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The commercialization of academic patents: black boxes, pipelines, and Rubik's cubes

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Abstract Drawing on histories of technological innovation originating from research by faculty at The Pennsylvania State University and Johns Hopkins University, this paper presents evidence for a "technology" as well as an "intellectual property rights" research approach to the commercialization of academic patents. By describing how inventor and firm activities and strategies affect the technical development and commercial positioning of university patents, a technology focus adds depth to the general proposition that university patents are embryonic technologies. It likewise serves as an analytical probe to reconsider other mainstream propositions about university technology transfer.

Keywords Commercialization · Academic research · Technology transfer · Patents and licenses

JEL Classification O31 · O33 · O34

1 Problem statement

Squeezed and at times ill-fitting between the extensive research literature on post-1980 activities of United States universities and their faculty in patenting, licensing, and spin-offs and recurrent litigious flare-ups over academic patents (e.g., *University of California and Eolas v. Microsoft*; *Florida State v. American BioScience*) (Kerbeshian 2004) is an analytical black box containing the events and relationships that affect the conversion of university intellectual property into commercially offered technological innovations.

That such a gap exists is implicit in the mainstream proposition that university patents are embryonic technologies (Thursby and Thursby 2003). Analytical use of this proposition though has centered about the importance of the (faculty) inventor's tacit knowledge and

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subsequent negotiations related to valuation of academic patents, leading to industry's oft-made contention that universities overstate the economic value of their intellectual property. As argued, for example, by an Industrial Research Institute (IRI) committee, "Ownership and/or the rights to developing technology are probably the most contentious issues in the preparation of agreements between universities and industrial companies. When ownership and IP rights issues interfere with industry's aim to gain competitive advantage, then these issues impede open communications and collaboration" (IRI 2002, p. 2). Moving on to a discussion of the issue of how compensation for university intellectual property is to be calculated, the report notes that the road to commercialization is a path requiring multiple steps—eight are identified, including activities such as manufacturing design and marketing. It then argues that, "In most collaborations, the university participates only in the very first step (idea generation) with little or no cost or risk. It is not attractive to an industrial partner to share a large royalty after assuming all of the risk and executing most of the work, while the university is responsible for only the basic research" (p. 6).

However, other than sketching out these steps, the report does not enter into how these steps affect the transformation of a patent into a technology, or the technology into the product. A similar assessment may be made of the coverage of the compendious body of research on the economic, legal, behavioral, and institutional impacts of Bayh-Dole and connected post-1980 events on the patenting, licensing, and related technology transfer activities of US universities. To refer only in general to this work, theoretical models and empirical research have examined evolving faculty and university attitudes, policies, and behaviors in seeking patents, negotiating licenses, and forming start-up firms. (For recent reviews, see Rothaermel et al. 2007; Siegel et al. 2007; Geiger and Sa 2008). Also extensively examined have been the organization, objectives, and strategies of technology transfer offices, with frequent use made of production function relationships between various sets of inputs (e.g., resources; organizational attributes) of technology transfer offices and outputs (e.g., patents, licenses, revenues, start-ups). A related set of studies has examined the role of academic patents in the start-up of new firms, generally from the perspective of inquiries into the characteristics of faculty entrepreneurs, sources of capital to start-up firms, and the regional economic impact of such establishments.

However, with few but notable exceptions, such as the multipart University of California, Stanford University and University of Columbia study (Colyvas et al. 2002; Mowery et al. 2004), little of this literature extends its empirical span into the development of discrete, marketable, technological innovations. It is difficult in most studies to connect findings about university patenting and licensing behavior or the performance of technology transfer offices to what Niosi has described as "down-to-earth" questions about the commercial introduction and subsequent diffusion of university-based innovations (2006, p. 400). Commercialization processes—the eight or so steps identified in the IRI report tend to be subsumed within the observation that academic patents are embryonic products, or if noted, are used as case study examples to explicate relationships defined and tested in aggregate, quantitative form.

Data on the number of licenses, the amount and size distribution of revenue streams, or the forms of these streams (e.g., royalties, sale of equity holdings), however, at best are partial indicators of how a university's patent and licensing strategies affect processes of commercialization. They provide only limited understanding of how the patented invention is used and by whom, and of the dynamics and vagaries of technical, market and firm-specific variables that populate most histories of technological innovation (Mowery and Rosenberg 1998). Most starkly, they omit the actions and strategies of firms with respect to

the embryonic technology, and how these in turn feedback upon the actions and strategies of faculty inventors in their institutions.

The approach adopted here is different. It works through the several steps identified in the IRI report, further refining some of them. It thus connects events beginning with the genesis of the academic patent or other form of intellectual property through efforts to introduce the resulting technology into a commercial product. Detailing these steps illuminates the distinction between technology transfer and technological innovation.

That the paper is an explanatory probe intended to highlight the richness of a broadened analytical framework is obvious in the limited number of observations upon which it draws and its citation of US experience only. But what the six case histories presented below point to is the complexity of the processes of technological innovation based on academic patents. This complexity confounds exisiting interpretations of the contribution of such patents and licenses to the emergence of a new product or products. Further downstream, it may also confound aggregate relationships between measures of university technology transfer activities and estimates of the contribution of academic r&d to regional or national economic growth or competitiveness. In effect, by moving from measures of intellectual property inputs to measures of associated outputs, contemporary research tends to measure end points but to omit the middle. It is this middle that the case histories are designed to fill in.

2 Research design

The paper draws upon findings from case histories of technological innovation from the Pennsylvania State University (PSU) and Johns Hopkins University (JHU). The approach represents a combination of what Helper (2000) has described as learning "just by watching" (or, in this case, listening), and what Weick (1995) has termed "theorizing" about a problem, that is, "an interim struggle in which people intentionally inch towards stronger theories", rather than a formal model. It is in the methodological tradition of using field research and case studies to build, and as appropriate to question existing theory and empirical findings (Yin 2003).

The initial focus of the study—the unit of analysis—was the patented technology. Thus, it skips over questions relating to the effects of Bayh-Dole on academic patenting (Mowery et al. 2001), as well as the starting point of the California-Stanford-Columbia and related inquiries (Rosenberg and Nelson 1994; Feller 1997) concerning the differential paths by which patented and unpatented academic inventions reach the market. Each of the case studies presented here centers around a patented invention or copyright; moreover, in each case, the faculty inventor emphasized that a patent was an important aspect of the commercialization process, albeit in three of the cases noting that the decision to seek a patent was not uppermost in their mind when they undertook the related line of research, but instead was requested of them by the firms that supported their research.

Of especial interest in constructing the case histories was examining in detail the proposition that follow-on R&D is frequently required to convert the knowledge embodied in a license into a commercial product. The need for follow-on R&D also has links to several well-established research questions: Were the initial expectations that firms had for entering into sponsored research agreements with universities met (Feller et al. 2002)? What strategies did firms use for acquiring and refining externally obtained technologies (Arora et al. 2001)? How important was the continuing role of academic inventors in the development of specific technologies (Gelijns and Rosenberg 1995; von Hippel 1976)?

