INNOVATION

Biomedical Innovation in Academic Institutions: Mitigating Conflict of Interest

Lita L. Nelsen[1]* and Barbara E. Bierer[2,3]*

As universities and research hospitals move increasingly toward translational research and encouragement of entrepreneurship, more attention must be paid to management of conflicts of interest (COIs) if the public trust is to be maintained. Here, we describe COI policies at two institutions that aim to structure an academic environment that encourages innovation while protecting academic values.

Translational medical research is an important, legitimate, and necessary enterprise for scientists in universities and research hospitals. Indeed, a central goal of academic medical institutions is to ensure that their innovations ultimately benefit patients. The translation of innovative technologies into clinical practice occurs through the creation and testing of diagnostics, therapeutics, and devices. This path may include drug screening, medicinal chemistry, product formulation, prototype development for devices, preclinical testing in cells or animal models, and early clinical trials. Depending on its capabilities and financial resources, an academic research institution may perform or outsource these functions or form industry partnerships. Such collaborations can include preexisting companies or ones that were created to focus specifically on the translation of an invention owned by the institution (start-up companies). The degree of collaboration between a research institution and a company may be minimal (for example, a simple license agreement) or may include joint research projects with or consulting by university investigators. Such research collaborations inherently present conflicts of interest (COIs), both for the investigators and their institutions, that are complicated further by differences between a nonprofit organization and a for-profit company. Here, we discuss policies and management procedures that our two institutions, and others, use to manage COIs.

The Massachusetts Institute of Technology (MIT) began granting exclusive licenses to and taking equity in start-up companies in 1987. Because this was a relatively new activity for universities at the time, MIT was cautious about possible consequences and decided on a conservative approach with fairly strict ground rules; these strict "experimental" policies have not changed over time and have served the university for more than two decades of technology licensing and the founding of several hundred companies (Fig. 1). The policies of Partners HealthCare and Harvard Medical School (HMS) evolved more gradually and include additional safeguards to protect patients and research subjects but otherwise are quite similar to those of MIT. As academic institutions increasingly engage in translational medicine research, questions will arise as to whether these policies continue to be sufficient, whether they need to be reframed in order to help bring new medicines and devices to the public, and whether additional safeguards are needed.

Fig. 1. Food for thought. Academic institutions have sharpened their focus on translational medicine research, which necessarily includes the promotion of biomedical innovation and encouragement of entrepreneurship. If they are to maintain the public trust, universities must manage the myriad COI challenges associated with translational science.

AVOIDING CONFLICT, NURTURING DISCOVERY

Although the policies described below are specific to our institutions and based on our experiences and environments, the principles elucidated are broadly applicable. COI policies and management processes are based on preserving academic integrity and the academic mission and broadly include the following parameters:

Preservation of discovery and public dissemination of research. Of great concern in academic institutions and among policy-makers and industry leaders is whether an emphasis on translational application (working toward a product) will lead to the neglect of fundamental scientific research and loss of the freedom to choose one's research focus and engage in curiosity-driven discovery—with long-term consequences for the academy and the public. Furthermore, increasing amounts of commercially driven research projects, particularly in collaboration with companies, may inhibit publication and lead to a culture of secrecy within the academic institution. As academic institutions become more and more dependent on industrial support, universities may be forced to succumb to industry's demands for confidentiality of data or to take on "work for hire" instead of allowing investigators to choose their own research directions.

A number of factors inherently, and institutional rules advertently, mitigate these potential concerns. Academic rewards, including promotion and funding from governments and foundations based on peer recognition, depend on performing innovative research and on publication of the results. Many institutions purposely do not factor patents or commercialization success into the promotion process and tenure review. In their collaborations with in-

[1]Technology Licensing Office, Massachusetts Institute of Technology, Cambridge, MA 02139–4307, USA. [2]Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA. [3]Harvard Medical School, Boston, MA 02115, USA.
*Corresponding authors. E-mail: lita@mit.edu (L.L.N.); bbierer@partners.org (B.E.B.)

