Managing innovation: university-industry partnerships and the licensing of the Harvard mouse

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DuPont's Oncomouse patent licensing program continues to cause a stir in academia and industry.

Over the last several decades, technology and technological innovation have gradually replaced manufacturing and agriculture as the main drivers of the US economy. The unparalleled system of American research universities[1] and their association with industry are important drivers of the new economy. The relationship between universities and industry is multifaceted, encompassing exchanges of knowledge, expertise, working culture and money. Whereas the transfer of technology from universities to industry has been going on for more than a century, ties between university and industry have grown during the past three decades, coinciding with the growth in biotechnology[2].

These university-industry interactions can generally be categorized as collaborations and research partnerships, with industry supplying financial support to universities in exchange for options on developed technologies and inventions. The most successful interactions result in discoveries being licensed to and developed by industry in exchange for upfront and downstream monies[3]. Indeed, the current paradigm for biotech development is based on such partnering[4]. These partnerships have been encouraged and stimulated by several factors: passage of legislation, most notably the Bayh-Dole Act of 1980, corporate restructuring in the 1980s resulting in reduced industry R&D spending and scarcer federal R&D funding. Increased technology transfer has sparked a debate on universities' roles in the national economy: on the extent to which these relationships affect the mission of universities to carry out and disseminate the results of basic research, and on how universities can manage their partnerships, collaborations and technology transfer without compromising their mission.

In the basic research paradigm, investigators' inquiries are directed toward developing an understanding of scientific phenomena. Results from basic research sometimes lay a foundation for advancements of enormous commercial significance. However, as technology-based industries have grown and become more complex, so has the relationship between universities and industry. Issues arising related to intellectual property, rights to publish research results and academic freedom have caused many to reexamine university-industry partnerships in relationship to their value to public health, education and the economy.

Much of the discourse concerns how and whether the partnerships and subsequent licensing can be strategically designed and managed to promote innovation, technology development, proper risk-rewards incentives and public health[5]. One aspect of this partnering that has come under scrutiny is deals that give the funding corporation 'first rights' to develop and commercialize results from sponsored university research discoveries.

Because substantial federal support is often used to develop academic research before industrial partnering, how can the agreements governing these partnerships be optimized for mutual near- and long-term benefits to the parties? Recently this dialog has been focused on DuPont's licensing of the transgenic 'Harvard mouse,' subsequently trademarked as the Oncomouse[6].

The Oncomouse patents

DuPont's patent licensing program for 'Oncomouse technology' has caused a stir in academia and industry for over a decade[7]. These patents broadly claim transgenic nonhuman mammals expressing cancer-promoting oncogenes, a basic research tool widely used in the fight against cancer. The Oncomouse technology provides an important tool useful for the initial testing of many new and promising cancer treatments. Balancing academic access to this tool with DuPont's rights to the technology has proved to be a challenging undertaking that presents an interesting backdrop against which policy considerations implicated by research tool licensing can be viewed. DuPont's increasingly aggressive approach to licensing Oncomouse technology ultimately made academic institutions and the US National Institutes of Health (NIH) cry foul in response to concerns that compliance with onerous license terms would seriously affect the basic research mission of universities and hinder the search for new cancer therapies. In 1999, after four years of negotiations[8], the NIH and DuPont arrived at a memorandum of understanding (MOU) that allowed NIH researchers and grantees to use the Oncomouse technology for basic research without charge, provided that the research did not directly benefit commercial interests or a for-profit institution[9]. However, this did not stop DuPont from continuing to make aggressive licensing demands on academic and research institutions.

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In response to such demands, the University of California asserted that it is entitled to the same royalty-free use of the Oncomouse technology accorded to the NIH. Citing specific provisions of the 1999 MOU, the University of California countered DuPont's demands with an offer to take a license to the Oncomouse technology on the same no-cost terms and conditions provided to the NIH as described in the MOU. On October 28, 2003, NIH informed DuPont that it felt that the University of California's position was "consistent with the intent, terms and conditions" of the 1999 MOU. With this pronouncement, the University of California and NIH have put into serious question DuPont's ability to collect royalties for the use of the Oncomouse technology by universities and nonprofit institutions conducting cancer research.