The case history technologies were identified through interviews with the technology transfer and sponsored research officers at the two universities.[1] These officials were asked to identify technologies that had been patented and licensed for a period of time long enough for products to be commercially introduced. Ruled out by the use of this selection criteria were patents that had been recently issued or licensed but for which no product had yet been commercially introduced. An attempt was also made the balance the heavy emphasis on biomedical patenting at JHU with the more dispersed pattern of patent activity in agriculture, manufacturing, and materials technologies at PSU. For each identified technology, initial interviews were conducted with the faculty inventor or member of the research team, and then in a snowball approach other firms and individuals identified in these interviews. Interviews were augmented by reviews of company histories and financial reports, archival material, and secondary sources. What emerged from this line of inquiry was a complex set of "business" decisions that affected both the commercial introduction of each patented technology and the involvement of the firm or firms that eventually brought the innovation to market. These decisions are recounted in the case histories presented in Sect. 3.

3 Case histories

3.1 Penn State heart assist devices

Penn State's development of heart-assist devices dates back to the mid 1970s, with the development by Dr. William Pierce, Milton S. Hershey College of Medicine, of a surgically implantable, pneumatic ventricular assist pump. The pump, designed to regulate blood flow to patients during open heart surgery, is more properly seen as a compound product consisting of patentable technologies, fundamental technical understandings of miniaturization and control mechanisms, and know-how based upon the contributions of a research team of surgeons, engineers and materials specialists at PSU's Hershey Medical Center.

In 1983, efforts began toward patenting the emerging technology. Echoing tensions reported in other accounts of the history of patenting at PSU, differences arose about whether the invention was patentable and whether or not it was worthwhile to pursue a patent between the PSU team and the Research Corporation, which at the time administered PSU's invention disclosures The initial technologies were patented. (These patents were subsequently followed by other patents for different components, such as control mechanisms and energy transmission.)

The initial Penn State patent was licensed to Thoratec Corporation, a California-based firm that specialized in research, development, manufacturing and marketing of medical devices for circular support. The medical and economic impact of these early pumps was limited. Problems were reported with the pump's performance in clinical trials; the prospective market for the use of the pump in transplant operations also proved to be small, leading Thoratec's management to pull back from continued interest in the PSU technology.

The technological trajectory of primary interest began in the mid 1980s when the PSU group applied for and received the first of a series of grants from the National Institutes of

[1] Extended accounts of the structure and strategies of the technology licensing offices at Penn State and Johns Hopkins are found in Bercovitz et al. (2001) and Feller et al. (2000).

Health (NIH) to develop an electrical artificial heart. The NIH program emphasized the manufacturability and reliability of university-based medical technologies—a theme emphasized in federal science agencies in the period of the international economic competitiveness challenge—and required a commercial partner. Sarns, Inc., a small-size manufacturer of a series of cardiac surgery medical devices located in Ann Arbor, Michigan was selected as the industrial partner, in part because of prior supplier-customer relationships (Sarns 1999). Another participant in the PSU effort was Abiomed, a Massachusetts-based firm that was also working collaboratively with the Texas Heart Institute on its own approach to an artificial heart under a counterpart NIH award.

For its part, prior to entering into a partnership with PSU, Sarns's management had "made a strategic decision to seek corporate partners with financial, technical and marketing resources which would enable (it) to offer state of the art products worldwide" (Sarns 1999). Following 2 years of discussion, in 1981, Sarns became a wholly owned subsidiary of the 3-M Corporation. Thus, during its second NIH grant, covering the period from approximately 1986 to 1999, PSU worked with 3-M. At this time, 3-M had a thriving cardiovascular business, and was considered one of the leading firms in the development of heart and lung machines. In terms of the strategy underlying the NIH program, 3-M's contribution was to bring expertise in design and feasibility to the work of the PSU research team so that pilot production could overlap with progress in the project's research phase.

3-M's orientation towards patenting and its patent expertise are reported as being important in PSU's movement towards patents. About 1996, 3-M's attorney suggested that the PSU team begin to file for patents on the emerging technologies. 3-M provided guidance to the researchers on which aspects of the technologies could and should be patented, and also provided funds for the patent filings. The research agreements between 3-M and PSU gave the firm rights of first refusal on use of any patented technologies, although no license agreement was ever negotiated. In 1999, however, at the time of animal testing and durability experiments on the PSU heart machine, 3-M, as part of a general strategic decision to concentrate on its core businesses, sold its entire cardiovascular business to Therumo Cardiovascular Systems, a Japanese-owned firm headquartered in Ann Arbor, Michigan. As part of this sale, 3-M gave up future claims on the PSU heart; its existing rights, however, were specifically excluded from the sale. Also, as part of 3-M's exit from the project, it provided funds for PSU to reorganize the project and for materials, as well as to pay for additional patent filings.

Therumo's engagement with the technology was short lived. In an almost textbook example of the importance of complementary assets (Teece 1987), one of the factors retarding the commercialization of PSU's left-assist ventricular device by the initial licensee was Therumo's concern that the technology used a component for which there was only one supplier. Not wishing to find itself vulnerable to monopoly pricing for a key input, the licensee found it necessary to develop an alternative material, one moreover that would meet FDA regulatory standards.

After 3-M's decision to exit the cardiovascular machine market, several of its former employees in the disbanded division decided to launch start-up firms based on the PSU heart. One former manager acquired 3-M's inventory of related patents and established a firm, BeneCor Heart, Inc., intending to become the prime manufacturer of the PSU heart. BeneCor also entered into an agreement with PSU for rights to its heart pump technology. BeneCor then set off to obtain the required angel funding, estimated at between $20 and 30 million to launch production. The effort to secure funding failed, and the firm never produced a product. Its prime asset was its rights to the PSU technology.

In 2000, Abiomed purchased BeneCor in a straight stock swap, becoming the holder of the license to the PSU heart technology. Under the sales agreement, BeneCor received 110,000 shares of Abiomed common stock, and warrants to purchase up to 400,000 additional shares of common stock at an exercise price of $0.01 per share. PSU received 55,000 shares of Abiomed common stock (valued by PSU in 2001 at about $1.3M), plus warrants to purchase up to 200,000 additional shares of Abiomed. The exercise of these warrants was made contingent on the achievement of certain clinical and regulatory milestones with the Penn State Heart by specified dates. Abiomed's agreement with PSU also gave it access to future advances in related implantable replacement heart technology generated by the PSU research and development team.

