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Present at the biotechnological revolution: transformation of technological identity for a large incumbent pharmaceutical firm

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Abstract

Management of successful incumbent firms experience difficulty in recognizing the need for, and effecting change in the firm's technological identity after an externally generated shift in the industry's technological trajectory. Nonetheless, some large pharmaceutical firms have transformed their technological identity in drug discovery from a chemical/random screening to biological/drug design model. We report how one of the world's most successful incumbents transformed. Technically sophisticated senior management championed the transformation. It was achieved primarily through hiring many new scientists embodying biotechnology; existing personnel acquired the expertise or left. Continual self-transformation is part of the corporate ethos. Some differences in incumbent and entrant technology remain: incumbents use a wider range of techniques consistent with their complementary assets. Publication and incentive compensation policies are driven by the need to attract and retain the best scientists. Professor–firm collaborations are ubiquitous, often non-public, and best identified in quantitative analyses by co-publishing. Collaborations with new biotechnology firms are used primarily to substitute for developing internal expertise judged of marginal value. No drug-discovery collaborations exist with other major incumbents. We identify another seven or eight incumbents similarly transforming as indicated by top scientific talent and patenting success. Published by Elsevier Science B.V.

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1. Introduction

Technological advance arising within an industry is an effective means of increasing sales and net income of the incumbent firms in an industry, although the gains of the firms leading the innovation may come at some cost in market share and profits of lagging firms. However, when a revolutionary breakthrough in technology originates outside the industry and uses a different set of skills from those required to practice the existing technology, new entrants may replace incumbent firms as a group, and even the definition of the industry may be transformed (e.g., from carriages to automobiles).

The wave of innovations in drug discovery associated with the advent of modern biotechnology—beginning in the 1970s, gaining strength in the 1980s, achieving dominance in the 1990s—appears to be an archetypal example of externally generated, incumbent-skill-obsoleting, discontinuous innovation, which the literature predicts leads to replacement of incumbents (pharmaceutical firms) by entrants (new biotechnology firms). There has been an ongoing process of consolidation among the incumbent drug-discovery firms, but a substantial number of incumbent firms surprisingly have flourished. We report here on the experience of one of the largest flourish-

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ing incumbents to enrich our understanding of the process by which incumbents are or are not supplanted by entrants in the face of an external technological discontinuity.

The paper is organized as follows: Section 1 reviews the literature on technological revolution and displacement of incumbent firms. Section 2 provides a primer on the biotech revolution as it applies to drug discovery. Section 3 presents the goals and methodology of the case study. We turn to Section 4 in reporting what we learned about how this major firm transformed its technological identity to the point that its scientists can claim that there is no difference between the best new biotech firms and itself in how research is done. We next report the firm's approach to collaborations with scientists at universities and at other firms in Section 5. In Section 6, we present some evidence on how generalizable the case study may be by comparing this and other major pharmaceutical firms with the dedicated biotech firms in terms of their access to leading-edge scientists and their genetic-sequence patenting success. Conclusions are drawn in Section 7.

2. Technological revolution and displacement of incumbent firms

The concept of the technological identity of the firm is basic to the issue of displacement of incumbent firms through technological revolution. In the simplest models, all firms have identical production and cost functions. Underlying the enormous population–ecology literature is the idea that each firm has a fixed technological identity, related to the broader concept of entrepreneurial capacity (Friedman, 1976, pp. 106–126), but these identities vary across firms. The entry or exit of the firm depends on how suited its technological identity is to the industry's competitive conditions at any given time (Baum, 1996 provides an excellent recent review of this literature). Kaufman (1971) (pp. 8–23) argues from an organizational point of view that it is extremely difficult for organizations to change. [1] If a firm's technological identity is fixed, then studies of entry or exit can tell us something about which technology is dominant, for the time being, but transformation for survival is impossible.

Nelson and Winter (1982) elaborate a concept of the firm that is amenable to transformation. They see an organization as separable from the sum of its parts because it embodies particular information about how to do things in a set of task routines that require little direct intervention by management to ensure that the work of the organization gets done. For organizations in technologically-based industries, these task routines and the embodied knowledge they represent will determine the technological identity of the firm. Thus, a firm can have a kind of organizational capital that provides a continuing competitive advantage. Unless conditions change, new entrants cannot eliminate this competitive advantage by hiring away individual employees (although there is occasional litigation over firms hiring a large number of employees in an attempt to replicate these task routines).

Demsetz (1988) sees the identity of the firm determined by the fields for which it has acquired organizational mastery of specialized bodies of knowledge. Individual actors—managers—can choose to enlarge or change the fields for which the organization incorporates mastery (see the review by Tolbert and Zucker, 1996). The technological identity of a great high-technology firm is recognized as the source of its strength, providing persistent high returns (Waring, 1993). It may be difficult to either recognize or effect any substantial change in what has worked so well and, for a time, will continue to produce supranormal earnings in the face of a breakthrough change in technology, which will ultimately convert that strength to an outmoded, uncompetitive technology. The question is when management of an incumbent firm will recognize a new dominant technology, and whether they will then choose to transform the firm's technological identity or gradually withdraw from the industry in the face of the new technology.

As suggested by Dosi (1982), an existing organization can achieve routine excellence in pursuit of a given technological trajectory that carries forward a shared technological paradigm, but this process does not lead to substitution of new technological trajectories and paradigms in the face of opportunities aris-

[1] Kaufman does allow for change to occur through personnel turnover.

ing from scientific breakthroughs (see also Klevorick et al., 1995 on the importance of technological opportunity). Lounamaa and March (1987) elucidate some of the difficulties in organizations attempting to learn adaptively in the face of a changing technological environment. (See March and Simon, 1993 for a more nuanced review of the literature on organizational learning.)

Tushman and Anderson (1986) present evidence that the survival of incumbent firms is enhanced by technological discontinuities introduced by incumbent firms, and based on their existing knowledge set while survival is threatened if the discontinuities are external in origin and require mastery of new fields of knowledge. Of course, the choice of exit in the face of new, unfamiliar technologies may be completely in line with rational wealth maximization. Henderson and Clark (1990) and Henderson (1993) elaborate the Tushman and Anderson hypothesis and present further evidence in its support. Reinganum (1983, 1989) also argues that since incumbents have monopoly rents whose value will be lost from radical innovations, such breakthroughs are most likely to come from entrants rather than incumbents.