Development of the Oncomouse at Harvard

Building on the original transgenic work of Gordon and Ruddle at Yale[10], the Oncomouse (or Harvard mouse) was developed in the laboratory of Harvard professor Philip Leder in the early 1980s (ref. 11). This transgenic mouse expressed the mouse mammary tumor virus (MMTV)-myc oncogene, and so was prone to developing a variety of different tumors[12]. In 1988, the Harvard mouse became the basis for the first US patent granted to a higher organism[13]. Subsequent patents broadly claimed an entire class of transgenic nonhuman mammals and methods to produce them[14]. These patents claim not only transgenic mice expressing c-myc, but essentially any nonhuman mammal that expresses any cancer-causing transgene. Thus, a transgenic mouse created at a university that expresses a different oncogene and develops different types of cancers would likely infringe the broader claims of the Harvard patent portfolio.

DuPont's contribution to the discovery of the Oncomouse was in the form of a $6 million donation it made to Harvard to support Leder's research. The grant was provided in 1981, when Leder left the NIH to join the faculty of Harvard Medical School. In 1981 and the subsequent year, Leder also received NIH funding to study the regulated expression of "genes of man and the mouse"[15]. By 1983, Leder and his colleagues had made the initial c-myc transgenic mice, characterized their propensity for developing cancer and filed their initial patent applications. The first patent, entitled "Transgenic nonhuman mammals," was awarded in 1988. Although the patents arising out of Leder's work were assigned to Harvard, DuPont was entitled to an exclusive license (with a right to sublicense) to all inventions in consideration of its financial support. Initially, DuPont's license fees for use of the mouse in basic research were nominal, and the license carried with it very few restrictions[16]. Use of the technology proliferated quickly. DuPont collaborated with Charles River Laboratories to further develop the Oncomouse and other transgenic cancer-prone mice. But in the mid-1990s, DuPont began negotiating licenses with substantial monetary fees from commercial entities and licenses from academics that were unusually restrictive[17], for example, requiring universities and their researchers to file frequent reports on their use of the technology. It also reportedly asked researchers to seek DuPont's approval before sharing the results of research performed using the mice with commercial or nonprofit entities[18].

On July 1, 1999, DuPont and NIH signed the memorandum of understanding allowing "public health service" scientists to use Oncomouse-related patent rights in biomedical research free of charge provided that such use was not "for any commercial purpose or for the direct benefit of any for-profit institution."

The NIH-DuPont MOU

The cancer research community, by now accustomed to using transgenic test subjects without significant charge or limitation, viewed DuPont's activities as a significant encroachment. Indeed, the licensing terms proposed by DuPont, one commentator noted, effectively allowed the company to "leverage its proprietary position in upstream research tools into a broad veto right over downstream research and product development"[19]. One of the most prominent voices among those decrying DuPont's actions belonged to the NIH. High-level negotiations ensued during which NIH emphasized the importance to public health in having unimpeded access to the research tool, and it was rumored, the use of public funds in the initial discovery.

On July 1, 1999, DuPont and NIH signed the memorandum of understanding allowing "public health service" scientists to use Oncomouse-related patent rights in biomedical research free of charge provided that such use was not "for any commercial purpose or for the direct benefit of any for-profit institution"[20]. The MOU went on to enumerate two specific activities that would fall into this exception if undertaken for a commercial purpose or the direct benefit of a for-profit institution: testing compounds or using the mice to produce products. The terms and conditions of the MOU were to apply to research conducted by the public health service or "recipient institutions," defined as organizations that received NIH funds to conduct research.

The University of California solution

Although this agreement apparently solved the problem for the NIH, DuPont continued to make demands on universities[21]. The importance of the mice as a basic testing tool created an uncomfortable situation for academic institutions, creating huge pressures for some to take a license from DuPont rather than jeopardize ongoing research.

Universities that DuPont approached received NIH funds, and therefore were properly considered "recipient institutions" covered by the MOU. But DuPont argued that university research sponsored by commercial entities, or "sponsored research," should be subject to license terms beyond the MOU. DuPont asserted that such research provided a "direct benefit" to sponsors that were commercial, for-profit entities. On this basis, DuPont refused to acknowledge the applicability of the NIH MOU terms to sponsored research projects.

The University of California disagreed. Sponsored research conducted at the university's campuses is for the "direct benefit" of the university and its research mission, it argued. Indeed, the university has a long-standing official policy of insisting that university research be conducted in an open academic environment, and in a manner consistent with the freedom to publish[22]. In addition, intellectual property derived from sponsored research is consistently assigned to the university. These policies, as well as the outcomes of collaborations, the university felt, support that the 1999 MOU, and nothing more, should govern the university's use of the Oncomouse technology[23]. In the university's view, the up-front licensing fees that DuPont requested in many circumstances dwarfed the overall value of the

sponsorship, and severely restricted the ability of universities to participate in sponsored research projects with companies interested in using mice that are arguably covered by Harvard's patent claims.