At Abiomed, PSU's technology both competed with and complemented other prototypes being developed by the firm. Abiomed's first major attempt to market an artificial heart was the AbioCor™. This product is described on the firm's website as incorporating "the best technologies of both the AbioCor™ and the Penn State heart". Abiomed's initial effort to gain FDA approval of its device was rejected. In 2005, an FDA Advisory panel by a 7–6 vote rejected AbioCor™ Implantable Replacement Heart for commercial distribution because it was deemed not to meet FDA's humanitarian-device exemption requirements.[2] FDA approval was subsequently granted in September, 2006 for patients suffering from heart failure on both sides of their heart and who had no other alternatives. Separate from the issue of the mortality data considered by the FDA Advisory Panel, the price of the Abiomed artificial heart (estimated at between $200,000 and $250,000) relative to the length of time it is projected to prolong life itself became an issue. A *Wall Street Journal* report on the initial 2005 FDA decision quoted Dr. Gerson Rosenberg, chief of the Division of Artificial Organs, Hershey Medical Center, as saying that an extra year of life might not be enough to satisfy expectations, and improvements in the devices were still needed before their use becomes as widespread as heart valves and pacemakers (Goldbarb 2005). The commercial future of the device after more than 30 years remains uncertain.[3]

3.2 PennMulch

PennMulch is a fiber-based, water-soluble product for mulching newly seeded areas. It is marketed as superior to straw as a ground cover in that it doesn't promote the growth of weeds or have to be raked once new grass takes hold. The technology transfer or commercialization history of PennMulch is that of an academic inventor seeking to obtain the necessary manufacturing and marketing capabilities to commercially introduce his new technology over an approximate 10-year period.

[2] A humanitarian device exemption application is similar to an FDA premarket approval application in requiring reasonable assurance of safety and probable benefit. The exemption pertains to the small size of the potential population to benefit from the device and to smaller size trials concerning the device's effectiveness.

[3] Throughout these years, PSU researchers at the Hershey Medical Center continued their research on artificial heart technology, receiving, for example, a $5M contract from the National Heart, Lung, and Blood Institute in 2004 to develop a pediatric heart-assist device. Also, at the same time that it was engaged in continuing research related to the implantable heart, Hershey researchers were engaged in complementary work on other heart-assist devices. One such line of research led to the "LionHeart", a completely implantable pump for use in individuals with congestive heart failure who didn't qualify for a heart transplant. The agreement with ABIOMED did not preclude Hershey researchers from continuing their work with Arrow International, Pennsylvania, which had licensed this technology. In 2005, Arrow announced plans to stop manufacturing the LionHeart, describing it as "not economically viable for the firm", having failed to sell any of the pumps in the previous 2 fiscal quarters.

PennMulch was invented by George Hamilton, then a senior lecturer in Penn State's Department of Agronomy, and subsequently Assistant Professor of Crop and Soil Sciences. The technology was intended to provide a low-cost method for mulching relatively small areas. The dominant turf grass technology prior to the introduction of PennMulch was hydroseeding. This technology employed wood fiber and required expensive machinery. It thus was economical only for large areas. Hamilton, whose position at Penn State involved extensive interaction with the professional turf grass industry, sought a means of providing the same mulch protection for small, newly seeded areas. He was familiar with pelleting technology and the difficulties of converting wood fibers into water-soluble pellets. His initial approach involved the use of polymers, which he was familiar with from earlier soil-related research.

Hamilton financed some of his early research by drawing on the discretionary funds available to him through grants-in-aid provided by chemical and seed firms that had longstanding ties to Penn State's College of Agricultural Sciences. These grants-in-aid were no-strings-attached awards, typically in the range of $5,000–$20,000, that permitted college faculty and research personnel to work on projects of their own choosing related to the research needs of the industry. The arrangement was described by Hamilton as based on good faith between the parties; it also had the advantage to the sponsor that gifts unlike industrial research grants entailed no university overhead charges.

Hamilton thought of PennMulch as a product in 1990, and filed a field invention disclosure in November of that year. He soon encountered technical difficulties in developing an operational approach. He quickly expended his discretionary research funds and began searching for other funding sources. At the time, the state of Pennsylvania had an Environmental Technology Fund, funded by tipping fees at landfill operations. The fund was administered by but operationally separate from the Ben Franklin Partnership program, Pennsylvania's version of the state government-university-industry cooperative R&D programs that had begun to emerge in the 1980s. The Ben Franklin Partnership program was organized into four regionally distributed centers of excellence, each tied to one or more universities. Penn State was the host university for one of these centers.

Under the terms of the Ben Franklin Partnership, grants were made to firms, not to university faculty. Penn Pro Corporation, a small start-up firm, received a $40,000 grant from the Ben Franklin Partnership, with Hamilton conducting the research as a subcontract under an agreement between the firm and PSU. At this point, the technical challenge was to determine if it was physically possible to pelletize paper. The state funds permitted Hamilton to experiment with various formulations of a fiber soluble product. Hamilton contracted with a firm in New Berlin, Pennsylvania that had experience in pelletizing grain, and proceeded in this manner to develop 10–12 prototypes. To obtain raw material, Hamilton drew on his previous contacts with a Proctor and Gamble plant in Pennsylvania and experimented with pelletizing paper diapers that were rejected during quality control checks. He also experimented with other sources of fiber sludge. Hamilton described the work at this stage as focused on formulation, not on production rates or scale-up.

In 1992–1993, a second grant of approximately $100,000 from the Pennsylvania Environmental Technology Fund permitted Hamilton to refine the product and begin addressing questions of manufacturability, such as the size of the pellet. Research at this point focused on developing a working model. By 1993–1994, the technology was "pretty well figured out".

As work progressed, a patent application was filed through PSU in late 1992 and a patent issued in 1995. The patent was seen as the key to the further development of

PennMulch. According to Hamilton, firms were uninterested in products protected by trade secrets because reverse engineering could easily imitate the product.

As Penn Pro and Hamilton moved from technology development to commercialization, they realized that considerable capitalization was required for manufacturing and marketing. They initially considered a strategy of arranging for the contract manufacturing of the product and then handling the marketing themselves, but recognized that such a strategy would give them no control over output, inventory and distribution.

In applying for the second Ben Franklin grant, Hamilton sought a larger partner than Penn Pro. He entered into an arrangement (in which he was the subcontractor) with Agri-Tech 2000, a Pennsylvania-based firm that was developing new technologies for the turf grass industry. Agri-Tech began marketing PennMulch by sending it to end users such as golf courses.

At this stage, manufacturing issues became a problem. The effort to go-to-scale was described as a "nightmare". Difficulties were encountered in getting custom pellet mills to work with the firm or to fit PennMulch's product needs into their production schedules. PennMulch did find a custom pellet manufacturer, but the price quoted by the mill was seen as too high and the lengthy production schedule conflicted with the terms of the Ben Franklin grant. After much effort, a recycling processor in the Pittsburgh area (whose main business was tire grinding) that had an idle pellet mill, was found. This firm became their subcontractor on the second Ben Franklin grant.