Kimberly and Quinn (1984) are more optimistic about the possibility of managers taking entrepreneurial actions that transform the organization. Kim (1997) reports numerous case studies in which top management has consciously created crises for organizational subunits to achieve innovative transformation in the rapidly developing Korean economy. In Zucker and Darby (1996a), we report evidence of extensive transformation of most of the world's top-twenty drug-discovery firms by the early 1990s, as evidenced by discovery of new biological entities, genetic sequence patents, and co-publishing with top academic biotech scientists. [2] Therefore, the drug-discovery pharmaceutical industry appears to present a case in which numerous firms have pursued a strategy of transformation of technological identity—adopting the new technological trajectory rather than pursuing 'underinvestment and incompetence as responses to radical innovation'. This surprising success might provide us the basis for better understanding which incumbent firms transform and which die in the face of an external technological discontinuity.

Good fortune—in the form of targeted support from the Alfred P. Sloan Foundation through the NBER Research Program on Industrial Technology and Productivity and personal intervention by NBER President Martin Feldstein—provided us access to the top research and policy management, as well as some archival material, of one of the most successful transforming firms. Section 3 provides a brief primer on biotechnology and its relation to the drug-discovery industry as required for interpreting what we learned about the process of transformation from investigating this firm.

3. The biotechnological revolution in drug discovery

The biotechnological revolution is an outstanding example of the type of technological breakthrough most likely to result in the replacement of previously dominant incumbent firms by newly created firms that encompass the new technology in their technical identity: the new technology's origin is in academic biological sciences, and its practitioners design drugs based on scientific hypotheses, while the drug discovery technology, dominant in the pharmaceutical industry in the 1970s and into the 1980s, was based on chemistry and involved nearly random screening of molecules to discover ones that were effective.

The major pharmaceutical firms of the type we are concerned with in this paper are creators, manufacturers and marketers of human therapeutics, vaccines, and diagnostics. An essential characteristic of this segment of the pharmaceutical industry is that they are involved in discovering new products that are protected for a time by patents. Purely generic manufacturers, whose incomes depend on being low-cost manufacturers and distributors of drugs once they go off patent are not really part of the drug-dis-

[2] As discussed below, many drug-discovery firms have pursued a strategy of using new biotechnological techniques to discover small-molecule drugs that can be synthesized by chemical methods rather than produced by living organisms. Thus, all their biotech-based drugs would be classed as new chemical entities, not new biological entities.

covery business. [3] The revolution in the biosciences has transformed technologies used in many other industries (including medical supply, chemical, agricultural, food-processing, and brewing), but none so rapidly and dramatically as in drug discovery.

3.1. What is the biotech revolution?

Broadly enough defined, biotechnology has been used as long as people have baked bread and drank wine. Crossbreeding of animals and growing penicillin are other examples of such traditional forms of biotechnology. Today, biotechnology, or biotech, is generally defined more narrowly in terms of using breakthrough technologies such as genetic engineering. An excellent working definition of biotechnology, as put forward by a respondent at the subject firm of the case study, would be as follows:

In discussing biotechnology at [the firm], I use biotechnology to mean the revolutionary breakthroughs in life sciences over the last two decades including especially, the use of recombinant DNA to create living organisms and their cellular, subcellular, and molecular components as a basis for producing both therapeutics and targets for testing and developing therapeutics. Recent developments focus on structural biology, combinatorial chemistry, and gene therapy.

In ongoing research with a number of associates, we have found it useful to date the beginning of the biotech revolution in bioscience with the 1973 discovery by Stanford professor Stanley Cohen and University of California-San Francisco professor Herbert Boyer of the basic technique for recombinant DNA (Cohen et al., 1973). The commercial applications of biotechnology followed quickly in new biotechnology enterprises formed as early as 1975 and 1976. Sindelar (1992, 1993) provides a useful introduction to these applications in the pharmaceutical industry. [4]

The revolution in bioscience is not completed nor is it entirely clear what will ultimately prove its most important areas of applications in the pharmaceutical industry. It is clear, however, that biotech is a dominant technology for at least some areas of production of biological agents, for creation of targets for screening and evaluating potential pharmaceutical products, and as a methodological base for creating potential pharmaceutical products. Currently, firms in the industry are undergoing a shakeout both as it becomes easier to separate the most effective from the less effective of those firms using the new technologies, and also as government and regulatory initiatives and health-care market restructuring impact anticipated future and current profitability in the pharmaceutical industry. Nonetheless, it is clear that biotech is a dominant technology even as it is unclear what will be the makeup of the industry in which it will be utilized.

3.2. Intellectual human capital and the evolution of industrial biotechnology

In a series of papers recently summarized and extended in Zucker and Darby (1996b), we have shown that the top-producing or 'star' scientists—as measured by frequency of appearance in GenBank,

[3] For some purposes, it might be preferable to exclude also diagnostics from the definition of the pharmaceutical industry. However, many new firms aiming to enter the therapeutics and vaccines industry first produce diagnostics as a faster source of revenues utilizing their technologies. The economics of this industry was reviewed extensively by Comanor (1986).

[4] Sindelar (1992) (pp. 3–4) notes in reference to pharmaceuticals that modern biotechnological techniques can be divided "into three broad areas..." Recombinant DNA techniques "take identified gene sequences from one organism and place them functionally into another to permit the production of protein medicines such as human insulin, alpha interferon, and colony-stimulating factors. Second, methodologies have been developed for producing monoclonal antibodies, ultrasensitive immune system-derived cells designed to recognize specific substances known as antigens that are uniquely associated with chemicals found in foreign organisms and/or humans. Developments in this field have led to their use as diagnostic agents for laboratory and home use in pregnancy tests and ovulation prediction kits and in the design of site-directed drugs such as OKT-3 for kidney transplant rejection. Finally, the development of technologies to study DND–DNA and DNA–RNA interactions has led to the formation of DNA probes (antisense technology) for a variety of research purposes with potential uses as diagnostics and therapeutics."

the universe of all genetic-sequence discoveries, up to 1990—played a crucial role in determining where and when firms entered biotechnology, and which of them were most successful. Furthermore, during their periods of active publication as or with employees of firms, the stars are more productive (both in terms of articles per year and citations per article) than they are before or after that time. The star effect on firm success is large: an otherwise average firm with five articles co-authored with a local university star is estimated to have 5 more products in development and 3.5 more products on the market by 1991, and 860 more employment growth from 1989 to 1994 (Zucker et al., 1997a,b). The number of universities with top-quality bioscience departments and the number of scientists supported by federal grants in the local region also affect the rate of entry of firms into biotech, but the number of collaborators (co-authors of the stars) does not (unless marginally late in 1980s).

