success: ranking firms by their linked articles up to 1989 does about as well as ranking by 1989 employment at predicting the 1989–94

Table 2
Relation of Employment in New Biotech Firms to Links to High Science as Represented by Articles Coauthored with Scientists in Top 112 Research Universities

	Number of firms	Employment in 1989 (%)	Employment change 1989–94 (%)	Core links to top universities (%)	Other links to top universities (%)
By 1989 employment					
Top decile	21	53.8	53.2	76.4	79.4
Next decile	21	15.0	9.4	6.2	4.0
Bottom 80%	169	31.2	37.4	17.4	16.6
Totals	211	100.0	100.0	100.0	100.0
By core links					
Top decile	21	48.7	53.4	94.0	81.5
Next decile	21	7.1	4.6	5.1	7.7
Bottom 80%	169	44.2	42.0	0.9	10.7
Totals	211	100.0	100.0	100.0	100.0

SOURCE: Calculations of the authors for the biotech-using firms that disclosed employment for 1989 and 1994 and were formed after 1975 in the Zucker et al. (2002) database.
NOTES: Core links are a count of articles published through 1989 in journals directly related to biotechnology indexed by the Institute of Scientific Information and with one or more authors affiliated with the firm and one or more authors affiliated with any of the top 112 U.S. research universities in terms of receipt of federal research funding. Other links are a count of articles published through 1989 in journals not directly related to biotechnology indexed by the Institute of Scientific Information and with one or more authors affiliated with the firm and one or more authors affiliated with any of the top 112 U.S. research universities in terms of receipt of federal research funding.

employment increase. Put another way, an investor who restricted his or her biotech portfolio at the end of 1989 to only the 22.7% of firms with any linked firm-research university core biotech publications or the 10.9% with more than one or two of these would include all of the top 10 firms and nearly all of the base-hit firms. The message of these simple correlations holds up in the context of poison regressions which allow for other determinants. Figure 5 reports the strong estimated effects of these linked articles on firm research productivity in California and Japan.[14]

Fieldwork—supported by analysis of the timing of the academic scientists' first articles with a firm and its founding—indicates that these academic-firm copublishing relationships most often connote that the academic scientist was a firm founder or at least presently has a significant financial interest in the firm.[15] Indeed, Herbert Boyer, of the Cohen-Boyer team who discovered recombinant RNA or genetic engineering, and entrepreneur Robert Swanson founded the first of the new biotech firms (Genentech). Similarly, Torero (1998) finds that a few hundred top scientists and engineers account for a large part of the patenting in the semiconductor industry, and firm success depends heavily on the degree of involvement of those stars in a firm. Where and when these star semiconductor

Figure 4
Concentration of New Biotechnology Firms' Links to Top Research Universities for 1989 Employment Deciles

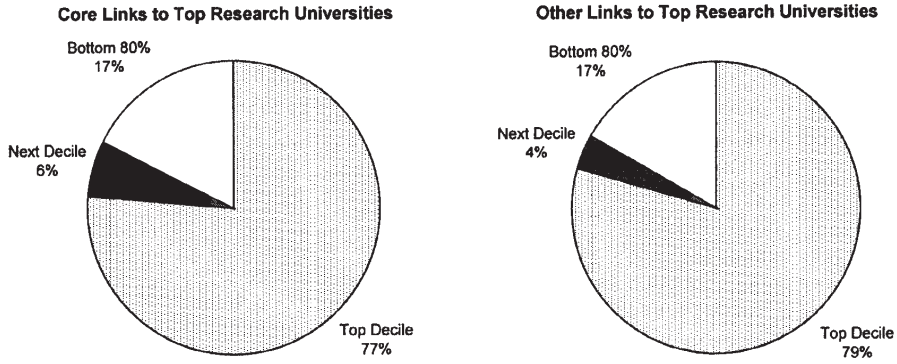
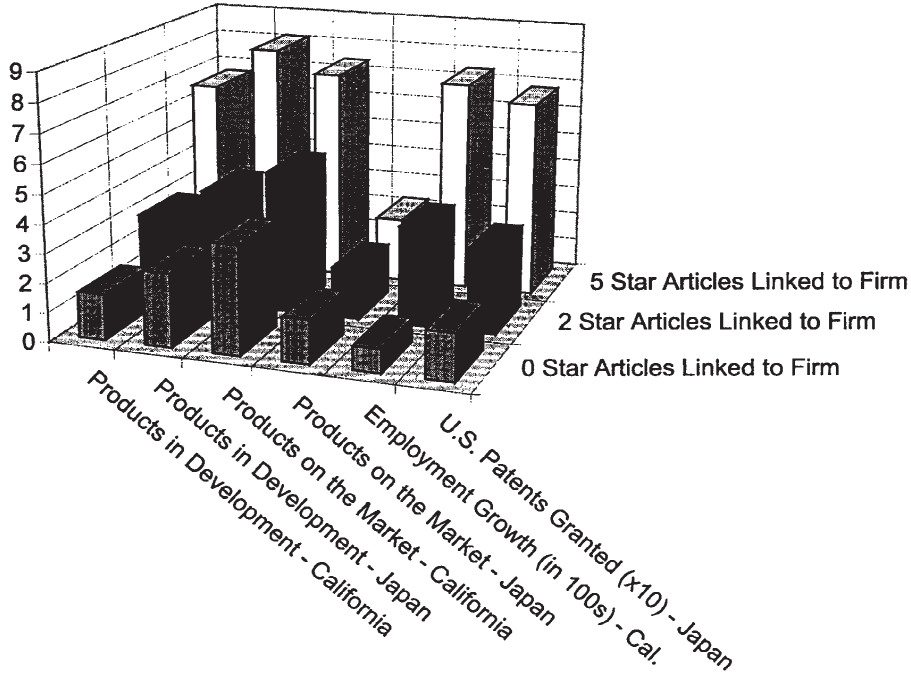


Figure 5
Estimated Effects of Number of University Star-Firm Linked Articles on Success of Californian and Japanese Biotechnology-Using Firms



scientists and engineers are working is an important determinant of where and when new semiconductor firms are established (Torero et al., 2001).

IV. NATURAL EXCLUDABILITY AND THE DIFFUSION OF METAMORPHIC BREAKTHROUGHS

The central role of a relatively small number of scientists and engineers in determining success of high-technology firms forces us to rethink the nature of technology. Economists have traditionally analyzed technology as if it were a public good with a marginal cost of (re)production of zero (Nelson, 1959; Arrow, 1962). Despite the seminal works of Stigler (1961) and Becker (1964) spawning the vast literatures on the economics of costly information and human capital, most analyses of technology including the "new" endogenous growth models typically conceive of technology as information that can be recorded on a floppy disk and then be costlessly reproduced and applied. Romer (1990), for example, acknowledges that this nonrivalrous characterization is an idealization but argues that it is much more expensive to create a new technology than learn it and that the idealization is harmless. We disagree.

When a major scientific breakthrough occurs and creates the opportunity for a corresponding incumbent-enhancing or entry-generating technological breakthrough, it may be very difficult for anyone other than the discovering scientists or their close working associates to reduce the discovery to technological practice. The ideas are far from codified and even the discovering scientists are not sure exactly what it is that they are doing, which is crucial. Published results—including those in a patent—may not be reproducible unless the reproducing scientist goes to the discoverer's lab and learns by doing with him or her.[16] In biotechnology, patent disclosures are often made by deposit of a cell line with an independent agent so that they will be publicly available at the expiration of the patent term: it is simply not possible to write down what a person skilled in the art would have to do to obtain the same organism.

Breakthrough discoveries leading to metamorphic growth are often of the same nature as Griliches's (1957, 1960) classic case of corn hybridization: *an invention of a way of invention.* Such platform technologies involving new techniques and instrumentation are typically hard to work with at first, and their diffusion is based on learning-by-doing-with at the laboratory bench: that is, by immediate observation and practice with someone who holds the tacit knowledge of how to make the technique work.

Not only are breakthrough discoveries often characterized by extensive tacit knowledge, only a relatively few top scientists near the frontier of the area are likely to be able to figure out how the discovery might be used to actually produce something of economic value. Although everyone might want to pluck the newly available low-lying fruit, not everyone can see where they are. The

late Robert Swanson, founding CEO of Genentech, liked to tell the story of how the firm obtained such a favorable royalty deal for Humulin® (human insulin produced by genetically modified bacteria) from the usually shrewd bargainers at Eli Lilly and Co. The scientists there were so sure that Herbert Boyer and Genentech were attempting the impossible that no serious bargaining was done until Genentech notified Lilly that they were holding a press conference announcing success in three days.

We say that this embodied knowledge—transferred slowly only by learning-by-doing-with—is characterized by *natural excludability*. Even if the university is assigned a patent to the discovery, most of the value accrues to the discoverers because without their cooperation the patent cannot be used. Our fieldwork for biotechnology and more general studies by Jensen and Thursby (2001) and Thursby and Thursby (2002) support the natural excludability hypothesis. For example, in the Jensen and Thursby (2001, 243) survey of Technology Transfer Office managers, "For 71 percent of the inventions licensed, respondents claim that successful commercialization requires cooperation by the inventor and licensee in further development."

Diffusion with Natural Excludability

If new metamorphic technologies were really like software on a disk, diffusion of this highly profitable knowledge would be limited only by the speed with which people realize the value of the new processes (Mansfield, 1961; Griliches and Schmookler, 1963). In contrast to this potentially infinite rate of adoption, natural excludability limits the extent of diffusion to an exponential times the number of discoverers.

To see this, consider biotechnology in 1973 and suppose that six people in two laboratories knew how to do genetic engineering (recombinant DNA). Suppose one knowledgeable person can transfer the knowledge to at most one person per year. Then the maximum number of potential practitioners of the art in year t ($t = 0$ in 1973) is $6 \cdot 2^t$. Even if this rapid rate of diffusion were possible, there would only be $6 \cdot 2^{10} = 6{,}144$ potential practitioners of genetic engineering in 1983, each of whom would still be earning a very large shadow wage. Over time, the value of the knowledge declines as the number of practitioners increases until new apprentices earn only the normal human capital return to their investment in learning the knowledge.

Thus there is a varying period of time during which the discoverers and early learners derive supranormal returns from practicing their knowledge and also benefit from lower-cost assistants due to the implicit tuition chain. This period of time can be long enough to significantly impact the formative period of a new industry, such as biotechnology or nanotechnology, or transformative periods, such as have occurred in semiconductors. We have formulated a much

more elaborate model involving multiyear learning in a lab with the number of learners in the lab and their probability and lag to leading their own lab, all as a function of the value of the knowledge, but the basic message of at most exponential growth from a small base remains intact. Zucker et al. (2002) illustrate both the geometric growth in scientists publishing their first paper reporting a genetic-sequence discovery and the continuing tacit nature of the knowledge.[17]

Discovering and other top scientists and engineers play a key role in metamorphic progress as we have seen so far for biotechnology and semiconductors, lasers as described by Sleeper (1998), and nanotechnology (based on our new research). We believe that natural excludability makes this role a frequent feature of metamorphic progress. Note that even where university professors follow the rules and promptly disclose inventions for patenting by the university under the Bayh-Dole Act, the value of those patents is impacted by the usual necessity to license the patent to a firm and on terms such that the discovering professors are willing to cooperate in the commercialization process.

V. UNSETTLED WELFARE AND POLICY ISSUES

Academic purists often express concerns about faculty involvement in commercialization of their discoveries. These concerns include: (1) lost scientific productivity of the scientists, (2) reduction in the amount of science contributed to the common pool by publishing, (3) deflection of the development of science toward more commercially relevant problems, (4) conflict of interest leading to scientists' distorting their findings, and (5) conflict of commitment to the university. Our research can shed light on some of these concerns, but others remain open issues. We do not consider more radical objections to scientific progress and productivity growth because we believe that these are well answered in more general debates.

Lost Scientific Productivity of the Scientists

One of the initial motivations of the biotechnology study that spawned our current larger growth, science, and technology project was to examine the cost in lost scientific productivity of commercial involvement of the very best academic bioscientists. Surprisingly, we found robust evidence that scientific productivity of these scientists increases during their commercial involvement (as compared to their own productivity before or after) on the standard measures of publications and citations to those publications (Zucker and Darby, 1995, 1996). To give an extreme example, the most commercially involved star scientists (those ever affiliated with a firm and with patents) have nine times as many citations as do star scientists who are never affiliated or linked to a firm and have no patents. About half of that difference reflects the fact that those who

become involved are more energetic to begin with, and the rest reflects the increase in publications per year and citations per publication during their years of firm involvement.

In the half-decade since we first published those findings, we have further tested them on an expanded U.S. data set using improved methodology and replicated them for Japan. Because publishing increases robustly for scientists working with firms, we were forced to reconsider our initial assumptions. First, the delays in publication required for patenting by firms are typically on the order of three months, and universities also require delay while they prepare patent applications with possibly less efficiency. Furthermore, purely academic scientists also may prefer to delay publication for strategic reasons; one respondent put it this way: "When I was a pure academic, I didn't exactly throw away my lead by publishing rich discoveries until I put together three or four articles following them up." We may not only have overestimated the increased returns to secrecy but also missed two factors that seem to swamp any higher value for secrecy.

The first countervailing factor is that commercial involvement gives the scientists much more resources to do their work. Not only are venture capitalists and investment bankers easier funding sources (per dollar) than the National Institutes of Health or the National Science Foundation, but it permits scientists the luxury of research assistants who are highly experienced and skilled long-term employees instead of first-year graduate students performing an assay or protocol for the first time.

The second countervailing factor is that the best scientists really love doing science! That is, doing science is a luxury good for which the income elasticity is greater than 1. When their company goes public, they consume not only more Ferraris but more experiments.[18]

Reduction in the Amount of Science Contributed to the Common Pool by Publishing

These concerns in part refer to publishing activities by scientists who are commercially involved and those have been addressed. There is, however, a broader concern that the commercialization of science will reduce the amount of publishing by scientists generally—thus reducing the positive externalities that enrich the entire enterprise. Put another way, extensive faculty involvement in the commercial world may import commercial norms of trade secrecy into the academy. Our evidence suggests that just the opposite is true and that the new biotech firms—largely started with active faculty as principals—have exported academic values of publishing to the industries in which they are involved. The new biotech firms were a major organizational form/design innovation that forced the surviving incumbents to permit and reward journal publication to

compete for the best and brightest scientists who are needed for the firm to survive and prosper. As the top research executive at one of the largest pharmaceutical firms put it:

> We see some danger of losing our competitive advantage by publishing, but a much greater danger if we do anything that deters the best scientists from coming here. Further, we need for our scientists to have great reputations in order to bring others like them to [the firm]. We are the beneficiaries of world-wide scientific research, and thus we also need to contribute to this pool of scientific knowledge, creating a public good....Relative to new biotechnology firms, [we] may believe more strongly in the commonality of research tools because we have a wider array of methodologies and products. (Zucker and Darby, 1997, 438–39).

Table 3 is an extract of the top and other references (i.e., nonpatent references) section from Goeddel and Heyneker's (1982) U.S. Patent 4,342,832, assigned at issue to Genentech. The patent was applied for in July 1979 and cites related work by the inventors (Goeddel et al., 1979). Note the extensive citations to other work published in leading academic journals, indicating the continuity between basic science and new intellectual property in the science-driven industries. Indeed, much research done at firms is openly published either without a patent or shortly after one is applied for. In the most successful firms, world-class scientists are more likely to follow high-stakes, high-return R&D strategies instead of more predictable incremental strategies, as indicated by the larger jump-size in their stock price when success or failure is revealed (Darby et al., 2002).

The evidence is clear that the involvement of university faculty in commercialization of their discoveries has widened the norms of publication of research results into the very science-driven industries where there is the most to be learned from firm research. It is hard to credit that other university scientists are publishing less while those directly involved are publishing more; so we conclude that there has likely been an overall increase in the propensity to publish research results rather than the hypothesized decrease.

Deflection of the Development of Science Toward More Commercially Relevant Problems

We believe that the trajectory of science is bent to a degree toward more commercially relevant problems. Just as provision of government research funding targeted to politically important issues would seem to have some impact on the trajectory of science, we would expect that the availability of commercial funding should also have an impact. However, it is very hard to develop a counterfactual trajectory for science, so our evidence is indirect: Zucker et al. (2002)

Table 3

Extract from U.S. Patent 4,342,832, Assigned to Genentech Illustrating Close Ties to Academic Science

United States Patent 4,342,832
Goeddel et al. August 3, 1982

Method of constructing a replicable cloning vehicle having quasi-synthetic genes

Abstract

Described are methods and means for the construction and microbial expression of quasi-synthetic genes arising from the combination of organic synthesis and enzymatic reverse transcription from messenger RNA sequences incomplete from the standpoint of the desired protein product. Preferred products of expression lack bio-inactivating leader sequences common in eukaryotic expression products but problematic with regard to microbial cleavage to yield bioactive material. Illustrative is a preferred embodiment in which a gene coding for human growth hormone (useful in, e.g., treatment of hypopituitary dwarfism) is constructed and expressed.

Inventors: Goeddel; David V. (Burlingame, CA); Heyneker; Herbert L. (Burlingame, CA)
Assignee: Genentech, Inc. (South San Francisco, CA)
Appl. No.: 055126
Filed: July 5, 1979

...

Other references

Technology Review, pp. 12 and 13, Dec. 1976.
Martial et al., *Science*, vol. 205, Aug. 10, 1979.
Shine et al., *Nature*, vol. 285, Jun. 12, 1980, pp. 456–461.
The Economist, pp. 87 and 88, Jul. 14, 1979.
Time, Jul. 30, 1970, p. 70.
Newmark, *Nature*, vol. 280, pp. 637 and 638, Aug. 23, 1979.
Villa-Komaroff et al., *Proc. Natl. Acad. Sci.*, vol. 75, pp. 3727–3731, Aug. 1978.
Seeburg et al., *Nature*, vol. 276, pp. 795–798, Dec. 1978.
Itakura et al., *Science*, vol. 198, pp. 1056–1063, Dec. 1977.
Crea et al., *Proc. Natl. Acad. Sci.*, vol. 75, pp. 5765–5769, Dec. 1978.
Klenow et al., *Proc. Natl. Acad. Sci.*, vol. 65, pp. 168–175, Jan. 1970.
Sutcliffe, *Cold Spring Harbor Symposium* 43, pp. 70–90 (1978).
Curtis et al., *Molecular Cloning of Recombinant DNA*, by Scott et al., pp. 99–111 (1977).
Ullrich et al., *Science*, vol. 196, pp. 1313–1319, Jun. 1977.
Bolivar et al., *Gene* 2, pp. 95–113 (1977).
Goedel et al., *Proc. Natl. Acad. Sci.*, vol. 76, pp. 106–110, Jan. 1979.
Chang et al., *Nature*, vol. 275, pp. 617–624, Oct. 1978.
Maxam et al., *Proc. Nat. Acad. Sci.*, vol. 74, pp. 560–564 (Feb. 1977).
Kornberg, *DNA Synthesis*, pp. 87 and 88, pub. by W. H. Freeman & Co., 1974.
Razin et al., *Proc. Natl. Acad.*, vol. 75, pp. 4268–4270, Sep. 1978.
Wickens et al., *The Journal of Biological Chemistry*, vol. 253, No. 7, pp. 2483–2495 (1978).

find that bioscientists working in areas more directly relevant to human disease are more likely to become linked to firms, and, as noted, scientists who are linked to firms are both generally more productive of articles and citations to those articles and are significantly more productive during their linkage than they were previously. Thus there must be some impact of commercial relevance on the course of science. However, because more science is being done in total and progress in one area depends partly on progress in other areas, we cannot conclude unambiguously that there is less progress in the less commercially applicable areas than there would have been in the absence of commercial involvement.

Even if there were less science in the less commercially applicable areas, it does not follow that this is a cost rather than a benefit. In the case of biotechnology, it means that more people are being spared from death and spared from suffering from disease and starvation due to high food costs. Possibly it is appropriate that scientists weigh these benefits directly and in terms of their financial implications in choosing which problems to work on. Even in economics, there are some distinguished practitioners who argue that their science would be healthier if empirical relevance played a greater role in allocation of rewards and hence choice of problems.

Conflict of Interest Leading to Scientists' Distorting Their Findings

From time to time cases of scientific fraud emerge, and the fear is that this frequency is inevitably increased where scientists can profit directly from selling products or shares of stock based on such claims. This is probably a very small risk for star scientists who are likely at a robust corner solution due to reputations of immense value and realistic prospects for the Nobel and other major prizes. Where reputation value is less, one would expect that fraud increases with the returns. However, we do not normally argue against wealth creation on the grounds that it increases the incentives for theft and fraud.

Conflict of Commitment to the University

Finally, there is an argument that the opportunity to commercialize discoveries distracts faculty from the roles for which they are paid: to instruct, do research, and attend committee meetings. We can leave out any threat to research because that unambiguously increases in quantity and quality during commercial involvement, so the threat is concentrated in the areas of teaching and collegiality. Even for teaching, the issues are complicated by the extraordinarily high value of training received by apprentice researchers in the laboratories of scientists making valuable discoveries with natural excludability. If the possibility of working with such scientists increases the applications to the university in the relevant department(s) or school(s), can we truly say that their teaching output has decreased?

Moreover, in addressing the question of diversion from commitment to the university, we must face the issue that the roles or commitments of a professor are not standardized and are traditionally subject to individual negotiation as discussed by Stigler (1950) and Stinchcombe (1990). This immediately raises the issues of incentive packages and compensating differentials in wages of professors who—if they make a commercially valuable discovery—will tend to profit from the discovery as well as do more research and less teaching and collegiality. Normally, we would suppose that markets handle these contracting

issues rather efficiently, although not perfectly compared to a costless world (Darby and Karni, 1973; Aghion and Tirole, 1994). Possibly the complaints about conflict of commitments reflect more the feeling of some faculty in other departments that they work just as hard and should be equally rewarded by the market.

VI. CONCLUSIONS: A DRAFT RESEARCH AGENDA

The endogenous growth literature assumes that technology is a nonrivalrous recipe that is costly to discover but costless to replicate. We saw in section IV that for many industries undergoing metamorphic progress, technology instead possesses natural excludability, resides in particular individuals, and diffuses by learning-by-doing-with. That is, breakthrough technologies are better thought of as rivalrous human capital, not a recipe on a disk capable of free copying. It follows that the focus of the endogenous growth literature should shift from the theory of the firm toward understanding the motivations of discovering scientists to report or bootleg discoveries, to found new firms or cooperate with existing firms in commercializing their discoveries, and most important to do the initial research that creates the opportunity for a commercial breakthrough. Key issues largely ignored in the current growth literature include compensating wage differentials, incentive pay, rents and quasi-rents, and moral hazard along the lines of Aghion and Tirole (1994). Jensen and Thursby (2001), Thursby and Thursby (2000), and Zucker et al. (2002) explicitly pursue those issues.

If the most important breakthrough technologies are typically embodied in individual scientists and transferred or diffused by learning-by-doing-with, then the incentives to discover are considerably higher than conventionally analyzed even if the university or firm gets nominal ownership of the intellectual property rights in the discovery through a patent. The discoverers and patent owner have an interesting bargaining problem because the patent is worthless unless the discoverers cooperate with the licensee(s), often firms in which the discoverers have founders' interests. On the other hand, the angel investors and venture capitalists financing discovers' firms want to be sure that the intellectual property is secure and tied down, so the discoverers must either negotiate a reasonable agreement with their employers (the patent owners) or take extraordinary steps to document that the discoveries were not made with, say, university resources. Hence, the plethora of firm laboratories very near campuses and the attraction of university-adjacent science parks to ensure that follow-up discoveries clearly belong to the firms and not the universities.

Our approach also suggests that the analysis of spillovers (the science and technology literature's term for positive externalities) is basically flawed. The spillovers from the ivory tower that are widely used to explain geographically localized knowledge (i.e., increased research productivity for firms) in the

neighborhood of great research universities do not hold up to rigorous empirical analysis. Increased research productivity is very large in firms with specific identifiable links to discovering university scientists and engineers and otherwise nil or insignificant. The more important positive externalities associated with commercialization of university discoveries have been neglected in the literature. These are the *nonlocalized* spillovers associated with increased publishing by the university scientists working with the firms and by the scientists and engineers employed by the firms.[19]

We know from a great deal of empirical research in the field of growth accounting that technological progress together with growth in the average level of human capital are the ultimate determinants of growth in output per capita. The endogenous growth literature has started the important work of understanding the determinants of technological progress in an aggregate model. The aggregate models to date are oriented toward explaining what we call perfective progress—based on incremental R&D performed by incumbent firms. We argue that metamorphic progress is an equal or greater source of technological progress and that most often (but not always) metamorphic progress involves discoveries made by scientists and engineers external to the existing industry and involves embodied knowledge that is protected by natural excludability and diffused by learning-by-doing-with. We believe that building on these ideas will strengthen both the science and technology and the endogenous growth literatures with the ultimate result that we understand what institutional arrangements are most conducive to growth in the standard of living.

NOTES

An earlier version of this article was delivered as Michael R. Darby's presidential address at the Western Economic Association International Meetings, San Francisco, CA, July 6, 2001. The research has been supported by grants from the University of California's Industry–University Cooperative Research Program, the University of California Systemwide Biotechnology Research and Education Program, and the Alfred P. Sloan Foundation through the NBER Research Program on Industrial Technology and Productivity. We are indebted to many coauthors, postdoctoral fellows, and graduate and undergraduate research assistants who have contributed to the development of these ideas over the past decade. This article is part of the NBER's research program in productivity. Any opinions expressed are those of the authors and not those of their employers or the National Bureau of Economic Research.

[1] Abba Lerner (1953) also propagated the Crusonia plant.

[2] See, for example, the papers collected in Federal Reserve Bank of Kansas City (2001).

[3] If it were the point of the article, we would do a full analysis of productivity growth taking account of changes in capital, labor-quality adjustments for the hours worked, and procyclical movements in productivity (see Darby 1984a, 1984b). Before undertaking such an effort, we would want to see evidence of an interesting anomaly in cruder measures of productivity growth. Cen-

tral bankers saying that the economy works differently from before so that they can ignore the usual signs of monetary overstimulus hardly qualify as an anomaly.

[4] Rudebusch (2000) clearly walked a tight line between professional and institutional loyalty: "As noted above, there is, of course, always a large amount of uncertainty about estimates of the growth rate of potential output. Indeed, based on a strict statistical interpretation of Figure 1, there is a one in five chance that there has been no change in the growth of potential output in the 1990s."

[5] Growth in overall industry size can be attributed to movement down an elastic demand curve as more efficient, lower-cost producers replace higher-cost producers. The question is why it takes so long for the low-cost producers to emerge and drive out the others.

[6] Zucker (1989), Baum and Powell (1995), as well as the review articles by Baum (1996) and by Singh and Lumsden (1990), raise significant questions about the directions of theory and research in organizational ecology, while also stressing the value of particular empirical studies done under the ecology banner.

[7] Compare infant mortality in Wedervang (1965) to liability of smallness, ruling out age effects, in Freeman et al. (1983).

[8] New industries may eliminate or greatly reduce the size of other industries previously satisfying the fundamental function—for example, the advent of the automobile industry all but eliminated both the buggy and buggy whip industries. In principle, we could view the present automobile and vestigial buggy industries as a transformed personal land transportation industry, but it is not apparent what would be gained from such semantic niceties.

[9] The range and impact of incumbent-enhancing metamorphic change is suggested by Harberger's ongoing work on major cost reductions in existing industries.

[10] This process may interact with waves of optimism and pessimism about the future of an emerging industry. For example, despite a promising and ultimately successful pipeline of drug discoveries, Cetus faced a cash shortage during a phase of biotech pessimism and merged into Chiron.

[11] Note that we maintained the decile sorting by *level* of 1989 employment in Figure 3. If we had instead sorted by employment change along the lines of Harberger (1998), the top and second deciles so defined would account for 75.8% and 17.4% of the *net* employment change with only 6.7% left for the other firms. The bottom 80% (169 firms) on this basis includes 63 firms with negative change, 10 with no change, and 96 firms with positive employment change.

[12] See especially Dorfman (1988), Jones and Vedlitz (1988), Smilor et al. (1988), and Bania et al. (1993). There are, of course, other important sources of geographic agglomeration (see, for example, Head et al., 1995).

[13] Publications involving scientists at two firms are extremely rare. Furthermore, the scientists practice serial monogamy, usually writing with only one firm during his or her career and, in the alternative, writing with only one firm at a time.

[14] We introduce major methodological innovations in Zucker et al. (2002), exploiting a substantially broadened database, so that simple comparisons are not possible although the results are very supportive of the importance of academic-firm linked articles.

[15] In Japan, explicit principal status in a firm is forbidden to professors at the national universities. However, continuing unreported cash payments on the order of the scientist's salary are com-

mon (and rarely prosecuted, but see *Japan Times*, 1999, for a counterexample) as are lucrative corporate directorships promised when the professor "descends from heaven" at age 55 or 60 (i.e., postretirement).

[16] Sometimes when an important result is difficult to reproduce in another location, the entire laboratory is reproduced, including the placement of equipment down to the coffee urn. If the result can then be obtained, detective work ensues to figure out what features are crucial. In a similar vein, during our fieldwork we heard one distinguished scientist grumble that another "had stolen [his] best cloner." This is not a remark applicable to something easy to learn from material written on a floppy disk!

[17] Tacitness is indicated by the fact that the bulk of new authors reporting genetic-sequence discoveries for the first time were writing as coauthors with previously published discoverers, and this continued to the end of the data set (1994), as reported in Zucker et al. (2002).

[18] Milton Friedman reminds us that economists are not immune to this science as (tax-exempt or conspicuous?) consumption phenomenon: Irving Fisher amassed a fortune inventing a visible file system and founding one of the constituents of Remington-Rand. He used it to hire a sizable staff of assistants to compute $(X'X)^{-1}X'y$ in the days before electric calculators. The ability to estimate multiple regressions was a powerful professional advantage in the 1920s.

[19] We are indebted to Milton Friedman for this point.

REFERENCES

Adams, J. D., and A. B. Jaffe. "Bounding the Effects of R&D: An Investigation Using Matched Establishment-Firm Data." *Rand Journal of Economics*, 27(4), 1996, 700–21.

Aghion, P., and J. Tirole. "The Management of Innovation." *Quarterly Journal of Economics*, 109(4), 1994, 1185–209.

Aldrich, H., and U. H. Staber. "Organizing Business Interests: Patterns of Trade Association Foundings, Transformations, and Death," in *Ecological Models of Organizations*, edited by Glenn R. Carroll. Cambridge: Ballinger, 1988, 111–26.

Aldrich, H. E., and R. Waldinger. "Ethnicity and Entrepreneurship." *Annual Review of Sociology*, 16, 1990, 111–35.

Arrow, K. J. "Economic Welfare and the Allocation of Resources for Invention," in *The Rate and Direction of Inventive Activity: Economic and Social Factors*, edited by R. R. Nelson. Princeton: Princeton University Press, 1962.

Audretsch, D. B. "New-Firm Survival and the Technological Regime." *Review of Economics and Statistics*, 73(3), 1991, 441–50.

Audretsch, D. B., and M. P Feldman. "R&D Spillovers and the Geography of Innovation and Production." *American Economic Review*, 86(3), 1996, 630–40.

Bania, N., R. Eberts, and M. Fogarty. "Universities and the Startup of New Companies: Can We Generalize from Route 128 and Silicon Valley?" *Review of Economics and Statistics*, 75(4), 1993, 761–66.

Barnett, W. P., and T. L. Amburgey. "Do Larger Organizations Generate Stronger Competition?," in *Organizational Evolution: New Directions*, edited by J. V. Singh. Newbury Park, CA: Sage, 1990, 78–102.

Baum, J. A. C. "Organizational Ecology," in *Handbook of Organization Studies*, edited by S. R. Clegg, C. Hardy, and W R. Nord. London: Sage, 1996, 77–114.

Baum, J. A. C., and W. W. Powell. "Cultivating an Institutional Ecology of Organizations: Comment on Hannan, Carroll, Dundon, and Torres." *American Sociological Review*, 60(4), 1995, 529–38.

Becker, G. S. *Human Capital: A Theoretical and Empirical Analysis, with Special Reference to Education*. Chicago: University of Chicago Press, 1964.

Bernardo, A. E., and B. Chowdhry. "Resources, Real Options, and Corporate Strategy." *Journal of Financial Economics*, 2002, in press.

Brittain, J. W., and J. H. Freeman. "Entrepreneurship in the Semiconductor Industry." Paper presented at the 46th Annual Meeting of the Academy of Management, New Orleans, 1986.

Carroll, G. R., and M. T. Hannan. "Density Dependence in the Evolution of Populations of Newspaper Organizations." *American Sociological Review*, 54(4), 1989, 524–41.

Caves, R. E. "Industrial Organization and New Findings on the Turnover and Mobility of Firms." *Journal of Economic Literature*, 36(4), 1998, 1947–82.

Cohen, S., and H. Boyer. "Process for Producing Biologically Functional Molecular Chimeras." U.S. Patent number 4,237,224, granted December 2, 1980.

Cohen, S., A. Chang, H. Boyer, and R. Helling. "Construction of Biologically Functional Bacterial Plasmids in Vitro." *Proceedings of the National Academy of Sciences*, 70(11), 1973, 3240–44.

Darby, M. R. *Labor Force, Employment, and Productivity in Historical Perspective*. Los Angeles: UCLA Institute of Industrial Relations, 1984a.

———. "The U.S. Productivity Slowdown: A Case of Statistical Myopia." *American Economic Review*, 74(3), 1984b, 301–22.

Darby, M. R., and E. Karni. "Free Competition and the Optimal Amount of Fraud." *Journal of Law and Economics*, 16(2), 1973, 67–88.

Darby, M. R., and L. G. Zucker. "Change or Die: The Adoption of Biotechnology in the Japanese and U.S. Pharmaceutical Industries." *Comparative Studies of Technological Evolution*, 7, 2001, 85–125.

Darby, M. R., Q. Liu, and L. G. Zucker. "High Stakes in High Technology: High-Tech Market Values as Options." UCLA Working Paper, April 2002.

Davis, S. J., and J. Haltiwanger. "Gross Job Creation, Gross Job Destruction, and Employment Reallocation." *Quarterly Journal of Economics*, 107(3), 1992, 819–63.

Dorfman, N. S. "Route 128: The Development of a Regional High Technology Economy," in *The Massachusetts Miracle: High Technology and Economic Revitalization*, edited by D. Lampe. Cambridge, MA: MIT Press, 1988, 240–74.

Ericson, R., and A. Pakes. "Markov-Perfect Industry Dynamics: A Framework for Empirical Work." *Review of Economic Studies*, 62(1), 1995, 53–82.

Federal Reserve Bank of Kansas City. *Economic Policy for the Information Economy*. A Symposium Sponsored by the Federal Reserve Bank of Kansas City. Kansas City: Federal Reserve Bank of Kansas City, 2001.

Freeman, J., G. R. Carroll, and M. T. Hannan. "The Liability of Newness: Age Dependence in Organizational Death Rates." *American Sociological Review*, 48(5), 1983, 692–710.

Goeddel, D. V., and H. L. Heyneker. "Method of Constructing a Replicable Cloning Vehicle Having Quasi-Synthetic Genes." U.S. Patent number 4,342,832, granted August 3, 1982.

Goeddel, D. V., D. G. Kleid, F. Bolivar, H. L. Heyneker, D. G. Yansura, R. Crea, T. Hirose, A. Kraszewski, K. Itakura, and A. I. Riggs. "Expression in *Escherichia coli* of Chemically Synthesized Genes for Human Insulin." *Proceedings of the National Academy of Sciences*, 76(1), 1979, 106–10.

Greenspan, A. "Technology and the Economy." Remarks before the Economic Club of New York. New York, NY, January 13, 2000a.

———. "Technological Innovation and the Economy." Remarks before the White House Conference on the New Economy. Washington, DC, April 5, 2000b.

———. "Economic Developments." Remarks before the Economic Club of New York. New York, NY, May 24, 2001.

Griliches, Z. "Hybrid Corn: An Exploration in the Economics of Technological Change." *Econometrica*, 25(4), 1957, 501–22.

———. "Hybrid Corn and the Economics of Innovation." *Science*, 132(3422), 1960, 275–80.

Griliches, Z., and J. Schmookler. "Inventing and Maximizing." *American Economic Review*, 53(4), 1963, 725–29.

Haltiwanger, J. C. "Measuring and Analyzing Aggregate Fluctuations: The Importance of Building from Microeconomic Evidence." *Federal Reserve Bank of St. Louis Review*, 79(3), 1997, 55–77.

Harberger, A. C. "A Vision of the Growth Process." *American Economic Review*, 88(1), 1998, 1–32.

Head, K., J. Ries, and D. Swenson. "Agglomeration Benefits and Location Choice: Evidence from Japanese Manufacturing Investments in the United States." *Journal of International Economics*, 38(3–4), 1995, 223–47.

Henderson, R. "Underinvestment and Incompetence as Responses to Radical Innovation: Evidence from the Photolithographic Alignment Industry." *RAND Journal of Economics*, 24(2), 1993, 248–70.

Henderson, R., A. B. Jaffe, and M. Trajtenberg. "Universities as a Source of Commercial Technology: A Detailed Analysis of University Patenting 1965–1988." *Review of Economics and Statistics*, 80(1), 1998, 119–27.

Jaffe, A. B. "Technological Opportunity and Spillovers of R&D; Evidence from Firms' Patents, Profits, and Market Value." *American Economic Review*, 76(5), 1986, 984–1001.

———. "Characterizing the 'Technological Position' of Firms, with Application to Quantifying Technological Opportunity and Research Spillovers." *Research Policy*, 18(l), 1989, 87–97.

Jaffe, A. B., M. Trajtenberg, and R. Henderson. "Geographic Localization of Knowledge Spillovers as Evidenced by Patent Citations." *Quarterly Journal of Economics*, 63(3), 1993, 577–98.

Japan Times. "Professor Guilty in Drugs Bribes Case." *Japan Times International Edition*, April 18, 1999.

Jensen, R., and M. Thursby. "Proofs and Prototypes for Sale: The Tale of University Licensing." *American Economic Review*, 91(1), 2001, 240–59.

Jones, B. D., and A. Vedlitz. "Higher Education Policies and Economic Growth in the American States." *Economic Development Quarterly*, 2(1), 1988, 78–87.

Jovanovic, B. "Selection and the Evolution of Industry." *Econometrica*, 50(3), 1982, 649–70.

Jovanovic, B., and G. MacDonald. "The Life-Cycle of a Competitive Industry." *Journal of Political Economy*, 102(2), 1994, 322–47.

Klepper, S. "Entry, Exit, Growth, and Innovation over the Product Life Cycle." *American Economic Review*, 86(3), 1996, 562–83.

Klepper, S., and J. H. Miller. "Entry, Exit, and Shakeouts in the United States in New Manufactured Products." *International Journal of Industrial Organization*, 13(4), 1995, 567–91.

Knight, F. H. "Diminishing Returns from Investment." *Journal of Political Economy*, 52(1), 1944, 26–47.

Lamoreaux, N. R., and K. L. Sokoloff. "Inventive Activity and the Market for Technology in the United States, 1840–1920." Paper presented at the Second Annual Roundtable for Engineering Entrepreneurship Research, Atlanta, Georgia, March 21–23, 2002.

