

Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises

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The number of American firms actively using biotechnology grew rapidly from nonexistent to over 700 in less than two decades, transforming the nature of the pharmaceutical industry and significantly impacting food processing, brewing, and agriculture, as well as other industries. Here we demonstrate empirically that the commercialization of this technology is essentially intertwined with the development of the underlying science in a way which illustrates the significance in practice of the localized spillovers concept in the agglomeration literature and of the tacit knowledge concept in the information literature. Indeed we present here strong evidence that the timing and location of initial usage

by both new dedicated biotechnology firms (*“entrants”*) and new biotech subunits of existing firms (*“incumbents”*) are primarily explained by the presence at a particular time and place of scientists who are actively contributing to the basic science as represented by publications reporting genetic-sequence discoveries in academic journals.

By quantifying separable effects of individual scientists, major universities, and federal research support we provide specific structure to the role of universities and their faculties in encouraging local economic development through what are conventionally described in the literature as geographically localized knowledge spillovers.¹ Such localized knowledge spillovers may play fundamental roles in both economic agglomeration and endogenous growth (Paul M. Romer, 1986, 1990; Gene M. Grossman and Elhanan Helpman, 1991). However, our evidence, like the other literature cited here, specifically indicates localized effects without demonstrating that they can be characterized as spillovers (or externalities).

Section I lays out our basic hypothesis. The data are described in Section II. Empirical results are reported and discussed in Section III. A summary and conclusions section (Section IV) and Data Appendix complete the article.

I. The Hypothesis

Innovations are generally treated in the growth literature as a nonrivalrous good—freely useable by an unlimited number of potential

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¹ Zvi Griliches (1992) has surveyed the importance of R&D spillovers as a major source of endogenous growth in recent “new growth theory” models and the difficult empirical search for their existence. Despite these difficulties, there have been a number of articles reporting evidence of geographic localization of knowledge spillovers, including Adam B. Jaffe (1989), Jaffe et al. (1993), and Edwin Mansfield (1995).

users at a zero marginal cost (Richard R. Nelson and Romer, 1996). A complementary literature recognizes that some information requires an investment of considerable time and effort to master. The human capital developed by this investment is seen as earning a normal return on the cost of the investment, both direct costs and foregone earnings. We believe that some innovations, particularly a breakthrough "invention of a method of inventing" (Griliches, 1957), may be better characterized as creating (rivalrous) human capital—intellectual human capital—characterized by natural excludability as opposed to a set of instructions for combining inputs and outputs which can be protected only by intellectual property rights. This natural excludability arises from the complexity or tacitness of the information required to practice the innovation (see Nelson [1959], Kenneth J. Arrow [1962], Nelson and Sidney G. Winter [1982], and Nathan Rosenberg [1982]).

Based on both extensive interviews and empirical work summarized in Zucker and Darby (1996), we believe that, at least for the first 10 or 15 years, the innovations which underlie biotechnology are properly analyzed in terms of naturally excludable knowledge held by a small initial group of discoverers, their co-workers, and others who learned the knowledge from working at the bench-science level with those possessing the requisite know-how. Ultimately the knowledge spread sufficiently widely to become part of routine science which could be learned at any major research university. After the initial 1973 discovery by Stanley Cohen and Herbert Boyer of the basic technique for recombinant DNA—the foundation of commercial biotechnology as well as of a burst of scientific innovation—the financial returns available to talented recombinant-DNA scientists first rose dramatically as the commercial implications became widely appreciated and then more gradually declined as more and more scientists learned the techniques, until knowledge of the new techniques per se earned only the normal return for the time required for a graduate student to master them. Further, mere knowledge of the techniques of recombinant DNA was not enough to earn these extraordinary returns; the knowledge was far more productive when embodied in a scientist with the genius and vision to con-

tinuously innovate and define the research frontier and apply the new research techniques in the most promising areas.

We hypothesize that entry of firms into biotechnology in a given year thus will be determined by the geographic distribution of stars and perhaps others then actively practicing the new science as well as by the geographic distribution of economic activity. Stars are properly viewed as locationally (semi-)fixed since few star scientists who knew how to do recombinant DNA were willing to abandon their university appointments and laboratory teams to pursue commercial applications of biotechnology. The primary pattern in the development of the industry involved one or more scientist-entrepreneurs who remained on the faculty while establishing a business on the side—businesses which, where successful, resulted in millions or even billions of dollars for the professors who acquired early ownership stakes. Thus, we see the university as bringing about local industrial benefits by permitting its professors to pursue private commercial interests while their faculty appointments tie them to the area. In preliminary work not reported here, we tried to develop measures of local economic activity for industries, like pharmaceuticals, specifically impacted by the new technology, but these attempts never added significantly to the measures of general activity used in the empirical work below. The *local* availability of venture capital is widely believed to play a significant role in the birth of new biotech entrants (Martin Kenney, 1986; Joshua Lerner, 1994, 1995); so we also include that variable in our regressions.

II. The Data

Data has been collected in panel form for 14 years (1976–1989) and 183 regions (functional economic areas as defined by the U.S. Department of Commerce, Bureau of Economic Analysis [BEA], 1992b). Frequently, the data are aggregates of data at the zip code or county level.² Lagged variables

² The BEA's functional economic areas divide all the counties in the United States into regions including one or more cities, their suburbs, and the rural counties most closely tied to the central city.

include data for 1975 in the unlagged form. See the Data Appendix for more details.

A. Firms

Our data set on firms was derived from a base purchased from the North Carolina Biotechnology Center (NCBC) (1992) which was cleaned and supplemented with information in *Bioscan* (1989–1993) and its precursor (Cetus Corp., 1988). We identified 751 distinct U.S. firms for which we could determine a zip code and a date of initial use of biotechnology. Of these 751 firms, 511 were entrants, 150 incumbents, and 90 (including 18 joint ventures) could not be definitively classified. By 1990, 52 of the 751 firms had died or merged into other firms.

We then calculated the number of births in each region by year of initial use of biotechnology for all 751 firms as well as for their identified subcomponents of entrants and incumbents. We also have the stocks of surviving firms, entrants, and incumbents by region and year.

