

**Finding the Endless Frontier:
Lessons from the Life Sciences Innovation System for Energy R&D**

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Though the Federal government initiated significant commitments to *both* life sciences research and alternative energy research during the 1970s, there has been a sharp divergence in the growth and performance of these two innovation systems over the past three decades. This paper considers the drivers of the structure and evolution of the life sciences innovation system. The growth and performance of this system reflects the interaction between abundant scientific and technological opportunity, a reasonably effective and adaptive institutional and property rights framework, and a reservoir of unmet demand for therapies and technologies that significantly enhance human health care. Examining the evolution and dynamism of the life sciences innovation system, this paper emphasizes three central foundations: a long-term, slowly growing commitment of financial and human resources by both the public and private sector, an institutional framework that encourages competition on the basis of innovation across multiple dimensions, and the promise of significant financial rewards for private sector innovators leveraging publicly funded scientific discoveries. While there have been calls that energy innovation should focus on a one-off, centrally managed “Manhattan Project” approach to identify and commercialize climate change technologies, the experience of the life sciences suggests this emphasis may be misplaced. A productive and dynamic energy innovation system is more likely to emerge in an environment where both public and private resource commitments are growing at a reasonable and stable pace, competition between technologies, institutions and individuals is pervasive and oriented around innovation, and significant (and well-defined) financial rewards are available for those innovators who offer practical and general approaches to reduce or mitigate the impact of carbon-intensive energy technologies.

I. Introduction

Over the past 30 years, the evolution and performance of the biopharmaceutical sector has been remarkable. Combined with related advances in medical practice, new pharmaceuticals and biologics have delivered extraordinary economic and health benefits, from drugs that offer proactive treatments against conditions such as hypertension to the development of life-saving drug regimens to combat AIDS and cancer. Biopharmaceutical innovation has been linked to significant improvements in mortality and clinical outcomes (Lichtenberg, 1996, 2008), and offers cost savings and productivity gains over alternative treatments (Garthwaite, 2009). Moreover, the biopharmaceutical industry has been a reliable source of high-wage, high-skilled employment, and until the recent past, has generated persistently high returns to investors (Burrill, 2008). Widely regarded as a success story for government support of R&D, this sector has attracted increasing policy attention as a potential source of regional and national economic development (Cortright and Mayer, 2002; Feldman, 2003; Hermans, et al, 2008).

This paper outlines some key features of the life sciences innovation system – the set of interdependent firms, markets, institutions, and regulatory and legal frameworks responsible for this strong record of innovation – and draws some lessons from this sector for innovation policy in energy and climate change. While we recognize that the nature of energy and climate change innovation is in many respects different in some fundamental ways from life sciences innovation (and we discuss these differences below), we nonetheless argue that the evolution and structure of the life sciences innovation system offers an instructive comparison. Most notably, the genesis and evolution of the life sciences innovation system is the consequence of a set of policy choices and a microeconomic environment that has allowed the United States to leverage a set of embryonic scientific discoveries into a platform for sustained innovation which has had a significant impact on human health and welfare.

By any measure, technological progress in biopharmaceuticals over the past 30 to 40 years has been impressive. Figure 1 shows the decline in mortality in the U.S. in recent decades. While factors such as public health, nutrition, access to medical care, and progress in other medical technologies have played an important role, much of this can be attributed to innovation in biopharmaceuticals, with major breakthroughs in treatment of leading causes of death such as

heart disease, cancer, and HIV.¹ Indeed, much innovation in this sector can be characterized as radical, with remarkable advances made in treating disease through the identification and exploitation of new physiological mechanisms or new classes of drugs, from SSRIs in the 1980s to HIV/AIDS drugs in the 1990s and genomic therapies in the current decade. But incremental innovation in the form of development of “follow-on” drugs with differentiated properties, or efforts to enhance the effectiveness of existing drugs through reformulations or more effective treatment regimens, has also been pervasive, and has been a significant source of economic and health benefits (Cockburn, 2007). Though a low rate of FDA approvals over the last several years has led to significant concern over the “biopharmaceutical R&D productivity crisis,” most scientists and analysts forecast continued evolution and significant growth into the future: an unprecedented numbers of drug candidates are in the early stages of the clinical development process, and new cohorts of clinically relevant (and commercially profitable) new drugs and therapies are emerging from the significant basic research investments made over the past two decades in areas such as genomics and stem cells. Importantly, despite dramatic shifts in the nature of the underlying scientific base of the industry, changes in the nature and locus of demand (from cash payers to managed care), and realignments in both vertical and horizontal industry structure, the life sciences innovation system has, at the macro level, continued to grow and evolve over time.

While the commercialization of new drugs and therapies is by and large undertaken by the private sector, a distinctive attribute of the life sciences innovation system is that the biopharmaceutical industry draws upon (and complements) an exceptionally large publicly funded basic research effort in the life sciences. Life sciences now account for more than 60% of all academic R&D expenditures (NSF, 2008, Figure 5-6), with the vast majority of support for academic R&D coming from the budgets of the NIH, NSF and other agencies. These expenditures contribute to the development of skilled and specialized life sciences workforce, a high rate of sustained advance in “upstream” science performed in academic and government laboratories, and the development of platform technologies, datasets, and research materials that serve as a foundation for commercial applications. In some areas such as cancer and viral

¹ While the link between innovation and improved disease outcomes is subtle (demographic and behavioral shifts play a very important role), there is considerable evidence that improvements in outcomes are closely linked to disease categories and conditions that have seen significant biomedical innovation. *See* Lichtenberg (1995; 2001; 2005) and Duggan and Evans (2008).

outbreaks, government also has been directly involved in the identification of new potential therapies and drugs.

Federal involvement in biopharmaceutical innovation has not been confined to underwriting the development of a body of scientific knowledge and an army of specialized human capital. The industry is highly regulated (arguably one of the most regulated sectors of the economy), with the FDA controlling new product introductions and production processes, and federal and state legislation and regulation governing the marketing, distribution and reimbursement rules for drugs. Significantly, while these regulatory structures are a significant, and costly, constraint on commercial innovation, they also play an important role in shaping competition. Though the high costs of meeting FDA requirements and managing the FDA approval process lowers the direct returns realized by any one successful drug, these costs (and strong patent protection) creates significant barriers to entry; as a result, innovators are insulated from direct price competition and competition can be premised on innovation and the improvement of patient care and product quality.

What are the forces driving innovation in this sector? How has the life sciences innovation system been able to yield such a high and sustained rate of scientific discovery and technological innovation? While scientific and technological opportunity in this sector has been very high in the aftermath of discoveries such as Watson and Crick's elucidation of the structure of DNA, the principal contention of the paper is that the economic and technological dynamism of the life sciences sector over the past 30 years does not simply reflect unusual scientific opportunity. Rather, the performance of the life sciences innovation system is grounded in the microeconomic and institutional environment, which has, by and large, been conducive to long run scientific and technical progress.

Our analysis focuses on six key elements. First, and perhaps most importantly, the life sciences innovation system is built on a stable foundation of high levels of public support for basic research over the long term. Public funding for academic biomedical research through the NIH, together with other granting agencies, has been sustained at a high level for many decades. While political considerations (and direct policy choices) have led to occasional "surges" in the overall NIH budget (as occurred from 1998-2003) and occasional rapid shifts in financial resources across research programs (such as during the focus on HIV in the late 1980s and early

1990s), the NIH has, by and large, been able to maintain a relatively steady funding growth rate for both intra- and extra-mural research over long periods of time.

Second, innovation in the life sciences innovation is grounded in the development of a large and specialized R&D workforce. Over time, universities have expanded and developed graduate and post-graduate training programs, particularly within academic medical centers, allowing each new generation of researchers to develop the specialized human capital required to innovate at the life sciences frontier. Federal and state policies have reinforced this emphasis on human capital investment, through programs that specifically fund training and provide universities with incentives to conduct research that utilizes graduate and postdoctoral researchers. Over time, there has been a significant increase in both the public and private life sciences innovation workforce over time (National Science Foundation, 2008). Moreover, this increase in size has been accompanied by a significant increase in the degree of specialization by individuals: while researchers share undergraduate training in a few core disciplines such as biology and chemistry, doctoral and postdoctoral training emphasizes the development of specialized expertise. Over time, the organization of both public and private research has evolved into (often quite large) collaborative research teams composed of highly specialized individual team members; together, these teams bring together knowledge, expertise and specialized tools and materials from related (but distinct) scientific research fields.

Third, the nature of demand for biopharmaceuticals has had a profound impact on the life sciences innovation system. Inherently high willingness to pay for products that extend life or improve the quality of life has been translated into relatively price-inelastic and stable demand, increasingly controlled by insurers and government, but nonetheless driven to a large extent by physician and patient preferences. “Blockbuster” products have by and large been those which are the first to offer safe and effective treatment for poorly served medical conditions, or those with demonstrably superior clinical attributes, rather than price-competitive alternatives to existing products. At the same time, government regulation of approval of generic products and of retail dispensing of drugs has supported a very efficient distribution channel for generics, creating a powerful “push” motive for R&D-based companies to innovate. Notwithstanding increasing emphasis by some companies on incremental improvement of existing products, or on marketing to expand their use, and concerns about whether payers will continue to reward innovative product introductions, biotechnology and pharmaceutical firms have been able to

secure significant returns over a long period of time by focusing on the development and commercialization of innovative novel biotherapeutic compounds.

Fourth, notwithstanding the political priorities reflected in appropriations bills, and occasional large scale “top down” initiatives, the allocation of public funding for biomedical research has been primarily focused on investigator-initiated, peer-reviewed projects. Most public research funds support extramural research, primarily conducted at universities, where researchers face explicit incentives and social norms that reward individual creativity and academic freedom. Alternative sources of support such as the Howard Hughes Medical Investigator program further reinforce an orientation in which the direction of research is controlled largely by researchers themselves and the quality of research is judged through peer review. With relatively few exceptions, government-sponsored research has rarely taken the form of “Manhattan Project” initiatives. Instead, biomedical science has been largely driven by a robust and independent scientific community focused on the intellectual merit and novelty of investigator-generated research proposals, balanced by input concerning social or governmental priorities. Indeed, the most notable “big science” projects within the life sciences innovation system such as the Human Genome Project have been initiated within the scientific community (with the objective of providing a platform for investigator-initiated follow-on research projects).

Fifth, intellectual property rights (IPR) – most notably in the form of patents – plays a fundamental (if occasionally controversial) role in this sector, and there is considerable evidence that the patent system is relatively more effective in the life sciences than in many other areas of the economy. Relative to the formal IPR available for other sectors, IPR in biopharmaceuticals is relatively unambiguous, visible, and enforceable, and, by and large, is closely synchronized to product lifetimes and to relevant product market regulation. Biopharmaceutical firms rely heavily on strong IPR to protect innovations during the product development process and during a period of time after FDA approval; in most circumstances, these innovators then face intense generic competition once the patent underlying a compound or treatment expires. The availability of IPR for final products during the early years of the product lifecycle and intense competition driving price to marginal cost after patent expiration simultaneously induces significant consumer welfare and powerful incentives for firms to launch new products over time. Over the last decade, a vigorous debate has emerged over the role of patents for more upstream discoveries in the life sciences. While this debate is ongoing, an emerging body of

evidence suggests that the role of patents is quite complex; while it is possible to identify particular cases where patent grants have been associated with what seems to be significant inefficiencies, the more general pattern seems to be that, over time, strong patents operate in parallel (and are complementary to) a large and vigorous domain for open science. Notably, the patent system plays an important role in facilitating a market for technology that promotes the commercialization of publicly funded research discoveries.

Finally, the life sciences innovation system is characterized by intense competition on the basis of innovation. While price competition in the product market for biopharmaceuticals is relatively muted (at least until generic entry occurs after patent expiration), competition between researchers, institutions, and firms is focused on discovery, innovation and the commercialization of new technologies. Individual scientific research teams compete with each other for scientific “kudos,” universities compete with each other to attract faculty, students, and resources, biotechnology firms compete with each other to attract scientists, venture capital, and commercialization partners, and product market competition is by and large oriented around quality and innovation rather than cost. In other words, despite FDA regulation and the presence of strong patents, competition within the life sciences innovation system is pervasive and operates at multiple levels and at different stages of the product development process.

In concert, these drivers seem to have been instrumental in shaping the structure and evolution of the life sciences innovation system. To draw out the lessons (and points of difference) for energy and climate change innovation, we begin in the next two sections with an historical overview. This historical narrative emphasizes that the evolution of the life sciences innovation system over time does not simply track shifts in scientific or technological opportunity, but instead reflects specific episodes and instances of institutional and economic experimentation. We use this background to then analyze in greater detail the six distinctive characteristics of the now-mature life sciences innovation system previewed above. The final section of the paper draws out the lessons from the life sciences for a potential climate change innovation system.

II. The War on Cancer and Project Independence

A useful starting point for analysis is to compare the origins of innovation systems for life sciences and alternative energy in the United States. In particular, while the rise of American hegemony in science and engineering after World War II was concentrated in areas such as computing, petrochemicals, and aeronautics (Nelson and Wright, 1992; Mowery and Rosenberg, 1998), the 1970s saw novel sustained efforts to devote significant and sustained funding to fundamental challenges in both life sciences and energy.