Landefeld, J. S., and B. M. Fraumeni. "Measuring the New Economy." *Survey of Current Business*, 81(3), 2001, 23–40.

Lerner, A. P. "On the Marginal Product of Capital and the Marginal Efficiency of Investment." *Journal of Political Economy*, 61(1), 1953, 1–14.

Lippman, S. A., and R. P. Rumelt. "Uncertain Imitability: An Analysis of Interfirm Differences in Efficiency under Competition." *Bell Journal of Economics*, 13(2), 1982, 418–38.

Mansfield, E. "Technical Change and the Rate of Imitation." *Econometrica*, 29(4), 1961, 741–66.

———. "Academic Research Underlying Industrial Innovations: Sources, Characteristics, and Financing." *Review of Economics and Statistics*, 77(1), 1995, 55–65.

Marrett, C. B. "Influences on the Rise of New Organizations: The Formation of Women's Medical Societies." *Administrative Science Quarterly*, 25(1), 1980, 185–99.

McCarthy, J. D., M. Wolfson, D. P. Baker, and E. Mosakowski. "The Founding of Social Movement Organizations," in *Ecological Models of Organizations*, edited by G. R. Carroll. Cambridge: Ballinger, 1988, 71–82.

McKelvey, B. *Organizational Systematics: Taxonomy, Evolution, Classification*. Berkeley: University of California Press, 1982.

McKelvey, B., and H. Aldrich. "Populations, Natural Selection, and Applied Organizational Science." *Administrative Science Quarterly*, 28(1), 1983, 101–28.

Miner, A. S., T. L. Amburgey, and T. M. Stearns. "Interorganizational Linkages and Population Dynamics: Buffering and Transformational Shields." *Administrative Science Quarterly*, 35(4), 1990, 689–713.

Nelson, R. R. "The Economics of Invention: A Survey of the Literature." *Journal of Business*, 32(2), 1959, 101–27.

Pakes, A., and R. Ericson. "Empirical Implications of Alternative Models of Firm Dynamics." *Journal of Economic Theory*, 79(1), 1998, 1–46.

Romanelli, E. "The Evolution of New Organizational Forms." *Annual Review of Sociology*, 17, 1991, 79–103.

Romer, P. M. "Endogenous Technological Change." *Journal of Political Economy*, 98(5), part 2, suppl, 1990, S71–S102.

Rudebusch, G. D. "How Fast Can the New Economy Grow?" *FRBSF Economic Letter*, number 2000–05, February 25, 2000.

Schumpeter, J. A. *The Theory of Economic Development*, translated by R. Opie. Cambridge, MA: Harvard University Press, 1934.

Singh, J. V., and C. J. Lumsden. "Theory and Research in Organizational Ecology." *Annual Review of Sociology*, 16, 1990, 161–95.

Sleeper, S. D. "The Role of Firm Capabilities in the Evolution of the Laser Industry: The Making of a High-Tech Market." Ph.D. dissertation, Carnegie Mellon University, 1998.

Smilor, R. W., G. Kozmetsky, and D. V. Gibson. *Creating the Technopolis: Linking Technology, Commercialization, and Economic Development*. Cambridge: Ballinger, 1988.

Stigler, G. J. *Employment and Compensation in Education*. New York: National Bureau of Economic Research, 1950.

———. "The Economics of Information." *Journal of Political Economy*, 69(3), 1961, 213–25.

Stinchcombe, A. L. "Organizations and Social Structure," in *Handbook of Organizations*, edited by J. G. March. Chicago: Rand McNally, 1965, 142–93.

———. "University Administration of Research Space and Teaching Loads: Managers Who Do Not Know What Their Workers Are Doing," in *Information and Organizations*, edited by A. L. Stinchcombe. Berkeley: University of California Press, 1990, 312–40.

Thursby, J. G., and M. Thursby. "Who Is Selling the Ivory Tower? Sources of Growth in University Licensing." *Management Science*, 48(1), 2002, 90–104.

Torero, M. "Analyzing the Spillover Mechanism on the Semiconductor Industry in the Silicon Valley and Route 128," in *Essays on Diffusion of Technical Change*, edited by M. Torero. PhD diss. UCLA Economics Department, 1998, 6–48.

Torero, M., M. R. Darby, and L. G. Zucker. "The Importance of Intellectual Human Capital in the Birth of the Semiconductor Industry." UCLA Working Paper, January 2001.

Tushman, M. L., and P. Anderson. "Technological Discontinuities and Organizational Environments." *Administrative Science Quarterly*, 31(1), 1986, 439–65.

Wedervang, F. *Development of a Population of Industrial Firms: The Structure of Manufacturing Industries in Norway, 1930–1948*. Oslo: Universitetsforlaget, 1965.

Zucker, L. G. "Combining Institutional Theory and Population Ecology: No Legitimacy, No History." *American Sociological Review*, 54(4), 1989, 542–45.

Zucker, L. G., and M. R. Darby. "Virtuous Circles of Productivity: Star Bioscientists and the Institutional Transformation of Industry." National Bureau of Economic Research Working Paper No. 5342, November 1995.

———. "Star Scientists and Institutional Transformation: Patterns of Invention and Innovation in the Formation of the Biotechnology Industry." *Proceedings of the National Academy of Sciences*, 93(23), 1996, 709–16.

———. "Present at the Biotechnological Revolution: Transformation of Technical Identity for a Large Incumbent Pharmaceutical Firm." *Research Policy*, 26(4, 5), 1997, 429–46.

———. "Capturing Technological Opportunity via Japan's Star Scientists: Evidence from Japanese Firms' Biotech Patents and Products." *Journal of Technology Transfer*, 26(1/2), 2001, 37–58.

Zucker, L. G., M. R. Darby, and J. Armstrong. "Geographically Localized Knowledge: Spillovers or Markets?" *Economic Inquiry*, 36(1), 1998a, 65–86.

———. "Commercializing Knowledge: University Science, Venture Capital, and Firm Performance in Biotechnology." *Management Science*, 48(1), 2002, 138–53.

Zucker, L. G., M. R. Darby, and M. B. Brewer. "Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises." *American Economic Review*, 88(1), 1998b, 290–306.

Zucker, L. G., M. R. Darby, and Y. Peng. "Fundamentals or Population Dynamics and the Geographic Distribution of U.S. Biotechnology Enterprises, 1976–1989." National Bureau of Economic Research Working Paper No. 6414, February 1998c.

Zucker, L. G., M. R. Darby, and M. Torero. "Labor Mobility from Academe to Commerce." *Journal of Labor Economics*, 2002, in press.

The Benefits to Society of New Drugs: A Survey of the Econometric Evidence

Frank R. Lichtenberg

Many economists believe that "new goods are at the heart of economic progress" (Bresnahan and Gordon 1997) and that "innovative goods are better than older products simply because they provide more 'product services' in relation to their cost of production" (Grossman and Helpman 1991). An industry whose propensity to generate new goods is among the highest is the pharmaceutical industry. It is one of the most R&D-intensive industries in the economy. Moreover, due in part to extensive FDA regulation, we have unusually good data about the launch and diffusion of new pharmaceutical goods. I have used these data to perform a number of econometric studies to assess the health and economic impacts of new drug development and use.

I hypothesize that people may obtain several kinds of benefits from using newer, as opposed to older, pharmaceutical products: longer life, improved quality of life, and reduced total medical expenditure. My studies have been designed to estimate the magnitude and value of these benefits and compare them with the cost of using newer drugs.

I have used a number of complementary approaches and data sources to address these issues. One study uses aggregate U.S. data to determine the contribution of new drug approvals to longevity increase. Several others use disease-level data that I constructed to evaluate the effect of pharmaceutical innovation on hospitalization rates and quality of life indicators (activity limitations, disability days). And several other studies have used individual-level data—or even data *below* the individual level.

Virtually all of my research is based on large, publicly available data sets, most of which were produced by federal agencies. These include the Vital Statistics—Mortality Detail files, the National Ambulatory Medical Care Survey, the National Hospital Discharge Survey, the National Health Interview Survey, the Medical Expenditure Panel Survey (MEPS), and unpublished FDA data obtained

via the Freedom of Information Act. The mortality data are based on a complete census of deaths in the United States, and most other data sets are based on large, representative samples of health care providers and households.

My studies are based on data covering all medical conditions (diseases) and all drugs. They therefore provide evidence about the health and economic impacts of new drugs *in general*, not the impacts of specific drugs or on particular diseases. While the methods I use could, in principle, be applied to specific drug classes or diseases, the number of observations about particular drugs and diseases in publicly available data sets is generally too small to obtain statistically reliable results.

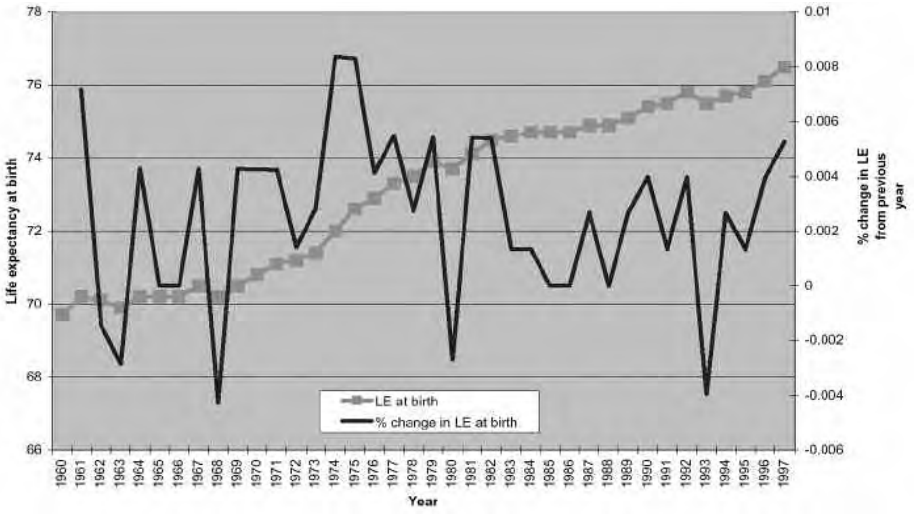
In the first section of this article I will describe some of my research about the impact of new drugs on longevity. In the next section, I will discuss quality-of-life effects, and in the third section, I will review my findings concerning the impact of new drugs on medical expenditure.

LONGEVITY

Between 1960 and 1997, life expectancy at birth increased approximately 10 percent, from 69.7 to 76.5 years. Nordhaus (2003) estimates that the value of life extension during this period nearly equaled the gains in tangible consumption.[1]

While life expectancy has tended to increase since 1960, as Figure 1 indicates, there have been substantial fluctuations in the rate of increase. Life

Figure 1
Life Expectancy at Birth, 1960–97: Trend and Fluctuations

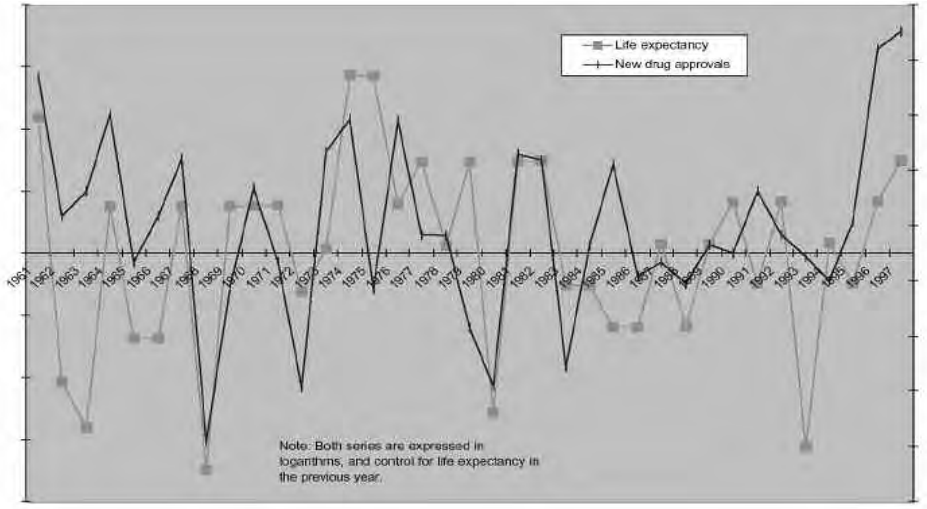


expectancy increased at an average annual rate of 0.25 percent; it increased more than 0.70 percent in 1961, 1974, and 1975, and declined more than 0.25 percent in 1963, 1968, 1980, and 1993. Measurement error is unlikely to account for much of the fluctuation in life expectancy. As noted in Anderson (1999, 34), "The annual life tables are based on a complete count of all reported deaths," and there are about 2 million deaths per year. Growth in real per capita income (GDP) also doesn't account for these fluctuations. The period in which life expectancy increased most rapidly (1973–75) was a period of dismal macroeconomic performance.

There is, however, a highly statistically significant relationship between the number of new molecular entities (NMEs) approved by the FDA and longevity increase: *The periods during which the most new drugs have been approved by the FDA tend to be the periods in which longevity grew most rapidly.*[2] This is consistent with the hypothesis that the greater the number of drugs that are available to physicians and consumers, the higher longevity will be.[3] The number of drugs available in a given year is not simply equal to the sum of the number of drugs approved in all previous years, since the introduction of new drugs may render older drugs obsolete. I estimate that the obsolescence rate of drugs is about 5 percent per year.

Figure 2 displays the relationship between life expectancy and the number of new drug approvals, holding constant life expectancy in the previous year, which, on theoretical grounds, it is appropriate to do. The estimates indicate that the average new drug approval increases the life expectancy of peo-

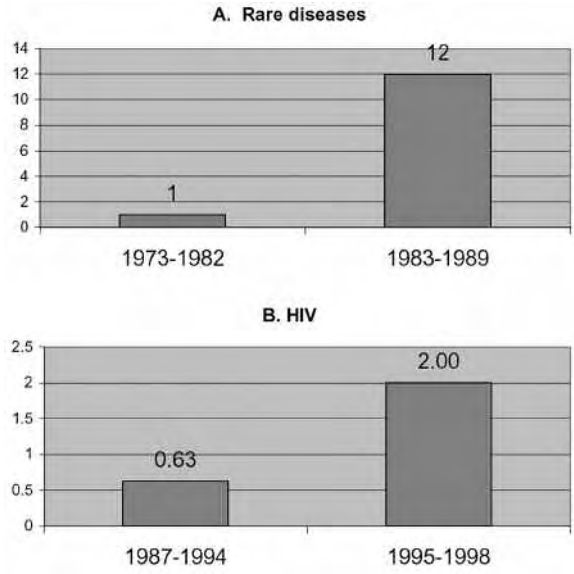
Figure 2
New Drug Approvals and Life Expectancy at Birth, 1961–97



ple born in the year that the drug is approved by 0.016 years (5.8 days). This may sound insignificant, but since there are approximately 4 million births per year in the United States, the average new drug approval increases the total expected life-years of the cohort by 63.7 thousand years (4 million births times .016 years/birth). New drug approvals in a given year also increase the life expectancy of people born in future years, but by a smaller amount (due to obsolescence of drugs).[4] I estimate that the average new drug approval increases the total expected life-years of current and future cohorts by 1.2 million. In other words, *current and future generations will live a total of 1.2 million life-years longer due to the average new drug approval.* The cost to the pharmaceutical industry of bringing a new drug to market is often estimated to be about $500 million. Hence cost per life-year gained is $424 ($500 million/1.2 million life-years). According to Murphy and Topel (2003), this is a small fraction of the economic value of a life-year, which they estimate to be on the order of $150,000.

Increased longevity, while desirable for its own sake, may also have positive implications for medical expenditure. A recent National Academy of Sciences study showed that costs in the final two years of life were lower for people who lived longer. "The older you are when you die, the less expensive the last two years are," said the study's principal author, Kenneth G. Manton, director of the Center for Demographic Studies at Duke University.[5]

Figure 3
Average Annual Number of Drugs Brought to Market



Case Studies of Orphan Diseases and HIV

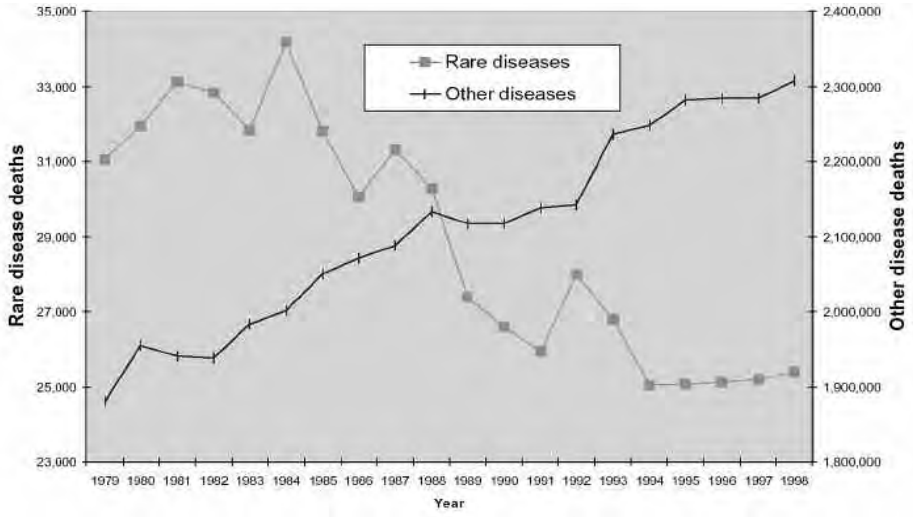
During the last two decades, there have been large, sudden increases in the number of drugs available to treat two kinds of diseases: "orphan" (rare) diseases and human immunodeficiency virus (HIV). As Figure 3 indicates, the average annual number of drugs for rare diseases brought to market during 1983–99 was twelve times as great as it was during 1973–82,[6] and the average annual number of HIV drugs brought to market during 1994–98 was three times as great as it was during 1987–93.

These increases occurred for different reasons and under different circumstances. The increase in drugs for rare diseases occurred because Congress passed the Orphan Drug Act in January 1983. The increase in drugs for HIV occurred because AIDS was first reported in 1981, was identified as being caused by HIV in 1984,[7] and (in the 1990s) the average length of time required to develop a drug was about 15 years.[8]

Both increases provide a good opportunity to investigate the effect of pharmaceutical innovation on mortality. In Lichtenberg (2001a, 2003a), I investigated the effect of increases in the number of drugs available to treat these diseases on mortality associated with them.

Before the Orphan Drug Act went into effect (between 1979 and 1984), mortality from rare diseases grew at the same rate as mortality from other diseases (*Figure 4*). In contrast, during the next five years, mortality from rare dis-

Figure 4
Number of Deaths from Rare Diseases and Other Diseases, 1979–98



eases grew more slowly than mortality from other diseases. I estimated that one additional orphan drug approval in year t prevents 211 deaths in year $t + 1$ and ultimately prevents 499 deaths, and that about 108,000 deaths from rare diseases will ultimately be prevented by all of the 216 orphan drugs that have been approved since 1983.

Consistent with previous patient-level studies of HIV, I find that new drugs played a key role in the post-1995 decline in HIV mortality (*Figure 5*). I estimate that one additional HIV drug approval in year t prevents about 6,000 HIV deaths in year $t + 1$ and ultimately prevents about 34,000 HIV deaths. HIV drug approvals have reduced mortality both directly and indirectly (via increased drug consumption). HIV mortality depends on both the quality and the quantity of medications consumed, and new drug approvals have a sizeable impact on drug consumption: One additional HIV drug approval in year t results in 1.2 million additional HIV drug units consumed in year $t + 1$ and ultimately results in 3.6 million additional HIV drug units consumed.

As summarized in Figure 6, mortality from both diseases declined dramatically following increases in drug approvals.

Effect of Increased Drug Use Associated with Medicare Eligibility

Most people become eligible for Medicare suddenly, the day they turn sixty-five. Although Medicare does not pay for most outpatient drugs, Medicare

Figure 5
HIV Drug Approvals and HIV Mortality Reduction

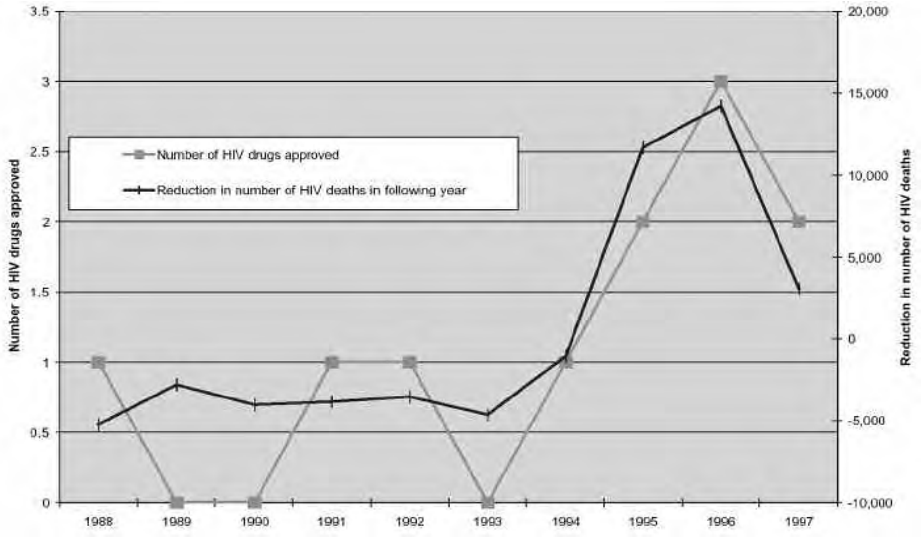
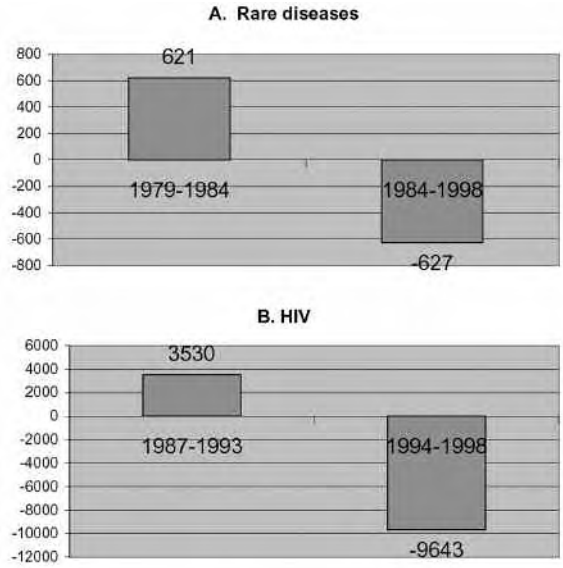


Figure 6
Average Annual Change in Number of Deaths



subsidizes a service that people must use in order to obtain prescription drugs: physician care. In Lichtenberg (2002), I show that utilization of ambulatory care increases suddenly and significantly at age sixty-five, presumably due to Medicare eligibility. The evidence points to a structural change in the frequency of physician visits precisely at age sixty-five.[9] Attainment of age sixty-five marks not only an upward shift but also the beginning of a rapid upward trend (up until age seventy-five) of about 2.8 percent per year in annual physician visits per capita.

The number of physician visits in which at least one drug is prescribed also jumps up at age sixty-five (*Figure 7*). Data from the 1996 Medical Expenditure Panel Survey indicate that people between the ages of sixty-six and seventy-five consume about 66 percent more medicines per person than people between the ages of fifty-six and sixty-five (*Figure 8*).

I examined whether this increase in utilization leads to an improvement in outcomes—a reduction in mortality—relative to what one would expect given the trends in outcomes prior to age sixty-five. The estimates were consistent with the hypothesis that the Medicare-induced increase in health care utilization leads to slower growth in the probability of death after age sixty-five (*Figure 9*). Physician visits (which are highly correlated with prescription drug utilization—physicians prescribe drugs in over 60 percent of office visits) are estimated to

Figure 7
Number of Physician Visits in Which at Least One Drug Was Prescribed, 1985 and 1989–98

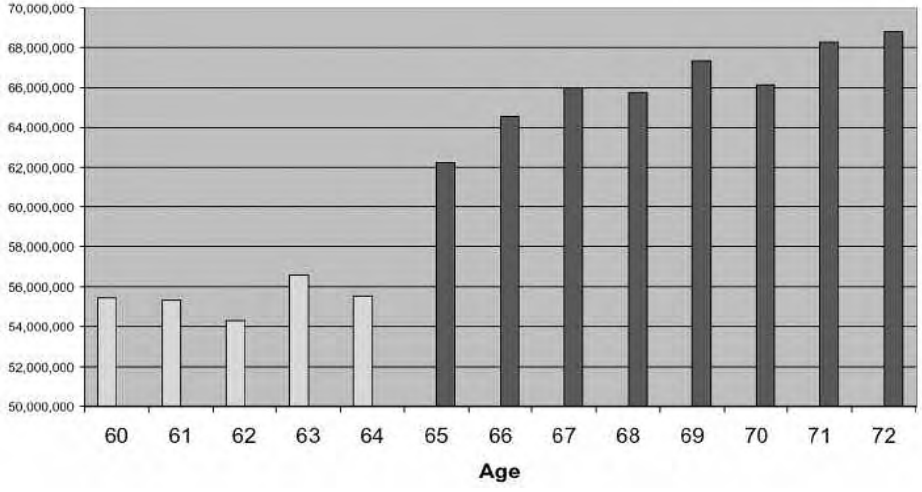


Figure 8
Median Number of Prescriptions, by Age, 1996

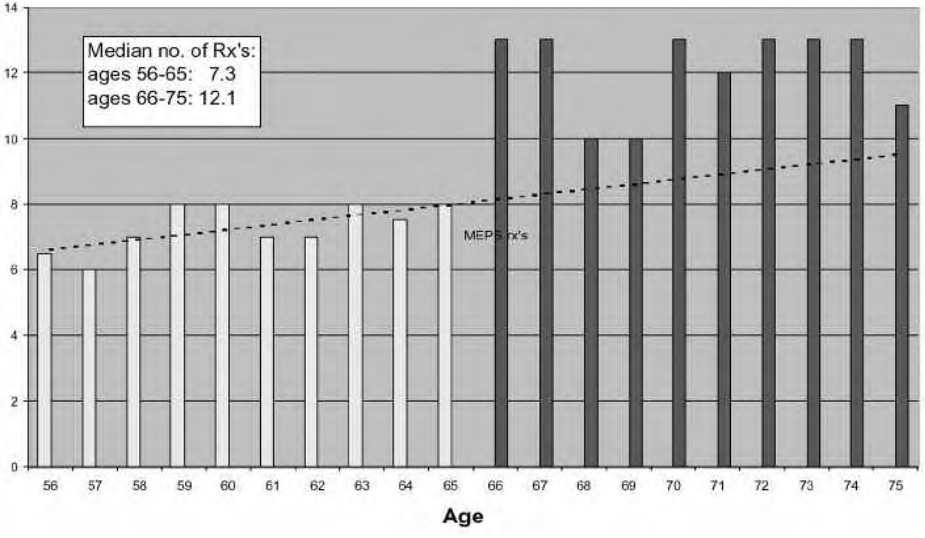
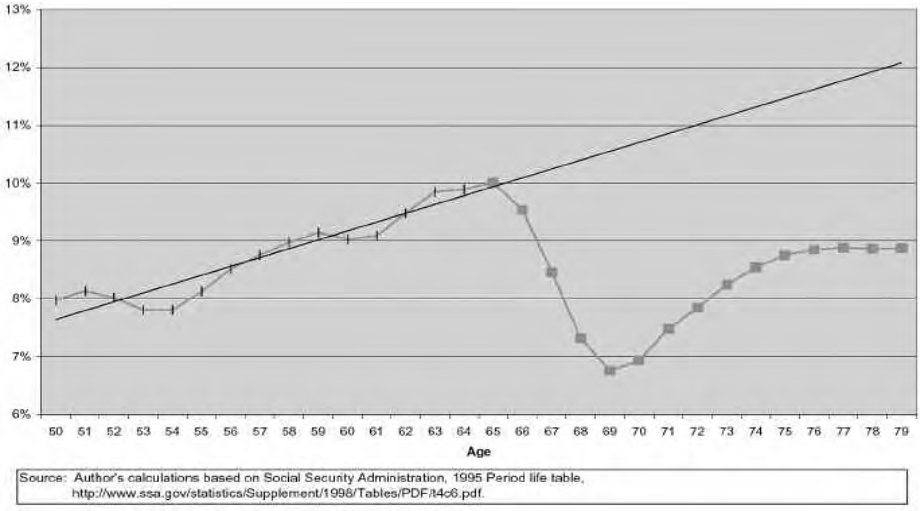


Figure 9
Percentage Increase from Previous Year in Probability of Death: Men



Source: Author's calculations based on Social Security Administration, 1995 Period life table, http://www.ssa.gov/statistics/Supplement/1998/Tables/PDF/t4c6.pdf.

have a negative effect on the male death rate, conditional on age and the death rate in the previous year: A permanent or sustained 10 percent increase in the number of visits ultimately leads to a 5 percent reduction in the death rate.

Data on age-specific death probabilities every ten years back to 1900—i.e., before as well as after Medicare—were enacted to provide an alternative way to test for the effect of Medicare on longevity and provide strong support for the hypothesis that Medicare increased the survival rate of the elderly, by about 13 percent.

QUALITY OF LIFE

In this section I present some new evidence about the impact of new drugs on quality of life ("health"), as measured by ability to work, activity limitations, and disability days. The analysis was performed using a combination of individual-level and medical-condition-level data. Most of the analysis is based on samples of over 300,000 observations spanning more than a decade (1985–96). I examined the following health indicators:

- Whether a person is *limited* in work, and a given condition is the main or secondary cause of the limitation
- Whether a person is *unable* to work, and a given condition is the main or secondary cause of the limitation

- Whether the person has *activity limitation*, and a given condition is the main cause of the limitation
- The total number of *restricted activity days* in the last two weeks for a given condition
- The number of *work-loss days* in the last two weeks for a given condition (for currently employed workers ages eighteen to sixty-nine)

I investigated the effect of drug *vintage*—defined as the year in which the FDA first approved a drug—on health. In particular, I tested the hypothesis that a person's health is an increasing function of the (mean) vintage of the drugs he consumes, *ceteris paribus*. If the hypothesis stated above is true, then the average health of a group of people is an increasing function of the average vintage of the drugs they consume, and the *change* in average health is an increasing function of the *change* in average drug vintage.

The estimates indicate that changes in mean drug vintage have highly statistically and economically significant effects on activity limitations and disability days. The magnitudes of these effects can be illustrated by calculating the costs and health benefits that a ten-year increase in mean drug vintage would have. Suppose that the average FDA approval year of the drugs consumed by a person in 1996 increased from 1970 to 1980. Newer drugs generally cost more than older drugs, and this switch to newer drugs would increase the person's drug expenditure by 27 percent, or $71, on average. However, the estimates imply that the switch to newer drugs would yield a number of benefits, whose value would exceed the increase in drug cost:

For employed people:

- The mean number of work-loss days per person per year would decline by 21.3 percent, or 1.02 days. Average daily employee compensation is about $140, so the value of this reduction is about $143.

For all people:

- The mean number of restricted-activity days per person per year would decline by 12.0 percent, or 1.74 days.[10]
- The probability of having an activity limitation would decline by 9 percent.
- The probability of being completely unable to work would decline by 10.8 percent. Average annual employee compensation is about $40,000, so the value of this reduction could be as high as $300.

I am currently engaged in another study of the impact of drug vintage on quality of life. This study, which is restricted to the Medicare population, is based on the Medicare Current Beneficiary Survey for the years 1992–96, conducted by the Health Care Financing Administration. That survey contains a number of questions concerning the ability of respondents to engage in various

activities of daily living (ADLs), such as walking two to three blocks, lifting ten pounds, stooping/kneeling, reaching over head, and writing. I have examined the relationship between the vintage of the drugs consumed by an individual and his or her ADL limitations, controlling for the person's age, sex, race, education, income, insurance status, total medical expenditure,[11] medical history, the therapeutic class of the drug, and other attributes. Preliminary findings indicate that *Medicare beneficiaries consuming newer drugs have significantly fewer ADL limitations than people consuming older drugs.*

TOTAL MEDICAL EXPENDITURE

Case studies of a number of specific drugs have shown that these drugs reduced the demand for hospital care. For example, according to the Boston Consulting Group (1993), operations for peptic ulcers decreased from 97,000 in 1977, when H2 antagonists were introduced, to 19,000 in 1987; this is estimated to have saved $224 million in annual medical costs. The Scandinavian Simvastatin Survival Study indicated that "giving the drug simvastatin to heart patients reduced their hospital admissions by a third during five years of treatment. It also reduced the number of days that they had to spend in the hospital when they were admitted, and reduced the need for bypass surgery and angioplasty." But treatment with the $2/day pill that lowered cholesterol did not actually save money: Hospital costs were $8 million lower among the 2,221 volunteers who got the drug, but the medicine itself cost $11 million (*The New York Times* 1995a). On the other hand, the clot-dissolving drug TPA "costs $2,000 to administer to each stroke victim, but has the potential to save much more in long-term care for those who are helped" (*The New York Times* 1995b).

Other case studies have indicated that government-imposed rationing of pharmaceuticals led to increased use of hospital care. Soumerai et al. (1991) analyzed the effect of limits imposed by the New Hampshire Medicaid program on the number of reimbursable medications that a patient can receive on rates of admission to nursing homes and hospitals. Imposition of the reimbursement cap resulted in an approximate doubling of the rate of nursing home admissions among chronically ill elderly patients.

While these studies are valuable, the extent to which their findings apply to pharmaceutical use in general is unclear. Moreover, these studies have yielded mixed results about (or have not addressed) the issue of whether the reduction in hospital cost was outweighed by the increase in pharmaceutical cost. I have performed several studies to assess the impact of pharmaceutical use in general on the demand for inpatient hospital care and overall medical expenditure.

My first study on this issue was based on disease-level data: I constructed a database containing information about utilization of pharmaceuticals, ambulatory care and hospital care, by disease, at two points in time (1980 and 1991 or

1992). I controlled for the presence of "fixed (diagnosis) effects" by analyzing relationships among growth rates of the variables. The main findings of this study were as follows:

- The number of hospital bed-days declined most rapidly for those diagnoses with the greatest increase in the total number of drugs prescribed and the greatest change in the distribution of drugs.
- An increase of 100 prescriptions is associated with 16.3 fewer hospital days.
- A $1 increase in pharmaceutical expenditure is associated with a $3.65 reduction in hospital care expenditure (ignoring any indirect cost of hospitalization), but it may also be associated with a $1.54 increase in expenditure on ambulatory care.
- Diagnoses subject to higher rates of surgical innovation exhibited larger increases (or smaller declines) in hospitalization.

My second study on this issue was based on individual-level data, most of which were obtained from the 1996 Medical Expenditure Panel Survey, a nationally representative survey of health care use and expenditures for the U.S. civilian noninstitutionalized population. This survey collected extremely detailed data from 23,230 people on use and expenditures for office and hospital-based care, home health care, and prescribed medicines. MEPS contains data at three different levels of aggregation: the person level, the condition level (77,000 conditions), and the event level. A person may have several conditions (e.g., hypertension, diabetes, and glaucoma); a given condition may be associated with a number of events.

The unit of observation in my analysis was a prescribed-medicine event. I had data on over 171,000 prescriptions. Over 90 percent of the prescriptions are linked to exactly one medical condition, and the 1996 Medical Conditions file contains summary information about these medical conditions, including the number of hospital events, emergency room events, outpatient events, office-based events, dental events, and home health events associated with the condition. Expenditure (and charges) associated with each condition, by event type, can be computed from the records contained in the respective medical event files. For example, one can compute total hospital expenditure associated with individual x's hypertension. In addition to calculating expenditure, by event type, we calculated total nondrug expenditure—i.e., the sum of expenditures on the six event types listed above. The MEPS data enable us to control for many important attributes, including sex, age, education, race, income, insurance status (whether the person is covered by private insurance, Medicare, or Medicaid), who paid for the drug, the condition for which the drug was prescribed, how long the person has had the condition, and the number of medical conditions reported by the person.

By controlling for condition, we are in effect comparing individuals only with other individuals with the same condition. We do not control for drug class, however, since we do not want to rule out comparisons between people consuming drugs in one class (e.g., SSRI antidepressants) and people consuming drugs in another class (e.g., tricyclic antidepressants) for the same condition.

My objective was to determine the effect of drug age—the number of years since the FDA first approved the drug's active ingredient(s)—on outcomes and expenditure, controlling, in a very nonrestrictive fashion, all of these factors cited above. But in addition to those observed individual differences, there may be other, unmeasured determinants, such as the physician's "practice style": Physicians prescribing older drugs might be less well trained, less likely to keep up with advances in medicine, and more likely to practice in substandard facilities. Fortunately, the fact that many individuals in the sample have both multiple medical conditions and multiple prescriptions means that we can control for *all* individual characteristics—both observed and unobserved—by pursuing a second approach. This involved estimating a model that includes "individual effects."

Table 1 shows the number of 1996 MEPS events, by type, and their associated average expenditures. Figure 10 depicts the frequency distribution of MEPS prescriptions, by the date the active ingredient was first approved by the FDA. About one-quarter of prescriptions consumed in 1996 were for drugs approved before 1950; more than half of the drugs consumed were approved before 1980.

First I analyzed the relationship between the age of the drug and the amount paid for the prescription. Not surprisingly, I found that new drugs are, on average, more expensive than old drugs prescribed for the same condition. For example, if a fifteen-year-old drug were replaced by a 5.5-year-old drug, the cost of the prescription would increase by about $18.

Then I examined the relationship between the age of the drug and the number and cost of nondrug medical events associated with the condition. Hospital

Table 1
Frequency of and Expenditure on MEPS Events

Event type	No. of events	Avge. Expenditure	Total expenditure	% of total expenditure
Inpatient visit events	2,207	$7,587.60	$16,745,833	41.5%
Office-based visit events	100,320	$81.45	$8,170,815	20.2%
Prescribed medicine events	171,587	$32.77	$5,623,511	13.9%
Outpatient visit events	9,957	$412.55	$4,107,802	10.2%
Dental visit events	22,165	$142.92	$3,167,747	7.8%
Emergency room visit events	3,899	$345.34	$1,346,490	3.3%
Other medical expenditure events	6,402	$189.70	$1,214,484	3.0%
All	316,537		$40,376,682	100.0%

stays are the most important of these, since they account for almost 42 percent of total medical expenditure. The estimates revealed that *people consuming newer drugs had significantly fewer hospital stays than people consuming older drugs*. Replacing an older prescription with a newer drug as in the previous examples would reduce the expected number of hospital stays by 0.0059—i.e., about six fewer stays per thousand prescriptions. Since the average expenditure on a hospital stay in MEPS is $7,588, one might expect a reduction in hospital expenditure of $44 (0.0059 × $7,588), compared with an increase in drug cost of $18. However, the reduction in hospital expenditure from the use of newer drugs is even larger than this—$56—because newer drugs are associated with shorter, as well as fewer, hospital stays.

The estimates indicate that reductions in drug age tend to reduce *all* types of nondrug medical expenditure, although the reduction in inpatient expenditure is by far the largest. This reduction of $71.09 in nondrug expenditure is much greater than the increase in prescription cost ($18), so *reducing the age of the drug results in a substantial net reduction in the total cost of treating the condition*.

I estimated the nondrug medical expenditure model separately, for those under and over sixty-five years of age. Nondrug medical expenditure is positively related to drug age for both groups, and drug age appears to have similar effects, in percentage terms, on nondrug expenditures of the elderly and the nonelderly.

