Accounting for emergence and novelty in Boston and Bay Area Biotechnology[*]

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All happy families resemble one another, each unhappy family is unhappy in its own way.
-- Leo Tolstoy

Tolstoy's epigrammatic comparison of families is not as far removed from research on innovative, high-technology clusters as one might expect. We contend that existing studies of innovation and propinquity all too often begin with Tolstoy's insight; that successful regions resemble one another, while those that falter do so more idiosyncratically. This conjecture, however, is rarely an a priori proposition. Instead, we suggest it is a substantive artifact of reliance on methods that emphasize comparative statics over analyses that focus on emergence and dynamics.

Recent efforts illustrate the need for closer focus on both the genesis and evolutionary trajectories of regional high-technology clusters (Breschi and Malerba 2001). New attention is being turned to both the origins of regional networks and variations in their capacity with an eye toward understanding the necessary inputs for cluster formation, as well as the inital conditions that shape their trajectories (Bresnahan, Gambardella, and Saxenian 2001). Indeed, studies that link entrepreneurship during times of crisis to regional characteristics and capacities open the possibility that very similar outcomes may emerge from widely disparate processes (Feldman 2001).

Such a claim reverses the causal order implied by static comparisons that treat the characteristics of successful regions as foregone outcomes of similar processes. In what follows, we offer a thought experiment that highlights the very different trajectories followed by two successful high-technology regions. Drawing upon a dataset that tracks strategic alliance networks in human therapeutic and diagnostic biotechnology over a twelve-year period (1988-1999), we examine patterns in the development of two canonically successful biotechnology clusters in the Boston/Cambridge Massachusetts

metropolitan region and the San Francisco Bay Area. We emphasize the extent to which interesting variations in the form and substance of innovative activity are apparent when viewed with a dynamic lens. Broad similarities in ascendant clusters, we contend, can be outcomes of divergent patterns of development. Moreover, we suggest that these patterned variations can shape the nature of innovations produced by firms.

Our empirical analyses proceed from a trio of analytic staring points. One, network structure and co-location are necessary characteristics of clusters. Successful high-tech clusters are not merely jumbled congeries of organizations, resources, and skills; they require both propinquity and cohesion (Owen-Smith and Powell 2004). Two, inter-organizational networks are simultaneously the locus of innovation in biotechnology (Powell, Koput, and Smith-Doerr 1996) and the skeleton on which the varied institutional and social arrangements that support innovation interact (Powell, White, Koput, and Owen-Smith 2005). Three, the form and substance of innovation in successful clusters vary over time and with patterns of emergence (K. Porter 2004). In short, understanding how successful clusters generate substantive novelty requires attention to the dynamics of the networks that weave small, science-based biotechnology companies, investors, and nonprofit research organizations into a coherent regional 'community.'

In the sections that follow we turn to descriptive data to highlight variations in the trajectories and outcomes of two key biotechnology regions. We first introduce the biotechnology industry and the regions that are our substantive focus. Next we turn to description and discussion of the inter-organizational networks that underpin innovation in both clusters. Variations in the evolution of those networks, we contend, are

consequential precisely because they leave lasting impacts on the form and substance of innovations by the firms that are embedded in them. In order to flesh out this claim, we draw on patent citation data to establish that the forms innovation takes differ by region. Boston and Bay Area biotechnology innovations depend upon distinct sets of antecedents and rely to disparate degrees on internal R&D.

Next, we draw upon FDA approval data to demonstrate differences in the substantive focus of successful innovations by biotechnology firms in Boston and the Bay Area. We conclude with a comparison of the patents and citations underlying two successful treatments for remitting and relapsing multiple sclerosis: Betaseron, developed by Bay Area firm Chiron, which was approved in 1993 and Avonex, developed by Boston stalwart Biogen, which received FDA approval in 1996. The therapies are direct competitors as they share an initial therapeutic indication, rely on extremely similar biological compounds and have been the subject of several comparative clinical trials. Yet the patented innovations that support each therapeutic rely on only partially overlapping sets of precursors. These intellectual antecedents, we suggest, reflect lasting distinctions between the topology, infrastructure, and culture of the regions in which the firms developed these comparable products.

The San Francisco Bay area and Cambridge/Boston are the world's largest and most commercially successful biotechnology regions. The attributes and successes of these regions are widely studied and their efforts broadly emulated. Despite similarities in scale and outcomes, however, each region emerged through a distinctive process that continues to influence its outputs. These variations, in turn, suggest that there are multiple

pathways to similar outcomes and offer a corrective to efforts to transpose a 'standard' model of regional innovative success that may never have existed.

Regional Advantage and Industrial Development in Biotechnology[1]

We focus on the commercial field of biotechnology, which developed scientifically in university labs in the 1970s, saw the founding of hundreds of small science based firms in the 1980s, and matured in the 1990s with the release of dozens of new therapeutics. The field is notable for both its scientific and commercial advances as well as for the diverse cast of organizational players -- universities and other public research organizations (PROs) government laboratories, venture capital firms, large multi-national pharmaceutical corporations, and smaller dedicated biotechnology firms (DBFs) – involved in its development.

In this field, where the sources of scientific and technical leadership are widely dispersed and rapidly developing, and where the relevant skills and resources necessary to produce new medicines are scattered, collaboration among organizations became a necessary component of success. An elaborate system of private governance emerged to orchestrate the inter-organizational networks such collaborations constituted (Powell 1990; 1996), and the internal structure and practices of DBFs changed accordingly as firms co-evolved with the structures that characterize the industry.