Industry-sponsored research represents a vital source of funding for the University of California and for universities in general. As an example, such funding at the University of California San Francisco increased nearly fivefold from 1992 to 1999 (ref. 24). Nationwide, sponsored research represented 9% of overall research funding at universities in 2000 (ref. 25).

Against this backdrop, and on behalf of its ten campuses and five medical centers, the University of California addressed the issue with DuPont head on. The University of California argued that the university, as a recipient of NIH funding, was entitled to take a license under the same terms 1999 DuPont/NIH agreement. As the university pointed out, the MOU specifically provided that "DuPont agrees that it shall make Harvard Patent Rights available for use by nonprofit recipient institutions under separate written agreements in accordance with the terms and conditions outlined above." DuPont asked the University of California to solicit NIH's opinion on this argument. The director of the office of technology transfer at the NIH responded to the University of California's request in late October 2003, concluded that the university's interpretation of the MOU was correct and that, "The PHS-DuPont MOU clearly provides for NIH nonprofit recipient institutions to be offered the same terms and conditions as those in the PHS agreement"[26].

A solution for all academic institutions?

Although other institutions may have already signed licenses with DuPont, the MOU expressly provides that its terms supercede those of any other agreement: "DuPont agrees that any nonprofit recipient institutions currently licensed under the Harvard Patent Rights may amend its license, in a separate written agreement, in accordance with the terms and conditions outlined above." The NIH has essentially stated that the University of California institution can license the Oncomouse technology on the same terms and conditions as the NIH, as provided for in the MOU. Applying this same logic, other "recipient institutions" may also avail themselves of these license terms and even apply them in place of terms that may already exist. DuPont has not conceded to the applicability of the MOU terms to sponsored research at UC, however, so the issue presently remains unresolved.

The current situation highlights many of the issues raised by the growing ties between university and industry. These ties have come under increased scrutiny in the United States and abroad, as institutions and governments try to maximize innovation, advance public health and stimulate the economy. Although the outcomes of these closer relations have generally been viewed positively, one byproduct has been increasing scrutiny of, and as the Oncomouse case shows, threats to academic research environments. As the narrow scope of the common law research exemption has recently been clarified[27], many academic institutions are finding the task of fulfilling their basic research mission vulnerable to legal problems. As the Oncomouse case illustrates, nowhere is this problem more pointed than in the case of research tools, which are often much more difficult to "work around." The potential for society to lose out when access to these tools, which themselves enable further advances, is restricted is arguably much greater than in the case of more conventional inventions that have limited applications.

The ramifications of limiting access to research tools reach far beyond the academic laboratory. Fears that the hold-up costs to society of limiting access to Oncomouse technology would be too great originally motivated the formation of the NIH MOU to make the technology widely available at no cost to public health researchers and their affiliates. Now in this latest chapter, similar concerns have led the University of California to position the academic community, as affiliates of the NIH, and the general public, as beneficiaries of its work, to reap the benefits of the MOU.

In the case of the Oncomouse, the progress of cancer research is advanced by making the technology widely available to all researchers, including those working in industrial settings, on commercially reasonable terms. Providing significantly disparate access to the technology as between research institutions, academic campuses and industry laboratories could prevent the development of a 'gold standard' mouse to be used in cancer testing across settings. Licensing agreements should be structured to encourage, rather than suppress, widespread use of such technologies while also providing just rewards to DuPont and others taking risks in the ventures that produce them. The success met by the licensing scheme set by another seminal set of research tools, recombinant DNA technologies, could be instructive in this regard. Patent-holders Stanford University and the University of California licensed these technologies on terms that included a small upfront payment and reasonable royalties. It is thanks to schemes such as this that the biotech industry was allowed to develop in its early years, producing numerous life-saving and health enhancements and growing into the multi-billion dollar industry it is today.

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22. See, for example, Policy Guidelines Governing Openness and Freedom to Publish (http://www.spo.berkeley.edu/Policy/ucmemos/publish.html), and Principles Regarding Rights to Future Research Results in University Agreements with External Parties (http://www.ucop.edu/ott/preamble.pdf).
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