The changing role of universities and research institutions in a global economy: lessons drawn from the US biotechnology sector

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The global economy places great emphasis on science-rooted technologies. Hence university-educated students and university–industry research collaborations have become the focus of future plans of both government and industry worldwide. Traditional academic and business cultures have begun to accommodate each other in mutually supportive arrangements in the larger interests of a global economy. In this respect the biotechnology sector has set some pioneering examples.

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TILL recently, the industry had little effect on the university system. In the US, formal technology transfer from the universities really began with the spread of scientific agricultural practices through the land-grant university system[1]. Most of academia otherwise resisted getting involved with the problems of the real world, preferring the seclusion of their ivory towers. However, the World War II brought about a major change. The governments of Germany, England, Canada and the US turned to their universities for the development of technologies needed to win the war. In the US, MIT's Radiation Laboratory contributed to anti-aircraft gun control, radar and electronics; Columbia physicists I. I. Rabi, George Pegram, Enrico Fermi, and John Dunning served the war effort through the Manhattan Project in building the atomic bomb[1]. So when Vannevar Bush, at the behest of President Franklin D. Roosevelt, prepared his famous plan for the future of research in the US[2], in 1945, it was in the backdrop of the spectacular successes of the academicians who had descended patriotically from the ivory tower to dirty their hands in designing weapons of war. What followed after the war were several decades of steadily rising federal funding of academic research (both military and non-military). In retrospect, the fear that such funding would eventually lead to federal control of academia, now back in its ivory tower, turned out to be ill-founded[1].

In the 1970s, the US Government discovered that many of the inventions that resulted from its funding, although freely available to the public, were languishing for lack of additional investment needed to turn them into marketable products[3]. In 1980, the US Government found that it held approximately 28,000 patents; yet fewer than 5% of these was licensed to industry for development of commercial products[4]. The government sought to redress the problem with the Bayh–Dole Act of 1980 (codified as amended at 35 USC Sections 200–212)[5]. Its purpose: 'to use the patent system to promote the utilization of inventions arising from federally funded research or development'. Under the provisions of the Act, non-profits (including universities) and small businesses gained handsomely. They were allowed and encouraged to retain the title to inventions developed under federally funded research programmes. Universities, in particular, were exhorted to collaborate with and promote utilization of their inventions by commercial concerns, especially small businesses, through licensing. Descriptions of inventions were given legal protection from public dissemination and from requests under the Freedom of Information Act[6] for a reasonable period to enable patent applications to be filed. In return, the government retained a royalty-free, non-exclusive license to practice such inventions throughout the world (including use by government contractors) and held march-in rights. However, the exercise of march-in rights requires cumbersome and elaborate administrative proceedings and exhaustion of court appeals.

The Bayh–Dole Act of 1980 has played a stellar role in bridging the great divide between the university system and industry in the US. Before 1981, universities sought and received fewer than 250 patents annually; a decade later[3] they were averaging 1600. Of those, nearly 80% came from federally funded research. But more remarkable was the fact that in 1992, 200 universities had at least one patent granted annually[7]. Academic and research institutions have since become keen seekers of patents. Instead of looking for just pioneering physical sciences and engineering inventions to patent as in the past, they have begun to encourage invention disclosures from computer science departments and business schools. Some already

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have active technology transfer offices, focused on building portfolios, and developing strategies to protect their patents and to avoid infringement claims by others. The Act is widely believed to have energized State Governments into targeting universities as engines for economic growth. *The Economist*, in its 14 December 2002, issue wrote:

> 'Possibly the most inspired piece of legislation to be enacted in America over the past half-century was the Bayh–Dole Act of 1980. Together with amendments in 1984 and augmentation in 1986, this unlocked all the inventions and discoveries that had been made in laboratories throughout the United States with the help of taxpayers' money. More than anything, this single policy measure helped to reverse America's precipitous slide into industrial irrelevance.'

The 1984 amendment to the Bayh–Dole Act was the Trademark Clarification Act of 1984. The 1986 augmentation relates to the Federal Technology Transfer Act of 1986 which amended the Stevenson-Wydler Act of 1980 and empowered each federal agency to give the directors of government-owned, government-operated laboratories the authority to enter into cooperative R&D agreements and negotiate licensing agreements for inventions made at the laboratories; it also formed the Federal Laboratory Consortium for Technology Transfer. Indeed, it mandated that technology transfer be considered a part of employee performance evaluation. The law now requires federal laboratories to actively seek opportunities for transfer of technology to industry, universities and State and local governments. The result has been that universities – the major recipients of federal grants – have become significant players in the biotechnology patenting arena.

