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LOCAL ACADEMIC SCIENCE DRIVING ORGANIZATIONAL CHANGE: THE ADOPTION OF BIOTECHNOLOGY BY JAPANESE FIRMS

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ABSTRACT

The local academic science base plays a dominant role in determining where and when biotechnology is adopted by existing firms or -- much more frequently -- exploited by new entrants in the U.S. In Japan this new dominant technology has almost exclusively been introduced through organizational change in existing firms. We show that for the U.S. and global pharmaceutical business -- biotechnology's most important application -- the performance enhancement associated with this organizational change is necessary for incumbent firms to remain competitive and, ultimately, to survive. Japan's sharply higher organizational change/new entry ratio compared to the U.S. during the biotech revolution is related to Japan's relatively compact geography and institutional differences between the higher-education and research funding systems, the venture-capital and IPO markets, cultural characteristics and incentive systems which impact scientists' entrepreneurialism, and tort-liability exposures. Both local science base and pre-existing economic activity explained where and when Japanese firms adopted biotechnology, with the latter playing a somewhat larger role. *De nova* entry was determined similarly as if entry and organizational change are alternative ways of exploiting the scientific base with relative frequency reflecting underlying institutions. While similar processes are at work in Japan and America, stars in Japan induce entry or transformation of significantly fewer firms than in the U.S. and preexisting economic activity plays a greater role. We find no such significant difference for entry of keiretsu-member and nonmember firms within Japan.

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Geographically localized knowledge -- especially academic-derived knowledge -- plays a major role in the geographic distribution of American industry.[1] In the United States, professors are often involved in start-up firms, but Japanese institutions discussed below largely precluded this role during the biotechnological revolution in Japan. Even significant consulting relationships with incumbent firms were difficult or illegal for Japanese professors. This paper shows that, nonetheless, the *local* availability of the best academic scientists remains an important determinant of the speed with which existing firms adopted the new dominant technology, although the magnitude of the effect is less than in the U.S.

Adoption of modern biotechnology requires profound organizational change in the R&D function and is necessary for performance improvement or even survival in industries in which competitors are adopting the new dominant technology. Biotechnology is best understood as an "invention of a method of inventing" analogous to the development of hybrid-seed technology (Zvi Griliches 1957). In most applications (genetic engineering), genes from one organism are inserted in cells from another organism (of the same or different species) and the resulting new organism is grown and reproduced. Thus, biotechnology can "merely" increase the speed and precision of traditional cross-breeding or produce more novel life forms such as, for example, easy-to-grow bacteria which produce human insulin.

These invented organisms or their products may serve directly as inputs into the productive process (as in pharmaceuticals, food, beer, and other fermentation-based products) or serve as R&D tools (e.g., producing particular receptors as targets to identify promising drug candidates in pharmaceutical discovery). For firms whose profits depend on discovery of new and better drugs, seeds, yeasts, and the like, adoption of modern biotechnology often required a profound change in power relations and relevant scientific base. For example, pre-biotech drug discovery was dominated by chemists at both bench and managerial levels with biological sciences playing a subsidiary role at best. Adoption of biotechnology at a major U.S. pharmaceutical firm entailed massive hiring of outstanding biological scientists for both functions and forcing out over a short time those scientists -- whose prior discoveries were paying for the new hires -- who could not work effectively with the new technology (Zucker and Darby 1997, pp. 435-436). Thus, adoption of biotechnology by an existing firm simultaneously represented and required radical organizational change to obtain the performance improvement which could provide ongoing competitive advantage in some industries or, in other industries, avoid ongoing competitive disadvantage and ultimately exit.

Section I demonstrates quantitatively the major performance-enhancing significance of the radical organizational change inherent in adoption of biotechnology to incumbent-firm survival in the U.S. and global pharmaceutical industry, the new technology's most important area of application to date. Section II reports findings of extensive Japanese fieldwork which identified institutional differences between Japan and the United States which have promoted Japanese organizational change relative to replacement of existing firms by new firms in comparison to the U.S. In Section III, we show that the timing and location of these organizational changes appear to be driven by the prior development of a local science base -- measured by publications of outstanding "star" bioscientists in local universities -- as opposed to simply reflecting the prior distribution of economic activity. Section IV examines the relative importance of local science base to organizational change in existing firms and entry of new firms attempting to use the new technology to capture market share from the existing firms. Keiretsus have played a significant role in the Japanese economy; we examine whether keiretsu membership promoted or retarded this form of organizational change in Section V. Section VI examines the relative importance of local science base to organizational change in existing firms and entry of new firms in

Japan versus in the United States. We summarize our results and draw conclusions in Section VII. An extensive Data Appendix completes the paper.

I. The Performance-Enhancing Significance of Adopting Biotechnology: Survival

Michael L. Tushman and Philip Anderson (1986) have argued that major technological discontinuities originating outside the established industry are threatening to the incumbents, who thereafter often exit, unable to keep up with the new technology outside the scope of their knowledge. Indeed, Rebecca Henderson (1993) has pointed to "Underinvestment and Incompetence as Responses to Radical Innovation" by incumbent firms. Examining the pharmaceutical industry, Zucker and Darby (1996a, 1997) have argued that while there is support for this pessimistic view of the survival of incumbents faced with an external technological breakthrough, a sizable number of these firms have been able to successfully transform their methodology of drug discovery to the point that they are in that regard difficult to distinguish from the most successful dedicated biotechnology firms. In this section, we present new evidence of the substantial performance-enhancing significance of adopting biotechnology in terms of increased probability of survival of the firm.

Major pharmaceutical firms carry out five distinct, important activities: drug discovery, clinical testing, obtaining regulatory approval, manufacturing drugs, and marketing drugs. Biotechnology profoundly alters drug discovery and may affect manufacturing as well. An industry leader will perform all these activities well, but there is little scope for the other activities if drug discovery is not done well. Indeed membership in the Pharmaceutical Research and Manufacturers of America (PhRMA -- formerly known as Pharmaceutical Manufacturers Association or PMA) requires an active program of drug discovery.[2] Since biotechnology has dramatically increased the productivity of drug discovery activities by replacing more or less random screening of compounds with cloned targets, smart drug design, and other advances, we expect that the probability a firm will survive the radical restructuring of the industry in response to the innovation depends on the degree to which it has successfully adopted the new technology.

We operationalize our measure of adoption of biotechnology by examining whether any of the firm's scientific publications are authored by a "star scientist" writing either as or with an employee of the firm. We use star scientists to mean one of the 327 top-producing genetic sequence discoverers identified and validated for biotechnology entry or adoption and for subsequent firm success in Zucker, Darby, and Brewer (1998) and Zucker, Darby, and Armstrong (1998). We assume based on our prior field work that any major pharmaceutical firm which has converted its drug discovery has the resources to identify and hire or at least work with one of the top scientists in the field at the bench level.

Our principal survival test is based on the 38 members of the Pharmaceutical Manufacturers Association in 1975 for which we could find CUSIP numbers either for themselves or their ultimate parent. The founding discovery for biotechnology was made by Cohen and Boyer in 1973 and the first firms began to use biotechnology in 1975 or 1976; so this list provides a reasonable basis for identifying the incumbent firms at the time of the technological discontinuity. Essentially all these firms applied chemistry-based drug-discovery technologies in 1975. Fifteen of these 38 firms survived in the sense that the firm continued to 1999 as an independent firm (or division or subsidiary of the 1975 parent) or the dominant partner in any merger. There is a slight ambiguity in how to treat the Upjohn case which entered into an equal merger with Pharmacia of Sweden to form Pharmacia and Upjohn, but we count this as a clear survival case since the merged company is in the process of moving its global headquarters from "neutral" London to New Jersey.

As indicated in the first three lines of panel A of Table 1, only 16 or 42.1 percent of these 38 firms have survived the past 24 years. However, among firms adopting biotechnology to the extent of developing star ties, 12 or 80.0 percent of 15 adopting firms survived, while only 4 or 17.4 percent of the 23 firms without ties managed to survive. The $\chi^2(1)$ statistic for the hypothesis that the difference in survival rates is due to chance is 14.6 implying a p-value much less than 0.001. Thus it appears that adoption of biotechnology was so performance-enhancing in drug discovery that non-adopters were effectively forced from the field by adopting incumbents (and new entrant dedicated biotechnology firms).

George Baker has argued that this apparently strong finding could be the spurious result of two independent processes in which those that happen to survive longer will have more years in which their scientists might write in collaboration with a star scientist. This hypothesis is not borne out by the data, however. The fourth and fifth lines of panel A show that the average exit rate per year for firms which do not then have star ties is double that for firms that have then written with stars. Annual observations on exit rates -- the ratio of firms exiting in the year to their numbers at the beginning of the year -- are plotted in Figure 1 according to whether the firm did or did not have any prior star ties at the beginning of the year in question. We note that the exit rate of firms with ties exceeded the exit rate of firms without ties in only one year, and is generally much smaller. The significance level of this difference in mean exit rates depends on the dating of the ties: by year of publication or, as we have argued elsewhere (Zucker and Darby 1996b), some two (or more) years earlier when the work was actually done and the firm must have already adopted biotech drug discovery. Even allowing for a two year publication lag, which reduces (increases) the per year exit rate for firms with (without) star ties by increasing (decreasing) the number of years in the denominator, the significance level for a one-sided difference in means test is only 0.06.

Fortunately, we can obtain more precise estimates of the effects on firm survival of biotech adaption as indicated by star ties by estimating Weibull loglinear survival models.[3] In the results reported in Table 2, the two variables considered to effect the survival probability are whether the firm in the current year is marked as adopting biotechnology by having worked with a star and whether the firm was listed as among the top 20 firms in the world in terms of drug discovery in 1981-1982 (discussed below). Regardless of whether the Top-20 variable is included in the model and regardless of whether a two or zero year publication lag is assumed, the probability of survival is increased at better than the 0.05 significance level in years in which Has-ties marks the firm as having adopted biotechnology.

We also examined the survival of the world's 20 leading companies in the development of new drugs in 1981-1982 as identified by the California Department of Commerce (1986), extending our previous analysis of these firms in Zucker and Darby (1996a). This set of firms has the advantage of being international (9 American based, 1 British, 2 French, 3 German, 2 Japanese, and 3 Swiss) but the disadvantage that most (70 percent) of these outstanding, science-based firms did adopt biotechnology (as indicated by star ties) and 90 percent of these 20 firms survived from 1982 to 1999. Fortunately, since sample size and the rarity of exit prevented our obtaining stable Weibull estimates, the Baker argument does not apply in this case: All the firms that were ever tied to a star had published results with stars by 1992, indicating adoption likely occurred at the latest in 1990; the two exits occurred in 1995 and 1996, long after all the firms we count as adopting biotech drug discovery had done so. Although the significance of the difference in means tests is a bit shy of conventional levels, we can rely on the contingency table χ^2 test to reject at the 0.025 level the hypothesis that *prior* adoption of biotech drug discovery did not affect survival.[4]

We conclude that the quantitative evidence supports the everyday observation of industry experts such as Dr. Francois L'Eplattanier (in 1995 as 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."[5] So far, eighty three percent of the 23 PMA members of 1975 which we identified as failing to adopt biotechnology successfully have exited with one and three quarters year left until 2001.