B. Scientists

Early in our ongoing project studying the scientific development and diffusion of biotechnology, we identified a set of 327 star scientists based on their outstanding productivity through early 1990. The primary criterion for selections was the discovery of more than 40 genetic sequences as reported in *GenBank* (1990) through April 1990.³ However, 22 scientists were included based on writing 20 or more articles, each reporting one or more genetic-sequence discoveries.⁴ In the 1990's,

sequence discovery has become routinized and is no longer such a useful measure of research success. These 327 stars were only three-quarters of one percent of the authors in *GenBank* (1990) but accounted for 17.3 percent of the published articles, almost 22 times as many articles as the average scientist.

We collected by hand the 4,061 articles authored by stars and listed in *GenBank* and recorded the institutional affiliation of the stars and their coauthors on each of these articles. These coauthors are called "collaborators" if they are not themselves a star. Some data on the stars and collaborators who ever published in the United States is given on the left side of Table 1, where the scientists are identified by the organization(s) with which they were affiliated on their first-such publication. The higher citation rate for firm-affiliated scientists is explored at length in Zucker and Darby (1996).

Figure 1 illustrates the time pattern of growth in the numbers of stars and collaborators who have ever published and the total number of firms using biotechnology in the United States. There was a handful of stars who published articles reporting genetic-sequence discoveries before the 1973 breakthrough, but even after 1973 their number increased gradually until taking off in 1980. The numbers of collaborators and firms lagged behind the growth in stars by some years.

To identify those scientists clearly working at the edge of the science in a given year, we term a star or collaborator as "active" if he or she has published three or more sequence-discovery articles in the three-year moving window ending with that year. As seen in the right side of Table 1, this stringent second screen provides an even more elite definition of star scientists as well as identifying some very significant collaborators. We count for each year the number of active stars and active collaborators who are affiliated with an organization in each region.

The locations of active stars and firms are both concentrated and highly correlated geographically, particularly early in the period. Figure 2 illustrates this pattern for the whole period by accumulating the number of stars who have ever been active in each region up to 1990 and plotting them together with the

³ See Zucker et al. (1993). As will be obvious, much of the time between 1990 and the initial submission of this paper was spent in developing reasonable measures of intellectual human capital and in collecting and coding data necessary to locate the authors of the discoveries reported in the articles in question and to trace the diffusion process.

⁴ Scientists advised that some sequence discoveries are more difficult than others and thus merit an article reporting only one sequence. Therefore we included scientists with 20 or more discovery articles to avoid excluding scientists who specialized in more difficult problems.

TABLE 1—DISTRIBUTION OF STAR SCIENTISTS AND COLLABORATORS WHO HAVE EVER PUBLISHED IN THE UNITED STATES

Organization type ^a	Full data set		Ever active in U.S. ^b	
	Number of scientists	Citations ^c /scientist/years	Number of scientists	Citations ^c /scientist/years
<i>Stars:</i>				
University	158	85.5	108	110.8
Institute	44	63.0	26	98.7
Firm	5	143.7	1	694.3
Dual	0	n/a	0	n/a
Total	207		135	
<i>Collaborators:</i>				
University	2901	10.4	369	30.6
Institute	776	13.7	88	35.8
Firm	324	29.2	43	99.1
Dual	3	7.2	0	n/a
Total	4004		500	

^a The organization type refers to the affiliation listed on their first publication with a U.S. affiliation.

^b Ever active in the U.S. means that in at least one three-year period beginning 1974 or later and ending 1989 or earlier, the scientist was listed on at least three articles appearing in our data set of 4,061 articles which reported genetic-sequence discoveries and were published in major journals and that the affiliation listed in the last of the three articles was located in the United States.

^c Citation counts are for 1982, 1987, and 1992 for all articles in our data set (whenever published) for which the individual was listed as an author.

location of biotech-using firms as of early 1990.

C. Other Measures of Intellectual Human Capital

Active stars and collaborators may be incomplete measures of location of the scientific base because there are techniques other than recombinant DNA which have played an important role in commercial biotechnology. Some skeptical readers might also think that some simpler measures of regions' relevant academic resources would contain all the information which we have laboriously collected. We found two measures of regional scientific base which entered separately in regressions reported below, but none which were capable of eliminating the effects of the star scientists.

One measure is a count of the number of "top-quality universities" in a region where top quality is defined by having one or more "biotech-relevant" (biochemistry, cellular/molecular biology, and microbiology) departments with scholarly quality reputational ratings of 4.0 or higher in the 1982 National Research Council survey (Lyle V. Jones et al., 1982). There are 20 such universities in the United States.⁵ Our second measure, "federal

⁵ The 20 universities were: Brandeis University, California Institute of Technology, Columbia University, Cornell University, Duke University, Harvard University, Johns Hopkins University, Massachusetts Institute of Technology, Rockefeller University, Stanford University, University of California-Berkeley, University of California-Los Angeles, University of California-San Diego, University of California-San Francisco, University of

