Academic-Industrial Relationships: Opportunities and Pitfalls*

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ABSTRACT: *Over the past 50 years, academic-industrial collaborations and technology transfer have played an increasingly prominent role in the biomedical sciences. These relationships can speed the delivery of innovative drugs and medical technologies to clinical practice, creating important public health benefits as well as income for universities and their faculty. At the same time, they raise ethical concerns, particularly when research involves human subjects in clinical trials. Lapses in oversight of industry sponsored clinical trials at universities, and especially patient deaths in a number of trials, have brought these issues into the public spotlight and have led the federal government to intensify its oversight of clinical research. The leadership of Harvard Medical School convened a group of leaders in academic medicine to formulate guidelines on individual financial conflicts of interest. They and other groups are working to formulate a national consensus on this issue.*

INTRODUCTION

In 1959, C.P. Snow described the clash of "The Two Cultures", the humanities and the sciences. A similar cleavage might be discerned between academia and industry, very different cultures with two very different missions. The academic mission is education and discovery driven by intellectual curiosity, what we in academia like to regard as "pure motives". In industry, the mission is translational research, commercialization, and profit making [Figure 1].

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In the 20th century, a series of breaches arose in the wall between these two worlds, resulting in an increasingly porous interface that has been admired by many and abhorred by some. The first breach came in the fields of technology, engineering, and computer science, when major research universities began to engage in patenting, licensing, and the earning of royalties [Table 1]. During the last 50 years, with the National Institutes of Health and the biomedical research enterprise growing at a rapid pace, the same process has occurred in the biological sciences. New ethical issues have emerged, particularly with regard to agents and devices that must be tested in clinical trials for efficacy and safety before they are approved for general use.

As part of the evolution in academic-industrial collaboration over the past 25 years, most universities have adopted a "20% rule", allowing faculty one day a week to engage in outside activities for which they can be remunerated by honoraria, consultant fees, stock options, or equity. Faculty members have increasingly been permitted, even encouraged, to start companies, and these initiatives have generally been accepted as part of the "new" academic world. Although worries have been expressed about conflicts of commitment, only in rare instances have these relationships been actively monitored.

During the same period, industry has been a growing source of support for basic science research in many leading academic institutions. These relationships with medical schools began most visibly with the Monsanto contracts with Washington University in St. Louis and with Harvard and its affiliated Children's Hospital in the mid-1970s [Figure 2]. The agreement between Massachusetts General Hospital (MGH) and the German pharmaceutical firm Hoechst, formulated in the early 1980s, had by 2000 contributed over $100 million to basic research at the hospital and resulted in the formation of the Department of Molecular Biology comprising basic scientists working on a range of topics from plant to human genetics.

Other academic-industrial collaborations have since evolved. MGH negotiated a major contract with Shiseido to study the basic science of cutaneous biology and the Dana-Farber Cancer Institute has negotiated deals with Novartis. The controversial relationships between the Scripps Research Institute and Novartis have led to intense scrutiny by the federal government, and the involvement of Novartis in supporting basic research in plant genetics at UC-Berkeley has faced opposition from many faculty members. In general, these relationships have been controversial in the beginning, but are now judged to have been successful and productive, providing value to both the academic community and to industry.

As a matter of perspective, despite its prominence in current policy discussions, corporate funding of academic research represents only about 7.5% of total research funding [Figure 3]. In the last decade, however, academic institutions have come to realize that little money is made from licensing agreements and royalties. Only eight universities in the country made more than $20 million in licensing income in 1999. Columbia tops the list at $89 million and the University of California system is second at $74 million. Harvard University brought in about $10 million in 1999 [Table 2]. With the promise of increasing the financial return on academic-industrial relationships, many universities have accepted equity in start-up companies or more

established commercial enterprises. Many start-up companies have become very successful, and stock ownership improves the chances of a more substantial economic return to the research enterprise. This becomes particularly attractive at a time the revenue margins in hospitals have declined precipitously and the subsidy of research from clinical revenues can no longer be counted on. Most large research universities, including Columbia, Johns Hopkins, and Harvard, now permit equity in start-up companies, as do most of the Harvard-affiliated hospitals.

A concurrent nationwide development over the past decade has been the enormous growth of the clinical research enterprise. The clinical trials listing service CenterWatch estimates that about 60,000 U.S. trials were under way in 1998, up from 33,000 in 1990 and 14,000 in 1980. Many for-profit clinical research organizations (CROs) have formed during the past five years, and an increasing number of faculty members are involved in clinical trials of new drugs and medical devices. And with gene therapy and gene transfer, we have for the first time introduced into people biological agents with unpredictable effects—as exemplified tragically by the patient death at the University of Pennsylvania, probably caused by abnormal and unexpected immunological events.