II. Why Did the Japanese Biotech Revolution Occur via Organizational Change?

Over 1993-1998 we have done fieldwork involving interviews with nearly 100 university and research-institute scientists, executives and scientists at Japanese biotech and financial firms, and government officials. The purpose of the fieldwork was to better understand the industry and its constraints in order to develop hypotheses for quantitative analysis, not to test any hypotheses *per se*.

Our respondents identified a number of structural differences between Japan and the United States, differences which they primarily saw as impediments on the Japanese side explaining the lag of their industry behind that in the U.S. (A particularly well organized version of the consensus Japanese view was provided for use in our discussions by one of our respondents and appears as Appendix Table A.) From our reading and observations, we have identified several other factors that may affect the process of entry of new firms and adoption by incumbent firms. We shall discuss what appear to be the key underlying differences after summarizing what is known about the industry and its scientific base in the two countries.

Science Base and Its Commercial Application

As indicated previously, there is a unified data base (GenBank) reporting all genetic-sequence discoveries. The GenBank accession number is normally required by editors as a condition of publication, and scientific and commercial incentives for demonstrated priority ensure that scientists promptly report their discoveries.[6] There is no such universe to provide a frame for identifying the firms exploiting the new biotechnology by commercially applying the breakthroughs in recombinant DNA and other basic technologies. In our terminology, biotech-using firms are either newly-formed "**entrants**" or pre-existing "**incumbents**". Depending on the directory or directories a researcher uses, for example, there are between 500 and perhaps 2500 biotech-using firms in the U.S. alone. Using a more stringent definition of whether the enterprise is actually involved in using the breakthrough technologies, Zucker, Darby, and Brewer (1998) dated the inception of 751 U.S. biotech-using firms from 1976 to April 1990. As used here "**inception**" refers to the formation of biotech-using entrants and the initial adoption of biotechnology by incumbents. For larger incumbents, this initial adoption of biotechnology frequently occurs in particular identifiable subunits or subsidiaries -- the proverbial "skunk-works."

We have attempted to apply a similar definition to biotech-using firms in Japan, and have identified 368 biotech-using firms either born or beginning use of biotechnology between 1975 and 1989 inclusive as described in Data Appendix A.1. We are not confident that the definitions are strictly comparable, nor is a simple count of biotech-using firms our preferred measure of the total activity in the area. Unfortunately, however, many entrants are nonpublic and report very little information while most incumbents do not report information with sufficient detail to distinguish between activities involving traditional technologies and the new biotechnologies.

In the U.S. data, Zucker, Darby, and Brewer (1998) could definitively classify only 661 of their 751 biotech-using firms, 511 as entrants and 150 as incumbents, with the remaining 90 biotech-using firms lacking data to classify or (in 18 cases) being problematic joint venture cases. For Japan we did not have the ability to definitively investigate the origins of entrants and adopted a convention which we believe overstates the frequency of true *de nova* entry and accordingly understates the frequency of adoption of biotechnology by incumbent firms: Any biotech-using company with a founding date after 1974 is counted as an entrant while any company with an earlier founding date is counted as an incumbent. On this basis we count 23 Japanese entrants and 345 incumbents. Thus, only 6.3 percent of Japanese biotech-using firms are entrants compared to 77.3 percent (511/661) in the U.S. Based on our fieldwork, we believe that most of these Japanese entrants are unidentified affiliates of incumbents or groups of incumbents and that essentially all inceptions in Japan amount to organizational changes in incumbent firms rather than true entry.[7]

Figures 2 and 3 plot the number of stars ever active and the number of biotech-using firms born up to early 1990 by the functional economic areas defined by the Bureau of Economic Analysis (for short, '**BEAs**") for the U.S. and by prefectures for Japan.[8] We see in both the U.S. and Japan that there is a high correlation in the locations of biotech-using firms and star scientists. Of course, this apparent correlation cannot prove causation since it may reflect the effects on each of third factors such as population or employment distribution which might determine where both stars and biotech-using firms are located.

Geography

The U.S. is characterized by a rich variety of patterns across the BEAs: Some large areas have great universities and others do not, the same is true for medium and smaller regions. Nor do all great universities, even those among the strongest in the biosciences, have similar numbers of star scientists as we define them. All together, the U.S. geography provides us with sufficient variation to characterize as a natural experiment. In Japan, people, firms, and universities are much more concentrated, particularly in the Tokyo area and around Osaka and Kyoto in the Kansai. This makes it more difficult statistically to distinguish the effects of stars and other measures of intellectual human capital from measures of economic activity. Fortunately, we do have information not only on where stars have been active but also when and thus are able to draw some conclusions where otherwise it might be impossible.

The simple map in Figure 3 illustrates in a substantive as well as statistical way in which Japan's geography might result in different impacts of local stars on regional development: With the population and economy concentrated like a dumbbell along the Tokaido shinkansen line, few stars are located more than three hours from some 90 percent of the existing firms. Thus, it is conceivable that Kyoto's scientists could contribute actively to commercial applications of biotechnology at biotech-using firms located in Tokyo and vice versa. These issues are particularly important in explaining inception into biotechnology. Once we know the firms which are actively using the new technology, we can look at specific linkages between stars and biotech-using firms to predict the success of those biotech-using firms (see Zucker, Darby, and Armstrong 1998), but that is the subject of another paper.

Institutional and Cultural Differences between Japan and the United States

As noted above, interview respondents acutely sense that Japan has lagged behind the United States in creating and commercially applying their scientific base. They point to three main areas of concern: (a) university structure, policies, and culture, (b) financial market support for venture firms, and (c) cultural differences with respect to entrepreneurialism. We would add that Japanese firms have faced a distinctly lower threat of product liability litigation.

<u>University structure, policies, and culture</u>

Japanese respondents point to the hierarchal nature of Japanese universities with funding, personnel, and laboratory space primarily allocated equally to each professor regardless of their current or prospective research productivity as retarding the development of the scientific base. They also note that it is illegal for national university professors, where essentially all the stars are located, to earn additional labor income from firms or start a firm as is common in the U.S. However, a number of respondents noted that those laws are widely evaded, ignored or otherwise worked around, but the less secure property rights for professor-firm collaborations may interfere with their effectiveness. Furthermore, cultural inhibitions on professor's entrepreneurial activity were said to reinforce the legal bans on profiting from consulting with or starting a firm.

A significant difference in treatment of patent rights between Japan and the U.S. is an important institutional factor favoring more Japanese star-firm ties. In the U.S., if the underlying work is done at a professor's university laboratory, a patent is normally assigned to the university although the inventing scientist(s) may have significant shares of any income from the patent. In Japan, such a patent is almost always assigned to the inventing scientist(s) who may make a donation to his university or department.[9] Furthermore, top researchers sent (with funds for equipment and supplies) to stars' university laboratories by firms as "students" are an important means of increasing the size of the laboratory since professors cannot use research grants to increase staff because of lifetime employment at the universities. Thus, in Japan star-firm joint work is customarily done in the star's university laboratory while in the U.S. a star must physically go to a firm laboratory and establish a second team there to secure full patent rights.

These latter advantages apparently more than offset the deterrents to working with firms, and Japanese academic scientists do so to a remarkable degree. In fact, 40 percent of Japanese stars at some time in their publishing career up to 1990 either have published as or (much more frequently) with an employee of a firm, a higher rate even than the 33 percent figure for the United States. Stars in Japan and the U.S. show substantially more such ties than those in any other country.[10] While the quantity of collaborations between academic scientists and firms if anything favors Japan, it may be that these ties are not as deep or significant to the firm as in the U.S. where the scientists are frequently motivated by substantial equity interests in the firms with which they work.

Financial market support for venture firms

There are about 1.3 million corporations active in Japan, which is nearly three quarters the American rate of 3.5 million after adjustment for population differences. Despite the special deterrents to starting biotech firms for reasons of university policy and cultural inhibitions (discussed below), clearly some Japanese are willing and able to start businesses.

Respondents attribute the capital market inhibitions to creation of venture firms as due to the interaction of four distinct but reinforcing attributes of these markets: the lack of American-style venture capital firms, the prohibition of initial public offerings (IPOs) for firms without an established record of substantial profitability, the fact that the keiretsu will not buy small firms unless at distress prices, and the lack of bank financing for risky ventures without collateral.

About 120 venture capital firms exist in Japan, but they are all focussed in bringing established small and medium sized companies to the point of making the IPO. These firms had assets of about $5.5 billion by May 1993 with another $2.5 billion raised through sponsored partnerships. The largest of these venture capital firms by far is Japan Associated Finance Co., Ltd. (JAFCO) with about $2 billion under management. However, there appear to be no U.S. style venture capital firms which will finance a new biotech firm located in Japan for the first ten years or so before the firm either makes an IPO or is sold profitably to a large firm.[11]

The lack of venture capital firms financing start-up companies does not appear to reflect a shorter horizon on the part of venture capital firms in Japan. In the United States, too, a typical venture capital firm is looking to something like a ten year relationship. The difference is that American firms can rely on making an IPO or profitable sale at a much earlier stage of development than in Japan. In effect, the more complete American capital markets allow the venture capital firms to act farsighted because they know that once substantial research and development results have been obtained, their investments can be sold to other investors who will discount the future profitability to the present.[12]

The Japanese capital markets and especially the Ministry of Finance did not accept IPOs for firms which do not have a track record of proven profitability. The second section of the Tokyo Stock Exchange for smaller companies requires a minimum before tax profit of ¥400 million ($3.6 million). On the over-the-counter (OTC) market JASDAQ which began on October 23, 1991, the smallest before tax profit reported by a firm making an IPO was ¥258 million ($2.3 million).[13] Only in 1995 under pressure from the Ministry of International Trade and Industry (MITI), was a second OTC market established to permit high-technology companies without proven profits to go public, but the first such IPO did not occur until 1996 (for an intranet software firm ATL Systems Inc.) and even in 1999 there are only one or two true venture biotech firms in Japan. Thus a Japanese IPO market which could take biotech venture firms public before profitability is only now emerging and its absence in the 1970s, 1980s, and most of the 1990s, meant that there was no venture capital firms financing start-ups in the golden age for biotech during the 1980s. In this way we see a vicious circle of no financing for start-ups and no start-ups to lead the way as with the Genentech IPO in the U.S. in 1982.

In principle, the large groups of Japanese companies (the keiretsus) could substitute for an effective IPO market by bidding vigorously for the winners of an R&D race among independent venture firms. Indeed, this is a common outcome of successful venture capital investments in the United States. For reasons that are not clear to the authors, none of the respondents reported any such bidding and indeed indicated that if firms were bought, it would be only at distress prices.[14] Thus, one alternative means of fostering bio-ventures in Japan was eliminated.

Respondents also point to a lack of uncollateralized bank financing for risky ventures as a deterrent to growth in new enterprises, in effect requiring all growth to be self-financed. While this would seem to stretch out the period of growth relative to other countries, it seems unlikely to us that bank financing would anywhere be a real alternative to venture capital firms.