During the very early years of the industry, from the early 1970s to the late 1980s, most DBFs were very small start-ups that relied, of necessity, on external support. Lacking the skills and resources needed to bring new innovations to market, they became involved in elaborate lattices of relationships with universities and large pharmaceutical

[1] This section draws upon our earlier work on biotechnology (c.f. Powell et. al. 2005; Bunker-Whittington, Owen-Smith & Powell 2004).

firms (Kenney 1986; Powell and Brantley 1992). Lacking a knowledge base in the new scientific field of molecular biology (which was the industry's wellspring), large companies were drawn to start-ups by the latter's capabilities in basic and translational science (Galambos and Sturchio 1996; Gambardella 1995). Asymmetries in technological, regulatory, and financial muscle drove early collaborative patterns in the industry (Hagedoorn and Roijakkers 2002; McKelvey 1996; Orsenigo 1989; Orsenigo, Pammolli, and Riccaboni 2001).

Despite arguments that the new field would undergo a 'shake-out' as large pharmaceutical firms developed the technical competencies that would allow them to assert dominance over weaker small firm partners (Sharpe 1991; Teece 1986), the founding of new firms accelerated. Established firms' efforts to 'cherry-pick' promising new ventures faced significant obstacles imposed by deeply collaborative R&D efforts and a mobile scientific labor force. Instead of consolidation and shakeout, the industry's later years witnessed the give-and-take and mutual forbearance characteristic of relational contracting (Macneil 1978), which became the dominant practice in the field.

By the late 1980s, several DBFs (e.g. Biogen, Genzyme, Chiron, Genentech, Amgen, Immunex) had become large and formidable organizations in their own right, and numerous pharmaceutical firms had created in-house molecular biology research programs (Henderson and Cockburn 1996; Zucker and Darby 1997). Even when mutual need declined as a spur to collaboration, the pattern of dense inter-connection deepened, suggesting that the original motivation of exchanging complementary resources had shifted to a broader focus on mining innovation networks to explore new forms of collaboration and product development (Powell et al. 2005).

An analytic story that places networks alone at the heart of biotechnology's development misses an important component of the story, however. Despite the evolution of dense and expansive networks, geography played an essential role in the industry's development and remains an important feature even today. The evidence for salutory effects of geographic concentration in high-technology industries is compelling. Studies drawing on multiple methods and data sources have demonstrated the positive effects of propinquity in high technology regions (Almeida and Kogut 1999; Audretsch and Stephan 1996; Feldman and Audretsch 1998; Jaffe, Trajtenberg, and Henderson 1993; Prevezer 1997; Zucker and Darby 1996), and the U.S. biotechnology industry is no exception.

The networks that now characterize this complex commercial field emerged from distinct geographic roots. Beginning in the Bay Area and Boston, then spreading to such areas such as San Diego, Seattle, and Bethesda, MD, clusters of DBFs, venture capital firms, and public research organizations forged local networks that reached out to other areas as they developed, creating a national industry network from regional origins (Owen-Smith, Riccaboni, Pammolli, and Powell 2002). Yet these regions remain important to understanding conditions in the industry. Indeed, evidence is mounting that the network effects that drive much of the action in biotechnology vary with the geographic location of partners (Owen-Smith and Powell 2004; Bunker Whittington, Owen-Smith, and Powell 2004). Networks, then, played an essential role in the development of stable regional clusters, but those clusters seeded the geographically dispersed structures that have come to be characteristic of the field. We thus turn to analyses of network connections in the two largest and most successful U.S.

biotechnology regions in order to demonstrate that collaborative arrangements help to underpin successful clusters. Those regional communities vary in their character, evolutionary path, and approach to innovation.

We draw upon a dataset of strategic alliance ties involving 482 Dedicated Biotechnology Firms (DBFs) and their more than 2,000 partner organizations over the period 1988-1999 to illuminate patterns in the structures connecting regionally co-located biotechnology firms. Data are drawn from *Bioscan*, an independent industry directory published quarterly. We focus on DBFs -- independently operated, profit-seeking entities involved in human therapeutic and diagnostic applications of biotechnology – but omit companies involved in agricultural and veterinary applications as those sectors draw on different scientific capabilities and operate in different regulatory environments.

Our dataset, like the industry it represents, is dominated by U.S. firms, although recent years have seen considerable expansion in Europe. The sample of DBFs includes both public and privately held firms, and the former include companies with minority or majority investments by other firms as long as their stock is independently traded. Large pharmaceutical companies, investors, government agencies, and public research organizations enter the data-set as partners that collaborate with DBFs. We link these relational data to patent grant and citation information for the period 1976-1999 drawn from the NBER patent citation database (Jaffe and Trajtenberg 2002). In total, there are 10,067 U.S. utility patents issued to the 482 DBFs in our sample over this time period. Organizations are identified by type and location, which enables us to isolate ties among co-located organizations in two established biotechnology regions.

The San Francisco Bay Area and Boston are well-studied examples of densely connected and intensely innovative regional economies. In our dataset, Boston is home to more than 14% (N=57) of U.S. DBFs in our sample. Bay Area biotechnology firms account for almost 21% (N=82) of U.S. firms. Together, these regional DBFs were issued 51.5% (N=5182) of the patents assigned to U.S. biotechnology firms through 1999 and developed 32% (N=17) of all biological therapeutics approved by the U.S Food and Drug (FDA) administration between 1988 and May, 2004.[2] Five of the ten best-selling biotechnology drugs in 2001 were developed by firms in these two regions. Boston and the Bay Area thus represent notable success cases for biotechnology regions.

The Bay Area and Boston Networks.

In order to examine the evolution of Boston and Bay Area networks, we identify all organizations located in the two regions that have contracted with a local biotechnology firm. Our dataset includes four types of formal inter-organizational connections and five types of organizations. In addition to DBFs, we include venture capital firms, government agencies, large multinational pharmaceutical corporations, and public research organizations in the partner sample. These diverse organizational forms are connected by four varieties of contractual ties. R&D connections represent agreements for shared research and development efforts. Finance ties reflect investments in one organization by another. Licensing ties are agreements that transfer the rights to intellectual property across organizations. Commercialization ties include downstream product development activities, ranging from manufacturing to sales and marketing.