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dustry, academic institutions contractually insist on the right to publish (at least their own research results) without censorship by the industrial collaborator or undue delay in publication (*1*).

Several institutions, including our own, have entered into novel comprehensive, multiproject, multiyear "umbrella" agreements with industry. Specific research projects initiated by principal investigators in the institution's academic laboratories are selected by a steering committee with equal representation from company executives and independent academic faculty. The faculty committee members are charged with ensuring that the projects have academic merit and contribute to fundamental discovery.

In addition, many institutions review and regulate sponsored research support for faculty members who have an equity interest in the company that provides the support. With a single (historical) exception for Phase I Small Business Innovation Research grants and Small Business Technology Transfer grants from the U.S. government, MIT will not accept research support from private or small public companies in which the investigator or the institution holds equity, whether the funds come from the company itself or from collaborative government grants. At HMS and Partners HealthCare, a faculty member may not receive sponsored support for research in which he or she or a family member has equity in the company, private or public, above a certain de minimus threshold. Ensuring that the funds that support research are segregated from personal financial interests is an important control against the perception of, or actual, bias.

Protection of students and trainees. Faculty members are expected to ensure that graduate students and postdoctoral fellows engage in research projects of sufficient academic merit that the students' research training and publication opportunities are not compromised. In sponsored research with industry, our institutions insist that students not be burdened with confidential information that would prevent free discussion of their research within the institution or credible publication. Institutions mandate that students will not be asked to work on projects for their supervisors' companies, and policies specifically forbid part-time or summer hiring of students by a faculty member's company while that student is under the faculty member's academic supervision. Further, institutions often require disclosure of any COIs of a supervising faculty member and will provide an independent institutional resource from which students can seek guidance.

Protection of patients and transparency. Of greatest concern, however, is the protection of patients and research subjects and preservation of the public trust. Although individuals and the public can benefit greatly from academic-industry partnerships, there is growing concern that the financial interests of faculty and institutions may engender subtle coercion in the management of clinical trials and research (for example, trial-enrollment decisions), compromise professional decision-making and evaluation of data, and jeopardize scientific integrity. The concern is most evident in clinical trials but is applicable to preclinical research (for example, efficacy and toxicity experiments in animal models) because these data form the basis for applications for clinical trials and ultimately for new product marketing submitted to the U.S. Food and Drug Administration (FDA). Adding to the concern is the observation that reports of product-related scientific studies that are supported by industry are more likely to be published and contain positive results than are studies funded by the federal government (*1*, *2*).

Fundamental to any appropriate management is the periodic and complete reporting of all relevant financial relationships with industry by each faculty member, coupled with institutional review of individual and institutional COIs, delineation of management plans as appropriate, and adequate oversight for compliance. Many institutions have adopted a zero-dollar threshold for reporting to avoid any confusion or misunderstandings as to reporting expectations. Further, reporting is both annual and transactional so as to ensure that each faculty member reviews their financial interests at the appropriate time to determine relevance and importance. The cornerstone of any management plan is disclosure of any relevant financial interests—including licensed and filed patents, payments for consulting or other industry services, equity, and other financial interests—to trainees, collaborators, and institutional review boards (IRBs) and, as dictated by the IRB or institution, to potential research subjects and in all publications. HMS and Partners HealthCare uphold an outright ban on faculty participation in clinical research on a technology developed by a company in which the faculty or a family member has a consulting relationship (above a de minimus threshold), holds equity or ownership (in any publicly traded company above a de minimus threshold or in any private business), or has any other business interest. Postmarket royalties obtained through the inventor's institution are excluded from this consideration, although the institution is expected to manage the relationship in this event. Most other medical research institutions do not have an outright ban on participation in such clinical trials; rather, they endorse careful oversight and a rebuttable presumption—one that is assumed to be true unless shown otherwise.

Participation in company-related research is not allowed except in rare and compelling circumstances (for example, the individual's participation is essential for the research, and adequate measures exist to ensure the integrity of the research), and this strict and restrictive policy holds for all individuals responsible for the design, conduct, and reporting of clinical trials. Institutional COIs, including conflicts of senior officials, in proposed research are similarly evaluated, and mechanisms for management of the conflicts are devised by an appropriate institutional committee and the IRB—groups that have appropriate independence and authority.