On the one hand, prompted by a combination of public furor over the prevalence of cancer (at that time the second leading cause of death among Americans) and optimism on the part of researchers over recent advances in immunology and oncology, the Nixon Administration initiated the War on Cancer. In his 1971 State of the Union Address, Richard Nixon staked out innovation-oriented progress on cancer and the life sciences more generally as a priority: "I will also ask for an appropriation of an extra \$100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal." (Nixon, *State of the Union*, 1971). Bipartisan support for this initiative led to the 1971 National Cancer Act, which significantly increased the budget for the National Cancer Institute and established the Frederick Cancer Research and Development Center (which would ultimately become an important home both to cancer research and the development of tools, materials, and data infrastructures important to cancer research). The funding and policy commitments initiated by the War on Cancer (and related scientific and technological developments discussed in the next section) were the foundations for a slow but steady growth in the Federal commitment to basic life sciences research, grounded by and large in advances in molecular biology and genetics. Over time, the National Institutes of Health ended up being responsible for a disproportionate share of all Federal research expenditures on basic research within two decades (Stern, 2004).

A similar combination of public concern and technological optimism fueled Project Independence, an innovation-oriented energy independence initiative proposed by the Nixon Administration only three years later in response to the 1973 oil crisis. In the 1974 State of the

Union, Nixon prioritizes innovation and new technology as a solution for energy independence: “As we move toward the celebration 2 years from now of the 200th anniversary of this Nation's independence, let us press vigorously on toward the goal I announced last November for Project Independence. Let this be our national goal: At the end of this decade, in the year 1980, the United States will not be dependent on any other country for the energy we need to provide our jobs, to heat our homes, and to keep our transportation moving. To indicate the size of the Government commitment, to spur energy research and development, we plan to spend \$10 billion in Federal funds over the next 5 years. That is an enormous amount. But during the same 5 years, private enterprise will be investing as much as \$200 billion--and in 10 years, \$500 billion--to develop the new resources, the new technology, the new capacity America will require for its energy needs in the 1980's. That is just a measure of the magnitude of the project we are undertaking.” (Nixon, *State of the Union*, 1974). Not simply a matter of political rhetoric, both the Nixon and Carter Administration indeed invested significant Federal resources in alternative energy initiatives throughout the 1970s, primarily through the Department of Energy projects such as the Clinch River Breeder Reactor and exploratory basic and applied research into synthetic fuels. Indeed, while the level of Federal support declined after 1980, there is a case to be made that the foundations for an American alternative energy system began to be established, in a tenuous way, at that time.

In other words, both the life sciences and alternative energy innovation systems were at roughly similar levels of development and scale in the United States in the mid to late 1970s. However, starting in the late 1970s (and particularly after the beginning of the Reagan Administration), there was a dramatic and sharp divergence in the growth and evolution of each of these systems. On the one hand, the alternative energy innovation system was largely dismantled, characterized by scattered and isolated projects. In contrast, the life sciences innovation system embarked s on a long period of systematic growth, founded on an innovation orientation and a commitment to a step-by-step research process involving complementary investment utilizing both public and private sector resources.

III. The Life Sciences Innovation System

We now turn to a more systematic analysis of the growth and evolution of the US life sciences innovation system, building on the innovation system literature (Nelson, 1993; Lundvall, 1992; Mowery and Nelson, 1998). In particular, we present a brief narrative history that focuses first on the combination of economic, institutional, and technical conditions that allowed the life sciences innovation system to emerge in the 1970s and 1980s, and then consider the key drivers of the growth and evolution of that system over the past two decades.

Our analysis begins by defining what we mean by the life sciences innovation system. Simply put, an innovation system consists of the interrelated and interdependent web of institutions and entities that contribute to the exploration, development, commercialization and diffusion of new knowledge and technology. The overall productivity of life sciences research and commercialization efforts depend on the structure of the innovation system, including the participation and role of public and private institutions, and the nature of the relationships among institutions (and the people within them). Within the US life sciences innovation system, these institutions include, but are not limited to, (a) sources of capital and funding such as the National Institutes of Health, private philanthropy, venture capital, and the investment activities of public companies (b) sources of research performance including basic university science departments, academic medical centers that combine basic research, clinical research, and patient care, private biotechnology start-up innovators, and the research activities of established pharmaceutical and medical device companies and (c) sources of commercialization capability including downstream pharmaceutical firms, and the activities of supporting sectors such as the clinical research organizations. As we describe in some detail below, this system has realized an extraordinary rate of scientific discovery and nascent technological innovation; at the same time, there are concerns about the ability of this system to translate these promising scientific and technical developments into products and tools that are able to overcome regulatory barriers and achieve a high level of diffusion.

The section can be divided into the various “eras” of the life sciences innovation system. Up until the 1970’s, the pharmaceutical industry was mostly isolated from the molecular biology and genetics, producing a very different environment than the current life sciences innovation system. In the 1970’s, we see a distinct shift in public and private funds for basic research in

molecular biology and related fields. From 1980-1995, the development of a skilled and specialized workforce combine with the “biotech gold rush” to create an emerging innovation system (though the number of products and therapies that are commercialized remains quite limited). From 1995 onwards, the life sciences innovation system has matured as more stable platforms and institutions for cumulative research emerge. Over the past decade, the US life sciences innovation system has served as a dynamic source of commercial applications for new technologies for pharmaceuticals, medical devices, and agricultural biotechnology.

Pre 1970's: The Divide between the Pharmaceutical Industry and Molecular Biology

While the period after World War II saw the rise of the US pharmaceutical industry and the emergence of molecular biology and related disciplines, these two areas of activity remained largely distinct from each other until the early 1970s. By and large, the pharmaceutical industry focused on large scale “random-screening” of drug candidates (Schwartzman, 1976; Cockburn, Henderson, and Stern, 2001). As a practical matter, this involved work by medicinal chemists who tested thousands of compounds for evidence of a physiological reaction in animal tests (e.g., measuring whether or not a particular compound lowers the blood pressure of hypertensive rats (Henderson and Cockburn, 1994). Large, vertically integrated firms relied on (essentially) serendipity in the earliest stages of the drug development process. As Maxwell and Eckhardt note in their conclusions to their detailed study of 32 drug innovation histories, “screening...appears to be all but indispensable to the discovery of innovative drugs, having been involved in the discovery of 25 of the 32 case histories covered by us.” (Maxwell and Eckhardt, (1990, p. 409)). Indeed, during the early 1980s, many researchers expressed strong appreciation for screening methods in the absence of biological theory,

In some cases it is surprising how well medicinal chemistry can do without knowing the biological system involved. The narcotic analgesics may serve as an example. By means of rather simple screening methods an enormous number of potent and specific analgesics were being and could be developed.

(Carlsson, in Gross, (1983, p. 35))

This brute force approach to innovation was profitable in an environment where the availability of relatively few effective pharmaceutical products, stringent FDA regulation, and broad patent protection resulted in inelastic demand and the ability to charge significant premiums for those drugs that were able to reach the marketplace. In particular, the 1962

Kefauver-Harris FDA amendments (and subsequent regulatory infrastructure developed by the FDA) led both to the systemization of the clinical trial process (including randomized treatments and control groups) and to the erection of significant barriers to entry for those firm that were able to successfully navigate the drug approval system (Thomas, 1990). While drug companies did draw on individual scientific findings (through reading journals, etc.) or by hiring skilled graduates, the pharmaceutical industry was primarily engaged in applied industrial research and development activities, and competitive advantage was earned through control over proprietary random-screening techniques and effective clinical trial management (Henderson and Cockburn, 1994; Gambardella, 1995).

Though emerging at a similar time as the pharmaceutical industry, molecular biology and genetics remained distinct and separate from commercial drug development. Founded in the 1930s, molecular biology focused on fundamental theoretical and empirical questions concerning the function and structure of genetic material. The proposal of a double helix structure for DNA by Watson and Crick in 1953, the most public achievement of molecular biology, ensured the place of molecular biology as among the most elite and basic type of pure science. Prior to the early 1970s, the “distance” between fundamental research in molecular biology and drug development was significant.

In contrast to the chemistry-oriented “random screening” approach, molecular biologists sought to address fundamental research questions, even when compared to mainstream biochemistry. While mainstream biochemists focused on characterizing biochemical pathways among eukaryotes (higher organisms (most notably humans or related species)), molecular biologists focused almost exclusively on careful studies of the molecular genetics of prokaryotes (lower organisms lacking cell nuclei) (Kenney, 1986; Stern, 1995). Though these discoveries were important in a scientific sense (resulting in multiple Nobel Prizes), as long as the tools and techniques of molecular biology were limited to lower organisms, the utility of this fundamental research for biopharmaceutical innovation was essentially nil. Moreover, this gap between molecular biology and drug development was not simply a matter of scientific distance: the bulk of the advances in molecular biology were conducted within “classical” academic biology departments that had few if any connections to industry. Academic medical centers such as those that emerged at Stanford were the exception rather than the norm, and the commercialization of any discoveries would have been constrained by perceived limitations on

patenting Federally funded research and unresolved issues in patent law governing the ability to obtain patents on living organisms or genetically modified biological materials.

1970-1980: The Foundations of Biotechnology

The linkage between pharmaceutical (and medical device) innovation and molecular biology – the foundation of biotechnology and the origins of the life sciences innovation system - - can then be traced to a collection of complementary technical, economic, and institutional shifts during the 1970s and early 1980s that bridged the earlier divide: the development of recombinant DNA technology and complementary scientific and technical advances, a significant increase in funding and resources for life sciences research (both public and private, both in the US and abroad), and a set of policy decisions – such as the 1980 *Diamond v. Chakrabarty* Supreme Court decision and the Bayh-Dole Act – that allowed the assertion of intellectual property rights over innovations based on genetic engineering, even those funded by the public sector.

From a technical perspective, critical advances in technique, instrumentation, and theory overcame many of the barriers that had slowed the application of molecular genetics. The most public of these advances was the gene-splicing technique pioneered by Stanley Cohen and Herbert Boyer in 1973. Along with work by Jackson, Symons, and Berg, the Cohen-Boyer technique gave researchers the ability to manipulate—to change—the genetic code and subsequent protein production of an organism (Johnson, 1983). While the Cohen-Boyer was the most public advance, complementary technical advances such as gel electrophoresis and gene synthesis were also achieved during this period. Together, these advances greatly enhanced the potential to exploit molecular biology as a tool or methodology for commercial applications and served as the nascent foundations for biotechnology.

Equally importantly, institutional and policy shifts facilitated the emergence of biotechnology at the university-industry divide. Three policy shifts stand out. First, the Bayh-Dole Act allowed and encouraged researchers at universities to seek patents rights for government sponsored research (Mowery, et al, 2004). The Bayh-Dole Act was meant to increase the benefits to society of public research by incenting inventors to patent and commercialize their work. Around the same time, *Diamond v. Chakrabarty* upheld that genetically engineered organisms were eligible for patent protection, thereby allowing patents on a significant amount of biological sciences research. These decisions had a profound impact on universities, which began to set up technology transfer offices to commercialize their research.

The impact on university researchers was equally important, who now saw reduced barriers to patenting and licensing their inventions. These two policy decisions were instrumental in laying the foundations for the dynamic early-stage commercialization environment characteristic of the life sciences innovation system. Third, there was a significant increase in access to private sector risk capital as the result of the growth of the venture capital model. Not simply a private sector “financial sector” innovation, the growth of venture capital was grounded in policy decisions: the 1979 amendment to the Prudent Man rule allowed pension funds to invest in venture capital, substantially increasing the money available to commercialize technologies. In addition, the National Institutes of Health (NIH), emerged as a central player in financing and supporting extra-mural early stage research. The scale of funding, and its focus on extramural basic research helped to define the NIH’s role and sustain its importance in the innovation system. In particular, starting with the War on Cancer, the NIH and related Federal life sciences funding grew at a rapid but relatively steady pace, culminating in a funding surge during the late 1990s (Figure 2).

Extramural NIH funding created a high-level of competition for funds and supported the development of departments in universities focused on the biosciences. Grant-supported training of PhD and postdoctoral students engaging in frontier research helped to create a mobile, knowledge based workforce that moved between industry and academia.

By the early 1980s, therefore, the stage was set for rapid growth in innovative activity at the interface of academic science and commercial research. In universities, revolutionary discoveries showed the promise of a new frontier for basic science to investigate—and a substantial “payoff” to public funding. In industry these advances highlighted the viability of making drug-discovery and the early stages of the commercialization process more science-intensive. And a new form of organization, science-intensive venture-backed entrepreneurial firms closely linked to universities and government laboratories had begun to emerge as credible and critical players in the innovation system. This increased focus on basic science set the stage for the development of an entirely new innovation system.