Interestingly, the largest concentrations of the intellectual human capital providing the scientific base for biotechnology was located in California and the Boston area. This distribution was quite different from that of incumbent pharmaceutical firms, although there was another concentration in New York City, which was reasonably close to some of the incumbents. Therefore, a key question for exploration in the case study below is how the firm accessed the scientific base, particularly in view of both geographic impediments, and the ability of star scientists to participate in founding new biotechnology firms, which made many multimillionaires when the new entrants went public.

4. Goals and methodology for the case study

Our earlier empirical work was grounded by case studies of new biotechnology firms in the US and the UK, and fieldwork on four Japanese incumbent firms that had adopted biotechnology (Liebeskind et al., 1996; Darby and Zucker, 1966). In the Japanese fieldwork, we repeatedly heard the view that Japan's system was inhospitable to biotechnology, in part, because of the institutional barriers to founding new biotechnology firms, so that transformation of incumbent firms was the only unsatisfactory alternative. Accordingly, we were delighted by the opportunity to explore the transformation of one of the five largest US pharmaceutical firms, although permission to do so was granted only on condition that the firm not be identified.

This firm is widely and correctly regarded as one of the most successful pharmaceutical companies in the world, with an enviable record of science-based drug discovery and development, outstanding abilities in the management of clinical testing, excellent ability to shepherd a New Drug Application (NDA) through the FDA in as short a time as possible, and a first-rate marketing group to effectively distribute the products when they are approved. It is one of a handful of such firms in the US, each endowed with loyal employees who are both proud of their company, which they believe the best among some outstanding competitors, and very pleased that their personal success is in direct proportion to their ability to contribute to reducing suffering and death among victims of disease.

Given these company attributes, it is easy to see why economists and management strategists would hypothesize that it would prove difficult, if not impossible, to tamper with a proven formula for success. Nonetheless, we found that the ethos of this science-driven company valued innovation and that there was great pride taken in the firm's ability to continuously change how it did its research and development, so that ongoing technological change appeared to be an integral part of the firm's identity. [5]

4.1. Goals

In our experience, lengthy discussions with knowledgeable participants with reinterviews to discuss differences between the information provided and empirical research can lead to better understand-

[5] We note that American universities clearly dominate the global market for post-secondary education. This occurs, we believe, precisely because of their success in institutionalizing and rewarding continual self-transformation. Hedberg (1981) argues that such a process of continual learning and unlearning is possible in firms.

ing of the underlying processes, institutions and constraints; hence to new hypotheses and better empirical measures for the empirical work. It was necessary, nonetheless, to focus the discussions around some working hypotheses on what determines whether an incumbent firm transforms or dies as the result of an external technological discontinuity. Our first goal is to report what we heard in sufficient detail that readers may come up with their own hypotheses.

The thrust of the literature reviewed in Section 1 is that this sort of externally generated shift in the technological trajectory is most likely to lead to entrants supplanting incumbents. We formalized this null hypothesis as:

H0 immutability: Firms are born with a technological identity, and flourish when that identity has a competitive advantage. In the face of a radical technological breakthrough that makes another technology requiring different human capital dominant, previously successful incumbent firms will be unable to change, and will ultimately be replaced by new firms with the newly dominant technological identity.

With the advantage of hindsight, it was clear that some of the major drug-discovery firms were successfully transforming their technological identity. It seemed to us that preserving the value of organizational capital involved in clinical testing, acquiring regulatory approval, and marketing new drugs provided the incentive for firms to transform the complementary drug-discovery aspect of the business. Thus, we formulated the alternative hypothesis:

H1 Persistent success: In the face of a radical technological breakthrough which makes another technology requiring different human capital dominant, (at least some) successful incumbent firms will change the relevant part of their technological identity, bringing in new human capital, so that the value of their other assets is not wasted.

We knew from our relational database and prior empirical results, as well as the work of others, that the case-study firm would be an example of technological transformation supporting H1 relative to H0. So our practical goals were not to provide a counterexample of H0, which could be done with much less work, but to understand the organizational mechanisms of transformation, and whether the firm's possession of complementary organizational assets in R&D, as well as in the testing, regulatory, and marketing areas, led to differences in how the firm commercialized the breakthroughs in bioscience, as compared to the dedicated new biotechnology firms born lacking such assets. Since our earlier work had demonstrated that access to and working with top university bioscientists seems to be powerfully linked to success, we were particularly interested in seeing how this firm regarded and used such linkages.

Based on our prior case studies, we isolated three processes, to examine in this case study, that occur sequentially and at any step may lead to either immutability or to persistent success.

1. Detection of a change in the technological environment, with the best predictor the prior investment in R&D (Zucker and Darby, 1996a).
2. Decision to implement the new technology, often initially moving to involve star scientists in company operational decision-making and construction of new scientific teams (often combining new and old employees and thus techniques).
3. Ability to mobilize the necessary resources, either redeploying them from their prior use or raising new resources required to implement the new technology, where resources include scientific personnel, financial resources for product development, and management oversight in the selection of product targets.

We extend resource mobilization theory (developed in the nonprofit context; see McCarthy and Zald, 1977, McCarthy and Wolfson, 1996) to consider both the decision-maker's position within the firm and the availability of necessary resources (e.g., cash flow or external financing).