Many circumstances require the involvement of a potentially conflicted investigator or institution, and additional measures may be introduced to manage the apparent conflict. The permissibility of involvement and the management plan are adjusted according to the risk of the study, the necessity of the participation, and the level of the financial conflict. In addition to disclosure, measures used to ensure that patients and research subjects are protected include (i) disclosure as outlined above; (ii) limitation of the involvement of the individual in study design, subject selection (inclusion/exclusion) criteria, subject recruitment and enrollment (including process of informed consent), clinical intervention and care, data analysis, and manuscript preparation; (iii) independent review of data elements, adverse events, and data analysis; and (iv) limitation of the number (for example, <10% of the total) of enrolled subjects from the institution in a multisite trial. As with all research, reduction, restriction, or divestiture of the financial interest remains a potent management tool.

Protection of institutional credibility. Although academic institutions have long been careful to protect themselves

from legal liability in their technology licensing and commercialization programs, an additional concern is protection of the institutions' credibility and reputation as an honest broker in societal concerns. Any perception that an institution's recommendations, particularly in medical and scientific issues, might be influenced by commercial concerns would be harmful to the institution's faculty and students—and to society at large.

Start-up companies, particularly when equity is involved, present a particular hazard. MIT, for instance, is concerned to avoid any implication of control of its companies. When it holds equity, the institution is a minority owner—generally with far less than 10% ownership of the company. MIT does not invest in the first round of funding of its start-up companies (relying on "the market"—that is, outside investors—to set the value of the companies) and does not take a seat on their boards.

Our institutions are conscious of the power of our brand and trademarks, as they might be used to enhance public perception of the quality and value of products and companies. As a result, we license our trademarks only to insignia items (sweatshirts and key chains, for example) and will not include licenses to our trademarks with our licenses to patents for products or services.

THE FUTURE: TRANSLATIONAL RESEARCH

As research institutions increasingly engage in translational research, the traditional policies and COI management procedures may not be adequate or even relevant in some situations. As research moves further toward product development, traditional emphasis on "discovery" and publication becomes less relevant, and the safeguards discussed above offered by peer review become less influential. Different skills may be required of faculty and staff, and promotion and tenure may need to be based on criteria different from those currently used. And as financial returns become more relevant, new incentive systems for faculty, students, and staff need to be developed.

Students are now actively seeking training specifically in biomedical product design and development and may also seek opportunities to work toward a specific objective rather than dedicate their careers to basic discovery research. The convergence of biology, engineering, and technology initiatives has resulted in new avenues of research that are targeted to a specific medical need, rather than hypothesis-driven research in traditional programs oriented to future academic research careers. In order to better serve graduate students and postdoctoral fellows who aspire to engage in translational research or careers in industry, academic institutions should give serious consideration to developing educational tracks that are distinct from ones oriented toward research careers in academic institutions.

A further complicating issue is the availability of research funding. Most translational research funding has and will continue to come from industry or other private investors or the institutions' internal funds rather than from federal agencies. Some institutions have already developed their own venture or "accelerator" funds for such work, whereas others have invested in specialized laboratories. Whether the funds are from industry, outside venture capital funds, or the internal institutional funds, return on investment or financial sustainability is usually expected—although successful business models for this early stage of product research and development are not yet clear. It is apparent, however, that these models will require features more typically associated with business rather than academic strategy and management. Projects may be chosen more on the basis of their probability of financial success than social benefit, and academic researchers will have to learn to work with clear milestones, oversight, and discipline and not diverge into new directions that might be scientifically intriguing. Royalties or equity from technology transfer will be viewed as vital for sustainability rather than as unanticipated windfalls that are the by-products of basic research.

The increased interest in and emphasis on translational research in academic institutions is relatively new. Thus, the policies and management of COIs are evolving as the institutions become more aware of the differences that such research presents compared with the traditional discovery research model. Wisdom will be required.

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