It is sometimes suggested that because generic drugs tend to be less expensive than branded drugs, allowing people to use only generic drugs might

Figure 10
Frequency Distribution of MEPS Prescriptions, by Date Active Ingredient Was Approved by the FDA

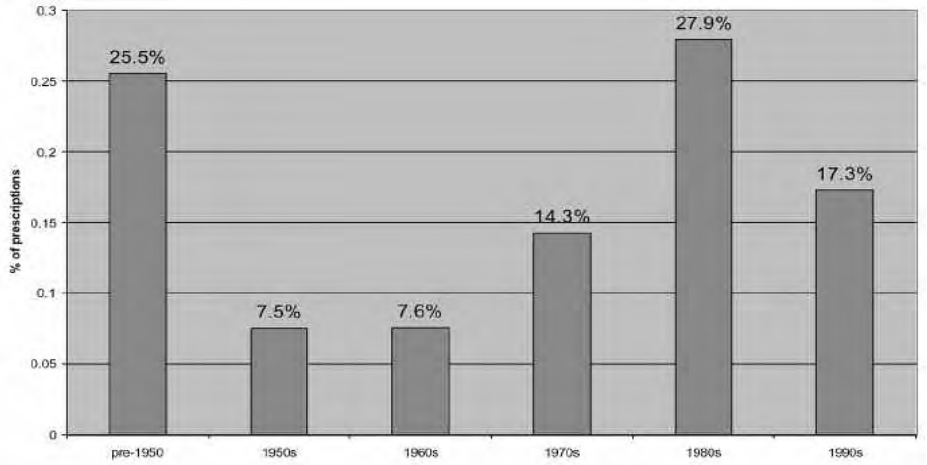
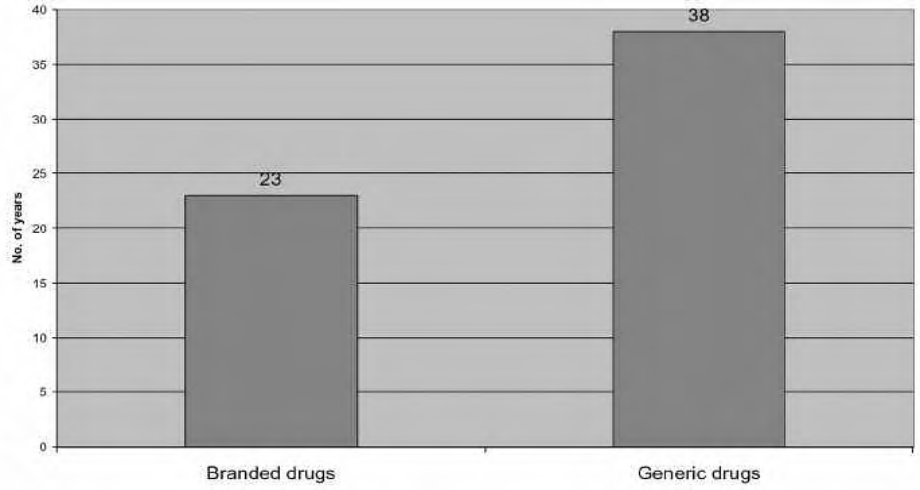


Figure 11
Mean Age (in Years) of Drugs Consumed in 1996



be an effective means of reducing health expenditure. As Figure 11 shows, generic drugs tend to be much older than branded drugs. Suppose that instead of consuming the actual mix of 60 percent branded and 40 percent generic drugs, people had to consume only generic drugs. This would increase the mean age of drugs consumed by 31 percent, from twenty-nine years to thirty-eight years. My estimates indicate that *denying people access to branded drugs would increase total treatment costs, not reduce them, and would lead to worse outcomes.*

Drug costs (and changes in drug costs) are visible to the naked eye; identification of drug benefits requires careful analysis of good data. People making drug policy decisions need to consider the full range of effects, not just the costs, of newer drugs.

NOTES

[1] Nordhaus (2003), along with Murphy and Topel (2003), offers parallel estimates of the value of recent increases in longevity. To the casual observer, it hardly seems possible—and may seem morally offensive—to put a dollar value on human life. But modern economics has devised a credible way around these imponderables, inferring the value people put on life from what they must be "bribed" in everyday settings to incur small but predictable increases in the risk of death. Let's say that moving from a factory line to outdoor construction increases a worker's chance of a fatal accident by one in 10,000 each year. In other words, if 10,000 workers made

the shift, expected on-the-job fatalities would rise by one per year. Suppose further that to induce 10,000 workers to play this death lottery voluntarily, an employer would have to pay an extra $500 annually to each worker, for a total of $5 million. One of these new construction workers is likely to die in return for the group gaining $5 million. Thus the value of one life in this example is said to be $5 million.

Estimates from the dozen or so work-related studies since the mid-1970s put the value of a statistical life in the relatively narrow $3 million to $7 million range. Using the relatively conservative estimate of $3 million for the average value of avoiding one death to calculate the value of extending life, Nordhaus estimates that in the 1975–95 period, the value of life extension nearly equaled the gains in tangible consumption.

[2] The rate of introduction of new drugs fluctuates considerably from year to year. Part of this is due to the inherent randomness of the drug development and approval process. But major changes in government policy have also clearly influenced the number of new drugs approved.

[3] Analysis of individual-level data (Lichtenberg 2001b) also indicates that people consuming new drugs are significantly less likely to die within a given period than people consuming older drugs.

[4] It takes about 18.5 years for half of the longevity effect of a new drug approval to occur.

[5] "Decrease in Chronic Illness Bodes Well for Medicare Costs," *New York Times*, May 8, 2001.

[6] "More than 200 drugs and biological products for rare diseases have been brought to market since 1983. In contrast, the decade prior to 1983 saw fewer than ten such products come to market." (Source: www.fda.gov/orphan/History.htm.)

[7] www.fda.gov/oashi/aids/miles81.html.

[8] DiMasi, J. A., "New Drug Development: Cost, Risk, and Complexity," *Drug Information Journal*, May 1995, cited in *PhRMA Industry Profile 2000*, Chapter 2, www.phrma.org/publications/publications/profile00/index.phtml.

[9] Reaching age sixty-five has a strong positive impact on the consumption of hospital services, but most of this impact appears to be the result of postponement of hospitalization in the prior two years.

[10] My study of the impact of Medicare, described in the previous section, indicated that average bed-days are lower after age sixty-five than one would expect from the pre-sixty-five trend. Increased use of drugs after age sixty-five may contribute to this.

[11] Total medical expenditure can serve as an indicator of the person's (pretreatment) medical condition or severity.

REFERENCES

Anderson, Robert (1999), "United States Life Tables, 1997," in *National Vital Statistics Reports*, vol. 47, no. 28 (Hyattsville, Md.: National Center for Health Statistics), Dec. 13.

The Boston Consulting Group, Inc. (1993), "The Contribution of Pharmaceutical Companies: What's at Stake for America, Executive Summary," September.

Bresnahan, Timothy, and Robert J. Gordon, eds. (1997), *The Economics of New Goods* (Chicago: University of Chicago Press).

Grossman, Gene, and Elhanan Helpman (1991), *Innovation and Growth in the Global Economy* (Cambridge, Mass.: MIT Press).

Lichtenberg, Frank R. (1996), "Do (More and Better) Drugs Keep People Out of Hospitals?" *American Economic Review* 86 (May): 384–8.

——— (2000a), "The Effect of Pharmaceutical Utilisation and Innovation on Hospitalisation and Mortality," in *Productivity, Technology, and Economic Growth*, ed. B. van Ark, S. K. Kuipers, and G. Kuper (Boston: Kluwer Academic Publishers).

——— (2000b), "Sources of U.S. Longevity Increase, 1960–1997," CESifo Working Paper Series 405, CESifo, Munich.

——— (2001a), "The Effect of New Drugs on Mortality from Rare Diseases and HIV," National Bureau of Economic Research Working Paper no. 8677 (December).

——— (2001b), "Are the Benefits of Newer Drugs Worth Their Cost? Evidence from the 1996 MEPS," *Health Affairs* 20(5) (September/October): 241–51.

——— (2002), "The Effects of Medicare on Health Care Utilization and Outcomes," in *Frontiers in Health Policy Research*, vol. 5, ed. Alan Garber (Cambridge, Mass.: MIT Press).

——— (2003a), "The Effect of New Drugs on HIV Mortality in the U.S., 1987–1998," *Economics and Human Biology* 1: 259–66.

——— (2003b), "Pharmaceutical Innovation, Mortality Reduction, and Economic Growth," in *Measuring the Gains from Medical Research: An Economic Approach*, eds. Kevin M. Murphy and Robert H. Topel (Chicago: University of Chicago Press).

Murphy, Kevin M., and Robert H. Topel (2003), "The Economic Value of Medical Research," in *Measuring the Gains from Medical Research: An Economic Approach*, eds. Kevin M. Murphy and Robert H. Topel (Chicago: University of Chicago Press).

The New York Times (1995a), "Cholesterol pill linked to lower hospital bills," March 27, A11.

The New York Times (1995b), "New study finds treatment helps stroke patients," Dec. 14, A1.

Nordhaus, William D. (2003), "The Health of Nations: The Contribution of Improved Health to Living Standards," in *Measuring the Gains from Medical Research: An Economic Approach*, eds. Kevin M. Murphy and Robert H. Topel (Chicago: University of Chicago Press).

Soumerai, S. B., D. Ross–Degnan, J. Avorn, T. J. McLaughlin, and I. Choodnovskiy (1991), "Effects of Medicaid Drug-Payment Limits on Admission to Hospitals and Nursing Homes," *The New England Journal of Medicine* 325 (15) (Oct. 10): 1072–7.

PART TWO

The Interdisciplinary Nature of Biotech Research

Harnessing New Technologies for the 21st Century

Malcolm Gillis

The Convergence of Disruptive Technologies Enabling a New Industrial Approach to Health Products

C. Thomas Caskey

Harnessing New Technologies for the 21st Century

Malcolm Gillis

The 20th century was a very good one for economic growth in the United States: Real GNP in 1999 was more than twenty times that of 1900. Replicating this performance—much less improving upon it—in the 21st century will not be easy. Science-based industry played a crucial part in 20th century economic expansion. This was most obviously so in the case of the chemical industry, the first major science-based industry to arise in the United States. Development of that industry helped accelerate growth in dozens of others, including oil and gas refining, pulp and paper, textiles, building materials, and, of course, pharmaceuticals.

If 21st century growth rates are to approach those of the past century, new science-based industries will have to play roles comparable with the chemical industry after 1900. Some of these are already appearing on the scene as infant industries. David Baltimore, Nobel laureate, now president of California Institute of Technology, correctly asserts that biotechnology is one of these infant industries.[1] The term *infant*, as applied to this industry, does not necessarily mean small; rather, it means that the young biotechnology industry today is not nearly as large or as pivotal as it is going to be within a few years.

Up until now, the principal application of the biotechnology industry has been in the development of drugs for the pharmaceutical industry. Credible estimates are that drugs and vaccines developed through biotechnology have already benefited more than 250 million people.[2]

Perhaps this is one reason why some tend to view the biotechnology industry as almost indistinguishable from the pharmaceutical industry, which itself accounted in 1997 for 1.2 percent of GDP.[3] Indeed, in an influential article as late as 1999, the biotechnology industry was defined essentially as a subsection of pharmaceuticals, specifically as "an industry that uses biotechnology to produce drugs or diagnostics previously unobtainable."[4] We will see that this definition no longer suffices.

Earlier presentations by Darby and Lichtenberg will have provided a comprehensive sketch of the macro importance of biotechnology. Here, I merely note that by the mid-'90s, the sales volume of the pharmaceutical industry was probably about fifteen times that of the biotech industry.[5] Sales of pharmaceuticals will doubtless grow apace, especially with the progressive graying of our population.[6] Sales of the now infant biotech industry, though, will surely grow even faster over the next two decades, as biotechnology applications extend further beyond pharmaceuticals, to the commonplace manipulation of DNA, proteins, and cells in fields ranging from agriculture, nutrition, and energy production to tissue engineering and, of course, gene therapy. Clearly, biotechnology will be an industry serving a very large market beyond that for drugs. For example, the near-term worldwide market for tissue engineering products has been estimated to be as high as $350 billion per year.[7] Moreover, the future flowering of biotechnology will not be limited only to advances in biosciences. Progress in biotechnology turns out to be no less dependent upon advances in information technology and nanotechnology. If I succeed today only in portraying the growing linkages between biotechnology, information technology, and nanotechnology, I will consider it a very good day's work. I have enlisted in my cause the testimony of several Nobel laureates, not only in medicine but also in economics.

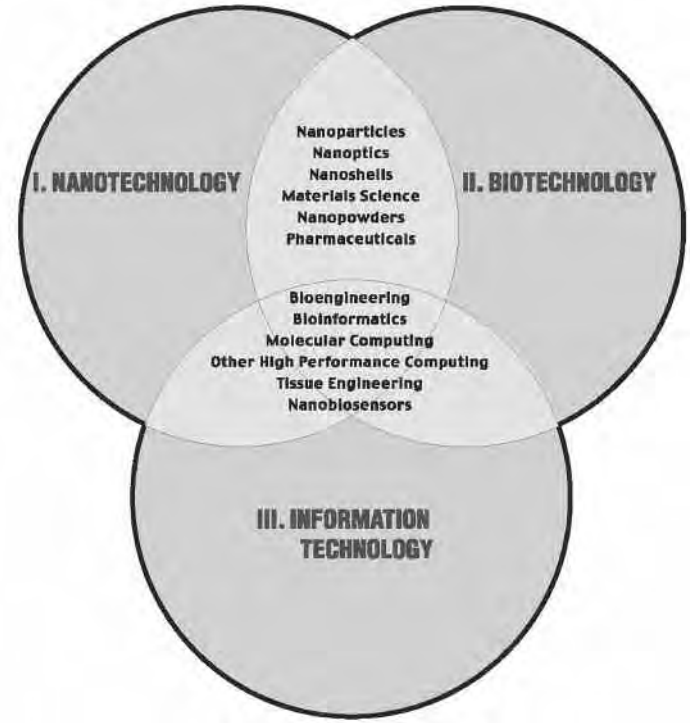
My remarks do not purport to cover all subfields of biotechnology but primarily the biotechnology I know best: that found today among Rice faculty and their research partners of the Texas Medical Center, just across the street. Necessarily, then, my comments are focused somewhat more on the longer-term societal payoffs from activity in research labs than upon near-term market prospects.

BIOTECHNOLOGY, INFORMATION TECHNOLOGY, AND NANOTECHNOLOGY

Pity those poor economists who will be specializing in national income accounting in the decades to come. In attributing economic activity to distinct sectors, how will they distinguish output in biotechnology from that in information technology and nanotechnology? To be sure, in 2050 we will still find individuals identifying themselves as biologists or information scientists or nanotechnologists. The economists could ask those people. But would those scientists be able to draw clear dividing lines for the economists? Probably not, because these rapidly evolving fields are becoming ever more closely linked. Not only that, but the nature of the linkages among the three is itself evolving rapidly. Figure 1 represents an attempt to depict intersections between them. The chart was probably obsolete by the time it was constructed in March.

The potential role of these technologies in reshaping our economy and society cannot be understood by examining each in isolation. We know quite

Figure 1
Linkages Between Key Technologies in Science and Engineering



well from the past two centuries of American economic history that technology-driven economic progress is almost never the result of a single invention or even a single set of technologies. Rather, rapid economic growth has generally been the outcome of the interplay between a collection of largely unanticipated discoveries, clumping and clustering in very different fields, not over months or years but usually decades. To illustrate: The economic progress often attributed to the steam engine unfolded over at least a century and a half after Watt. For example, in the United States even sixty-five years after Watt patented the steam engine—as you know, he did not discover it—almost all manufacturing was powered by water.[8] The steam engine began to yield truly revolutionary change only in the 19th century, when it was modified for use in transportation and in the textile industry's power looms. Watt's legacy was vastly magnified by the invention of the dynamo, pioneered by Faraday and Wheatstone and perfected by Edison in 1878. Even so, as late as 1940 electricity had not reached large swathes of the rural south in the United States. Herbert Simon, another Nobel

laureate,[9] was clearly right on the mark in postulating that the ramifications of any one technological innovation depend greatly upon the stimulation it provides to and receives from other, often quite independent, innovations.

Biotechnology Generally

Yet another Nobel laureate, economist–historian Robert Fogel,[10] published a series of papers in the '80s and '90s showing vividly the remarkable extent to which investments in biomedical research made seventy-five and a hundred years ago are still paying off handsomely today, in affecting how well we live and how long we live. More recently, the distinguished economist William Nordhaus has suggested that the medical revolution qualifies, on economic grounds alone, as the "greatest benefit to mankind." He has estimated that the heretofore unmeasured value of "health income" (the value not captured in the national income accounts) attributable to increases in longevity in the last hundred years is nearly as large as the value of measured income attributable to nonhealth goods and services.[11] Others offer findings paralleling those of Nordhaus. Lichtenberg estimates that just between 1960 and 1997, life expectancy at birth increased by about 10 percent, to 76.5 years,[12] attributable primarily to both medical innovation and rising expenditures—especially public spending—in medical care. The conclusions of Fogel, Nordhaus, and Lichtenberg are reinforced by research from a growing body of economists (Mark McClellan, David Cutler, Elizabeth Richardson among others) working in new traditions of analysis of health economics.[13] As impressive as were the gains of the past, tomorrow's biotechnology holds out the promise of benefits that could make those of the last century appear pale in comparison.

Only thirteen years have passed since scientist W. French Anderson fired the biotech shot heard around the world by administering the first artificial gene to cure a hereditary illness. Since then we have learned more about the workings of human genes than in the entire half century following the 1953 discovery of the double helix by two modern counterparts of Prometheus, Watson and Crick. As a result, biology has been transformed from a discipline centering upon the passive study of life to one allowing the active alteration of life almost at will. Virtually all the molecular rungs on the chemical ladders of the human genome have been identified, providing us with an almost complete parts list for a human. As David Baltimore says, "Now we can discover all the secrets of nature."[14]

The theoretical understanding developed in genetics and clinical advances in gene therapy over the past fifty years bid fair to render commonplace medical applications that were once viewed as unthinkable. This new world of possibilities arises from the joining of the insights of the geneticist with advanced tools of information and computational science and the rapidly growing skills of biomedical engineers and nanotechnologists.

The promise of biotechnology is, however, not at all unalloyed: The possible blessings are very obvious, while the potential banes are not.[15] Moreover, there is the possibility that both our expectations and our worries over the biotech revolution have been overinflated. Knowing all the secrets of nature could bring utopia, but it could also usher in a nightmare world resembling that limned in Aldous Huxley's remarkably prescient book *Brave New World*, published seventy years ago. That world boasted some innovations already here and one we still lack: genetic engineering of humans *in vitro*, powerful mood-altering pharmaceuticals, and body implants to complement "feelies," the ultimate in participatory entertainment. All of these wonders were developed to assure human happiness. But Huxley's totally homogenized world could hardly be either brave or happy, for it allowed no scope at all for the exercise of human choice or respect for fundamental human values. Huxley's world has yet to encroach much on ours, but at the very least, it stands as an unsettling reminder that today's biotechnology involves ethical thickets and moral issues that society has only just begun to plumb, much less resolve.[16] When, for example, does gene therapy spill over into eugenics? To what extent will the accumulation of genetic information stigmatize affected people?

The Biotechnology–Information Technology Interface

Mathematical, statistical, and computer methods have become indispensable in the analysis of biological, biochemical, and biophysical data. Moreover, the interactions also work in reverse: A growing number of projects in computational science are being driven by biological problems. No less a scientist than David Baltimore flatly asserts: "Biology is today an information science."[17] He goes on to note that "the human genome, as it might be recorded in a web site, is a string of three billion units over four letters.... Only computers can store such data, only mathematicians can understand how to take sequenced DNA fragments and put them together in appropriate order."[18] Indeed, the human genome has been reconstituted perhaps as much by advanced computational technology as in wet labs.

The field of bioinformatics weaves together biology and information science. Although the early commercial promise of bioinformatics, like that of the Internet, has thus far proven to have been oversold, this should not obscure the fact that bioinformatics is beginning to usher in another technological revolution. Whereas classical medical research depended to a great extent upon trial and error, the discipline of bioinformatics allows research to be based upon information about networks of molecular interaction that control diseased, as well as normal, life.

The emergence of bioinformatics is merely the latest testament to the fruitfulness of university-based research in drawing together several disciplines to work on vital questions. Arguably, the most fundamental advances in biomedi-

cine have come from advances in basic sciences in the academy. Virtually all the stunning advances in diagnostic and therapeutic tools of recent years were based on discoveries from the one place where one finds critical masses of questing physicists, biologists, chemists, mathematicians, engineers, and computer scientists, as well as clinicians: the research university.

Directly from physics came magnetic resonance imaging and laser surgery. From chemistry sprang fullerenes, first discovered at Rice University in 1985, as well as a host of pharmaceuticals. From mechanical engineering came robotics used in surgery. New insights from researchers in computer science and applied mathematics led to groundbreaking work in tomography, genomics, and now, proteomics.[19] The interrelationships between biomedicine and information sciences can be seen to be especially strong in the area of medical imaging. At Rice, at least a half dozen of our computational and mathematical scientists are involved in joint work in medical imaging with physicians from the Texas Medical Center.

Several subfields in bioinformatics are moving ahead at high speed. Computational physiology is one of these. The virtual heart is a very good example: A union of form and function on a computer screen, this heart is the result of the translation of thousands of mathematical equations and data points into a computer simulation. *The Economist* calls this a spectacular example of *in silico* biology that brings computing power to bear on a much wider range of biological problems from proteomic analysis to the re-creation of neural networks.[20]

Another new direction in the bio–info interface lies in computational cancer research. Clinicians at M.D. Anderson Cancer Center stress that cancer is not a hundred different diseases, but thousands of different diseases. At least five mutations may be required to create a cancer cell, each drawn from a repertoire of several hundred genes. Thus it is apparent that there is an overwhelming number of possible combinations and permutations of cancer-causing mutations.[21] This is exactly the type of problem that can be addressed only by biomathematicians, computational scientists, and biostaticians—that is to say, those in bioinformatics.

Finally, it is to be emphasized that new disciplines at the intersection of biotechnology and information technology have ample applicability to the mainstay of 20th century biotechnology: new pharmaceutical products. The difference is that for the 21st century, more and more pharmaceutical innovations will be IT-based.

The fusion of computational sciences with biochemistry and pharmacology has already given birth to the new discipline of pharmacogenomics, which promises to allow the personalization of much of medicine. This new field will augment and perhaps eventually replace traditional therapy based on the premise that "one drug fits all."

Pharmacogenomics, like its predecessor pharmacogenetics, deals with the genetic basis underlying variable drug response in different individuals. Phar-

macogenetics also relies on the study of sequence variations in genes thought to affect drug response. But pharmacogenomics goes further: It looks at the entire genome, enabling not only the identification of variant genes governing different drug responses across patients but also identifying genes that affect susceptibility to disease. Thus, pharmacogenomics may allow new insights into disease prevention as well as individualized application of drug therapy.[22]

For this promise to be realized, scientists must understand fully not only the genome but the proteome as well. That requires the development of increasingly more sophisticated and powerful computational methods. The Gulf Coast Consortium for Bioinformatics, embracing Rice and six other institutional members in Houston and Galveston, is one of the venues where such computational approaches to drug design are beginning to blossom. There, researchers are developing powerful new tools for use in computer-aided design of drugs.[23] Interdisciplinary approaches at the consortium have been very fruitful. Robotic path planning, developed in engineering, has been applied to modeling biomolecular interactions to help solve problems in drug design.

The Biotechnology–Nanotechnology Interface

Nano is derived from the Greek word for dwarf. Nanotechnology is the application of findings of the highly interdisciplinary field of nanoscale science, which deals with objects as small as one billionth of a meter: a nanometer. Nanotechnology refers to activity involving the measurement, manipulation, and fabrication of objects from less than one to about 100 nanometers across. Nanotechnology is not to be confused with the more widely known, top-down approach called miniaturization. Nanotechnology devices are built from the bottom up, one molecule, or even one atom, at a time.

My thumb is about 30 million nanometers wide. The nanometer, the width of about ten hydrogen atoms, has come to be the preferred unit of measure among scientists and engineers working at or very near the atomic scale in biology, electronics, and materials science. Naturally, these individuals have come to be called nanoscientists and/or nanotechnologists, working in either "dry" or "wet" nanofields. The dry side is, naturally enough, waterless. The wet side centers on the study of biological systems that exist in a water environment. By 2002, the wet side of nanotechnology had become virtually indistinguishable from molecular biophysics, structural biology, and biotechnology. Chemistry Nobel laureate Rick Smalley goes so far as to assert that 21st century biotechnology could be considered a subset of wet nanotechnology.

The nanoworld is where much of nature's weirdness resides—the borderland between the world of quantum mechanics and the more familiar macroworld of classical physics, where different laws apply. Navigation in this landscape is difficult indeed. Much of the most interesting work focuses on an

intermediate domain between the two worlds, involving structures too large to be easily understood with ordinary quantum mechanics but not large enough to escape fully the weirdness of quantum effects.[24]

Until quite recently, nanoscale science was on the leading edge of research, while nanotechnology was on the "bleeding" edge of applications: lots of money going out and not much coming in. That is now beginning to change, as we will see, as investors and governments have begun to turn on the financial taps.

Government support of nanoresearch has risen sharply in recent years, growing faster than that from private sources. At the federal level, the total nanotech budget for FY 2003 is proposed to increase by 17 percent, with a striking 57 percent increase for the Department of Energy. A similar pattern may be found in other countries, where total funding for nanotechnology has jumped from $316 million four years ago to $835 million last year.[25] New nanotechnology centers have been recently established, both in Cambridge and Oxford, one focusing on wet nanotech, the other on dry nanotech.

While the dry side of nanotechnology, especially that involving new materials, is not irrelevant for biotechnology, the wet side is by far more significant. Biomedical applications of nanotechnology were given a large boost after it was established that the two nanoparticles discovered at Rice—carbon 60 (the Buckyball) and carbon 70—are nontoxic.[26,27] These particles, commonly called "fullerenes," possess two other traits that make them especially suited for biomedical applications.

First, they are very, very small—about one nanometer wide. Second, their surfaces are particularly well suited for attaching therapeutic compounds. In the words of one of the discoverers, Rick Smalley, "They are molecular pincushions that can easily be decorated with other chemicals." Exploitation of these properties of fullerenes is proceeding. One promising anti-AIDS application capitalizes on three features of the Buckyball: its size, its ability to carry chemicals enabling delivery of drugs to specifically targeted sites, and its unique shape that facilitates binding with HIV-infected cells.

At least as promising are the efforts under way at Rice and nearby M.D. Anderson Cancer Center involving nanoparticles other than fullerenes: gold nanoshells. These are biocompatible devices with a gold surface adhered to a silica core. At 100 nanometers in width, they easily pass through the circulatory system. The optical properties of nanoshells may prove extremely useful in both diagnosis and treatment. Once inserted into the body and delivered to sites of individual tumors by virtue of antibodies attached to them, they are hit by infrared light and heated up to 55 degrees centigrade, enough to destroy cancer cells while leaving intact healthy ones. This highly localized therapy can penetrate up to 15 cm. in tissues and thus reach all organs without the serious side effects of chemotherapy or radiation therapy.

The Grand Interface: Bio–Info–Nano

We have come to the juncture of all three of the new technologies: the design and utilization of nanomaterials for biomedical engineering. Especially notable is the rapidly growing field of tissue engineering, which focuses primarily upon the development of biological substitutes to restore, maintain, or improve tissue function. Put another way, tissue engineering will allow fabrication, on a large scale, of a range of spare human parts to replace diseased or spent ones, with or without the help of embryonic stem cells.

Twentieth century forms of biomedical engineering will doubtless persist for a time, until the field is largely eclipsed by tissue engineering. Traditional bioengineering has already brought us biomechanical body parts, including unduly bulky whole organs, various joints, heart valves, stents, and the like. It is notable that in 2001, thirty-three years after Christian Barnard's first transplant of a living heart, an artificial heart has allowed a handful of patients to remain alive for several weeks.

Veterinarians have contributed as well, drawing on their experience with large animals to fashion ingenious, highly compact devices that not only augment the activity of damaged human left ventricles but also in some cases even allow damaged natural heart tissue to heal and resume functioning. Also, innovative research is exploring how metal and ceramics can be used in the fabrication of artificial lungs.

Progress in providing other organs much more complex than the lungs or highly specialized heart tissue will be longer in coming but is no longer the stuff of science fiction. The overwhelming share of those advances will come from newer approaches to tissue engineering, some of which rely on stem cells taken from adults. Experiments are already under way using living cells to make bioartificial pancreases and livers. Virtually every other part of the body has attracted researchers seeking ways to find bioartificial replications of body parts.

Traditional biomedical engineering uses metals, polymers, and ceramics to construct temporary or permanent replacements of body parts that interact minimally with surrounding tissue. Tissue engineers take exactly the opposite approach: They design materials to interact extensively with adjacent tissues in order to facilitate the regeneration process.[28]

In bone regeneration, for example, tissue engineers use biodegradable polymers to create scaffolding shaped like the lost bone. A biopsy is taken from the patient himself, the bone-forming cells are isolated and expanded in the laboratory and seeded onto a scaffold. The cell/scaffold construct is grown in a bioreactor and then grafted back into the patient. As the cells integrate with the body's own tissue, the polymer scaffold gradually melts away, leaving only living tissue behind. With the right signals, this newly formed tissue regenerates the missing bone.

Scientists and engineers at Rice and other Texas locations are engaged in promising research for deploying tissue engineering to deal with a multitude of other medical problems: atherosclerosis, thrombosis, inflammations, osteoporosis, cartilage regeneration, and repair of tissue.

The objectives of tissue engineering are not limited to bone and organ replacement. Tissue engineers have already developed quite serviceable blood substitutes. Most recently, protein engineers at Rice together with industrial collaborators surmounted one of the most vexing problems in the development of blood substitutes. Recombinant technology was used to design new hemoglobin molecules that eliminate the hypertensive side effects of previously available blood substitutes, traceable to nitric oxide scavenging. This work is being carried out under the auspices of the Gulf Coast Consortia, plural because it is an umbrella organization for cooperative research and education in structural biology, computational biology, and molecular biophysics.

This type of research requires the most resourceful efforts not only of biologists but also information scientists and nanotechnologists. Wet nanotechnology is used to create tissue analogs to grow skin, muscle, and organs. The computational and structural skills of engineers are required to construct the scaffolds on which bioscientists build, after having used mathematical models to image their work.[29]

Nowhere is the interplay between bio-, nano-, and information technology more striking than in new forms of health maintenance, diagnosis, and treatment. Already nanometer-sized biosensors can be inserted into the bloodstream. More advanced nanosensors could eventually monitor all bodily functions.

CONCLUSION: OF PARTS LISTS AND SPARE PARTS

The potential for truly staggering applications of biotechnology in the marketplace is in little doubt. Whether much of this potential will be soon realized is, however, yet unclear. Financial constraints on biotechnological transfer may be shrinking, but legal constraints loom somewhat larger than in past technological revolutions.

On the bright side, biotechnology looks to be the principal arena for an ongoing, far-reaching synthesis in science and engineering. As the infant industry of biotechnology reaches its adolescence and later adulthood, it can be expected to provide a wide array of products and services to fuel sharp increases in living standards in the 21st century. Pharmaceuticals will doubtless remain prominent in this picture, but other types of new products and services should grow steadily in importance.

From genomics, biotechnology has already provided us with a complete parts list for both animals and plant life. As a result of advances in wet nanotechnology and information technology, tissue engineering promises to pro-

vide widely available, inexpensive, and reliable spare parts for humans. There is, however, a darker side: a still unresolved and complex welter of ethical—and perhaps moral—issues raised by our fast-expanding capacities in biotechnology. These are just beginning to be systematically addressed on many university campuses across the nation—including my own—and in boardrooms and the halls of Congress. Considerable wisdom will be required to ensure that the potential of the biotechnological revolution is realized without erosion in fundamental human values. With resolution of these issues, the economic and social impact could be as profound and as positive as that wrought by any previous revolution in human history.

NOTES

I am grateful for comments from many Rice colleagues, especially Eugene Levy, Kathleen Matthews, Neal Lane, Tony Mikos, John Olson, Terry Shepard, and Moshe Vardi.

1 Baltimore (2001), 43–45.

2 Feldbaum (2002).

3 Landau (1999), xi.

4 Scriabine (1999), 271.

5 According to Landau, sales of the pharmaceutical industry in 1997 were $122 billion. Given ambiguities over the very meaning of biotech sales, few precise figures are available. Sales values for the biotech industry, according to leading biotech scientists, reached only $6 billion in 1993 and may have grown to $7.5 billion by 1997. See Landau (1999) and Rudolph and McIntire (1996).

6 Nearly 30 percent of biotech products in Phase III of chemical trials are for cancer and another 11 percent for the nervous system, including Alzheimer's.

7 As a measure of the potential present-day market for tissue-engineering products, consider that organ replacement therapies using standard organometallic devices constitute about one-twelfth of medical spending worldwide, or about $350 million. See McIntire (2002), chapter 1, 1.

8 Rosenberg and Trajtenberg (2001).

9 Simon (2001).

10 Fogel (1994).

11 Nordhaus (2002).

12 Lichtenberg (2002).

13 Cutler et al. (1998).

14 Baltimore (2001), 49.

15 This line of argument is developed skillfully at some length by Francis Fukuyama (2002) in his new book, *Our Posthuman Future: Consequences of the Biotechnology Revolution*. See also Wade (2002).

16 See, for example, Rothstein (1996).

[17] Baltimore (2001), 44, 49.

[18] Baltimore (2001), 48.

[19] Proteomics is the study of the proteome, an organism's total protein set.

[20] *The Economist* (2001).

[21] M. D. Anderson Cancer Center, "The Ross and Margot Perot Center for Computational Cancer Research" (undated, but written in January 2002).

[22] See Mancinelli, Cronin, and Sadee (2000).

[23] See, for example, Finn and Kavraki (1999).

[24] Roukes (2001).

[25] Stix (2001).

[26] Wilson (1999).

[27] Researchers at Rice and the Texas Medical Center in 1996 found that carbon 60 (the Buckyball) does accumulate in the liver since it cannot be oxidized in mammals. However, no toxic effects were noted.

[28] Antonios Mikos, bioengineer at Rice.

[29] Jackson (2002).

REFERENCES

Baltimore, David (2001), "How Biology Became an Information Science," in *The Invisible Future: The Seamless Integration of Technology into Everyday Life*, ed. Peter J. Denning (McGraw-Hill).

Cutler, David M., Mark McClellan, Joseph P. Newhouse, and Dahlia Remler (1998), "Are Medical Prices Declining? Evidence for Heart Attack Treatments," *Quarterly Journal of Economics* 108 (4).

The Economist (2001), "The Heart of the Matter," December 8, 21.

Feldbaum, Carl (2002), "Some History Should Be Repeated," *Science* 295 (Feb. 8): 975.

Finn, Paul W., and Lydia E. Kavraki (1999), "Computational Approaches to Drug Design," *Algorithmica* 25: 347–71.

Fogel, Robert W. (1994), "Economic Growth, Population Theory, and Physiology: The Bearing of Long-Term Processes on the Making of Economic Policy," Presidential Address, *American Economic Review* 84(3): 369–95.

Fukuyama, Francis (2002), *Our Posthuman Future: Consequences of the Biotechnology Revolution* (New York: Farrar, Straus and Giroux).

Jackson, Shirley A. (2002), "Interdisciplinary Research Is a Wise Investment in Our Future," *Trusteeship* 10(1) (Association of Governing Boards of Universities and Colleges).

Landau, Ralph (1999), "Introduction," in *Pharmaceutical Innovation: Revolutionizing Human Health,* eds. Ralph Landau, Basil Achilladelis, and Alexander Scriabine (Philadelphia: Chemical Heritage Press).

Lichtenberg, Frank R. (2002), "Sources of U.S. Longevity Increase, 1960–1997," NBER Working Paper Series, no. 8755 (Cambridge, Mass.: National Bureau of Economic Research), January.

Mancinelli, Laviero, Maureen Cronin, and Wolfgang Sadee (2000), "Pharmacogenomics: The Promise of Personalized Medicine," *AAPS PharmSci* 2(1): 1–20.

McIntire, Larry, V. (2002), "Introduction," in *WTEC Panel Report on Tissue Engineering Research* (Washington, D.C.: National Science Foundation), January.

Nordhaus, William (2002), "The Health of Nations: The Contribution of Improved Health to Living Standards," NBER Working Paper Series, no. 8818 (Cambridge, Mass.: National Bureau of Economic Research), March.

Rosenberg, Nathan, and Manuel Trajtenberg (2001), "A General Purpose Technology at Work: The Corliss Steam Engine in the Late 19th Century U.S.," NBER Working Paper Series, no. 8485 (Cambridge, Mass.: National Bureau of Economic Research), September.

Rothstein, Mark (1996), "Ethical Issues Surrounding the New Technology as Applied to Health Care," in *Biotechnology: Science, Engineering, and Ethical Challenges for the 21st Century*, eds. Frederick B. Rudolph and Larry V. McIntire (Washington, D.C.: National Academy Press), 199–207.

Roukes, Michael (2001), "Plenty of Room Indeed," *Scientific American*, September.

Rudolph, Frederick B., and Larry V. McIntire, eds. (1996), *Biotechnology: Science, Engineering, and Ethical Challenges for the 21st Century* (Washington, D.C.: National Academy Press).

Scriabine, Alexander (1999), "The Role of Biotechnology in Drug Development," in *Pharmaceutical Innovation: Revolutionizing Human Health*, eds. Ralph Landau, Basil Achilladelis, and Alexander Scriabine (Philadelphia: Chemical Heritage Press).

Simon, Herbert A. (1987), "The Steam Engine and the Computer: What Makes Technology Revolutionary," *EDUCOM Bulletin* 22(1): 2–5.

Stix, Gary (2001), "Little Big Science," *Scientific American*, September.

Wade, Nicholas (2002), "A Dim View of a Posthuman Future," *New York Times*, April 2, D-1.

Wilson, Lon J. (1999), "Medical Applications of Fullerenes and Metallofullerenes," *Electrochemical Society Interface* 8 (Winter): 24–28.

The Convergence of Disruptive Technologies Enabling a New Industrial Approach to Health Products

C. Thomas Caskey

I have prepared this talk to cover two areas. First, I want to present a convergence of disruptive technologies that are driving new therapeutics. I will then finish with the situation in the state of Texas with regard to the traction we have in biotechnology, the companies being created, and what strength our academic community is providing to stimulate the initiative.

Bear with me for a moment while I create a yachting analogy for the biotech industry. The Vendee custom yacht is a single-person-managed yacht with a maximum speed of about 35 knots and the capacity to go nonstop around the world. In the Vendee race, it goes south, following a southern arch. This is the same arch undertaken at the turn of the century by Shackleton, who needed twenty-four months and a substantial crew.

The difference between the experiences early in the century and the experiences with the Vendee Great South Yacht Race is the difference in technologies, which enables a single individual to achieve the objective. My message is that technology empowers. It is the focus on new technology by biotechs that allows them to sail faster than large pharmaceutical firms.