4.2. Methodology

Our contacts with firm employee's were coordinated by the executive in charge of public policy issues. To familiarize this executive and his colleagues in drug discovery with our interests, we provided first a series of papers reporting our previous research, and then a summary statement of goals (including shedding light on the two hypotheses above) together with a lengthy questionnaire that we

wished to use to guide our interviews during site visits to the main research facilities and the corporate headquarters. A few requests for personnel data were refused due to concerns over privacy of individual employees, but we soon agreed on the basic information to be sought and provided. This approach gave the firm the ability to identify appropriate respondents, and for these respondents to poll colleagues on issues in which they were uncertain. We interviewed a variety of respondents, including the executive vice-president in charge of drug discovery who was more than generous with his time in a sequence of face-to-face and telephone interviews. After each round of interviews, we analyzed what we learned and did preliminary empirical analyses, where indicated, to inform follow-up questions, usually preceded by questionnaires. Limited access to archival data, particularly on publications and presentations, was provided, and we used our copies of these records to test response accuracy. [6]

Upon completing these rounds of interviews, we provided an early draft of this report to our key firm contacts who corrected some misunderstandings, redacted some competitively valuable details of research strategy, and requested rephrasing of identifying passages. Our draft report and tentative findings were presented in a final meeting led by the executive vice-president in charge of drug discovery. We believe that what is reported in Sections 5 and 6 is as accurate an account of the firm's technological transformation as is possible in retrospect, given the proscription on access to personnel data on individual scientists.

5. Transformation as a response to technological revolution

The firm views itself currently as technologically indistinguishable in research and development from any of the best large dedicated biotech firms. The transformation from some involvement to state-of-the-art is seen as occurring between 1985 and 1990. While a few new biotechnology firms were founded between 1976 and 1979, most were founded in the 1980s, so this transformation might be characterized as lagging the commercial application of the new technology by no more than about five years. In terms of employment, this firm is one of the largest biotech enterprises based on its self-characterization.

5.1. Detection of the technological change

The firm actually was one of the first to market a biotech product, but this product was developed in large part by university scientists who themselves founded new biotechnology firms. Nonetheless, this alliance is evident of management awareness of the commercial importance of biotechnology very early in the 1980s.

5.2. The drivers of the transformation: decision to implement

Firm respondents clearly see the process of transformation as driven by top managers who were technically competent to evaluate the importance of the bioscience breakthroughs to the pharmaceutical industry, and had the vision to devote the resources necessary to ensure that the firm became a world leader in the use of those breakthroughs. [7] These managers included the firm's CEO and the head of the R&D group during the period of transformation. The individual who was the CEO had earlier played a leading role in initiating one of the first biotech collaborations at the firm (see discussion above of detection of the technical change).

5.3. Transformation process: resource mobilization within the firm

In the early 1980s, some research groups at the firm were utilizing biotechnology, but it was not a

[6] We are seeking funding to code this archival material in a form suitable for quantitative comparison with similar records acquired from two new biotechnology firms.

[7] In the fieldwork in Japan, we noted that senior research personnel at two major pharmaceutical firms were envious of the ability of American top management to understand and support the necessary technological transformation. In a third such firm, the only Japanese firm to have any star scientists as employees through 1990, senior research personnel attributed the firm's early adoption of biotechnology to the vision and adamant insistence of the CEO that these breakthroughs would transform their industry, if not indeed lead to replacement of the traditional industry.

general practice nor one consciously fostered. In 1985, with the appointment, as head of the research group, of a molecular biologist who had the full support of the CEO, the conscious effort to transform how the firm did drug discovery began. Biotechnology was introduced through focused groups, or SWAT teams, at this time. Over a period of three or four years, the firm's scientists generally switched to cloned human targets (receptors, proteins, enzymes, DNA) for initial testing of prospective drugs. [8] The firm's Japanese labs were operated independently and only recently have begun the same transformation under new leadership. By 1990, biotech had permeated the entire research organization, become 'central to the way we do drug discovery,' and the remaining SWAT teams were eliminated, as most of their members had already transferred to research teams focused on particular types of disease. In 1994, the firm hired another of our star scientists to lead developments in the area of gene therapy.

The firm's own biotechnology revolution was accomplished primarily by hiring people knowledgeable in the technology during a period of rapid growth throughout the 1980s and early 1990s:

The strategy was to hire many excellent people to grow our strength in bioscience in the late 1980s. [We] can hire from the best teams because the new biotechnology firms legitimized working in industry. We regularly compete with good university offers in our hiring. As with academic departments, some people already here got excited by what was being done by the new people and adopted the methods as well.

That is, the firm experienced rapidly expanding revenues based on discoveries made using the traditional technologies, and applied large parts of those new resources to acquire the intellectual human capital to replace the very technology that accounted for the current success. We cannot say from one case study how frequently such forward-looking decision-making occurs, but clearly it is possible that a commitment to continuous technological change is a major source of persistent success in high-technology industries. Even in the current period with a relatively stable research budget, the firm is using turnover to hire in targeted areas that go substantially beyond the initial bioscience breakthroughs discussed above.

5.4. *Incumbent / entrant differences in applications of biotechnology*

There is an ongoing controversy in the pharmaceutical industry as to whether incumbent firms have really adopted biotechnology, or only a part of it. As we have seen above, our respondents say that when one compares how recombinant DNA has been integrated in basic research drug discovery, their firm "is now indistinguishable from the best major biotech companies in how research is done." Biotech company executives sometimes assert that the major pharmaceuticals now use cloned targets to search for the same kind of 'small molecule' drugs they have always produced rather than really using biotechnology to produce 'large molecule' therapies. Major pharmaceutical firms (as seen below) do not accept the factual accuracy of this assertion, saying they do both. In part, this sort of self-conceptualization by advocates of new biotechnology firms can be interpreted as an attempt to define, for the financial markets, a view in which the entrants have a competitive advantage. If the new biotech firms do not dominate on science, few of them could hope to remain competitive with the incumbent firms that have outstanding track records in clinical testing, regulatory affairs, and marketing. One popular scenario for the pharmaceutical industry sees the major firms concentrating on the three latter activities, and increasingly buying their drug discoveries from the new biotechnology firms, thus converting a fixed to a variable cost.