Japanese venture capital firms such as JAFCO have concentrated on financing American and European bio-ventures and also on their strategic alliances with Japanese firms through joint ventures and other mechanisms.

Cultural differences with respect to entrepreneurialism

As alluded to above, many respondents commented on the differential status or honor given to the professor relative to the individual involved in commerce. This social distance was compounded at least through the early eighties by the radical or Marxist orientation of many students and some faculty in the major universities.

Several respondents also believed that business people do not want to reveal too much to university faculty because the faculty highly value open communication and may not keep their findings confidential until patent protection of intellectual property can be obtained.

One respondent went so far as to say that firms looked to the universities primarily to supply good Japanese brains. The demand for Japanese scientists, rather than scientists trained elsewhere, probably stems in part from the value of the social network formed in the universities, providing early and privileged access to new discoveries at the university where the scientist was trained. But there also may be an element of Japanese discrimination against *gaijin* (foreigners) that leads firms to avoid hiring non-Japanese whether because of prejudice or for fear that the foreigners will ultimately choose to leave Japan and the firm.

Other respondents suggested that the faculty's desire for honor and only covert relations with firms reduced the firms' costs of obtaining Japanese academic research -- that providing honor through creating foundations and institutes and perhaps making some informally agreed payments cost only a tenth as much as explicit payments for academic researchers in the U.S. and Europe.[15] On retirement from the university, a professor who has maintained a close relationship with a company can become a consultant to the firm or a member of its board -- but not an employee -- without losing honor.

A second cultural factor which inhibits the creation of bio-venture firms in Japan is the national career ideal of working for a single employer until retirement. Reinforcing this factor is the importance of social contacts within organizations which make it hard for a newcomer to enter a firm from outside. Thus, leaving a firm or university to start a new firm involves disrupting that firm-based or university-based social network and possibly labeling oneself as different if not unstable. If the firms succeeds, then there is probably a net gain on these dimensions to the individual, but biotechnology is inherently risky with the prizes from a search for a new drug mainly going to whomever gets there first and can raise enough capital along the way to keep the company afloat until there are some profits. If the new venture ultimately fails, the founding scientists' career pattern is disrupted and it may be very hard to find new lifetime employment or even to establish the social network within a new organization to be successful. Since lifetime employment is itself a culturally endorsed risk-avoidance strategy, the downside risk of starting a new firm must seem enormous compared to scientists used to the American system of employment often said to be based on the revolving door.[16]

Compounding the difficulties of the potential venture firm are the general difficulties with entry of new firms into the Japanese market place. These barriers to entry are well known and have been the subject of numerous international trade negotiations. They work for natives in much the same way as for foreigners and must deter biotech-using entrants as well. On the other hand, since the biggest returns are in the highly regulated pharmaceutical industry where track record and personal ties also play a major role in the United States, this factor probably should not be unduly stressed.

A cultural preference for group or team activity as opposed to the American ideal of rugged individualism may contribute to the relative evenness of allocation of funds within ranks at the national universities and the aversion to differential rewards for differential performance. The same cultural preference may restrain vigorous national competitions for scientific grants and the associated culture of scientific entrepreneurship which seems to be a short step away from starting a new firm in the United States. The Japanese government, nonetheless, is currently shifting national policy toward competitive, peer-reviewed research funding. Scientists in both countries, moreover, rely on the same mode of scientific production: the research team based in the laboratory of a distinguished senior scientist. It remains for us to see how these teams differ.

A final cultural trend in Japan is its eclecticism. One respondent noted a tradition of Japan's sending people to other countries to learn their best practices starting 1000 years ago with China. While the success of Japan in judging the best in foreign economies and cultures and incorporating it at home -- often in improved form -- is legendary, it may also lead to overestimation of foreign superiority in areas of innovation. We saw that Japanese firms and investors were eager to support the innovative work done in America but less willing to support and rely on the unique breakthroughs of Japan's own scientists. Sometimes Japanese firms ended up licensing applied technologies from the United States that were based on Japanese basic-science discoveries -- just the reverse of many American's fear of another VCR!

Threat of product liability litigation

Although Japanese observers have not remarked on the threat of product liability litigation as playing a role in the development of commercial applications of biotechnology, this may be because they were searching for factors which have retarded that development in Japan relative to the United States. Clearly, product liability has been, in contrast, a favorable factor for inception of biotech-using firms in Japan.

Viscusi and Moore (1993) demonstrate that higher liability exposure tends to reduce R&D expenditures for innovative products, so this is a positive difference for adoption of biotechnology in Japan. However, higher liability exposure works differentially for large and small firms since the most that can be forfeited (beyond insurance) is the value of the company itself. The greater the potential liability – as in the U.S. – the greater is the competitive advantage of carrying out risk innovation in small rather than large firms. So the liability difference reinforces the university, financial, and cultural explanations of why biotech-using firms are much more likely to be incumbents in Japan than in the U.S.

Conclusions on Why the Japanese Biotech Revolution Occurred via Organizational Change

As a practical matter, the structure of the Japanese capital markets (particularly the inability of firms without substantial accounting profits to go public) precluded the pattern of entrant formation seen in the U.S. (see Kishimoto 1989 and Zucker and Darby 1994 for details). At the same time, the structure of the universities has greatly reduced the number of potential founding scientist-entrepreneurs.

Thus, we understand why inception into commercial application of biotechnology in Japan has occurred nearly exclusively through adoption of the technology by pre-existing firms (incumbents). An alternative explanation is that the threat of product liability litigation was sufficiently severe in the U.S. that many incumbent firms left the field open for new entrants. In any case, Zucker, Darby, and Brewer (1998) show that in the U.S. the inception processes for entrants and incumbents are indistinguishable. We do not have sufficient numbers of Japanese entrants to make a similar comparison, but it appears likely that the effects of differential numbers of incumbents and entrants, if any, are on the comparative success of Japanese biotech-using firms and not on their total numbers.[17] We will explore the former issue in future work and here restrict our concern to the latter.

The structural differences between Japan and the U.S. raise questions as to whether the significant impact on biotech-using firm inception of where and when star scientists are publishing -- observed in the U.S. at the BEA level -- were also present in Japan and, if so, to the same extent. These questions are addressed in Sections III and IV below. Industrial groups known as keiretsus play a prominent role in Japanese industrial organization that is not present in the United States. Their risk-sharing and cross-financing aspects might have facilitated inception into biotechnology for keiretsu member firms compared to others, a possibility examined in Section V.

III. The Local Science Base and Where and When Japanese Firms Adopted Biotechnology

In this section we restrict our statistical analysis to incumbents -- firms already born as the commercialization of biotechnology began in 1975. We do so to examine a pure case, but will proceed in Section IV to examine inception for all Japanese biotech firms. Since we have already learned a great deal about the process of biotech-using-firm inception in the United States, we follow Zucker, Darby, and Brewer (1998) to the extent possible given the availability of data and the problems of multicollinearity which arise within the more limited geography of Japan where many of the explanatory variables used in the U.S. are highly correlated. Basically, we look to measures of intellectual capital and to other economic variables to explain inception of firms, entering them in groups both to give an idea of marginal contribution and stability of the prior coefficients.

Given the directory nature of our firm data sources, we were concerned whether the reported locations were the primary sites where biotechnology was done or merely the headquarters of the firm. Accordingly, we searched the *Science Citation Index* for biotech-relevant publications by scientists at each of the 368 Japanese biotech-using firms in order to correct instances in which corporate headquarters rather than laboratory or plant locations were reported in our directory source. Where another location was reported on a plurality of these publications, we used that location for the firm instead of the one in the directory.[18]

Analogous to Zucker, Darby, Brewer (1998), our data are in panel form for each of the 47 Japanese prefectures for each of the years 1975-1989 for a total of 705 observations. We are attempting to explain counts of inceptions by biotechnology-using firms for each prefecture and year. Since there are many zeroes among these non-negative integers, we estimate poisson regressions using LIMDEP (Version 7.0).

We measure intellectual capital both by counts of how many stars and their collaborators are "active" in each prefecture in each year and also by the number of main professors and the total resources for bioscience research institutes at major universities in the prefecture (see Data Appendix A.2 for details). As in the U.S., the economic variables are total employment in the prefecture as a measure of its size and average earnings in the prefecture as a measure of the skill level of its labor force (see Data Appendix A.3 for details).[19]

The first column (a) of Table 3 estimates a simple model of inception of incumbent firms into biotechnology based on the numbers of active stars and collaborators by year and prefecture. In Japan, stars have a strong positive effect and collaborators have a significant negative effect.[20] As in the U.S., there appears to be a nonlinear relationship which is captured in the second column (b) of Table 3 by adding the product of the number of stars and collaborators. This eliminates the negative direct effect of collaborators and instead the negative interaction coefficient suggests that the more new people to whom the stars are teaching the new technology the less is the effect of the stars on inception into biotechnology. However, the significance of both collaborators and the star x collaborator interaction term is unstable as the model is expanded to account for other resources in the area; so the influence of collaborators may not be reliably determined from the limited geography of Japan. We believe that geography's limits on the variation in Japanese conditions is the most likely explanation, in part because when we experimented with artificially limiting the U.S. inception analysis data set to only California BEAs, we found that similar instability resulted.

The final column (e) of Table 3 presents the full model, in which stars (as always) have a significantly positive effect on the probability of inception of biotech-using firms in the prefecture. Total employment and average earnings also have highly significant positive effects. The coefficients of the number of main professors and total research funding for bioscience labs in major university research institutes are insignificant in the full model, in contrast to model (c) which includes all the intellectual human capital variables only and in which they are both significant but have the wrong sign. We explored the multicollinearity among these two variables and the economic variables a bit further by dropping each in turn from models (c) and (e): We found that either the number of main professors or total research funding is highly significant and positive in model (c) if entered alone but neither is significant if entered alone in model (e) with the economic variables. Thus, the distribution of major universities is such that, unlike the U.S., we cannot find any stable effect for them separate from the areas in which they are located.

The fourth regression (d) in Table 3 indicates that, unlike the U.S. results in Zucker, Darby, and Brewer (1998) for the U.S., the explanatory factor of the economic variables alone is significantly greater than that of the intellectual capital variables as a group (compare the log-likelihoods for columns c and d). As in the U.S., where and when star scientists are active has a strongly positive and significant independent effect on where and when biotech-using firms entered into biotechnology, and this effect is always separate from and in addition to the effects of research support for university scientists and the general economic conditions of the prefecture.

Thus the Japanese data validate key qualitative conclusions in our previous work for the U.S. alone on the role of individual star scientists in promoting inception of biotech-using firms in an area and the regional economic development which they imply. The local presence of top-producing scientists contributes to the transformation and expansion of the local industry through organizational change in incumbent firms in Japan and also through new entrants in America.

IV. The Science Base and Organizational Change in Incumbents *versus* Entry of New Firms

We argued above that even the apparent Japanese entrants born after 1974 are in fact newly created affiliates of incumbents. Comparing Tables 3 and 4, we see that the results are essentially the same whether inceptions include all firms or only those born before 1975. This is consistent with the view that all inception of biotechnology in Japan through 1989 occurred by organizational change in incumbents rather than new entry. However, Zucker, Darby, and Brewer (1998) found that inception of incumbents and entrants follow a very similar process for the U.S. Thus the lack of change in coefficients moving from Table 3 to 4 might simply reflect similar processes governing births of incumbents and entrants.