The Vendee race also has some good analogies to business. Let me illustrate. Four yachts were sunk. Three were sunk under conditions in which they had full appreciation of conditions and their position. The fourth yacht knew where it was but not the surrounding conditions. It had lost its technology and thus was unable to estimate the surrounding conditions.

There were two categories of rescuers for these failing yachts. There was the individual, high-tech rescuer, as illustrated by Peter Gross, who found the failing boat in the vast southern ocean. He utilized GPS technology and had full knowledge of the conditions surrounding both single-man boats. In the second

example, the rescuer was disadvantaged because she lacked GPS position and knowledge of the surrounding environment. The third situation utilized a large interdisciplinary team. All came to the rescue of individual entrepreneurs and, in this case, individual sailors. The outcome of the race was one lost at sea, one racer-to-racer rescue (I equate that to biotech-to-biotech rescue), and two rescued by large organizations (I equate that to pharma). The overall outcome of the Great Southern Race: one winner, eight finished, four sunk, three rescued, and one lost. That is about the same outcome on biotechnology investment. I hope you remember this illustration as an example of what it takes for high tech to succeed.

I will now shift from this introductory illustration to discuss the technologies that are enabling or empowering smaller numbers of scientists to do more. HIV drugs have been discussed. It was my great pleasure to be senior vice president at Merck as we developed the reverse transcriptase inhibitors and proteinase inhibitors. I cannot recall a time in science that has been so rewarding. We were able to see these drugs safely introduced and death rates fall. It was an exciting, exciting time. We focused on the technologies necessary to achieve that objective in eight and a half years, which was a record time for drug approval by the FDA. No other drug development effort has ever matched that effort. It started with the isolation of the HIV virus, isolation recombinant DNA technology, cloning, sequencing, and understanding the structure and function of the HIV virus. Converging disruptive technologies were fundamental to the project; without them we would have had no product.

Never underestimate the power of cell biology. Those who criticize the Nixon era war on cancer, saying it achieved little, were wrong. The war on cancer gave the United States dominance in the area of cell biology. It was the ability to grow cells and use a virus's DNA to infect a cell that allowed us to satisfy Koch's postulates that the killing of a cell was caused by a virus. Then came the ability to study drug targets by genomic sequencing and predicting gene function and thus matching the cell biology to drug development.

We had lucky breaks in the first two HIV drugs. There were cancer products in development that were structurally similar to the inhibitors of the reverse transcriptase and the antihypertensive drugs. We were off and running, as were many other pharmaceutical companies. We were on target within a short period of time. Thus by recombinant DNA technology, Koch's hypothesis was satisfied by cell biology, followed by the lucky break of having the lead compounds. We are now developing new products (integrase inhibitors and CCR5 and 4 blockers). But this development is more difficult because we lack leads; thus we have to find them by combinatorial chemistry, leading to a longer development time.

Let me shift to replacement inhibitory proteins. Examples of replacement proteins would be Epos Factor 8, interferon, growth hormone, and insulin. Examples of the inhibitory proteins would be monoclonal antibodies now used

for anticoagulation, arthritis, and cancer. There are some very novel new protein products that I would put under the classification of a Trojan horse. It looks pretty friendly, but if you let it in the door to that receptor, it kills the receptor's function. Examples include emerging drugs for arthritis and cancer. These are true recombinant molecules that create a new event at the target receptor. Recombinant DNA technology and bioinformatics were used to predict functionality of these proteins and thus select them for drug development. We drew upon an accumulation of data from huge databases and bioinformatics that were critical to the identification of proteins and their corresponding monoclonal antibodies. If you examine the products from this arena, many of them are fashioned to a native molecule. We can, however, improve on nature for pharmaceutical products. We can make it an injectable, achieve a therapy peak, make a longer action, and add a safety factor. The study of proteins and monoclonal antibodies opened a new therapeutic area and created biotechnology.

Let me shift to HIV vaccines. Utilizing DNA technology, viral genome sequencing as well as delivery of viral vector constrictions, HIV vaccine strategy is directed at making a harmless virus that delivers the immunological challenge and creates the immune response protective from HIV. Such a safe virus was made possible by our understanding its genes and predicting what could be removed from these vectors to create the vaccine. Cell growth and cell transfer were critical to success.

HIV vaccines have been extremely difficult to develop. We had a poor understanding of how to protect against HIV infections. We had to discover the process by which the virus made cell entry, permanently established itself, avoided the immune protective system, and others. The creativity of individual scientists to understand this biology has made possible the new vaccines now in trial. There have been misjudgments made along the way. We know now that antibodies alone do not work to protect individuals. What worked for hepatitis B, human papillomavirus, and other viruses did not work for HIV. The entire strategy had to be changed to accommodate so-called viral cell killing. Last week we witnessed the first failure of this strategy that used a canary pox virus vaccine. Even with knowledge and good design, we still have a challenge on the use of these disruptive tools to achieve a vaccine. One trial I want you to follow now is one using a combination of a DNA-injectable, followed by a protected artificial virus construct for T-cell immune stimulation. It has protective effects for the primate with HIV. Such a vaccine may protect individuals from infection by clearing infected patients of their residual infected cells, those not eliminated by drug cocktails.

Next, I will focus on Alzheimer's. Consider where we were with Alzheimer's drug development ten years ago. Our efforts have been absolutely focused and put into logic by the discovery of disease genes responsible for inherited forms of Alzheimer's. The study of human genetics and the discovery of the disease–

gene associations set the field to work in a logical manner. Before these discoveries we had no conceptualization of the disease or logic for drug development. There are many more opportunities from human genetics. Humans have about 5,000 to 6,000 inheritable diseases whose causative genes are yet to be discovered. The disease–gene relationship represents the starting point for conceptualizing the disease process and removes the biologic chaos. Approximately forty disease–gene associations are being discovered per month. Ten years ago it was ten per year. This accelerated discovery rate can be connected to the scientific empowerment of the human genome project completed in 2003.

High-throughput drug screening and combinatorial chemistry have accelerated the discovery of lead compounds. In the past, pharmaceutical companies amassed vast collections of chemical compounds, without a strategy to move from one compound to others efficiently. All changed with the conceptualization and implementation of combinatorial chemistry, where one could begin to build platforms of space-occupying chemistry. This created large numbers of compounds. Now, a million-compound collection is not uncommon. Furthermore, rarely do the first compounds have the best properties. Medicinal compounds are modified for safety, drug distribution, dosage, etc. Combinatorial chemistry has that strategy to achieve such objectives. Scientists can move rapidly. A single scientist can develop from a single lead compound a new set of 100 or 500 related compounds within a week. Such productivity previously required teams of 100 to 500 chemists. Without high-throughput drug screening and computer analysis of large numbers of compounds, none of this would have been achieved. Each company now has adapted this integrated technology for drug development. Alzheimer drug development makes tremendous use of combinatorial chemistry, high-throughput screening, and human genetic gene leads to achieve the objective of new drugs.

The most important development involving descriptive technologies is that of disease models and the development of designer species. It makes use of genome sequences, human genetics, mouse genome sequences, and stem cells. We have known about the stem cell for over twenty years. It is the cell that can be manipulated to realize all the mouse models that we constructed over the past twenty years. Stem cells have been very much in the research forefront and are used very proactively. We are in the early stage of use of stem cells for human disease.

Let me illustrate a stem cell utility. Let us assume there are five genes involved in Alzheimer's. We know that for a single patient with Alzheimer's, we can identify one of four genes. By transfer of the patient's cell nucleus into a laboratory-friendly cell type, we would have the capacity to test a single drug for efficacy. This provides a preclinical test for therapy response and drug choice.

Let's focus on the creation of mouse disease models. Companies like Lexicon Genetics, located in The Woodlands, Texas, and several others have carried out gene knockouts in the mouse to create disease models, allowing a scientist to

examine a single gene and determine the disease. The hospitalization and examination rate of these mouse knockouts is a thousand per year. Thus Lexicon has industrialized disease–gene discovery for mice and man and accelerated drug development.

Let us now focus on Texas. Texas is a big agricultural state. Our northern neighbor, Canada, is also a large agricultural entity. Canada committed substantial resources to developing special species of advantage in fish, forest, commercial crops, and production animals. I use this as an example of how the empowering technology in genome science allows you to reach not only from the mammal but also into very important commercial species. We need to accelerate our Texas initiatives in biotechnology.

What has been achieved by biotechnology? Of the new therapeutics, 35 percent comes from innovative products being developed out of biotech corporations. That is a very aggressive pipeline of new therapeutics. We have numerous examples of biotech products being licensed and acquired by large pharma. The point to be made: Biotech can move faster and more focused than pharma. Big pharma is that locomotive preparing to have the switches thrown. Big pharma is powerful in development; biotechs are weak in development. Biotechs can prove the principle of the therapy, bring the product to the point of high likelihood of utility, but need big pharma to engage in development. Rarely can a biotech go to FDA approval with available funding.

What are the novel products coming out of biotechnology? I can assure you that few large pharmas would have taken on the uncertainty of these new therapeutics. They just will not take the challenge; there is too high a risk. There are many biotechs. Some will succeed. Some will fail. It is, however, biotechnology that will discover an important pathway for regulating cancer, controlling cancer, regulating diseases like type 1 diabetes, multiple sclerosis, and others—all based on cytotoxic T lymphocytes (CTLs).

There is not one pharma that would have touched antisense because of its novelty. The first ophthalmologic products are now in use. Isis Innovation started antisense therapy. Almost all vaccines are licensed from outside biotechs. Biotechs now lead the development of terrorism vaccines. No pharma would approach gene therapy—again based on risk. Wonderful opportunities now exist for organ and cell transplantation, and these will rely upon biotechs for advancement.

Let's examine the financial drivers for biotechnology in Texas. As shown in Table 1, the National Institutes of Health is the gorilla. The National Science Foundation is increasing in importance. Pharma exceeds these two because of the high cost of development. Venture capital, while small, is a key stimulator. State contributions are about a million nationally.

Diversification and building high-tech industry are critical to the state. Let's examine the fuel for the discovery engine in Texas (*Table 2*). Listed here are

Table 1
Financial Drivers of Biotechnology in Texas

National Institutes of Health	$23.0 million
National Science Foundation	$ 4.8 million
Pharmas	$26.0 million
Venture Capital	$ 3.3 million
State	$ 1.0 million

NIH numbers from 2001, and they are focused on the biologic sector. This does not include training, so it gives you an idea of the level of investment. You can see that Texas is doing extremely well. These are excellent numbers. This is an important engine for the state and reflects the state's wisdom in developing these academic institutions. We need to capitalize on this base. An example of how to capitalize would be the creation of the ability to transfer this technology into industrial parks. I favor development of a second Texas Medical Center for Industry, adjacent to the Texas Medical Center and the size of the Texas Medical Center. It is estimated such a campus would exceed the income of the Texas Medical Center within fifteen years. We are underachieving by almost tenfold the introduction of new corporations in the state based upon our investment. Before we rest on our achievements in our great state, there is competition to be considered. I have identified two substantial challengers—San Francisco and Boston. Their numbers (*Table 3*) are terrific. These are very powerful institutions that score beautifully in the ability of their scientists to draw in basic research numbers.

Table 2
Texas' 2001 Share of National Research Funds

Baylor College of Medicine	**$205,439,317**
M.D. Anderson	**$ 90,188,425**
Rice	**$ 4,436,938**
University of Houston	**$ 12,038,167**
Univ. Texas Houston	**$ 71,920,305**
Univ. Texas Austin	**$ 34,236,699**
Univ. Texas Southwestern	**$ 131,882,625**
Univ. Texas San Antonio	**$ 62,733,840**
Texas A&M	**$ 20,300,939 + $13,912,253**
Univ. Texas Galveston	**$ 61,319,476**

SOURCE: National Institutes of Health.

Table 3
Texas' Competition for National Research Funds in 2001

Univ. California San Francisco	$292,103,420
Stanford University	$204,766,474
Univ. California Berkeley	$ 78,245,614
Harvard University	$243,710,837
Brigham & Women's Hospital	$164,768,897
Boston University	$111,611,498
Dana-Farber Cancer Institute	$ 95,072,888
Whitehead Inst. for Biomedical Research	$ 91,914,328
Univ. Massachusetts Medical School	$ 77,018,828
Massachusetts Institute of Technology	$ 71,094,309
Children's Hospital (Boston)	$ 63,920,552

SOURCE: National Institutes of Health.

My favorite project on the West Coast is Mission Bay in San Francisco. It is the site of the old 1903 earthquake that has been reclaimed. This is a real estate-driven park. The funds are from the private sector. Everything from academic institutions to biotech clusters is located within it. Profit is made on the commercial side: commercial centers, townhouses, housing, hotels, and, incidentally, biotech parks in academic institutions. It is located adjacent to downtown. It is a beautiful opportunity for San Francisco to accelerate what is already a very powerful focus in the state.

The opportunities for expansion in our region are to increase the number of quality start-ups. We need to recruit pharma and biotech into our region, not just to grow them but to recruit them. We need to be looking for more opportunities for consolidation. The consolidations do not have to come out of Texas. We could take a Texas base and move a company from Seattle or Baltimore, for example. Consolidations are critical because of the large numbers of companies drifting down to smaller numbers of quality organizations.

It is clear that improvement in business plans and management is critical. The talent and skills are not at an optimal level in our state. To have talent and the opportunity for expansion, we need to build and recruit. We need larger VC investment firms. We need regional incentives such as is being done in Michigan, Ohio, Missouri, and others. I am extremely pleased with Governor Perry's initiative in the state of Texas. When you have the governor leading, others join the logic. His leadership has been critical. We are fortunate to have this leadership in the state. Finally, we need to advertise, advertise, advertise, and communicate with the VCs that are moving and driving biotech.

Table 4
Publicly Traded Biotech Corporations in Texas

Introgen ($95M)
Lexicon ($460M)
Luminex ($200M)
Tanox ($600M)
Texas Biotechnology ($250M)
Total: $1.605 Billion

Table 4 shows the Texas-based companies traded on the Nasdaq. All these companies are derivatives of academic institutions. The research engine of the institutions leads to the ideas that back these companies. We are doing well, but we can do better.

Lexicon Genetics, in The Woodlands, is an example of one of those Nasdaq-traded companies. It is now a 500-person pharmaceutical company. It has two divisions; the chemistry company is in New Jersey, and a biology division is in The Woodlands. Gordon Cain has to be given a lot of credit for this corporation. He stepped up to the plate to singularly fund the company. He told me several days ago he preferred single ownership. Few had his vision and resources. The public offering raised the necessary capital from the market to build a corporation in Texas and New Jersey. We can do more in Texas with leaders of the quality and confidence of Gordon Cain.

Let me finish with a few comments. First, we have abundant unsolved medical needs. The new technology enables innovative discovery. Second, we have an emerging set of new information from the genome project—all investigator empowering. Third, the biotechs can move faster and are more focused than pharmas. What are the challenges? I see the following challenges for biotech: Visualize your product. Manage the company to achieve that product. Value the product properly at the outset, and fund the company sufficiently to be able to drive to the end point you are trying to achieve in the development. Consistently look for the opportunity for consolidation, and wish good health to big pharma.

PART THREE

Legal and Regulatory Issues Facing Biotechnology

Patents and New Product Development in the Pharmaceutical and Biotechnology Industries

Henry G. Grabowski

Reaching Through the Genome

Rebecca S. Eisenberg

Patents and New Product Development in the Pharmaceutical and Biotechnology Industries

Henry G. Grabowski

Grilliches, in a 1992 survey paper, found that high social returns to R&D were a major factor underlying the growth in per capita income and consumer welfare during the twentieth century.[1] Many of the studies done by economists on this topic have found that the social returns to R&D are more than twice the private returns to R&D.[2] A primary reason for this finding is the positive externalities generally associated with industrial innovations. As F. M. Scherer stated in his leading graduate text in industrial organization, "Making the best use of resources at any time is important. But in the long run it is dynamic performance that counts."[3]

The pharmaceutical and biotechnology industries, which are among the most research-intensive industries, have been the focus of several studies on benefit cost and social return on R&D. Elsewhere in this symposium, Frank Lichtenberg has reported on his finding concerning the impact of new drugs on increased longevity, worker productivity, and savings in other types of medical expenditures.[4] He finds significant aggregate net benefits to society from new drug introductions. His analysis is consistent with more microeconomic analyses targeted to specific medical conditions such as cardiovascular disease, depression, and infectious disease. These studies have also found high incremental social benefits from new drug innovation.[5]

Another general finding of the academic literature is that public policy actions can have a significant influence on the rate of innovation in particular industries. Among the key industrial policies influencing the innovative process in pharmaceuticals are the public support of biomedical research, patents, FDA regulatory policy, and government reimbursement controls.[6] The focus of this paper is on the role and impact of patents and intellectual property protection in the discovery and development of new pharmaceutical and biotechnical products.

The importance of patents to pharmaceutical innovation has been reported in several cross-industry studies by economists. In particular, Richard Levin et al. and Wes Cohen et al. have undertaken surveys of U.S. R&D managers in a large cross section of industries to identify which factors are most important and necessary in appropriating the benefits from innovations.[7] These factors included the competitive advantages of being first in the market, superior sales and service efforts, and secrecy and complexity of productions and product technology, as well as patents. Both studies found that the pharmaceutical industry placed the highest importance on patents. By contrast, many other research-intensive industries, such as computers and semiconductors, placed greater stress on factors like lead time and learning-by-doing efficiencies in production accruing to first movers.

The findings of these studies are in accordance with an earlier study by the British economists Taylor and Silberston. Based on a survey of U.K. R&D managers, they estimated that pharmaceutical R&D expenditures would be reduced by 64 percent in the absence of patent protections. By contrast, the corresponding reduction was only 8 percent across all industries. Similar findings were reported by Edwin Mansfield from a survey of the research directors of 100 U.S. corporations.[8]

In the sections of this paper that follow, we examine the economic characteristics of the R&D process in pharmaceuticals that make patents so critical. The next two sections consider the costs of innovation relative to imitation in this industry. The following section considers whether the biotech industry is different from the pharmaceutical industry in terms of R&D costs. The paper then considers the distribution of returns on R&D in these industries. The final section presents conclusions and policy considerations.

R&D COSTS FOR A NEW DRUG INTRODUCTION

The explanation for why patents are more important to pharmaceutical firms in appropriating the benefits from innovation follows directly from the characteristics of the pharmaceutical R&D process. In essence, it takes several hundred million dollars to discover, develop, and gain regulatory approval for a new medicine. Absent patent protection, or some equivalent barrier, imitators could free ride on the innovator's FDA approval and duplicate the compound for a small fraction of the originator's costs. In essence, imitation costs in pharmaceuticals are extremely low relative to the innovator's costs for discovering and developing a new compound.

One of the reasons R&D is so costly in pharmaceuticals is that most new drug candidates fail to reach the market. Failure can result from toxicity, carcinogenicity, manufacturing difficulties, inconvenient dosing characteristics, inadequate efficacy, economic and competitive factors, and various other prob-

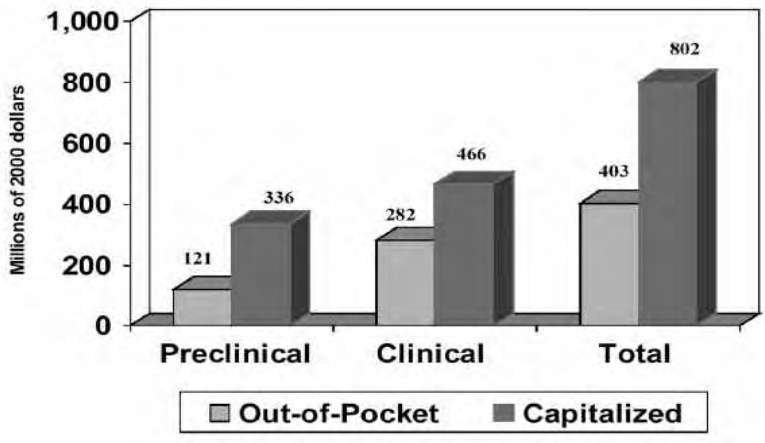
lems. Typically, less than 1 percent of the compounds examined in the preclinical period make it into human testing. Only 20 percent of the compounds entering clinical trials survive the development process and gain FDA approval.[9] Furthermore, the full R&D process from synthesis to FDA approval involves undertaking successive trials of increasing size and complexity. The preclinical and clinical testing phases generally take more than a decade to complete.[10]

In a recently completed study, Joe DiMasi, Ron Hansen, and I examined the average R&D cost for drugs introduced into the market in the late 1990s. Data were collected on R&D costs for a randomly selected sample of sixty-eight investigational drugs from ten multinational firms. We found the representative new product approval incurred out-of-pocket costs of over $400 million.[11] This includes money spent in the discovery, preclinical, and clinical phases, as well as an allocation for the cost of failures.

Figure 1 shows a breakdown of total R&D costs per approved drug that are incurred during the preclinical and clinical R&D phases. As shown in this figure, expenditures in the clinical period account for roughly 70 percent of total out-of-pocket expenditures. This reflects the fact that clinical trials are very expensive on a per patient basis, many drugs must be tested for every one approved, and drugs that do make it to the final testing phase and FDA submission typically require premarket testing on thousands of patients.

Figure 1 also shows R&D costs capitalized to the date of marketing at a representative cost of capital for the pharmaceutical industry of 11 percent. The average capitalized R&D cost for a new drug introduction during this period is

Figure 1
Out-of-Pocket and Capitalized Costs per Approved Drug



SOURCE: Tufts Center for the Study of Drug Development.

$802 million, or nearly double the out-of-pocket expenditure. Capital costs are high in this situation because of the long time periods involved in pharmaceutical R&D. More than a decade typically elapses from initial drug synthesis to final FDA approval. Since preclinical expenditures occur several years prior to FDA approval, these costs are subject to greater compounding at the industry cost of capital of 11 percent. Therefore, they account for a greater proportion of total capitalized compared with total out-of-pocket costs (42 percent versus 30 percent).

R&D costs per new drug approval were observed to have increased at an annual rate of 7.4 percent above general inflation when compared with the costs of 1980s introductions. A major factor driving this increase is the size, complexity, and number of clinical trials, which have increased significantly in the 1990s compared with the 1980s.[12] One important factor underlying this trend is the increasing focus of the pharmaceutical industry on chronic and degenerative diseases. These conditions require larger trial sizes to establish their efficacy and longer time periods for effects to be observed.

A number of factors could operate to alter the growth pattern for future R&D costs. Emerging discovery and technologies may have profound effects on R&D productivity in the next decade. The mapping of the genome, and related advances in fields like proteomics and bioinformatics, has led to an abundance of new disease targets. Nevertheless, some industry analysts have hypothesized that these developments may actually cause R&D costs to rise in the short run.[13] The basic reason is that these new technologies require substantial up-front investments, and to date they have generated many disease targets that are not yet well understood. Eventually this expansion in the scientific knowledge base should lead to substantial efficiencies in the R&D process for new pharmaceuticals.

GENERIC ENTRY AND COMPETITION

In contrast to new product introductions, the development costs of generic compounds are relatively modest. In the United States, since the passage of the 1984 Hatch–Waxman Act, generic products need only demonstrate that they are bioequivalent to the pioneering brand to receive market registration. Generic firms can file an abbreviated new drug application (ANDA). The ANDA process only takes a few years and typically costs a few million dollars.[14] The probability of success is also very high, as reflected by the fact that many generic firms file to receive FDA approval and enter the market within a short time window around patent expiration of the pioneer brand.

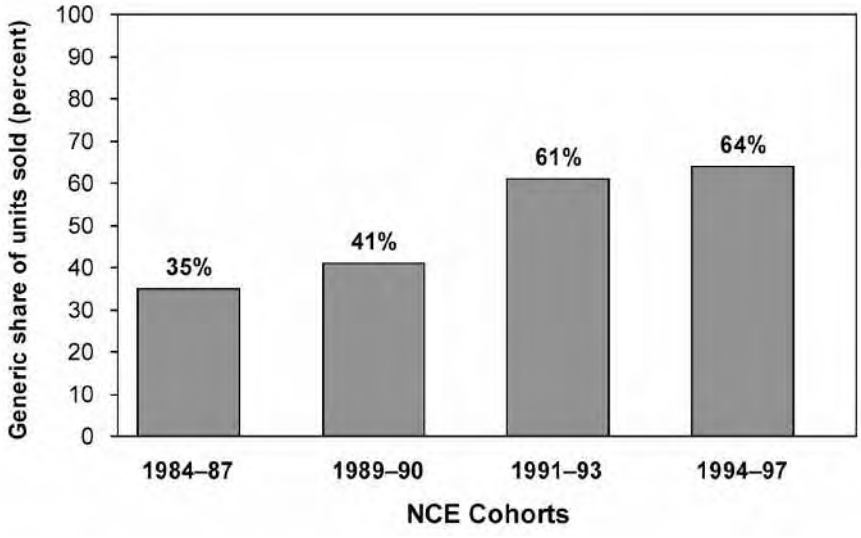
John Vernon and I have completed studies of generic competition during the 1980s and 1990s.[15] A distinctive pattern of competitive behavior for generic and brand name firms has emerged in the wake of the 1984 act. First, commercially significant products experienced a large number of generic entrants within

a short time after patent expiration. This was in sharp contrast to what occurred in the pre-1984 period. In the post-1984 period, we also observed a strong positive relation between the size of the market and the number of generic competitors, in accordance with expectations from economic theory.

Second, generics exhibited a high degree of price competition. The initial generic product entered the market at a significant discount to the brand name firm, and this discount grew larger as the number of generic competitors for a particular brand name product expanded over time. For our 1984 to 1989 sample of commercially significant products, generic prices averaged 61 percent of the brand name product during the first month of generic competition. This declined to 37 percent by two years after entry.

Third, we observed a more rapid rate of sales erosion by the brand name products in the case of more recent patent expirations. This is illustrated in Figure 2. This figure shows the growth in generic market shares during the first year on the market for four successive time cohorts. Market shares are measured in terms of pills sold for the most popular dosage size. The more recent time cohorts in Figure 2 are characterized by much more intensive generic competition. The observed trend is particularly striking for the 1994–97 cohort of brand name products. In particular, generic drugs captured a 64 percent share of total units sold after one full year on the market. This increased to 73 percent after the second year. Recently, Prozac was subject to its first generic com-

Figure 2
Generic Market Shares One Year After Entry



petition, in September 2001. Prozac lost over 80 percent of its U.S. sales to generics within the first month after their entry.

In sum, price competition and generic utilization have increased dramatically since the Hatch–Waxman Act was passed. In the mid-1980s, generic products accounted for approximately 19 percent of all prescriptions. By 1999, the figure was 47 percent.[16] The growth of managed care and other related demand-side changes also have been important factors underlying the rapid increase in generic usage that has taken place during the last decade. However, the passage of the 1984 act played a major role in relaxing the regulatory hurdles for generic firms and facilitating higher levels of generic entry.

ARE THE INNOVATION AND IMITATION COSTS OF NEW BIOTECH ENTITIES DIFFERENT?

Most of the analyses of R&D costs for new drug entities and their generic imitators have focused on small-molecule new chemical entities. This reflects the fact that the biotech industry is relatively young. New biologic entities were first introduced in the 1980s. By 1994, only twenty-nine new biologic entities had been introduced into the U.S. market, but this number has increased dramatically since then. In this regard, forty-one new biological introductions occurred between 1995 and 2001.

The newest R&D cost study by DiMasi et al. does include seven biotech compounds in the sample of sixty-nine entities for which data were obtained from ten major pharmaceutical and biopharmaceutical firms.[17] While this sample of biological entities is too small to say anything definitive about the cost of biotech drug development, the clinical phase costs in the DiMasi et al. study were similar for the biotech and pharmaceutical projects.

As discussed above, capitalized R&D costs per new drug introductions are influenced by a number of factors. These include out-of-pocket costs at the preclinical and clinical phase, the probability of success for new drug candidates at different stages of the R&D process, and the length of time it takes to move through all the stages of the R&D process and gain FDA approval. Recent studies of the probability of success and length of the R&D process for biotech drugs indicate a convergence in these parameters toward the values observed for small-molecule pharmaceuticals.

Two initial studies of success rates for biotech drugs were performed by Bienz-Tadmor et al. and Struck.[18] Both studies found that success rates for biotech drugs were substantially higher than success rates for new chemical entities. In particular, both studies projected success rates for biopharmaceuticals in excess of 50 percent. However, a basic assumption implicit in the methodology of both studies is that success rates for biotech drugs that entered development in the late 1980s and early 1990s are the same as for the biotech

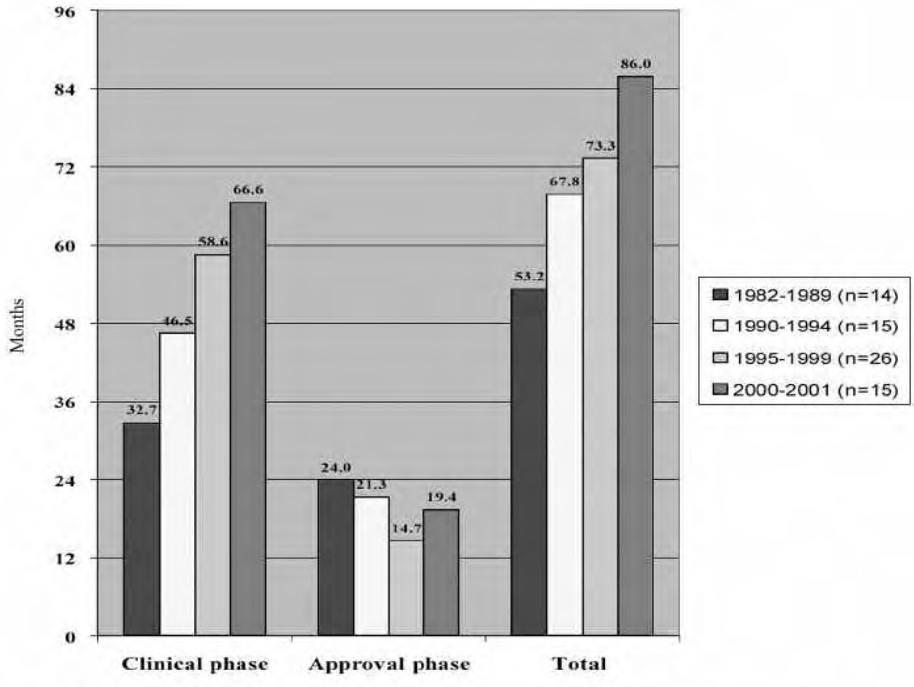
drugs that entered development in the early to mid-1980s. This was a very strong, and potentially hazardous, assumption, given that 90 percent of the drugs in their samples were still under active testing.

Subsequently, Gosse et al. analyzed a comprehensive sample of U.S. biopharmaceutical drugs and compared the success rates of older and newer biotech entities.[19] They found dramatic differences in the time pattern of success rates observed for early versus later biotech drug cohorts. In particular, for the investigational new drugs (INDs) filed in the early 1980s, the success rate for new recombinant entities is 38 percent. For the INDs filed during the late 1980s, the success rate was only 10 percent, based on approvals to date (i.e., six years after testing). At a comparable point in time, the new recombinant entities of the early 1980s had a success rate of 26 percent. In fact, the success curve of the recent recombinant entities more closely resembles that of new chemical entities rather than that for the early biological entities.

This result is consistent with the history of biotech research in the United States. The first biological entities introduced into the market were naturally occurring proteins that replaced purified nonrecombinant formulations already in general use as established therapies (e.g., insulin and human growth hormone). It is reasonable to expect that recombinant versions of established therapies would have high success rates, once the technology to manufacture these products was proven. Other earlier targets for biotechnology were naturally occurring proteins with well-known and defined physiologic activity (e.g., erythropoietin and filgrastim). As the biotech drugs moved to targets for which limited knowledge existed about clinical and pharmacological profiles, it is reasonable to expect that success rates would fall back toward those of conventional drug entities. This is consistent with the findings of the recent Gosse et al. study. The prospect of a long and uncertain discovery and development period for a new drug is another factor affecting costs and risks in the drug R&D process. The longer the development and approval process, the higher the interest and opportunity costs and the overall capitalized R&D costs of a new drug introduction. Recently, Janice Reichert of the Tufts University Center for the Study of Drug Development has done a historical analysis of clinical development time for successive cohorts of new biopharmaceuticals.[20] The results are presented in Figure 3. This figure shows that the earliest biopharmaceuticals had much shorter total clinical development times than more recent introductions. In particular, the cohort of 2000–01 new biopharmaceutical introductions had a total clinical development time (including FDA approval) of eighty-six months, versus 53.2 months for 1982–89 biopharmaceutical introductions.

Hence the experience with respect to development times parallels the experience observed with respect to success rates. In particular, there has been a convergence in clinical trial period times observed for new biological and new chemical entries. Of course, the biotech industry is still in the early stages of

Figure 3
Historical Comparison: Biopharms



SOURCE: Tufts Center for the Study of Drug Development *Outlook 2002*.

evolution. It may eventually produce higher success rates and shorter development times as a result of new technologies currently emerging in the discovery period. However, the best evidence at the current time is that biopharmaceuticals, like new chemical entities, are subject to very high rates of attrition and long gestation periods in the clinical development stage.

One aspect in which biopharmaceuticals may be different from small-molecule new chemical entities concerns the ease of generic entry when patents expire. To date, there have only been a few patent expirations involving biopharmaceuticals. One case in which there has been entry after patent expiration is human growth hormone. However, all the entry to date has been by other big pharma firms that have had experience supplying this product in Europe and Japan (Pharmacia, Novo Nordisk, and Ares-Serono). There are greater hurdles in manufacturing biopharmaceuticals at an efficient scale compared with new chemical entities, and in addition there are greater regulatory requirements for biologicals associated with the manufacturing process.[21] These factors may

moderate the degree of imitative competition for biopharmaceuticals compared with small-molecule chemical entities. Whether or not this is the case will become more apparent when some of the commercially important biopharmaceuticals are subject to patent expiration and potential competitive entry during the current decade.

RETURNS ON R&D FOR NEW DRUG INTRODUCTIONS

John Vernon and I have examined the distribution of returns for new drug introductions.[22] This work builds directly on the R&D cost analysis of DiMasi et al. and considers the sales and net revenues realized over the product life of new drug introductions during the 1970s, 1980s, and 1990s. A finding of this work is that the distribution of returns to new drug introductions is highly variable. This is another source of risks for firms developing new drug introductions.

Figure 4 shows the distribution for present value of net revenues (revenues net of production and distribution costs but gross of R&D investment outlays) for 1990 to 1994 new drug introductions. The distribution shows very strong skewness. Roughly one half of the overall present value from this sample of 118 compounds is accounted for by the top-ranked decile of new drug introductions. The top decile of new drug introductions has an estimated after-

Figure 4
Present Values by Decile: 1990–94 NCEs

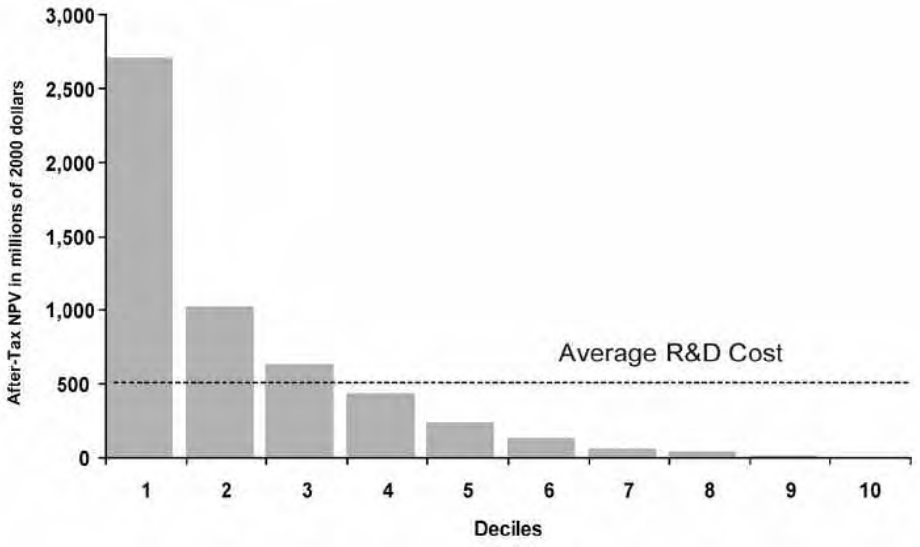
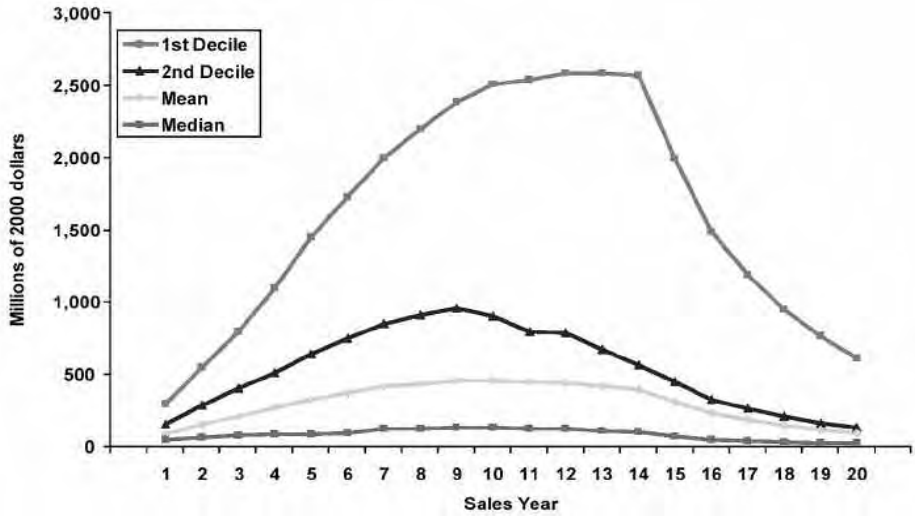


Figure 5
Sales Profiles



tax present value that is more than five times the present value of average after-tax R&D costs per approved introduction. Furthermore, only the top three deciles have present values that exceed average R&D costs.

A major factor underlying the skewed distribution observed in Figure 4 is the level of sales realized by new drug introductions. Figure 5 shows sales profiles for the top two deciles and also for the mean and median drug introduction for the 1990 to 1994 period. This figure illustrates the highly skewed nature of the sales distribution for new drug introductions. The sales peak of the top decile drugs is several times greater than the sales peak of the next decile. In addition, the mean sales curve is much higher than the median one. This latter result is also reflective of a highly skewed distribution. John Vernon and I have investigated other periods and time cohorts of new introductions and found that they are characterized by similar patterns.[23]

Our returns to R&D analyses confirm the fact that the search for blockbuster drugs is what drives the R&D process in pharmaceuticals. The median new drug does not cover the R&D costs of the average compound (including allocations for the cost of discovery and the candidates that fall by the wayside). A few top-selling drugs are really key in terms of achieving economic success in pharmaceutical R&D over the long run. This result implies that larger firms, which have the resources to develop a diversified portfolio of drugs simultaneously, will have lower overall risk of failure (e.g., bankruptcy) than small firms. The large fixed costs of pharmaceutical development and the skewed distribu-

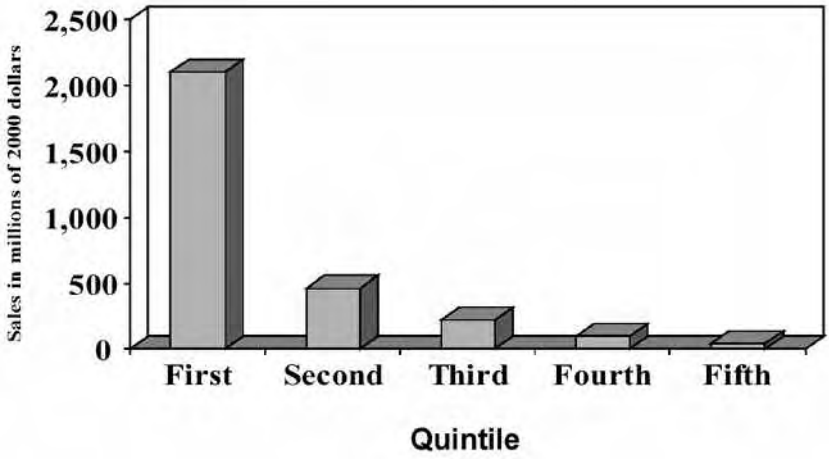
tion of outcomes help to explain the clustering of biotech firms at the research stage of the R&D process and the large number of alliances between biotech and big pharma firms at the development and marketing stages.