Following the post Bayh–Dole success of the US in promoting the utilization of inventions arising from government-funded R&D, other countries, including India, have adopted similar strategies. Not surprisingly, since the 1980s, in developed and in some developing countries, government funding for research has shrunk in percentage terms, while industry funding for research substantially exceeds that of government. Naturally, industries have begun to play godfather to scientific research and their funds carry considerable clout even in university research. Technology, and indeed any form of application-oriented knowledge, has become an important component of international trade. Naturally, industry expects a financial return, often in the form of intellectual property rights, from much of the research it funds.

The biotechnology industry paves the way

The biotechnology industry, in particular, is of great interest. It is heavily science-based, has close interactions with university researchers, requires huge funding, carries high business risk, and relies on patents for survival. Its successes and failures, and its innovative methods of overcoming or avoiding intellectual property-related problems, especially with respect to patent litigation, are being carefully studied so that practitioners of other emerging technology areas, such as nanotechnology, can derive lessons useful to them.

Basic research forms the backbone of the pharmaceutical industry. Traditionally, the development of pharmaceutical end-products has long been a proprietary enterprise in which patents play a crucial role. On the other hand, biochemical research has a strong tradition of open science. Since the 1950s, with the discovery of the DNA structure, there has been a continuous narrowing of the conceptual gap between basic research and commercial application. Drug discovery now depends critically on basic knowledge of genes, proteins and associated biochemical pathways, rather than on trial-and-error processes of the past[8].

Prior to the late 1970s, there was a clear division of effort between the upstream curiosity-driven basic research pursued by not-for-profit institutions and the downstream market-oriented applied research pursued by for-profit companies. Traditionally, upstream basic technology funded by the government and philanthropists and developed in government laboratories, universities, research institutes and teaching hospitals, has been available for free use by all. Only in rare cases were any patents filed[9].

In the late 1970s an intermediate sector – the biotechnology sector – emerged between academic research institutions and Big Pharma to become an important competitive force in the industry[9]. Companies such as Amgen, Genetech and Human Genome Sciences, leverage their insights and state-of-the-art knowledge of molecular biology to develop products for end-users and compete against Big Pharma. Interestingly, academic researchers were instrumental in the founding of many biotechnology companies; they either moved out of academic employment or participated in both worlds[9].

The deep university–industry relationship in the biotechnology sector seen today was made possible due to the convergence of several factors. Of singular importance was the patentability of DNA sequences, monoclonal antibodies, transgenic organisms and gene expression systems, isolation and purification of proteins, etc. Second, was the high cost of research in biotechnology and accompanying societal pressure to justify those costs. This led public institutions to focus more on applied research, seek patents and generate licensing revenues from those patents. Eventually, as scientists handling large budgets and complex cutting-edge research projects began developing managerial skills, their appetite for business ventures grew. The venture capital industry, sensing an opportunity, daringly chipped in to support inexperienced companies enter the market with a 7–10 year pro-

duct development cycle[9]. The academic-entrepreneur was thus born.

Bernadine Healy, a former director of the National Institutes of Health (NIH), USA, has credited the Bayh–Dole Act with the development of the entire biotechnology sector[3]. The biotechnology industry is now clustered around major US universities in a symbiotic relationship. Post Bayh–Dole, universities and other government-funded institutions have become not merely more tolerant of 'off-campus' commercial activity, but active encouragers of it[9]. Other countries have begun to follow the US example.

Understandably, these developments have caused concern in some quarters because basic research thrives on openness, whereas patenting of DNA sequences, research tools, etc. means stifling that openness for economic gain. Pressures to patent have resulted in greater secrecy, cumbersome technology-transfer agreements and complex licensing terms, making sharing of research data a legal maze. Without effective access to data, materials and publications, the scientific enterprise becomes nearly impossible.

The dilemma: How does one encourage innovation without eroding the vitality of the scientific commons? What is the right balance between private enterprise and public sharing? Should one seek a balance through free-market mechanisms or government intervention? Reforms in the patent system are undoubtedly warranted, but what those reforms should be are rather unclear.

The biotechnology industry on its part is not oblivious of the dilemma. Its growing maturity in this respect is amply visible in some of the research projects it has funded, with the clear aim of placing its research output in the public domain in the larger interests of both industry and society. Such efforts are attempts to address a core concern of researchers: that the intellectual property system 'locks up' new knowledge and information in contrast to the goals of science, which aims to put them in the public domain expeditiously. Other research-driven high-technology industries, such as those related to information technology, nanotechnology, robotics, etc. are no doubt learning from the experiences of the biotechnology industry.