In the following sections, where we examine the effect of keiretsu membership on inception and compare Japanese to U.S. results, it is appropriate to consider all 368 biotech-using firms in the statistical analysis.

V. Has Keiretsu Membership Promoted or Retarded This Form of Organizational Change?

Keiretsus, large groups of related firms typified by cross-shareholding and financial relations with a central bank, are generally viewed as a distinctive and important aspect of Japanese industrial organization. One hypothesis is that members of a keiretsu are more likely to engage in risky, long-horizon investments such as biotechnology because of their low cost of capital and implicit risk-sharing arrangements and superior information network for monitoring innovation. An alternative hypothesis is that management of keiretsu-member firms are more entrenched and less likely to be alert to new innovations such as biotechnology. In this section, we examine whether their inception pattern in fact differs significantly from that estimated for non-member firms.

Since keiretsus are largely informal groupings, there is no generally agreed definition or listing of which firms are members of which keiretsu. The situation is somewhat easier for vertical groupings more analogous to American conglomerates in structure, but it is debatable whether those groups should be counted as keiretsus at all. David Weinstein generously has provided us with the data set constructed for Weinstein and Yishay Yafeh (1995) which lists member firms for four different definitions of keiretsu: (a) The Big 6 are the DKB, Fuyo, Mitsui, Mitsubishi, Sanwa, and Sumitomo horizontal groups. (b) The Big 8 are the Big 6 plus the Industrial Bank of Japan and Tokai groups. (c) The Big 8 + Vertical definition is the broadest, combining firms that are members of vertical groups and the Big 8 firms. (d) The Big 6 Presidents Club definition is the narrowest, including only the inner circle of Big 6 firms whose CEOs belong to their group's Presidents Club.[21]

Using in turn each of these four definitions of keiretsu memberships, we divided our inception counts by prefecture and year into the number of inceptions by firms identified as members of a keiretsu and the number of inceptions by all other firms. We replicated Table 4 for the member and non-member counts separately for each definition, and also stacked the two count variables in a third regression for ease in testing the hypothesis that the coefficients of each of the variables -- but not the constants -- are the same in each regression pair.[22] We do not include the constant terms in the test as they will differ simply because keiretsu-member firms are relatively infrequent and thus should (as a group) have a different, lower base frequency of inception. For each Keiretsu definition, from broadest to narrowest, Table 5 reports the χ^2 statistics for these tests of equality for the coefficients of regression forms (b) through (e) from Table 4 together with a memorandum of the share of keiretsu-member inception to total inception into biotechnology.[23] Of the 16 different regression-form and keiretsu-definition combinations, in only one case does the χ^2 statistic indicate significant differences in regression coefficients. This is about what is expected by chance, so we conclude that the keiretsu and non-keiretsu coefficients are the same.

In Figure 4 we plot the cumulative inception as a percentage of type-specific total inception for keiretsu members and nonmembers separately. Note that a higher proportion of keiretsu members appear to have entered early in the process than is the case for nonmembers. Since the underlying processes are indistinguishable, these differences appear to be explained by subtle differences in geographical distribution by membership category.[24]

VI. Biotech Adoption and Entry in Japan versus in the United States.

A particularly interesting question is whether the structural differences between Japan and the

United States result in detectible differences in the linkage between the science base and its commercialization. Since it is difficult to find many variables which are strictly comparable across countries, we must address this question with stripped down models which consider only the numbers of stars and collaborators and total employment in the local area.[25]

The first column (a) of Table 6 reports the results from a pooled Japan-US poisson regression for biotech-using firm inception by year and area based on only a constant and the number of stars and collaborators in each. In this simple model, the number of stars but not the number of collaborators has a significantly positive effect on inceptions of biotech-using firms. In the remaining four columns of Table 6 we explore different models which include both the values of the variables for both countries and those values interacted with JDUMMY where JDUMMY is 1 for Japanese observations and 0 for U.S. observations. Thus, the interaction terms measure the *additional* impact of the variable in Japan compared to the U.S. Therefore, the combined coefficients for Japanese stars and collaborators in column (b) are 0.157 + 0.225 = 0.382 and 0.043 - 0.152 = -0.109, respectively. These differ from the values in column (a) of Table 4 only because of rounding.

Since on average Japanese prefectures have nearly twice as large populations as American BEAs, the probability of an inception in a prefecture might well be larger on average than in a BEA, so we want to test for structural differences that shift the coefficients of the variables in Japan relative to the coefficients in the U.S. For an individual coefficient, whether the value of the JDUMMY interaction coefficient is significantly different from 0 is an appropriate test if it is maintained that all the other coefficients are in fact different. The χ^2 JDUMMY interactions = 0 statistic near the bottom of the table reports the test of the hypothesis that there is no significant difference, except for the constant, in the inception process between Japan and the U.S. (i.e., that all the coefficients of the interaction terms are zero). In contrast to the similar analysis conducted in Section V above for members and non-members of keiretsus, in every case this χ^2 statistic confirms that there are significant differences between the processes in the U.S. and Japan.[26]

Considering first the full model in column (e), we see that stars and collaborators have weaker effects on local developments -- as measured by biotech-using firm inceptions -- in Japan than in the U.S. and that firms are more likely to enter in Japan where there is already more economic activity. This is certainly consistent with the arguments presented in Section II above which suggest that there are strong structural impediments in Japan to the deep involvement in commercialization characteristic of many U.S. professors/scientist-entrepreneurs. The greater importance of agglomeration factors in Japan, as indicated by the large coefficient on Total Employment x JDUMMY, may also reflect the institutional structure in which biotech-using firms often get what collaboration they can with star scientists at national universities by sending their employees to the stars' labs rather than the stars coming to the firms. (Recall that in the U.S., it is in both the biotech-using firm's and the scientist's interests for the university scientist to work at the firm in order to strengthen the case that the university does not have a property interest in the results of the research.) If the biotech-using firm's employees are working in the university lab, rather than vice versa, then it is less important that the biotech-using firm be located locally to conserve the star's time.

In columns (c) and (d), we see that even in the absence of internationally-comparable additional university-based measures of intellectual human capital, counts of stars and collaborators and their interaction alone make a somewhat greater marginal contribution as measured by increases in the log-likelihood than does total employment in explaining the pattern of inception of biotech-using firms into biotechnology in Japan and the U.S., with their combined explanatory power considerably greater than either alone. This reflects the much greater relative importance of intellectual human capital in the U.S. as compared to the importance of pre-existing economic geography in Japan.

Figure 5 shows the cumulative densities of Japanese and American biotech-using firm inception, where each is measured as a cumulative percentage of total inception for each country.[27] The patterns are very similar with a relatively small lead on the part of Japan apparently explicable by differences in definition of the start of the process with inception in Japan definitionally starting in 1975 and in the U.S. definitionally starting in 1976. Note, however, in Figure 6 that biotech-using firm inception by non-members of keiretsus virtually overlaps the U.S. pattern while inception by keiretsu members is concentrated in relatively earlier years. Again, we cannot determine whether this reflects some anomaly in reporting practices or whether it is a possible indication of a real timing difference in inception for keiretsu member firms relative to non-member firms in Japan and firms in the United States.

Given the relatively small coefficients on Japanese stars and collaborators reported in Table 6, an important issue for future research and for policymakers is whether structural differences in Japan in comparison with the U.S. have resulted in the under-utilization of the science base -- particularly the intellectual human capital embodied in the stars and their collaborators -- in terms of its impact on commercial development in Japan or whether instead these structural differences have only spread the impact of stars on commercialization more widely throughout Japan.

VII. Summary and Conclusions

Times of radical technological change are perilous for incumbent firms -- particularly when that change originates outside the firms' technological competencies. We have seen that incumbent pharmaceutical firms over the last quarter century have had to adopt biotechnology or die, and that the bulk of them in fact failed to survive. This illustrates that biotechnology so improved the performance of those incumbents and new entrants who could master it that other established firms were no longer able to compete effectively.

In the U.S. many new entrants emerged and successful incumbents opened or bought facilities near the academic centers where star scientists worked. Thus, both organizational change and replacement moved the geographic center of the affected industries. In Japan, we learned that institutional and geographic factors channeled the industrial transformation due to the biotechnological revolution almost exclusively into organizational change of incumbent firms. In the latter half of this paper we found that Japanese firms -- like their American counterparts -- have been significantly more likely to adopt biotechnology at a time and place where academic star scientists are actively publishing. So in Japan too the location of scientists making breakthrough discoveries has changed the overall industrial geography as well as the technological identity of particular firms.

This paper raises a number of questions for future research. Why did less than half of the American publicly owned pharmaceuticals develop ties to star scientists when they were near necessity for survival? Is the absence of new entrants in Japan a major explanation of Japan's lag in biotechnology relative to the U.S. or can incumbent firms change sufficiently to be equally effective? Is the significantly smaller estimated effect of stars on inception in Japan a reflection of relatively less utilization of the science base or merely that the effect is less geographically concentrated than in the U.S.? In the U.S. close ties between academics and firms is symbiotic for science, with stars publishing significantly more articles which on average are more highly cited during the time they work with firms. In Japan this symbiotic process appears to be weaker both in terms of the strength of ties between Japanese stars and firms and of the impact of those ties on star productivity. The causality is unclear and could reflect the smaller resources mobilized for star research in Japanese star-firm ties or the stars' rational expectations that the payoff will be less and so they are unwilling to become as deeply involved as is typical in the U.S.

We conclude that firms can engage in radical organizational change in response to a technological breakthrough which threatens the survival of firms that cannot improve their performance to meet the new competitive norms. Some observers may be more surprised by how many incumbent succeeded and others more by how many failed. We have shown that proximity to the very best academic scientists whether in an existing facility or through establishment of new facilities is characteristic of transformation of incumbents in both the U.S. and Japan, basically repeating the pattern observed for location and timing of new U.S. entrants. As any coach knows, great strategy can go only so far in making up for a bench weak in personnel.

Data Appendix

All data on stars and their collaborators was derived from the universe in *GenBank* (1990), and hand-pulled and coded records for each of the stars' articles therein as detailed in the Data Appendix to Zucker, Darby, and Brewer (1994), which also provides conceptual and procedural background on the variables detailed here.

A.1. Biotechnology-using firms

Attempting to develop a data set comparable to the one we developed for the U.S., we started by licensing a machine readable data base (North Carolina Biotechnology Center 1992). As with the U.S. biotech-using firm data set, we added additional biotech-using firms based on their listings in *Bioscan* (1989-1994). Next, we added additional biotech-using firms from Nikkei Biotechnology (1990) based on lengthy discussion with Mr. Mitsuru Miyata (Editor-in-Chief) and Ms. Ikuko Uchiyama (Staff Editor) of *Nikkei Biotechnology* which enabled us to distinguish firms actually using the new technologies from those which were listed as a courtesy to subscribers hoping to improve their stock price. Nikkei Biotechnology (1994) was used to fill in missing data. Finally, we searched each entry of Nikkei Biotechnology (1990) for firms with research projects or products using recombinant DNA technology.