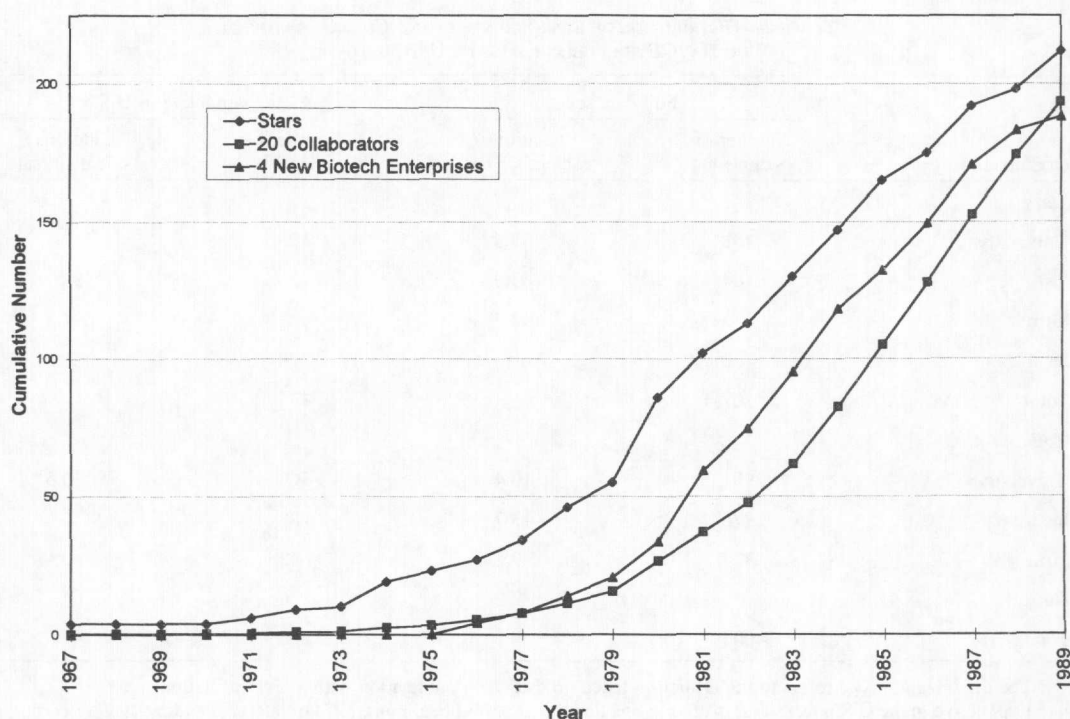


FIGURE 1. CUMULATIVE NUMBER OF U.S. STARS, COLLABORATORS, AND NEW BIOTECH ENTERPRISES, 1967–1989

support," is the total number (in hundreds) of faculty supported by 1979–1980 federal grants to all universities in each region for biotech-relevant research.⁶ These variables take on the same value for a given region in each year.

D. Other Variables

Using listings in Stanley E. Pratt (1982), we measure "venture capital firms" as the number of such firms in a region legally eligible to finance start-ups in each year up to 1981. For later years, the number of firms is fixed at the

number in 1981 to avoid possible simultaneity problems once the major wave of biotech founding began.⁷ (While great bookstores spring up around great universities, the former should not be counted as causing the latter.)

Since entry of biotech firms would be expected to occur where there is other economic activity, particularly involving a highly skilled labor force, we also include *total employment* in all industries (in millions of persons) and *average wages* (measured by deflated average earnings per job in thousands of 1987 dollars) for each region and year.

Finally, an increase in the (all-equity) cost of capital, as measured by the *earnings-price ratio* on the Standard & Poor's 500 Index would reduce the net present value of entry

Chicago, University of Colorado at Denver, University of Pennsylvania, University of Washington (Seattle), University of Wisconsin-Madison, and Yale University.

⁶ We also tried a measure of biotech-relevant research expenditures as reported by the universities, but this variable was too collinear with the federal support variable to enter separately and appeared to be less consistently measured across universities.

⁷ Instrumental variables would provide a more elegant approach to this problem if suitable instruments had been found.

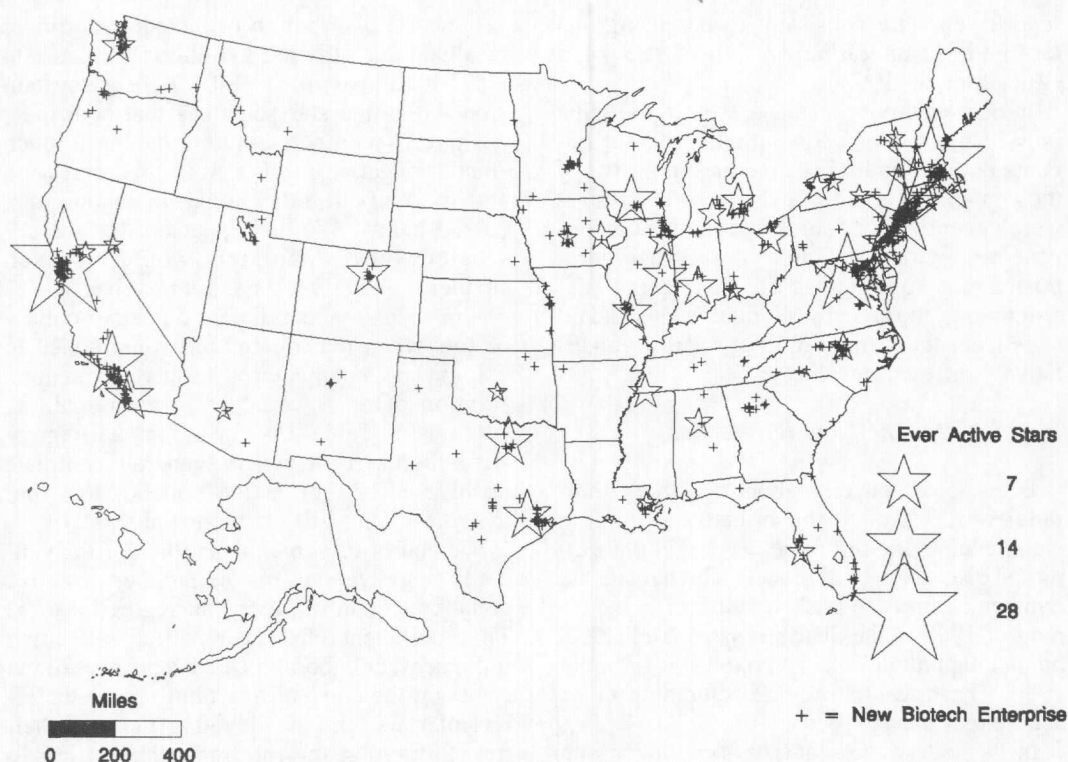


FIGURE 2. EVER ACTIVE STARS AND NEW BIOTECHNOLOGY ENTERPRISES AS OF 1990

and so should have a negative impact on birth of new firms, entrants or incumbents.