Such developments have led to an increase in the workload of our institutional review boards (IRBs) and the increased intrusion of federal regulators into the clinical research enterprise. Trials have been shut down at Johns Hopkins, Duke, the University of Pennsylvania, and other universities. Informed consent for clinical trial participants has been a subject of much debate, particularly in instances where the investigator or institution has financial ties to the company. Several study groups, committees, and investigations are currently in progress. These include the National Academy of Sciences' Committee on Assessing Integrity in Research Environments, the Association of American Medical Colleges' (AAMC) Task Force on Financial Conflicts of Interest in Clinical Research, the Association of American Universities (AAU) Task Force on Research Accountability, and a survey by the Department of Health and Human Services Office of the Inspector General.

Figure 1: The Two Cultures

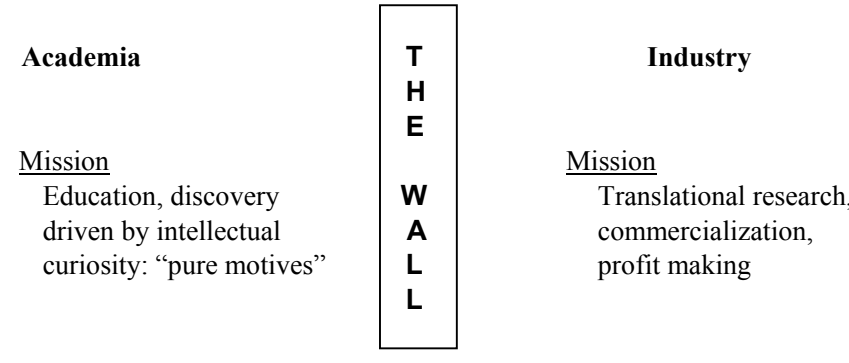
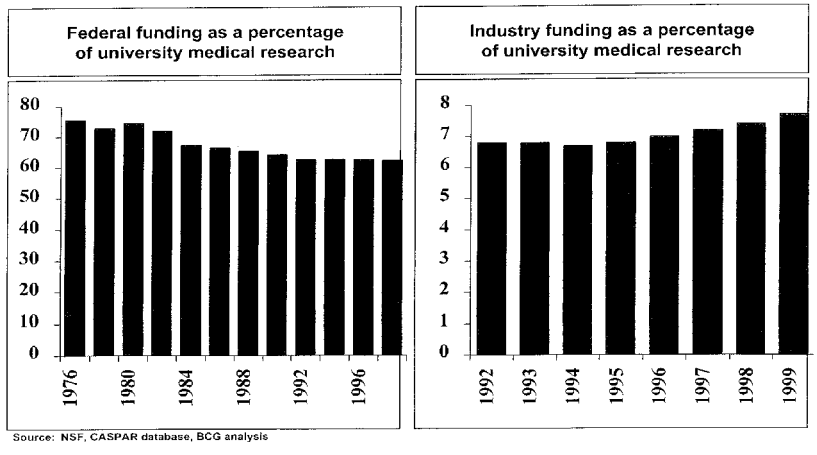


Figure 2: Previous Industry - Academic Affiliations

Washington University	⇨	Searle/Monsanto Merck SNP Consortium
Stanford	⇨	GSK SNP Consortium
Yale	⇨	Bristol-Myers
MGH/Harvard	⇨	Hoechst Shiseido Dupont, Millennium, others
MIT/Whitehead	⇨	Merck, Millennium SNP Consortium, others
Hopkins	⇨	SmithKline Beecham, BMS, others

Figure 3: Industry is an Increasingly Important Source of University Research Support



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ACADEMIC-INDUSTRIAL RELATIONSHIPS: PROS AND CONS

Breaches in the wall separating academic and industrial activities might be considered advantageous in a number of ways. Translational research has facilitated new therapies such as growth hormone, new devices like angioplasty, and new technologies like functional MRI [Table 3]. Interdisciplinary opportunities have been enhanced. At Harvard Medical School, the Institute of Chemistry and Cell Biology was supported with a $5,000,000 gift from Merck. The school has also benefited from discretionary funds from industry that have funded professorships, fellowships, and student scholarships.