In Figure 6, the distribution of worldwide sales in 2000 is presented for thirty new biological entities introduced into the U.S. market between 1982 and 1994. This includes new biological entities at different stages of their life cycle. However, all these compounds have been in the market at least seven years, and therefore they have progressed beyond the initial rapid growth phase of their life cycle. The sales data presented in Figure 6 indicate that new biopharmaceuticals also exhibit a high degree of skewness, similar to the much larger cohort of new drug introductions.

The high degree of skewness in the outcomes of pharmaceutical R&D projects indicates that there are substantial risks in this endeavor, both for big pharma firms as well as smaller biotech enterprises. Even though many big pharma firms spend billions of dollars per year on a diversified portfolio of in-house and outsourced projects, this does not guarantee a stable set of outcomes. In particular, the law of large numbers does not work very well in the case of skewed distributions.

If a firm invests in a large diversified portfolio of projects that are normally distributed, we expect that returns can be predicted with some confidence. When returns are highly skewed, however, individual companies experience highly volatile outcomes even when they invest in large numbers of independ-

Figure 6
New Biotech Introductions, 1982–94
Worldwide Sales in 2000



ent projects. To illustrate this point, John Vernon and I examined the new product sales for the U.S. drug companies that spent between $300 million and $500 million on their global R&D in the mid-1980s (the top-tier group in that period). We found subsequent new product sales emanating from these R&D efforts varied between $100 million and $3 billion (after seven years of market life).[24]

Finally, it is important to note that the distribution of outcomes from pharmaceutical R&D projects has similar characteristics to many other innovation samples, including venture capital funding of high-tech start-ups. In this regard, Scherer et al. have examined the size distribution of profits from investments in innovation projects using a diverse set of data samples.[25] Their analysis included two large samples of high technology venture capital investments, as well as a comprehensive sample of venture-backed start-up firms that had their initial public offering in the mid-1980s. A common finding was that the size distribution of profit returns from technological innovation is strongly skewed to the right. As in the case of new drug introductions, the most profitable cases contribute a disproportionate fraction of the total profits from innovation.

Table 1 summarizes the results from three data sets employed in Scherer's analysis. The first two data sets, assembled by Venture Capital Inc. and Horsley Keough Associates, involve an analysis of several hundred venture capital firm investments in high-tech start-up companies. Scherer's analysis indicates that roughly 60 percent of the returns, measured at the time of the final distributions to investors, are realized by the top decile of venture capital projects. At the same time, roughly half of the projects in these samples failed to earn positive returns. Similarly, an analysis of the stock market performance of the universe of high-tech companies that went public in the mid-1980s found that the top decile of companies realized 62 percent of the sample's total market value ten years later.

Table 1
Returns Distribution for Selective Innovation Samples

Data set	Percentage of value from top decile
Venture Capital (Start-ups)	62
Horsley Keough (Start-ups)	59
1980s IPOs— (1995 value)	62
1990s New Drugs (Grabowski–Vernon)	52

The corresponding value for our sample of 1990–94 new drug introductions is 52 percent. Hence these samples of risky, high-tech start-up companies exhibit similar skewed distributions of returns to the pharmaceutical industry.

CONCLUSIONS AND POLICY CONSIDERATIONS

Economic analyses of the R&D process in pharmaceuticals indicate that it is a very costly and risky process, even for large established firms. Most compounds in the R&D pipeline never reach the marketplace. The process takes a long time, and the distribution of profits among those that are marketed is highly skewed. A few blockbuster successes cover the losses on many other R&D investment projects.

Overall, then, a key implication of my work with John Vernon and Joe DiMasi is that the returns of research-intensive pharmaceutical firms are positive but are highly dependent on a relatively few highly successful new products. One important implication for public policy is that reimbursement, regulatory, or patent policies that target the returns to the largest-selling pharmaceuticals can have significant adverse consequences for R&D incentives in this industry.[26]

Many of the compounds in the top decile of the returns distribution involve the first mover, or other early entrants, in a new therapeutic class. The family of medicines in a given therapeutic class passes through a well-delineated life cycle. There is dynamic competition involving breakthrough, as well as incremental, advances among the branded products within that class. This dynamic competition, in turn, produces substantial consumer surplus and social returns, as discussed above. When the patents for established products expire, consumers also benefit from imitative competition from generic entrants, which provide social benefits in terms of significantly lower prices.

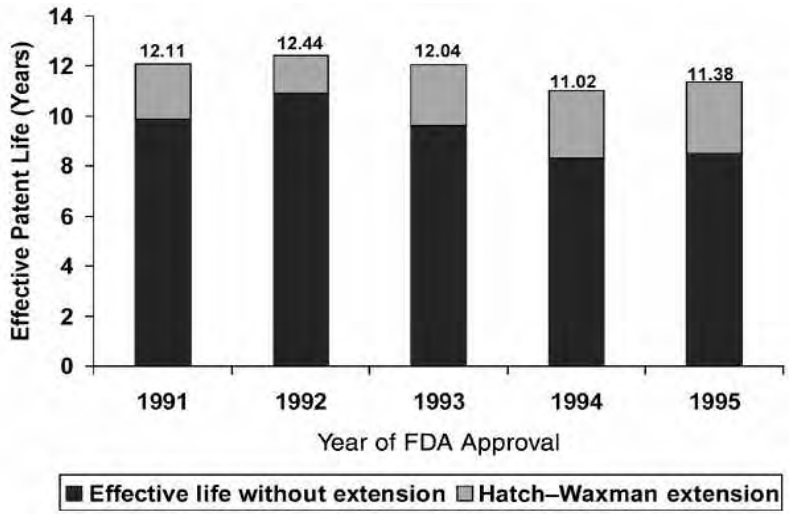
The patent system is the public policy instrument designed to balance the trade-offs inherent between these dynamic and generic forms of competition. Without a well-structured system of global patent protection, neither the research pharmaceutical industry nor the generic industry would be able to grow and prosper, as the rate of new product introductions and patent expirations would decline significantly.

Effective patent life (EPL), defined as patent time at a product's market launch date, is an important variable influencing R&D incentives in this industry because it takes many years to recoup the R&D costs and earn a positive return for a typical new drug introduction. Because firms apply for patents at the beginning of the clinical development process, significant patent time is lost by pharmaceutical products by the time of FDA approval. This implies a significant reduction in the effective patent life of drugs relative to the nominal life of twenty years.[27] In light of this, the United States, the European Community, and Japan have all enacted patent term restoration laws.

The U.S. law in this regard, the Hatch–Waxman Act, has been in existence since 1984. This law provides for patent term restoration of time lost during the clinical development and regulatory approval periods, up to a maximum of five years additional patent life.[28] This is also the law that facilitates generic entry by allowing generic firms to file abbreviated new drug applications, in which generic firms only have to demonstrate bioequivalence to the pioneer's products to obtain FDA approval. Prior to the passage of the act, generic firms had to submit their own proof of a compound's safety and efficacy, as well as show bioequivalence.[29]

John Vernon and I have investigated the effects of the 1984 act on both generic competition and effective patent lifetimes.[30] In this paper, I have summarized our analysis of the significant increases in generic competition that have taken place since the act's passage. We have also examined the impact of the law on effective patent lifetimes. Figure 7 shows the trends in EPLs by approval year for the new drugs introduced in the first half of the 1990s. This figure indicates that the average EPLs in the 1990s center around an eleven- to twelve-year range.[31] The mean for all 126 new drug introductions in the 1990–95 period is 11.7 years, with an average Hatch–Waxman extension of 2.33 years. In the last two years of this period, when virtually all of the drugs involve compounds that entered clinical testing after 1984, the average extension is close to three years in length. The mode of the frequency distribution of EPLs for this sample of annual new drug introductions is in the interval of twelve to fourteen years.

Figure 7
Effective Patent Life for 1991–95 NCEs



We also found that relatively few NCEs are marketed with effective patent lifetimes of less than ten years. The effective patent life on the top decile of compounds is particularly critical, given the highly skewed nature of the outcome distribution and the vital role that the top compounds play in sustaining the viability of the entire R&D enterprise. We found that effective patent life for these compounds tends to be a few years above the mean for the full sample as a whole. This suggests that firms are able to accelerate the development of commercially promising compounds by doing R&D in parallel and by undertaking other cost-increasing activities to marginally speed up the development process.

The Congressional Budget Office (CBO) has also done an analysis of the economic effects of the act.[32] As in our analysis, they found that generic competition has been a powerful force for price competition since 1984. The CBO estimated annual savings of $8 billion to $10 billion to consumers by the mid-1990s. In terms of R&D incentives, however, they found that the 1984 act has had negative consequences on the expected returns on R&D. In this regard, they estimated that the act, together with the increased demand-side incentives promulgated by managed-care organizations to utilize generic products in the 1990s, has resulted in steadily accelerating erosion in pioneer-brands' sales over time.

The CBO found that from the perspective of R&D returns, the much more rapid loss of sales in the period after patent expiration has dominated the patent term restoration aspects of the law. In particular, the CBO estimated a 12 percent lower expected value for the after-tax profits from R&D for the mean new drug compound as a consequence of the 1984 act. While the mean compound is still profitable in this analysis, the increased generic competition since 1984 can have adverse R&D incentives for compounds of above average riskiness or ones with shorter than average effective patent life.

Overall, the Hatch–Waxman Act has provided a relatively balanced approach to the trade-offs between pharmaceutical R&D and generic competition. Improvements on the margin could be considered by policymakers, such as a longer minimum exclusivity period before an ANDA could be filed for new drug introductions (currently five years in the United States but longer in Europe and Japan). Nevertheless, the law has provided a reasonably well-structured system of incentives for both innovative and generic firms. Both R&D activities and generic utilization have increased dramatically in the period since the passage of the 1984 act. Some groups have suggested that Congress consider changing the patent restoration aspects of the law in order to further increase generic competition in pharmaceuticals.[33] Given the critical role that patents and effective patent life play in terms of R&D incentives for this industry, this would not appear to be a desirable course of action on social welfare grounds.

NOTES

[1] Zvi Grilliches (1992), "The Search for R&D Spillovers," *Scandinavian Journal of Economics* 94 (Supplement): 29–47.

[2] Ibid., Table 1.

[3] F. M. Scherer (1980), *Industrial Market Structure and Economic Performance* (Chicago: Rand McNally), 407.

[4] Frank Lichtenberg, paper on social returns to pharmaceutical R&D, presented at April 19, 2002, Federal Reserve Bank of Dallas conference.

[5] See, for example, David M. Cutler and Mark McClellan (2001), "Is Technological Change in Medicine Worth It?" *Health Affairs* 20 (September/October): 11–29; Jack E. Triplett, ed. (1999), *Measuring the Price of Medical Treatments* (Washington, D.C.: Brookings Institution).

[6] Adrian Towse, ed. (1995), *Industrial Policy and the Pharmaceutical Industry* (London: Office of Health Economics).

[7] Richard D. Levin et al. (1987), "Appropriating the Returns from Industrial Research and Development," *Brookings Papers on Economic Activity*: 783–820; Wes Cohen et al. (1997), "Appropriability Conditions and Why Firms Patent and Why They Do Not in the American Manufacturing Sector," Carnegie Mellon University Working Paper (Pittsburgh).

[8] C. T. Taylor and Z. A. Silberston (1973), *The Economic Impact of the Patent System* (Cambridge: Cambridge University Press). In a follow-on study, Silberston categorized three groups of industries for when patents are essential, very important, or less important, based on both survey responses and objective analyses (patent and R&D intensity). He concluded that "the first category consists of one industry only, pharmaceuticals." Z. A. Silberston (1987), "The Economic Importance of Patents" (London: Common Law Institute of Intellectual Property). Edwin Mansfield surveyed the R&D directors of 100 U.S. corporations on what fraction of the inventions they introduced between 1981 and 1983 would not have been developed without patent protection. For pharmaceuticals, the value was 60 percent, while the average across all industries was 14 percent. Edwin Mansfield (1986), "Patents and Innovation: An Empirical Study," *Management Science* 32: 175.

[9] Joseph A. DiMasi (1995), "Success Rates for New Drugs Entering Clinical Testing in the United States," *Clinical Pharmacology and Therapeutics* 58: 1–14.

[10] Joseph A. DiMasi (1995), "Trends in Drug Development Costs, Times and Risks," *Drug Information Journal* 29: 375–84; Kenneth I. Kaitin and Joseph A. DiMasi (2000), "Measuring the Pace of New Drug Development in the User Fee Era," *Drug Information Journal* 34: 673–80.

[11] Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski (2003), "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22(2): 151–85. For an earlier study using the same methodology for 1980s new drug introductions, see Joseph A. DiMasi (1991), "Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10(2): 107–42.

[12] Ibid.

[13] Lehman Brothers (2001), "The Fruits of Genomics: Drug Pipelines Face Indigestion Until the New Biology Ripens" (New York, January).

[14] U.S. Congressional Budget Office (1998), "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry" (Washington, D.C.: U.S. Government Printing Office); U.S Department of Health and Human Services, Theodore Goldberg et al. (1986), "Generic Drug Laws: A Decade of Trial: A Prescription for Progress" (Washington, D.C.: NCHSR).

[15] Henry Grabowski and John Vernon (2000), "Effective Patent Life in Pharmaceuticals," *International Journal of Technology Management* 19: 98–100. This paper summarizes and extends our analyses of generic competition published in the *Journal of Law Economics* October 1992 and *PharmacoEconomics*, vol. 10, supplement 2, 1996.

[16] PhRMA (2000), *Pharmaceutical Industry Profile 2000: Research for the Millennium* (Washington, D.C.), 69.

[17] Joe DiMasi et al., "The Price of Innovation," op. cit., footnote 11.

[18] Brigitta Bienz-Tadmor, Patricia A. D. Cerbo, Gilead Tadmor, and Louis Lasagna (1992), "Biopharmaceuticals and Conventional Drugs Clinical Success Rates," *BioTechnology* 10 (May): 521–25; M. M. Struck (1994), "Biopharmaceutical R&D Success Rates and Development Times," *BioTechnology* 12 (July): 674–77.

[19] Marilyn E. Gosse, Michael Manocchia, and Toben F. Nelson (1996), "Overview of U.S. Pharmaceutical Development, 1980–1994," Tufts University Center for the Study of Drug Development, May.

[20] The data in Figure 3 were provided by Janice Reichert of the Tufts University Center, April 2002.

[21] Henry Grabowski and John Vernon (1994), *The Search for New Vaccines: The Effects of the Vaccines for Children Program* (Washington, D.C.: American Enterprise Institute), 13–35.

[22] Henry Grabowski, John Vernon, and Joseph DiMasi (forthcoming), "Returns on R&D for New Drug Introductions in the 1990s," *PharmacoEconomics*. For earlier studies of new drug introductions in the 1970s and 1980s, see (1994), "Returns to R&D on New Drug Introductions in the 1980s," *Journal of Health Economics* 13: 383–406; (1990), "A New Look at the Returns and Risks to Pharmaceutical R&D," *Management Science* 36: 804–21.

[23] Ibid.; see in particular Figure 8.

[24] Henry Grabowski and John Vernon (2000), "The Distribution of Sales from Pharmaceutical Innovation," *PharmacoEconomics* 18 (Supplement 1): 21–32.

[25] F. M. Scherer, D. Harhoff, and J. Kukies (2000), "Uncertainty and the Size Distribution of Rewards from Innovation," *Journal of Evolutionary Economics* 10: 175–200.

[26] Henry Grabowski and John Vernon (1996), "Prospects for Returns to Pharmaceutical R&D Under Health Care Reform," in ed. Robert Helms, *Competitive Strategies in the Pharmaceutical Industry* (Washington, D.C.: AEI Press).

[27] For data on effective patent time, see the 1998 CBO study cited in footnote 14, as well as my work with John Vernon cited in footnote 15.

[28] Title II of the Hatch–Waxman Act provided for partial restoration of the patent time lost during the clinical testing and regulatory approval periods. A formula for patent term restoration was embedded in the law. In particular, new drugs were eligible for an extension in patent life equal to the sum of the NDA regulatory review time plus one-half of the IND clinical testing time. The law capped extensions at five years and also constrained extensions to a maximum effective

patent lifetime of fourteen years. Drugs in the pipeline at the time the act was passed, in September 1984, were limited to a maximum extension of two years.

[29] For new drug products with little or no effective patent life, generic firms are prohibited from filing an abbreviated new drug application within the first five years of the product life. Most European countries prohibit such filing within the first ten years of market life.

[30] Grabowski and Vernon, "Effective Patent Life in Pharmaceuticals," cited in footnote 15.

[31] This includes any benefits from the international GATT agreement, passed by Congress in 1994, which harmonized U.S. patent laws with foreign countries', including setting the nominal patent life to twenty years from the date of patent application rather than seventeen years from the date of patent grant. It does not include any potential benefits of a six-month extension granted under the FDA Modernization Act in 1997, which can be awarded if the firm does additional testing and gains FDA approval for a pediatric indication.

[32] See the CBO study, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," cited in footnote 14.

[33] See, for example, National Institute for Health Care Management Foundation (2000), "Prescription Drugs and Intellectual Property Protection," NIHCM Foundation Issue Brief, Washington, D.C., August.

Reaching Through the Genome

Rebecca S. Eisenberg

The past two decades have been a period of rapid evolution in the science of biotechnology and therefore in patent strategies, if not in patent law itself. Patent law takes a long time to catch up with science, and commentators take a long time to catch up with the law, but patent lawyers don't have that luxury. They have to keep ahead of the game, figuring out claiming strategies that allow their clients to capture the value of future discoveries. I want to discuss some of these strategies today.

The patenting of DNA sequences is hardly a new thing, but rather an established practice that goes back at least two decades. It began with little fanfare and little controversy, in contrast to other first encounters of the patent system with new categories of invention in biotechnology and other fields. Considerably more public controversy accompanied the allowance of patents on microorganisms, animals, computer software, and business methods. The issuance of patents in each of these areas provoked immediate opposition, along with critical media commentary and congressional hearings.

In recent years we've seen similar attention focused on the practice of patenting genes, but nothing like that happened when people first started patenting genes in the early 1980s. At the time, public outcry over biotechnology patents was focused on living organisms rather than genes. We didn't see any significant controversy over patenting DNA sequences until the advent of high-throughput DNA sequencing in the early 1990s, when genomics started to look more like information technology than like chemistry. By this point, patenting genes was such a well-established practice that questions about whether DNA should be patentable seemed quaint and out of touch.

Even in the early 1980s, when the courts were still wary of protecting information technology,[1] they viewed DNA as a molecule, a chemical, a composition of matter, rather than as information.[2] Perhaps if the Patent and Trade-

mark Office (PTO) and courts had coded DNA as a storage medium for information, a metaphor that is more common in popular understandings today, the outcome would have been different. Instead, paradoxically, for a while it was far easier to patent *nature's* information technology than it was to patent *human-made*, electronic information technology.

Why was the patenting of genes so uncontroversial in the early days, and why has it become so controversial since then? In the early days, patenting genes looked like patenting drugs. Now it looks more like patenting scientific information. We have a clear story about why we should issue patents on drugs. It is less clear whether we want to issue patents on scientific information.

In fact, it was the scientific community, and not the usual antibiotech suspects, that first provoked public controversy over the patenting of DNA sequences. The focus of the controversy was the filing of patent applications by the National Institutes of Health in the early '90s on the first random gene fragments (expressed sequence tags, or ESTs) coming out of the laboratory of Dr. Craig Venter while he was at NIH.[3] But until the era of high-throughput DNA sequencing, the scientific community did not complain about patenting DNA.

The first generation of DNA sequence patents was directed toward genes encoding proteins of interest. They typically claimed:

1. An isolated and purified DNA sequence.
2. A recombinant vector that includes the DNA sequence.
3. A transformed host cell that includes the vector.

These claims all covered tangible materials used to make pharmaceutical products. The effect was similar to a patent on a drug, although the gene patent was directed to the recombinant materials used in production of the protein rather than to the protein product itself. The PTO and the courts treated these patents the same way they treated patents on new chemical compounds. The analogy may never have been perfect, but it worked, in the sense that it provided commercially effective patent protection that motivated investment in the development of new products.

This was important because in the biopharmaceutical industry the patent system does real work. In some industries, firms report that patents aren't really very important to their investment decisions, that other things matter more in determining the profitability of innovation, such as being first to market, that patents are just trading currency to get other patent holders to leave you alone.

That is not what one hears in the pharmaceutical industry. Empirical evidence indicates that this is a field where patents really matter.[4] Why? The standard account from the pharmaceutical industry is that new drugs cost a fortune to develop, and there are many costly failures for each successful product. If generic firms could compete and drive down prices on the successful products

without incurring all the development costs on the full range of successful and unsuccessful candidates, they would drive them out of business.

Early biotechnology firms saw themselves as "high-tech" pharmaceutical firms developing therapeutic protein products rather than small molecule drugs. They, too, wanted patents that would prevent free riders from destroying their profits. Patents on genes promised to provide that protection and allowed these new firms to raise capital and sometimes to get pharmaceutical firms to collaborate with them.

But in recent years the biotechnology and genomics industries have become much more diverse in their research and business strategies. As the Human Genome Project has generated vast quantities of DNA sequence information, with biological significance yet to be determined, many firms have emerged in a market niche that requires appropriating the value of information resources for use in future research and product development. Research that builds upon today's bioinformatics platforms can contribute to the development of products that are several steps removed from the genomic information base that helped researchers on the path to discovery. It's not obvious how to use patents to capture the value that upstream research platform technologies contribute to these discoveries. Firms are seeking strategies for reaching into the revenues from end product sales, especially drug sales. The introduction of new pharmaceutical products is typically the point at which bioscience starts to yield real money.

Needless to say, the pharmaceutical industry is viewing these strategies with concern. The industry has long relied on patents on drugs to make drug development profitable, but patents on drugs are not the only patents that accompany new drugs on the road to market these days. Patents on the prior "upstream" inventions that explain disease pathways and mechanisms and identify potential drug targets impose costs on drug development. They are like so many siphons at the feeding trough of new drugs, draining away profits in a lot of different directions.

From a strategic perspective, the issue for upstream firms is how to use intellectual property rights in advances that facilitate future research to capture a share of the commercial value of the future discoveries that they facilitate, and the issue for downstream drug developers is how to resist these strategies. From a public policy perspective, we can recast the issue as how to allocate intellectual property claims along the complex course of cumulative innovation in biomedical research.

When researchers identify the disease relevance of a gene or set of genes, perhaps identifying a new drug target, can or should they be able to get patent claims that dominate future products that bind that target?

Various strategies are available for achieving that goal. Each of these strategies depends for its viability upon legal rules that might be interpreted or fine-

tuned to promote, permit, inhibit, or forbid these strategies, depending on how we feel about them as a normative matter.

One approach is called "reach-through licensing." This is primarily a contract strategy, although often the contract involves a license to use a patented research platform technology or material. The basic idea is that the patent-holder restricts access to a patented research-enabling technology to users that agree, as a term in the license, to share a piece of the action in future products. Sometimes the piece of the action takes the form of a royalty on future product sales, and sometimes it takes the form of a license to use future inventions made in the course of the research. Many institutions resist these strategies, but some agree to them.[5]

Pharmaceutical firms will go to great lengths to avoid incurring reach-through royalty obligations, such as inventing around a patent or even going offshore to conduct drug screens. They will not sign a reach-through license agreement unless they absolutely have to. Universities are rarely targeted for reach-through royalties because they are unlikely to develop and sell products on which royalties might be collected. But firms often seek grant-backs of licenses to future inventions made in the course of university-based research as a license term when they provide research tools to universities. For their part, universities resist agreeing to grant-backs whenever possible. They view these provisions as compromising their stewardship over future discoveries and believe that firms should provide them with free access to research tools so that they can advance the frontiers of knowledge.

Both pharmaceutical firms and universities believe that reach-through rights overvalue the past contribution of tool providers relative to the work that remains to be done by themselves as tool users in order to advance the course of cumulative innovation. But for some institutions, particularly biotechnology firms, reach-through license terms make sense. Not only do they ask others to agree to pay them reach-through royalties, but they sometimes agree to pay them themselves.

The diverse institutions comprising the biopharmaceutical research community do not easily arrive at agreement on reach-through rights. They consume a lot of transaction costs in haggling about them, and if the haggling takes place far enough upstream, when the profitable end point of the research looks speculative and far away, they might conclude it's just not worth the costs of getting to yes. This risk enhances the attractiveness of reach-through strategies that don't require *ex ante* agreements. Two such strategies have been getting attention: reach-through remedies and reach-through claiming.

A reach-through remedy is a damage award for infringement that is measured as a reach-through royalty on sales of products developed through unlicensed use of a research tool. Janice Mueller has recently proposed such a remedy as a modified "research exemption" from infringement liability.[6] Under this pro-

posal, researchers who use a patented tool to develop a commercial product don't need to get permission in advance, provided they give notice, but if their research yields a product, they will be liable for reach-through royalties on that product. If reach-through royalties become common in license agreements for research tools, then they would arguably be an appropriate damage remedy under current law, on the theory that they approximate the value to which a willing licensor and licensee would have agreed. But in the present environment, with many would-be licensees putting up strong resistance to reach-through royalties, such a remedy seems to substitute a court's evaluation of fair license terms for that of the market.

Another strategy is called "reach-through claiming," which means issuing patents that are broad enough to cover future discoveries enabled by prior inventions. This strategy depends less on contract and more on patents. If the claims of a patent cover future products, the owner does not need to get the user to agree in advance to pay royalties on future product sales but can wait until the user has a product ready to bring to market before sitting down to bargain. Users that avoid patent owners at the research stage will still have to deal with them later, perhaps from a weaker bargaining position.

Patent claims that reach beyond the technological accomplishments of the patent holder are by no means unprecedented. It is common for pioneering inventions that open up new fields (in which there is little prior art) to receive broad patents that dominate future advances, including products that require significant further R&D. An example of an early advance in the biotechnology field that received broad reach-through claims is the Cohen-Boyer gene-splicing technique patented by Stanford University. The patent claims covered not only the enabling technology, subsequently put to use in many different academic and industrial laboratories across a broad range of R&D problems, but also any recombinant organisms created through use of the technology. The claims to recombinant organisms reached through the disclosed technology to cover later-developed starting materials used in recombinant production of proteins, giving the patent owner a dominant claim over a whole generation of biotechnology products.

But the history of patent law also includes many examples where the courts have held that a broad claim on a pioneering invention simply proves too much, including claims from such pioneering inventors as Morse and Edison.

Today the courts and the PTO seem to be viewing reach-through claims in genomics with some skepticism, but that doesn't stop inventors from continuing to pursue such claims, and some of them may be succeeding.

A stylized example illustrates how these reach-through claims work. Suppose a firm has identified a novel gene encoding a receptor, and based on similarities to previously characterized genes, it appears to be a new member of a known receptor family. Suppose further that based on what is known about

other members of this family of receptors, the inventor plausibly speculates that this new receptor might be a drug target. Let's suppose the applicant wants to patent:

1. The receptor itself, as an isolated and purified composition of matter.
2. A method of identifying a ligand that binds the receptor through screening procedures described in the specification.
3. Ligands identified by the screening method.

Is the applicant entitled to any of those claims? The applicant's best hope is for the first two claims—the claims to the isolated and purified receptor and the drug-screening method. The biggest obstacle to obtaining these claims is the requirement of utility (or industrial applicability, as it is known outside the United States). In order to get a patent, the inventor must have a useful invention and must disclose how to use it. All the claims will fail unless the application discloses a specific and substantial use for the receptor protein.[7]

Disclosure of a specific and substantial utility will be enough to permit the inventor to claim the isolated and purified receptor and the screening method to identify agonists. But it won't permit him to reach through to claim the as-yet-unidentified ligands. The primary obstacle to obtaining these reach-through claims is the *disclosure requirements* of the patent laws. To patent an invention, the inventor must provide a written description that is sufficient to enable a person of ordinary skill in the relevant field to make and use it without undue experimentation.[8] For product claims to meet this standard, one must supply information about the structure of products covered by the claim, and not just their function.[9] The hypothetical claims to ligands that bind the receptor fail to meet this standard because all the applicant has disclosed is the function of the molecules covered by the claim, without saying anything about their structure. The Federal Circuit has been particularly tough in applying the written description requirement to biotechnology inventions,[10] in contrast to its relatively light touch on the utility[11] and nonobviousness[12] standards.

Nonetheless, technology has advanced in ways that give some firms a strategy for addressing this written description problem. Researchers studying new proteins can sometimes crystallize the protein and determine its three-dimensional structure using X-ray crystallography. They can then obtain Cartesian coordinates permitting visualization of the target on a computer screen, creating a 3-D model of the target for use in designing ligands. Some patent claims have been issued for methods of identifying candidate inhibitor compounds that involve introducing crystal coordinates for a drug target into a computer program and superimposing models of inhibitor test compounds to identify those that fit spatially into an active site of the target.[13]

Might such an inventor also claim compounds identified through this computer visualization technique? Perhaps. Although the written description require-

ment is a potential problem, one might argue that the requirement is satisfied if the crystal coordinates provide enough structural information linked to the function of binding the target to permit visualization of the molecules falling within the scope of the claim. In other words, the applicant is not just claiming any molecules that do the job but actually describing what such molecules would look like.

Of course, the speculation might be wrong. Perhaps the shape of the receptor in the environment in which it interacts (or not) with the rationally designed compound is quite different than the shape found for the crystallized protein. Or perhaps a prior art compound will turn out to fall within the scope of the claims, rendering them invalid. A broad claim to a genus of compounds fails to meet the novelty standard if even a single member of the genus was disclosed in the prior art, even if the properties of the prior art compound that make it fall within the scope of the claim were merely inherent and not disclosed. Broad claims make big targets.

So while there are a lot of open questions yet to be resolved, there may be some claiming strategies that allow upstream inventors to get reach-through claims that will dominate future pharmaceutical products on the basis of preliminary genomics and bioinformatics work.

How should we be thinking about these reach-through practices as a normative matter? Should the law permit or promote practices that allow early-stage inventors to reach through to capture a share of the value of future discoveries? Should it discourage or prohibit these practices?

Critics argue that reach-through rights over-reward those who rest on their laurels at the expense of those who carry research forward. Moreover, mechanisms that permit leveraging of patents on early discoveries into control of future inventions raise potential antitrust concerns. To the extent that reach-through rights continuously augment the number of rights-holders at the bargaining table as cumulative research proceeds, they magnify risks of bargaining failures in a potential "tragedy of the anticommons."[14]

On the other hand, reach-through rights may be a valuable way to permit early innovators to capture the value that their discoveries contribute to subsequent research. Otherwise the stand-alone value of early innovations may be too low, undermotivating the initial investment that is necessary to identify and enable socially valuable research paths. A reach-through remedy may be a solution to the anticommons problem, permitting research to proceed without need for constant negotiations over access to each proprietary input.

How one weighs these competing concerns depends upon how one views the relative need for incentives at different points in the course of cumulative innovation. If one worries more about the adequacy of incentives for early-stage innovation and less about the adequacy of incentives for later-stage innovation, then reach-through strategies make a lot of sense. On the other hand, if one

worries more about the adequacy of incentives for downstream research and product development, then reach-through strategies are cause for concern. Judicial opinions about patent law reflect both of these perspectives.

Patent law sometimes rewards pioneers in a field with broad claims (and a broad range of equivalents), while giving only narrower claims to those who make follow-on improvements, even though the improvements may have more stand-alone commercial value than the primitive versions of the invention developed by the pioneer. Suzanne Scotchmer has argued[15] cogently that upstream research is both riskier and less likely to have a high stand-alone value than downstream research, which by definition is closer to market. She therefore argues for giving broad rights to early innovators that allow them to force subsequent improvers to deal with them. Giving a broad patent to the pioneer who invents, say, a primitive sewing machine allows her to capture some of the follow-on value created by those who tweak the invention and make it more user-friendly.

But one gets a very different picture of the relative contributions of early and subsequent innovators from observing biotechnology and genomics research. Of course, in biotechnology, as in other fields, there have been pathbreaking, pioneering discoveries that paved the way for lesser discoveries that were more financially viable. But many of these discoveries were paid for by NIH, raising questions about the need for strong patents to motivate and reward the work that generates that sort of basic research. In recent years some private firms have tried to figure out business models for generating biomedical research information to provide a platform for downstream discovery, especially in genomics, but often by the time private firms see such an opportunity, the so-called upstream research has become relatively mechanical. For example, when Celera decided they could take on the publicly funded Human Genome Project and complete their own version of the human genome sequence,[16] much of the pathbreaking work had been done already. Although much work remained, there was little question but that the job could be done. In this setting, the "upstream" work of sequencing the genome looks relatively routine, riskless, and uncreative compared with the "downstream" work of figuring out what it all means and how to use the information to develop new diagnostic and therapeutic products.

More generally, in the biomedical field, upstream research is relatively cheap and heavily subsidized with public funding. Downstream research is relatively costly and risky and relies primarily on private funding. This configuration of risk and cost argues for focusing on motivating and rewarding downstream research more than upstream research.

But other factors would support the opposite intuition. The biotechnology industry, already in its third decade, has mostly been unprofitable, while the pharmaceutical industry over the same time period has been extremely prof-

itable. Maybe this is partly because the pharmaceutical firms are smarter about business than the biotechnology firms, but perhaps this gross disparity in the bottom lines reflects in part a failure of the biotechnology industry to capture the social value that they have contributed to the pharmaceutical industry. If that is indeed what is going on, that cautions against disabling biotechnology firms from using legal strategies to get their fair share.

Persistent bargaining failures in the biomedical research community over the terms of access to research tools also caution against precluding reach-through strategies. Universities, biotechnology firms, and pharmaceutical firms describe these problems in different ways, each pointing the finger at the others, but they all report difficulties in agreeing about what is fair and reasonable when one institution provides another with resources that might facilitate future discoveries. In this environment it makes little sense for the law to foreclose options that might help the parties get to yes. Reach-through provisions can help with two big problems in the licensing of research tools: valuation and financing. If the parties cannot use reach-through provisions, they need to use pay-as-you-go terms for access to research tools. This suits the pharmaceutical industry just fine, because they have plenty of cash and would rather pay a relatively small amount upfront than agree to share profits later. But reach-through terms are more attractive to biotechnology firms that otherwise would be unable to pay enough to compete with the pharmaceutical industry to get access to research tools. In effect, reach-through agreements allow upstream and downstream biotechnology firms and universities to form joint ventures, sharing risks without draining cash at the research stage.

Reach-through grant-back licenses—i.e., precommitments to license future discoveries back to the provider of an upstream research platform—are more troubling but may also be a valuable contract option. What makes these provisions troubling is that they allow early innovators to exercise continuing control over future research and perhaps to suppress new innovation. On the other hand, such provisions may be a necessary defensive maneuver to permit early sharing of research tools without having to worry about facilitating domination by a competitor. Reach-through licenses can have a "copyleft" aspect to them, disabling subsequent innovators who have benefited from access to a predecessor's research platform from monopolizing their own subsequent inventions.

Given that these provisions have the potential to enhance efficiency and promote exchanges that are currently vexed by bargaining problems, it seems unwise to preclude the use of reach-through provisions as terms in voluntary agreements as a matter of law.

On the other hand, the case for reach-through royalties as a remedy for patent infringement is far weaker. Such a remedy (which amounts to a compulsory license in exchange for court-ordered payment of reach-through royalties) has the advantage of permitting research to proceed without compelling

researchers to get licenses in advance, when the transaction costs may loom large relative to the expected value of research that is far removed from commercial payoffs. But they present a danger that a court-ordered remedy will be too high or too low. The standard worry about compulsory licenses is that the court-ordered remedy will be too low. In this setting there is also a risk that a royalty rate determined *ex post*, when the research has proven successful and valuable, will be significantly higher than an *ex ante* valuation arrived at between the parties. If reach-through royalties become common in licenses, the terms of actual reach-through licenses negotiated *ex ante* will provide a benchmark to guard against overvaluation *ex post*. The law should follow, not lead, actual contracting practices and award reach-through royalties if and when they become common as a license term for research tools.

Reach-through claims raise all the problems of reach-through remedies and more. Approved by the PTO in the course of *ex parte* patent prosecution, patent claims are not tied even to a hypothetical agreement between prior and subsequent innovators. Patent examiners who speak only to patent applicants without hearing from future innovators may overvalue the importance of the applicant's invention relative to potential future discoveries. Multiple overlapping claims, already common even with the PTO viewing reach-through claims skeptically, will become much more common if reach-through claiming strategies become more commonplace, giving multiple owners hold-up rights over future products.

Patent law has a tradition of limiting patent protection to actual accomplishments and future variations that can be achieved through work that is routine and predictable. This is a sensible limitation that appropriately guides patent examiners away from acceding to unreasonable requests for patent claims that dominate future research that is itself fraught with risk and uncertainty.

There are good reasons for permitting prior innovators to use their intellectual property to capture a fair share of the value that their discoveries contribute to subsequent downstream innovation, but we can be more comfortable with strategies that are negotiated in the market for licenses than with those that are negotiated in the course of patent prosecution.

NOTES

[1] See generally Diamond v. Diehr, 450 U.S. 175 (1981).

[2] See, e.g., Amgen v. Chugai Pharmaceuticals, 927 F.2d 1200 (Fed. Cir. 1991). ("A gene is a chemical compound, albeit a complex one.")

[3] For a history of this controversy, see Robert Cook-Deegan (1994), *The Gene Wars: Science, Politics, and the Human Genome* (W.W. Norton).

[4] W. M. Cohen et al. (2000), "Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)," National Bureau of Economic Research Work-

ing Paper Series, no. 7552 (concluding on basis of survey results that "patents are used in substantially different ways across different technologies" and indicating that patent incentives are particularly important in motivating R&D in the pharmaceutical industry).

[5] See Rebecca S. Eisenberg (2001), "Bargaining Over the Transfer of Proprietary Research Tools: Is This Market Failing or Emerging?" in *Expanding the Bounds of Intellectual Property: Innovation Policy for the Knowledge Society*, ed. R. Dreyfuss, H. First, and D. Zimmerman (Oxford University Press), 209.

[6] Janice Mueller, "No 'Dilettante Affair': Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools," 76 Wash. L. Rev. 1 (2001). See also Jorge A. Goldstein (2001), "Patenting the Tools of Drug Discovery," *Drug Discovery World*, Summer, 9–18; James Gregory Cullem (1999), "Panning for Biotechnology Gold: Reach-Through Royalty Damage Awards for Infringing Uses of Molecular Sieves," *IDEA* 39 (4): 553.