[2] We base our calculations on approvals for initial indications by the U.S. Food and Drug Administration's Center for Biological Evaluation and Research.

During the period 1988-1999, the Bay Area network is the larger of the two, involving 159 organizations (82 DBFs, 12 PROs – most notably Stanford University and the Universities of California at Berkeley and San Francisco, one government laboratory – Lawrence Livermore Labs, and some 64 venture capital firms), connected by 243 local contractual ties. The Boston network is home to 113 organizations (57 DBFs, 19 PROS – including MIT, Harvard University, MIT, Massachusetts General Hospital, and the Dana Farber Cancer Center, and 37 venture capital firms), connected by 201 local contractual ties. Neither region was home to a multinational pharmaceutical corporation during this time period.[3] While the regions differ in scale and in the demography of organizational types that occupy them, most notably in the availability of local venture capital funds (Powell, Koput, Bowie, and Smith-Doerr 2002), both are characterized by organizationally diverse and structurally cohesive networks.

How, then, do the regions differ? Figures 1 and 2 track yearly changes in Boston and the Bay Area in terms of the distribution of dyads that comprise each region's main network component. The main component of a network is its largest connected subset. In practical terms, the main component represents the largest group of organizations in a structure that can reach one another through network paths of finite length and thus captures the minimal level of connectivity necessary to enable broad information diffusion (Owen-Smith and Powell 2004). Put colloquially, imagine drawing linkages among nodes without ever lifting your pen. These figures paint a very different evolutionary trajectory for the two regions.

[Figs 1 and 2 here]

[3] More recently, Pfizer and Novartis have moved R&D activities to Kendall Square in Cambridge, MA. The largest biotech firm, Amgen, has acquired a smaller Bay Area firm, Tularik, and created a beachhead in that region.

The most basic unit of a network is the dyad. In this case, a dyad is a pair of organizations connected by a formal R&D, finance, licensing, or commercialization tie. Figures 1 and 2 characterize dyads in terms of the types of organizations that comprise them, without regard to the class of activity connecting a given pair. Three types of dyads are possible in these main components: DBFs can connect with each other (a DBF-DBF dyad), with PROs such as universities or hospitals (a DBF-PRO dyad), or with Venture Capital firms (a DBF-VC) dyad.[4] In addition to the distribution of dyads, regional networks grow at different paces and in different patterns.

Consider figure 1, which tracks the growth of the Boston network. Note first the pattern of growth in ties (each dyad represents a single tie) implied by the height of the histogram bars. Our dataset begins in 1988, when we find a relatively large number of ties in Boston. The number grows slightly into the early nineties, then levels off for a several years before climbing again through the latter years of the dataset. The bars are colored to represent the relative prevalence of different dyads in the network. Note the bar that represents 1988, showing a remarkable reliance on public research organizations. Only a very small number of ties link DBFs to each other or to local VC firms in 1988 or 1989. Both DBF-DBF and DBF-VC ties grow as the network expands and these 'commercial' connections eventually dominate the network (though PROs remain consistently important) by the end of the end of our time frame.

Boston represents a case where a network grew from origins in the public sector (Porter, Bunker Whittington & Powell, 2005). Put differently, public science formed the foundation for commercial application (Nelson 1981,1986). Industries where

[4] Our data are structured as a two-mode network (Wasserman & Faust 1994) that tracks connections among DBFs and between DBFs and partner organizations. Linkages between non-DBF partners (e.g. PRO-VC collaborations) are exceptionally sparse and thus are not included.

commercially viable technical advances emerge from academic and public sector roots manifest more open technological trajectories than industries that rely more heavily on industrial R&D (Dosi 1982). The Boston biotechnology community is linked by shared connections to public research organizations early in its evolution. These connections remain an important part of the network, but increasing patterns of DBF to DBF and DBF to VC ties reflect the development of a commercial network that becomes structurally autonomous, while bearing the imprint of the public sector.

Contrast this trajectory with the different pattern illustrated by Figure 2. There is no dominant network component in the Bay Area in 1988, though a cohesive network forms in 1989. Unlike Boston's growth pattern, which saw a plateau in the early 1990s, the Bay Area grew markedly through 1996 before stabilizing in the late 1990s. These differences in volume and velocity are matched by very different dyad distributions. During the first two years when a main component existed, the Bay Area community was comprised entirely of ties linking DBFs to local venture capital firms. Where the stability and technical diversity of Boston PROs anchored that network and fostered a more open technological trajectory (Owen-Smith & Powell 2004), the Bay Area relied heavily on the prospecting and matchmaking efforts of venture investors.[5] Later years witnessed the increasing importance of VCs, a smattering of ties involving PROs, and – most importantly – dramatic growth in DBF-DBF connections. By 1999, direct links among Bay Area DBFs outweigh the other two types of dyads.

[5] This different trajectory may reflect left censoring in the data. If we had comparable data for the Bay Area for the late 1970s and early 1980s, we might well observe important DBF-PRO ties. In particular, we would expect more linkages connecting UCSF and Stanford to local DBFs. We do know that the Bay Area biotech community developed earlier than Boston (Robbins-Roth 2001), hence the direct comparison for the later 1980s and early 1990s may capture a slower takeoff in Boston.