New business start-up problems were encountered at this stage. Agri-Tech was a marketing and distribution firm but lacked skills in manufacturing. At this point, a new relationship was attempted with BFI, which was involved in recycling paper. BFI saw the PennMulch technology as a way to achieve downstream integration, finding a new market for its recycled paper rather than having to pay to dispose of it, as well as gaining political goodwill for being an environmentally friendly firm. However, at the same time, other markets developed for recycled paper and BFI walked away from the potential partnership with PennMulch.

The experience produced what was described as a steep learning curve about access to raw materials and the need to control its production process for PennMulch as it attempted to sustain its commercial operations. One residual positive outcome of the interaction with BFI was that a BFI representative informed PennMulch about the existence of an idle, commercial-size pellet mill in Arcadia, New York.

In 1994, Hamilton entered into discussions with Wally Snipes, a former Penn State faculty member and inventor of a major transdermal drug-dispensing technology. Snipes had earlier sold the firm, Zetachron, which had been formed to manufacture this technology, to Schering and had used the proceeds from the cash-out and other of his successful patents to form Technology Assessment & Development (TA&D). TA&D describes itself as focusing on proof-of-concept, providing capital and business development experience to faculty and students in launching R&D-based businesses. With PennMulch, proof-of-concept had been established; what was needed was proof-of-scale. Discussions between Hamilton and Snipes initially centered on marketing the product, but it soon became apparent that the primary issue was developing a reliable manufacturing source for a low cost, high-volume product. In the 1995–1996 period, as PennMulch continued to develop a commercial-scale operation, Snipes convinced Hamilton that Agri-Tech was not the right platform for commercializing the product. TA&D purchased Agri-Tech's license for PennMulch, giving the firm remaining short-term rights to serve as a sales and marketing organization. TA&D subsequently proceeded to buy the license from Agri-Tech and the New York pelleting plant, setting up PennMulch as a subsidiary. In the

first years of operation, the plant was used to make pellets in the winter and produce PennMulch using sawdust, in the summer. The product was sold to golf courses and professional landscapers in 50-pound bags at $7.50/bag. There were significant technical advances once large-scale, steady production began. The firm gained a better understanding of the mix of raw materials that could be used and how to make a consistent product.

About 1997 PennMulch approached Lebanon Chemical about a private label arrangement. Lebanon Chemical's initial response was lukewarm, characterizing the product as not well known, but after several months agreed to a private label contract. At that time, TA&D also suggested to Lebanon Chemical that the firm consider the possibility of acquiring PennMulch. Lebanon Chemical had become aware of Penn Mulch through meetings of distributors and other marketing channels. Firm representatives viewed the product as a breakthrough in seeding because of favorable comments about it from distributors.

Lebanon Chemical had a strong market presence in fertilizer and seed products in the Northeast and Mid-Atlantic, but considered itself lacking in real in-house R&D capabilities. Its business strategy however, was evolving from being a predominantly chemical manufacturing company to one known for product development: a company to which customers would look for new and improved products on a regular basis, whether developed internally or acquired. (As described by one firm representative, the firm was almost 60 years old but had received its first patent only a few years earlier).

As its seed business grew, Lebanon Chemical explored several sources of external technologies including similar acquisitions of grass seed varieties being developed at Rutgers University, which showed a responsiveness to new products developed by independent entrepreneurs. However, PennMulch was seen as a product more congruent with the firm's core manufacturing competencies, which were in granulation, formulation, and bulky processing, as well as its sales, marketing and distribution channels.

In 1998 Lebanon Chemical purchased PennMulch from TA&D, including its property, plant and equipment, the licensing agreement with PSU, (which provided for a running royalty on sales), the brand name, and the goodwill. Upon the acquisition, the PSU license was transferred to Lebanon Chemical. This transfer, however, was between Lebanon Chemical and TA&D and did not involve any discussions with PSU's intellectual property office. Upon acquiring PennMulch, Lebanon Chemical immediately began expanding its product line. They recognized that PennMulch was being marketed in professional outlets as a product for newly seeded lawns only, but was not readily available to consumers. They quickly changed the color of the product and began to market it as suitable for home gardening.

3.3 Air inhalation research/alkermes

David Edwards joined PSU's Department of Chemical Engineering in 1994, after completing his Ph.D. at MIT under the supervision of Robert Langer. Edwards' research centered on the then-novel concept of designing large porous particles, which "offered the promise of delivering drugs into the lungs with increased duration and at lower doses than was possible utilizing current available drug delivery technologies" (Garner 1999, p. 1). Edwards applied for an NIH grant to continue this research but was turned down as the proposal. in his view, was "so unlike what NIH was funding". As recounted by Edwards in an earlier Harvard Business School case history of Air Inhalation Therapy, "Based on our preliminary research, Langer and I approached a public delivery company to see if they

were interested in acquiring our technology. We offered to consult for them in exchange for research funding. They were interested, but wanted us to come back when the technology was more advanced." (Garner, op. cit.)

Edwards describes the availability of PSU's Food Science Laboratory spray dryer, which was located close to his own laboratory, as a "big thing" in the commercial development of his core technology. He sent his students to scour the university for equipment that could be used to test the applicability of his findings for commercial uses. Master's degree students did their thesis research on the formulation of the product.

Edwards continued to turn to Langer at MIT for research assistance. Langer's lab helped by providing polymers for use in Edwards' experiments. Edwards and Langer co-authored the fundamental paper, "Large Porous Particles for Pulmonary Drug Delivery," on their research, which appeared in *Science* (June 20, 1997: 1868–1871). They continued to collaborate on subsequent papers and patents, alternating names of lead patentee and author.

Edwards described his primary research goal as "science". Once he and Langer published their findings in *Science*, they became interested in showing the versatility of the findings for many particles. They wanted to show the pharmaceutical industry that their technology could be adapted to whatever the industry needed by working with different drug formulations. Since particles differ in their characteristics (e.g., fragility, stability), moving from the general to the specific constituted a series of research questions. Their research had led to a general purpose technology that could be used to produce streams of additional findings, patents and products. Once they demonstrated the generalizability of their technology, products became obvious. However, Edwards emphasized that this orientation was the antithesis of product development, and he wanted to show that his technology had broad applications. Conducting and publishing the research that showed specific applications led to additional papers and patents. Edwards also noted how an university setting stimulated research because it simultaneously provided the "open idea environment of sharing equipment" and a "low price tag for failure". Even if a research program led to no "good product", students still could do thesis-quality research.

Edwards initially thought of patents as a way to leverage additional research funds. He and Langer initially viewed venture capital firms as sources of additional research funds. The contacts benefited from Langer's prior involvement with a venture capitalist, Terry McGuire, who had founded Polaris Ventures. Polaris was willing to provide this support to a firm, but not as a grant or contract to a faculty member. The support was instrumental to the formation in 2002 of a new firm, Advanced Inhalation Research (AIR), which Edwards operated from his home. Polaris gave research grants to AIR, and AIR awarded the funds to PSU where it supported Edwards' work mainly through funding for a postdoc and purchase of equipment.