On the negative side, concerns have been expressed over "academic medicine for sale"[1] and "uneasy bedfellows",[2] over inadequate compliance with informed consent and the failure of IRBs to ask important questions. Questions have been raised about the effects of industry relationships on traditional academic values [Table 4]. Are students free to pursue their own interests in research? Are publications delayed over results unfavourable to a company? What happens to free and open academic exchange in an environment in which research is supported by for-profit entities? At the same time, researchers are wary of the expansion of federal regulations that has resulted from the concerns noted above.

The positive aspect of these relationships is that they facilitate the mission of all medical schools and teaching hospitals: to find treatments for the ills that afflict humankind. On the negative side is the real or perceived conflict of interest, personal or institutional gain, personal enrichment and fame that defiles the public trust in our endeavours, spawning suspicion and distrust from our patients and the public about our search for truth.

Table 1: Breaches in the Wall

- Institutions accept equity (1995-2000)
- Clinical research expands
  - IRB workload increases
  - Informed consent guidelines challenged
  - Conflict of interest disclosures critical
- Clinical research organizations formed (1995-2000)
  - Quintiles *et al.*
  - Increased participation of private practitioners in clinical trials
- Gene therapy: introduction of biologicals into humans (1995 -2000)
  - Gene therapy advocates move biologicals into human clinical trials

  Body responses to biologicals unpredictable

Table 2: Top 20 U. S. Universities by Licensing Income, Fiscal 1999

Institution	*Licensing Income (millions of dollars)*
Columbia U.	89.2
University of California system	74.1
Florida State U.	57.3
Yale U.	40.7
Washington Research Foundation, U. of Washington	27.9
Stanford U.	27.7
Michigan State U.	23.7
U. of Florida	21.6
Wisconsin Alumni Research Foundation, U. of Wisconsin (Madison)	18.0
Massachusetts Institute of Technology	16.1
Emory U.	15.3
State U. of New York Research Foundation	13.5
Baylor College of Medicine	12.3
New York U.	10.7
Johns Hopkins U.	10.4
Harvard U.	9.9
North Carolina State U.	7.8
Tulane U.	7.6
Washington U. (Missouri)	7.0
California Institute of Technology	6.5

Source: Association of University Technology Managers. Adapted from a more detailed data presentation that appeared in *The Chronicle of Higher Education,* Nov. 24, 2000, Vol. XLVII, No. 13, p. A49. Reproduced by permission of the Association of University Technology Managers.

Table 3: Breaches in the Wall: *Pros*

1. Translational research facilitated
   - new therapies (growth hormone)
   - new devices (angioplasty)
   - new technologies (fMRI)
2. Interdisciplinary opportunities enhanced
3. Discretionary money for academic programs: Institutions foster offices of technology licensing
4. Professorships, scholarships, fellowship support
5. Acculturation of the academic and industrial communities

Table 4: Breaches in the Wall: *Cons*

1. Conflict of Interest (money)
2. Conflict of Commitment (time)
3. Loss of Public Trust
   - "Academic medicine for sale"
   - "Uneasy bedfellows"
   - Inadequate compliance with informed consent, IRBs
4. Expansion of federal regulations including fines
5. Conflict of academic interests
   - students, publication delays
   - manuscript debates
6. Loss of freedom of academic exchange

CURRENT UNIVERSITY CONFLICT-OF-INTEREST PRACTICES

Several publications have reviewed institutional management of potential conflict of interest. Cho reviewed 89 of the top NIH-grantee institutions.[3] She found that 55% of institutions required disclosure from all faculty, 45% required disclosure from principal investigators only, 19% set limits on financial ties to corporate sponsors, and 70% specified sanctions for non-disclosure. Most university policies lacked specific guidelines on the sanctions for violations of the rules. None required disclosure to patients. The procedures these institutions used to manage conflicts included disclosure (89%), disclosure to the public (58%), monitoring of the conflict (68%), divestiture (57%), disqualification from the project (47%), modification of the protocol (36%), and placing equity into escrow (rarely done).

Boyd surveyed faculty at the University of California, San Francisco,[4] finding that 7.6 percent of UCSF faculty members reported financial relationships with industry. Approximately one third of this group reported each of the following: speaking fees (ranging from $250 to $20,000 per year); income from consulting ($1,000 to $120,000 a year); and membership on science advisory boards or boards of directors. Fourteen percent held equity, 12 percent had multiple financial ties, and a university review panel recommended managing about a quarter of the conflicts that were disclosed.