As noted, 93.7 percent of these 368 companies had founding dates prior to their inception into biotechnology and so were classed as incumbents. Apparent response bias led a number of early adopters to report 1975 as the date of inception, which we accepted as the earliest date of inception even though it is doubtful that inception occurred before 1976 given the lag observed in applying the key Cohen-Boyer discovery (Stanley Cohen, A. Chang, Herbert Boyer, and R. Helling 1973) in the U.S. In four cases, very early incumbent adopters gave dates of inception before 1975, apparently referring to earlier technologies; these were constrained to 1975.[28] This gave us dates of inception for 333 firms. For another 35 firms, no inception dates were available in any of our data sources. Since there was valuable location data associated with the firms, we estimated the inception date of these firms by drawing inception dates from the same distribution as recorded for firms in their prefecture with known inception dates.

Typically, these biotech-using firms were large enterprises with many locations and often the headquarters address was listed as the biotech-using firm's location regardless of where biotechnology actually was being applied. Akio Tagawa developed an ingenious method to locate biotech-using firms by searching the *Science Citation Index* online by firm name for 1983-1993 to see where scientists affiliated with each firm were writing bioscience articles. For those firms which could be thus located, the most frequent location was designated the site of inception. Otherwise, the listed location was retained.

A.2. Japanese University Research Resources

Our university research resources information is taken from a comprehensive directory published by the Japan Association for the Advancement of Science (Nihon Gakujutsu Shinkokai, 1990) which has listings for all of the scientific research institutions in Japan affiliated to universities. This source, in addition to general information such as institute names, addresses, phone numbers, and year of establishment, also contains very detailed information such as director names, numbers of researchers, research divisions within institutions, researcher names, research objectives, and information about research oriented resources. It is published yearly.

We first collected information from this directory about all of the research institutes that perform research in bioscience related fields, and compiled them. In particular, the numbers of full professors, associate professors, assistant professors, and other researchers, as well as the total resources for each relevant institute was recorded.

The relative size and structure of Japanese research institutes is quite clear from the way in which the entries are listed. Institutes generally are broken down into smaller research divisions, each of which has a specific research agenda, and each of which is led by what we call a "main professor," who is usually a full professor but often an associate professor. Thus, the number of main professors or research divisions gives us a very good indicator of how large the universities' institutes are. Typically, it would suffice to simply count the number of full professors who are affiliated to each institute, but in many cases, there was no full professor, and so an associate professor was counted. It is for this reason that we have used a variable No. Main Professors which counts their number by prefecture, in contrast to simply using "full" professor.

We also collected information about the total amount of yearly resources for each of the relevant institutes. This figure also is another measure of the relative size of the institutions. Because we were concentrating on relative size of the institutions based on university and ultimately location of the university by prefecture, we collected the information for the research institutes from the 1990 directory, which includes information for the years 1987 and 1988.

In the end, all of the data was combined and sorted based on the universities to which the various research institutes belong, and the cumulative data is what we used for this study. Because we were only interested in the top research oriented universities in the country, we used a minimum cut-off of three main professors per university to qualify for the analysis, and all others were considered too small to significantly contribute. Our variable Total Research Funding is the sum (in millions of yen) across all such universities in a given prefecture.

Note that both No. Main Professors and Total Research Funding have the same values for a given prefecture for each year in the analysis, thus serving together as a type of modeled fixed effect component in our regressions.

A.3. Japanese Economic Variables

The main prefecture-level economic variables used are Total Employment (total employment in the given prefecture in a given year) and Average Earnings (average earnings per employed person in the given prefecture in a given year). These variables were obtained for the years 1975-1990. At the sub-national level, we combined several sources to compile the necessary information for these variables: Policy Planning and Research Department, Minister's Secretariat, Ministry of Labour (1975-1990), Statistics Bureau, Management and Coordination Agency (1976, 1981, 1986, 1991), Asahi Shinbunsha (1975-1990), Kokuseisha (1988), and Bureau of Statistics (1991).

Total Employment (in thousands) was listed irregularly in the various sources, and while there was some overlap among sources which served for confirmational purposes, much of the information was obtained through the above sources in different editions. In the end, we were able to obtain consistent data only for the years 1975, 1977, 1979, 1980, 1985, 1987, and 1990. The remaining years were filled in by interpolation from the obtained data.

Average Earnings was calculated from the average cash earnings per worker per month over a twelve month period for all of the 47 prefectures in Japan and compared for consistency to the national average. Cash earnings is defined as the amount of money earned before deductions for income tax, for social insurance contributions, for union dues, and for payment for goods purchased. Cash earnings specifically include semi-annual bonuses, which in Japan are (or were) typically equivalent to another six months' worth of income. The yearly cash earnings were divided by 12 to find the average monthly cash earnings for each prefecture and year. Finally, we adjusted this amount for inflation by dividing by the consumer price index for the central city of each of the prefectures in Japan for each year during the period 1975-1990. The basic cash earnings data were found in successive annual editions of the Yearbook of Labour Statistics during this period.

We also experimented with a third economic variable, the Earnings/Price Ratio as an estimate of the (all-equity) cost of capital. This figure is the inverse of the price/earnings ratio as reported in Nihon Ginko Tokeikyoku (1975-1990) for the Tokyo Stock Price Index, or TOPIX, based on all First Section stocks on the Tokyo Stock Exchange.

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FOOTNOTES

1. Evidence of geographically localized knowledge, often attributed to knowledge spillovers, is reported by Adam B. Jaffe 1989, Jaffe, Manuel Trajtenberg, and Rebecca Henderson 1993, and Edwin Mansfield 1995, Lynne G. Zucker, Michael R. Darby, and Marilynn B. Brewer 1998, and Zucker, Darby, and Jeff Armstrong 1998.

2. This requirement excludes firms that specialize in low-cost manufacturing of generic versions of drugs discovered by other firms once their patents have expired.

3. These models were estimated using LIMDEP, Version 7.0.

4. The 18 firms counted as surviving include not only the Upjohn case of an equal merger but also the two Swiss companies that consummated an equal merger to form Norvartis. Even if we reduce the population reduced to 17 firms after excluding the equal mergers, we can reject the hypothesis that survival does not depend on adopting biotechnology at the 0.05 level.

5. As quoted in Clive Cookson (1995). Cookson reports that "[t]oday, genetic engineering is used daily as a laboratory tool by every research-based pharmaceutical and biotech company."

6. Each genetic sequence entering GenBank for the first time is assigned a primary accession number (our measure of a genetic-sequence discovery).

7. A number of respondents report that even apparent "venture firm" entrants in our data set (e.g., Hayashibara Biochemical and Nippon Gene) are more accurately characterized as continuations of and subunits of long existing family firms which provided their financing rather than new dedicated biotechnology firms comparable to the usual American form.

8. Prefectures are 92 percent larger than BEAs in population but only 16 percent as large in land area, although some of the latter discrepancy is eliminated if the few BEAs comprising Alaska and the desert southwest are excluded from the U.S. calculations.

9. The decision is made by a faculty committee. If the patent is not assigned to the professor(s) it goes to the government in which case the Ministry of Finance does not return any income to the university or department.

10. Copublication is generally agreed by scientists and executives to be an excellent indicator of alignment of interests and was shown in Section I to be an important predictor of incumbent firm success. Similarly, Zucker, Darby, and Armstrong (1998) show that copublication with stars is a powerful determinant of (primarily entrant) firm success in California. Zucker and Darby (1999) compare the frequency of star-firm ties across a number of countries.

11. These firms are sometimes involved with financing start-ups abroad as discussed below.

12. An alternative view of the Japanese situation is that the lack of start-up funding does not reflect incompleteness of the capital markets. Such funding vehicles, on this view, are not necessary in Japan because the keiretsu provide an efficient funding mechanism for new activities in a way which reduces shareholder-manager agency problems. On this view, the numerous American venture capital firms are due to American regulatory restrictions. We do not believe that this story holds up, however, since the banking regulatory system in Japan is even more restrictive than in the United States, there are no regulations preventing large American firms from establishing new sub-units to pursue new technologies, and venture capital firms funding startups was also a feature of the incubation of the U.S. electronics industry for which there were no significant liability issues (see footnote 6 above).

13. JASDAQ suffered from some early scandals which may have reinforced caution in standards for IPOs.

14. Stock prices of the major conglomerates do seem to react to the reputed success of their biotech subunits. On the other hand even remarkably profitable biotech-using subunits tend to be small relative to the core businesses of their parents. For example, Kirin Brewery reportedly earned ¥23 billion in 1993 on two very successful pharmaceutical products, but stock prices declined with overall sales of beer. Given the results in Section I above, these biotech subunits may play a vital role in determining a firm's long-run success as the Japanese economy transforms from medium- to high-tech production in the face of new competition in the globalized economy. Accordingly, we are puzzled by the general belief by Japanese experts that the value of such subunits would not get reflected in competitive bids for successful bio-ventures.

15. Recall, however, that Japanese industrialists appear to prefer dealing with American academic researchers so there may be significant elements of the cost-benefit relationship omitted from the simple cost comparison.

16. Note that the two university systems are similar in their reliance on an initial screening period followed by lifetime tenure guaranteed by the university. However, the practice appears to be different. U.S. faculty more often move -- with life tenure -- to other universities, and more often will resign tenured university employment for untenured opportunities in firms or research institutes. Perhaps significantly, in America only tenured university professors can take a leave of absence -- rather than being forced to resign previous employment -- when they accept appointment as an official of the federal government.

17. Zucker, Darby, and Armstrong (1998) present some evidence that entrants may be more successful in biotech research than incumbents.

18. In empirical work not reported in detail here, we tried an alternative definition of inception based on both the primary locations and any additional secondary locations where biotech-relevant research was reported. The results were substantially similar, but more difficult to interpret since we had to supply missing inception years for all the secondary locations.

19. Zucker, Darby, and Brewer (1998) also included a count of the number of venture capital firms in the BEA eligible to finance start-up entrants, but such a variable would be uniformly 0 in Japan during this period. In addition, we experimented in regressions not reported here with the (TOPIX) earnings-price ratio as a measure of the nationwide cost of capital. This variable performed even more poorly than in the U.S. case (see Zucker, Darby, and Brewer 1998) with perverse (positive) coefficients wherever it was entered. We believe that this occurred because, varying by year but not prefecture, it serves as a fixed effects proxy for the year and, in our sample, covaried positively with underlying factors impacting positively on biotech-using firm inception. It is frequently argued that the managers of Japanese firms are so insulated from stock-market pressure that the absence of a significant negative effect is not entirely surprising.

20. Zucker, Darby, and Brewer (1998) report that both stars and collaborators have positive effects in the corresponding model for the U.S. Differences between the U.S. and Japan will be explored in Section VI below. Note, however, that in long-run poisson regressions (not feasible here because of the smaller number of prefectures than U.S. BEAs) Zucker, Darby, and Brewer (1998) do find some evidence of negative effects of the number of active collaborators.