Both Boston and the San Francisco Bay Area evolved from dependence on a non-DBF organizational form to a state where significant portions of the network were made coherent by direct connections among science-based biotechnology firms. In other words, similar endpoints in the evolution of the networks were reached through different routes. While both relied on the inclusion of organizations different from biotechnology firms; Boston was anchored in the public sector, whereas the Bay Area was dominated by venture capitalists. The endpoints of these trajectories are similar as both regions came to depend heavily upon collaborations among ostensible competitors, but their different starting points and the lasting involvement of different partners may have produced distinctive patterns of innovation. Distributions of dyads, however, cannot tell the full story of a network's evolution, hence we turn to an assessment of the overall topology of the networks.

Figure 3 fleshes out differences across the regions with images of the networks in three distinct time periods. These snapshots were generated using Pajek,[6] a freeware program designed for the visualization and analysis of large networks. The relative positions of nodes in these images are meaningful and result from two spring-embedded, graph-drawing algorithms. The first treats a network as a physical system where nodes repel each other and ties act as 'springs' that pull connected nodes closer together (Fruchterman and Reingold 1991). This algorithm moves unconnected nodes to the periphery of the image, and separates components (groups of two or more nodes) from one another. A second algorithm relocates connected nodes so that the Euclidean distances among them are proportional to their graph theoretic distance (Kamada and

[6] A freeware program developed by Vlado Batagelj and Andre Mrvar and available for download online at http://vlado.fmf.uni-lj.si/pub/networks/pajek/ .

Kawai 1989).[7] These images, then, are replicable representations where the relative position of organizations is a function of the connectivity of the system and the degrees of separation among nodes.[8]

[Figure 3 Here]

Nodes in Figure e are colored to represent types of organizations. Cyan nodes are DBFs, Orange nodes are PROs and Gray nodes are venture capital firms. The colors of ties likewise represent different types of collaborations. Red links are R&D ties, green represent financial investments, black ties are licenses and blue linkages indicate commercialization deals. The width of a given tie reflects the number of connections linking a pair of partners. When multiple ties are present in a dyad, the color of the linkage reflects the most recent type of activity. To gain purchase on the differences between the two networks at given point in time, read across columns in Figure 3. To get a sense of the evolutionary pattern within each region, pick a column and read down.

Consider the first image of the Boston region, which bears out Figure 1's emphasis on ties between DBFs and PROs. Note the central role played by orange nodes and the relatively few connections linking cyan nodes to each other. The main component of this network stretches across the center of the image, most of the ties are single connections between different types of organizations. Tie colors are rather evenly dispersed, but Blue (commercialization) and Black (licensing) ties are in the majority. In the region's early years, DBF firms are stitched together into a coherent network by their shared connections to public research organizations. Harvard, the well connected orange node in the upper left hand corner of the image, and MIT the center of the 'star' in the

[7] This distance is a function of the number of 'steps' it takes to traverse a network path connecting a given pair of nodes. Organizations that are connected by a tie are a distance one.
[8] For more detail on network visualization using pajek, see the appendix of Powell et al. 2005).

lower right hand quadrant, are the primary entry points to the network and their relative distance from each other suggests that the early years of the Boston biotechnology community may have been shaped by different kinds of academic involvement. In related work, we show that while both Harvard and MT faculty have been active in founding Boston-based biotechnology firms, MIT scientists are much more active patentors, while Harvard faculty serve on more scientific advisory boards (Porter et. al., 2005).

The 1988 Bay Area image paints a very different picture as ties in that year did not aggregate to create a dominant component. Instead, the early years of the region appear to be characterized by small clusters of firms connected either to multiple venture capitalists or, less commonly, to Stanford University (the center of the three node 'chain' at the top of the image) or UCSF (the orange node in the dyad – with Genentech, whose founder was a UCSF scientist – near the center of the figure.)

The patterns suggested by the visualizations are echoed by careful archival research. In an analysis of the career histories of the founders of biotech firms in the Bay Area and Boston, Kelley Porter (2004) finds that Boston companies were often started by MIT and Harvard professors, many of the whom maintained their university affiliations. In contrast, founders in the Bay Area were much more likely to come from venture capital or other biotech firms. Another key contrast was that the Boston faculty were senior professors who had established reputations. When Bay Area faculty were involved in founding, they tended to be younger and much more likely to take a leave from their university positions. Almost all founders in Boston came from the region, while founders

in the Bay Area came from diverse locals. Indeed, east coast faculty -- from Yale, Columbia, and Duke -- came to California to start companies.

Turn your attention now to the second row of Figure 3, which represents the regional networks near the middle of our time series in 1994. The Boston network has grown, but maintains a reliance on PROs and both Harvard (now at the bottom of the image) and MIT (the well connected orange node at the top of the image) remain important, though less central players in the network. This image also suggests the growing importance of local venture capitalists (notably in the 'tree' structures that descend from Harvard's partners in the lower quadrant of the image) as well as the salience of DBF to DBF ties. Note the diamond (outlined by a dashed circle) formed by R&D connections among four Boston firms -- Genzyme, Genzyme Transgenics (one several spinoffs from Genzyme), Autoimmune (whose research tie to the Dana Farber Cancer keeps this nascent cluster attached to the larger network) and Creative Biomolecule. These firms, particularly Genzyme -- a large and successful 'first generation' biotechnology company, seed the development of a dense DBF-DBF region in the Boston network.