PSU's technology transfer office played a supportive role in creating AIR. In contrast to the earlier, stand-offish policy of accepting equity described in the PennMulch case, the office was described as adopting a flexible stance towards the potential conflict of interest of having Edwards conduct the same research in his laboratory and his company. Patent filings and licensing, however, were conducted through MIT's Technology Transfer Office. Edwards described MIT as having a better track record in negotiating licenses with firms than their Penn State counterparts, and as more willing than PSU to file for patents that did not have an immediate licensee. PSU and MIT were to share intellectual property revenues on a 50–50 basis. Both universities had equity in AIR as well as a royalty claim on future sales. Both MIT and PSU sold their holdings in AIR at the time of its sale to Alkermes.

As conflict of interest issues associated with his joint role as head of AIR and a faculty member became more pressing, Edwards left PSU in 1998 to concentrate on AIR. Added pressure in this direction came from the pharmaceutical firms that were funding Edwards' research, who were concerned about insuring the confidentiality of the research, especially as it was conducted by students working under Edwards' supervision. Edwards subsequently returned to academic life, joining the Harvard faculty in 2001.

3.4 CD34

CD34+ selection (CD34 positive selection) represents a process for isolating and purifying stem cells and then returning them to the blood streams of cancer patients undergoing chemotherapy. This technique can reduce the risk of relapse following an autologous transplant for patients with diseases such as leukemia, breast cancer and lymphoma cancer, thus both prolonging and improving the quality of life for patients.

CD34 was discovered by Dr. Curt Civin, Professor of Oncology and Pediatrics at the Johns Hopkins University (JHU). Civin began his research on stem cells at JHU's Oncology Center in the early 1980s. He and his research team started with the assumption, controversial at the time, that stem cells, the master cells from which all other cells in the blood and immune system develop, have their own unique antigens. The idea was that if the antigen could be identified, then antibodies could be created to target these antigens and isolate the stem cells, like a magnet drawing away iron filings (Keiger 2000). Civin's initial efforts to secure NIH funding for this research were unsuccessful. "In the early 1980s, when he first tackled the problem of stem cells, he had trouble getting the work funded. 'Too many untested assumptions', people said. The problem was just too hard" (Hancock 1996). His initial work was supported by foundation grants, philanthropy and departmental contributions that helped advance the research to the point that it successfully competed for NIH funding.

Civin drew on earlier and parallel research begun in the early 1980s by Koeffler and Golde, who, working under a federal grant at the University of California at Los Angeles, had developed the KG-1a cell line. Since then, this cell line has been widely used as a disease model by scientists to look for new antibodies and utmost for cure solutions. Making use of KG-1a cell line, Civin discovered the My-10 antibody, one in a series of monoclonal antibodies against the cell line KG-1a,[4] which, in turn, led to the discovery of the CD34 antigen (CD for Cluster Designation).

In May 1982, Civin received the first of two-three-year NIH grants for further research on the antibody and the stem cell antigens. This award allowed Civin to expand his lab and also conferred legitimacy to the investigation. The research results, which introduced a new way to isolate large quantities of elusive stem cells, were published in the *Journal of Immunology* (Civin et al. 1984).

Civin filed the invention disclosure in 1983 at the same time that he submitted his manuscript for publication. In 1984, JHU filed a patent application for *Human Stem Cells* based on this disclosure. The patent application was subsequently split into four separate patents, which were issued between 1987 and 1992. The first two, which would later be the focus of many legal battles, are US Patent Nos. 4,714,680 (the '680 patent, which covers cell suspensions substantially free of mature cells) and 4,965,204 (the '204 patent, which covers the use of CD34 antibodies). The other two are US Patent Nos. 5,035,994 (the '994

[4] http://www.biotech.ist.unige.it/cldb/cl3024.html.

patent) and 5,130,144 (the '144 patent). Collectively these four patents are referred to as "the Civin Patents".

The onset of the commercialization of CD34 also began in 1984. At that time, JHU did not have a technology transfer office. Based on his prior involvement with the firm, Dr. Civin initiated contact with Becton Dickinson (BD) about the possibilities of the firm's licensing of the technology. Soon after, JHUC issued an exclusive license to BD for the Civin patents. Civin's approach to BD was a logical outgrowth of preexisting relationships. Much of the experimental laboratory equipment used by Civin had been made by BD, and Civin assumed it would be interested in his invention. In addition, he knew people who worked at BD as well as faculty members from Boston that had licensed with them.

BD obtained an exclusive license for the CD34 patent(s) in 1984. In addition to provisions calling for royalty payments until 2012, the license came with three additional conditions sought by Civin. These were: (1) an initial grant to support his ongoing research; (2) the setting aside of a portion of the royalty income for further research and investigation; and (3) a consulting agreement that would allow Civin to use BD's resources and equipment. All three conditions were met. The consulting agreement led to some twenty academic articles and one patent coauthored with Michael R. Loken. The Loken/Civin and Shah patents resulted from collaboration with the Becton Dickinson scientists from research that accompanied the CD34 licenses.

Becton Dickinson began marketing the first anti-CD34 antibody in 1985, and has sold anti-CD34 antibodies worldwide since then. However, the firm's efforts to develop diagnostic applications or therapeutic products were unsuccessful. In 1990, it abandoned these efforts, selecting instead to sublicense its rights to develop therapeutic products based on CD34 to Baxter Healthcare Corporation. The logic of the sublicense was that BD has a corporate focus on diagnostics while Baxter Healthcare, a unit of a major pharmaceutical firm, has expertise in therapeutic applications. The patent rights were licensed exclusively to Baxter for $1.25 million plus a running royalty at 11% on future sales.

Baxter had developed a prototype stem cell selection device by late 1991 and started clinical trials by Dr. Civin in 1992. In January 1995, Baxter received regulatory approval in Europe for its Isolex 300 System for cell selection. In February 1997, after controlled and monitored clinical trials in the United States, Baxter filed an application for pre-market approval for the Isolex system with the Food and Drug Administration (FDA). Shortly thereafter, Baxter spun off its Immunotherapy Division as Nexell Therapeutics, Inc. Baxter conveyed both license rights to the Civin patents and Isolex product development to Nexell.

Since that date, Nexell has carried the torch for commercialization of the CD34 technology. Isolex 300 & 300i Magnetic Cell Selection System received FDA approval in July 1999. The indication for use is identified as "Processing autologuous peripheral blood progenitor cell (PBPC) products to obtain a CD34+ cell enriched population intended for hematopoietic reconstruction after myeloablative therapy in patients with CD34-negative tumors."[5]

To this point, CD34+ appears as a paradigmatic case of a university discovery of a biomedical invention, with basic research findings being handed off to firms that engage in subsequent product development, marketing, and responsibilities for securing regulatory approvals. The history, however, is complicated by the interjection of a set of parallel university discoveries, parallel university involvement with established and start-up firms and a labyrinth set of patent infringement cases and court decisions.