21. The two broader definitions (b) and (c) were based on "Dodwell Marketing Consultants' *Industrial Groupings in Japan*." The narrower definitions (a) and (d) were based on '*Keizai Chosa Kyokai's Keiretsu no Kenkyu* (KNK)." (Weinstein and Yishay Yafeh 1995, p. 367.)

22. See Section VI below for details on the stacked regressions and associated Wald test as the technique is applied to testing for equality of coefficients for inception in Japan and the U.S.

23. These stacked regressions are not reported in full since the coefficient estimates are identical to those in the separate regressions, representative examples of which are reported in Table 5 below.

24. Alternatively, the differences which are visually apparent may not be statistically significantly so. Further, these differences may reflect remaining differential reporting bias in which larger firms are more likely to claim to have been doing biotechnology from the beginning since nearly 10 percent of keiretsu firms report entering biotechnology in the earliest possible year.

25. In the United States we use functional economic areas (BEAs) as the local areas corresponding to prefectures in Japan.

26. The χ^2 statistic is not reported for column (d) since in that case there is only one interaction term and the significant coefficient for Total Employment x JDUMMY is sufficient to demonstrate structural differences.

27. There are a relatively small number of incumbents in the U.S. for which secondary locations are included among the biotech-using firms if separate inception dates could be obtained for inception at each location.

28. Inception dates for incumbents are generally less reliable than for entrants, and this is especially so in

Japan where many firms declare themselves early adopters of biotechnology referring to older fermentation and other production methods based on living organisms, and not to the "new" biotechnology based on recombinant DNA, monoclonal antibodies, and other new techniques.

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Table 1
Adoption of Biotechnology and Survival to 1999 of Publicly Traded Companies with

A. Pharmaceutical Manufacturers' Association Membership in 1975 (38 Firms)

	Indicator of Adoption		All Firms	Test for = exit rates
	No Star Ties	Had Star Ties[a]		
Firm Did Not Survive	**19**	**3**	22	-
Firm Survived[b] to 1999	**4**	**12**	16	-
All Firms	23	15	38	-
Exit rate (2-year publication lag)	3.92%	1.56%	3.25%	z=1.558, p=0.060[c]
Exit rate (0-year publication lag)	3.69%	1.85%	3.25%	z=1.150, p=0.125[c]

Contingency table $\chi^2(1) = 14.6$ ($p \leq 0.001$)

B. World's Leading Companies in the Development of New Drugs in 1981-1982 (20 Firms)

	Indicator of Adoption		All Firms	Test for = exit rates
	No Star Ties	Had Star Ties[a]		
Firm Did Not Survive	**2**	**0**	2	-
Firm Survived[b] to 1999	**4**	**14**	18	-
All Firms	6	14	20	-
Exit rate (2-year publication lag)	1.13%	0.00%	0.57%	z=1.414, p=0.078[c]
Exit rate (0-year publication lag)	0.98%	0.00%	0.57%	z=1.212, p=0.113[c]

Contingency table $\chi^2(1) = 5.2$ ($p \leq 0.025$)

Note: [a]Had star ties indicates that one or more genetic-sequence-discovery articles was written by a star scientist with or as an employee of the listed firm or a predecessor or controlled firm.
[b]Survived means that the firm continued to 1999 as an independent firm (or division or subsidiary of the 1975 parent) or the dominant or equal partner in any merger.
[c]z and p values of one-sided test of hypothesis that exit is binomial process independent of ties.

Sources: A. Pharmaceuticals Manufacturers Association, 1975 membership list; COMPUSTAT, CRSP; Securities Data Corporation Mergers and Acquisition data base; Bioscan various issues; world wide web company web pages. B. California Department of Commerce (1986), Tables 11 and 12; COMPUSTAT, CRSP; Securities Data Corporation Mergers and Acquisition data base; Bioscan various issues; world wide web company web pages.

Table 2
Effect of Adoption of Biotechnology on Survival
Pharmaceutical Manufacturers' Association Membership in 1975 (38 Firms)
Weibull Loglinear Survival Models

Variables	Coefficients (standard errors)			
	2-year publication lag		0-year publication lag	
Constant	2.967*** (0.109)	2.828*** (0.107)	3.001*** (0.110)	2.852*** (0.107)
Has-ties	0.815** (0.297)	0.644* (0.281)	0.743* (0.293)	0.578* (0.280)
Top-20	-	1.039* (0.460)	-	1.062* (0.462)
Sigma	0.451*** (0.088)	0.435*** (0.086)	0.451*** (0.088)	0.437*** (0.086)
Log-likelihood	-88.35	-82.78	-89.51	-83.62

Significance level: $*p \leq 0.05$, $**p \leq 0.01$, $***p \leq 0.001$

Table 3
Poisson Regressions for Inception of Use of Biotechnology by 345 Incumbent Firms
by Year and Prefecture in Japan, 1975-1989

	(a)	(b)	(c)	(d)	(e)
Constant	-1.049***	-1.158***	-1.479***	-4.112***	-5.975***
	(0.040)	(0.043)	(0.060)	(0.621)	(0.584)
Active Stars	0.388***	0.405***	0.167***	-	0.108***
	(0.023)	(0.018)	(0.019)		(0.028)
Active Collaborators	-0.111***	-0.003	-0.045**	-	-0.088***
	(0.014)	(0.012)	(0.017)		(0.023)
Active Stars x Active Collabs.	-	-0.008***	-0.003*	-	-0.001
	-	(0.001)	(0.001)		(0.002)
No. of Main Professors	-	-	-0.086***	-	0.024
			(0.008)		(0.014)
Total Research Funding-University	-	-	-0.023***	-	-0.003
			(0.001)		(0.003)
Total Employment in Prefecture	-	-	-	0.563***	0.479***
				(0.066)	(0.075)
Average Earnings in Prefecture	-	-	-	0.058**	0.110***
				(0.019)	(0.017)
Log-likelihood	-671.4	-658.3	-586.7	-531.9	-509.0
Log-likel. restricted	-869.3	-869.3	-869.3	-869.3	-869.3

Significance levels: * < 0.05, ** < 0.01, *** < 0.001
Notes: Standard errors (adjusted by Wooldridge 1991, Procedure 2.1) are in parentheses below coefficients. N = 705.

Table 4
Poisson Regressions for Inception of Use of Biotechnology by 345 Incumbent and 23 Entrant Firms, by Year and Prefecture in Japan, 1975-1989

	(a)	(b)	(c)	(d)	(e)
Constant	-0.962*** (0.037)	-1.059*** (0.040)	-1.364*** (0.055)	-3.901*** (0.580)	-5.661*** (0.552)
Active Stars	0.383*** (0.021)	0.398*** (0.018)	0.168*** (0.018)	-	0.108*** (0.026)
Active Collaborators	-0.109*** (0.013)	-0.010 (0.012)	-0.051** (0.016)	-	-0.093*** (0.023)
Active Stars x Active Collabs.	-	-0.008*** (0.001)	-0.002 (0.001)	-	-0.0002 (0.002)
No. of Main Professors	-	-	-0.084*** (0.007)	-	0.026** (0.013)
Total Research Funding-University	-	-	-0.022*** (0.001)	-	-0.004 (0.003)
Total Employment in Prefecture	-	-	-	0.560*** (0.061)	0.473*** (0.071)
Average Earnings in Prefecture	-	-	-	0.055** (0.018)	0.105*** (0.017)
Log-likelihood	-711.3	-699.8	-628.1	-567.2	-544.5
Log-likel. restricted	-915.5	-915.5	-915.5	-915.5	-915.5

Significance levels: * < 0.05, ** < 0.01, *** < 0.001
Notes: Standard errors (adjusted by Wooldridge 1991, Procedure 2.1) are in parentheses below coefficients. N = 705.

Table 5
Wald Tests for Equality of Coefficients for
Inception of Use of Biotechnology by 368 Keiretsu and Non-Keiretsu Members
in Poisson Regressions by Year and Prefecture in Japan, 1975-1989

Variables Included -- Equality of Coefficients Tested Groupwise[a]	χ^2 Statistics[a] by Definition of Keiretsu[b]			
	Big 8 + Vertical	Big 8	Big 6	Big 6 Pres. Club
Active Stars, Active Collaborators, Active Stars x Active Collaborators.	2.24 [3]	2.60 [3]	3.30 [3]	5.54 [3]
Above variables + No. of Main Professors, Total Research Funding-University	7.60 [5]	8.62 [5]	7.59 [5]	9.71 [5]
Above variables + Total Employment, Average Earnings in Prefecture	10.56 [7]	12.81 [7]	9.76 [7]	16.48* [7]
Only Total Employment in Prefecture, Average Earnings in Prefecture	1.05 [2]	1.36 [2]	3.65 [2]	3.70 [2]
Memo: Share of Keiretsu-Members in Total Entry	0.307	0.291	0.293	0.139

Significance levels: * < 0.05, ** < 0.01, *** < 0.001

Notes: [a]The reported statistics are distributed χ^2 with the degrees of freedom reported below each in square brackets on the null hypothesis that the coefficient for each variable is the same for entry of keiretsu-member and non-member firms in poisson regressions in which the number of births of each type are counted separately.

[b]Keiretsu membership is defined by comparing our firms with those listed as in a keiretsu of a particular type for four different definitions in a data set generously supplied by David E. Weinstein and described in Weinstein and Yishay Yafeh (1995). The Big 6 are the DKB, Fuyo, Mitsui, Mitsubishi, Sanwa, and Sumitomo horizontal groups. The Big 8 are the Big 6 plus the Industrial Bank of Japan and Tokai groups. The Big 8 + Vertical definition adds firms that are members of vertical groups. The Big 6 Presidents Club definition is the narrowest, including only Big 6 firms whose CEOs belong to their group's Presidents Club.

Table 6
Poisson Regressions for Inception of Use of Biotechnology by Incumbent and Entrant Firms
by Year and Local Area in Japan (1975-1989) and the U.S. (1976-1989)

	(a)	(b)	(c)	(d)	(e)
Constant	-1.414***	-1.591***	-1.858***	-1.793***	-1.971***
	(0.024)	(0.030)	(0.035)	(0.035)	(0.047)
JDUMMY	-	0.629***	0.799***	-0.344***	-0.152
		(0.054)	(0.064)	(0.068)	(0.092)
Active Stars	0.204***	0.157***	0.250***	-	0.147***
	(0.016)	(0.019)	(0.016)		(0.024)
Active Stars x JDUMMY	-	0.225***	0.148***	-	-0.057
		(0.032)	(0.027)		(0.035)
Active Collaborators	0.011	0.043**	0.229***	-	0.208***
	(0.010)	(0.012)	(0.012)		(0.015)
Active Collaborators x JDUMMY	-	-0.152***	-0.239***	-	-0.222***
		(0.020)	(0.020)		(0.023)
Active Stars x Active Collaborators	-	-	-0.014***	-	-0.011***
			(0.001)		(0.001)
Active Stars x Active Collabs. x JDUMMY	-	-	0.007**	-	0.007***
			(0.002)		(0.002)
Total Employment in area	-	-	-	0.431***	0.183***
				(0.010)	(0.028)
Total Employment x JDUMMY	-	-	-	0.300***	0.526***
				(0.022)	(0.044)
χ^2 JDUMMY interactions=0	n/a	71.9***	185.2***	n/a	375.4***
		[2]	[3]		[4]
Log-likelihood	-2474.0	-2388.2	-2162.4	-2316.4	-1973.4
Log-likel. restricted	-3192.0	-3192.0	-3192.0	-3192.0	-3192.0

Significance levels: * < 0.05, ** < 0.01, *** < 0.001

Notes: Standard errors (adjusted by Wooldridge 1991, Procedure 2.1) are in parentheses below coefficients. N = 3220.