1980-1995: The Emergence of the Life Sciences Innovation System

By the late 1980’s and early 1990’s, life sciences research had developed a foothold in universities across the U.S. and the early stages of what we now refer to as the life sciences innovation system developed. It is useful to focus on three key elements of the system during

this period: the development of a skilled and specialized R&D workforce, the introduction of the first generation of biotechnology products, and the emergence of institutions and policies that have reshaped the university-industry interface.

The Development of a Skilled and Specialized R&D Workforce. A distinctive attribute of the molecular biology and genetics communities during the early 1970s was its small size. In key areas, only a small number of researchers and laboratories had the specialized training and tools to take advantage of technologies such as the Cohen-Boyer technique, and this small community was responsible for the bulk of the early activity and advances (Hall, 1988; Hsu and Lim, 2009). Over the 1980s and early 1990s, however, there was a very significant increase in the size and nature of the life sciences workforce, in both the public and private sector (National Science Foundation, 2008). Figure 3 illustrates these trends. Between the early 1970s and today, the number of life science doctorate holders employed in academia has more than doubled (areas such as the physical sciences and engineering have realized a much smaller percentage gain over time), and there was also a significant expansion in the relative number of bachelors levels students who receive a degree in the life sciences fields. Notably, during the first half of the 1990s, areas such as engineering and computer science experienced absolute declines in the number of bachelor degrees awarded, while life sciences overtook engineering as the leading field of study in the “hard sciences and engineering.” These are not isolated trends: life sciences consistently graduates the highest number of doctorates of any field, accounts for more than half of all postdoctoral researchers working in universities, and is by far the area with the highest number of academic publications (National Science Foundation, 2008).

In part, these trends reflect more qualitative institutional shifts: the 1980s were marked by a significant increase in the number and scope of graduate programs in molecular biology, genetics and related bioscience fields, and many universities established new institutes and departments to take advantage of the new technologies. For example, while MIT had long maintained a small but high-quality presence in biology and related fields, the establishment and growth of the MIT Whitehead Institute (and related initiatives) during the 1980s changed the character of teaching and research at MIT, with a shift from a dominant emphasis in the physical sciences and engineering towards the development of a large, diverse and highly productive life sciences faculty. Along with leading research universities, the NIH helped to develop well-defined training and career paths, including the sponsorship of graduate and postdoctoral

fellowships, encouraging significant entry by young researchers into the fields that were able to take advantage of the rapidly improving technology.

A Biotechnology “Gold Rush.” The rapid expansion in the scale and scope of biotechnology was driven, at least in part, by the early introduction of a few key “blockbuster” biotechnology drugs that raised exceptionally high expectations for the commercial potential and near-term human health impact of the new technologies. Importantly, the early biotechnology industry was marked by the founding of numerous companies with strong ties to leading university researchers (Zucker, Darby and Brewer, 1998), many of which received significant capital from the still-emerging venture capital sector or from new public risk capital programs such as the Small Business Innovation Research (SBIR) program.

Genentech is an illustrative and particularly important example of the types of companies emerging during this period (Hall, 1988; McKelvey, 1996; Stern, 1995). Founded by UC-SF researcher Herbert Boyer (of the Cohen-Boyer gene splicing technology) and venture capitalist Bob Swanson in the mid-1970s, Genentech was able to rapidly develop (and patent) two particularly promising applications of the new technologies – human insulin and human growth hormone. These innovations attracted extraordinary interest because they represented a very different type of commercial product (i.e., the genetically engineered production of human proteins) that met an important and unmet human health need. For example, prior to the introduction of Humulin (human insulin) in 1982, the insulin needs of patients suffering from Type I diabetes were met primarily with insulin extracted from pigs or cows (and some human cadavers), with significant clinical limitations (e.g., a significant fraction of patients had adverse reactions to non-human insulin products). Interestingly, a distinctive feature of these early Genentech innovations was that the actual commercialization of new products arising from the technology was achieved through cooperative commercialization with established pharmaceutical firms (e.g., Humulin was commercialized in a (contentious) partnership with Eli Lilly, which had long dominated the market for non-human insulin products). Most notably, even before *any* products were on the market, Genentech was able to attract significant venture capital funding (including a seed-stage investment by Kleiner Perkins) and a liquidity event for these venture capital investors with an enormously successful IPO in 1980.

The success and excitement of the Genentech IPO led to the first biotechnology “gold rush,” with rapid increases in venture capital (and public equity market) funding of

biotechnology during the early 1980s, followed by a “bust” period during the mid 1980s as the number of new biotechnology products stagnated. On the one hand, these investments reflected the belief that the ability of Genentech to identify a few straightforward and important applications of the new technology implied a rapid increase in the number of products that would be commercially viable. In actuality, the ability to exploit the new technology was confined to the relatively small community of researchers that had specialized expertise, and there were only a small number of viable target applications. Indeed, in many areas (such as monoclonal antibodies), multiple companies raced against each other to achieve particular technical milestones (for which patent protection would be available). Ultimately, the combination of a rapid influx of capital and the fact that only a very small number of new products were actually introduced implied that average private sector returns were low, resulting in a period of investor disillusionment and declines in private sector funding. This boom-and-bust financing cycle is recurrent, with at least four distinct cycles between 1980 and 2000. In each case, the promise of a new application of biotechnology seems to have resulted in significant overshooting by private sectors investors, resulting a highly variable rate of private investment environment over time. Importantly, this variation in private funding was buffeted by the every-increasing and less variable level of Federal support for life sciences innovation research, including funding specifically directed to start-up innovators through programs such as the SBIR. By the late 1980s, life sciences research funding was about evenly split between Federal funding and other sources (mostly private sector risk capital) (Figure 4).

Emerging Institutions at the University-Industry Interface. The final shift in the life sciences innovation environment during this period was the development and evolution of a set of complex and interdependent set of institutions supporting the life sciences innovation system. While a comprehensive accounting of these institutions is beyond the scope of this paper, it is useful to highlight some key examples, including the development of the modern academic medical center as a locus of research and the establishment of innovation-oriented industry organizations such as the Biotechnology Industry Association. By and large, these new institutions served as extraordinarily effective mechanisms for harnessing the new types of research that were being conducted in the life sciences, and, over time, promoted the development of a new pattern of academic and commercial interactions between universities, start-up innovators, and more established firms in the emerging innovation system.

Consider the rise of academic medical centers (AMCs) (Rosenberg, 2008). While academic teaching hospitals had long played an important role in physician training and clinical research, most basic research in molecular biology and genetics was conducted in university biology departments that were largely insulated from practical applications (and were focused on research that had little near-term practical application). During the late 1950s and 1960s, a small number of universities, such as Stanford and UC-SF, pioneered an alternative approach in which basic life science research disciplines such as molecular biology were established as independent departments within the medical center, supported by a range of programs from NIH and private foundations. In the case of Stanford, the transformation of the medical school to an academic medical center began with the move in 1959 from a San Francisco location to the main Stanford campus, and the recruitment by Fred Terman of a range of biochemists and molecular biologists such as Arthur Kornberg and Paul Berg, and geneticists such as Joshua Lederberg. Each of these researchers was drawn from a traditional science department. While AMCs such as Stanford were considered oddities at the time of their initial inception, these centers turned out to be extraordinarily productive basic research environments (resulting in numerous Nobel Prizes) that additionally created technologies and tools with significant practical application (including the founding of successful companies adjacent to the Stanford campus that aimed to commercialize these discoveries) (Rosenberg, 2008). This new organizational model allowed frontier researchers to pursue life sciences research that increasingly took place in “Pasteur’s Quadrant,” where a single research finding can be a fundamental scientific discovery and serve as the basis for a commercially oriented new technology (Stokes, 1996; Murray and Stern, 2007).

By the 1980s, there was a significant shift towards the AMC model across leading American universities. To highlight but one notable example, the Harvard University Biology Department had long been a leader in fundamental biological research, under the long-term leadership of James Watson, and leading researchers from that department such as Walter Gilbert had been involved in the early years of the Biotech Gold Rush as a co-founder of Biogen (Hall, 1988; Stern, 1995). However, during the 1980s, the locus of a significant fraction of research activity and talent at Harvard shifted towards the Harvard Medical School, with the establishment of new basic research departments. In many cases, these new departments received significant support from industry (along with NIH and foundations), occasionally raising key challenges for the management of the university-industry interface. For example,

one of the first discoveries of the newly formed Genetics Lab at Harvard Medical School was the Oncomouse (a mouse genetically engineered to be predisposed to cancer developed by Phil Leder and Tim Stewart), which became the genetically engineered mammal to receive US patent protection (Murray, 2009). Though the discovery was made at Harvard, the funding agreement underlying the research resulted in an exclusive license to DuPont, which enforced its IP rights aggressively (even threatening enforcement against follow-on academic researchers), resulting in a significant controversy within the life sciences community that was only resolved by an agreement between DuPont and the NIH in 1998 in which DuPont agreed to allow academic researchers free access to the technology. The granting, licensing, enforcement, and NIH settlement regarding the Oncomouse patent was emblematic of the novel challenges that arose as life sciences research increasingly came to have a dual existence on both sides of the university-industry divide (Murray, 2009).

At the same time, the nascent biotechnology industry began to build more durable institutional structures that reflected its orientation around innovation and the translation of basic life sciences research. Most notably, while the pharmaceutical industry had long supported an extremely strong industry association (PhRMA) that was largely focused on facilitating a more effective regulation of drug introduction, marketing, and reimbursement, the Biotechnology Industry Association (BIO) focused on nurturing more effective collaboration between universities and industry, and between venture capitalists, start-up innovators and more established downstream partners. For example, the annual BIO meeting began to combine a wide range of frontier scientific research presentations alongside panels and discussions of best-practices for intellectual property management, licensing, and effective clinical trial management. By the early 1990s, BIO began to develop specific practices encouraging a “market for technology” for biotechnology tools and discoveries, with explicit disclosure rules, and the provision of forums for effective collaboration.

The rise of academic medical centers and the development of a distinctive and innovation-oriented industry association are but two key developments in the institutional framework undergirding the emerging life sciences innovation system during the 1980s and early 1990s. Among other developments, there has been significant entry and growth of specialized suppliers of biomedical materials and tools (including gene sequencers, biomaterials, etc), the development of contract research organizations that can provide expertise in areas such as early-

stage clinical trials, and the development of specialized managers, lawyers, and venture capitalists who provide expertise and reputation facilitating more effective transactions in what became an increasingly complex web of relationships between academe, entrepreneurs, and downstream firms.

The Mid-1990s onwards: A Mature Life Sciences Innovation System

By the mid 1990s, the mature structure of the modern life sciences innovation system began to emerge. While there is no single event or marker delineating this more mature system from its earlier incarnation, several events during the mid-1990s altered the character and ultimate scope of the system. First, several enabling platform technologies such as PCR became cost-effective across a range of applications, greatly expanding the scope of biotechnology-oriented research and innovation. Second, the institutional shifts from the 1980s transformed the structure of interaction between public and private life science research organizations, resulting in an extraordinarily complex research network structure. Finally, the significant and sustained investment in the system began to pay off – the number of new therapies with their origins in biotechnology increased after a long period of stagnation, and an increasing share of all new drug development began to be grounded in biotechnology and the life sciences innovation system.

Platforms for Cumulative Research and Innovation. While the discoveries of the the 1970s and 1980s represented fundamental scientific breakthroughs and offered isolated commercial applications (such as the development of synthetic insulin and human growth hormone (Stern, 1995; McKelvey, 1996), the growth the life sciences innovation system has ultimately relied not on prototypes but on a cumulative series of complementary technological and scientific breakthroughs. The maturation of the life sciences innovation system was marked by rapid improvements in several enabling technologies that dramatically shifted the productivity and potential scope for life sciences research, including (but not limited to) the development of rapid genetic sequencing methods, the widespread availability of animal research models (such as knock-out mice) that allowed for precise experimentation and inference, and the development of powerful databases such as GenBank (and the data from the Human Genome Project) and ever more sophisticated bioinformatics tools to exploit and analyze this data explosion.

Consider the case of polymerase chain reaction (PCR), the single most important advance in genetic sequencing technology. Originally developed in the early 1980s by Kary Mullis (a

researcher at Cetus Corporation), the use of PCR and the power of genetic sequencing was still quite expensive (perhaps as much as \$50 per base pair of a gene) and so was used mostly for small-scale experiments throughout the 1980s. However, PCR was subject to a constant and rapid rate of improvement, so that by the mid-1990s, the cost per base pair had been reduced by more than an order of magnitude, and has been additionally reduced by two additional orders of magnitude over the last 15 years (Figure 5). In other words, while PCR was available as a technology during the 1980s (indeed, Kary Mullis won the Nobel Prize in 1993 for his discovery, and the key patent rights to the technology were purchased for more than \$400 million by Roche in the early 1990s), the dramatic improvements in PCR over time, resulting from a long stream of incremental improvements, have transformed the potential applications and scope for research using this technology. While the Human Genome Project – the largest “early” sequencing project using PCR -- required sustained investment by thousands of scientists over the entire course of the 1990s, the cost of sequencing an individual human genome is now below \$50,000, with strong expectations that individualized genome sequencing will be available as a mass market application within the next three years.