Lo *et al.* surveyed conflict-of-interest policies at the top 10 NIH grantees: Baylor, Columbia, Harvard, Hopkins, Penn, UCLA, UCSF, Washington University, University of Washington, and Yale.[5] Four of these institutions required disclosure from all research staff and five required disclosure for any amount, including amounts below the federal threshold of $ 10,000. Six institutions required disclosure to the Institutional Review Board in some way or another, and four had stricter policies when clinical and

patient-oriented research was involved. The authors wrote that "The conflict of interest clauses at most leading universities are substantially weaker than policies adopted in large industry-sponsored clinical trials." This means that the companies testing agents in clinical trials are often more strict about limiting participation by investigators who held a financial interest in the research than are the academic institutions involved.

CONFLICT-OF-INTEREST DISCUSSIONS AT HARVARD MEDICAL SCHOOL

Several years ago, Harvard Medical School was faced with the question of what the school's position should be on financial conflicts of interest. A committee deliberated vigorously about this issue over a period of about 18 months, and in the end was split in its recommendations. The school's leadership decided to put on hold any changes, and wait to see whether a national consensus would develop on this issue In a published commentary,[6] Dennis Kasper and I summarized our position as follows:

- We believe that the public deserves to know that the biomedical research they support will be a search for truth uncontaminated even by a perception of bias.
- They deserve to expect that discoveries with the potential to improve health are rapidly translated in practice to clinical trials.
- They deserve to feel confident that their participation in the development of new therapies will be safe, with full informed consent obtained at the outset and access to outcome data provided afterwards (something rarely done in clinical trials).
- The public deserves to be assured that neither the decision to ask patients to participate in clinical trials nor the assessment of the risks that patients may incur will be prejudiced by an investigator's personal profit motives.

The next steps for Harvard Medical School will include the formation of a faculty/trustee advisory committee that will be charged with reviewing the school's current conflict-of-interest policies, considering the AAMC guidelines, and recommending revisions to the school's policies. Another major task will be to consider issues of institutional equity.

ACADEMIC HEALTH CENTERS WORKING GROUP

In November 2000, Harvard Medical School convened leaders from about 20 institutions, including the top 10 NIH-grantee universities surveyed by Lo, several state universities, and Memorial Sloan-Kettering Cancer Centre. The group, which convened in November 2000 and released its findings in January 2001, made the following recommendations:

Statement of Purpose

Protecting human participants in research and maintaining the integrity of biomedical research are of paramount importance to American medical schools, teaching hospitals, and research institutes. Industrial collaborations are essential if patients are to benefit

from the translation of biomedical research into clinical practice. However, the potential financial conflicts of interest that may arise from these relationships require that we have consistent and adequate standards for managing such conflicts. We therefore propose a set of principles and guidelines to be used by American medical schools, teaching hospitals, and research institutes as they review and refine their own institutional policies. In proposing these principles and guidelines, we note that we are addressing potential conflicts of interest on the part of individuals and not of institutions. Issues of institutional conflict of interest are also important ones, which merit separate and careful review and consideration. We have organized the proposed guidelines into three areas: policy issues, disclosure, and implementation and review.

Proposed Guidelines on Policy Issues

Every medical school, academic teaching hospital, and research institution should have a written policy on financial interests related to research.

The policy should apply to individuals who are directly involved in the conduct, design, or review of research including faculty, trainees, students and administrators.

The policy should include both a statement of general principles and a clear delineation of the activities and the levels and kinds of research-related financial interests that are and are not permissible, and those that require review and approval. The policy should specifically address the special circumstances surrounding research involving human subjects. Individuals involved in the conduct, design, or reporting of research involving human subjects should not have more than a clearly defined minimal personal financial interest[a] in a company that sponsors the research or owns the technology being studied.

Financial interests covered by the policy should include fees, honoraria, gifts, and other emoluments for consulting or lecturing; equity interests including stock options and expectations of receiving equity interests; and directorships, executive roles, and other special relationships with companies having the potential for personal material gain.

The policy should stipulate whose financial interests, in addition to those of an individual involved in the research, could pose a conflict of interest for that individual.

All key terms in the policy, such as "family" and "financial interests", should be clearly defined.

Any financial interests deemed by the institution to be allowable, such as equity interests in mutual funds, should be clearly delineated in the policy. The policy should clearly state the procedures to be followed in disclosing financial interests, reviewing disclosure forms, implementing the policy, appealing decisions concerning the policy, and sanctioning non-compliance with the policy.

The policy should clearly define the range of possible sanctions for non-compliance, up to and including dismissal, and reference the procedures to be followed in the sanctioning process.

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a. This statement reflects the inability of the group to reach consensus on financial limits.