III. Empirical Results

We test our hypothesis using both the full panel data and by regressing the geographical distribution of the data in 1990 on values of the independent variables circa 1980. The former more fully exploit the available information while the latter avoid problems of possible simultaneity which might arise after 1980 when commercial biotechnology became a significant economic factor in some regions. All the regressions reported here, as well as an extensive sensitivity analysis noted below, were estimated in the poisson form appropriate for count variables with numerous zeroes using LIMDEP (William H. Greene, 1992 pp. 539–49), with the Wooldridge regression-based correction for the variance-

covariance matrix estimates.⁸ The poisson regressions estimate the logarithm of the expected number of firm births; so the signs and significance of coefficients have the usual interpretation. Although OLS regressions are inappropriate for our count dependent variables with most observations at zero and the rest tailing off through small positive integers, we

⁸ As discussed in Jerry Hausman et al. (1984), the poisson process is the most appropriate statistical model for count data such as ours. In practice, overdispersion (possibly due to unobserved heterogeneity) frequently occurs. Given the problems with resort to the negative binomial (A. Colin Cameron and Pravin K. Trivedi, 1990), Jeffrey M. Wooldridge (1991) developed a flexible and consistent method for correcting the poisson variance-covariance matrix estimates regardless of the underlying relationship between the mean and variance. We are indebted to Wooldridge and Greene for advice in implementing the procedure in LIMDEP.

reported broadly consistent results using that technique in an earlier version of the paper (Zucker et al., 1994).

In our sensitivity analysis, we ran the same poisson regressions for entrants and incumbents defined both exclusive and inclusive of the arguable case of joint ventures. The results were generally very similar to the subcomponent regressions in Table 4. In other unreported poisson regressions, we found that eliminating those regions with no firms and no stars from the sample did not result in qualitatively different results.

A. *The Long-Run Model*

Because of concerns about possible simultaneity biases once the industry became a significant economic force, we begin our empirical discussion with models which relate the number of firms in each region at the beginning of 1990 to the distribution of intellectual human capital and other variables as of about 1980. These results provide something of an acid test of our approach.

In Table 2, we present cross-section poisson regressions across the 183 regions explaining the number of firms in each at the beginning of 1990 when our data set ends.⁹ Column (a) restrains the analysis to only the numbers of stars and collaborators ever active in each region at any time up through 1980, while columns (b) and (c) add first their squares and then our other intellectual human capital variables. Column (d) considers alternatively other economic variables which might explain entry, and column (e) combines the variables in (c) and (d). Column (f) adds to this model the number of biotech firms existing in 1980.

Column (a) in Table 2 indicates that the number of stars and collaborators active through 1980 is a powerful predictor of the

geographic distribution of biotech enterprises in 1990, since the log-likelihood increases to -871.9 compared to -1401.7 for a constant alone. It is the star scientists that contribute positively, with collaborators having a much smaller negative coefficient in this regression and most of the other long-run models discussed below. We had expected that the coefficient on collaborators would be much smaller than that on stars, but positive. We do obtain a positive coefficient on active collaborators when the squared terms are added in column (b), but that turns negative again upon addition of other variables in the remaining columns of Table 2.¹⁰ (In the annual regressions discussed below, we generally estimate positive effects of active collaborators, but they are often statistically insignificant.)

We can offer two explanations for the generally negative sign on the number of active collaborators in the long-run regressions: (i) This coefficient reflects two partially offsetting influences; collaborators have a positive direct effect on the entry of firms but reduce the effect of stars who are devoting more of their time to training students and relatively less to starting their own firms. Training collaborators is surely a useful and rewarded activity—particularly for the academic stars—but it may take more of the stars' energy than it is worth if firm birth were the only criteria.¹¹ (ii) The sign and magnitude of the coefficient on collaborators may simply reflect significant multicollinearity among the intellectual human capital variables in the very early years. This is especially likely since when we examine the

¹⁰ In column (b) of Table 2 (and Table 3), the negative coefficient on the squared term indicates that as the number of stars or collaborators increases, their marginal contribution diminishes eventually passing through zero. For collaborators, in columns (c)–(f) of these tables the sign pattern reverses so that the partial derivative of the log probability of birth with respect to collaborators starts out negative, and increases as their number increases, eventually becoming positive.

¹¹ In support of this explanation, we note that in our sensitivity analysis we tried regressions which substituted interaction terms multiplying the numbers of active stars and collaborators for the squared terms. In those regressions, we obtain significant positive coefficients on the numbers of stars and collaborators and a significant negative coefficient on their interaction.

⁹ In an earlier version of this paper we included an alternative form of Table 2 (available from the authors upon request) in order to forestall interpretations that the results in Table 2 may reflect reverse causality. This alternative table reported regressions which explain the number of firms alive at the beginning of 1990 that were born after 1980. Nearly identical results were obtained, reflecting the fact that bulk of new biotechnology enterprises were founded after 1980.

TABLE 2—POISSON REGRESSIONS ON THE STOCK OF BIOTECH-USING FIRMS AT THE BEGINNING OF 1990 BY REGION

	(a)	(b)	(c)	(d)	(e)	(f)
Constant	0.911*** (0.014)	0.644*** (0.015)	0.468*** (0.033)	-2.595*** (0.086)	-2.718*** (0.256)	-2.607*** (0.345)
Number stars active at any time during 1976–80	0.567*** (0.029)	0.587*** (0.072)	0.466*** (0.090)	—	0.877*** (0.076)	0.649*** (0.084)
Number collaborators active at any time during 1976–80	-0.076*** (0.012)	0.175*** (0.033)	-0.183** (0.068)	—	-0.333*** (0.045)	-0.261*** (0.037)
(Number stars active at any time during 1976–80) ²	—	-0.028*** (0.007)	-0.019 (0.014)	—	-0.049*** (0.012)	-0.024* (0.012)
(Number collaborators active at any time during 1976–80) ²	—	-0.005*** (0.001)	0.002 (0.003)	—	0.007** (0.003)	0.001 (0.002)
Number top-quality universities in the region	—	—	1.388*** (0.150)	—	1.594*** (0.107)	0.442* (0.195)
Number faculty with federal support in the region	—	—	0.263 (0.143)	—	0.752*** (0.088)	0.711*** (0.051)
Number venture capital firms in the region in 1980	—	—	—	0.017*** (0.002)	-0.045*** (0.003)	-0.013** (0.004)
Total employment (all industries) in the region in 1980	—	—	—	0.222*** (0.019)	-0.009 (0.043)	-0.213*** (0.049)
Average wages per job in the region in 1980	—	—	—	0.166*** (0.004)	0.143*** (0.014)	0.139*** (0.019)
Cumulative births of biotech firms during 1976–80	—	—	—	—	—	0.300*** (0.025)
Log-likelihood	-871.9	-707.3	-543.2	-753.9	-416.0	-350.7
Restricted log-likelihood	-1401.7	-1401.7	-1401.7	-1401.7	-1401.7	-1401.7