A similar case can be made for each of the other foundational enabling technologies of the life sciences innovation system. While genetically engineered knock-out mice were available in small quantities and a small number of varieties during the 1980s, the late 1990s saw an exponential explosion in the rate of development of specialized research mice (more than 13,000 different mice have now been developed and disclosed in the public scientific literature). Similarly, while bioinformatics was an exciting basic research area during the 1980s, the development of data infrastructure systems such as GenBank, alongside the dramatic expansions in processing power (and connectivity through the Internet) have transformed the ability to use precise genetic sequencing information in more applied research projects. Overall, the modern life sciences system is marked by a relatively constant rate of cumulative technical progress in a collection of key enabling technologies, allowing for dramatic improvements over time in the scope and potential applications that are able to be addressed by these technologies.

The Life Sciences Innovation Network. The mature life sciences innovation network is also marked by an extraordinarily complex network of structured relationships among research organizations. While a loose network structure of entrepreneurial firms often characterizes industries during their earliest stages that is then followed by a period of consolidation

(Utterback, 1995), the life sciences has been marked by sustained and ever-growing interaction and interdependency between university researchers, start-up innovators, and downstream firms engaging in both research and cooperative commercialization. Three features stand out.

First, university research continues to be a central input into the life sciences innovation system. The earliest development of the life sciences innovation system was characterized by the development of start-up innovators in a relatively small range of narrow application areas (such as the commercialization of particular hormones such as insulin) and the increased reliance of a “rational” approach to drug design grounded in biology by pharmaceutical firms (Cockburn and Henderson, 1995; 1998). Over time, the potential scope for commercial applications arising from university research has expanded considerably and now covers a wide range of background disciplines and potential application areas. To highlight but one example, developmental biology was long a fundamental area of science with little scope for potential commercial application; with the discovery and characterization of human stem cells in the late 1990s (a key advance in developmental biology itself), fundamental scientific findings in this area became enmeshed in Pasteur’s Quadrant, and there was a rapid increase in seeking out formal intellectual property protection for discoveries that were traditionally disclosed exclusively through the scientific literature, the founding of numerous start-up firms seeking to develop these insights for the purposes of licensing and commercialization, and significant new investments by existing biotechnology firms and more established pharmaceutical firms in developing commercially oriented research programs to take advantage of new developments in stem cell science. In other words, rather than the role of basic science receding over time as firms turned their attention towards process improvements and more incremental innovation, the life sciences innovation system has been characterized by a state of “perpetual immaturity” in which university research continues to spawn an ever wider range of potential avenues for commercial application.

Second, while the traditional pharmaceutical industry had been largely vertically integrated in research, production, and distribution, the modern life sciences innovation system is marked by a diverse range of specialized R&D firms who engage in cooperative development and marketing with more established downstream players (Gans and Stern, 2003). The continuous flow of scientific innovations and the fragmentation of the value chain encourages the biotechnology sector to continuously create new companies. Over time, the biotechnology sector had seen the founding of more than 1,300 companies in the US and around 5,000

worldwide (Burrill & Company, 2004). Although some successful biotechnology companies have ultimately transformed into large firms with a downstream market presence -- Genentech and Amgen being prime examples -- the sector as a whole is a study in dynamism, with new entrants appearing on the scene every year, and commercialization most often achieved through partnerships and cooperation with more established companies for development and distribution. Over time, the number of alliances between biotechnology companies and downstream firms has continued to grow, with rapid growth in these arrangements from the early 1990s onwards (Figure 6). An important implication of the presence of a large “market for technology” is that, though the life sciences system is highly innovative, the sector has *not* experienced the widespread creative destruction of established firms in the pharmaceutical industry. Rather than overturning the market power of established companies, university-based entrepreneurship in the life sciences has largely reinforced the market power of the pre-existing pharmaceutical industry (Gans and Stern, 2003).

Finally, the modern life sciences innovation network is characterized by an extraordinarily high degree of complexity and interdependency, and is clustered in a small number of key locations. Not simply composed of bilateral relationships between individual organizations, the life sciences innovation network is highly decentralized and involves multiple linkages between and among different institutions, including universities, start-up firms, established biotechnology companies, pharmaceutical firms, government, and venture capitalists (Figure 7, drawn from Powell, 2004). Both public institutions and private firms play key roles in the network (though there is no one influence that dominates), and the network structure has become considerably more complex and interdependent over time (the 1998 network in Figure 7 is considerably denser than the network structure from 1988). Importantly, this highly evolved system is centered in a few key locations (such as the Boston area, the San Francisco Bay Area, and the area around San Diego), and each of these regional clusters is marked by a network with a high level of overlap between public and private research organizations of different sizes and maturity. An important implication of this emergent network structure is that the performance of the system is mostly independent of the actions and strategies of any one organization or firm but depends crucially on the effectiveness of the institutions that support structured knowledge production and transfer between and among research and development organizations.

Biotechnology as the Foundation for New Drug Development. The final key indication of the maturity of the life sciences innovation system from the mid-1990s is simply that the system came to serve as the dominant source of knowledge in new drug development. While the first 20 years of the biotechnology industry were marked by a small number of products, mostly in areas that had not been a traditional focus of the pharmaceutical industry (Lerner, 1995), there was a sharp increase in the number of drugs with their origins in biotechnology in the mid-1990s (Figure 8). By the early 2000s, between 25-40% of all pharmaceutical sales came from products with their origin in the biotechnology sector, and the vast majority of all new drug candidates were closely linked to biotechnology and the life sciences revolution. Over the last several years, a relatively low rate of new drug approvals, alongside some visible product recalls, has led some to question the efficiency of the life sciences innovation system to effectively serve as the primary knowledge source for downstream pharmaceutical innovation; however, a careful look at the overall pharmaceutical product pipeline (particularly the large number of new therapies working their way through the product approval process) and accounting for the significant improvements that are made over time in existing products through the discovery of new indication and improved drug delivery suggests that the significant investment in life sciences research over the last 30 years has begun to pay off in terms of a wide range of new and improved therapies with significant human health and welfare benefits (Cockburn, 2008).

More generally, this narrative history suggests that the the life sciences innovation system has ultimately *replaced* the traditional divide between university science and pharmaceutical innovation with a system that depends on interdependent and collaborative knowledge development spanning both public and private organizations.

IV. The Drivers of the Life Sciences Innovation System

We now build on this narrative history to identify some of the key drivers of the foundation and growth of the life sciences innovation system over the last 30 years. In particular, we focus on those institutions and environmental conditions that have allowed the system to achieve its high level of dynamism and growth, and identify some of the broad innovation policy choices that have impacted the system over time. By characterizing the driving forces underlying the (now mature) system within the life sciences, we are able to turn in the next section to draw out some innovation policy lessons for the (much more nascent) energy

and climate change innovation system. We focus in on two broad types of factors: (a) broad supply and demand conditions, and (b) the institutional and strategic environment.

Supply and Demand Conditions. We first highlight the broad supply and demand conditions that have shaped the growth of the system, including the high level and (mostly) stable growth in the level of public funding, the development of a skilled and specialized life sciences workforce, and the presence of a high willingness to pay for breakthrough innovations that address human needs.

The High Level and Growth of Public Funding. While the particular structure and institutional aspects of the life sciences innovation system are undoubtedly important, an extremely important driver of its performance has been the sustained and growing long-term public investment in life sciences research, primarily through the expansion of the NIH. Whereas most other areas of non-defense Federal R&D funding have either stagnated or declined (in real terms) since the 1980s, life sciences funding has more than tripled (and nearly quadrupled) in real terms (Figure 9). Strikingly, the entire increase in the real non-defense R&D budget over the past 30 years can be attributed to increases in funding for life sciences research. Where life sciences research was a relatively minor component of Federal R&D spending (less than 25%), life sciences research makes has made up the majority of all non-defense R&D funding since 2000.

Three interrelated features of this funding should be emphasized. First, from 1980 through the late 1990s, the growth rate in NIH funding experienced very little variability, a sharp contrast to the more volatile private funding environment for biotechnology investment. This steady rate of growth allowed universities and other research organizations to make consistent and coherent long-term planning investments, particularly given that this was an era where the physical capital infrastructure of academic medical centers was considerably expanded. The funding pattern since 1998 has been more variable, with a doubling of the NIH budget in nominal dollars between 1998 and 2003, followed by a flat nominal budget from 2003 through 2008. By 2008, the real declines in funding from 2003 onwards implied that the NIH budget had again reached the level it would have reached along the stable growth path that had characterized the 1980-1998 period.

At the same time, while the overall NIH budget had a relatively low level of variation in growth (at least until 1998), the funding within the NIH was much more variable. Over time,

there have been significant shifts in the particular focus and emphasis of the NIH budget. For example, while funding for the emerging AIDS crisis during the early 1980s was essentially non-existent (with political resistance for several years), AIDS funding received dramatic increases starting in the mid-1980s and ultimately came to account for a significant share of the overall NIH budget. Similarly, in response to the opportunities afforded by high-throughput sequencing enabled by technologies such as PCR, the NIH and Congress were able to direct significant increases in funding to genetics and bioinformatics research, both through the peer-reviewed grant system as well as through special initiatives such as the Human Genome Project. While there is of course a reasonable level of persistence in the funding for each NIH institute and area on a year-to-year basis, the ability of the NIH and Congressional funders to reallocate the NIH budget over time to emerging scientific opportunities and to address particular healthcare needs has nurtured a system with a high level of adaptability alongside the stability required for infrastructure and human capital investment planning.

Finally, the “surge and retreat” pattern of NIH funding over the last decade offers a cautionary lesson about the impact of public funding on research activity (Freeman and van Reenen, 2009). During the 5-year doubling of the NIH budget, a large number of universities and other research organizations (including the NIH intramural campus) engaged in significant investment in dedicated physical capital investment in laboratories (often with cost-sharing from the NIH) as well as in the expansion of graduate programs and postdoctoral positions in those areas that were receiving the largest increases in NIH funding (such as genomics). These physical and human capital investments occur over far more than a 5-year window (particularly in terms of exploiting the investment in terms of research activity), and many of these investments were made under the expectation that the NIH would continue to grow after the 2003 period, albeit at a slower rate. The subsequent reduction in the size of the NIH budget thus resulted in systematic distortions in funding and research activity that likely have reduced research productivity. The unanticipated increase in the share of costs for physical capital investments falling on universities significantly reduced the ability of universities to provide funding for research and graduate student support. More importantly, the reduction in real terms of the NIH budget has essentially created a “budget squeeze” that is particularly salient for the generation of young investigators that were trained during the boom period. In particular, the surge and retreat pattern had the consequence of inducing a significant increase in the number of

tenure-track junior faculty at precisely the time when the NIH grant pool for new investigators became far more limited (Freeman and van Reenen, 2009). While significant excess returns to the endowment at leading universities mitigated some of these effects (at least at those schools with large endowments that performed well), an emerging body of evidence suggests that the high level of variability in the aggregate NIH budget over the past decade has likely resulted in a less productive innovation system and distorted the incentives and career dynamics of an entire research generation.

Slow and Steady Growth of a Skilled and Specialized R&D Workforce. Both the overall NIH funding regime as well as the organization of leading university program has nurtured the development of a skilled and specialized R&D workforce. During the 1980s, numerous universities expanded their graduate training programs to adapt to new technologies through the creation of new disciplines, including bioinformatics, genetics, and bioengineering. The slow and steady growth of this workforce, and the interdependencies between public sector and private sector research had distinct implications for the structure and performance of the life sciences innovation system.

First, the large size of the emerging discipline meant that individual researchers could become highly specialized, and collaborate with other researchers (as co-authors) on particular projects (Jones, et al, 2006). The combination of specialization and opportunities for collaboration cannot be overstated. In the absence of norms and institutions that encouraged widespread collaboration, individual scientists would have to master a much wider range of skills and knowledge in order to work on any one project; this requirement for breadth would come at the expense of depth, lowering research productivity (Jones, 2008).

At the same time, this highly specialized graduate training could result in a range of alternative employment opportunities, including a traditional tenure-track position within a biology department, a research position within an academic medical center that might involve a heavier reliance on sponsored research activities (as opposed to the “freedom” of a pure biology department), or employment with a biotechnology, pharmaceutical or medical device firm where basic research responsibilities would be complemented with direct concerns about the commercialization of discoveries. Moreover, the highly interdependent nature of the life sciences innovation network has the consequence that a period of employment in the private sector need not come at the expense of returning to public sector scientific employment in the

future. Researchers on both sides of the university-industry divide publish heavily in the scientific literature, collaborate with each other on projects, and engage in more structured interactions in the context of commercialization (Cockburn and Henderson, 1998). Indeed, the career concern incentives to participate in this system on an ongoing basis may be an explanation for why scientists seeking private sector employment are willing to accept lower wage income for jobs that permit some freedom in research project choice and permit ongoing publication in the open scientific literature (Stern, 2004).