[5] http://www.fda.gov/cber/pma/P970001.htm.

In 1984, soon after the filing date of the Civin patents, a research team led by Dr. Ronald Berenson at the Fred Hutchinson Cancer Research Center in Seattle, Washington, was engaged in stem cell research under a different NIH grant.[6] As a result of their research, they discovered a monoclonal antibody called 12.8, which like My-10 and other subsequently discovered antibodies in the CD34 cluster, binds to an antigen on the surface of stem cells.

Berenson's cell separation technology is similar to what was disclosed in the Civin patents; however, the monoclonal antibody developed for this purpose was designated as the 12.8 antibody, another monoclonal antibody that binds to the antigens in the CD34 cluster. What excited the scientists at the Hutchinson Center was that the 12.8 antibody has some advantages over the My-10 antibody. Specifically, the 12.8 antibody binds in ten places in the CD34 cluster, while My-10 only has two binding places; further, the My-10 only binds solely to human stem cells but the 12.8 antibody also binds to baboon stem cells. This allowed the possibility of animal studies in baboons, which subsequently led to approval of the 12.8 antibody for human use. The promising results encouraged Dr. Berenson and others at Hutchinson and outside venture capitalists to form CellPro in 1989 to bring their technology into the market.

In July 1990, CellPro created a working cell bank to produce the 12.8 antibody and marketed two machines, the Ceprate LC and the Ceprate SC, which allow customers to use the 12.8 antibody to perform Berenson's cell separation method. In 1990, CellPro raised an additional $7.5M from investors and in 1991 issued its public offering. CellPro believed that the Civin patents are invalid and unenforceable. As an intellectual property protection strategy, however, CellPro also set aside $3M as a reserve for potential litigation involving the Civin patents, and its financial forecasts included provision for possible litigation as well as the possibility of being ordered, were they to lose the case, to pay a 'stiff royalty' of 15% as damages.

CellPro was charged almost immediately by Baxter with patent infringement. In January 1992, Baxter claimed that CellPro's technology infringed on its patents and proposed a payment of $750,000 and 8% royalty on future sales. The two firms negotiated but were unable to reach any agreements. (In this same period, two other companies, Applied Immune Sciences [later RPR Gencell] and Systemix [later acquired by Novartis],[7] came to terms with Baxter to sublicense CD34 technology.)

As a defensive move, in April 1992, CellPro filed suit against Baxter and BD for unfair competition and antitrust violations in federal court in the state of Washington. The remedy sought was the inva1idation of the CD34 patents. JHU and Baxter reiterated their licensing offer, but CellPro refused. The CellPro case was dismissed by the Federal judge on the grounds that the court lacked jurisdiction over JHU because it had no presence in Washington State.

After several failed attempts to negotiate shared rights to CD34 technology with CellPro in 1994, Baxter, Becton-Dickinson and JHU sued CellPro for patent infringement of certain claims of the '204 patent in Federal court in Wilmington, Delaware. CellPro counterclaimed for a declaratory judgment of the invalidity of '204 patent and no infringement of certain claims of the '680 patent. The counterclaim prompted JHU to sue CellPro for infringement of '680 patent as well. In 1995, a jury in Delaware returned a

[6] Petition letter to the honorable Donna E. Shalala, March 3, 1997 from Lloyd Cutler and Birch Bayh at http://www.nih.gov/icd/od/foia/cellpro/index.htm.

[7] NAT'L INSTS. of Health, Determination in the Case of Petition of CellPro, Inc. (Aug. 1, 1997) at http://www.nih.gov/icd/od/foia/cellpro/pdfs/foia_cellpro39.pdf.

verdict entirely favorable to CellPro, indicating that all of the asserted claims of the two patents were invalid for both obviousness and lack of enablement, and therefore CellPro did not infringe on them.[8] In an effort to resolve this continuing series of suits, Baxter offered CellPro a license but CellPro refused during mediation.[9]

In July 1996, Judge Roderick McKelvie, United States District Court Judge for the District of Delaware, overturned the verdict and ordered a new trial. The judge upheld the validity of the patents and subsequently ruled that CellPro had engaged in patent infringement, leaving open only the question of whether the infringement was willful. In March 1997, the new jury ruled that CellPro had indeed acted willfully. Judge McKelvie ordered CellPro to pay a total of $ 15.6M for damages, of which $7.6M was for infringement damages and $8M for attorneys' fee (Bar-Shalom and Cook-Deegan 2002). CellPro made a last-ditch appeal. In August 1998, the United States Court of Appeals for the Federal Circuit granted JHU's motion for judgment that CellPro infringed claims of 1–5 of the '680 patent and claims 1 and 4 of the '204 patent.

Even before the verdict, in 1997, CellPro began marshalling its political and legal forces to petition for NIH march-in rights for a compulsory license to allow CellPro to develop their own products by using their 12.8 technology.[10] It was the first time under the Bayh Dole Act that NIH was asked to exercise its march-in rights. In 1998, NIH declined CellPro's petition and decided to enforce JHU's patent against CellPro.[11] CellPro faced bankruptcy.

In 1999, Nexell, the spun-off company from Baxter, acquired technology rights from Baxter International, Inc. and at the same time acquired CellPro. Pursuant to the CellPro Acquisition Agreement, CellPro filed a petition for reorganization under Chapter 11 of the Federal Bankruptcy Code on October 28, 1998. Among other things, the Acquisition Agreement[12] required CellPro (1) to withdraw its citizen's petition(s) before the FDA, and otherwise to refrain from attacking NCI's premarket approval application for the Isolex cell separation systems, and (2) to withdraw its petition before the Department of Health and Human Services (HHS) requesting the exercise of so-called march-in rights with respect to the patents underlying the CD34+ sublicense.[13] Nexell reverted sales rights of the Isolex instrument to Baxter in June 2001. Baxter is still selling Isolex Cell Selection System under their cellular therapies products. The use of CD34 stem cells was approved by the FDA in 1996.

Since then, thousands of patients have been treated worldwide using the CD34+ selection technology, and CD34 cells have been studied extensively in over 10,000 research articles.[14]

[8] Email correspondence from Howard Califano, Director of the Office of Technology Licensing to David Blake, dean of the Medical School (August 7, 1995: 11:22 a.m.).

[9] Declaration of Dr. Jerry A. Hausman mentioned that CellPro repeatedly refused Baxter's 1992 offer of a license for $750,000 and an 8% royalty.

[10] Letter to Donna E. Shalala, Secretary of Department of Health and Human Services. 1997.

[11] http://www.nih.gov/news/pr/aug97/nihb-01.htm. NIH determination in the case of petition of CellPro, Inc.

[12] 10 K report, Nexell, about their march in the Baxter's cancer therapy and acquire of CellPro. http://sec.edgar-online.com/2000/03/30/15/0000898430-00-001062/Section2.asp.