Notes: $N = 183$. Standard errors (adjusted by Wooldridge, 1991 Procedure 2.1) are in parentheses below coefficients.

* Significantly different from 0 at the 5-percent level.

** Significantly different from 0 at the 1-percent level.

*** Significantly different from 0 at the 0.1-percent level.

full cross-section/time-series results just below we obtain (we think more reliable) zero or positive coefficients on collaborators, so the puzzle largely disappears.

The full “fundamentals” model (excepting the decade-lagged dependent variable) is presented in column (e) of Table 2, where all the coefficients are significant except that for total employment. Leaving aside the question of the negative collaborator coefficient, we note the strong, positive, separate effects of stars, top-quality universities, and federal research

grants at universities on birth of firms in a given geographic region. The intellectual human capital variables alone increase the log-likelihood ratio from -1401.7 to -543.2 [see column (c)], with the final three variables bringing this quantity up to -416.0. As to the last three variables, the quality of the labor force, measured by average wages per job, seems much more relevant than its size. Surprisingly, to some observers, the number of venture capital firms in a region enters, but with a significantly negative sign. We interpret

the negative sign as evidence that venture capitalists did play an active role in the formation of entrant firms, but they apparently resulted in fewer, larger firms being born in the areas in which they were more active.¹²

This sign of the coefficient of the number of venture capital firms in a region is robust in sensitivity experiments with other forms (not reported here) except for regressions which exclude the intellectual human capital variables such as in column (d). That regression looks good in terms of significance and expected sign pattern although it has a much lower explanatory power than the intellectual human capital variables alone [column (c)]. Just below, we report very similar results in a cross-section/time-series context. Thus, it is certainly easy to see why the evidence for an important positive impact of venture capital firms on the birth of biotech firms may have appeared stronger in previous work than seems warranted based on fuller models: Since venture capital firms have developed around a number of great universities, their presence proxies for intellectual human capital in the absence of more direct measures; if they are the only variable indicating presence of great universities and their faculties, they enter positively even if their packaging activities result in a negative direct effect on births.

The decade-lagged dependent variable is added to the full fundamentals model in column (f) of Table 2. Doing so primarily has the effect of weakening the significance of the top-quality universities variable (but, see the annual model below) due to significant multicollinearity between the variables.¹³ One interpretation of this positive coefficient on the lagged dependent variable is that agglomera-

tion effects strengthen the impact of fundamentals on regional development. However, the statistical properties of poisson regressions with lagged dependent variables are somewhat problematic so such regressions and their estimated standard errors should be viewed cautiously.

In conclusion, the intellectual human capital variables play a strong role in determining where the U.S. biotech industry developed during the 1980's. We have been able to identify particular star scientists who appear to play a crucial role in the process of spillover and geographic agglomeration over and above that which would be predicted based on university reputation and scientists supported by federal grants alone. The strong positive role of venture capital variable reported previously is not supported for firm births. Indeed, the data tell us that there were fewer firms founded, other things equal, where there more venture capital firms. It is left to future research to explore whether firms which are associated with particular star scientists or were midwived by venture capitalists are more successful than other firms.¹⁴

B. The Annual Model

We next report analogous poisson regressions exploiting the panel nature of our data set with observations for the 183 regions for each of the years 1976 through 1989. Tables 3 and 4 report poisson regressions for this entire panel.

Column (a) of Table 3 reports the results using only the counts of stars and their collaborators active each year in each region. As with the long-run models in Table 2, examination of the data suggested that these effects—particularly for stars—were nonlinear so we add squared values in column (b). Again, as the number of stars increases, their marginal contribution diminishes eventually passing through zero.

These nonlinearities might reflect the declining value over time of the intellectual human capital as we have measured it. Basically,

¹² This hypothesis was derived from anecdotal evidence, but note that the top nine of Ernst & Young's list of top-ten companies by 1993 market valuation (G. Steven Burrill and Kenneth B. Lee, Jr., 1994 p. 54) were located and founded in regions richly endowed with venture capital firms: Boston (3), San Francisco (3), Los Angeles (1), San Diego (1), and Seattle (1).

¹³ In the alternative version of Table 2 (see footnote 9 above), the coefficient on the lagged dependent variable was nearly as large as in Table 2, so the significant positive coefficient does not arise from firms born 1976–1980 appearing in both the current and lagged dependent variables.

¹⁴ See Zucker et al. (1994) for our first effort to assess the determinants of success of firms after birth.