However, this scenario does not recognize the considerable value of integrating testing, regulatory and marketing considerations with decisions on areas

[8] A firm scientist explains the advantages of this change: "For example, schizophrenia is a disease involving excess dopamine, and existing drugs operate by suppressing the action of dopamine. This is effective, but results in difficulties with motor function also controlled by dopamine. We can now identify subtypes of dopamine receptors and develop drugs which operate on the relevant subtypes without interfering with the operation of other subtypes. Thus, using biotech permits us to develop effective drugs which are safer and have fewer side effects."

of concentration for research, and on which drug candidates to continue working. [9] Perhaps more importantly, the R&D out-sourcing scenario does not recognize that it is all but impossible for a firm to be an intelligent buyer of research unless the firm has an ongoing capability of doing leading-edge research: [10]

[Our] basic strategy is excellent in-house research. This lets us make better decisions with respect to establishing relationships with new biotechnology firms and, if the right occasion were to arise, purchasing a new biotechnology firm. We have internal evaluators who can adequately assess their research quality, and, therefore, feel that we have effectively turned down deals that were less compelling scientifically.

Nor does the view that this major incumbent firm is indistinguishable in its research technology from the major new biotechnology firms adequately allow for the very real strengths that this sort of firm may have which are not available, without substantial additional investment, to the entrants. Such additional assets could well induce the incumbent firm to use technologies available to it, either in addition to, or as a substitute for those available to the entrants.

We found some evidence in our interviews that there were indeed technologies possessed by the incumbent firm that were viewed by its scientists as providing competitive advantage.

[We have] a competitive advantage as a result of a great history in chemistry. This could have been a disadvantage if there were great resistance to change. It is sometimes suggested, and I believe inappropriately so, that less thought is required [using combinatorial chemistry] than traditional methods. So leadership has been required to support those who adopt the new technology, and to reward those who accelerate the process of drug discovery. [The firm] also has a very significant collection of chemicals that other companies do not have.

Certainly, having more technologies available has the potential to reduce costs. The issue is whether the firm optimizes over the full range of opportunities, and at least this respondent acknowledges the dangers at the root of the immutability hypothesis, and indicates that he believes that they have been overcome. In complementary field work on drug manufacturing (rather than discovery), Pisano (1994) found that large pharmaceutical firms could shorten the process development time by laboratory experimentation for chemical-based drugs, but not for biotechnology-based drugs. This suggests that the manufacturing strengths of these firms are not easily transferred to other technologies.

Research executives at this large incumbent firm state that in fact they try both ends, constructing or identifying targets for drugs and production of drugs by biological processes. They believe that recently "there have not been a lot of successful new proteins; so it looks like the 'low-hanging fruit' was picked early. The remaining areas of application, like septic shock, have proved to be very complex." Indeed, they would argue that "the biotechs have themselves become less optimistic about proteins as therapeutics, and thus, have moved away from proteins and set up combinatorial chemistry groups of their own."

At this point, we see no yardstick to measure the differences in research strategy between any entrant/incumbent pair much less a typical one. We do believe that the case illustrates that the differences may be smaller than popularly believed, and that there is no necessary presumption that any differences favor the new entrants over the incumbents.

5.5. Incumbent / entrant differences in providing information to financial markets

Discussions with firm executives suggested that the Zucker et al. (1997a,b) finding—that significantly higher numbers of products in development are reported by entrants relative to incumbents, other things equal–may reflect different financial reporting approaches conditioned by different financial circumstances:

... biotech firms seem to announce drugs in development earlier. We want to avoid raising hopes that are

[9] See also Aghion and Tirole (1994) for an illuminating analysis of the advantages and risks of integrated vs. out-sourced R&D.

[10] Arora and Gambardella (1994) consider the case of biotechnology and point to differences among incumbents in ability to evaluate information and profit from collaborations as a significant competitive factor.

very often disappointed and so release relatively little information until the principle is proven in humans near the end of Phase II clinicals. Publications by scientists early on are fine, but as a company we try not to raise expectations since we neither want to raise patients' hopes without being able to deliver nor to violate our fiduciary responsibilities to not make unfounded claims. It also is something of a competitive advantage not to discuss at an early stage what seems to be promising...

And in another context:

We don't do a lot of public relations aimed at the current price of our stock. We believe that if we deliver the fruits of excellent research the stock price will take care of itself. The strategic orientation is rather different when you aren't pressed to raise money to cover the burn rate... [11] On the other hand, because of the importance of breakthroughs in the area of AIDS, we broke our usual policy and have been disclosing information about our AIDS drug development earlier than normal...

This sort of reported difference in announcement policies suggest that caution is warranted with respect to interpreting products-in-development differences as due to greater research productivity by the entrant new biotechnology firms.

5.6. Human resource policies during the transformation

Our previous research (Zucker and Darby, 1996b) indicates that star scientists combining genius and knowledge of emergent technologies are the gold deposits around which firms and their success were built subsequent to the biotech breakthroughs. These scientists had the ability to become a founder of a new biotechnology firm, earning in some cases literally hundreds, if not thousands of millions of dollars when the firm was taken public. In addition, star scientists may be pursuing personal goals of scientific achievement, including perhaps the Nobel prize. Japanese respondents point to factors making it impossible there to either start one's own firm, or to pursue scientific achievement outside the university as factors holding back their country's commercialization of biotechnology (Darby and Zucker, 1966). The ability of university-based scientists to start their own firms in the 1980s, and continue affiliation with their university and active scientific publication, provided opportunities that could not be offered by any major pharmaceutical company. However, the ability of a biotech star to break the bank declined dramatically in the latter half of the 1980s as the techniques diffused more widely.

By 1985, when this incumbent firm launched its effort to transform its technological identity, it could offer an overall employment package that was attractive to a number of the best scientists.

5.7. Publication policy

Unlike the reported case for Japan, this firm—and they believe much the same is true at other major pharmaceutical firms—follows a very liberal policy on scientific publication. Beyond a possible brief delay to prepare patent filings, the firm encourages publication of research results. [12] The policy is rationalized as follows:

We see some danger of losing our competitive advantage by publishing, but a much greater danger if we do anything that deters the best scientists from coming here. Further, we need for our scientists to have great reputations in order to bring others like them to [the firm]. We are the beneficiaries of worldwide scientific research, and thus we also need to contribute to this pool of scientific knowledge, creating a public good.... Relative to new biotechnology

[11] The 'burn rate' is the term used by analysts specializing in new biotechnology firms for the [negative] "sum of the net cash flow from operating activities per month, plus net cash flows from investing activities per month, plus capital spending per month." (Lee and Burrill, 1994; p. 54) The survival index is the "burn rate divided into existing cash, cash equivalents, short-term investments, and long-term marketable securities. This calculation reflects the number of months a company can survive at its existing net burn rate" in the absence of off-book resources or commitments, regulatory approvals which can dramatically alter operating cash flows, or sales of fixed assets or debt or equity.

