Medical Innovation and Institutional Interdependence
Rethinking University-Industry Connections

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Few persons would challenge the social value of medical innovation in promoting long-term health and improving quality of care or would want it seriously curtailed. However, sharp critical questions have recently been posed about the “adverse effects” of highly productive means of encouraging innovation. Concerns center on blurring lines between academic research and the commercial world, closer ties between universities and business, and the implications of universities’ newfound readiness to behave as profit-seeking entities. The Atlantic Monthly published a 4-part article on “The Kept University.”1 The opening lines declare that “commercially sponsored research is putting at risk the paramount value of higher education—disinterested inquiry. Even more alarming... universities themselves are behaving more and more like for-profit entities.” In a recent editorial, Angell contended that “the claim that extensive ties between academic researchers and industry are necessary for technology transfer is greatly exaggerated, particularly with regard to clinical research. There may be some merit to the claim for basic research, but in most clinical research, including clinical trials, the ‘technology’ is essentially already developed. Researchers are simply testing it.”2

Is growing intimacy between industry and academia in the discovery and development of medical advances eroding the traditional mission of universities, as charged? The risks of university-industry interaction deserve careful consideration, which they have received in several recent articles.3-5 Productive debate, however, should focus not only on threats to the institutional mission but also on balancing risks against benefits. Crucial to illuminating that balance is clearer insight into the division of labor that defines the current roles and contributions of organizational partners (universities, industrial firms, and government) in the various stages of medical innovation. This question has been surprisingly seldom studied. The traditional image—academic faculty generate fundamental knowledge...
that industry in turn develops and markets—does not do justice to the subtle production functions of medical innovation, and thus offers a flawed foundation for unraveling increasingly salient institutional perplexities. This article explores the dynamics of medical innovation and draws some implications for organizational and public policies.

Research Types and Institutional Roles

Innovation emerges from the interplay of universities, national laboratories, and industrial firms in an environment shaped by a growing body of governmental rules and incentives. Following World War II, the United States witnessed an explosive increase in federal medical research and development funding and by 1997 an astonishing 54% of the overall public research budget was spent in the life sciences. Most of these dollars were allocated to academia. To ensure that resulting discoveries would not lie fallow in academic or governmental laboratories, Congress enacted numerous pieces of legislation during the 1980s. Most notable were the Bayh-Dole Act of 1980 and the Federal Transfer Act of 1986, which provided universities and federal laboratories strong incentives to patent the findings of publically funded research. In 1980, these incentives were strengthened by the US Supreme Court’s landmark decision to allow the patenting of new life forms created by biotechnology techniques. Partly in response to these policies, university-industry interactions increased substantially over the past 2 decades. The first step to an understanding of this expanding interface is to recognize important distinctions among the research activities conducted at these institutions.

Fundamental Sciences of Health: A 2-Way Street

Advances in the fundamental sciences underlying health, such as biology, behavioral sciences, and physics, are critical to the development of new diagnostic and therapeutic technologies. Over the past 50 years, for example, about 50% of Nobel Prizes in Medicine or Physiology were awarded to researchers who discovered the structure and function of DNA and 7 Nobel Prizes in Chemistry were awarded to related work. Most of this work, though academic in origin, has had substantive industrial implications. The revolution in genetics and molecular biology spawned the biotechnology industry, which has from its inception been intimately tied to academic scientists. The industry’s tendency to locate close to research universities acknowledges the value of star academic scientists in biotechnology. Today, academic scientists continue to serve 3 key functions in the biotechnology industry: they facilitate knowledge transfer, signal the quality of the firm’s research to capital markets, and help chart the scientific direction of the firm.

The academic research that spawned the biotechnology industry catalyzed similar basic research in the pharmaceutical industry, where advances in molecular biology enhanced discovery of conventional small molecule synthetic chemical drugs, such as the cloning of target receptors against which new compounds could be screened. The efficiency of drug development has been further increased by industrial application of academic advances in combinatorial chemistry, which allow the rapid, automated synthesis of hundreds of thousands of experimental substances for preliminary screening. Moreover, insights from computer-assisted structural biology, using x-ray crystallography and nuclear magnetic resonance, allow definition of active sites within biological molecules and thus more precise molecular design of drugs. Chip technology, using complementary DNA assays, permits molecular separation of indistinguishable phenotypes and may have important diagnostic and therapeutic implications.