There should be coordination among the various offices of the institution dealing with research and conflict of interest, including committees on human subjects protection, institutional review boards (IRBs), offices of technology transfer, and other administrative units.

Proposed Guidelines on Disclosure

Faculty, trainees, students, and staff who participate in research should periodically and prospectively disclose all related financial interests; interim updates should be required whenever situations change.

Disclosure of related financial interests should be made to specifically designated institutional offices and to the research funder. In the case of funding by a federal agency, disclosure should be made in conformance with federal requirements.

Faculty, trainees, students, and staff who participate in clinical research should disclose related financial interests to IRBS. Each IRB should have responsibility for ensuring that patients are informed of such relationships as the IRB determines is appropriate.

Faculty, trainees, students, and staff should disclose all related financial interests in any publications and presentations, including presentations made both within and outside the institution.

Biomedical science journals should require the disclosure of related financial interests as a condition of publication.

Proposed Guidelines on Implementation and Review

Every institution must have a mechanism to assure dissemination of the policy to faculty, staff, and students, and to provide appropriate education and training in the policy.

Faculty and research staff should be required to acknowledge formally that they have read and understood the policy.

There should be requirements for regular periodic reporting as well as interim updates utilizing a reporting disclosure form.

Disclosure should be made at multiple levels within each institution. These should include disclosure to the Dean, CEO, or the equivalent individual who has ultimate responsibility for monitoring the activities of the faculty, staff, and students; and disclosure to the department chair(s).

Each institution should have an advisory policy oversight committee which has broad representation of faculty, administrative staff, and possibly lay representatives. The committee should be charged with:

- providing oversight of the policy
- reviewing cases brought before the committee
- recommending monitoring procedures for exceptional cases when appropriate.

Monitoring policies and procedures should be prospectively defined.

The conflict of interest (COI) oversight committee should be advisory to the dean, CEO, or equivalent individual. The dean or other responsible party may also appoint ad

hoc monitoring committees on a case-specific basis, and should have final authority to determine the need for monitoring in specific circumstances. Overall institutional compliance with the policies should be monitored using the institution's internal audit mechanisms.

Conflicts between faculty should be resolved by the COI oversight committee with recommendations to the Dean, CEO, or equivalent individual who has the ultimate authority to define the terms of a final resolution.

There have been several important developments regarding conflict-of-interest policy in recent months. Greg Koski was appointed in September 2000 to head the newly restructured Office of Human Research Protections within the Department of Health and Human Services (DHHS). He has aggressively proposed new regulations for IRBs and the reporting of adverse effects. His office has been aggressive in shutting down clinical research at some of our most prestigious institutions. The most dramatic recent action was taken against Johns Hopkins University in July 2001 after the tragic death of a volunteer in a trial of pharmacologically induced asthma.

In December 2001, the Association of American Medical Colleges (AAMC) released the first report of its Task Force on Financial Conflicts of Interest in Clinical Research.[7] The task force includes leaders in academic medicine, clinical investigators, patient representatives, drug and device company executives, former legislators, and journalists. The report offers a model for baseline standards and practices for the oversight of individual financial interests in human subjects research, and is designed to cover faculty, staff, students, fellows, and trainees at AAMC member institutions. It includes core principles to guide policy development, suggests the appropriate scope and substance for such a policy, and defines key terms. Among its principal recommendations are that academic institutions presume that a 'financially interested individual'—defined as any researcher holding a significant, financial interest in human subject research—may not conduct the research in question, and that the researcher may rebut this presumption only by demonstrating to a review body compelling reasons to do so.

The AAMC task force has now begun to consider the equally important issue of institutional conflicts of interest: the disposition of equity by institutions that may have a stake in the outcome of a developing pharmaceutical product or medical device, or the financial holdings of institutional board members. Its second report, scheduled for release later in 2002, will address institutional financial interests in human subjects research.

The Association of American Universities (AAU) also convened a blue ribbon committee to develop guidelines, which were published and circulated in October 2001.

Moses and Martin suggested that a separation of these holdings from the leaders of the institution would serve the public's interest.[8] We proposed several models. One would place the holdings at arm's length in a "mutual fund" type of portfolio with holdings of more than one institution held in a shared arrangement, as some of our leading institutions currently do with malpractice insurance.

CONCLUSION

In closing, a few points deserve special emphasis, First, collaboration between academic institutions and the industrial community is essential. Many drugs and devices that benefit our patients have arisen from these collaborations. Faculty members are often energized by collaboration and are, as a result, more entrepreneurial and productive. However, the public loses trust in our institutions if they fail to effectively police these collaborations.

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