Compare this view to the image of the Bay Area, whose large main component reflects the dramatic pattern of growth captured in Figure 2. This image is dominated by ties linking DBFs to venture capitalists, while PROs play a minimal role in the network. The single orange node at the bottom left is Stanford, which is linked to a young biotechnology firm by a license.[9] Note, however, the robust cluster of (often multiple) DBF to DBF ties outlined by a dashed circle at the top of the figure. This group, centered

[9] To be sure, this isolation does not imply that Stanford is not active in technology transfer, but at the point in time the bulk of its formal licensing activities are to firms outside the region.

on Genentech – one of the first and most successful biotechnology firms – and Chiron – another large and established player in the industry – is characterized by diverse and repeated ties that directly link biotech firms to one another. Boston's 'Genzyme triangle' and the Bay Area's 'Genentech cluster' represent the beginnings of a network centered on collaborations among ostensible competitors. The size of these ties relative to those connecting younger DBFs to venture captital firms suggests a process by which newcomers are identified by investors and then linked into the DBF-DBF segment of the network by forging ties with incumbents or their partners. Where PROs are still the entry way and the gatekeepers of Boston circa 1994, Bay Area VCs prospect for new talent, and established firms usher promising newcomers into an increasingly connected segment of the network.

These patterns became more robust in 1999, the final year of our data. In both networks the pattern of DBF-DBF linkages expands and deepens (relevant regions are outlined by dashed ellipses) and both sections of the network remain centered on the region's largest and most successful firms (Biogen and Genzyme in Boston and Genentech and Chiron in the Bay Area). Despite the clear emergence of purely commercial portions of both networks, however, the regions still manifest significant differences. While VC firms are important players in the Bay Area network, they only rarely form multiple connections to the same partner and (as one would expect) their ties are overwhelmingly financial. The field of green in the lower left quadrant of the 1999 Bay Area image exemplifies this trend. VCs play an important connective and prospecting role in this network, but their one dimensional network portfolios suggest

that much of the innovative action may emerge from the dense and multiplex cluster of biotech to biotech ties.

Public research organization linkages shrink in importance in the Boston network in 1999 (recall Figure 1). The distributional decline, however, masks the continued importance of these research-oriented public sector organizations. Universities, nonprofit research institutes and hospitals forge repeated (and multiplex) ties to biotechnology firms (evidenced by the thicker connections linking orange and cyan nodes), and thus play a very different role in the region than do VC firms (who dominate a small portion of the Boston graph in the lower left segment of the image). Boston PROs remain important structural components of the network as well. Note the orange nodes at the center of the image (just to the right of the dotted ellipse) that represent MIT and Massachusetts General Hospital. Both regions developed tightly interconnected DBF-DBF commercial networks, but they did so from different starting points and with very divergent types and levels of involvement from non-DBF partners. Though similar on many dimensions, we suggest that these disparate evolutionary trajectories have lasting effects on the nature of innovation in these regions.

The form and substance of regional innovation.

How do varied starting points and evolutionary trajectories leave lasting imprints on regional innovation patterns? We contend that the networks more clearly dominated by 'open' public sector organizations will result in innovations that rely less heavily on internal R&D, and that draw more on research conducted in organizations other than biotechnology firms. In short, we expect patents assigned to Bay Area DBFs, a region whose network was always based more on commercial firms to cite proportionally less

non-DBF prior art and to rely more heavily on self citations than do patents assigned to Boston firms.

We turn to data on citations made by patents assigned to Boston and Bay Area DBFs to examine how regional effects may shape the process of innovation. We begin by presenting information on the R&D outputs of regional firms in the aggregate from 1988-1999. We then turn to consideration of shifting patterns in prior art citations by DBF patents. Next we consider the substance of regional innovation by assessing differences in rates of FDA approvals, as well as variation on Orphan Drug Indications[10] by region. Finally, we compare the patented innovations underpinning two comparable treatments for multiple sclerosis: Cambridge-based Biogen's Avonex and Emeryville-based Chiron's Betaseron.

The differences in regional scale that we identify are matched by differences in the volume of innovation. Table 1 presents a comparison of R&D outputs by region for the period 1988-1999. The 82 Bay Area DBFs in our sample generated some 3,800 U.S. utility patents in this time period; which is an average of slightly more than 46 patents per firm. This contrasts dramatically with Boston DBFs' average of slightly more than 24 patents per firm. In contrast, biotechnology firms located outside of these two regions produced only slightly more than 14 patents on average, suggesting the relative fecundity of both Bay Area and Boston DBFs.

These output differences also mask a highly skewed distribution of patents within regions. Bay Area outputs are more stratified than those in Boston. The five most prolific

[10] An Orphan Indication is conveyed by the U.S. Food and Drug Administration for products that treat rare diseases and thus have little potential to become huge commercial successes. Orphan indications are valuable to firms in that they convey tax breaks and reduced regulatory fees as well as short-term market exclusivity.

Bay Area patentors account for 63% of regional patents, while the top five Boston patentors were issued 42% of the region's patents. Despite these patterns, patents assigned to regional firms had very similar citation impact. Two-tailed t-tests discerned no significant difference between the impact of Bay Area and Boston DBF patents ($t=0.774$, $p=0.439$), but did suggest that firms in these regions higher impact intellectual property than those located elsewhere ($t=3.837$, $p<.0001$).[11] The similar impact of Boston and Bay Area innovations masks broad differences in the distribution of highly cited patents within the regions. Patents assigned to Boston firms manifest a much higher variance in forward citations than do Bay Area patents, suggesting that Boston firms may more routinely engage in 'exploratory' innovative search, which typically yields a few very high impact patents at the expense of numerous innovations with lower than average future effects (Fleming and Sorenson 2001; Leavitt and March 1988). On this view, the Bay Area's lower citation variance is indicative of a more directed and incremental 'exploitative' strategy, which is what one might expect of firms that are supported by investor networks that are interested in demonstrable progress. Firms that pursue exploitative strategies generally develop numerous related improvements on established components of their research trajectories. Such incremental innovations are less valuable on average than the riskier outcomes of more broad-ranging innovation efforts, but convey important benefits in terms of overlapping ownership rights. Exploitative patents, then, will have lesser variance in their impacts than will patents that result from more exploratory efforts to develop blockbuster technologies.