[12] "Sometimes there is a delay due to patenting, but when I was in academe, I observed a tendency to delay and skim the cream using new discoveries before publishing them."

firms, [we] may believe more strongly in the commonality of research tools because we have a wider array of methodologies and products.

Zucker et al. (1997a,b) show that star scientists affiliated with firms, particularly those with patented discoveries, are typically much more highly cited by other scientists than stars working in universities; [13] so the ability to pursue and publish scientifically interesting and important research would not appear to disadvantage this firm relative to new biotechnology firms, where, arguably, the scientist–entrepreneur must devote more of his or her time to management activities.

One of the firms we studied in Japan, as well as some other large pharmaceutical firms, have attempted with some success to attract top scientists by establishing a quasi-independent, almost academic bioscience research institute that has some interaction with the separate applied R&D group. Separate basic and applied groups had existed for a time at the subject firm, but were integrated prior to and independently of the decision to adopt biotechnological methods company-wide. Our respondents viewed the independent institute model as a less productive approach, and reported no conflict between the integrated research group approach and recruitment of top scientists.

5.8. Incentives

A large pharmaceutical firm like the one studied here can offer a very attractive compensation and working-conditions package for outstanding scientists. Research teams, organized around a specific target and led by a champion, operate internally as 'mini-companies;' so the leader can enjoy much of the research independence experienced by the scientist–entrepreneur in a firm without the same risk, initial sacrifice, and pressures.

The manager with operational responsibility for research is certainly supportive of individual initiative:

> An important part of my job is to avoid bureaucracy at all costs so as to keep the science productive. The research teams in effect are many 'small companies.' My job is to nurture these small units, identify leaders, try to add in the areas that will be important, and to convince people to stop projects that aren't going anywhere without squelching creativity.

Further the firm has the ability to very quickly shift substantial resources to support promising ideas.

While the firm certainly does not offer the upside potential one enjoys in one's own firm, neither is there the downside, and there are very substantial financial incentives for top scientists. The corporate compensation philosophy is to reward for success. "There is a single basic measure of research productivity: Are you finding therapeutic compound candidates?" For those who are successful, incentive compensation in the form of bonuses and stock options can form a very substantial portion of the total package.

A key incentive plan for research scientists was instituted in 1985 in addition to the corporate-wide plans. Under this drug-discoverer system, several scientists, who played a major role in identifying a new drug candidate, are granted stock options that vest at specific mileposts in the development of the new drug candidate. The option price of the stock is the market price at time of issue. Recently, the program has been expanded to include other team members who have made important contributions to the discovery and development of the compound. These options would also vest in line with the milepost schedule.

Economists cannot help noting that under such a stock option system, managers profit from lower current stock prices so long as favorable news eventually emerges and is reflected in the stock price at the time they exercise their options. Thus, except for employees about to leave the firm, the incentive system is consistent with the policy of not discussing products in development (except in scientific journals) until they have been successfully proven in humans.

[13] The ratio is 6.5 times as many citations comparing firm scientists with patents to university scientists without patents, where, in each case, the comparison is restricted to the elite group of star scientists.

6. Collaborations of the firm with external scientists

6.1. Collaborations involving university faculty and students

Collaborations with university professors, their students, and their departments are common, often quite informal, and rarely publicly acknowledged:

Nearly every research program [here] has at least one university collaboration. Our scientists are told that its their job to find out what is important in their field worldwide and bring it into [the firm]. That is, scientists [here] should think about themselves as running the research for the whole world, and then bring in those other people who are needed to do that research.

...

Co-publishing is about as good an indicator as you can get of commonality of interests between [the company] and an academic collaborator. Although formal relationships are on a publicly available list, many relationships are not publicly acknowledged. We focus on a group of major universities which we support and whose students we actively recruit, so recruitment of students would not generally indicate collaboration with their professor. We don't hire collaborators just because they were collaborators.

In this and other fieldwork, we have repeatedly validated the usefulness of linking academic scientists to firms by bibliometric research on patterns of co-publication. As indicated in Section 2, this concept of linkage is powerfully predictive of firm success when academic star scientists are involved.

The company provides support for students, junior faculty, and relevant departments, as well as entering into direct collaborations with particular professors. The collaborations may involve a little more than informal exchanges of reagents needed in each other's research, to more elaborate and long-lasting efforts with particular therapeutic goals. The firm's expertise in knocking out particular genes through recombinant DNA, and in using drugs that knock out their effects, tools which get at gene expression, makes the firm a particularly attractive collaborator for university scientists.

6.2. Collaborations with other firms

While involved in multiple marketing arrangements with large and small firms and basic-research collaborations with small firms, the firm generally does not collaborate on basic research with other large firms. This lack of collaboration with large firms is not a matter of policy, but rather reflects the difficulties involved in working out complicated issues on marketing rights and other terms that are not so difficult with the small biotechs.

With respect to research collaborations with small new biotechnology firms, the firm is especially interested in collaborations where the particular expertise held by others is needed for a particular project, but is not thought worthwhile to build up internally. Sometimes successful collaboration reverses that judgement and leads the firm to undertake acquisition of the capability internally. Collaborations are not seen as shortcuts to acquiring new technologies for internal use. As discussed above, since the firm's strategy emphasizes excellent in-house research, collaborations with other firms do not play a central part in their effort to identify new drugs.

7. Evidence on generalizability of the transformation experience

We have seen that the incumbent firm started a bit late in the biotech revolution, but then devoted enough resources to transform its research technology to state-of-the-art. There is a natural question as to whether this is a peculiarity of the particular firm which we studied, or whether this pattern might have been followed more generally by major pharmaceutical companies. A definitive analysis of these issues is beyond the scope of the present paper, but it is possible to shed some light on the generalizability, as well as provide some useful information by considering patterns of affiliation and linkage of stars with incumbents and entrants, and also patterns of patenting of genetic sequences by the different types of firms.