In other words, a distinctive feature of the life sciences innovation system is that individual researchers are (by and large) able to make very specific human capital investments early in their career, and are able to realize the benefits of those investments by obtaining diverse types of employment that are nonetheless closely related to their human capital investments, and are able to collaborate with researchers (across organizational boundaries) with complementary human capital over the course of their career.

Significant Financial Rewards Innovative Clinical Breakthroughs. A third driver of the growth and evolution of the life sciences innovation system is the prospect for significant financial rewards for successful innovation. Most consumers have a very high intrinsic willingness to pay for drugs (as for other medical innovations), particularly when the alternative to drug therapy involves suffering from a painful, debilitating, or even deadly medical condition. While multiple therapies may exist to treat a condition, most innovative products are strongly differentiated from each other in terms of pharmacological or therapeutic characteristics (Ellison, et al, 1997; Stern, 1996).

Several interrelated features shape the product market rewards available for innovative products. Consider the environment within the United States (by far the single largest market). First, in terms of the demand for a therapy, pharmaceutical demand is determined largely through physician prescribing choices (who are therefore insulated from the pricing impact of their decisions), and a significant portion of patients receive some form of public or private insurance coverage for pharmaceutical purchases. While insurance companies constrain both physician discretion and patient insurance through the use of formularies, it is nonetheless the case that the key decisionmakers for many pharmaceutical purchases are insulated from the full cost impact of those decisions, and in any case have a high intrinsic willingness-to-pay. At the same time, the FDA regulatory framework alongside broad and enforceable patents implies that the substitution

choices for an innovative new product are often limited during the time of FDA exclusivity. In particular, the Hatch-Waxman Act of 1984 provided the modern regulatory framework that ensured a reasonable period of exclusivity (for the marketing and sales of a compound) for innovating firms after FDA approval, and encouraged the entry of generic firms to promote competition after that exclusivity period had expired (Grabowski and Vernon, 1996). The Hatch-Waxman Act was a significant policy success, simultaneously sharpening the incentives for breakthrough innovation while ensuring diffusion and low-cost access after patent expiration. Similarly, for conditions in which there are only a small number of patients (and so the incentives to innovate may not be sufficient), the Orphan Drug Act provides a less costly path towards regulatory approval and an enhanced exclusivity period. Many biotechnology firms have indeed targeted their efforts at markets covered under the Orphan Drug Act, both to take advantage of the favorable regulatory framework and because many of underlying disease conditions are particularly well-suited to therapies using the tools of biotechnology. Finally, while public payers such as Medicare are the single largest payers within the market, current policy prohibits explicit price controls. Within this framework, for innovative therapies addressing significant health and welfare challenges, demand is highly inelastic, and innovators are in many cases able to charge high prices (particularly compared to marginal cost), and so realize very significant margins during the time of FDA exclusivity. Once the patent expires, drugs are subject to very rapid and effective imitation by a now-mature and effective generic sector.

Of course, the United States is not the only product market, and biopharmaceutical firms are able to realize returns on their innovations on a global basis. While the incomplete globalization of pharmaceutical products is something of a puzzle (Kyle, 2007), the opportunities of a global market are nonetheless considerable. While most countries outside the United States impose some form of price controls (and other institutions regarding insurance and generic licensing also vary), most countries outside the United States provide a significant price premium for truly innovative products or those that address a significant condition for which there is no substitute. With that said, particularly for the experimental therapies emerging from the life sciences innovation system, most biotechnology companies (and their commercialization partners) emphasize opportunities for drug development and introduction into the United States, while at the same time seeking to build a global presence.

Finally, it is important to emphasize that the rewards for innovation are highly skewed, even for those products that are able to navigate through the regulatory system. A small number of “blockbuster” products realize very high sales, with the top 100 products accounting for about one-third of all global revenue, and nearly two-thirds of drugs do not generate sufficient market returns to recoup their development costs (Grabowski and Vernon, 1996).

Overall, the combination of intense demand on a global basis and limited competition during a period of exclusivity provide powerful incentives for innovation (Thomas, 2005). The “pull” of high margins and sales volumes for successful products and the “push” of intense generic competition work together to generate high returns for successful commercialization of biomedical research in the form of significantly improved products (Finkelstein, 2004; Acemoglu and Lin, 2004; Scherer, 2001). In other words, even though there is a significant level of public research for the US life sciences innovation system, the incentives provided by commercialization provide an equally large incentive, resulting in the (roughly) balanced level of total research expenditure between the public and private sector (Figure 4).

The Institutional and Strategic Environment. Beyond the broad supply and demand factors already highlighted, the growth and evolution of the life sciences innovation system have been powerfully shaped by the underlying institutional and strategic environment, including a transparent and competitive peer-reviewed grant system grounded in the norms of open science, the availability of formal intellectual property rights to protect innovations and provide opportunities for cooperative commercialization, and the presence of innovation-oriented competition along multiple dimensions and domains.

Peer Review and the Norms of Open Science. By definition, the life sciences innovation system is encompassed with the domain of open science (Merton, 1973; Dasgupta and David, 1994; Stern, 2004). The institutions of open science are subtle and interrelated, but are ultimately grounded in three distinctive features: academic freedom, the priority-based reward system, and the freedom to collaborate. By and large, life science researchers in public sector institutions are free to choose their own research agendas and are given broad latitude in how to approach a particular scientific research question (subject to ethical requirements such as human subjects regulation). By giving researchers freedom to choose their own agenda, a more diverse range of questions and experiments are undertaken (Aghion, et al, 2008), with the potential for significant surprises from “unexpected” directions. At the same time, the priority-based reward

system gives researchers credit for the prompt and full disclosure of their discoveries (usually in academic journals, but sometimes in other outlets such as databases like GenBank), accomplishing several interrelated objectives. The priority-based reward system complements academic freedom (researchers have incentives to come up with their own solution to problems that others within their field find interesting), encourages prompt disclosure (as one does *not* get credit if someone else discloses the discovery before you publish), and provides a transparent means for access by future scientists to the body of knowledge in a particular area. As an economic institution, open science encourages a high rate of cumulative knowledge production, and, importantly, offers no enduring monopoly rights over the *use* of that knowledge by future researchers (Dasgupta and David, 1994; Aghion, et al, 2009).

Federal policy towards the life sciences builds upon and reinforces the norms of open science in fundamental ways. While the allocation of public funding for biomedical research, like all Federal expenditures, are driven to some degree by the political priorities reflected in appropriations bills, to a great extent the allocation of public funding for biomedical research to specific projects and investigators has been controlled by peer-review of investigator-initiated projects, and has responded as much to supply of interesting ideas as it has to demand for solutions to health problems. In other words, the NIH peer-reviewed grant system is embedded within a system that encourages academic freedom and disclosure, and reinforces those institutions by providing ongoing incentives for participation and appropriate scientific behavior (e.g., prompt disclosure, a high level of ethical conduct, etc). While there are of course exceptions to these norms (e.g., occasional instances of outright scientific fraud, and, almost more troubling, a more pervasive pattern of limited data withholding in some scientific communities), perhaps the most striking feature of the life science innovation system is how rarely such exceptions occur; most scientists place a high degree of weight on the maintenance of their reputations, and behave in ways that protect those reputations and promote the transparency and priority rules for scientific research.

With relatively few exceptions, government-sponsored research has rarely taken the form of “Manhattan Project” initiatives. Rather the progress of science has been largely driven by a robust and independent scientific community focused on the intellectual merit and novelty of investigator-generated research proposals, balanced by input concerning social or governmental priorities. In the few cases where the life sciences innovation system has focused on a “big

science” project, such as the Human Genome Project, the impetus has often come from the recognition of the need for such a project from the scientific community itself.

Intellectual Property as an Incentive Device and an Enabler of a Market for Technology..

The nature of IP, specifically patents, has played a very important role in driving innovation in the sector. Several features have been particularly salient. First, in contrast to other sectors, in biopharmaceuticals the patent system appears to be working relatively well. In other technologies and industry sectors patents have become highly controversial, with many economists increasingly skeptical that the patent system is actually promoting technical change. Critics argue that poor standards of examination, growth of patent thickets, and increasingly sophisticated strategic use of IP are raising costs imposed by patents (Jaffe and Lerner, 2005). But in biopharmaceuticals, these problems have, at least historically, been much less severe.

To a great degree this is a function of the nature of technical knowledge and of pharmaceutical products. As products, drugs are normally a single molecule, or simple mixture of molecules, not complex devices comprising hundred, or thousands of distinct patented (or patentable) components. At the same time, innovation has taken place largely in the realm of the “chemical arts,” a highly systematized and codified domain of knowledge within which widely accepted conventions for nomenclature and technical practice, extensive professional training of participants, a large and exhaustively indexed scientific literature, and a long tradition of patenting make it straightforward to establish the novelty and patentability of new inventions. Patent rights over new molecules are therefore generally straightforward to obtain, to delineate, and to defend. Compared to other technologies, infringement of patents is generally easy to observe (and to establish in court) and “freedom to operate” i.e. the absence of others’ IP that could be used to hold up new products is relatively easy to establish.

Since most pharmaceutical products are also relatively easy to imitate, patents play a critical role in allowing innovators to appropriate returns from R&D. This creates a strong incentive for innovators to submit high quality applications. At the same time, the nature of product market regulation and competition creates extraordinary rewards from invalidating or inventing around a single patent, and competitors have a similarly powerful incentive to weed out “bad” patents.

Industrial R&D is unusually tightly linked to academic science, traditionally driven by “Mertonian” norms and incentives which are generally thought to be antithetical to exclusion-

based intellectual property rights. Thus as patenting in this sector has increasingly moved upstream from the product market and into the domain of basic science, the spectre of a “biomedical anticommons” has been raised. Concerns have been widely expressed about the inappropriate scope or blocking power of patents on fundamental physiological processes or genetic sequence information, of decreased knowledge sharing among scientists, or the potential for transactional “gridlock” as products rely increasingly the integration or combination of many pieces of independently owned IP. But evidence of a serious negative impact on innovation is thus far relatively weak. (Cohen, et al, 2002; Murray and Stern, 2007). The prominence and scale of open science also serves to vigorously delineate the public domain in biomedical science. And although patenting of research tools, drug targets, genes, and fundamental biological and chemical processes remains controversial, these property rights are the foundation of a very active “market for technology” which has promoted extensive dis-integration of R&D organizations, a high degree of specialization, and injected market pricing and entrepreneurial energy into the research process.

Second, in this sector patents work along side other mechanisms to generate extraordinarily high rewards to innovative individuals across multiple domains. Successful researchers can expect to gain both high social and professional status (awards, peer recognition, influence), significant intrinsic rewards from their work (curing disease), and substantial financial benefits (tenure, salaries, equity).

Third, patent protection and incentives are closely tied (in the US, at least) to a regulatory system that controls access to the product market. The Hatch-Waxman framework protects innovators through patent term extensions, data exclusivity provisions, and automatic 30 month stays preventing the FDA from approving the sale of allegedly infringing generic versions of a drug. But at the same time it provides incentives for imitators to challenge weak patents (180 days of exclusive generic status for the first entrant that successfully challenges and incumbent’s patent), forces clarification of the patent status of a drug (innovators must list relevant patents), and substantially lowers entrants’ costs of obtaining FDA approval for their product by allowing them to use the innovator’s health and safety data in preparing an abbreviated “ANDA” application. Together with state laws requiring automatic brand-generic substitution and widespread use of tiered copayment schemes and formularies by insurers and third-party payers, these provisions facilitating deep and rapid loss of sales once patent protection is lost. Thus the

“carrot” of effective and workable IP combined with the “stick” of intense post-patent competition create powerful incentives to compete through innovation.

Competition Along Multiple Dimensions and Domains. A distinctive feature of the life sciences innovation system, and one of the key drivers of its innovation performance, is the pervasiveness of competition at multiple levels of analysis. This competition occurs in many dimensions, and throughout the value chain. First, consider the “upstream” domain of basic research and scientific discovery. Here, individual researchers compete for priority in discovery, and for reputation within their peer community. A rich literature in the economics and sociology of science has identified the key elements of the governance and reward systems in “Open Science” (Merton, 1973; Dasgupta and David, 1994). While the social norms of these communities place a premium on collegiality, co-operation, and sharing, the highly skewed distribution of rewards (grants, promotion, status, power, “parking”) and relatively free entry into the academic labor market, results in vigorous competition among researchers (Dasgupta and David, 1994; Nelson and Rosenberg, 1994). At higher levels of organization, reputation-based competition is equally vigorous between research groups (“labs”) and between universities and other non-profit research institutions to attract resources and talent. Notwithstanding the “Matthew Effect” and other competitive dynamics that tend to cumulatively reinforce small performance differences, academic research activity is remarkably “atomistic” and fragmented, with several hundred institutions playing a significant role. At an even higher level of aggregation, states, regions, and countries can be understood as competing in the domain of basic research through policy choices and provision of physical and institutional infrastructure intended to attract human capital and investment. Consider competition between California and Massachusetts in the era of restricted federal funding for stem research, or initiatives such as the Singapore “Biopolis.”