[7] 35 U.S.C. §§ 101, 112. See U.S. Patent and Trademark Office, Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

[8] 35 U.S.C. § 112.

[9] See U.S. Patent and Trademark Office, Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001).

[10] E.g., Enzo Biochem. v. Gen-Probe, 2002 U.S. App. LEXIS 5642 (Fed. Cir. April 2, 2002); University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997).

[11] E.g., In re Brana, 51 F.3d 1560 (Fed. Cir. 1995).

[12] E.g., In re Deuel, 51 F.3d 1552 (Fed. Cir. 1995).

[13] U.S. Patent 6,083,711.

[14] M. Heller and R. Eisenberg (1998), "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *Science*, May 1, 698–701.

[15] See Suzanne Scotchmer (1991), "Standing on the Shoulders of Giants: Cumulative Research and the Patent Law," *Journal of Economic Perspectives* 5 (Winter): 29–41; Jerry R. Green and Suzanne Scotchmer (1995), "On the Division of Profit in Sequential Innovation," *RAND Journal of Economics* 26 (Spring): 20–33.

[16] J. Craig Venter et al. (1998), "Shotgun Sequencing of the Human Genome," *Science*, June 5, 1540.

PART FOUR

Financing Biotech Research

Financing Biotechnology Research: A Firsthand Perspective

Timothy F. Howe

Drawing on my experience with a health care venture capital firm and on much of what I teach at Columbia University's School of Business, I will focus on several practical aspects of the venture capital funding of biotechnology. These include how venture firms that invest in biotechnology operate, how this market evolved, and what areas of biotechnology research hold much promise. I will address these topics from the perspective of Collinson Howe & Lennox (CHL), a Northeast-based venture firm that my partners and I operate.

HOW CHL OPERATES AND HOW THE VC INDUSTRY HAS EVOLVED

In describing how our venture firm operates and how this form of investing has evolved, I will first provide some background on our company as a way to describe the talents that venture firms need from senior management and staff in order to successfully invest in biotechnology.

Some Background on CHL Medical Partners

Our partnership makes early-stage and seed investments in companies operating in the medical sector, defined to include biotechnology, pharmaceuticals, medical devices, and health care services. We are active, hands-on investors who are typically responsible for defining strategy at the companies in which we invest. We often manage these start-ups until we hire a complete management team to run them, and we are often responsible for their financing before they go public. We believe we add value by bringing top financial, scientific, and clinical expertise to bear on managing such ventures (*Table 1*).

Since the emergence of the institutional venture industry in the early 1980s, venture capital firms have generally become more specialized, a trend that char-

Table 1
Collinson Howe & Lennox: Classic Venture Capital

- Seed and early-stage investors
- Using an active hands-on approach
- Responsible for setting strategy, hiring management teams, raising capital
- Bringing to bear top financial, scientific, and clinical expertise
- Well-connected in health care and financial communities

acterizes the nature of the funds that we have managed over the years. In line with most venture capital funds, the ones we have managed are ten-year limited partnerships using capital raised from outside investors. During the 1980s, our activities were widely disbursed amongst leveraged buyouts, specialty retailing, biotechnology, information technology, communications, and just about anything one could imagine. Since then, the world has become a lot more complex and specialization has become necessary in order to identify the best investment opportunities. Our latest fund is called CHL Medical Partners II LP and is $160 million in size. Over the years, we have been involved in making private investments in about 150 companies, approximately forty of which have been biotechnology firms. Since 1989, we have focused 100 percent of our time on the medical sector.

Some of our portfolio companies might be familiar, including Incyte Genomics, Genetic Systems, Chiroscience, DNA Plant Technology, Procyte, Leukosite, Neurogen, Alexion, and Nova Pharmaceuticals. About 86 percent of our companies historically have completed initial public offerings (IPOs) and been successfully traded (not including the most recent, 1998 vintage, fund). The top one-third of our ventures have generated returns in excess of four times our initial investments; half of those have generated more than ten times, and half of those, more than twenty times.

Our investments with Texas-based companies are Texas Biotech, whose technology came from the Texas Heart Institute, and Gene Medicine (now known as Valentis), built upon research at Baylor University. We also have invested in two Texas start-ups: Odyssey Health Care, which provides home health and hospice care, and SemperCare, which operates long-term, acute-care hospitals.

Senior Management at Health-Oriented Venture Firms

The trend toward sector specialization among venture funds has reinforced the need for venture firms to couple specialized scientific knowledge with the managerial and financial expertise needed to develop a new business. At CHL

Medical Partners, our technical specialty is medical science. Of the three partners, Ron Lennox, with a Ph.D. in cellular biology and a B.S. degree in molecular biology, has a considerable scientific background, along with an M.B.A. from Wharton. On the financial side, Jeff Collinson has over twenty-five years of experience in private equity investing, along with an M.B.A. from Harvard and a B.A. from Yale; and I have worked in venture capital for about seventeen years, since earning a B.A. and an M.B.A. from Columbia. We are not atypical. Among senior management at venture firms, it is quite common to see a blend of business experience built upon considerable scientific and financial training.

Overall, there are nine people involved with our firm, and there is considerable scientific and business expertise among our future partners as well. For example, Greg Weinhoff is an M.D. who has an M.B.A. from Harvard, and Goga Vukmirovic, our latest addition, majored in molecular biology at Princeton, where she wrote a senior thesis on a topic in functional genomics. Looking through our firm, one sees a great depth of venture capital and medical-oriented experience.

Specialization, Diversification, and Sector Selection

At CHL Medical Partners, we try to balance the gains from specialization with the need to diversify across medical solutions. Although approximately half our business is biotechnology, our strategy is to diversify across the health care marketplace because we believe the solutions to medical problems could arise not only from biotechnology but also from medical devices and services concepts. Within biotechnology, we have invested in biotechnology tools, biopharmaceutical development, genomics, proteomics, and drug delivery technology (*Figure 1*).

Figure 1
Collinson Howe & Lennox: Sector Analysis

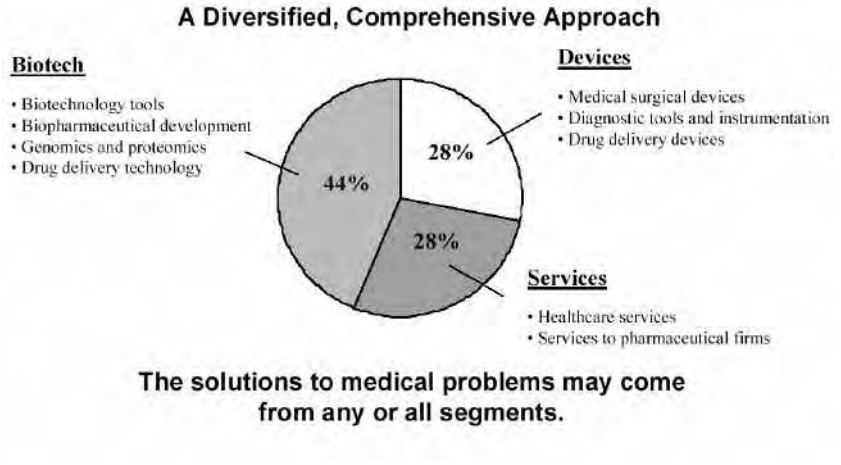
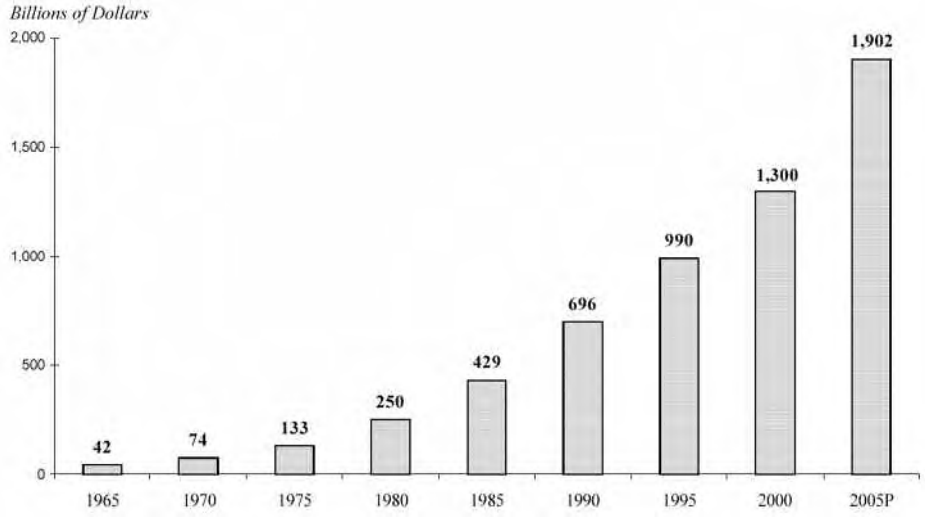
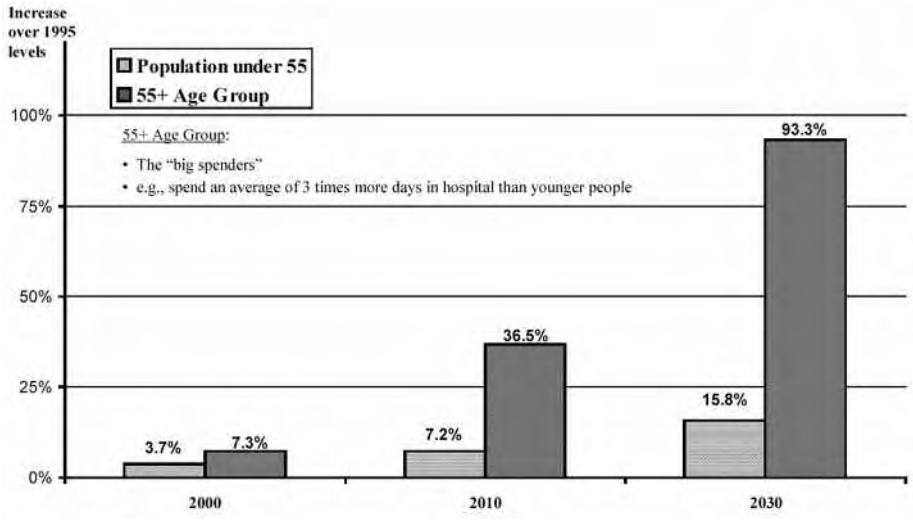


Figure 2
U.S. Health Care Expenditures



SOURCE: Centers for Medicare & Medicaid Services, Office of the Actuary.

Figure 3
The Aging of the Population: The Baby Boomers Move Through



SOURCE: U.S. Administration on Aging.

Investing in health care is attractive to us because health care expenditures have grown to become a large part of the U.S. economy, amounting to nearly 15 percent of GDP. Figure 2 depicts U.S. health care spending in billions of dollars over five-year increments.

Most of these expenditures are service-oriented, with only 10 to 12 percent spent on pharmaceuticals. The primary reason health care expenditures are growing at an increasing pace is the aging of the population, portrayed in Figure 3. The right-hand bars depict the percentage increase in the population that is over age 55 relative to the 1995 levels, while the left-hand bars depict population growth of those under age 55. This figure shows that the over-55 age population segment, which accounts for most medical spending, is growing about five times the pace of the rest of the population. This is a fundamental force that is propelling growth in health care spending. Moreover, with better development of drugs, this increased demand could be accommodated with much less expense to the system.

We see the opportunities in biotechnology as building off of advances in molecular biology, genomics, and proteomics, listed in Table 2. Currently, all the drugs on the market act on a total of about 500 targets, but there are upwards of 35,000 genes in the human genome, and many new targets for drug therapy remain to be identified. What we are really trying to do as investors is get a little bit closer to the ultimate goal of personalized medicine. More specifically, the goal is to really understand the genetic basis of disease and how an individual's genetic makeup influences the effectiveness of drug therapies. Such advances would hopefully lead to better, more specific therapies with fewer side effects.

Table 2
Human Genome Opportunities

- All the drugs on the market today act on a total of about 500 targets.
- There are around 35,000 genes in the human genome.
- Many new targets for drug therapy remain to be identified.

The genetic code is not the end point but **the beginning of a new phase** in medicine.
(*Money*, September 2000)

In the long run, genomics and proteomics will probably **transform** the pharmaceutical business, helping drug makers to develop better drugs faster and with fewer side effects.
(*Economist*, Feb. 17, 2001)

- Understanding the genetic basis for disease and how an individual's genetic makeup affects drug metabolism and toxicity will lead to better, more specific therapies.

The Role of Universities in Biotechnology Ventures

The critical role of science in the biotechnology arena naturally leads us to work closely with universities. With our headquarters in Stamford, Conn., Yale University is a natural partner. As Table 3 shows, we have worked closely with the Yale technology transfer office to establish and fund seven start-up companies.

Mirroring the experience of other medical-oriented venture funds, we have seen a shift in how the returns from joint ventures are shared with universities. While Yale-based technologies and expertise led to the creation of two of our biotechnology companies in the early '90s, Alexion and Neurogen, the financial returns to Yale consisted mostly of licensing fees for their technologies as opposed to equity ownership, which was typical of the environment at the time. Both of these companies became public, and depending on how their stock prices have traded, their market values have ranged anywhere from $150 million to over a billion dollars. Recently, in contrast to these initial ventures, our last five venture deals with Yale, made between 1998 and 2002, involved companies founded with the technology transfer office at Yale, whereby Yale University received an equity stake in exchange for licenses to technologies invented at Yale. So while it is still too early for these companies to consider initial public offerings, we are hopeful those days will come and Yale's returns, though riskier, could be substantially greater than had they just taken licensing fees. This exemplifies an important emerging trend of ventures involving tech-

Table 3
CHL Medical Partners: The Yale Relationship

- **Numerous Companies**

Neurogen Corp. Inc. (1988)
Founding investor; active director

Alexion Pharmaceuticals Inc. (1994)
Early investor; active director

polyGenomics Inc. (1998)
Founding investor; active director

Molecular Staging Inc. (1998)
Founding investor; active director

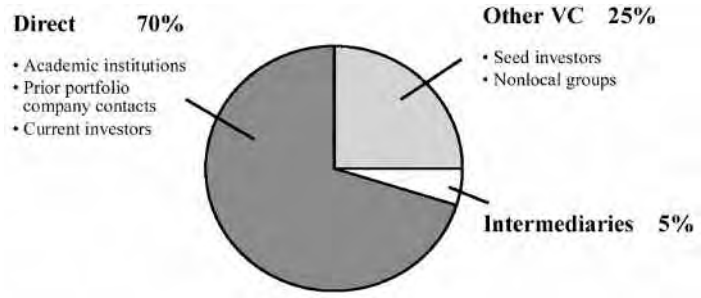
Cellular Genomics Inc. (1998)
Founding investor; active director

Protometrix Inc. (2001)
Founding investor; active director

VaxInnate Inc. (2002)
Founding investor; active director

- "Active" means we strive to create value through management recruitment, financing, identification of corporate partners and negotiation of collaborations, inlicensing key technology from elsewhere; strategic guidance aimed at commercialization and long-term value creation.

Figure 4
CHL Medical Partners: Portfolio Analysis, Deal Sources



nology transfers from universities, and Yale has emerged as one of the leaders in making this transition. Nevertheless, many other institutions remain reluctant to take equity and continue to prefer royalties.

There are other benefits to universities from venture deals. For example, we tend to situate the companies we fund from Yale around New Haven in order to benefit from the local talent pool, and Yale has been very pleased about bringing new companies and all the employment they help generate to the city of New Haven. From just our last five equity-share ventures alone, over $100 million of capital has been brought into the region thus far, and close to 100 new jobs were created, contributing both to the university's bottom line and to local development.

I would like to point out that most of our deals come directly from inventors, academic institutions, or from people in successful, earlier ventures. From Figure 4, one can see how few opportunities we have generated through intermediaries. It is important for us that the source of technology makes contact directly with us.

WHERE ARE THE FUTURE OPPORTUNITIES FOR BIOTECH VENTURE FIRMS?

Later, I will discuss the particular opportunity facing venture capitalists in the area of proteomics; however, first I'd like to provide the following introduction to how we develop biotech venture opportunities. Broadly speaking, we have found that important venture investment opportunities continue to emerge when one considers the vertically integrated pharmaceutical industry from the perspective of the potential of developing large horizontal players.

Drawing on the transformation of the computer industry illuminated by Andy Grove in his 1996 book *Only the Paranoid Survive*, where he describes

how the computer industry transformed itself from being vertically integrated to being dominated by horizontal players, we see some parallels in the pharmaceutical industry. Figure 5 illustrates the vertically integrated pharmaceutical industry on the left-hand side, with the activities broken down into five categories: sales and distribution, manufacturing, clinical research, compound discovery and development, and research/target discovery.

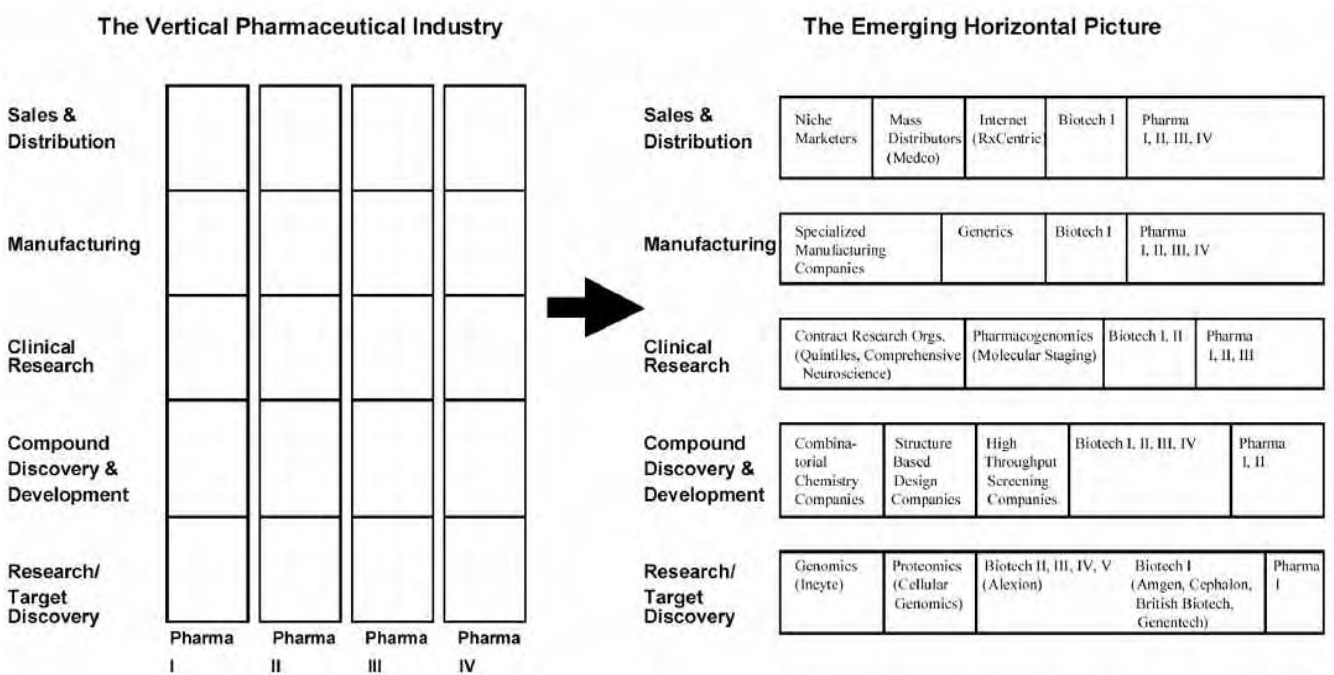
Historically, large pharma houses have been justifiably proud of their own research and target discovery capabilities, which they housed internally. Prior to the advent of combinatorial chemistry technologies, the pharmaceutical companies could also be very proud of their own proprietary compound libraries. Many big pharmaceutical firms continue to house their own clinical research, to manufacture all of their own pills, and to maintain huge sales and distribution forces. Recently, however, a number of venture-backed companies have emerged as potentially significant horizontal players that are transforming the way pharmaceuticals are discovered, developed, and brought to market.

For example, we founded Incyte Genomics to serve as a source for much of the research and target discovery for the pharmaceutical industry. Specifically, Incyte Genomics focused on sequencing the human and other species' genomes and providing access to its database to pharmaceutical industry clients who pay sizeable annual subscription fees under multiyear contracts. Currently, most of the top pharmaceutical companies subscribe to Incyte's databases. In addition to subscription fees, Incyte Genomics is also entitled to royalty payments on discoveries made using the databases that eventually get developed and sold in the marketplace. We believe that a company such as Incyte has the ability to dominate a horizontal segment of the pharmaceutical industry, much as Intel did within the chip sector of the computer industry.

Similarly, combinatorial chemistry, structure-based design technologies, and high-throughput screening tools are enabling more efficient compound development, and companies that have these technical capabilities have the potential to become horizontal leaders and integral parts of the industry's drug discovery and development process. Outsourcing clinical research to clinical research organizations has already become commonplace, but we expect many additional opportunities to arise with the emergence of pharmacogenomics and advances toward personalized medicine.

Within the sales segment, we have yet to see an outsider or newcomer grow into gaining a dominant position. Nevertheless, Medco Containment (prior to its acquisition by Merck) opened up a significant position as a mass distributor of drugs. We believe that the Internet could fuel further change by giving doctors easier access to drug information and pharmaceutical firms. In particular, we can conceive of lowering the cost of selling drugs by enabling pharmaceutical firms to introduce therapies to physicians at the physicians' own convenience over the Internet. Those companies that can provide these efficient systems for

Figure 5
The Horizontal View



pharmaceutical firms to reach physicians may become significant companies; hence we have invested in RxCentric.

Opportunities Posed by Advances in Proteomics

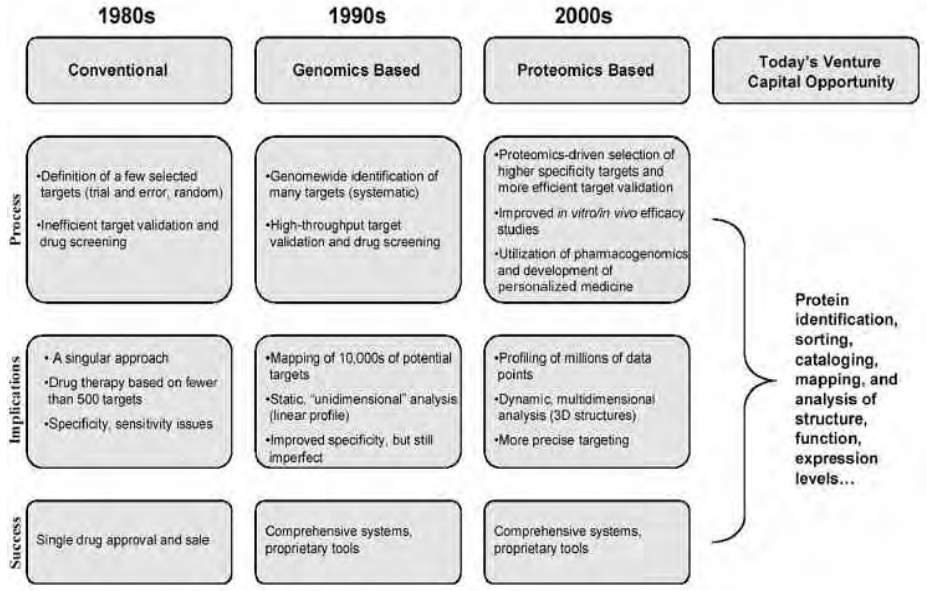
We see the coming proteomics era as potentially presenting a number of exciting venture opportunities. Over the past decade, the sequencing of human and model organism genomes has resulted in an enormous proliferation of information, transforming biology from a data-poor to a data-rich science. Historically, to understand the form and function of organisms, scientists have had to increasingly define more narrowly the unit of study. Looking at the entire animal gave way to a focus on increasingly smaller parts—from organs, to cells, to molecules. The reductionist approach of dissecting the whole into its constituent parts and studying each part independently has dominated the field of molecular biology over the past century; with the discovery of the structure of DNA, the unit and focus of study became the molecule. This approach has been a powerful strategy that will continue to have a role in scientific research. Yet today, with the genome sequencing efforts for humans and numerous model organisms nearly complete, there has been a shift away from the reductionist approach in research in favor of genomewide, context dependent, global analysis. The promise of genomics and proteomics has been fueled by the promise of holistic, whole-genome- and proteome-based approaches that generate and integrate sequence data, expression profiles, protein interaction maps, and protein structural and functional information.

Significant opportunities for venture capital investors exist in funding the development of technologies to understand and exploit this flood of information and data, and proteomics in particular has the potential to enhance pharmaceutical productivity and tremendously impact the drug discovery and development process.

Over the last twenty years, our biotechnology investing practice has changed as the focus of and the technology involved in drug R&D process changed (*Figure 6*). In the 1980s, a single drug target or a drug that was pretty interesting could be developed and sold at a significant profit, provided it was an important therapy. Fundamentally, success was defined by a bottom line driven by a single drug approval and sale.

In the 1990s, our investments shifted more into genomics-based research, where the success of a venture was based on the development of comprehensive systems and proprietary tools that enabled pharmaceutical companies to utilize the massive amount of information coming from the genome-sequencing projects. The overabundance of raw information, and lack of adequate tools to interpret and leverage it into marketable products, became the bottleneck in drug development. Hence our companies were designed to provide the tools

Figure 6
The Transformation of the Drug R&D Process



that mine the genome sequence information and generate a wealth of novel therapeutic targets. Genomics offered pharmaceutical firms a promise to decrease time to drug development, increase the success rate in clinical trials, and lower R&D costs. As investors, we were now taking pure technology risks rather than drug development risks. This was an important feature of the genomics era ushered in during the 1990s. Enormous investment returns were available for those who developed the successful proprietary genomic tools and systems and sold them effectively to the pharmaceutical industry.

Yet many of the early promises of genomics (such as decreased time to drug development, increased success rate in clinical trials, and lower R&D costs) have not materialized. It has become clear that medical breakthroughs do not follow from the genome sequence information itself. Rather, the breakthroughs will come from focusing on understanding the function and relationships among gene products (i.e., proteins) in a changing environment. Going from knowing the coding sequence to understanding the protein function is not a trivial task. Identifying any sequence feature is not necessarily indicative of its function, and the function of a particular gene product is highly context dependent and is rarely unique, as there are numerous instances where there is a "backup" system (i.e., redundancies in signaling pathways) in place that can compensate for

a particular loss of function. Dynamic, multidimensional analysis is needed to understand the structure and function of proteins, as particular proteins can be present in varying amounts at different times and in different locations within a cell. While the identification, sorting, cataloging, and analysis of structures and functions of proteins will be more important and difficult to undertake than was the case with genomics, leveraging proteomic information could alleviate many bottlenecks in drug discovery and development and potentially enhance pharmaceutical productivity.

Investing in technological tools continues to present attractive investment opportunities because researchers need increasingly more complex and sensitive technologies to carry out proteomic analysis, and the data management requirements alone supercede those of genomics by at least four- to fivefold. The tools market is attractive because it is unregulated (no FDA approvals necessary), businesses can scale quickly, and products are patent protected. Moreover, for investors, exit alternatives are wide ranging. There has been substantial M&A activity by large, publicly traded tool companies seeking new technologies to complement their existing portfolios, and numerous pharmaceutical and biotechnology companies seeking technologies that complement and extend their R&D efforts, offering them unique, proprietary techniques for drug development.

Genomics and proteomics have brought about a revolution in the field of biology and have the potential to fundamentally transform the pharmaceutical industry. Increasingly, diseases will be diagnosed and treated based on a greater understanding of both the disease pathology and the mechanism of particular drug action, further integrating drug discovery with disease characterization and diagnosis. With advances in proteomics, we are many steps closer to fulfilling the promise of personalized medicine to offer more effective and less toxic therapies to individuals. But even before personalized medicine becomes a reality, opportunities abound for creating significant value by developing enabling technologies and utilizing them in drug discovery and development.

Biotechnology and Government Funding: Economic Motivation and Policy Models

Michael S. Lawlor

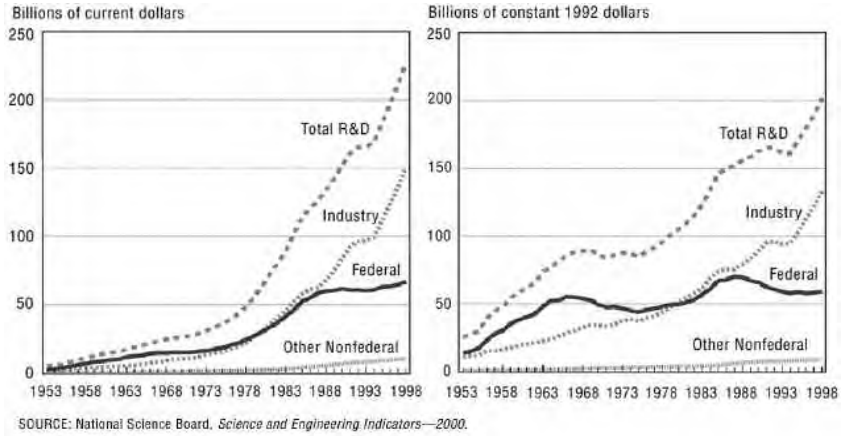
The United States is clearly the world leader in the emerging field of biotechnology—the application of breakthroughs in biochemistry and molecular biology to new products and health care therapies. It is no exaggeration to say that this world leadership position is the result of the superiority of the human and physical capital of the U.S. science and technology base in the nation's university, government, and nonprofit labs. Most of this base has been nurtured and sustained since the end of World War II by the generous support of the American taxpayer. The economic and political motivations upon which the U.S. research system was designed and operates, the special features of the biomedical research community, its history up to the present era of tremendous advance, and some lessons that lie therein for public policy toward science are the subjects of this paper.

OVERVIEW OF R&D FUNDING

Figure 1 shows the total funding for research and development in the United States from 1953 to 1998 in both current and constant (1992) dollars. Concentrating on the constant dollar values, roughly four eras of total funding are evident from these data. From 1953 to 1970, there were large, sustained increases in research funding, led by federal government efforts that corresponded to the arms and space races. In the '70s, public support for both these goals waned. It is important to note, though, that while total funding stagnated in the 1970s, this decade also saw the advent of new biomedical initiatives, such as the federally sponsored "war on cancer," which laid the groundwork for much of the bioscience of today.

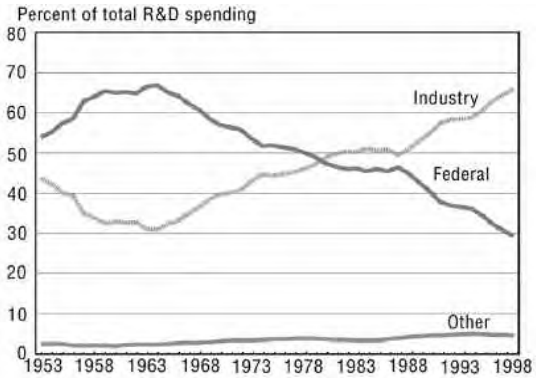
The third era of funding, in the 1980s, saw a brief resurgence of federal spending, mostly fueled by the Reagan administration's defense program, espe-

Figure 1
National R&D Funding, by Source, 1953–98



SOURCE: National Science Board, *Science and Engineering Indicators—2000.*

Figure 2
National R&D Expenditures, by Source of Funds



SOURCE: National Science Board, *Science and Engineering Indicators—2000.*

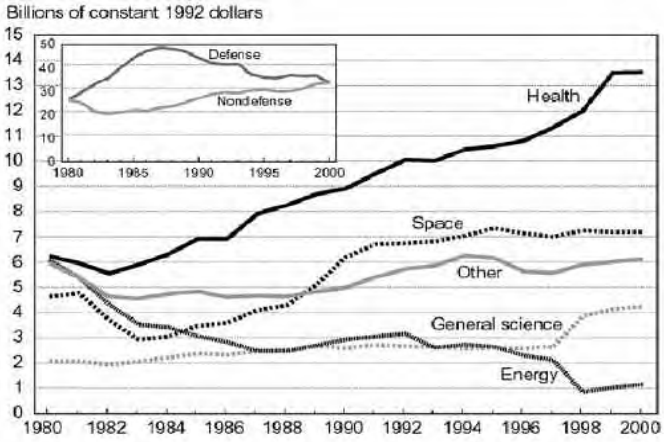
cially the effort to develop a space-based missile defense system. But the real story of the '80s is the rapid increase in private research expenditures. As can be seen in Figure 2, by the end of the decade, the federal role as the leader of funding had shifted to the private sector. Much of this was spent on drug discovery by the pharmaceutical industry. It was directed at the biological targets of the pregenetic biotechnological era that public basic science was then discovering. This research is largely responsible for most of the blockbuster drugs on the shelf today.

Finally, referring to Figure 1 again, a fourth stage in total national research and development spending began in the late 1980s with the end of the Cold War. The lack of any ambitious new nondefense initiative at this time saw total federal funding decline again. In terms of total federal government research spending, this decline has still not been reversed. Perhaps the recent military and biological defense spending increases called for by President Bush, in response to the threat of terrorism, may be the next large focus for public support of research spending. An important message to take away from this is the pervasive influence of current political interests, such as the Cold War science race, for instance, on the public funding of research and development activity. The variability of postwar public funding for science research is largely a story of changes in this political commitment.

Given the unpredictable nature of science, potentially *all* past federal science research has contributed to the biotechnology era. Consider, for instance, the fact that the techniques employed in the Human Genome Project were a complex combination of basic breakthroughs in theoretical biology, enabled by developments in imaging stemming from high-energy physics and kept track of by advanced computing technology (bioinformatics). Yet the original funding for the basic investigations that went into these seemingly unrelated advances, if they could all even be traced, came from sources originally thought to be unrelated to biomedical research.

Nevertheless, it is useful to see a breakout of public funding by category (*Figure 3*). First we should set aside defense research, much of which is directed

Figure 3
Federal R&D Funding, by Budget Function

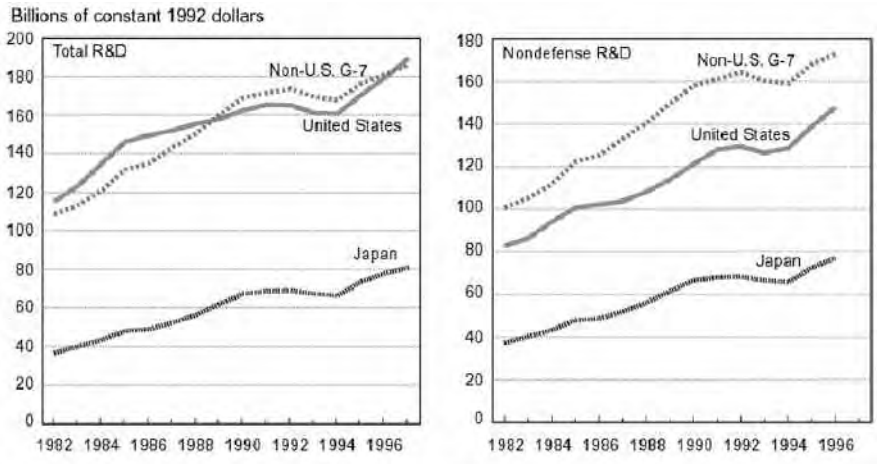


SOURCE: National Science Board, *Science and Engineering Indicators—2000*.

to weapons development, not to basic science issues at all. Aside from defense-related research, it is evident that most federal research funding is for "health" related activities. The majority of the funds in this category support the National Institutes of Health. If one were to further isolate the specifically biotechnology-related funding in the remainder of this breakout, it would span all the other categories shown in Figure 3, in addition to the obvious amount labeled "health." The majority of nonmedical, basic science training and research funding falls under the "general science" category (predominantly for the National Science Foundation). Additionally, various small programs that target specific biotechnology industries and/or types of technology are here included in the category "other" (for instance, the Department of Agriculture's research budget). Overall, because of the dominance of nondefense research by the health share, it has become customary to focus on the NIH budget when discussing biotechnology. By this measure, a good rough and ready indicator of the current health of publicly funded biotechnology research is the recent rapid increase in the NIH budget. If the proposal submitted by President Bush in April 2002 for the 2003 budget is passed by Congress, President Clinton's 1998 pledge to double the NIH budget over five years will have been met.

Finally, Figure 4 displays an international comparison of total U.S. science and technology expenditures. On a country-by-country basis, no single state comes close to the U.S. level of total spending. Japan, the closest, expends about half of the U.S. total. All of the non-U.S. G-7 countries combined spend an amount about equal to what the United States does. If we subtract defense

Figure 4
U.S. and Other G-7 Countries' R&D Expenditures



SOURCE: National Science Board, *Science and Engineering Indicators—2000*.

commitments though, an area in which none of these countries really competes, the United States does not stand out quite so dramatically. We are outspent on total nondefense research and development when compared with the whole group of our fellow G-7 partners. But we still outspend any one country by a large amount. This does not tell the whole story though, because for reasons discussed below, we also get more productivity—in terms of new breakthroughs, patents, marketable products, Nobel Prize winners, etc.—per dollar spent on research and development than any of these countries. Thus at present, the United States is the undisputed leader in almost every basic science area related to biotechnological research. Our universities, especially those with research-intensive medical schools, are the preferred place to train for a career in these fields. Every year sees a net inflow of talent from other countries of scientists wishing to work in these institutions. For these reasons, and despite the fact that much valuable research is conducted in Europe and Japan, all major international pharmaceutical companies feel the need to establish research relationships or laboratory locations to keep abreast of the new developments in the United States.

THE ECONOMIC MOTIVATION FOR PUBLICLY FUNDED RESEARCH

The basic economic motivation for public funding of scientific research lies with what economists call a market failure. The failure is caused by the degree to which the process of creating new scientific knowledge and technological innovation may be insufficiently appropriable—i.e., difficult to establish property rights to—to provide profit-seeking investment with sufficient rationale to pursue such research (Nelson 1959, Arrow 1962). At the root of this failure is the problem of the ease of spillover effects from new knowledge. Knowledge production requires real resources, and if the fruits of one's investment in those resources are freely available to anyone, then they make poor investment targets. Add to this the uncertainty, risk, and long-term nature of the knowledge production process and it is likely that many forms of research will not meet investors' minimum expected return hurdles. Even so, this is only a market failure of an important public good, one that requires public intervention, if the activity would also yield social returns greater than the cost of the investment in them.

Much empirical research by economists has established that this is in fact the case for investments in science. Two types of studies have been undertaken. At the microeconomic level, on an industry or case study basis, specific technological innovations have been demonstrated to display more benefits for the ultimate users of technology, consumers, than for the original innovating firms (Mansfield et al. 1977; Scherer 1982; Griliches 1992, 1995; Hall 1996; Jones and Williams 1998; and Lichtenberg's contribution to this conference). Thus the *public* rates of return on investment in the research to produce such new knowledge tend to be many multiples of the rates for *private* investors. This is because as

the benefits spill over to other producers and consumers, the private investor is not compensated. A second type of study, at a macroeconomic level, consistently finds that the rate of productivity growth of the whole economy is importantly linked to the invention and adoption of new technology. (See Ruttan 2001, ch. 2 and Steil, Victor, and Nelson 2002, ch. 1 for useful summaries of this literature.) Here the proposed linkage is both the effect on productivity of the spread of new ways of doing things across industries and products and the increased skill of a workforce trained in the new technology. Note that this evidence also indicates that the investment value of new scientific knowledge is greater for society in general than for any one firm. Thus both types of evidence combine in an argument that the private sector can be expected to underinvest, relative to what would be an optimal level for society, in the types of scientific research for which the difficulty of appropriating specific new knowledge is substantial.