Industry and open source

Industry, in general, is experimenting with various pragmatic approaches to find an appropriate balance between open-source (public domain) and proprietary knowledge to suit its specific business needs. The ubiquitous fear of litigation and production choking injunction is also partly responsible for some of the open-source activities of the industry. Here one finds broadly two classes of industry: one, whose products depend on many patented technologies not all of which are easily identifiable or held by one company, such as in the software industry; the other, whose products depend on a few and hence readily identifiable patents, such as the pharmaceutical industry. The former class of industries is more vulnerable to production choking injunctions should they even accidentally infringe a patent they are unaware of, than the latter.

To mitigate legal and operational problems, companies have evolved various measures, such as creating and sharing intellectual property (IP) within communities of collaborators to enhance the scale, scope and speed of innovation; using cross-licensing, patent pools, and patent exchanges to lower the cost of exchanging IP; embracing open standards to enhance inter-operability and encourage collaboration; and investing in pre-competitive information-commons to boost their downstream product development. The last has been the focus of the biotechnology sector.

Pre-competitive information-commons in the biotechnology sector

The biotechnology sector has made substantial investments in several pre-competitive information-commons. For an industry heavily dependent on intellectual property rights (IPR) for its survival, increased openness and collaboration is a breakthrough model, requiring a delicate balance between open and closed innovation. The insights the biotechnology industry gains will be valuable to other industries where open and closed innovation models could be fused to create powerful combinations[9].

Merck Gene Index

In February 1995, Merck & Co Ltd and Washington University jointly announced the collaborative Merck Gene Index (MGI) project to produce a gene index of the human genome, a non-redundant set of clones and sequences, each representing a distinct gene. In essence, it would be a public database of gene sequences corresponding to expressed human genes. The project immediately placed 15,000 expressed human gene sequences into the public domain, and promised to place more as quickly as possible. By 1998, 800,000 gene sequences had been placed in the public domain[9].

For Merck, the MGI project makes excellent business sense. The expressed gene sequences are inputs for their end-products. By placing them in the public domain, it prevents others from seeking patents on those gene sequences and thereby restricting Merck's access to this vital input, while it simultaneously increases the possibility of discovering new knowledge by not-for-profit researchers that may lead to new remedies for a wide range of diseases.

Merck-sponsored project to create patent-free transgenic mice

In 1997, Merck Genome Research Institute sponsored a project to Lexicon Genetics to create 150 patent-free trans-

genic mice, to make it easier for the research community to get access to transgenic mice[10].

SNP Consortium

In 1999, following Merck's example, the SNP Consortium was established by eleven (highly competitive) pharmaceutical firms, a non-profit institution (the Wellcome Trust), and two information technology firms. Its immediate goal was to prevent various biotechnology companies from patenting large numbers of SNPs (single nucleotide polymorphisms), fearing the potential for balkanization of IPR in this important resource. Its long-term goal was to produce 'a public biological blueprint for all human life', so as to spur a new era of 'personalized medicine' in which treatment is tailored to an individual's unique genetic profile. At the completion of the project in 2001, 1.8 million SNPs had been mapped and placed in the public domain, and the Consortium had spent about $50 million mainly to support university researchers[9].

The Consortium also filed patent applications to establish priority and obtain legal standing to contest other filings with the avowed goal of defeating patent claims to SNPs. However, patent applications were abandoned once the SNPs were securely in the public domain. With the SNPs mapped, the harder interpretive discovery work that could lead to new diagnostics and therapies has now begun[9]. There is a minority view that the activities of the Consortium were a concerted attempt to sabotage biotech competitors. It is difficult to please everybody.

International HapMap Project

The success of the SNP project inspired other similar projects, one of which was the International HapMap Project (haplotype map of the human genome), initiated in 2002. It is a 'partnership of scientists and funding agencies from Canada, China, Japan, Nigeria, the United Kingdom and the United States to develop a public resource that will help researchers find genes associated with human disease and response to pharmaceuticals'[11]. The objective of the project was to identify and catalogue genetic similarities and differences in human beings and place the catalogue in the public domain. The haplotype map is crucial for the development of personalized medicine. An analysis of the entire dataset was published[12] in October 2007. Once again, the for-profit members of the consortium avoided competing with biotechnology firms in basic research and freed themselves to pursue their real interests, which is in personalized medicine, where they were willing to compete with each other. A publicly accessible HapMap also eases the task of the US Food and Drug Administration and its counterparts elsewhere, because the map has been accepted by the scientific community[9].