Another important arena is the “market for technology” (Arora, et al, 2001; Gans and Stern, 2002, 2003; Cockburn). This trade in “technology” (frequently candidate molecules, but also research tools and data) across institutional boundaries has become a critical aspect of the innovation system. Licensing deals, collaborative research, and corporate M&A are one of the most salient features of the biomedical landscape. Many institutions compete actively on the supply and demand sides of this market, with universities and academic medical centers, government labs, biotechnology companies and some parts of big pharma companies competing

in the supply of out-licensed technology, and downstream specialists in commercialization (principally big pharma, but increasingly big biotech) competing to acquire the most promising discoveries to fill development pipelines and maximize utilization of their manufacturing, distribution, and marketing capacity. A distinct set of institutions and marketplaces are emerging to facilitate and govern this trade, such as university TLOs and industry-wide gatherings such as the BIO conference.

Lastly, there is competition in the product market. As described above, the nature of demand, and the regulatory framework controlling access to the market have focused commercialization activity on product-oriented innovation. The increasing role of generics, and the maturation of that part of the industry focused on therapeutic proteins which are very costly to produce, may result in greater emphasis on process innovation and lowering production costs. But for the most part commercialization activity is directed towards developing novel, premium priced molecules, and generates intense “Schumpeterian” dynamic competition between innovative products. Lichtenberg and Philipson (2002) show that a typical drug is launched in the face of 25 existing molecules in its therapeutic classes, and faces entry by a further 7 to 10 new molecules introduced during the time it is still patent protected. As with the basic research sector, competition is generally fragmented and atomistic. Notwithstanding ongoing consolidation among big pharma companies, relatively few therapeutic categories are dominated by a single producer.

This complex, multifaceted competition has a powerful influence on the rate and direction of innovation within this sector. Several aspects are worth noting. First, with the singular exception of generic manufacturing, competition for resources throughout the system is consistently oriented around innovation, priority and the creation of new knowledge. Second, compared to other sectors, the nature of competition and of innovations that results is highly transparent. There is a pervasive culture of codification and disclosure of new knowledge through scientific publication and patenting. This supports a research environment that is strongly cumulative and highly efficient in the sense of avoiding duplication. Third, competition and experimentation thrive in the absence of a single bottleneck, dominant platform, or monopoly player. Ironically, it is the industry where property rights over innovation are likely strongest that we see perhaps the highest sustained levels of innovation-oriented competition in an unconcentrated market. Simply put, there is no Microsoft.

One particularly interesting, and important, aspect of competition has been institutional and economic experimentation. Though much innovative activity continues to take place within large, stable organizations, this sector has seen dramatic industrial restructuring and the emergence of new and interesting organizational forms such as AMCs that combine bench research with clinical practice (Rosenberg, 2008), the “just off-campus” biotechnology firms founded by academic “star scientists,” non-academic non-for-profit research institutions such as the Jackson Laboratories, CROs, specialized venture capital firms, large scale “hands-on” funding by philanthropies such as the Wellcome Trust and the Gates Foundation, patient advocacy groups, and hybrid private-public entities such as OneWorld Health. Just as there is no monopoly on scientific discovery or entrepreneurship, there is no monopoly on the institutional approach to encouraging an effective life sciences innovation environment. This diversity encourages competition and experimentation over time facilitates systematic learning regarding the “science of science management.”

V. Lessons for Alternative Energy and Climate Change Innovation

The principal contention of this paper is that the relative dynamism and performance of the life sciences over the past twenty years does not simply reflect scientific and technological opportunity. Instead, the performance and character of the life sciences innovation system is grounded in the microeconomic and institutional environment, and, by and large, these factors have been conducive to significant and pervasive growth. Moreover, the life sciences innovation environment did not arise by chance but reflect a long set of public policy choices and an institutional framework that provides a robust supply of innovation inputs (in terms of money and people), the potential for significant rewards from breakthrough innovation, an engagement with the norms of open science that nonetheless allows for effective intellectual property protection, and opportunities for competition along multiple dimensions.

There is, of course, an ongoing and vibrant policy debate about how to ensure and enhance the vitality of the life sciences innovation system. In particular, in light of the relatively low rate of drug approval over the past several years, there are increased concerns about whether the system has sufficient capacity and incentive structures to translate scientific discovery into clinical applications that have a significant human health benefit. At the same time, there is a broader health care reform debate that focuses in large part on the ability to reduce the rate of

growth of medical costs over the long term; this broad policy objective may conflict with the historical commitment to reward breakthrough innovations through significant price premiums during the time of FDA exclusivity.

Despite these ongoing challenges, we argue that the history of the life sciences offers an instructive lesson regarding the growth and evolution of science-based innovation systems. It is of course important to recognize that there are fundamental differences between the environment for innovation in the life sciences and climate change. For example, in the absence of an effective and durable set of policies for carbon pricing (whether in the form of a carbon tax or a cap-and-trade system), the incentives for innovation and commercialization will be muted relative to the significant rewards available for innovative breakthroughs in the life sciences. As well, while the life sciences revolution was spurred by the development of particular discoveries and technologies from the early 1970s that pointed the way towards biotechnology applications, the impetus for a climate change innovation system is grounded in a specific social challenge that has so far resisted “easy” technological solutions, and there is no one technological paradigm on which to focus. Despite these differences, it is nonetheless true that both life sciences and alternative energy innovation have their origins in the early 1970s, and, while investments and progress in alternative energy innovation have been elusive, the life sciences innovation system has come to occupy a dominant role in non-defense public funding and a leading role in the overall American innovation system.

Lessons from the Life Science Innovation System

First, the returns to life sciences investments by both private and public entities have taken *decades* to pay off, and are only now coming to occupy a central role in the delivery of most new therapeutics. In contrast to a “Manhattan Project” approach in which a single burst of focused investment yields a single technological “fix,” the life sciences innovation system has been characterized by steady and cumulative progress over time and the development of complementary platform technologies. A single R&D “surge” with no follow-through might actually be counterproductive in terms of long-term technical progress, as specialized investments are undertaken during the boom period, resulting in significant distortions as funding is cut back. Moreover, the importance of stable and long-term public funding of research is particularly important in environments that are likely to be characterized by a high degree of interaction between public and private research funders. The private funding of innovation-intensive sectors

is notoriously fickle, and an often overlooked benefit of a stable pattern of public funding is the ability to buffet the variability of private sector investment. More generally, it is likely that any systematic and robust effort towards alternative energy must instead be grounded in a long-term commitment involving the development of specialized human capital, and the evolution of institutions that allow for effective public-private interaction. It is often remarked that Rome wasn't built in a day -- more importantly, the design principles and technologies that comprised ancient Rome took centuries to develop. While the social challenges and time constraints presented by climate change have led to considerable pressure to engage in an accelerated innovation process, effective long-term solutions to climate change and energy requirements are more likely to be grounded in a systematic and long-term research and development commitment.

Second, life science innovation has been driven by investigator-initiated and peer-reviewed science rather than a “command-and-control” approach. Even when particular public health priorities have emerged (as in the case of AIDS), the source of the ultimate solutions have been grounded in the open scientific community and are dependent on the exercise of intellectual freedom and scientific openness, and opportunities for experimentation and diversity at the level of individual researchers and institutions. Obviously, product market incentives steer resource allocation in commercial science, but these have been complemented and counterbalanced by the robustness and scale of “blue sky” research – with long run benefits to all. An environment that encourages academic freedom and entrepreneurship will of course be less focused than a command-and-control approach, as different researchers and firms experiment with alternative approaches based on individual perceptions and beliefs. Of course, most of these ideas and approaches will fail, and, even in the life sciences, there is significant pressure to reduce the rate of failure through a more top-down approach. However, the history of the life sciences suggests that attempts to significantly reduce the freedom of investigators and entrepreneurs, precisely because it reduces the diversity of experimentation, rarely results in important breakthroughs. Efforts to manage the direction of research in a centralized manner, rather than through a peer-reviewed investigator-initiated system, and a single-minded focus on short-run product market incentives are unlikely to provide a cumulative stream of innovation addressing the need to mitigate global climate change.

Third, competition is intense and pervasive throughout the value chain. Despite consolidation among Big Pharma companies, the product market is relatively fragmented and driven by “Schumpeterian” competition to introduce new molecules, and price/cost competition by generics within existing molecules. In the “market for technology”, thousands of smaller science-based entrepreneurs compete for capital, human resources and opportunities to license to or collaborate with downstream partners. In the publicly funded sector, Darwinian competition for resources prevails between many hundreds of institutions and thousands of PIs. Whether directed towards Nobel prizes or blockbuster drugs, this competition is focused on novelty and priority rather than pre-emption of scarce resources or control of distribution. Competition at multiple levels and multiple domains enhances the level of experimentation within an emerging innovation system, and mitigates the potential for hold-up and rent-seeking. Lack of competition within innovation does not simply engender the traditional static losses of monopoly pricing, but reduces the level of diversity and experimentation of the research community itself, with negative consequences for the rate and productivity of cumulative technical progress.

Fourth, though providing significant rewards for innovators and firms who effectively commercialize important innovations is extremely important, the dynamism of the life sciences depends on more than simply setting the right “price” for innovative therapies. The life sciences, almost by definition, rely extensively on the norms of open science and engagement with the scientific community, including university researchers. While scientists are of course motivated by potential financial returns, scientists are *also* motivated by innate curiosity and the potential for recognition (in the form of prestige, positions, and awards). In some cases, placing an extreme emphasis on financial incentives may actually reduce engagement and participation by the scientific community, particularly if the scientific community perceives that the exploitation of intellectual property rights or financial incentives are getting in the way of “good science.” A fundamental feature of open science is indeed its openness – the (mostly) prompt disclosure of new discoveries through scientific publication (and perhaps complemented by patenting), and the development of open-access institutions and infrastructure (such as GenBank or the Jackson Laboratories) to enhance the productivity of all scientists. While individual scientists do of course engage in strategic behavior (e.g., by only engaging in partial disclosure in order to limit rivals’ access to knowledge), the policy choices of the NIH, and the governance of academic societies and universities have created powerful norms that enhance the transparency of the

knowledge accumulation process. By facilitating access to prior discoveries and providing incentives for the disclosure of new discoveries, open science serves as powerful institutional framework for step-by-step scientific and technical progress.

Fifth, whether by accident or design, the interaction between the patent system, the FDA regulatory process, and the payer environment provide salient incentives for breakthrough innovation. The combination of a high willingness-to-pay for products (combined with insurance which insulates purchasers from the marginal price) and the Hatch-Waxman regulatory framework provide firms incentives for develop blockbuster therapies (particularly focused on the largest markets) and to develop a stream of innovations over time (as the monopolies generated by the system are transitory). The Hatch-Waxman framework helps to ensure that innovators are able to recoup the costs of the drug discovery and development process, while also enhancing the diffusion of valuable therapies at low prices after patent expiration. Finally, the relative strength of the patent system in this environment not only enhances incentives for innovation but also encourages the development of a “market for technology” so that therapies discovered within academe or by start-up firms are able to leverage the complementary assets and resources of firms more experienced at navigating the FDA process (reducing the time to approval) and with a larger presence in the product market (enhancing diffusion). Importantly, it seems that the discovery, development, and diffusion of new drugs is more efficient when there is significant overlap between the types of innovations that can be covered by a patent and the scope of exclusivity offered by FDA regulation. While the precise institutional framework for drug development is likely an ineffective analogy for climate change technology, the experience of life sciences innovation suggests that regulation governing product market access can play a crucial role in shaping innovation incentives, and that product market regulation and intellectual property rights policy can be powerful complements to one another.

Sixth, notwithstanding product lifecycles and research agendas that operate on a time scale of decades, and the very large scale of entities such as NCI or large pharma companies, the spectrum of organizations and institutions that make up the life sciences sector have demonstrated considerable flexibility and adaptation to an evolving environment. Incumbent firms have by and large not shown the structural rigidity and organizational inertia that appear to have been so costly in other sectors such as the US automobile industry. Rather than engage in systematic resistance to the emerging biological sciences, established firms accommodated and adjusted to

entry of new biotech firms (and the expansion and greater engagement of universities and AMCs), ultimately becoming enmeshed in a web of collaborative institutions and partnerships with both public and private firms. While the management of such research networks is daunting, an effective approach to cooperative commercialization is grounded in an effective set of institutions (balancing the norms of open science with an effective intellectual property rights) that allow for specialization in the division of innovative labor and commercialization activity, and the exploitation of distinctive complementarities between public science, science-based entrepreneurship and traditional pharmaceutical companies.

Our final lesson concerns the nature of life sciences innovation. While most discussions of potential technological solutions for climate change effectively envision a single “quantum leap” that offers a cost-effective substitute to carbon-based energy sources or an ex post mitigation scheme for removing emitted carbon from the environment, the history of life sciences innovation is that most “breakthrough” technologies depend on a long line of step-by-step innovation. However, the ultimate performance of a technology depends on whether the technology experiences significant and sustained improvements over time. While the power of cumulative innovation is obvious in areas such as information technology, the life sciences are also characterized by a process in which embryonic prototypes provide little indication as to the ultimate social impact of a given technology. To take but one striking example, sustained reductions in the costs of genetic sequencing have ultimately enhanced access to that technology, and have facilitated applications across diverse application areas from criminology to public health (characterizing different flu virus) to personalized medicine. Rather than considering whether there is a single “magic bullet” for climate change (and offering a single large prize for “success”), the experience of the life sciences suggests that sustained investments over time, powered by general-purpose platform technologies, and encompassing a diverse range of experiments are more likely to result in a stream of powerful innovations to address pressing social and human challenges.