Research in physics, material sciences, mathematics, and engineering has also been critical to the evolution of medical devices. University departments have discovered new scientific and technological principles, identified new designs, developed new materials, and advanced the computer sciences. Fundamental research has also occurred in the research laboratories of the electronics industry, such as IBM, General Electric, and AT&T. Scientists at AT&T’s Bell Laboratories won 3 Nobel Prizes in physics within 40 years and IBM scientists won 2 in the 1980s alone, a feat unequaled by most academic laboratories. By comparison, medical device firms have not invested heavily in basic research. These firms tend to exploit the fundamental research conducted in academia, and research and new technological capabilities developed by the electronics industry and firms manufacturing essential, specialized materials. The laser is a case in point. Work by Townes at Columbia University in 1951-1953 resulted in the invention of the Maser, a device that creates a focused microwave beam using stimulated emission. Townes then collaborated with Schawlow of Bell Laboratories on a theory of how stimulated emission might work at the wavelength of visible light—from maser to laser. Bell Laboratories got a patent for the laser in 1960 and applications to medicine ensued quickly. This case underscores the bidirectional interactions between academia and industry in fundamental research. In recent years, however, many large firms in the electronics industry have started to downsize their basic research laboratories, making the contributions of academic research in this domain more critical.

Research Into Basic Mechanisms of Disease: Overlapping Roles, Collaborative Gains

Breakthroughs in the molecular and genetic bases of disease have opened up vast therapeutic opportunities, underscoring the importance of research that can translate fundamental biological insights into clinical progress. Such research into the basic mechanisms of disease delineates pathways and targets for clinical intervention. Understanding the electrophysiology of the heart, for example, has critically shaped the design of pacemakers and defibril-
lators, and the discovery of the renin-angiotensin cascade has spurred development of angiotensin-converting enzyme inhibitors, so important in secondary prevention of heart disease.

Academia is a major source of such translational research, drawing on its infrastructure of animal laboratories for physiological research and its large and specialized patient base, which is critical for identifying genetic abnormalities and their varied expression patterns in subpopulations of patients. An especially important academic research output is the development of research tools, such as transgenic mice or gene knock-out models, which guide the identification and validation of targets for therapeutic intervention. Medical invention reports between 1980 and 1997 at Columbia University indicate that nearly 40% of faculty inventions, nearly 40% of patents, and more than 50% of licenses can be classified as research tools.

Universities are by no means the sole source of translational research. Over the past 3 decades, industrial scientists have posed questions of a very basic nature: What are the mechanisms of gastric acid secretion? How does the human immunodeficiency virus attach to lymphocytes? What are the mechanisms of insulin sensitivity or resistance of cells? Industrial scientists at SmithKline French, under the leadership of James Black, discovered an additional histamine receptor and a substance capable of blocking it. This research, and the availability of histamine 2 antagonists, enhanced academic research in the physiology of peptic ulcer disease. The overlapping assets of industry and academic laboratories in translational research make collaborations very fruitful. Indeed, coauthorship by industrial and academic scientists has been found to increase research productivity in the pharmaceutical and biotechnology industries.14,18

**Development and Modification of Technology: Counterintuitive Collaboration**

Contrary to common perception, both industry and academia are prominent players in the development and modification of medical technology. Universities play an active but decidedly secondary role in the development of new pharmaceutical agents. A recent analysis of 15 important drugs, introduced between 1967 and 1992, found that publicly funded researchers isolated, synthesized, and patented only 2 drugs.18

Universities play a more prominent role in the development of medical devices. Academic clinicians have invented and built a range of device prototypes, such as magnetic resonance imaging machines, the fiber-optic gastrointestinal endoscope, laparoscopic tools, and coronary angioplasty catheters. If a device originates in academia, however, researchers typically discover at some point that they cannot advance a project further, because enabling technologies are missing or are too specialized technically to be developed within the university, and partnerships with industrial firms ensue. The device itself is not the only dynamic part of the innovation process. The early development stage of a new device typically exhibits huge variations in operator techniques and skills. Clinicians are indispensable in refining and standardizing techniques, which can lead to significant improvements in outcomes, as reductions in operative mortality and driveline infections with left ventricular assist devices illustrate. This standardization is reinforced by industrial modifications that render devices more teachable, learnable, usable, and perhaps less expensive.