To move closer to a socially optimal level of investment in research, then, requires that the government intervene in some fashion. One such intervention could be the establishment of a government-regulated system of property rights on intellectual "inventions," such as the patent and copyright laws. This has been vigorously pursued in the United States since the time of the founding fathers. (See Grabowski's contribution to this conference.) A second possible policy could be to subsidize private research efforts by a tax credit. Research-intensive industries in the United States have lobbied for this incentive for decades, and since the 1980s it has become a permanent feature of our corporate tax code. Nevertheless, economists generally view tax incentives as a weak and ineffective tool, due to the undifferentiated incentive it presents to all kinds of research and development efforts. The problem is that it is difficult to target just the kind of basic research for which there is a market failure, and much applied and developmental research that could attract sufficient private funding on its own also ends up being subsidized. This is also inefficient from a social point of view. Thus the most direct and effective tool available to governments to fund research that is expected to be socially beneficial, but that is not likely to be done by the private sector, is to fund it directly. A long-term program of such funding also has the beneficial effect of keeping in place a system that will be uninterrupted over the long-run cycles of private funding. Providing infrastructure to nurture the cumulative and unpredictable nature of research programs, and the institutionalization of training grounds for reproducing the next generation of scientists, are additional benefits of this system.

SCIENCE VERSUS TECHNOLOGY, BASIC RESEARCH VERSUS APPLIED

Implicitly, we have assumed above that *basic* research into *scientific* questions represents the appropriate target of public research expenditures. Why?

Generally because such research is so broadly defined and so generally applicable and/or difficult to write into a legally binding patent application that it cannot be protected from spillover effects in sufficient degree to make it attractive to private investors. *Applied* research into *technology* would, in this framework, be such research as can be adequately appropriated to encourage private investment. But this tells us nothing essential about the qualities of these two types of activities that can be identified independently of what private initiative will or will not fund. Since, particularly at the basic science level, one cannot know in advance what scientists pursuing a particular line of research might have discovered or produced unless we let them try, there will always be a difficulty attached to identifying the correct (optimal) amount of total research spending. Additionally, public policy is faced with a need for ranking research goals to provide for the allocation of public funds between particular lines of research. Thus to some extent basic research will always depend on a degree of confidence—perhaps even bordering on "faith"—in the possible future life-enhancing usefulness of what must remain at some level the unforeseeable results of scientific research.

Nevertheless, the distinction between bioscience and biotechnology plays an important role in both investors' minds and in thoughtful public policy. Investors are reasonably suspicious of the probability of commercial success of an early and uncertain line of research. Policymakers, beholden to their constituencies, often want to direct funds to areas of greatest public interest or concern. Thus here is a good place to briefly review attempts by scholars to draw theoretical distinctions between the activities of science and technology research. We shall see that though this effort has added insight into the process of scientific research that is useful and interesting, the distinction is a shifting and slippery one to maintain in practice.

The most common view of the essential distinction between science and technology is based on the intended use of the new knowledge that is being pursued by research. By this view, science is new knowledge intended for knowledge's sake alone. Alternatively, technology is the "useful" application of new ideas for commercial, military, clinical, etc., uses. With regard to basic science activity, this captures something of the element of curiosity often proclaimed by scientists as the crucial element of research that has led to new breakthroughs (see Kornberg 1997). A more economic extension of this distinction was put forward by Dasgupta (1987). He distinguished between the alternative incentive systems involved in the production of each type of knowledge. Scientific discovery, situated largely in nonprofit settings and conducted by academic scientists, is motivated by the "rule of priority," according to Dasgupta. She who is first wins in this contest. A notable aspect of this system is that its focus on early achievement also serves to encourage rapid and complete disclosure of new knowledge. Thus this system advances the social function of the diffusion of

new ideas. Technology, in Dasgupta's view, is motivated quite differently. A profit-oriented firm that employs scientists to develop new clinical products, for instance, is motivated by the "rents" that can be appropriated from the new knowledge. It is not in the interest of the firm to see a rapid dissemination of its new knowledge. Private knowledge production, alternatively, encourages secrecy and hoarding of information.

An interesting feature of the current biotechnology era, where academic science and commercial development fluidly intermix, is the degree to which these distinctions have been breaking down. Most new biotechnology is already a mix of what Ruttan (2001, 536) calls "doing science" and "doing technology" years before it ever hits the marketplace. (Indeed, most biotechnology has yet to reach the marketplace!) Both the fundamental *idea* of the structure of DNA and the useful *method* of gene splicing have been integral to the development of molecular biology, for instance. Thus the distinction between scientific ideas and technological applications of them is more of interactive feedback loop. New ideas often lead to new technology that itself aids the next stage of discovery. Moreover, today the dual feedback loop between bioscience and technology extends quite far into the development stage, where new product development is itself a scientific endeavor. Consider, for example, that the average biotechnology start-up firm is a small group of scientists and laboratory technicians trying to develop a commercially viable prototype of a previous scientific result.

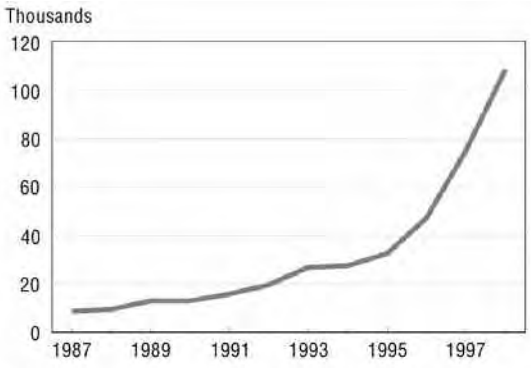
The same blurring of lines affects Dasgupta's taxonomy. Academic researchers who are winning the priority prize have also been patenting their discoveries and starting new commercial ventures to bring them to market. (See Darby's and Zucker's contributions to this conference.) For instance, Cohen and Boyer's gene-splicing technique, developed in a university lab, became the basis upon which the most commercially successful biotechnology firm to date, Genentech, was founded. This was the original model for the now numerous academic-science-entrepreneur firms that have sprung up in the biotech field. This cross-fertilization between basic science and technological development has also spread to the patenting process. Not only are many scientists and universities patenting the results of their research with greater frequency, but also many patent applications are citing scientific publications in their applications to establish both prior knowledge and the rule of priority. Figure 5 demonstrates this increasing link between new technology and new science in the rapid increase of references to scientific paper on applications for new patents since the mid-1980s. Another aspect of the breakdown of Dasgupta's distinction is the growing controversy over the clash of academic and commercial interests in disseminating the results of scientists who are also commercially funded or have a vested interest in future commercial applications. Thus not only are the worlds of science and technology increasingly intermixed, so are the motivations and roles of researchers in academic institutions and private industry laboratories.

One important public policy lesson of the ambiguous results academic investigation reveals about the distinction between science and technology is that there may be an additional role for public funding in certain cases of what might seem to be applied research. The rationale in this case concerns the possibilities that in relatively new technological areas there may be an additional market failure as firms find the difficulties of translating new laboratory science results into industrially viable technology too risky for private investment hurdles. In many cases, as biotechnology firms today are finding, for instance, established firms like large pharmaceutical companies find it an intolerable risk to nurture such new technologies as their own research investments. This is why the pooling of risk and consequent benefits of portfolio diversification through the characteristics of the venture capital fund have become so important in biotechnology.

But even venture capital may not be willing to assume all of the risk of wholly new science for which there is as yet no technology. Crossing this "death valley" of lack of funding along the way from laboratory science to engineering viability is a major hurdle today for many bioscience firms. Part of the problem is that certain types of premarket, generic, process technologies will possibly become commonly used by other firms in ways that are difficult for the original investor to lay claim to. But just as often it is the uncertainty of success in ramping up a basic science result to an industrial scale. An instructive historical example of this difficulty can be seen in the World War II–era attempt to produce penicillin. Penicillin mold was originally identified as an antibiotic by Alexander Fleming in 1928. Then followed a decade of work by British scientists at Oxford University in isolating the essential agent, producing it in labora-

Figure 5

Number of Citations on U.S. Patents to Scientific and Technical Articles, 1987–98



SOURCE: National Science Board, *Science and Engineering Indicators—2000.*

tory quantities, and proving its clinical efficacy in small numbers of risky experiments on patients. Only when the war arrived and it was expected that a successful antibiotic would save thousands of lives did the effort to industrially produce the product receive attention. When it did, the British turned to America for help. What turned out to be the crucial technological breakthrough came from agricultural scientists working for the U.S. Department of Agriculture on fermentation technology in Peoria, Illinois. The expertise of the agriculture scientists and engineers in the seemingly unrelated area of fermented food production led to an economically viable process by minimizing the ratio of "feedstock" input of mold to output of finished penicillin in industrial scale fermentators. (See Bud 1993, 103–7.) It was largely from these publicly funded results that the technological problem of penicillin was solved. This process then became the basis for a vast commerce in a wide spectrum of commercial antibiotics after the war.

Though some have called for more of this type of effort in the biotechnology field (Tassey 1999), already there is evidence that the U.S. government has been moving in the direction of providing some funding for just such generic technology development. For one, since the mid-1980s, it has been the policy of the federal government to encourage the transfer of any federally funded research to the private sector. This encouragement may occur in the form of cooperative research agreements (CRADAs) by which federally funded laboratories are authorized to establish research links for their own profit with commercial firms using their results. Similarly, all federally funded scientists are now authorized and encouraged to patent the results of their research by the opportunity for the scientists and the institutions to which they belong to share the royalties such patents might generate in the private sector. More directly, the Department of Commerce's National Institute of Standards and Technology has initiated a small-scale program of directly funding research into the development of a new generic process for emerging high-technology industry. This Advanced Technology Program (ATP) has launched projects on such questions as laboratory reproduction of stem cells, regeneration of human tissue, and the possible growth of insulin-producing cells in the pancreases of diabetics (Martin et al. 1998). Its mission is to investigate the feasibilities of such enabling technologies and then turn them over to the private sector for further use. If they can avoid, as they seem to be carefully doing, the problem of favoring particular firms, this small program has the potential to help bridge a crucial gap in the move of biotechnology from public science to viable commercial products.

POLITICAL AND SOCIAL MOTIVATION FOR PUBLICLY FUNDED RESEARCH

As our brief overview of public funding for scientific research in the previous section suggests, the market-failure rationale from economics has not

been the prime mover of science policy in the United States. Indeed, throughout history it has been much more likely that political considerations such as national prestige, military security, and social needs have been the main motivators of public funding for scientific research. There is no reason to expect that this will change in the near future. Since it is particularly the long-term nurturing of the broad basic science base that has produced the United States' competitive edge in biotechnology, it is instructive to understand how this system was founded and what qualities are responsible for its many successes.

In fact, it is something of a historical fluke, born of the political conditions of the 1940s, that the United States established what is an internationally unique system of noncentralized, government-funded, but largely university-performed, basic research in science and technology in the postwar era. That fluke is the story of what has come to be called the Vannevar Bush-inspired era of national science policy.

Vannevar Bush, formerly the dean of the MIT School of Engineering and then the president of the Carnegie Foundation, was selected by President Roosevelt in 1941 to head the Office of Scientific Research and Development. His task was to harness the skills of the academic science community for the war effort. The spectacular successes of this effort in the war—including, to name just three of many possible examples, the creation of a feasible synthetic rubber to replace the natural supplies cut off by the Japanese, the mass production of penicillin, and the creation of the atomic bomb—convinced Bush that the same type of work should be harnessed for peacetime needs in the postwar era. In 1945 he authored a Carnegie Foundation report, *Science: The Endless Frontier*, which laid out a plan for establishing a permanent federal science policy. Bush's report was couched in the inevitable military rhetoric of its era, with accounts of logistical needs, personnel available and needing to be trained, chains of command, budgets, and a plan of action that would have made a field general proud. No doubt this added to his report's enormous influence. But more important is the vision that his plan put forward. It called for an ambitious and comprehensive National Research Foundation, which would support primarily basic research in the life sciences, physical science, medicine, and what he called "basic military research," meaning research prior to actual weapons development. (He no doubt had atomic energy in mind.)

All of this research was to be funded at the federal level and performed largely by state and private university scientists. Most important for Bush, the scientists themselves would control the allocation of the funds. This would be accomplished, he suggested, by a peer review system by which proposals would be granted to projects and individuals deemed both capable and scientifically promising by other scientists. Yet though Bush made glowing comments on the potential applied social uses of scientific knowledge, he implicitly seemed to reject the rate of return reasoning we have just outlined as the economic argu-

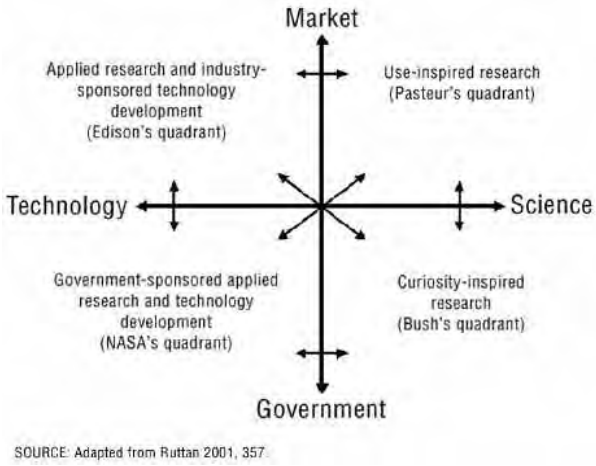
ment for public funding. In rejecting the "investment" criterion, as he called it, he articulated the humanistic argument still heard today, that scientists do their best work when motivated by curiosity alone, not practical application. Curiously, though, like the economics argument this led him also, for different reasons, to reject funding for any applied research. His objection was that too much political or commercial direction of scientific research would inhibit the free play of idle curiosity. Thus he did not envision federal support for industrial product development, and he wanted actual weapons development to be the responsibility of the armed forces separately. Also, curiously, his discussion of medical research (Bush 1945, appendix 2) only briefly mentions clinical research.

It is fair to say that Bush's vision of a science establishment innocent of other interests was politically naïve. Bush's historical role was to use his enormous influence to lobby for perhaps as much freedom for science from political, commercial, or military control as it has been given anywhere, anytime in history. In this he was largely pitted against the forces arrayed behind Senator Harley Kilgore of West Virginia, who sought a more centralized control of government-funded scientific research (see Kleinman 1995). Though Bush is often credited with being the architect of the postwar federal policy, it is important to note that his was not an unqualified political success. First of all, his advocacy of noninterference with scientists by either defense, social, or commercial interests was not to become a complete reality. It would be more correct to say that the purest example of the Bush model has been the National Science Foundation, founded in 1950. The NSF has stridently avoided attempts by Congress over the years to direct or widen its mission to applied research and any outside interference with its peer review system. Yet, possibly because of the NSF's sponsorship of this pole of pure curiosity-driven science, the NSF's budget has remained relatively small throughout the postwar era. It has, for example, received only a fraction of the NIH's funding.

In fact, the creation of a separate vehicle for biomedical and clinical research at the NIH is itself an example of the only partial success of Bush's ideal. Additionally, the military establishment was not about to hand over the direction of its research program to a group of scientists. Consequently, the Department of Defense's own applied weapons development projects, working largely with commercial defense contractors and the Atomic Energy Commission, often focused on big projects like the Oak Ridge facility, which are examples of Kilgore's favored centralized, state-controlled research policy. Later, when space exploration became a serious concern of the government, it also was organized along similar lines—as a centrally controlled, explicitly mission-based, applied research project.[1]

Bush's vision, then, is just one of many ways the government can and does fund science. Figure 6 (borrowed from Ruttan 2001, 537, and altered for this paper) illustrates, both conceptually and by reference to actual examples, a con-

Figure 6
Possible Interactions Between Basic Science and Applied Technology and Between the Market and Government



SOURCE: Adapted from Ruttan 2001, 357.

tinuum of possible combinations of ways that the government, the market, applied technological work, and new scientific knowledge might be organized and interact. In the upper quadrants of this diagram, there are purely applied attempts, based mostly on trial and error, by commercial "inventors" like Edison to invent new products. Alternatively, it is possible that investigation of a practical problem, like Pasteur's work on alcohol fermentation, might inadvertently lead to significant new scientific knowledge, such as the identification of the role of microorganisms in organic processes. The government has also been known—sometimes spectacularly successfully, as in some defense technology, agricultural science, and the space race; sometimes dismally, as in alternative energy research in the '70s—to organize, fund, direct, and either disseminate or use the skills and methods of science to meet a predetermined social need. This is illustrated in the lower left quadrant. Finally, Bush's vision is illustrated in the lower right quadrant. In this model, the government funds basic research but otherwise leaves its direction to the curiosity of the funded scientist.

How does this discussion relate to the current biotechnology era? First, recall that the major player in the fundamental developments of bioscience has been the NIH. In light of our discussion of the pervasive role of political considerations in generating support for science, the NIH represents a highly successful compromise model. It broadly represents the motivations of the public by its system of twenty-five institutes organized around body systems (e.g., the National Heart, Lung, and Blood Institute) and diseases (e.g., the National Can-

cer Institute). Moreover, as illustrated in Table 1, there is a rough and ready concordance between the nation's major health threats and the relative proportions of the NIH budget devoted to them. Yet within each institute, and in accordance with the Vannevar Bush vision, an extensive peer review system sorts out the particular researchers and projects that will be funded.

It would be a mistake to say that NIH policy is perfect. That is an unachievable goal for any public policy. There has continued to be debate in both the political and scientific communities about the proper balance between NIH funding of basic science and more applied clinical activities. But in broad perspective, considering both its successes and in its more realistic (compared with Bush's utopian ideal of science funded by the taxpayer but run only by scientists) political model, it is a fine example of a good policy that trumps a theoretically "best" one. Policymakers should be mindful that its success is based on so delicate a balance of social and intellectual forces. It is this system we have to thank for the efforts that have made the United States the world leader in biomedical science.

Table 1
Top Ten Diseases and Conditions by Level of NIH Funding, Fiscal Year 2000

Disease or condition	NIH funding
Cancer	$3.86 billion
HIV/AIDS	$2.01 billion
Heart research	$1.42 billion
Mental disorders	$853 million
Digestive diseases	$731 million
Drug abuse	$697 million
Diabetes	$525 million
Eye diseases	$485 million
Alzheimer's disease	$466 million
Smoking	$393 million

SOURCE: National Institutes of Health.

NOTE

[1] A nice illustration of the political and organizational tensions that surround the methods of public research fund allocation is recounted by Ruttan (2001, 568, note 23), who attributes the following comment to former Surgeon General Jesse Steinfeld: "If the space program had been conducted by NASA on an investigator-initiated project basis, we might now have 60,000 space scientists, each 80 miles on the way to the moon." Steinfeld's comment was made in light of his efforts to focus more of the NIH budget on disease-oriented clinical research, as opposed to basic science. Though amusing and true enough about the space race, we should be careful to note that it doesn't tell the whole story. The space race had a relatively stable goal in mind (put a man on the moon) and was working with relatively known scientific tools (rocket technology and planetary physics, etc.). Thus a centrally controlled crash program was feasible but, of course, not guaranteed. It is not clear that we know enough yet about cancer, for instance, to justify putting all of our scientific eggs into one basket.

REFERENCES

Arrow, K. J. (1962), "Economic Welfare and the Allocation of Resources for Invention," in *The Rate and Direction of Inventive Activity* (New York: National Bureau of Economic Research).

Bud, R. (1993), *The Uses of Life: A History of Biotechnology* (Cambridge: Cambridge University Press).

Bush, V. (1945), *Science the Endless Frontier: A Report to the President by the Director of the Office of Scientific Research and Development* (Washington, D.C.: U.S. Government Printing Office).

Dasgupta, P. (1987), "The Economic Theory of Technology Policy: An Introduction," in *Economic Policy and Technological Performance*, ed. P. Dasgupta and P. Stoneman (Cambridge: Cambridge University Press).

Griliches, Z. (1992), "The Search for R&D Spillovers," *Scandinavian Journal of Economics* 44: 29–41.

——— (1995), "R&D Productivity: Econometric Results and Measurement Issues," in *Handbook of the Economics of Innovation and Technological Change*, ed. P. Stoneman (Oxford: Basil Blackwell), 52–89.

Hall, B. H. (1996), "Private and Social Returns to Research and Development," in *Technology R&D and the Economy*, ed. B. R. Smith and C. E. Barfield (Washington, D.C.: Brookings Institution Press), 148–55.

Jones, C. I., and J. C. Williams (1998), "Measuring the Social Return to R&D," *The Quarterly Journal of Economics*, 1119–35.

Kleinman, D. L. (1995), *Politics on the Endless Frontier: Postwar Research Policy in the United States* (Durham, N.C.: Duke University Press).

Kornberg, Arthur (1997), "Support for Basic Biomedical Research: How Scientific Breakthroughs Occur," in *The Future of Biomedical Research*, ed. C. E. Barfield and B. L. Smith (Washington, D.C.: American Enterprise Institute and The Brookings Institution).

Mansfield, E. et al. (1977), *The Production and Application of New Industrial Technology* (New York: Norton).

Martin, S. A., D. Winfield, A. Kenyon, J. Farris, M. Bala, and T. Bingham (1998), *A Framework for Estimating the National Economic Benefits of ATP Funding of Medical Technologies* (Research Triangle Park, N.C.: Research Triangle Institute). Available at www.rti.org/publications/cer/6715-001.pdf.

Nelson, R. R. (1959), "The Simple Economics of Basic Scientific Research," *Journal of Political Economy* 67: 297–306.

Scherer, F. M. (1982),"Inter-industry Technology Flows and Productivity Growth," *Review of Economics and Statistics* 64: 627–34.

Ruttan, V. W. (2001), *Technology, Growth and Development: An Induced Innovation Perspective* (New York and Oxford: Oxford University Press).

Steil, B., D. G. Victor, and R. Nelson, eds. (2002), *Technological Innovation and Economic Performance* (Princeton, N.J.: Princeton University Press).

Tassey, G. (1999), *R&D Trends in the U.S. Economy: Strategies and Policy Implications. A Planning Report of the National Institute of Standards and Technology* (Washington D.C.: National Institute of Standards and Technology, U.S. Department of Commerce). Available at www.nist.gov/director/prog-ofc/report99-2.pdf.

PART FIVE

Local Determinants of Biotech Research

Commercializing Knowledge: University Science, Knowledge Capture, and Firm Performance in Biotechnology

Lynne G. Zucker, Michael R. Darby, and Jeff S. Armstrong

Commercializing Knowledge: University Science, Knowledge Capture, and Firm Performance in Biotechnology

Lynne G. Zucker, Michael R. Darby, and Jeff S. Armstrong

1. INTRODUCTION

Our research program over the past 10 years has focused on the use of basic science knowledge in commercial firms and the impact of that knowledge on firm performance. In our earlier research, we have found substantial consistent evidence that top academic science, specifically the star scientists who make most of the defining discoveries, provides intellectual human capital that defines the technology of the firm—at least following scientific breakthroughs. Although there are likely to be considerable spillover effects when knowledge is created or employed (Jaffe 1986, 1989), and perhaps also an important symbolic and legitimating function of high quality science for commercial activity (Stephan and Everhart 1998), our empirical work identifies the main and robust empirical effects due to real scientific labor contributions of star scientists to performance of the firm.

To "detect" stars and quantify their labor contributions to firms, we identified 327 "star" bio-scientists worldwide based on their publications of genetic-sequence discovery articles up to early 1990 before gene-sequencing machines were in widespread use. Stars were those cumulatively reporting more than 40 genetic-sequence discoveries or on 20 or more articles reporting any genetic-sequence discoveries in *GenBank* (1990). We identified every "star" article on which

Reprinted by permission, Lynne G. Zucker, Michael R. Darby, and Jeff S. Armstrong, "Commercializing Knowledge: University Science, Knowledge Capture, and Firm Performance in Biotechnology," *Management Science*, 48(1), 2002. Copyright 2002 the Institute for Operations Research and the Management Sciences (INFORMS), 901 Elkridge Landing Road, Suite 400, Linthicum, MD 21090 USA.

the star, or (more frequently) a co-author, was affiliated with a firm. The numbers of these articles was our measure of the depth of star involvement in the firm.

Before turning to new results reported in this article, a brief summary of our prior results will be useful for readers not already familiar with our work:

- Location of top, "star" scientists predicts location of firm entry into new technologies (both new and existing firms), shown for the United States and Japan in biotechnology (Zucker, Darby, and Brewer 1998, Darby and Zucker 2001) and replicated for the semiconductor industry in the United States (Torero et al. 2001).
- Ties that involve actual work at the science bench between star scientists (mostly academics) and firm scientists consistently have a significant positive effect on a wide range of firm performance measures in biotechnology (Zucker, Darby, and Armstrong 1998, Zucker and Darby 2001) and in semiconductors for number and quality of patents (Torero 1998). Ties to stars also shorten the time to IPO (firms are younger) and increase the amount of IPO proceeds (Darby et al. 2001).
- As the quality of an academic star bio-scientist increases and his/her research becomes more relevant to commercialization, the probability increases that the scientist conducts joint research or moves to a firm. As expected scientific returns increase—measured by citations to other local star scientists working with firms—the probability that the next star will begin working with a firm also increases (Zucker et al. 2001). Quality is also positively related to working with firms in Japan, but only number of articles predicts significantly with this smaller sample (Zucker et al. 2000).

Our findings on the importance of basic university science to successful commercialization of important scientific discoveries are confirmed in other research, especially the importance of intellectual human capital (Di Gregorio and Shane 2000). Faculty are a key resource in creating and transferring early, discovery research via commercial entrepreneurial behavior (Yarkin 2000). Jensen and Thursby (2001) confirm that active, self-interested participation of discovering professors is an essential condition for successful commercial licensing of university inventions. Thursby and Thursby (2000) find that the sharp increase in university-industry technology transfer has not resulted so much from a shift in the nature of faculty research as from an increased willingness of faculty and administrators to license and increased interest on the part of firms.

In this article, we continue our research program on the economic value of knowledge, especially tacit knowledge at the time of commercially relevant scientific breakthroughs. We compare the real effects on the performance of biotech firms of two overlapping groups of academic scientists who collaborate with firm scientists: the stars who made significantly more genetic sequence discoveries, and all relevant scientists (including the bulk of the stars) employed at

one of the top 112 U.S. research universities ranked by federal research funding. Our overall results again support the strong effects of academic science on the success of firms. Both science measures have strong positive independent effects on most performance measures. The patent panels show that the labor effort of the stars has a significant incremental impact on firm performance above and beyond the effects of all scientists from top research universities working with the firm. In cross-section estimates, we find significant positive effects from either star or top 112 faculty linkages but efforts to enter both sets of variables in the same regressions are confounded by multicollinearity. We conclude that affordable bibliometric measures are good but not perfect substitutes for the costly-to-construct star measures.

The article is organized as follows. In §2 we develop our theoretical approach to (a) the sources and implications of the information advantage—common to most scientific breakthrough knowledge—held by the discovering scientists, (b) the difficulties inherent to the transfer of tacit knowledge that lead to joint research, and (c) the amount of *knowledge capture* necessary for firms to offset sunk commercial development costs. In §3 we sketch the history of scientific development and the rise of the biotech industry, focusing on the ties between academic science and commercial firms. Since data are the plural of anecdote, we present qualitative evidence of the importance of ties to star scientists for the performance of the most successful firms. In §4 we briefly review the variables and their sources and then present and discuss the empirical results. We estimate Poisson regressions (and linear-least squares for employment) that explain the performance of a panel of biotech firms for patents and citation-weighted patents, and cross-sections for products in development, on the market and employment. In these regressions, we systematically test the predictive power of science (stars and top 112 university scientists tied to the firm via co-authoring of scientific research, as well as all local academic scientific publishing by stars), venture capital, and other firm characteristics such as use of the dominant technology (rDNA or genetic engineering). In §5 we offer our conclusions. Details on the data set and supplementary analyses are compiled in a separate appendix, which is cross-referenced and available from the authors on request.

2. THE REAL EFFECTS OF KNOWLEDGE CAPTURE

Academic-to-industry technology transfers may be rare, but we believe they can still account for the bulk of technological progress. These are not pure "transfers," but necessarily knowledge captures to the degree necessary to offset sunk development, marketing, and other costs invested in moving a discovery into a commercial innovation. Many fundamental industry transformations or technological breakthroughs can be traced to specific advances in science.

While the industries experiencing technological discontinuity are a distinct minority in our economy, we argue that a distinct minority of firms within this distinct minority of industries account for a large part of the aggregate technological progress conventionally measured in productivity studies (Harberger 1998, Darby and Zucker 2002).

Knowledge and the Market for Information

Our argument starts from the classic Stigler (1961) observation that information is a valuable and costly resource and that individuals are thus motivated to adopt strategies, such as search, that weigh the expected costs and benefits of acquiring information. For example, if individuals' search involves unique goods, then costs of search are sufficiently high that transactions are commonly localized as a device for identifying potential buyers and sellers. Stigler pointed out that medieval markets were an example of actual localization; advertising is an example of a "virtually" localized market.

We argue that another mechanism of "virtual" localization is a profession, or more commonly, a subspecialty within a profession.[1] Here, the buyers and sellers of knowledge, including new or "breakthrough" discoveries, are brought together in a highly balkanized market in which the participants share a reasonably similar endowed knowledge base that makes the new knowledge potentially understandable and useable. The size and geographic distribution of that knowledge base determines the extent of initial demand for the new knowledge. For the purposes of our argument here, information and knowledge are equivalent.

From Tacit to Codified Knowledge

New information tends to be produced in tacit form, increasing in tacitness as a function of distance from prior knowledge (hence, especially breakthrough knowledge), and requires resources to codify. Tacit knowledge tends to be highly personal, initially known only by one person (or a small team of discovering scientists) and is difficult to transfer to others (Polyani 1962, Schutz 1962).

As knowledge increases in complexity, the probability increases that deviation from "textbook" description of action will be required (Nelson 1959, Nelson and Winter 1982). For example, internal bleeding during surgery requires decisions about whether and how to deviate from the textbook that cannot be fully prescribed in advance. This kind of complexity leads to knowledge remaining tacit longer, perhaps remaining an "active task" that changes its nature in response to contingencies in contrast to an "inert task" such as a secretary typing a letter written by his/her boss (Scott et al. 1967).

Knowledge becomes shared (intersubjective) to the extent that codes or formulas are borrowed from pre-existing knowledge and/or are newly created.

Relevance to earlier knowledge allows borrowing of codes, mathematical expressions and relations, and even machines that "embody" those codes/math. Such knowledge is cumulative and can be easily understood and transferred, relying on references to the well-understood prior scientific literature.

But new knowledge that cannot be readily grafted on old is likely to offer more opportunities. Opportunity can shift incentives—increasing them along a continuum from incremental change to breakthrough discoveries (Klevorick et al. 1995). Increased incentives to enter arise from these greater opportunities.

Discovering scientists become important in technology transfer when a new discovery has both high commercial value and a combination of scarcity and tacitness that defines *natural excludability*, the degree to which there is a barrier to the flow of the valuable knowledge from the discoverers to other scientists. Tacit, complex knowledge provides partial natural protection of information, both separately and jointly with more formal property rights. Those with the most information about breakthrough discoveries are the scientists actually making them, so there is initial natural scarcity. To the extent that the knowledge is both scarce and tacit, it constitutes intellectual human capital retained by the discovering scientists, and therefore they become the main resource around which firms are built or transformed (Zucker, Darby, and Brewer 1998; Zucker, Darby, and Armstrong 1998). Hence, tacit knowledge can be viewed as at least partially rivalrous and excludable information and thus "appropriable" as long as it remains difficult (or impossible) to learn it.

As tacit knowledge becomes increasingly codified—or translated into "recipe knowledge" as Schutz (1962) terms it—tacitness decreases and knowledge transfer is easier. But significant barriers stand in the way of codification. Relevance between old and new knowledge can be difficult to determine (Schutz 1970), increasing the demand for social construction of new codes, formulae, and machines. The greater the discontinuity, the more difficult it is to anchor in prior systems of knowledge.

Until there is a reliable indicator of the value of the new knowledge, the size of the market for codification is unlikely to be large enough to cover the cost of developing the new codes. Paradoxically, once the value is known,

- If the value is low relative to alternative uses of scientific talent, then there are few incentives to codify it.
- If it is high, those few scientists who hold the new knowledge will have to weigh returns to codification against returns to time invested in scientific research, a trade-off that pits knowledge transfer against knowledge creation.

Hence, the average scientific discovery is never codified, and valuable discoveries experience a significant codification lag that tends to increase with their value.

Knowledge Capture via Team Production

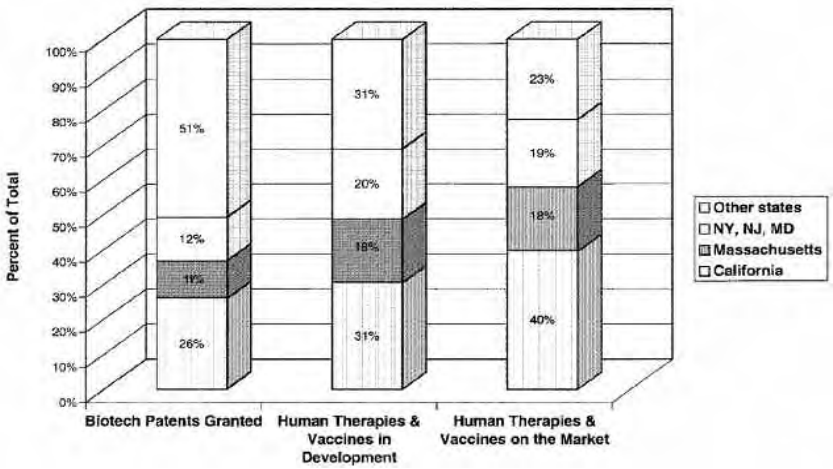
Knowledge that is cumulative builds on an existing set of words and symbols, and hence involves less or no barrier to communication: Listening to a lecture or reading a text can suffice. But tacit knowledge often requires that one of those already holding that knowledge works with the novices to teach them in a hands-on process. For example, 81% of the new authors enter GenBank by writing with old authors, and new authors write exclusively with new authors a significant 36% less than "old," experienced authors write exclusively with other "old" authors after excluding all sole authored papers (Zucker et al. 2001). Transfer may be very effective—there are well-documented effects of cumulative experience on performance improvement (Pisano et al. 2001)—but it is slow and requires the active participation of the holder of the tacit knowledge.

Discovering scientists are typically willing to transfer knowledge primarily in the context of their ongoing laboratory work. At the extreme, when tacitness is high, it is their collaborators on their research team who are the recipients of this knowledge; others are excluded through lack of access. Thus, the initial cost of entry is high. But entry cost tends to decline over time, and the probability of an error in the initial discovery also declines as others replicate it, thus reducing risk to the new entering scientist.[2]

This restricted process of transfer will more often than "normal science" lead to sufficient knowledge capture to justify the cost of commercial development by a firm. Knowledge capture explains why tacit knowledge tends to be highly localized: It will be concentrated geographically around where the discoveries are made (or where the discoverers move). As shown in Figure 1, there is considerable concentration of patented inventions, as well as human therapies and vaccines, in development and on the market. Just two states, California and Massachusetts with 14% of the U.S. population, have a disproportionate share especially of U.S. products in development (49%) and on the market (58%). Patenting is somewhat less concentrated; since patenting is both an input and an output of the innovation process, this may suggest a lessening of geographic concentration, perhaps as the discoveries mature and are codified. Generally patents provide a useful incentive to the codification of knowledge, but in the case of patented cell lines, a novel technique—deposit in an approved depositary to be publicly available on patent expiration—acknowledged the difficulty in codifying exactly how the new organisms could be created.

Understanding the role of scientific teams in tacit knowledge transfer extends the arguments for team production: (a) Team organization makes routine the transfer of tacit knowledge from the discoverer to other team members, and if team members cross organizational boundaries, then tacit knowledge is efficiently transferred—in the present case, most interestingly from university discovering scientists to firm scientists (Zucker, Darby, and Armstrong 1998). (b) Through

Figure 1
The Geographic Distribution of Biotech Patents and New Products as of 1991



team organization, more productive cooperation is often achieved via specialization than possible through the linking of individual efforts across impersonal markets (Demsetz 1995, p. 17).

The greater the labor effort of the discovering university scientist(s) with teams containing firm scientists, the greater the amount of tacit knowledge transfer. In bench level collaboration, you can actually see how the science is done. As tacit knowledge transfer increases from the discovering scientists, the success of the firm also increases. Thus, managers of high tech firms have incentives to hire the top-discovering scientists if their discoveries have commercial value. Discovering scientists also have incentives to found a new firm. In sharp contrast, in industries where "normal science" reigns, hiring of below average, acceptably competent scientists at a low wage is the typical practice (Kornhauser 1962). Obviously, each can be a market-value–maximizing strategy for the firms facing different knowledge frontiers.

3. SCIENTISTS' LEADERSHIP AND INDUSTRY SUCCESS: COMMERCIALIZING KNOWLEDGE

Biotechnology is a preeminent example of an industry undergoing very rapid growth associated with radical technological change initiated in academe and based on basic science breakthroughs. The key attributes can be summarized concisely:

- *Breakthrough discovery:* Professors Stanley Cohen (Stanford) and Herbert Boyer (University of California–San Francisco) reported the basic

technique for recombinant DNA, also known as rDNA, genetic engineering, or gene splicing (Cohen et al. 1973).

- *University scientists:* We identified star bio-scientists based on genetic sequence discoveries reported in *GenBank* (1990), an online reference file, and in this article introduce bio-scientists identified in ISI's electronic file of research articles written by at least one author located at one of the top 112 U.S. research universities.[3] Star articles are (nearly) a subset of top 112 articles (U.S. stars not in a top 112 university and conference papers—less than 1% of the total star articles—are not included in the ISI article files).
- *Links/collaborations with firms:* Articles that are co-authored by firm employees and top scientists, including "stars" and the top 112 university scientists, indicate the intensity of involvement with the firm's research effort.[4] Most of these scientists "wear two hats," one as professor at a university and one as a leader or lab head at a firm (confirmed through interviews at universities and firms on both coasts).

Firm Success and Knowledge Capture

The degree to which an open scientific literature can produce such strong apparent "knowledge capture" effects on firm success rests on (a) characteristics of tacit, complex knowledge that lead to natural excludability, and (b) selection by firms of discoveries for which the degree of knowledge capture is likely to offset sunk costs incurred in making the scientific discovery a commercial innovation.

To provide some intuition for our regression results, we first briefly review examples of the prominent positions that top academic scientists are given in the most successful biotech firms, identify their copublishing with the firm, and finally explore the impact that top scientists' copublications with firm scientists have on success.