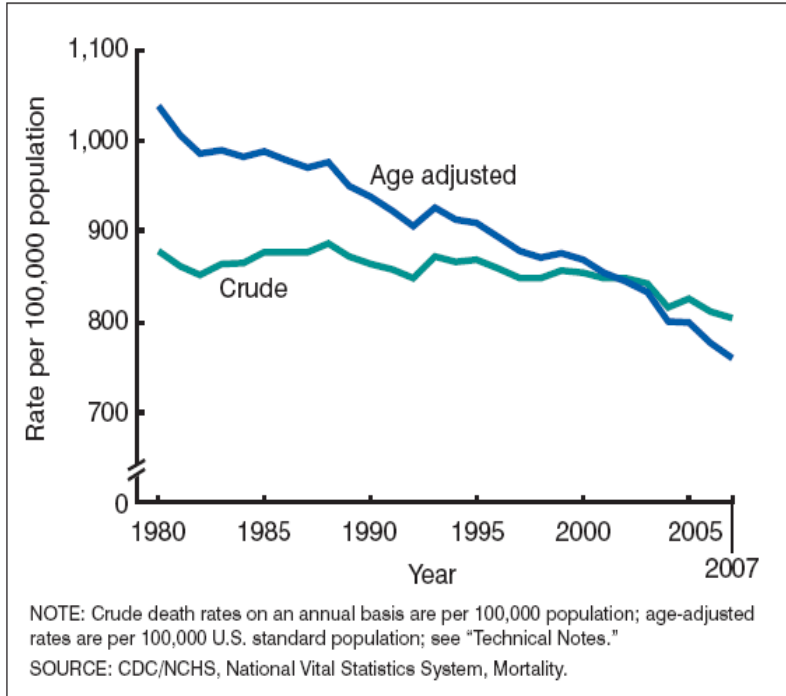


Figure 1. Crude and age-adjusted death rates: United States, 1980–2006 final and 2007 preliminary

Drawn from Xu, et al (2009), “Deaths: Preliminary Data for 2007,” *National Vital Statistics Reports*, National Center for Health Statistics.

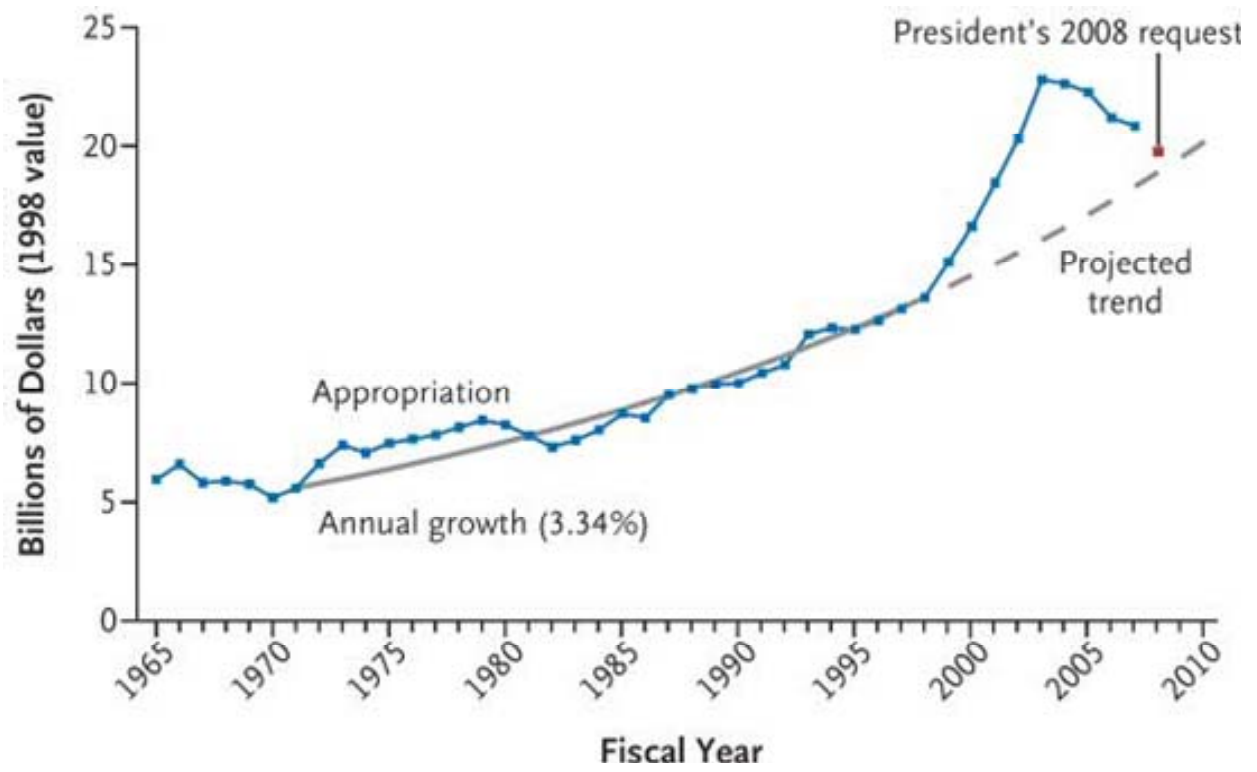


Figure 2: Federal Funding of NIH over time

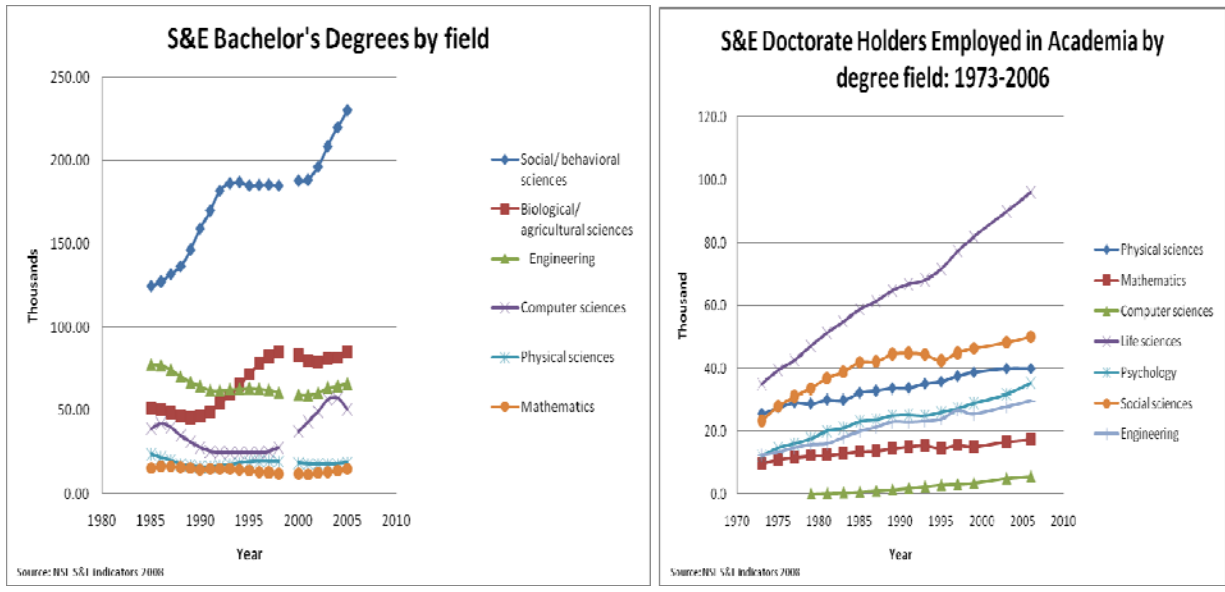
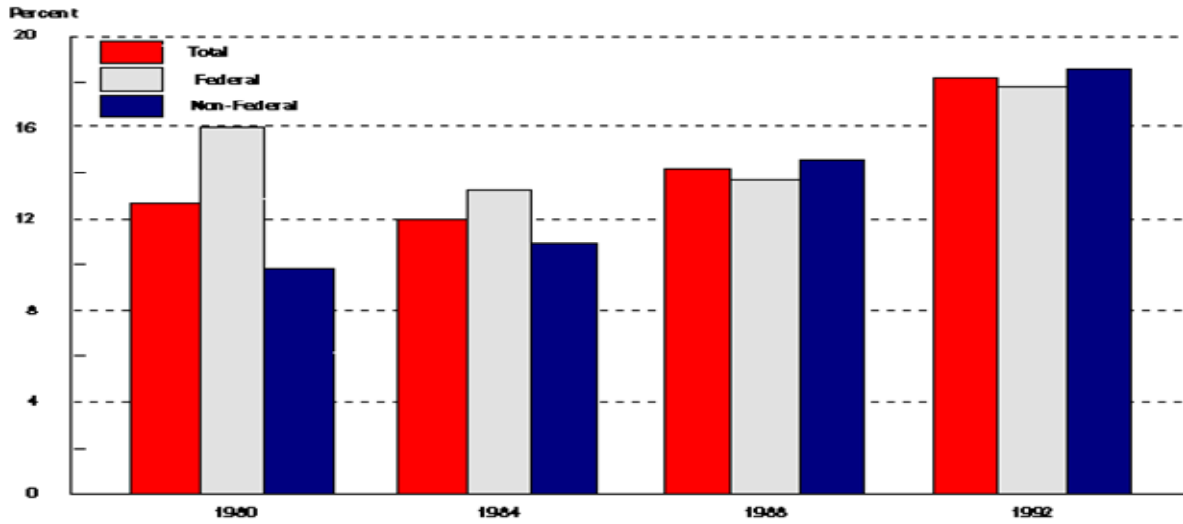


Figure 3 – S&E bachelor’s degrees by field 1985-2005 and S&E doctorate holders employed in academia by field 1973-2006

Figure 4-11.
Funding of health R&D as a percentage of total R&D, by source



See appendices 4-4 and 4-28.

Science & Engineering Indicators - 1997

Figure 4: Funding of health R&D as a percentage of total R&D by source

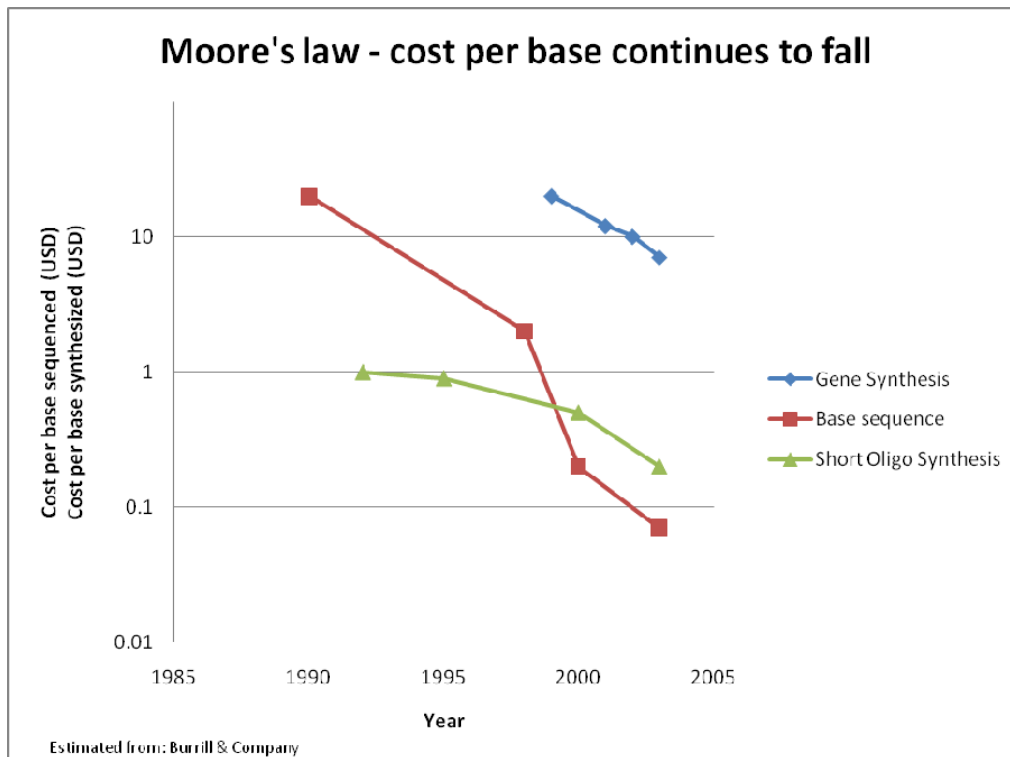


Figure 5: Cost per base synthesized and sequenced; highlights the emergence of a cumulative innovation environment driven by GPTs including PCR and IT Apps