**Clinical Evaluation and the Discovery of New Indications: Partners in Development**

Well beyond the stage at which prototypes develop, academic health centers (AHCs) are major players in the clinical evaluations that are critical to the commercial success of products. These evaluations yield clinical data that not only illustrate desirable changes in the design of products but also furnish the foundation for Food and Drug Administration approval and coverage by payers. Clinicians also regularly discover new indications of use. Widespread use is often a precondition for identification of these new uses. Learning by doing in AHCs, which may suggest modifications in the technology and the design of confirmatory trials, has had broad health and economic benefits. In 1995, our study of 20 of the top-selling drugs from 1993 found that secondary indications exceeded 40% of revenues and that a similar pattern held for medical devices.19 The evolution of technology requires lines of communication that allow information to flow freely from clinicians back to the research enterprise, both in academia and industry.

In recent years, for-profit contract research organizations (CROs) have assumed much of the role of AHCs in the design and conduct of clinical trials; the academic share of industry-sponsored clinical trials diminished from 75% in 1991 to less than 50% in 1993.20 Currently, the pharmaceutical industry outsources an estimated $5 billion to CROs, whose comparative advantage is efficiency in institutional review board approval, patient recruitment, and data management.

The efficiency advantages of CROs are undeniable, but such bottom-line considerations are not the last word. Clinical scientists in AHCs offer a rich source of patients with a variety of well-documented disorders, unique expertise in new surgical and implantable device procedures, informed feedback for design modifications, backup for managing potential adverse events related to experimentation, and identification of new indications of use.21 Clinical scientists also bring methodological expertise to the novel design of sophisticated trials, which typically add quality of life, quality-adjusted survival, and cost-effectiveness outcomes to traditional survival and physiological end points. Major issues in measurement and interpretation need to be resolved, not only in pharmaceutical trials but also in the design, conduct, and analysis of surgical and innovative device trials, which contend with unique technical and methodological chal-
lenses. Academic health centers can address these challenges and independently evaluate new technologies, but most lack the integrated infrastructure of people with expertise in statistics, clinical trial management, quality of life, and economics needed to tackle these roles.

Transfer Mechanisms
The different types of knowledge outlined above move between academia and industry by various routes. Academic research advances enter the public and industrial domain through publications or presentations at conferences. Interorganizational links also hinge strongly on the movement of personnel between academic and industrial settings, which can range from the hiring of graduate students by industrial firms to consultancy agreements with faculty. In fact, one of the most important long-term transfer mechanisms of knowledge from academia to industry may be the training of clinicians and scientists, skilled in modern research techniques. These transfer mechanisms, publications, presentations, as well as clinicians and scientists, are probably still the most common channels of knowledge and technology transfer.

More recently, the spotlight has illuminated university patenting as a transfer mechanism. New state and federal initiatives, such as the Bayh-Dole Act, have sharply stimulated university patenting and licensing agreements. Between 1991 and 1997, university licensing revenue increased from $186 million to $725 million. Over the past 15 years, the number of patents that universities have filed in the medical sciences grew markedly, as did the number of licensing agreements with industrial firms. Part A of the FIGURE charts the growth of inventive activity at Columbia University in New York and shows that the medical center is Columbia’s main locus of inventive activity, generating 75% of university invention reports with less than 60% of the faculty and budget. Part B shows that the medical school accounts for nearly 85% of all licensed inventions. Licensing income is heavily concentrated in a few inventions; 5 inventions yield around 95% of revenues at Columbia. It is important that, despite some notable exceptions, the majority of university technology transfer offices hardly break even.