[Table 1 here]

[11] Forward citations, citations from future patents to current innovations are a commonly used measure of impact. We standardize citation counts by year and technical class to avoid heterogeneity across time and technical areas (Jaffe and Trajtenberg 2002; Trajtenberg 1990).

While differences in impact variation are suggestive of different patterns of search in innovation, patterns in the prior art citations provide more direct insight into the precursors that firms rely on in developing new intellectual property. Such 'backward' citation data allows us to expand upon the relationship between regional networks and innovation in biotechnology.

Consider two ideal-typical possibilities: (1) Firms embedded in networks composed largely of competitors and investors are primarily concerned with speed and with commercial development, hence they pursue a more focused innovation process that relies heavily on internal R&D and attention to the efforts of direct competitors (e.g. other DBFs). As they are embedded in networks that lack a significant PRO involvement, such firms may be less likely to rely heavily upon innovations developed externally. In contrast, (2) firms that are embedded in networks anchored by public research organizations and that lack strong investor involvement may feel somewhat less overt pressure to pursue immediate commercial returns.

To the extent that 'open' public sector research organizations alter the norms that govern information flow within a network, firms in such networks may reach more freely across organizational boundaries in efforts to develop new innovations and may evince less attention the research efforts of competitors (Owen-Smith and Powell 2004). Again, we stress that these different patterns may reflect divergent time scales. Were we to have full data on Bay Area firms from the 1970s, we might well find patterns of relationships comparable to Boston in the 1980s and 1990s. We cannot rule out the possibility that these regional differences stem from the earlier start and success of Bay Area firms in bringing new medicines to market. Moreover, in their early years, several notable

Boston-based firms opted to license their earliest lead products to large pharmaceutical companies in return for royalty payments (Robbins-Roth 2001).

If these two conjectures have validity, we would expect innovations by firms in more overtly commercial networks – such as those in the Bay Area – to rely less heavily on prior art developed by organizations other than DBFs and to rely more strongly on citations to their own prior patents. In contrast, innovations made by firms situated in more 'open' networks dominated by academic and public sector organizations – such as those in Boston – will rely on a broader cross-section of prior art sources and less extensively on internal R&D. Table one provides descriptive support for these claims.

The 1,376 Boston inventions make 12,659 citations to prior U.S. patents, while the 3,806 Bay Area patents acknowledge 41,389 links to prior art (an average of 9.2 cites per patent in Boston and 10.9 cites per patent in the Bay Area. Firms outside these regions cite just under nine pieces of prior art per patent). Similar levels of reliance on prior art, though, masks significant variation in terms of the sources from which precursors are drawn. Patents assigned to Boston firms rely more heavily on non-DBF prior art -- a full 71% of citations -- than do either Bay Area patents, which make 45% of their citations to non-DBF prior-art, or non-regional patents. In contrast, slightly more than 1/3 (35%) of citations made by Bay Area patents are to their own prior art.[12] Boston firms do cite their own prior art, but at a much lower (12%) rate that more closely accords with the overall trend in the industry. In sum, the R&D portfolios of Bay Area and Boston firms rely on quite different sources of knowledge, and these patterns appear to map onto the structure of the collaborative networks in the each region.

[12] Despite a greater reliance on self citations, 65% of Bay Area prior art citations are to patents developed outside of the firm. The majority of innovative work goes on through networks.

The form innovation takes, then, is related to the characteristics and trajectories of the networks that support it. While both regions have been quite successful in biotech, and are emulated across the globe, we have shown that their respective origins and paths of development are rather dissimilar. This pattern may continue at the level of market outcomes as well as patents. To explore this possibility, we draw on FDA approval records to identify the 58 new drugs developed by Boston and Bay Area DBFs. Fifty-three (53) of those medicines were approved between 1988 and 2004. All five of the drugs that appeared on the market prior to that period were developed by two Bay Area Firms, Alza and Genentech. Again, these early approvals reflect the commercialization strategy pursued in a region with a strong venture capital community.

Eighteen (18) of these products are the work of Boston firms and 40 stem from work by Bay Area DBFs. Another 89 therapeutics were developed by the 343 DBFs located outside of these regions, but well established firms such as Los Angeles' Amgen, Philadelphia's Centocor, and Seattle's Immunex account for much of the action. In terms of market outcomes, the Bay Area appears to be both quicker and more prolific than Boston and both regions represent concentrations of success. This outcome is to be expected given a more commercially focused network and a development-oriented strategy that relies heavily on internal R&D. Indeed, 17 of the first twenty of these drugs to come to market were produced by Bay Area firms.

These differences in market outcomes, though, are much more suggestive of variations in strategy and focus than of competency. Consider another source of information about the development of therapeutics, Orphan drug designations. The 1983 Orphan Drug Act was designed to enable the FDA to speed the development of therapies

for rare diseases, and orphan designations offer tax breaks and regulatory assistance to organizations that develop such medicines. One hundred and eleven (111) orphan designations have been approved for Bay Area and Boston DBFs since 1985 (when the first such approval went to Boston's Genzyme for the drug Ceredase for patients with Gaucher's disease). Both Bay Area and Boston firms make use of orphan designations, but Boston firms, as one might expect for companies enmeshed in networks dominated by universities and hospitals, rely more heavily on indications for relatively rare diseases.

The focus on orphan drugs reflects another difference as well. The Boston-based firms build their product portfolios with an initial focus on smaller markets and medicines that have the added security of orphan drug exclusivity. These medicines, while targeted at relatively small populations, are very much desired by their patient communities. In contrast, Bay Area firms favor medicines for larger markets in which the potential patient population runs in the tens of millions, and for which there is likely to be product competition from other DBFs and major pharmaceutical corporations. This high-risk, high-reward strategy demands speed in product development, and shows the obvious imprint of the venture capital mindset.