Degrees of freedom are in brackets under the χ^2 statistics.

Local areas are prefectures in Japan and the B.E.A.'s functional economic areas in the U.S.

Appendix Table A
Comparative Analysis of Factors Related to Biotechnology Enterprise
between United States and Japan

	US	Japan
Academic activities		
national/state and private univ	both strong	mostly national
autonomy	strong	weak
government control	modest	influential
scientist mobility MD univ to univ	high	low
univ to company	high	very rare
PhD univ to univ	high	not frequent
univ to company	high(any size OK)	high(mostly big company)
support by company	expensive	inexpensive
by venture capitalist	frequent	so far zero
scientist entrepreneurship	aggressive, rewarded	essentially not allowed
innovative mind	aggressive	
Company		
size	large to small	large to middle
top management	relatively not age related	markedly age related
scientist mobility	high	very low
decision making	individually led	group consensus
challenge spirit	risk taking	modest
Society		
bank/venture capitalist	risk taking/frontier technology	don't take risk/asset based
popular view	appreciate small company	appreciate large company only
commerce law	relatively deregulated	strongly need deregulation
research cost(gvmt:company)	45:55	27:72
Patent		
priority	date of the invention (made only in US)	date of the submission
claim	broad(doctrine of equivalency)	limited
number of bio-pharm in 1991	140	18

Source: Ryuzo Sadahiro, Ph.D., Executive Director, Pharmaceuticals Group, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan.

Figure 1. 1975 PMA Members - Exit Rates by Star TIes, 1976-1999

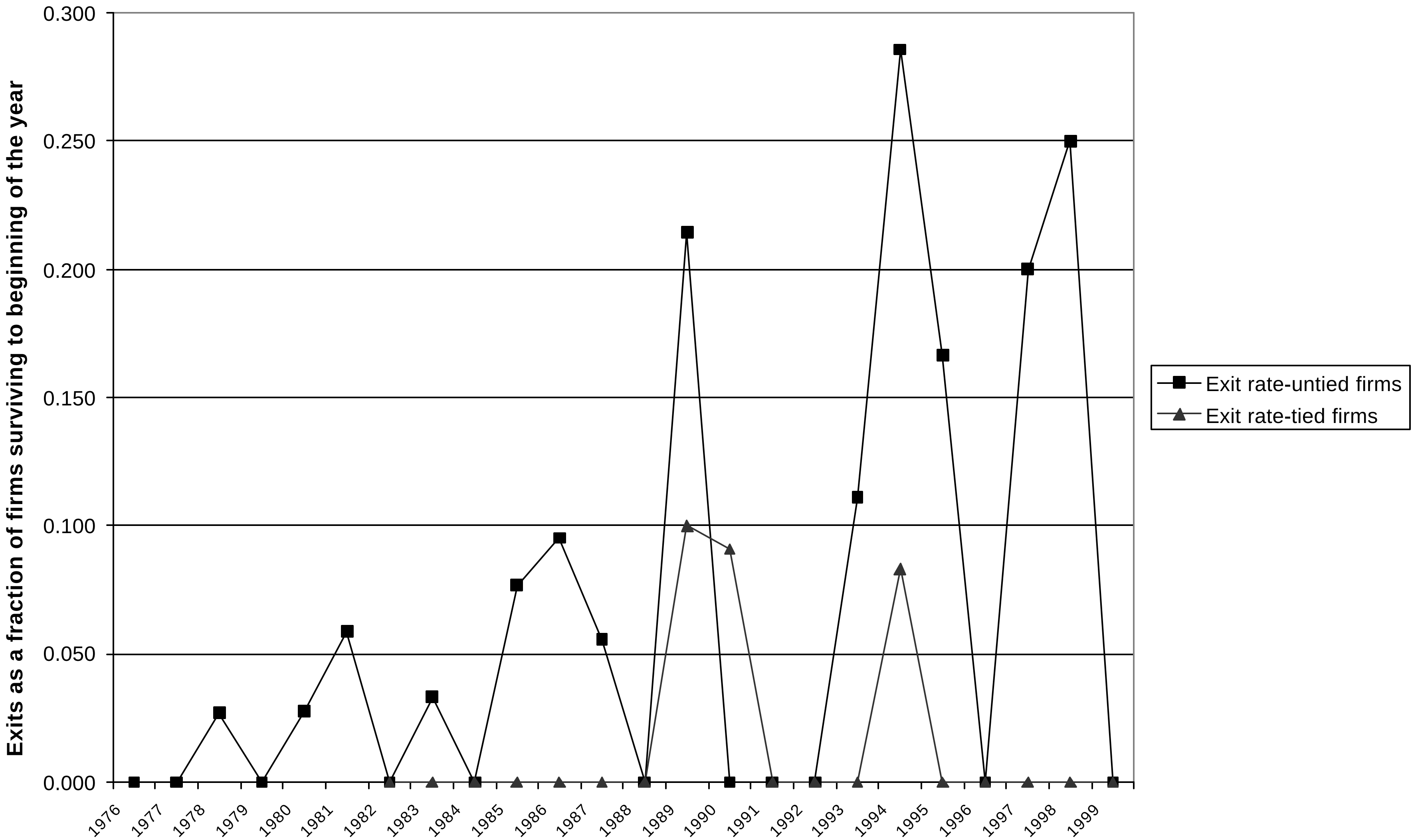


Figure 2. Ever-Active Stars and New Biotechnology Enterprises as of 1990 in the U.S.

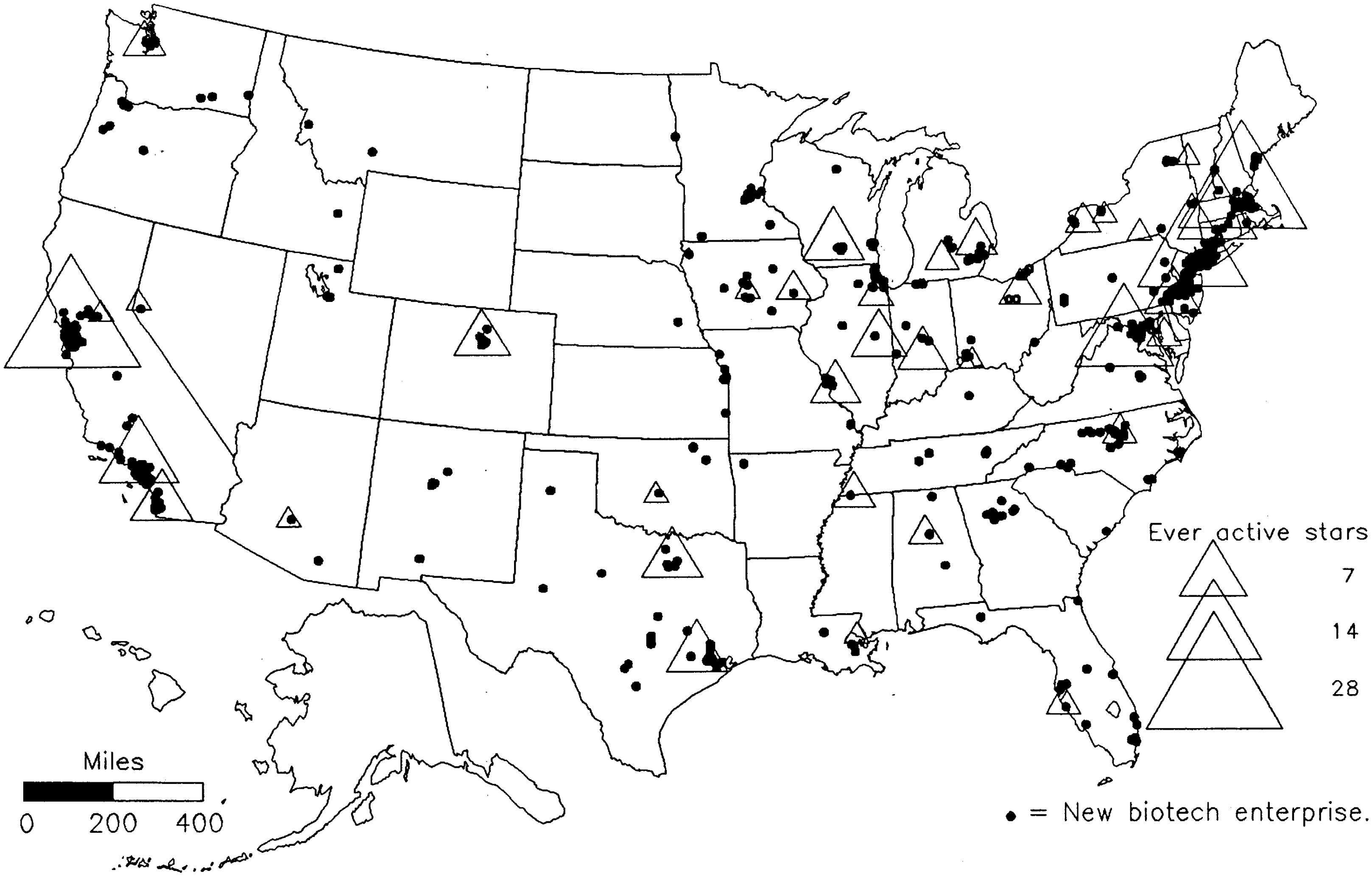
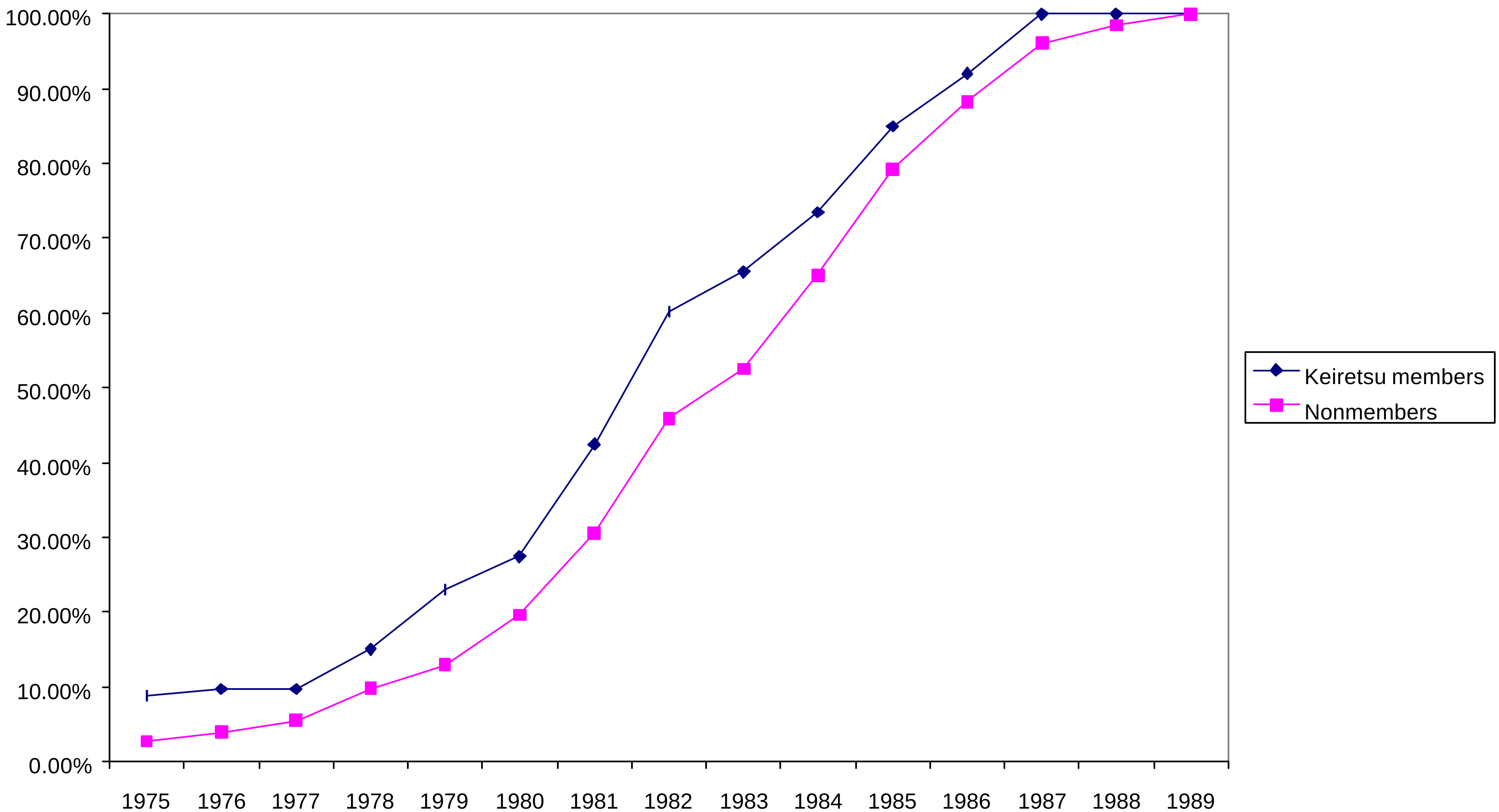