Faculty members, and sometimes their universities, also increasingly participate in the formation of new, start-up companies. Many universities have developed “incubator space,” where university researchers can collaborate with start-up companies. In 1998, at least 364 new firms were started based on academic discoveries. Long-term research contracts and agreements are providing substantial industry research funding for universities. In fact, the Hoechst–Massachusetts General Hospital agreement and the Harvard Medical School–Monsanto agreement in molecular biology and cancer research lasted for more than 20 years.

These long-term arrangements are not problem-free. Natural tension exists between academicians wishing to pursue fundamental knowledge in an unencumbered way and firms seeking new products or processes as a return on investment. The distinct organizational and cultural environments of the partners may impede communication of new knowledge. Furthermore, recruitments, promotions, mergers, and acquisitions may disrupt successful interactions. These long-term arrangements have been successful in the transfer of knowledge and technology, particularly through the training of scientists for industry. They have less frequently enhanced applications of new knowledge and have not much altered the time course for the development of new technologies. The experience of these arrangements teaches the importance of continual effort on both sides, personal commitments of leaders and scientists, and has stimulated experimentation with newer models of university-industry collaboration.

Organizational and Policy Challenges
Medical innovation depends on extensive interactions between universities and industry, with knowledge and technology transfer flowing in both directions. Important roles and contributions on both sides have been neglected.

Figure. Inventive Activity at Columbia University


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in much commentary. In particular, the familiar image of members of university faculties exclusively engaged in generating basic knowledge and commercial firms as simply those who carry these subtle roles and interchanges. Reality is messier and more intriguing. The goal of AHCs—to make health care better and thus people healthier—is eminently practical, including the development and modification of medical technology. Beyond product development, manufacturing, and marketing, industrial firms are engaged in both translational and more basic kinds of research. In today’s knowledge-based economy, where lines between science and technology steadily blur, innovations arise within complex organizational networks of both public and private sector institutions. However, many of these university-industry interactions remain ad hoc, each party goes its own way and they merge, if at all, after learning of potentially exploitable activities of the other party.

The institutional patterns of innovation reviewed above disclose several benefits of close university-industry interactions. They allow policy makers to increase the public health and economic pay-off of their investments in academic research. Academic research also contributes to the creation of new industries, opening of new markets, and development of new or modified products or procedures to manage disease. Mansfield, for example, showed that among several high-technology industries, academic research contributed most to the drug and medical product industry. Between 1986 and 1994, 31% of new products and 11% of new processes could not have been developed, without substantial delay, in the absence of recent academic research. Transfer of knowledge is bidirectional; these institutions have complementary and overlapping intellectual and technical assets. Both universities and industry gain from accelerated knowledge generation, new opportunities for learning, quicker development of new technologies, access to a partner’s superior capacities or capabilities (eg, new materials, research tools), and in the case of shared assets, creation of a critical mass to conduct research and development.

The costs of the university-industry interface might exceed the benefits, if the cultural and ethical principles of one partner overwhelm those of the other. Universities and industry have different missions and cultures, and critical concerns have been expressed that excessive closeness of academia to industry may decrease openness of communication, bias reporting of research results, and perhaps even affect the type of academic research that is conducted. Moreover, serious questions have been raised about biases in the design of industry-supported clinical trials and inappropriate enrollment of patients based on financial incentives.

These risks deserve careful and, in view of the dynamic nature of university-industry interactions, continuing consideration and discussion. Much activity is indeed taking place. The Public Health Service developed financial conflict of interest regulations in 1995, which are being updated for human research, and the Food and Drug Administration introduced financial disclosure rules in 1998. The Association of American Medical Colleges has created a new task force on this issue in clinical research and most academic leaders have begun to actively manage potential risks by revising conflict of interest guidelines and establishing new oversight mechanisms. But universities almost universally seem to neglect sustained strategic deliberation about the larger dimensions of the interface with industry: How can medical school and hospital leadership maximize the upsides of collaboration and minimize the downsides?