Top 10 Biotech Firms

Individual scientists are often highlighted in an IPO prospectus.[5] These scientists typically achieved prominence in both their university and private sector appointments. Examples of distinguished academics from the top-112 universities[6] that were appointed to corporate officer positions in one of the top 10 biotechnology firms (as of 1994) include: (a) Herbert Boyer to the position of vice president and director of Genentech Inc.;[7] (b) Edward Penhoet, former faculty member of the Biochemistry Department at UC–Berkeley and co-founder of Chiron, to the position of president, CEO, and director of Chiron; (c) Walter Gilbert, the American Cancer Society Professor of Molecular Biology at Harvard

Table 1

The 10 Most Highly Valued Biotechnology Firms in 1994: Leading Academic Scientists Appear on Their IPO Prospectus and as Joint Authors

		Star Scientists		Top-112 University Professors	
Company[a]	IPO Date	Listed on the Prospectus[b]	Linked Articles	Listed on the Prospectus[b]	Core Collaborations
Genentech, Inc.	October 1980		√	√	√
Centocor, Inc.	June 1982	√	√	√	√
Chiron Corporation	August 1983	√	√	√	√
Biogen N.V.	March 1983	√	√	√	√
Amegen, Inc.	June 1983	√	√	√	√
Immunex Corp.	July 1983		√	√	√
ALZA Corp.[c]	December 1985				
Genzyme Corp.[d]	June 1986			√	√
Genetics Institute, Inc.	May 1986		√	√	√
IDEXX Laboratories, Inc.	June 1991				√

[a] Top 10 biotechnology firms in terms of market value as identified in Lee and Burrill's (1995) ninth annual industry report for Ernst & Young. [b]Listed on the IPO prospectus as an executive, director, or member of the company's scientific advisory board. [c]ALZA Corp. was founded in 1968 before genetic engineering and has successfully pursued a specialized niche R&D strategy by concentrating on developing sophisticated drug delivery systems rather than drug discovery. [d]Genzyme Corp. had an extensive long-term contractual relationship with BioInformation Associates (BIA). BIA was owned by a group of eight academic scientists: George Whitesides at Harvard and seven MIT professors: Charles Cooney (also appointed as a Genzyme director), Harvey Lodish, Chokyun Rha, William Roush, Anthony Sinskey, Graham Walker, and Christopher Walsh.

University and 1980 Nobel prize winner, to several of Biogen's boards, with Phillip Sharp, professor of biology at MIT, and Daniel Wang, professor of chemical and biochemical engineering at MIT, on its scientific board; (d) two founders of Genetics Institute were university faculty, who also were executive officers and directors of the company, as well as members of its scientific advisory board; and (e) Amgen included on its scientific board prominent university professors from UCLA, CalTech, and Stanford, all members of the National Academy of Sciences.

Table 1 shows that 40% of these top 10 biotech companies reported at least one star on their team when going public, while 70% had linked articles (star copublishing with at least one firm employee). Not surprisingly, because of the much broader coverage of both scientists and universities, these top 10 biotech companies reported a higher percentage of top 112 university scientists: 80% reported at least one top 112 scientist on their team when going public, and 90% had core collaborations with one or more of these scientists. The advantage of the publishing measure is that it weights the amount of involvement of the scientist: For example, Centocor had only 1/20 as many core collaborative research articles as Genentech.

IPOs listed many former or current university professors as company founders, officers, directors or key members of scientific advisory boards (see Appendix Table A1). Almost every scientist holding a top management position had done so since the company's founding. These scientists were not brought in as part of the preparation for the IPO to merely "signal" the firm's success, contrary to a suggestion in Stephan and Everhart (1998).

Is Success in the Stars?

Certainly, scientists in high-ranking positions in these now public firms provide scientific control and are important for firm success. However, the majority of firms in our sample do not go public before the end of our time period. In any case, we are interested in the actual work that top scientists do that is joint with the firm. We measure this joint work by the cumulative number of collaborative articles.

Using the total number of joint articles, drawing on both of our science measures, we can take a preliminary look at our findings by graphing the mean values of the cumulative number of tied articles: for the stars, articles that involve a star scientist and a firm scientist (where the star can also be an employee of the firm) and for scientists at the top 112 universities, articles that involve joint work by at least one university and one firm scientist. These values are shown in Figure 2a. The differences are particularly striking at the 10+ article level. The mean success by tied star articles is consistently and markedly higher than for top 112 university scientists across our major success measures: patents, products in development, and products on the market.

Figure 2a

Biotech Firms Are More Successful if Tied to Star Scientists or if Linked to Top Research University Faculty

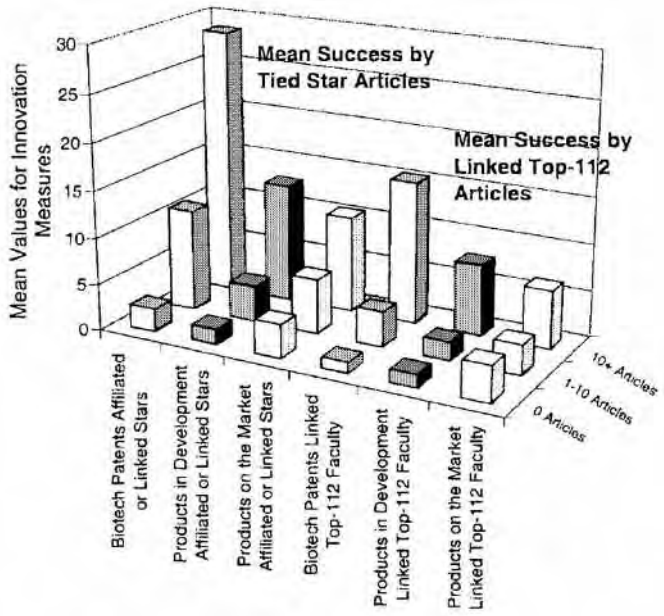


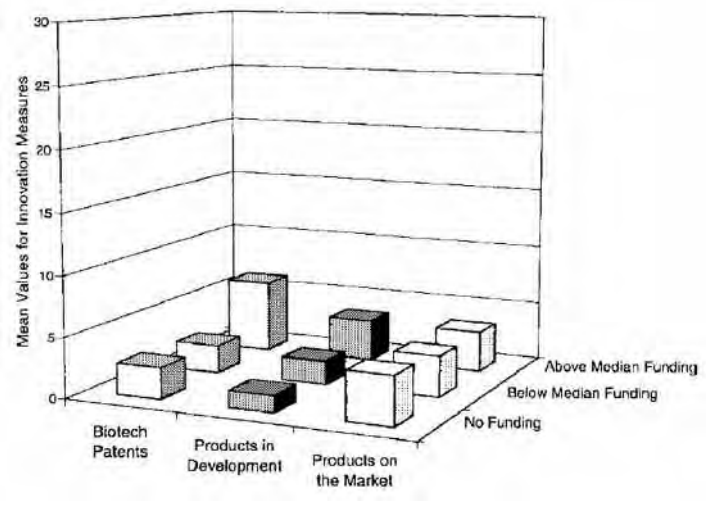
Figure 2b presents the comparable data on venture capital funding (data from Venture Economics). The amount of venture capital funding is less consistent in its effects compared to tied/linked science results. While increasing cumulative amount of venture financing generally increases both patents and products in development, the magnitude of differences is small relative to the tied/linked science effects shown in Figure 2a.

Concentration of Success

Darby and Zucker (2002) argue that much if not most of technological progress is accounted for by relatively few firms operating in relatively few industries undergoing rapid change. We will just touch on examples of concentration here:

- *Industry Success Concentration:* Top-decile biotech firms account for 64% of the total number of human therapies and vaccines in development (485 as of 1991), 43% of all patents, and dominated human therapies and vaccines on the market (82%). (See Appendix Figure A1.)
- *Geographic Concentration:* 64% of the total products in development are concentrated in the top five states (Appendix Table A2); 58% of the total products on the market are concentrated in those same five states (Appendix Table A3).

Figure 2b
Biotech Firms Are More Successful if Funded by Venture Capitalists



4. EMPIRICAL RESULTS

The Data

The Zucker-Darby star-scientists/articles database has been a powerful tool for exploring the co-evolution of life sciences and biotechnology. However, that methodology involves an expenditure of resources justifiable only for pioneering academic efforts or sophisticated financial institutions. As the ISI databases are increasingly available, the extent to which electronic bibliometry can substitute for hand coding and specialized technical knowledge is a question of practical importance to both academic researchers and industry practitioners.

Here we use the basic tool of copublishing between academic and firm scientists as a detector of joint research and (often two-way) university-industry technology transfer. The Institute of Scientific Information (ISI 2000) *U.S. University Science Indicators* database on CD-ROM has extensive information on all the scientific articles with at least one author at any of the top 112 U.S. research universities.

Table 2 defines all the variables used in the empirical estimates and provides summary sample statistics for each. As in Zucker, Darby, and Armstrong (1998), we classify each article in *GenBank* of which a star scientist is an author relative to each firm as affiliated with the firm, as linked to the firm if the star is unaffiliated but writing with the firm's employees, and otherwise as untied to the firm. Aggregating over all stars and time for each firm gives the first six variables in Table 2. The "local" in local untied articles refers to articles by stars affiliated with universities or research institutes in the firm's functional economic area (metro area plus exurbs as defined by the U.S. Bureau of Economic Analysis).

We attempted to find all articles written by any employee of each of our biotech firms in the ISI (2000) database; these articles also must have at least one top 112 university author to be included. Among these joint articles, we focus on the "core collaborations" in the four central biotech fields catalogued by ISI: biochemistry and biophysics, cell and developmental biology, molecular biology and genetics, and microbiology. To control for variation in quality of the collaborators, we also collected the number of citations in ISI-indexed journals in the current plus next four years for each article.

The firm characteristics and the last five dependent variables were mostly collected from paper directories and industry studies used by industry participants when looking for suppliers and customers. This methodology is tedious, but it is one of the few available for analysis of large numbers of privately (as well as publicly) held firms. As described in other papers referenced in Table 2, considerable effort was expended in ensuring that uniform coding procedures were applied to obtain quantitative variables from text records.

The primary exception was the venture-funding data obtained by licens-

Table 2
Definitions and Sample Statistics for Variables

	Definitions	*m*	SD	Min.	Max.	*n*
	Independent variables					
Cumulative star authorships of	Articles to date written by a star scientist:					
Local united articles	not firm-affiliated/not linked to this firm	120.0	125.3	0	387	3,152
Affiliated articles	affiliated with this firm	0.40	6.25	0	139	3,152
All linked articles	not firm-affiliated/with this firm's emp.	0.19	1.39	0	20	3,152
Star authorships of	Articles to 1990 written by star scientist:					
Local united articles	not firm-affiliated/not linked to this firm	164.5	149.5	0	382	342
Affiliated articles	affiliated with this firm	0.50	7.596	0	139	342
All linked articles	not firm-affiliated/with this firm's emp.	0.281	1.732	0	20	342
Cumulative top 112 university authorships	For articles to date with any author(s) at an ISI-defined top-112 university:					
All core collaborations	number with this firm's employee(s)	1.57	10.36	0	271	3,152
Citations to articles	mean citations in 5 years to above	5.45	18.24	0	254	3,152
Top 112 university authorships	For articles through 1990 with any author(s) at an ISI-defined top-112 univ.:					
All core collaborations	number with any this firms's employees	5.918	26.27	0	337	342
Citations to articles	mean citations in 5 years to above	10.23	24.87	0	225	342
Firm characteristics						
NBF indicator	1 if entrant firm; otherwise 0	0.746	0.436	0	1	342
Years in biotech	Year +1—year firm began using biotech	7.216	3.117	1	14	342
Recombinant DNA indicator	1 if firm uses recomb. DNA; otherwise 0	0.479	0.500	0	1	342
Cumulative venture capital funding	Amount of venture capital received by this firm to date in 100,000s of 1984 $s	24.26	65.65	0	899.5	3,152
Cumulative venture capital funding as of 1990	Amount of venture capital received by this firm to 1990 in 100,000s of 1984 $s	42.92	94.49	0	899.5	342
	Dependent variables					
Cumulative patents granted	Number of biotech patents applied for to date and assigned at issue to this firm	0.97	4.56	0	96	3,152
Cumulative patents granted as of 1991	No. of biotech patents applied for by end of 1991 and assigned at issue to this firm	2.652	9.337	0	120	342
Cumulation citation-weighted patents granted	Number of citations received up to year 1997 to biotech patents applied for to date and assigned at issue to this firm	8.881	41.69	0	820	3,152
Cumulation citation-weighted patents granted as of 1991	No. of citations received up to year 1997 to biotech patents applied for through 1991 and assigned at issue to this firm	19.68	70.63	0	820	342
Total products in development	Count of Total Products in Development in 1990 *Bioscan*	1.895	3.231	0	22	342
Total human therapies and vaccines in development	Count of Human Therapies & Vaccines in Development in 1990 *Bioscan*	1.418	3.031	0	22	342
Total products on the market	Count of Total Products on the Market in 1990 *Bioscan*	3.781	5.326	0	37	342
Total human therapies and vaccines on the market	Count of Human Therapies & Vaccines on the Market in 1990 *Bioscan*	0.547	1.591	0	13	342
Total employees as of 1994	Employment reported in 1994 *Bioscan*	926.2	7983	1	110,400	233

Note. Panel variables ($N = 3,152$) have observations by firm and year; others are observed only once per firm.
Detailed definitions and sources in text and data appendices in NBER Working Papers 4653, 4949, and 6360 (draft versions of Zucker, Darby, and Brewer 1998, Zucker, Darby, and Armstrong 1998, and Zucker and Darby 2001).

ing the Venture Economics database and deflating dollar amounts by the GDP deflator. We also had the list of licensees of the UC–Stanford Cohen-Boyer patent as an alternate indicator of the use of recombinant DNA technology. We bought our list of biotech patents from CHI Research, Inc., in 1997. We ensured that the CHI list included all those on U.S. Department of Commerce, Patent and Trademark Office (1993) and appropriate others. Counts of citations to date by other patents were included.

Table 3
Panel Estimates for Patenting-Success Models for All U.S. Firms and Years 1976–1991

Dependent Variables (across)	Cumulative Patents Granted (to current year)				Cumulative Citation-weighted Patents Granted (to current year)			
Explanatory Variables (down)	Model a	Model b	Model c	Model d	Model e	Model f	Model g	Model h
Constant	−2.6793***	−2.2509***	−2.1731***	−2.1444***	−0.6679***	−0.0767***	−0.0643***	−0.0285***
	(0.0358)	(0.0350)	(0.0297)	(0.0343)	(0.0046)	(0.0039)	(0.0035)	(0.0037)
Cumulative star authorships of								
Local untied articles		0.0001		0.0000		−0.0001***		−0.0002***
		(0.0001)		(0.0001)		(0.00001)		(0.00001)
Affiliated articles		0.0037***		−0.0092***		0.0049***		−0.0006***
		(0.0002)		(0.0007)		(0.00004)		(0.0001)
All linked articles		0.0872***		0.0237***		0.0904***		0.0510***
		(0.0016)		(0.0027)		(0.0004)		(0.0005)
Cumulative top 112 university authorships								
All core collaborations			0.0058***	0.0099***			0.0058***	0.0039***
			(0.0002)	(0.0005)			(0.00003)	(0.0001)
Citations to articles			0.0092***	0.0084***			0.0093***	0.0079***
			(0.0002)	(0.0002)			(0.00004)	(0.00003)
Firm characteristics								
NBF indicator	−0.7808***	−0.8849***	−0.9267***	−0.9357***	−0.9654***	−1.1240***	−1.1703***	−1.1735***
	(0.0242)	(0.0253)	(0.0245)	(0.0245)	(0.0028)	(0.0032)	(0.0031)	(0.0031)
Years in biotech	0.3265***	0.2829***	0.2762***	0.2713***	0.3364***	0.2806***	0.2777***	0.2760***
	(0.0027)	(0.0021)	(0.0023)	(0.0021)	(0.0003)	(0.0003)	(0.0003)	(0.0003)
Recombinant DNA indicator	1.4487***	1.2301***	1.1701***	1.1305***	1.5961***	1.3463***	1.2812***	1.2657***
	(0.0185)	(0.0217)	(0.0213)	(0.0219)	(0.0025)	(0.0029)	(0.0028)	(0.0029)
Cumulative venture capital	0.0034***	0.0030***	0.0025***	0.0028***	0.0049***	0.0047***	0.0045***	0.0047***
funding as of 1990	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0000)	(0.0000)	(0.0000)	(0.0000)
Log-likelihood	−5117.46	−4838.21	−4770.46	−4738.38	−38692.04	−35381.40	−35093.21	−34870.10
Restricted log-likelihood	−8228.78	−8228.78	−8228.78	−8228.78	−73148.71	−73148.71	−73148.71	−73148.71
Sample size	3,152	3,152	3,152	3,152	3,152	3,152	3,152	3,152

Note. All models were estimated as a Poisson process with standard errors (in parentheses) corrected following Wooldridge (1991).
Significance levels:
*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

The Estimates

In a technology-intensive industry like biotechnology, patents are a crucial measure of success. Patents serve as a measure of output from a firm's "knowledge production function" (Griliches 1990). The patent permits knowledge capture by establishing ownership rights to the invention's commercial rewards until the patent expiration date and even beyond expiration to the extent the firm establishes brand recognition. Patenting success also impacts the firm's ability to raise public equity capital.[8] Because patent acquisition is key to both financial and nonfinancial measures of success and citations data are available with which to quality-adjust a firm's patents, the patenting success models are a key testing ground for the electronic version of our star methodology.

Table 3 reports standard Poisson regression estimates for panel data on U.S. patenting by U.S. biotech firms. The standard errors are corrected using the procedure of Wooldridge (1991).[9] Models a and e in Table 3 indicate that simple firm characteristics available for both private and public firms do a good job

of explaining patenting. Entrants are generally at a disadvantage, experience helps, and use of the dominant technology (recombinant DNA or genetic engineering) is a positive factor for both quantity and quality of patenting. As always with forward-looking financial variables, the positive effect of the cumulative amount of venture capital investment may confound real R&D productivity of the investments with forecasting the effects of other, omitted variables.

Firms that have many articles with star scientists also tend to have many articles with top 112 university faculty—indeed nearly all the linked star articles are also included in the top 112 core collaborations count of joint faculty-firm articles. If one adds either the star variables used in Zucker, Darby, and Armstrong (1998) or core collaborations and their mean citations (a quality measure) as in Models b and c or f and g, we see that either set of indicators improves the explanatory power of the models. In the current case of patents and patent citations, the fit is a little better with the new variables than with the star-based variables, but we will see below that just the opposite is true for all products and for human therapeutics and vaccines on the market. The failure of local untied star articles to enter significantly positively reaffirms our (1998) result that localized knowledge impacts of universities on industry are associated with market transactions rather than uncompensated spillovers from the ivory tower. The coefficients on cumulative venture capital investment are only mildly reduced by inclusion of either (or both) of the star or top 112-based measures of the firm's science base. This suggests that venture capitalists in the 1980s were not discriminating much among biotech firms on the basis of scientific depth, so we obtain independent effects on research productivity of both intellectual and financial capital. The significance of the knowable science-base information implies that the capital markets were not fully incorporating it in allocating capital.

Models d and h in Table 3 experiment with adding both sets of science indicators at once. Since linked star articles are generally included in the top 112 core collaboration counts, the coefficient on linked articles measures the additional impact of stars on firm research output over and above that of the "average" joint authorship with a professor from a top 112 university. The coefficients for all core collaborations and their mean citations as well as this additional star impact are positive and significant for patents and patent citations. The negative coefficient on affiliated star scientists in these full regressions appears to reflect the special circumstances of one or two firms that have the bulk of affiliated articles.

Unfortunately, the smaller samples for the cross-section results in Tables 4, 5, and 6—comparable patent cross-sections are in the appendix available on request—seem more confounded by the near multicollinearity of the science variables observed cumulatively up to 1990: For the full Models d and h, where both the star and top 112 article faculty-firm coefficients are significant they have opposite signs. We would prefer panel estimates for products in development

Table 4
Estimates for Products-in-Development Models for All U.S. Firms

Dependent Variables (across)	Total Products in Development as of 1990				Total Human Therapies and Vaccines in Development as of 1990			
Explanatory Variables (down)	Model a	Model b	Model c	Model d	Model e	Model f	Model g	Model h
Constant	−0.9294***	−0.6682***	−0.5976***	−0.5148***	−1.4714***	−1.2688***	−1.0479***	−1.0725***
	(0.0782)	(0.0757)	(0.0772)	(0.0778)	(0.0898)	(0.0839)	(0.0877)	(0.0877)
Star authorships of								
Local untied articles		0.0003		0.0003		0.0013***		0.0012***
		(0.0001)		(0.0001)		(0.0002)		(0.0002)
Affiliated articles		0.0013**		−0.0315***		0.0013**		−0.0375***
		(0.0004)		(0.0019)		(0.0004)		(0.0021)
All linked articles		0.0959***		−0.0177		0.1006***		−0.0352***
		(0.0034)		(0.0072)		(0.0032)		(0.0074)
Top 112 university authorships								
All core collaborations			0.0061***	0.0227***			0.0066***	0.0269***
			(0.0005)	(0.0015)			(0.0005)	(0.0015)
Citations to articles			0.0056***	0.0029***			0.0075***	0.0037***
			(0.0006)	(0.0008)			(0.0006)	(0.0007)
Firm characteristics								
NBF indicator	0.2329***	0.2292***	0.2101***	0.1852***	0.2309***	0.2242***	0.1947**	0.1571**
	(0.0487)	(0.0531)	(0.0542)	(0.0534)	(0.0538)	(0.0579)	(0.0610)	(0.0603)
Years in biotech	0.1108***	0.0742***	0.0720***	0.0585***	0.1255***	0.0771***	0.0763***	0.0581***
	(0.0067)	(0.0066)	(0.0068)	(0.0070)	(0.0075)	(0.0074)	(0.0078)	(0.0079)
Recombinant DNA indicator	0.7369***	0.5549***	0.5189***	0.4218***	0.8829***	0.6164***	0.5991***	0.4449***
	(0.0439)	(0.0484)	(0.0474)	(0.0502)	(0.0480)	(0.0533)	(0.0529)	(0.0562)
Cumulative venture capital	0.0022***	0.0022***	0.0018***	0.0019***	0.0027***	0.0026***	0.0022***	0.0023***
funding as of 1990	(0.0001)	(0.0001)	(0.0002)	(0.0002)	(0.0001)	(0.0001)	(0.0002)	(0.0002)
Log-likelihood	−834.98	−792.83	−789.10	−765.98	−765.52	−709.36	−709.90	−677.12
Restricted log-likelihood	−936.40	−936.40	−936.40	−936.40	−872.49	−872.49	−872.49	−872.49
Sample size	342	342	342	342	342	342	342	342

Note. All models were estimated as a Poisson process with standard errors (in parentheses) corrected following Wooldridge (1991).
*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

and on the market and employment also, but each observation is very costly to obtain from old paper directories for these predominantly private start-up firms. As with the patent panels, we get generally significantly positive coefficients for linked and affiliated star articles (Models b and f in Tables 4, 5, and 6) or for top 112 core collaboration articles and their mean citations. Employment is the one dependent variable without many zeroes; in Table 6 we estimate the log of 1994 employment in accord with Gibrat's Law (Sutton 1997).

In summary, the empirical work strongly supports the central message that university-firm technology transfer for breakthrough discoveries generally involves detectable joint research between top professors and firms that they own or are compensated by. We have shown that our electronic bibliometry provides good but imperfect substitutes for the more costly to obtain and difficult to operationalize star measures. In particular, in large samples where we can obtain separable impacts, star linkages appear to have a significantly larger effect on firm research productivity than the average article written jointly by top research university professors and firm employees.

Table 5
Estimates for Products-on-the-Market Models for All U.S. Firms

Dependent Variables (across)	Total Products on the Market as of 1990				Total Human Therapies and Vaccines on the Market as of 1990			
Explanatory Variables (down)	Model a	Model b	Model c	Model d	Model e	Model f	Model g	Model h
Constant	0.4715***	0.6581***	0.4881***	0.6211***	−1.4588***	−1.0649***	−1.0252***	−1.0201***
	(0.0424)	(0.0491)	(0.04298)	(0.0456)	(0.1262)	(0.1252)	(0.1155)	(0.1263)
Star authorships of								
Local untied articles		−0.0010***		−0.0011***		0.0003		0.0003
		(0.0001)		(0.0001)		(0.0002)		(0.0002)
Affiliated articles		−0.0037***		0.0070*		0.0083***		−0.0129**
		(0.0006)		(0.0029)		(0.0009)		(0.0046)
All linked articles		0.0630***		0.0858***		0.1072***		0.0329
		(0.0057)		(0.0114)		(0.0072)		(0.0204)
Top 112 university authorships								
All core collaborations			0.0009***	−0.0070***			0.0103***	0.0146***
			(0.0002)	(0.0021)			(0.0005)	(0.0035)
Citations to articles			0.0010	0.0016**			0.0045***	0.0019
			(0.0006)	(0.0006)			(0.0011)	(0.0013)
Firm characteristics								
NBF indicator	−0.0855**	−0.0982***	−0.0848**	−0.0854**	−0.3431***	−0.3574***	−0.3515***	−0.3734***
	(0.0277)	(0.0286)	(0.0276)	(0.0275)	(0.0795)	(0.0851)	(0.0865)	(0.0856)
Years in biotech	0.1189***	0.1145***	0.1166***	0.1178***	0.1087***	0.0600***	0.0594***	0.0539***
	(0.0036)	(0.0040)	(0.0038)	(0.0039)	(0.0111)	(0.0102)	(0.0107)	(0.0106)
Recombinant DNA indicator	0.0544	0.0294	0.0338	0.0447	0.5854***	0.3515***	0.3547***	0.2904***
	(0.0232)	(0.0263)	(0.0249)	(0.0254)	(0.0771)	(0.0829)	(0.0845)	(0.0839)
Cumulative venture capital	−0.0007***	−0.0006***	−0.0007***	−0.0006***	−0.0009**	−0.0019***	−0.0031***	−0.0023***
funding as of 1990	(0.0002)	(0.0002)	(0.0002)	(0.0002)	(0.0003)	(0.0004)	(0.0005)	(0.0004)
Log-likelihood	−1317.71	−1296.09	−1316.81	−1293.83	−440.58	−418.77	−420.01	−416.54
Restricted log-likelihood	−1406.43	−1406.43	−1406.43	−1406.43	−456.72	−456.72	−456.72	−456.72
Sample size	342	342	342	342	342	342	342	342

Note. All models were estimated as a Poisson process with standard errors (in parentheses) corrected following Wooldridge (1991).
*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

5. CONCLUSIONS

Breakthrough discoveries in gene splicing set off a revolution in bioscience and created the biotechnology industry. These discoveries set the stage, then, for increased opportunity and increased incentives to enter. But significant natural barriers to the communication of new knowledge often exist. New knowledge tends to be developed in tacit form and requires resources to codify. New codes and formula to describe discoveries develop slowly—with insufficient incentives if value is low and too many competing opportunities if the value is high. Hence new knowledge tends to remain uncodified, difficult to obtain except through hands-on learning at the lab bench, and hence naturally excludable and appropriable. Our basic argument is that knowledge close to breakthrough discoveries needs to be transformed into words, codes, and/or formula before it can be easily transferred.

Difficulties inherent to the transfer of tacit knowledge lead to joint research: Team production allows more knowledge capture of tacit, complex discoveries by firm scientists. A robust detector of tacit knowledge capture by

Table 6
OLS Estimates for 1994 Employment for All Reporting U.S. Firms, Dependent Variable: Natural Logarithm of Total Employees as of 1994

Explanatory Variables (down)	Model a	Model b	Model c	Model d
Constant	4.416***	4.3516***	4.6815***	4.5195***
	(0.3379)	(0.3449)	(0.3338)	(0.3454)
Star authorships of				
Local untied articles		0.0015*		0.0014*
		(0.0007)		(0.0007)
Affiliated articles		0.0074		−0.0236
		(0.0118)		(0.0191)
All linked articles		0.1201*		−0.0148
		(0.0543)		(0.0734)
Top 112 university authorships				
All core collaborations			0.0179*	0.0315*
			(0.0070)	(0.0156)
Citations to articles			0.0116*	0.0081
			(0.0053)	(0.0056)
Firm characteristics				
NBF indicator	−1.2023***	−1.1656***	−1.1666***	−1.1879***
	(0.2477)	(0.2424)	(0.2394)	(0.2399)
Years in biotech	0.0199	−0.0040	−0.0238	−0.0256
	(0.0317)	(0.0317)	(0.0322)	(0.0321)
Recombinant DNA indicator	0.7636***	0.6452**	0.5631**	0.5453**
	(0.0439)	(0.1987)	(0.1994)	(0.1988)
Cumulative venture capital	0.0062***	0.0058***	0.0053***	0.0052***
findings as of 1990	(0.0012)	(0.0011)	(0.0011)	(0.0011)
Standard error of estimate	1.473	1.433	1.421	1.412
R^2 (adjusted)	0.208	0.250	0.263	0.272
Sample size	233	233	233	233

Note. Sample size was reduced because of nonreporting for 109 firms. Standard errors (in parentheses).
*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

the firm (and strong predictor of firm success) is the number of research articles written jointly by scientists working at a firm and the discovering, "star" scientists, nearly all working at top universities. For firms to commercialize new discoveries, there must be sufficient knowledge capture by the firm to offset sunk commercial development costs.

We find the results reported in Zucker, Darby, and Armstrong (1998) to be replicated to a major extent in the whole United States. The principal finding in our earlier paper, covering only California firms, was that research collaborations between firm scientists and university star scientists (the *ties*) had a robust significant positive effect on firm performance. The local pool of bioscience knowledge generated by nearby but noncollaborating scientists had no positive effect, providing further evidence for embodied technology transfer through markets rather than "knowledge spillovers." But this article is not simply a replication and scale-up.

In this article we add a generalized form of our star measure: the collaborative research articles between firm scientists and top U.S. university scientists.

In panel analyses, firms whose scientists collaborate with stars and/or top 112 U.S. university scientists have more patents and more highly cited patents. Further, star articles have an incremental positive effect above top 112 university scientists' articles on the number and quality of patents. Our cross-sectional analyses of products and employment show a generally similar pattern of positive effects on firms' success of collaborations with stars or top university scientists, but the incremental effects are less systematic. This nonrobustness appears to be due to multicollinearity. As predicted, untied star articles are either nonsignificant or oscillate between significant positive and negative effects. Venture capital funding amounts were always significant and usually positive.

The overall importance of ties, compared to lack of significance or instability of untied star effects, suggests that working jointly at the lab bench is a crucial transfer mechanism when knowledge has an important or large tacit component. Further, our findings suggest that, as we predicted, tacit knowledge is embodied in individual, discovering scientists. Telephone interviews conducted by Jeff Armstrong of university star scientists revealed that their relationships with firms were governed by tight contractual arrangements, academic scientists typically being "vertically integrated" into the firm in the sense of receiving equity compensation and being bound by exclusivity agreements. This evidence that star scientists were either fully employed by firms or were governed in their relationships with firms by explicit contracts supported our conclusion that firm success was not the result of a general knowledge "spillover" from universities to firms but due to star scientists taking charge of their discoveries.

ACKNOWLEDGMENTS

This research has been supported by grants from the University of California's Industry–University Cooperative Research Program, the University of California Systemwide Biotechnology Research and Education Program, the Alfred P. Sloan Foundation through the NBER Research Program on Industrial Technology and Productivity, and the National Science Foundation (SES 9012925). The authors also appreciate very useful comments from Scott Shane, Scott Stem, and other conference participants. The postdoctoral fellow David Waguespack prepared the series on all publishing between firms and the top 112 research universities for biotechnology firms based on ISI data. This article is part of the NBER's research program in productivity. Any opinions expressed are those of the authors and not those of the National Bureau of Economic Research.

NOTES

[1] Most commonly, there are multiple virtually localized markets organized around competing perspectives or models employed within the subspecialty. There is also geographic localization within the professions, with advantages to universities or cities with a "critical mass" of scientists who can interact. Thus, UCSF with its critical mass of molecular biologists and related sciences, and nearby strong universities, was "ripe" for a breakthrough.

[2] Note that when multiple teams are racing for a "ripe" discovery and publish their results almost simultaneously, we have much more rapid confirmation/validation of the discovery, which promotes faster learning by others. Gina Durante, graduate student at the Anderson School at UCLA, suggested this point.

[3] The top 112 universities are defined in terms of rank order on federal research funding received. The top 112 are defined by the Institute for Scientific Information, and the data were purchased from them.

[4] In 1994, Jeff Armstrong conducted a telephone survey of randomly selected linked stars in California and found that most possess a significant equity or founding interest in the firm.

[5] The prospectuses were obtained from Thomson Financial Services. The 10 companies in the table were the top biotechnology firms in 1994 as reported by Lee and Burrill (1995, p. 16).

[6] Due to human subjects' restrictions, we cannot reveal the identity of the star scientists. The following scientists may or may not be included in our list of U.S. stars.

[7] It is interesting that Genentech—with the largest number of star scientists of any firm—appeared to avoid mentioning stars on its prospectus resume unless the star had a formal corporate position. The one leading scientist who was listed on the prospectus was Dr. Boyer, who made it a policy never to publish a genetic-sequence discovery article as or with a Genentech employee.

[8] See Darby et al. (2001).

[9] The significance of key variables in these regressions is generally not sensitive to the Wooldridge correction, but to achieve an estimate of the variance-covariance matrix that is not restricted by first-moment parameter estimates, we apply the Wooldrige method as we did in the California study. An alternative would be to implement a binomial specification, but as explained in Wooldridge (1991), this procedure may bias both first- and second-moment estimates, whereas the Poisson process potentially biases only the second-moment parameters.

REFERENCES

Bioscan. 1989–1998. Volumes 3–12. The Oryx Press, Phoenix, AZ.

Cohen, S., A. Chang, H. Boyer, R. Helling. 1973. Construction of biologically functional bacterial plasmids *in vitro*. *Proc. Nat. Acad. Sci*. 70(11): 3240–3244.

Darby, M. R., L. G. Zucker. 2001. Change or die: The adoption of biotechnology in the Japanese and U.S. pharmaceutical industries. *Res. Tech. Innovation, Management, Policy* 7: 85–125.

———, ———. 2002. Growing by leaps and inches: Creative destruction and the Crusonia plant. *Econom. Inq*. 40 (forthcoming).

———, I. I. Welch, L. G. Zucker. 2001. Going public when you can in biotechnology. Working paper, UCLA Anderson School, Los Angeles, CA.

Demsetz, H. 1995. Agency and nonagency explanations of the firm's organization. *The Economics of the Business Firm: Seven Critical Commentaries*, Cambridge University Press, Cambridge, U.K.

Di Gregorio, D., S. Shane. 2000. Why do some universities generate more start-ups than others? Working paper, University of New Mexico and University of Maryland, College Park, MD.

GenBank. 1990. Release 65.0, machine readable database. IntelliGentics, Inc., Palo Alto, CA.

Griliches, Z. 1990. Patent statistics as economic indicators: A survey. *J. Econom. Lit.* 28(4): 1661–1707.

Harberger, A. C. 1998. A vision of the growth process. *Amer. Econom. Rev.* 88(1): 1–32.

Institute of Scientific Information (ISI). 2000. *U.S. University Science Indicators*. Machine-readable database on CD-ROM. Institute of Scientific Information, Philadelphia, PA.

Jaffe, A. B. 1986. Technological opportunity and spillovers of R&D: Evidence from firms' patents, profits, and market value. *Amer. Econom. Rev.* 76(5): 984–1001.

———. 1989. Real effects of academic research. *Amer. Econom. Rev.* 79(5): 957–970.

Jensen, R., M. Thursby. 2001. Proofs and prototypes for sale: The tale of university licensing. *Amer. Econom. Rev.* 91(1): 240–259.

Klevorick, A. K., R. C. Levin, R. R. Nelson, S. G. Winter. 1995. On the sources and significance of interindustry differences in technological opportunities. *Res. Policy*. 24(2): 185–205.

Kornhauser, W. 1962. *Scientists in Industry: Conflict and Accommodation*. University of California Press, Berkeley, CA.

Lee, K. B., Jr., G. S. Burrill. 1995. *Biotech 95: Reform, Restructure, Renewal*. Ernst & Young, San Francisco, CA.

Nelson, R. R. 1959. The economics of invention: A survey of the literature. *J. Bus.* 32(2): 101–127.

———, S. G. Winter. 1982. *An Evolutionary Theory of Economic Change*. Harvard University Press, Cambridge, MA.

Pisano, G. P., R. M. J. Bohmer, A. C. Edmondson. 2001. Organizational differences in rates of learning: Evidence from the adoption of minimally invasive cardiac surgery. *Management Sci.* 47(6): 752–768.

Polanyi, M. 1962. *Personal Knowledge: Towards a Post-Critical Philosophy*. University of Chicago Press, Chicago, IL.

Schutz, A. 1962. On multiple realities. *Collected Papers* 1: 207–259. Martinus Nijhoff, The Hague, The Netherlands.

———. 1970. *Reflections on the Problem of Relevance*. Yale University Press, New Haven, CT.

Scott, W. R., S. M. Dornbusch, B. C. Busching, J. D. Laing. 1967. Organizational evaluation and authority. *Admin. Sci. Quart.* 12: 99–117.

Stephan, P. E., S. S. Everhart. 1998. The changing rewards to science: The case of biotechnology. *Small Bus. Econom.* 10(2): 141–151.

Stigler, G. J. 1961. The economics of information *J. Polit. Econom.* 69(3): 213–225.

Sutton, J. 1997. Gibrat's legacy. *J. Econom. Lit.* 35(1): 40–59.

Thursby, J. G., Marie Thursby. 2000. Who is selling the ivory tower? Sources of growth in university licensing. *Conf. Tech. Transfer Univ. Entrepreneurship*, Georgia Institute of Technology, Atlanta, GA.

Torero, M. 1998. Analyzing the spillover mechanism on the semiconductor industry in the Silicon Valley and route 128. *Essays on Diffusion of Technical Change*. Unpublished Ph.D. dissertation, UCLA Economics Department, Los Angeles, CA.

Torero, M., M. R. Darby, L. G. Zucker. 2001. The importance of intellectual human capital in the birth of the semiconductor industry. Working paper, UCLA Anderson School, Los Angeles, CA.

U.S. Department of Commerce, Patent and Trademark Office. 1993. *Patent Technology Set: Genetic Engineering*. Machine readable database on CD-ROM. U.S. Department of Commerce, Office of Information Systems, Washington, D.C.

Wooldridge, J. M. 1991. On the application of robust, regression-based diagnostics to models of conditional means and conditional variances. *J. Econometrics* 47: 5–46.

Yarkin, C. 2000. Assessing the role of the University of California in the state's biotechnology economy. *The Economic and Social Dynamics of Biotechnology*. Kluwer Academic Publishers, Boston, MA.

Zucker, L. G., M. R. Darby. 2001. Capturing technological opportunity via Japan's star scientists: Evidence from Japanese firms' biotech patents and products. *J. Tech. Transfer.* 26(1/2): 37–58.

———, ———, J. S. Armstrong. 1998. Geographically localized knowledge: Spillovers or markets? *Econom. Inq.* 36(1): 65–86.

———, ———, M. B. Brewer. 1998. Intellectual human capital and the birth of U.S. biotechnology enterprises. *Amer. Econom. Rev.* 88(1): 290–306.

———, ———, M. Torero. 2000. Determinants of embodied technology transfer from stars to firms. Working paper, UCLA Anderson School, Los Angeles, CA.

———, ———, ———. 2001. Labor mobility from academe to commerce. *J. Labor Econom.* 20: 629–660.