[13] http://sec.edgar-online.com/2000/03/30/15/0000898430-00-001062/Section2.asp. Nexell 10 K reprot filing March 30, 2001.

[14] Capturing the stem cell. Winter 2004. Johns Hopkins Medicine. Promise and Progress. http://www.hopkinskimmelcancercenter.org/publications/publication.cfm?DocumentID=436&publicationID=15&publicationtypeid=1.

3.5 Adjusted clinical groups (ACG) case-mix system

Software is copyrighted rather than patented, and thus at times omitted or subsumed in mainstream reporting series on university technology transfer. Yet a software copyrighted product, Adjusted Clinical Groups (ACG) Case-Mix System (US Trademark 2376232), constitutes Johns Hopkins University's largest single license in terms of total intellectual property revenue.

ACG grew out of university research and was developed as an analytic tool. It was a relatively low-cost invention as its development involved writing computer code that codified knowledge already presented in academic articles. As such, it is an example of von Hippel's concept of a user-defined innovation that subsequently wends its way into commercial use.

The ACG Case-Mix System originated as the Ambulatory Care Group Case-Mix System and grew out of clinical observations made by Barbara Starfield, M.D., M.P.H. at the JHU School of Public Health. Research by Dr. Starfield and her colleagues in the early 1980s examined the relationship between morbidity and health care services utilization among children in managed care settings. Dr. Starfield theorized that children with the highest health care expenditures were not those with a single chronic illness but rather with multiple, seemingly unrelated conditions. To test her hypothesis, she grouped illnesses within pediatric HMO populations into five discrete categories:

- Minor illnesses which are self-limited if treated appropriately (e.g., the flu, or chicken pox);
- Illnesses which are more major but also time limited if treated appropriately (e.g., a broken leg or pneumonia);
- Medical illnesses which are generally chronic and which remain incurable even with medical therapy (e.g., diabetes or cystic fibrosis);
- Illnesses resulting from anatomical problems that are generally not curable even with adequate and appropriate intervention (e.g., cerebral palsy or scoliosis); and
- Psycho-social conditions (e.g. behavior problems or depression) (Starfield et al. 1991).

Her subsequent research demonstrated that the clustering of morbidity is a better predictor of health services resources used than the presence of specific diseases. These findings, financed by NIH, led to the series of highly cited academic articles. The perspective underlying Dr. Starfield's research, namely that it was possible to predict health care costs, was timely and fit with a larger movement of health cost containment.

Consistent with the then prevailing norms of science that dominated JHU's research culture until recently (Feldman and Desrochers 2003), Starfield did not focus on the potential commercialization of her research. However, Jonathan P. Weiner, then an assistant professor and one of Starfield's co-investigators on her later more applied work, immediately saw the potential for a commercial product. Starfield and Weiner had started working together on this research in 1985. Their first manuscripts on ACG were completed in 1989 and published in 1991 in the respected journals *Health Services Research* and *Medical Care*. Weiner and Starfield distributed the software to other academics. The interest they received from HMOs, state government health agencies and other insurance organizations indicated that there was commercial demand for the software. Another of the co-authors, Walter Stewart, an Adjunct professor of epidemiology, established a consulting business around this idea, thus creating another start-up from this work.

Weiner first considered starting a company to distribute the software but decided against it because he was not sure how it might affect his academic career, given the then

prevailing negative attitude towards commercialization of academic research prevalent at JHU. Instead, in 1989 he sent five letters to health care companies to see if they were interested in licensing the product. Computer Sciences Corporation (CSC) was the only company that responded. CSC provided earnest money of about $40,000 for further development of ACG. Weiner also received encouragement through a $1M grant to develop a Medicare module. This money came from HCFC through a local connection. HCFC was one of several companies started by Carl Schram, a JHU health economist who had left the School of Public Health to pursue entrepreneurial activities.[15] The ACG System was introduced by CSC for commercial sale in 1991. CSC is still the exclusive reseller of the JHU ACG System. CSC has approximately 90,000 employees worldwide with revenues of $11.3B for FY2003. Currently more than 175 organizations worldwide use ACG.

JHU receives about $3M annually from CSC in licensing revenues from ACG. In keeping with its mission to enhance public health and welfare, JHU also makes the software available in a streamlined version to state Medicaid agencies, which help allocate health resources to state Medicaid populations at no cost for rate-setting/capitation purposes. Since the free ACG-Medicaid system does not come with technical support, JHU has trained consultants to provide installation and support functions. Five JHU staff members are assigned to working on enhancing the system, among their other research. Updates are released approximately every 18 months with new enhancements that reflect changing regulatory and institutional requirements and incorporate user suggestions. For example, the 2003 version of ACG incorporated predictive modeling that allows identification of high-risk patients who may benefit from case management and other targeted services. Weiner's lab also continues to work on the updates and assistance from CSC.

3.6 MiniMed

Treatment of diabetes and other chronic medical conditions requires the controlled release of medication into the bloodstream over extended periods of time. A shortcoming of conventional methods is that they do not prevent ingested or injected drugs from concentrating in the blood, resulting in uncontrolled peaks and rates of decay of the medication. A more effective approach is to release medication directly into the bloodstream at a programmed rate in order to achieve the desired dosage of insulin. The need for such continuous and time-sensitive control provides significant advantages in the treatment of diabetes.

The Programmable Implantable Medication System (PIMS), developed by researchers at the JHU Applied Physics Laboratory, provides this capability. This solid-state device allows precisely controlled doses of medication to be released into the bloodstream or through the blood-brain barrier at user-programmable rates. PIMS is surgically implanted in the diabetic's abdomen to continuously deliver insulin. When an insulin refill is needed (about four times a year), it can be injected without surgery via a special hypodermic needle. Both patient and physician can adjust the insulin delivery rate via digital telemetry, a technique developed by NASA to communicate with a spacecraft from Earth. By holding a small radio transmitter over the implant and dialing one of ten preprogrammed codes, the

[15] Schramm left JHU to head the Health Insurance Association of America and later became executive vice president of Fortis (now Assurant) and president of its health insurance operations. Schramm, was an active entrepreneur and co-founded HCIA, Inc. and Patient Choice Health Care and founded Greenspring Advisors.

diabetic can change the infusion rate or ask for a supplemental dose of insulin before meals or when blood sugar levels are elevated. Another code allows the physician to access information from the pump's stored memory, reprogram insulin delivery, and generate computer records of the pump's performance.