When should universities and industries build on informal networks, fashion more formal cooperation, or remain detached? The considerable capabilities of both universities and industrial firms in translational research and technology development make this a promising area for cooperation. By comparison, clinical evaluative research may need to be more hands-off. Clinical investigators involved in the design and interpretation of trials should have no equity, stock options, or decision-making positions in companies affected by their research.

Workable collaborations may require internal organizational change. Because innovation requires recurring exchanges among different types of researchers, one promising development is the creation of interdisciplinary research centers, organized by technological capabilities or by disease that bring together different parts of the university. For example, the Center for the Integration of Medicine with Innovative Technology is a collaboration between the Massachusetts General Hospital, the Brigham and Womens Hospital, Harvard Medical School, the Massachusetts Institute of Technology, and Draper Laboratory, forging collaboration among biological, physical, engineering, and medical scientists in an interdisciplinary setting. Its mission is to integrate clinical and technological excellence to develop and rapidly implement innovations in minimally invasive diagnosis and therapy. Industry collaboration, an important component of the Center for the Integration of Medicine with Innovative Technology, allows companies to avoid negotiations with numerous academic departments. Effective as it is, this model requires levels of cross-disciplinary and cross-institutional exchange that are difficult to establish and monitor and significant infrastructure to move new ideas to industrial partners and into production.

Beyond internal organizational changes, accelerating the exploitation of knowledge may require newer models of university-industry collaborations; several experiments are under way. Scientists in academia and industry who share complementary and overlapping knowledge can form an intellectual partnership. Partners Health Care System (an academic health care system) and Genzyme Corporation (a leading biotechnology firm) bring their scientists together in regular meetings to discuss and address each others’ scientific problems. These joint efforts aim to speed
knowledge transfer, enhance the problem-solving capacity of each side, and expand and accelerate new applications.

The virtual research organization is another option. If each party has distinct intellectual and technical assets that would be prohibitively expensive or impossible for the other to duplicate, they could collaborate to expand their capabilities. An AHC, with its broad patient base and strong biologic and clinical abilities in translational research, could build a research enterprise with a company that has great technical and scientific strength in genomics and proteomics. If each party has knowledge that complements the other, an intellectual partnership may be formed with a multiyear scientist-to-scientist collaboration. Enhanced transfer of knowledge and technology should follow from this arrangement, in which management of time is but one obvious benefit.

Although we have focused here on university-industry relations, it is important to remember that government is a crucial part of the regulatory and market environment in which these relations evolve. Until recently, US policies to promote the development and transfer of technologies have been focused heavily on the alleged virtues of patents. But it is far from clear how effective, in comparison to other transfer mechanisms, university patents have been in stimulating the transfer of technologies that would otherwise remain locked in university laboratories. Would the licensed technologies have been used by industry anyhow? And what are the unintended consequences of these policies? Is exclusive licensing of research tools, an important research output of universities, defensible? Suppose Stanford University had exclusively licensed the Cohen-Boyer patent on ribosomal DNA technology? Any serious restriction of access to research tools can only be damaging to the collective research enterprise. And even if these types of inventions are widely licensed, patenting could dramatically raise the transaction costs of research.

Enhanced generation of new knowledge, technology, and applications will require more effective collaboration across institutional boundaries, enabling academic and industrial scientists to cooperate as colleagues, address mutual problems in real time, and begin to understand each other’s cultures. The economic, organizational, ethical, and political challenges in forging these institutional partnerships are many and complex. Experimentation with many trials and errors has been occurring in partnerships all over the country. We need to study what works and what fails, and draw inferences about the pros and cons of different transfer strategies. The for-profit and not-for-profit sectors differ deeply in their missions, cultures, resources, and incentives, and these differences deserve respect. That respect is best demonstrated not by offering prescriptions based on one-sided images of institutional dynamics but by recognizing that creative bridging of traditional divisions of labor is vital to medical innovation, and that this deeply felt practical need is generating exciting ventures in organizational collaboration that deserve close and dispassionate scrutiny.

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