Descriptive patterns in prior art citations, forward citation impact, and market outcomes are complementary with observed variations in the evolution of the two regional networks. Despite sharing an industry and scientific base, Boston and Bay Area DBFs appear to differ systematically in the substantive focus of their R&D efforts. To further explore these differences in the focus of innovative activity, we turn to a "natural experiment" and compare the citation patterns for patents underlying two fairly similar biotechnology drugs.

Betaseron and Avonex are competing therapies for remitting and relapsing multiple sclerosis and several clinical trials have directly compared their efficacy. Both drugs began life with orphan designations and both are variants of the biological compound interferon-beta, which differ only slightly in chemical makeup.[13] The processes by which these compounds are produced are also very similar, and rely on Chinese hamster ovaries, though their differences are manifest enough that an infringement lawsuit between Avonex's developer and Betaseron's manufacturer (*Biogen v. Berlex Laboratories)* resulted in a judgment of no infringement. Both drugs were approved during the 1990s (Betaseron in 1993 and Avonex in 1996). In short, these two drugs share notable scientific, clinical, and regulatory similarities, but they differ in the physical and organizational location of their development.

Betaseron is based on research done by Cetus, an Emeryville, CA biotech firm that was acquired by Chiron, another Berkeley-based DBF. Chiron did the development work on Betaseron and shepherded the drug through the FDA approval process. Betaseron is manufactured and marketed under an arrangement with Berlex Laboratories, an American subsidiary of the pharmaceutical firm Schering-Plough. Avonex, in contrast is based on research done by Boston-based Biogen who also developed, manufactures and markets the drug. We use FDA labeling information to identify the patents that underpin these drugs. We then turned to the NBER patent citation database to trace prior art citations by those patents and identify the sources of such prior art. In both instances we trace precursor inventions to three generations. Table 2 presents summary data for the innovations underlying these two drugs.

[13] Interferon beta-1a (Avonex) is a recombinant compound whose amino acid sequence is identical to natural interferon-beta. Interferon beta-1b (Betaseron) in contrast is a recombinant compound that differs from natural Interferon-beta by one amino acid.

[Table 2 here]

The patterns suggested by Table 2 are in line with the overall results in prior art citations by region, and with our expectations based on the evolution of each cluster's network. Betaseron relies on a set of four related patents initially assigned to Cetus (three were re-assigned to Chiron following the merger of the two firms; the fourth, a process patent for producing interferon, was re-assigned to Berlex Labs). These four patents cite a small group of prior art patents (4). Those four 'first-generation' precursors make another 31 second generation citations and those cite a further 16 linkages to prior art. All told, then, Betaseron rests upon a history of some 55 interlocking patents. Avonex, which is based on a single compound patent, reaches more broadly into the prior art, relying on 155 separate pieces of intellectual property. None of the prior art on which Avonex depends is owned by Biogen. This last finding is particularly telling, as it suggests that Biogen developed its market leading therapeutic without the benefit of a thicket of intellectual property rights, relying instead on a mix of partner's intellectual property and public domain science.

Differences in these two citation networks are instructive. Betaseron's underlying IP network includes six patents developed by Cetus. Avonex, in contrast, relies on a single Biogen-owned patent that makes no citations to other intellectual property owned by that firm. While internal R&D was surely not sufficient to the development of Betaseron, that drug relied much more heavily on a single DBF's research effort than did its competitor. Both innovation networks reach well beyond the regions in which the two firms are situated. Betaseron cites only two patents held by other Bay Area organizations, but it is notable that both are biotechnology firms (Genentech and ICN).

The Avonex citation network, in contrast, cites four patents held by Boston organizations, but none are owned by DBFs. Three belong to public research organizations with whom Biogen has network ties (MIT holds two patents the Massachusetts General Hospital a third). The fourth belongs to a non-DBF firm, a purification company called Ionics.

While the citation networks are fairly small, comparing these two very similar drugs offers a natural experiment that holds constant important technical, clinical and regulatory features of biotechnology innovations. Even when such factors are very similar, the patent citation networks underlying these two drugs differ in a fashion that reflects aggregate differences in regional innovation patterns and expectations based on the inter-organizational networks that characterize each region. The Bay Area-based drug relies more heavily on internal R&D and on the research efforts of other DBFs. In contrast, the Boston-based therapy draws on a broader cross-section of past IP owned by a wider range of organizational types.

Conclusion and Implications.

The Boston and Bay Area biotech communities became more similar over the 12 year period under examination, shedding their respective reliance on PROS and VCs, and developing a strong firm to firm component. But these divergent roots have a notable impact on the innovation process, with Boston-based companies heavily reliant on external sources of knowledge, opting to favor more exploratory efforts at discovery. This signature is captured by our measures of patent volume and impact, and by patterns of patent citations. Bay Area biotech firms were more self-reliant in terms of knowledge generation and more persistent in their efforts to further development of in-house intellectual property.

Similarly, Bay Area firms were faster and more prolific in terms of new product development, as well as more likely to pursue novel medicines for larger markets where they might face stiff competition. In contrast, Boston firms were more deliberative in their commercial strategies and more likely to focus on medicines for identifiable and active patient populations in need of relief from specific illnesses. Most remarkably, these differences persisted even when we held constant market, scientific and regulatory factors by examining Chiron and Biogen's approaches to the development of similar treatments for multiple sclerosis. Clearly, the continuing impact of venture capital in the Bay Area and public research organizations in Boston is significant.