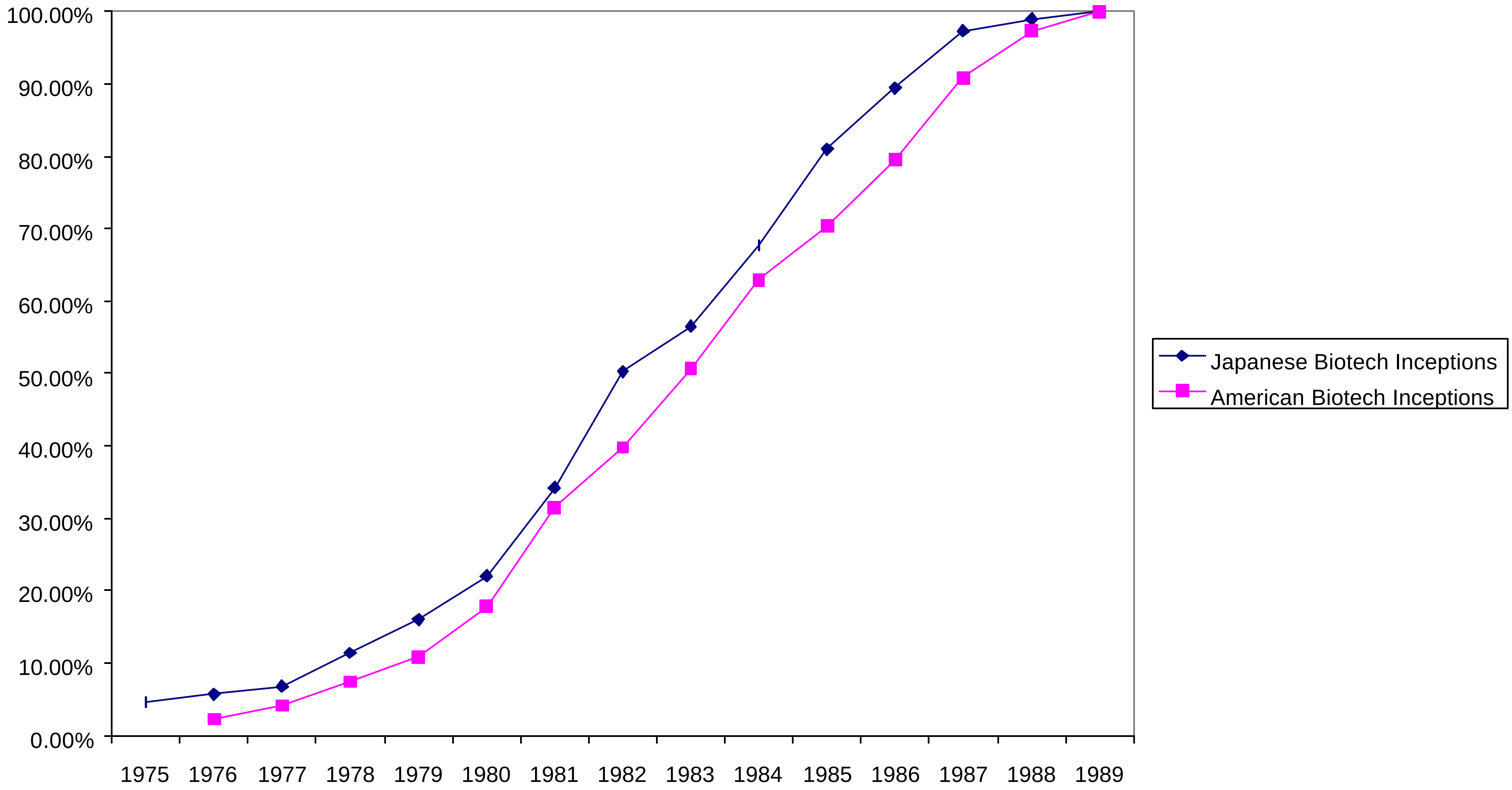
Figure 3. Ever-Active Stars and New Biotechnology Enterprises as of 1990 in Japan

Figure 4. Cumulative Densities for Inception of Keiretsu Members and Nonmembers into Biotechnology, 1975-1989



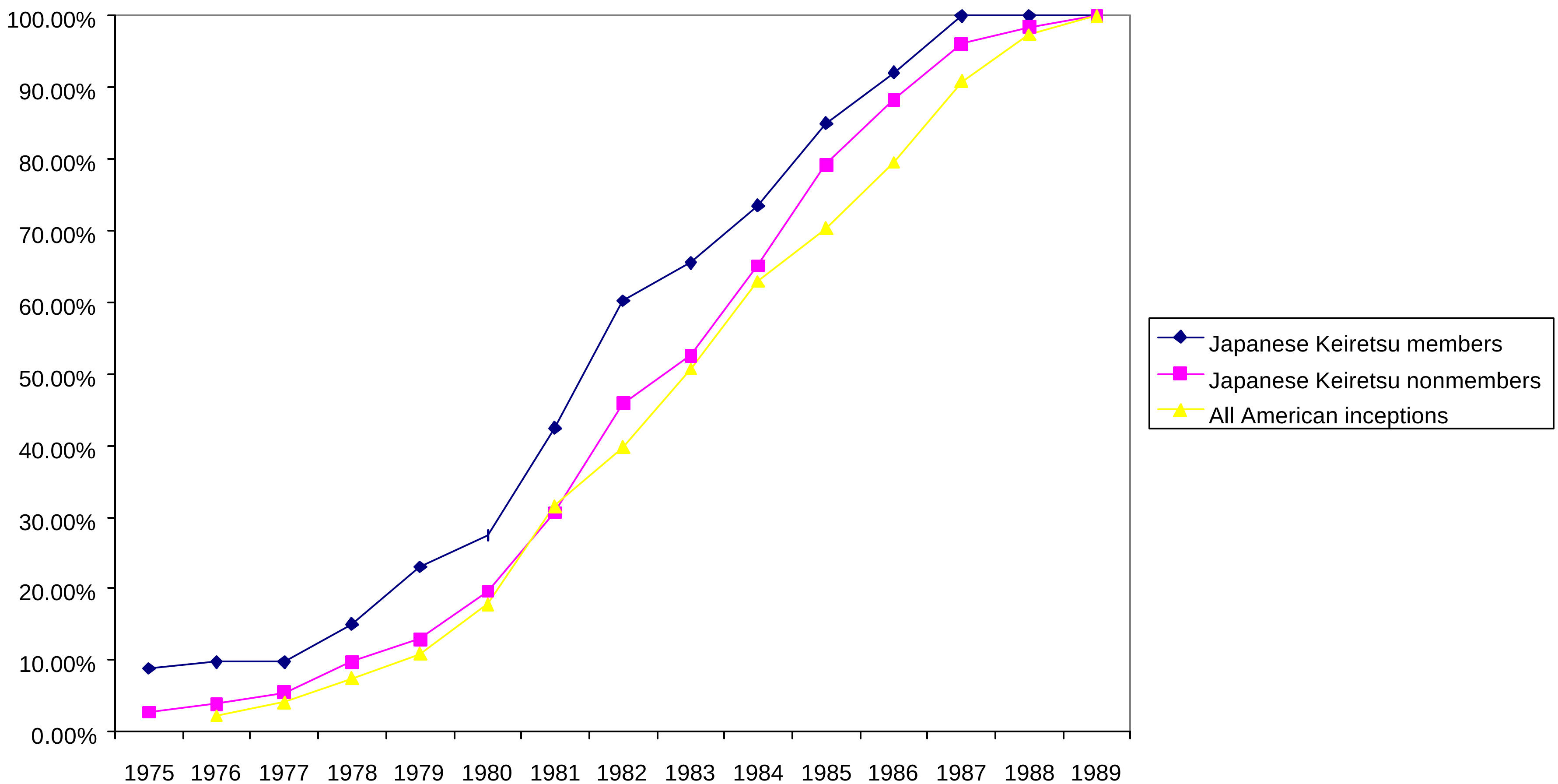
Note: Keiretsu Members are defined as Big 8 plus Vertical groups. All others are nonmembers.

Figure 5. Cumulative Densities for Inception of Japanese and American Firms into Biotechnology, 1975-1989



Note: The data sets define Japanese inceptions as beginning in 1975 and American inceptions as beginning in 1976.

Figure 6. Cumulative Densities for Inception of All American Firms vs. Japanese Keiretsu Members and Nonmembers into Biotechnology, 1975-1989



Notes: Keiretsu Members are defined as Big 8 plus Vertical groups. All others are nonmembers. The data sets define Japanese inceptions as beginning in 1975 and American inceptions as beginning in 1976.