TABLE 3—ANNUAL POISSON REGRESSIONS ON THE BIRTH OF BIOTECH-USING FIRMS BY REGION AND YEAR, 1976–1989

	(a)	(b)	(c)	(d)	(e)	(f)
Constant	-1.591*** (0.032)	-1.918*** (0.041)	-2.148*** (0.057)	-4.447*** (0.226)	-4.491*** (0.349)	-4.687*** (0.565)
Number stars active in the region and year	0.157*** (0.020)	0.529*** (0.051)	0.270** (0.088)	—	0.361*** (0.080)	0.282** (0.103)
Number collaborators active in the region and year	0.043*** (0.013)	0.083* (0.035)	0.047 (0.049)	—	0.013 (0.047)	0.032 (0.052)
(Number stars active in the region and year) ²	—	-0.022*** (0.002)	-0.014* (0.006)	—	-0.015** (0.005)	-0.014 (0.008)
(Number collaborators active in the region and year) ²	—	-0.001 (0.001)	0.000 (0.001)	—	0.000 (0.001)	0.001 (0.002)
Number stars active in the region and year × DUMMY1986–89	—	—	-0.219 (0.113)	—	-0.298** (0.102)	-0.245 (0.128)
Number collaborators active in the region and year × DUMMY1986–89	—	—	0.117 (0.067)	—	0.115 (0.064)	0.027 (0.081)
(Number stars active in the region and year × DUMMY1986–89) ²	—	—	0.006 (0.007)	—	0.009 (0.006)	0.007 (0.008)
(Number collaborators active in the region and year × DUMMY1986–89) ²	—	—	-0.001 (0.002)	—	-0.001 (0.002)	0.001 (0.002)
Number top-quality universities in the region in 1981	—	—	0.444*** (0.125)	—	0.472*** (0.095)	0.462*** (0.109)
Number faculty with federal support in the region in 1979–80	—	—	0.625*** (0.093)	—	0.982*** (0.094)	0.930*** (0.093)
Number venture capital firms in the region and year ^a	—	—	—	0.019** (0.007)	-0.028*** (0.006)	-0.024** (0.008)
Total employment (all industries) in the region and year	—	—	—	0.173*** (0.051)	-0.081 (0.048)	-0.117* (0.055)
Average wages per job in the region and year	—	—	—	0.153*** (0.010)	0.125*** (0.016)	0.132*** (0.017)
Earnings-price ratio (Standard & Poors 500) for year	—	—	—	-0.024 (0.016)	-0.026 (0.026)	-0.017 (0.039)
Number firms active in the region at end of previous year	—	—	—	—	—	0.020 (0.013)
Number firms active in all U.S. at end of previous year	—	—	—	—	—	-0.000 (0.000)
Births of biotech firms in the region for previous year	—	—	—	—	—	0.054 (0.034)
Log-likelihood	-1677.0	-1429.1	-1274.3	-1669.5	-1202.3	-1184.6
Restricted log-likelihood	-2238.5	-2238.5	-2238.5	-2238.5	-2238.5	-2238.5

Notes: $N = 2562$. Standard errors (adjusted by Wooldridge, 1991 Procedure 2.1) are in parentheses below coefficients.

^a For years after 1981, the number of venture capital firms in a region is held constant at the 1981 level to avert simultaneity problems.

* Significantly different from 0 at the 5-percent level.

** Significantly different from 0 at the 1-percent level.

*** Significantly different from 0 at the 0.1-percent level.

as the knowledge diffuses we expect that more and more stars will result in less and less pay-off to any one of them if he or she were to start a firm, and indeed stars are less likely to result

in birth of firms after 1985 than before. This is illustrated in column (c) of Table 3 where we add four interaction terms in which these counts and their squares have been multiplied

by a dummy DUMMY1986–89 equal to 1 during 1986–1989 and 0 otherwise, as well as the other intellectual human capital terms. During 1986–1989 the positive effect of stars is sharply reduced while that of collaborators more than triples.¹⁵ Nonetheless, we should view this inference cautiously since the significance values of the interaction terms for stars and collaborators with DUMMY1986–89 fall between 0.10 and 0.05, except for stars in the full fundamentals model in column (e) where the stars interaction term is significant at the 0.01 level.

Thus, we see that (at least during the first decade of this industry) localities with outstanding scientists having the tacit knowledge to practice recombinant DNA were much more likely to see new firms founded and preexisting firms begin to apply biotechnology. There is some evidence that as knowledge about gene splicing diffused and the tacit knowledge lost its scarcity and extraordinary value, the training function of universities became more important relative to the attraction of great scientists to an area. It is interesting that the quadratic term for stars is negative, suggesting diminishing returns (or possibly just proportionately fewer, larger firms) rather than the increasing returns suggested by standard views of knowledge spillovers which posit uninternalized, positive external effects from university scientists.¹⁶ In the same regression in column (c), we see that, beyond the identified stars and collaborators, university quality and federal support are also significant measures of intellectual human capital relevant to firm founding.

¹⁵ To compute the effects of stars in the 1986–1989 period, we need to add the coefficients of the number of active stars and the coefficient of the same variable interacted with DUMMY1986–89 and then do the same for the two terms involving the squared values of these variables. An analogous approach yields the effect of collaborators during 1986–1989. We examined also interactions with dummy variables for 1976–1980 and with a time trend. Since the coefficients were very small and statistically insignificant for interaction terms involving 1976–1980 dummies, we believe the reported form more accurately reflects the time or diffusion dependence than a negative trend throughout the period.

¹⁶ We are indebted to Jeff Armstrong for this point.

Column (d) of Table 3 leads to the same conclusions with panel data as found for the same column in Table 2: The economic variables enter significantly with the expected sign if the intellectual human capital variables are omitted from the regression. However, unlike the previous long-run case, we can now enter the earnings-price ratio.¹⁷ Here this variable enters with the correct sign, but does not even reach the 0.10 level of significance.

Column (e) of Table 3 presents the annual full fundamentals model incorporating the intellectual human capital and other variables. The results for the intellectual human capital measures are robust while the sign of the venture capital variable turns significantly negative as in the long-run model and the employment variable becomes insignificant (and negative).

Column (f) of Table 3, analogously to Table 2, adds a lagged dependent variable to the full fundamentals model. We also included the one-year lagged regional and national counts of firms using biotechnology as dynamic influences reflecting local agglomeration effects and market competition effects, respectively. None of the three dynamic variables enter significantly although their signs are consistent with some geographic agglomeration.

Thus, taken as a whole the results summarized in Table 3 support the strong role of intellectual human capital variables in determining the development of the American biotech industry.

The role of the economic variables, particularly the number of venture capital firms in the region, is explored further in Table 4. This table presents representative results for births in the entrant and incumbent subcomponents of firm entry into biotechnology. We see in columns (a) and (b) that if only the economic variables are introduced we get all the expected signs at appropriate significance [except for employment in (a) and the earnings-price ratio in both], including a result consistent with conventional wisdom that the number of venture capital firms has a signifi-

¹⁷ The earnings-price ratio had to be dropped from these analyses because it is available only nationally over time.