The Genographic Project

On 13 April 2005, the National Geographic Society and International Business Machines (IBM) launched a unique five-year research initiative called the Genographic Project[13] that will trace the migratory history of the human species, i.e. how humankind went around populating the earth. With funding from the Waitt Family Foundation, DNA samples from hundreds of thousands of people, including indigenous peoples and members of the general public, are being collected. Sophisticated laboratory and computer analysis of the DNA samples are being used to determine the genetic roots of modern humans. It is expected that this will reveal rich details and new understanding about the connections and differences that make up the human species. 'The Project is anonymous, non-medical, non-political, non-profit and non-commercial and all results will be placed in the public domain following scientific peer publication'[13].

Information-commons and NIH

In February 1996, the National Human Genomic Research Institute (NHGRI) of the NIH, the Wellcome Trust and academic researchers at major human genome mapping centres resolved that 'all human genomic DNA sequence information, generated by centers funded for large-scale human sequencing, should be freely available and in the public domain in order to encourage research and development and to maximize benefit to society'[14]. This pledge is known as the 'Bermuda resolution'. In April 1996, NHGRI followed up with a policy statement that made 'rapid release of data into public databases' a condition for grants for large-scale human genome sequencing[15]. In December 1999, NIH adopted a more general statement of 'Principles and Guidelines for Sharing of Biomedical Research Resources'. *Inter alia* the principles state that[16]: 'the use of patents and exclusive licenses is not the only, nor in some cases the most appropriate, means of implementing the [Bayh–Dole] Act. Where the subject invention is useful primarily as a research tool, inappropriate licensing practices are likely to thwart rather than promote utilization, commercialization, and public availability'.

The Guidelines appear reasonable in the case of broad enabling inventions useful to many researchers or to multiple companies in developing multiple products, or if the invention can be used as is. In addition, the Guidelines encourage unencumbered transfer of unpatentable research tools to other researchers needing them. In view of the Bayh–Dole Act, the Guidelines were careful not to forbid the grantees from filing patent application. NIH's preference for open-access norms is understandable since its top leadership is typically drawn from academia and the research community with a hallowed tradition of open

access. However, the pressure to patent inventions with high-commercial potential or with the potential to provide market leadership to a company resulting from university–industry collaborative research may sway many away from the Guidelines. It is unlikely that the NIH can enforce its Guidelines on grant applicants, if challenged in court.

Alliance for Cellular Signaling

The Alliance for Cellular Signaling (AFCS)[17], initiated in 1999 is expected to end in 2009. This is a large university–industry collaborative project in which NIH provides two-thirds of the funds and industry the remaining third. AFCS participants have agreed not to patent their research[9]. The project promises significant breakthroughs in our understanding of the inner workings of cells by mapping complex signalling networks. These networks comprise pathways along which different molecules travel as messengers within a cell. The project is important because signalling networks play a crucial role in creating unintended side effects that cause many drugs to fail. Eventually, the goal is to generate a computational model of signaling within the cell. Such a model could become an incredible drug discovery engine[9].

Final remarks

As science-based industries, such as those in biotechnology, nanotechnology, robotics, etc. continue to grow and become more complex, so will their evolving relationship with the universities. Various contentious IP-related issues that arise in such university–industry partnerships and possible solutions to those issues, which balance the need to place information in the public domain and the need to protect information for limited periods for commercial purposes, will continue to require careful thought.

The post-Bayh–Dole experiences of the biotechnology sector in the US in terms of university–industry collaborative R&D has been keenly watched by many national governments. Countries such as South Korea, Singapore, Japan, Germany and others, have begun implementing well-conceived plans that focus on innovation-driven industry sectors such as biotechnology, where initial investments are high, required knowledge and skill levels are at the cutting edge, and costs of copying by experts are low. Their plans essentially require creating cutting-edge technologies and protecting them with patents or selectively placing them in the public domain, as appropriate. They have reoriented their national economic policies from being investment-driven to being innovation-driven. To support those policies they have focused on providing high-quality education and training, developing first-class research universities and related infrastructure, and nurturing and sourcing creative talent globally by relaxing immigration laws. Given the high investments needed, they have tried to avoid R&D duplication and practice economies of expertise by excelling in specific research areas. Most such countries are aiming to spend 3% (roughly 1% from the government, and 2% from the private sector) of their GDP on R&D by 2010.

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