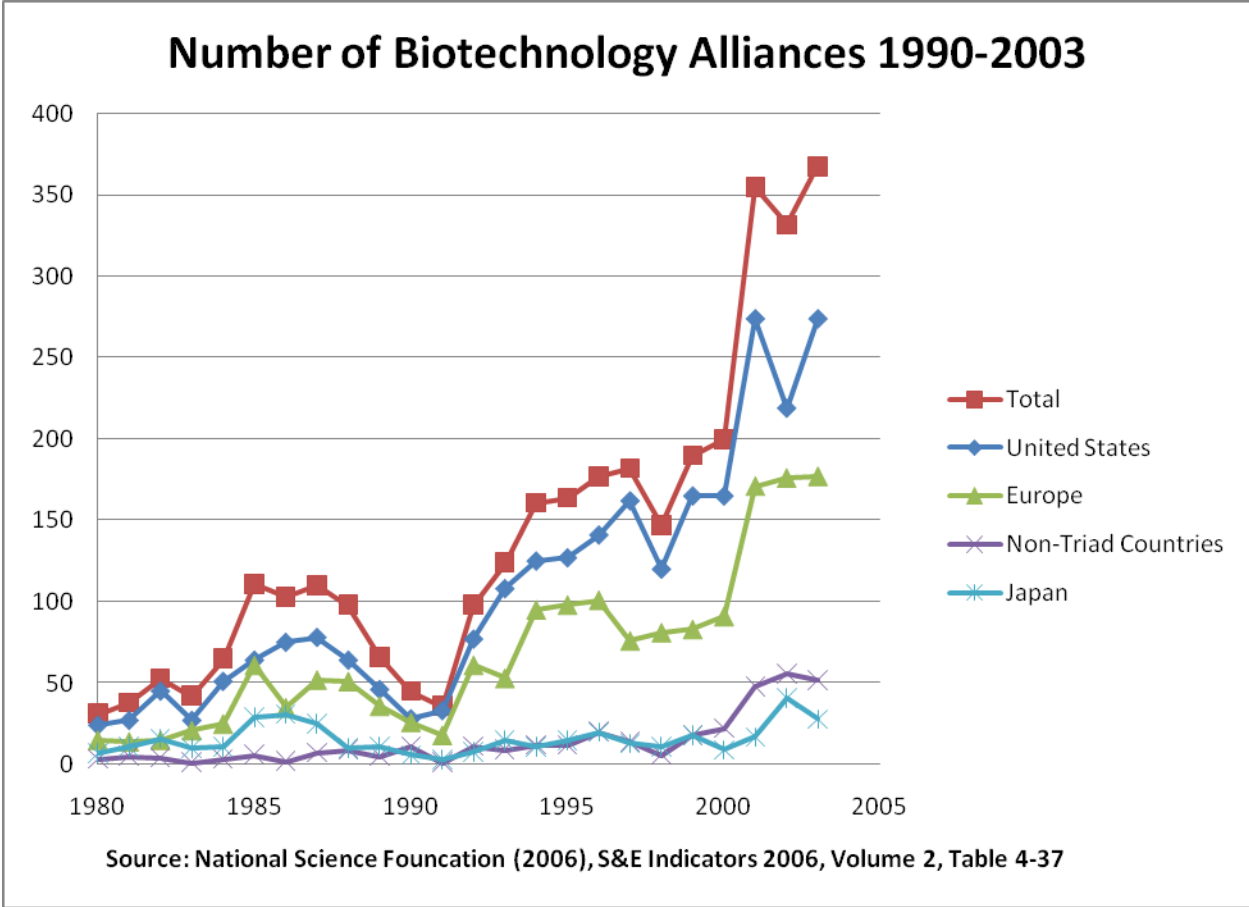


Figure 6: Biotechnology Alliances over Time.

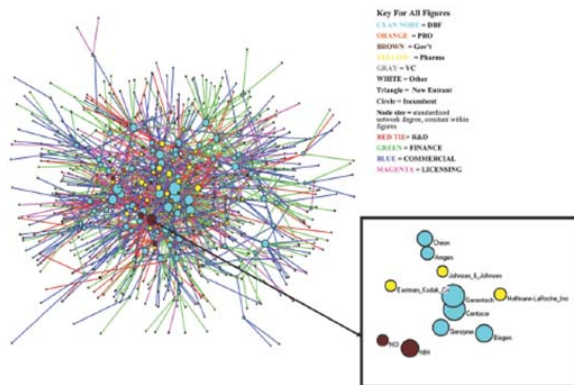


FIG. 4.—1988 main components, all ties

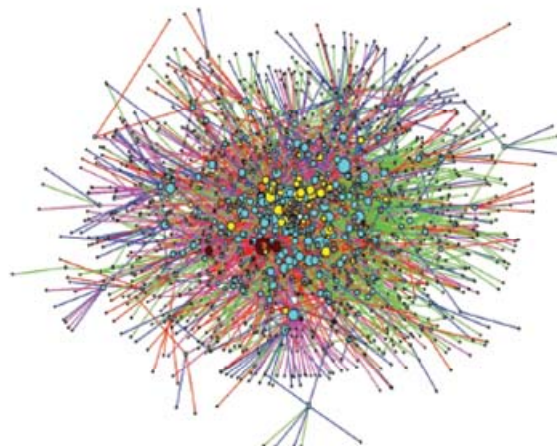


FIG. 8.—1997 main component, all ties

Figure 7 – Drawn from Powell, et al, 2004. The Life Sciences Innovation Network, 1988 and 1997

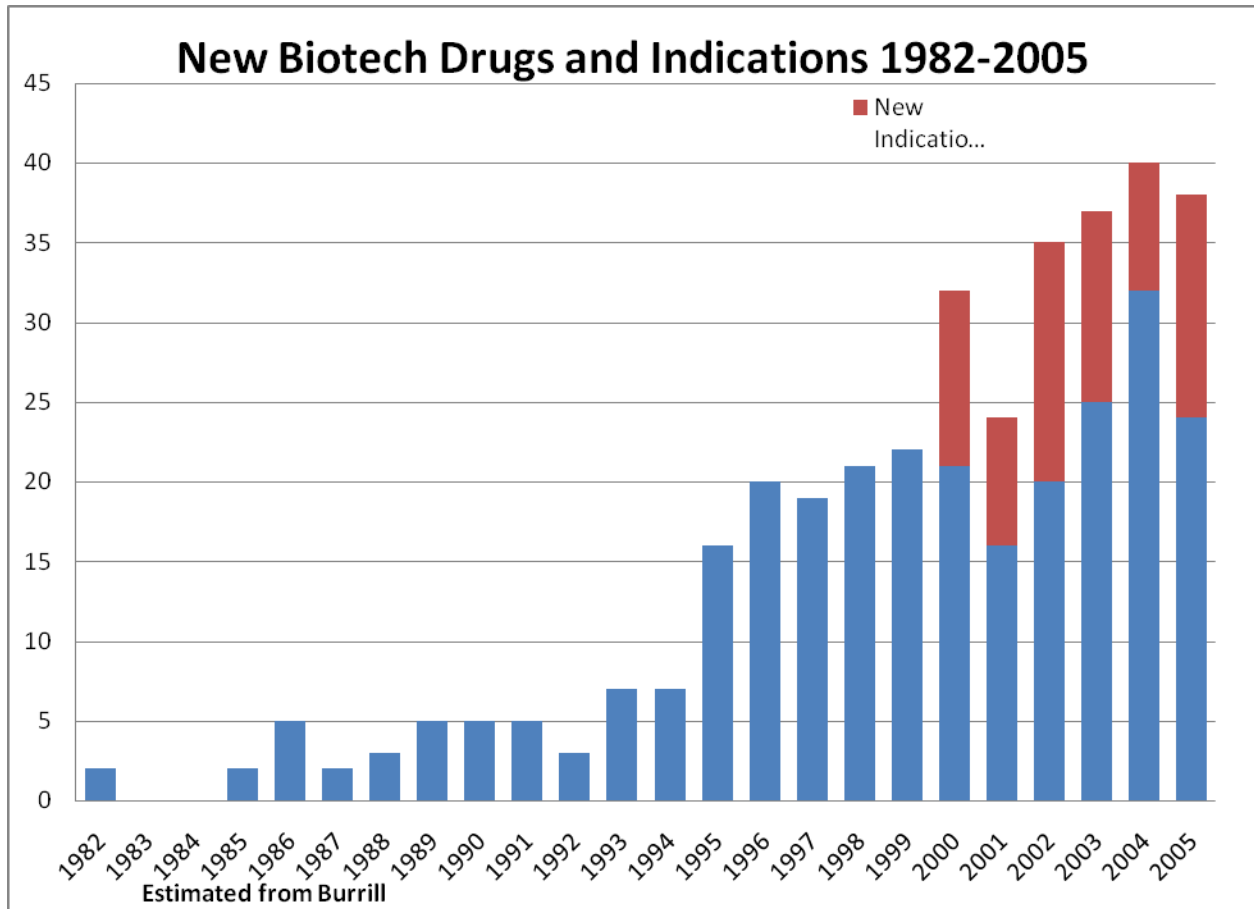


Figure 8 – Number of new drugs (and new approved indications) with their origin in biotechnology. Adapted from Burrill, 2009.

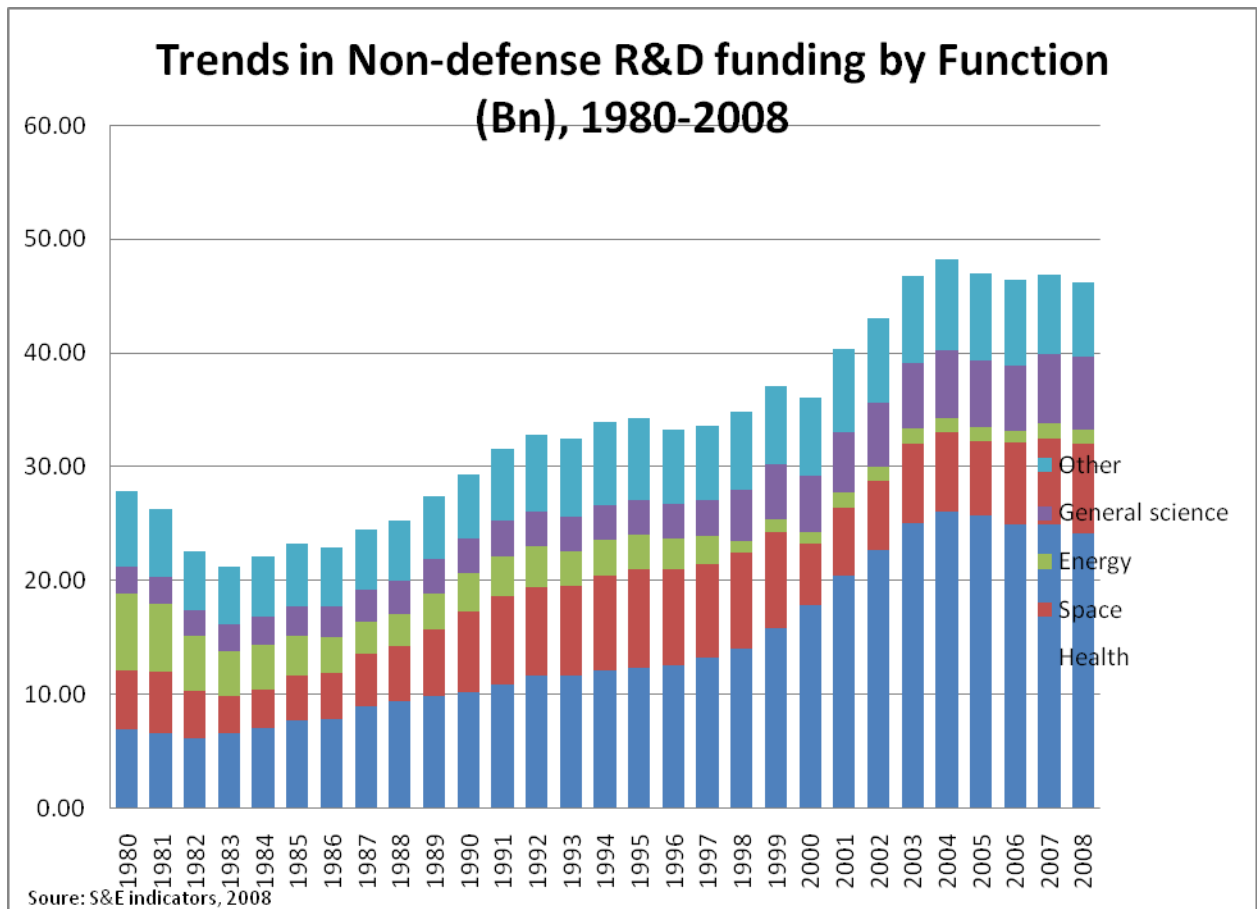


Figure 9. Trends in Non-Defense R&D, Adapted from AAAS (2009).

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