TABLE 4—ANNUAL POISSON REGRESSIONS ON THE BIRTH OF BIOTECH-USING ENTRANTS AND INCUMBENTS BY REGION AND YEAR, 1976–1989

	(a) Entrants	(b) Incumbents	(c) Entrants	(d) Incumbents	(e) Entrants	(f) Incumbents
Constant	-4.726*** (0.284)	-5.798*** (0.563)	-4.843*** (0.409)	-5.673*** (0.902)	-4.928*** (0.669)	-5.228*** (1.285)
Number stars active in the region and year	—	—	0.414*** (0.095)	0.323 (0.165)	0.351** (0.124)	0.242 (0.169)
Number collaborators active in the region and year	—	—	-0.006 (0.053)	0.000 (0.105)	0.012 (0.059)	0.019 (0.101)
(Number stars active in the region and year) ²	—	—	-0.016** (0.006)	-0.016* (0.008)	-0.017 (0.009)	-0.015 (0.011)
(Number collaborators active in the region and year) ²	—	—	0.001 (0.002)	0.002 (0.003)	0.000 (0.002)	0.001 (0.003)
Number stars active in the region and year × DUMMY1986–89	—	—	-0.227* (0.113)	-0.519* (0.237)	-0.196 (0.147)	-0.456 (0.251)
Number collaborators active in the region and year × DUMMY1986–89	—	—	0.096 (0.071)	0.233 (0.141)	0.011 (0.090)	0.144 (0.153)
(Number stars active in the region and year × DUMMY1986–89) ²	—	—	0.007 (0.007)	0.018 (0.010)	0.006 (0.010)	0.015 (0.013)
(Number collaborators active in the region and year × DUMMY1986–89) ²	—	—	-0.001 (0.002)	-0.004 (0.003)	0.001 (0.003)	-0.002 (0.004)
Number top-quality universities in the region in 1981	—	—	0.440*** (0.110)	0.479* (0.205)	0.410** (0.126)	0.447 (0.238)
Number faculty with federal support in the region in 1979–80	—	—	0.973*** (0.112)	1.114*** (0.296)	0.932*** (0.107)	1.041*** (0.295)
Number venture capital firms in the region and year ^a	0.023** (0.009)	0.006 (0.013)	-0.029*** (0.007)	-0.027* (0.012)	-0.024** (0.009)	-0.024 (0.013)
Total employment (all industries) in the region and year	0.128 (0.067)	0.296** (0.098)	-0.110 (0.058)	-0.052 (0.098)	-0.149* (0.067)	-0.078 (0.103)
Average wages per job in the region and year	0.156*** (0.012)	0.139*** (0.024)	0.123*** (0.018)	0.113** (0.039)	0.127*** (0.020)	0.114** (0.040)
Earnings-price ratio (Standard & Poors 500) for year	-0.036 (0.021)	-0.033 (0.043)	-0.022 (0.031)	-0.056 (0.070)	-0.016 (0.046)	-0.082 (0.092)
Number firms active in the region at end of previous year	—	—	—	—	0.023 (0.015)	0.024 (0.025)
Number firms active in all U.S. at end of previous year	—	—	—	—	-0.000 (0.000)	-0.001 (0.001)
Births of biotech firms in the region for previous year	—	—	—	—	0.037 (0.041)	0.055 (0.061)
Log-likelihood	-1265.1	-486.3	-945.9	-386.8	-935.8	-382.9
Restricted log-likelihood	-1628.7	-607.9	-1628.7	-607.9	-1628.7	-607.9

Notes: $N = 2562$. Standard errors (adjusted by Wooldridge, 1991 Procedure 2.1) are in parentheses below coefficients.

^a For years after 1981, the number of venture capital firms in a region is held constant at the 1981 level to avert simultaneity problems.

* Significantly different from 0 at the 5-percent level.

** Significantly different from 0 at the 1-percent level.

*** Significantly different from 0 at the 0.1-percent level.

cantly positive effect on the birth of new firms but an insignificant effect on the birth of subunits of existing firms which would not normally be financed by venture capital firms. The full fundamentals model is reported in columns (c) and (d) for births of entrants and incumbents, respectively, which is to be compared to column (e) for all firm births in Table 3. Again, in the presence of intellectual human capital the simple economic story does not hold up: the coefficients of venture capital firms and total employment turn negative, significantly so in the former case. Similar results are obtained in the dynamic versions of the full model reported in columns (e) and (f) of Table 4. The robustness of the negative venture capital coefficient remains a puzzle for future work, particularly in view of Yolanda K. Henderson's (1989) evidence that, despite some significant localization, most investments by venture capitalists cross regional boundaries.

IV. Summary and Conclusions

The American biotechnology industry which was essentially nonexistent in 1975 grew to 700 active firms over the next 15 years. In this paper, we show the tight connection between the intellectual human capital created by frontier research and the founding of firms in the industry. At least for this high-tech industry, the growth and location of intellectual human capital was the principal determinant of the growth and location of the industry itself. This industry is a testament to the value of basic scientific research. The number of local venture capital firms, which appears to be a positive determinant when intellectual human capital variables are excluded from the regressions, is found to depress the rate of firm birth in an area, perhaps due to the role of these venture capital firms in packaging a number of scientists into one larger firm which is likely to go public sooner.

We conclude that the growth and diffusion of intellectual human capital was the main determinant of where and when the American biotechnology industry developed. Intellectual human capital tended to flourish around great universities, but the existence of outstanding scientists measured in terms of research pro-

ductivity played a key role over, above, and separate from the presence of those universities and government research funding to them. We believe that our results provide new insight into the role of research universities and their top scientists as central to the formation of new high-tech industries spawned by scientific breakthroughs. By being able to quantitatively identify individuals with the ability both to invent and to commercialize these breakthroughs, we have developed new specificity for the idea of spillovers and in particular raised the issue of whether spillovers are best viewed as resulting from the nonappropriability of scientific knowledge or from the maximizing behavior of scientists who have the ability to appropriate the commercial fruits of their academic discoveries.