The PIMS resulted from group efforts begun in the 1970s at NASA's Goddard Space Flight Center, located near JHU's Applied Physics Laboratory (APL); MiniMed Technologies, a California-based manufacturer of medical equipment; and several private companies founded by Alfred E. Mann. After studying physics at UCLA, Mann began two aerospace companies, Spectrolab and Heliotek, which were both sold to Textron and are now owned by Hughes Electronics, a unit of the General Motors Corporation. One of the main technologies Mann developed in these companies was satellites. In 1969, Mann was approached by JHU scientists who were working on designing longer lasting batteries for pacemakers. Pacemakers were a hot technology at the time and involved collaborations between scientists from the Medical School and APL. The idea was that the space technology had a dual use for medical technologies. Upon the completion of this research, Mann and Robert Fischell, who was on the faculty at APL, founded a new company called Pacesetter Systems to further commercialize the rechargeable pacemaker batteries that they had developed. The company, which was privately held, was sold to Siemens of Germany for $150M in 1985 and is now owned by St. Jude Medical, Inc. Pacesetter Systems, behind Medtronics, is the second largest supplier of pacemakers in the world.

In 1979, Mann, then CEO of PaceSetter Systems,[16] was demonstrating a new pacemaker design to clinicians at the University of Alabama when the discussion turned to the severity of heart complications due to diabetes and the difficulties in monitoring insulin levels. This suggested a new business opportunity to Mann. In 1979, he started MiniMed as a firm dedicated to commercializing insulin pumps. The company funded research at the JHU APL to adapt the miniaturized pumps, originally developed under NASA funding, to monitor and deliver an insulin supply to the human body.

MiniMed introduced its first insulin pump, the MiniMed 502, at the 1983 American Diabetes Association convention. Little more than a rudimentary product, the 502 was soon followed by the 502A, which represented a major technological advancement in both reduced size and increased programmability over previous prototypes for insulin pumps. The early MiniMed products were external, usually clipped to a belt or other part of the user's clothing and worn around the clock. The 502A was about the size of a credit card, weighing just 3.8 ounces, containing a microprocessor, a long-life battery, and a syringe reservoir filled with insulin.[17]

MiniMed continued to develop external monitors while refining the JHU-APL PIMS. Christopher Saudek, a JHU endocrinology professor implanted the first MiniMed pump in a patient at Johns Hopkins Hospital in November 1986. Saudek's research on the pump had been funded by grants from the company. Within 4 years, the implantable pump was in wide-scale testing in the United States and France. In 1995 approval to market the implantable pump throughout Europe was granted, and the pump became the most successful implantation device ever sold in Europe.

[16] MiniMed was formed as a subsidiary of Pacesetter and spun off in 1985 when Pacemaker was acquired by Siemens. Mann also started and controls the Advanced Bionics Corp., which makes implants that allow deaf people to hear, and Medical Research Group Inc., which is doing research on the artificial pancreas for MiniMed. All the companies are next to one another in Sylmar, Calif., north of Los Angeles.

[17] In related marketing and product developments, MiniMed conducted user surveys to identify the most desirable features that people wanted to see in insulin pumps. Thus, the products were well received as they provided a set of attributes such as menu driven programming and style that consumers valued.

In June 1992, with its many R&D projects taking distinctive directions, MiniMed divided into three companies. An intravenous pump, the MiniMed III, was acquired by Siemens and became Siemens Infusion Systems. A neural stimulation project became Advanced Bionics Corporation, and developed the Clarion, a cochlear implant that provides a hearing aid for the profoundly deaf. The microinfusion product segment continued as MiniMed, Inc., chartered to develop devices and products to aid people with diabetes and other chronic diseases.

In 1992, MiniMed continued to advance the external pump technology with the introduction of the MiniMed 506, which was developed in house. This pump was a major redesign over earlier pumps in its programming, electronics and mechanics, and delivered many advanced features, such as meal bolus memory and daily insulin totals. Innovation continues with MiniMed's work on the next-generation implantable pump, which contains several technology improvements, such as improved memory, a longer battery life, and less weight.

MiniMed successfully went public in July 1995. At the time MiniMed dominating the US insulin pump market with a share above 75%. In 1996 Mann was the Ernst and Young Entrepreneur of the Year. In August 2001, MiniMed was acquired by and became a division of Medtronics. At the time the original research was conducted, Johns Hopkins University did not actively pursue patents and in the absence of a patent there was no basis for a license. Hopkins was in negotiations with Alfred Mann and the Mann Foundation for a $100,000,000 endowment. The negotiations broke down over intellectual property issues.

4 Discussion

Rather than the one-to-one, pipeline, correspondence between an academic patent and a technological innovation, as suggested by the subtitle, *25 Innovations that Changed the World*, of AUTM's 2006 report, *The Better World Report*, the case histories highlight the dependence of the commercialization of a university-based patent on a complex, daisy-chain set of relationships involving faculty inventors, firms that may sponsor the academic research that leads to an university patent, firms that initially license the patent (at times to form a start-up firm) and those that bring the technology to market. Indeed, as illustrated by the CD34 case, distribution of first the scientific credit and then of the economic benefits from a patent can depend on legal and political contests. (Civin and Ware 2001). If any metaphor seems appropriate to describe the commercialization of academic research, it is that of a Rubik's cube.

The case histories also suggest that the behaviors of university TTOs and entrepreneurial faculties with respect to patents and spin-offs are functions not only of their own strategies and cultural norms but also of the strategies and experiences of the firms with which they are engaged. 3-M was an active, experienced participant in PSU's decision to seek patents on its artificial heart technology. Likewise, the hesitancy of the firms that were support Edwards's research to have it conducted as part of the "open" system of faculty and student research was a factor in his decision to leave PSU to form a start-up firm, only to return to a university setting after a few years.

Perhaps most importantly, the case histories imply that aggregate data or theoretical formulations data related to intellectual property variables, such as patents, licenses, royalty revenue, R&D expenditures, and size and characteristics of technology licensing offices, by themselves provide incomplete information about the contribution of the knowledge embedded in a university patent to the generation of a commercially viable

technological innovation. These mainstream approaches provides little information about how intellectual property is transformed into technological innovations, by, by whom, in what markets, and in accord with what business strategy. How, for example, does one account for the contribution of a university patent to a technological innovation when the patent is combined with a firm's in-house R&D, or combined with other patents, be they from the same group of faculty inventors or other universities?

In a related manner, central to the elongated process affecting the travails of bringing the Penn State artificial heart to a marketable stage was 3-M's exit from the cardiovascular machine business. This decision stemmed from a general rethinking of the firm's corporate strategy, yet it was the precipitating event that set in motion the business transactions, including efforts to use the license to the Penn State heart as the magnet for venture capital, that led to its ultimate and current acquisition by Abiomed, where it became part of the firm's effort to entrench and expand its market position. In a contrary manner, PennMulch has evolved from a niche product controlled by a regionally based venture capital firm into a more broadly marketed consumer product by Lebanon-Chemical, whose acquisition of the relevant license and firm assets stems from its decision to reposition itself as a commodity producer of bulk chemicals to a product development company.

The larger research questions that emerges from these cases are how to best link analysis of the markets for intellectual property rights with those of technological innovation and business strategy. The cases reported here are only a start, but they do point to the need for an expanding the scope of research on university technology transfer activities.

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