7.1. Patterns of affiliation and linkage of star scientists

Zucker et al. (1997a,b) validated a method of measuring the strength of connection between star scientists and commercial enterprises by counting the number of publications written by a star giving the particular firm as an affiliation—or, if the star lists another affiliation—written by a star with a co-author who gives the firm as his or her affiliation (in which case the star is said to be linked to the firm). There is some evidence that scientists who are nearby are likely to be more involved with the firm than those farther away, so we classify linked stars by whether they are affiliated with an organization which is located in the same region (functional economic area as defined by the US Bureau of Economic Analysis) as the firm, in another US region, or in a foreign country. Firms with access to leading-edge science as evidenced by such affiliations and linkages perform significantly better than the vast majority of enterprises that lack such access.

Table 1 reports the history of such affiliations and linkages of stars to particular firms classified as dedicated biotech firms (entrants), major pharmaceutical firms, and the remaining incumbents for the periods 1976–1980, 1981–1985, 1986–1990. As we see, during the first five years of the biotech revolution, only one well-known entrant had the intellectual human capital that we are measuring here. In the second five years, 17 firms had demonstrated substantial access to intellectual human capital of which almost 24% were major pharmaceutical firms, and the remainder were entrants. Quantitatively, the pharmaceuticals lagged further, however, with all 97 articles by affiliated stars being published by stars affiliated with entrants, and only 19% of 52 linked articles linked to pharmaceutical firms. In the third five-year period 1986–1990, there appears to be evidence of a general catch-up effort by pharmaceutical firms. Pharmaceutical firms (including the subject of our case study) begin to have star scientists publishing as their employees (11%) and their share of linked articles rises to 24% (excluding the nascent

Table 1
Publications by star bioscientists affiliated with or linked to US firms

Variables	No. of firms	Publication counts of stars			
		Affiliated stars	Linked in region	Linked in other US	Linked foreign
1976–1980					
Dedicated biotech firms	1	9	0	0	0
Major pharmaceutical firms	0	0	0	0	0
Other incumbent subunits	0	0	0	0	0
Total for all firms	1	9	0	0	0
1981–1985					
Dedicated biotech firms	13	97	20	12	10
Major pharmaceutical firms	4	0	2	7	1
Other incumbent subunits	0	0	0	0	0
Total for all firms	17	97	22	19	11
1986–1990					
Dedicated biotech firms	19	68	16	30	6
Major pharmaceutical firms	8	8	3	9	4
Other incumbent subunits	3	0	2	2	0
Total for all firms	30	76	21	41	10
1976–1990					
Dedicated biotech firms	22	174	36	42	16
Major pharmaceutical firms	9	8	5	16	5
Other incumbent subunits	3	0	2	2	0
Total for all firms	34	182	43	60	21

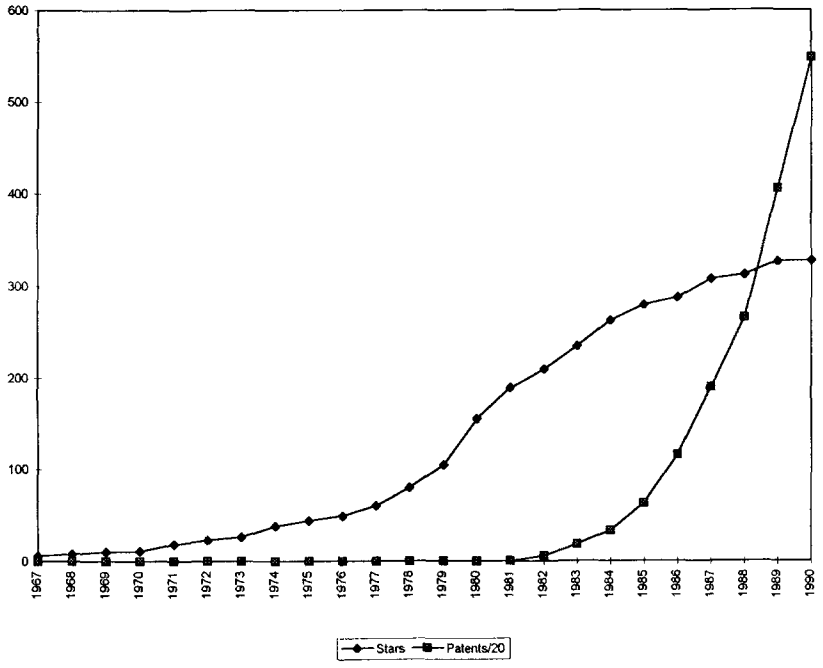

Fig. 1. Cumulative number of stars and genetic-sequence patents granted in the world. Source: GenBank™, Release 81.0, February 15, 1994, and calculations by the authors.

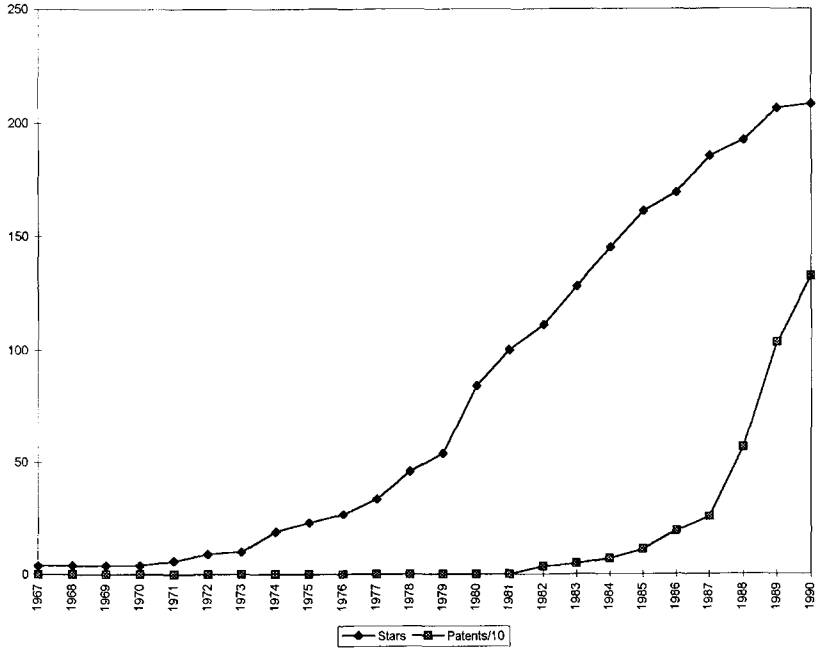

Fig. 2. Cumulative number of US stars and US genetic-sequence patents granted. Source: GenBank™, Release 81.0, February 15, 1994, and calculations by the authors.