DATA APPENDIX

The data used here are generally in panel form for 14 years (1976–1989) and 183 regions (functional economic areas as defined by the BEA). Frequently, the data are aggregates of data at the zip code or county level. Lagged variables include data for 1975 in the unlagged form. These data sets, part of our ongoing project on "Intellectual Capital, Technology Transfer, and the Organization of Leading-Edge Industries: Biotechnology," will be archived upon completion of the project in the Data Archives at the UCLA Institute for Social Science Research. A full description of the data is available from the authors upon request.

Biotechnology Firms

The starting point for our firm data set covered the industry as of April 1990 and was purchased from NCBC (1991), a private firm which tracks the industry. This data set identified 1075 firms, some of which were duplicates or foreign and others of which had died or merged. Further, there were a significant number of firms missing which had exited prior to April 1990. For these reasons, an intensive effort was made to supplement the NCBC data with information from *Bioscan* (1989–1993) and an industry data set provided by a firm in the industry which was also

the ancestor of the *Bioscan* data set (Cetus Corp., 1988).

We generally counted entry of firms by adding up for each year and region the number of entrants founded and incumbents first using biotechnology. A few special cases should be noted: Where a firm enters the data set due to the merger of a entrant and another firm, we count it for the purposes of this paper as a continuation of the original entrant and not a new birth (the older entrant if two are involved). If firms already in the data set merge and one continues with the other(s) absorbed, the enterprise is counted as the continuing enterprise and not a new birth.

Scientists

Star scientists and their collaborators were identified as described in the text. Individual scientists are linked to locations through the institutional affiliations reported in their publications in the article data set. The discovery of genetic sequences is recognized by *GenBank*'s assignment to an article of a "primary accession number" to identify each. The 22 additional stars added to the 315 with more than 40 primary accession numbers thus had 20 or more articles with at least one primary accession number and 20–40 primary accession numbers total.

Articles

Our article data set consists of all 4,061 articles in major journals listed in *GenBank* as reporting genetic-sequence discoveries for which one or more of our 327 stars were listed as authors. (A small number of unpublished papers and articles appearing in proceedings volumes and obscure journals were excluded to permit the hand coding detailed below.) All of these articles were assigned unique article ID numbers and collected by hand. For each article, scientist ID numbers are used to identify the order of authorship and the institutional affiliation and location for each author on each article. This hand coding was necessary because, under the authorship traditions for these fields, the head of the laboratory who is often the most prestigious author frequently appears last. Our stars, for example, were first

authors on 18.3 percent of the articles and last authors on 69.1 percent of the 4,031 articles remaining after excluding the 30 sole-authored articles.¹⁸ Unfortunately, only first- and/or corresponding-author affiliations are available in machine-readable sources.¹⁹

The resulting authorship data file contains 19,346 observations, approximately 4.8 authors for each of the 4,061 published articles. Each authorship observation gives the article ID number, the order of authorship, the scientist ID number of one of our stars and collaborators, and an institutional ID number for the author's affiliation which links him or her to a particular institution with a known zip code as of the publication date of the article.

Citations

We have collected data for 1982, 1987, and 1992 on the total number of citations to each of our 4,061 published articles listed in the Institute for Scientific Information's *Science Citation Index* (1982, 1987, 1992). These citation counts are linked to the article and authorship data set by the article ID number. The citations were collected for articles if and only if they appeared in the article data set; so scientists are credited with citations only insofar as they are to the 4,061 articles reporting genetic-sequence discoveries and published in major journals.

Universities

Our university data set consists of all U.S. institutions listed as granting the Ph.D. degree in any field in the Higher Education General Information Survey (HEGIS), Institutional Characteristics, 1983–1984 (U.S. Department of Education, National Center for Education

¹⁸ This positional tradition holds across national boundaries: As a percentage of articles coauthored by their fellow nationals, American stars are 16.4 percent of first authors and 71.2 percent of last authors, compared to 21.2 percent and 63.1 percent, respectively, for Japanese, and 19.7 percent and 69.2 percent for other nationalities.

¹⁹ The *Science Citation Index* lists up to six of the affiliations listed on the paper but only links the corresponding author to a particular affiliation.

Statistics, 1985). Each university is assigned an institutional ID number, a university flag, and located by zip code based on the HEGIS address file. Additional information described in the text was collected from Jones et al. (1982) for those universities granting the Ph.D. degree in biochemistry, cellular/molecular biology, and/or microbiology which we define as "biotech-relevant" fields.

Research Institutes and Hospitals

For those U.S. research institutions and hospitals listed as affiliations in the article data set, we assigned an institutional ID number and an institute/hospital flag, and obtained an address including a zip code as required for geocoding. No additional information has been collected on these institutions.

Venture Capital Firms

We created a venture capital firm data set by extracting from the Pratt (1982) directory the name, type, location, year of founding, and interest in funding biotech firms. This information was extracted for all venture capital which were legally permitted to finance startups. This latter requirement eliminated a number of firms which are chartered under government programs targeted at small and minority businesses. This approach accounts includes founding date of firms appearing in the 1982 Pratt directory, excluding those firms that may have either entered thereafter or existed in earlier years but exited before the directory was compiled.

Other Economic Variables

Total employment and average earnings per job by region and year are as reported by the Bureau of Economic Analysis based on county level data in U.S. Department of Commerce (1992b): Total employment is from Table K, line 010 (in millions of persons). Average earnings is from Table V, line 290 (wage & salary disbursements, other labor income, and proprietors income per job in thousands of current dollars), deflated by the implicit price deflator for personal consumption expenditures. The annual

data for the implicit price deflator for personal consumption expenditures were taken from U.S. Department of Commerce (1992a p. 247, line 16) as updated in the July 1992 *Survey of Current Business*, (p. 92, line 16). The S&P 500 earnings-price ratio was taken from *CITIBASE* (1993), series FSEXP.

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