Table 2
Patents granted to US firms with affiliated or linked stars, 1980–1990

Period	Major pharmaceutical firms	Dedicated biotech firms	All firms
1980	0	2	2
1981	0	4	4
1982	4	17	21
1983	0	9	9
1984	1	29	30
1985	4	34	38
1986	3	49	52
1987	10	18	28
1988	45	101	146
1989	43	152	195
1990	7	79	86
1980–85	9	95	104
1986–90	108	399	507
1980–90	117	494	611

group of incumbent firms in other industries with significant scientific capital).

7.2. Patterns of patent production

Fig. 1 indicates that, while the science diffused rapidly in the late 1970s in terms of initial publications of stars, patenting of genetic sequences did not boom until the mid-1980s. [14] Fig. 2 provides the data indicating a similar pattern when the quantities are limited to US values only. GenBank has data on 3353 patents granted through the end of 1990, of which we were able to link 611, or 18.2% of the world total, to 21 of the 34 firms examined in Table 1. [15] Table 2 provides annual data for total numbers of genetic-sequence patents granted to the major pharmaceuticals with ties to stars, to the corresponding entrants, and their sum. For convenience, the sums are provided for 1980–1985, 1986–1990, and 1980–1990. Again, we find that the major pharmaceuticals lagged behind the dedicated biotech firms but then began catching up quickly in the late 1980s: they had only 8.7% of total patents for 1980–1985, but this rose to 21.3% in 1986–1990. Given an average lag of perhaps two or three years between application and granting of the patent, this performance is even more remarkable.

7.3. Tentative conclusions on generalizability

In the early years of the biotech revolution, a few great scientists, who were also great entrepreneurs, recognized the value in the pharmaceutical industry of the scientific breakthroughs being made. Few if any outsiders could adequately judge whether their vision was right and probably none would or could pay a conventional compensation package that would match their true worth when the tacit knowledge essential to biotechnology was held in very few hands and brains. Some of these scientists proved right in their vision and became multimillionaires or billionaires. Others, although perhaps equally able and visionary, proved unlucky in their choice of problems or approaches and did not do as well, although we have found few star scientists who became principals of firms before 1986 and are not, by now, multimillionaires. Certainly, some very good scientists who do not have the record of achievement of our stars were also lucky and are very rich men and women today, but their odds were considerably diminished from those of equally situated stars.

After 1985, the science diffused rapidly and such extraordinary returns do not appear to have been there for the star scientists, and empirically, Zucker, Darby and Brewer (1997) report that the stars no longer played such a key role in determining the location of new entrants using biotechnology. It is certainly reasonable that the combination of technological successes and the more affordable compensation demands of top biotech scientists made this period an attractive one for the firm in our case study, and the other firms highlighted in Tables 1 and 2 to begin a wrenching and still expensive transformation of their technological identities.

Clearly not all major pharmaceutical firms have transformed their technological identity. However, the firm we studied has, and we find quantitative

[14] The availability of patent protection for genetically engineered organisms was doubtful until the US Supreme Court's 1980 decision in Diamond v. Chakrabarty; see Eisenberg (1987).

[15] We matched genetic-sequence patents to 8 of the 9 major pharmaceutical firms, 13 of the 22 dedicated biotech firms, but found no genetic sequence patents for the 3 other incumbents. Of course, the latter group were late on the scene and may appear in patent data after the 1990 cutoff in the data which we have so far analyzed. The case-study firm was in the middle of its group in terms of frequency and onset of patenting.

evidence that a number of such firms have followed a similar path in terms of both timing and success. Cookson (1995) reports that "[t]oday, genetic engineering is used daily as a laboratory tool by every research-based pharmaceutical and biotech company" and quotes Dr. Francois L'Eplattanier, head of R&D for Ciba of Switzerland: "Genetic engineering is absolutely essential for us. If we were not active in genetic engineering, we would be out of the game entirely by the beginning of the next century." Of course, recognition of the competitive necessity to transform the firm's technological identity is not the same thing as achieving that transformation in an effective way, so that the firm's superior performance is maintained. In future research, we shall test possible determinants of ability to transform suggested by the case study, such as top management's technical expertise.

8. Conclusions

We can draw a number of significant conclusions from the case study reported here.

(a) We have evidence that in one major incumbent firm, the biotechnology revolution fundamentally changed the firm's technology identity, a counter-example to the hypothesis that these identities are immutable; and consistent with the hypothesis that persistently successful firms maximize their wealth by transforming their technological identity as required to remain competitive in the face of technological revolutions.

(b) Senior management with the scientific ability to assess the breakthroughs championed the technological transformation.

(c) The technological transformation was achieved primarily through hiring new personnel embodying the new technology and incorporating them into the existing structure. Special subunits played only a transitional role, and collaborations and joint ventures with university scientists and new biotechnology firms were used primarily to augment internal expertise with explicit decision-making on the issue of whether this expertise was worth developing internally.

(d) There is some evidence that biotechnology applications in the incumbent firm are more likely to be used in combination with other technologies than in entrants which tend to use biotechnology for both discovery and production of new therapeutic entities. This difference in emphasis may result in value-enhancing synergies for the incumbent firm because of the wealth of related knowledge that makes for more effective, possibly different, applications of the new technologies.

(e) University–firm collaborations are ubiquitous, often non-public, and best identified in quantitative analyses by co-publishing. Hiring is not significantly related to such collaborations.

(f) The firm is capable of recruiting star scientists with an overall working-conditions/employment package which includes, for those with identifiable contributions to drug discovery, stock options which vest as the drug candidate progresses through clinical trials and FDA approval.

(g) While not all incumbent major pharmaceutical companies have changed their technological identities, we were able to identify another seven or eight such firms that seem to be following a similar path, both in terms of involving top scientific talent and in terms of patenting success.

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