We lack data on the early scientific roots of technical advance in the life sciences in Boston and the Bay Area. Perhaps the patterns we have observed are the outcroppings of diverse academic approaches to scientific research in the life sciences. Boston is home to the remarkable institutional combination of MIT, a powerful basic science institution that lacks a medical school, Harvard, another powerhouse institution in basic science whose medical school is located across the Charles river at a considerable remove from the main campus, and a number of research-oriented hospitals and institutes. The upshot of this institutional mix appears to us to be a corporate focus on expansive science and on patients. In contrast, the biotech community in the Bay Area has its earliest origins in the 'marriage' of Herbert Boyer, a UCSF scientist, and Robert Swanson, a prominent venture capitalist, who joined together to create Genentech, one of the very first biotech companies.

UCSF is an unusual institution, lacking disciplinary departments and a full panopoly of research program and students. The organizational model at UCSF was an

inter-disciplinary, cross-functional approach to medicine, with an emphasis on translating basic science into clinical application (Varmus and Weinberg 1992). Genentech adopted and refined this interdisciplinary 'team' model, adding the impatience and restlessness of venture capital financiers and the attendant focus on 'swinging for the fences' by developing products for such major illnesses as heart disease, cancer, and diabetes. Here, an approach to translational R&D pioneered at an elite PRO is transferred by founding scientists to a region's leading firm, eventually becoming a dominant arrangement for the region.

Universities, regions, and the paradox of deliberateness. Linking innovative outcomes in regions to contingent patterns in the evolution of collaborative networks raises a set of interesting questions for firm and non-firm participants alike. In our view, one of the fundamental features distinguishing between the Boston and Bay Area networks is Boston's early and continuing reliance upon the region's public sector research organizations. MIT, Harvard, Massachusetts General Hospital, the Whitehead Institute, Dana Farber Cancer Center, and other PROs anchored this network, catalyzed its development, and shaped its impacts on DBF innovation and product development. The imprints of evolutionary patterns, then, are a joint function of PRO roles *and* the particular institutional features that characterize such public sector organizations. In addition to providing stable anchors for networks, universities and hospitals contribute to more open information flows, to more expansive innovative trajectories, and, possibly, more patient-driven product development strategies. In short, PRO involvement is efficacious precisely because PROs operate in different environments and under different rules and constraints than their proprietary DBF partners.

The argument that the effects of PROs on networks are generated largely by their institutional characteristics is consonant with our descriptive findings for Boston and the Bay Area. This clear implication, however, raises a perplexing set of questions. In Boston, universities, research institutes, and hospitals -- organizations institutionally committed to open information flow, science, and public-health based business strategies -- altered the efforts of Boston firms precisely by maintaining a formal and deliberate role in their region's networks. In short, Boston area PROs 'opened' their local networks using precisely the tools (formal contractual arrangements that structure collaboration and the transfer of intellectual property rights) developed to control and direct information transfer. In contrast, Stanford and UCSF's lack of formal involvement, and preference for more informal, non-contractual ties in their regional network, an approach that seems to more clearly complement the institutional mission of universities, enabled financiers to shape innovative and organizational strategies. The implications are paradoxical: deliberate efforts by PROs to control and shape information and resource flows in networks result in more open and expansive structures, while more informal, 'hands-off' approaches help create networks that are more tightly controlled and commercially directed. The role that universities play in regional development, then, appears more complicated than a simple model of technology transfer and technical training would suggest.

The co-evolution of innovation, strategy, and structure. The paradoxical roles public research organizations play in the industrial and technological development of regions are illuminated by a joint focus on the evolution of structures (in this case regionally bounded inter-organizational networks), organizational strategies (approaches to product

development and commerce), and patterns of innovation (differential reliance upon expansive and streamlined R&D logics). Tracing the emergence and dynamics of regional structures provides new insights into firm-level arrangements and strategies, but those strategies help to reproduce the landscapes that generated them. This co-evolutionary dynamic is suggestive of important sources of regional variation, but also highlights the potential consequences of organizational action in evolving networks. DBF strategies in Boston and the Bay Area bear the characteristic footprints of their most important partners. At the same time, the partners' possibilities for action are constrained by the actions of local DBFs. Consider two brief examples. If success in the competitive arena of Bay Area biotechnology depends upon early access to venture capital and that access smooths entre into collaborations with established firms that are key to innovative and commercial success, then savvy venture capitalists will seek to invest in newcomers whose strategies and arrangements match dominant patterns in the region: the very patterns that VCs' early efforts helped generate and sustain. Not surprisingly, then, Stuart and Sorenson (2003) find that while VC support became abundant in the Bay Area in the 1990s, the odds for success declined. One possible reason is lock in around a dominant model.

Universities and PROs face a similar dynamic complicated by potential conflicts between their institutional arrangements and those of their for-profit partners. University strategies for controlling and coordinating their industrial collaborations altered the networks in which their future interactions would occur. While the data we present in this paper are only suggestive of feedback loops across structures and strategies, one can imagine that such recursive effects might shape both participants and the environments in

which they exist. Recall the paradox of PRO legalism and open information flows. Such a dynamic could conceivably result in situations where Boston DBFs embedded in open networks may pressure their PRO partners to loosen-up, with the eventual effect of constraining information flows. In contrast, Bay Area DBFs concerned with innovative speed and access to property rights that support product competition may push more free-wheeling academic partners to formalize their involvement. The dynamics of structures and strategies, then, inform one another and their co-evolution may generate unintended consequences that reshape both participants and their environments.

Co-evolution and the perils of emulation. The contrast of Boston and the Bay Area, the most prolific biotechnology clusters in the world, should give pause to policy makers who look to successful clusters for models to emulate. Without awareness of underlying institutional variations and distinctive approaches to the development of new medicines, one could easily draw the incorrect inference that combining public research organizations, venture capital and small firms provides the ultimate recipe for successful economic development. We emphasize that similar approaches may be very deceiving and mask sharp differences in underlying causes of institutional and technical development.

Figure 1. Boston Main Component ties by Dyad and year, 1988-1999

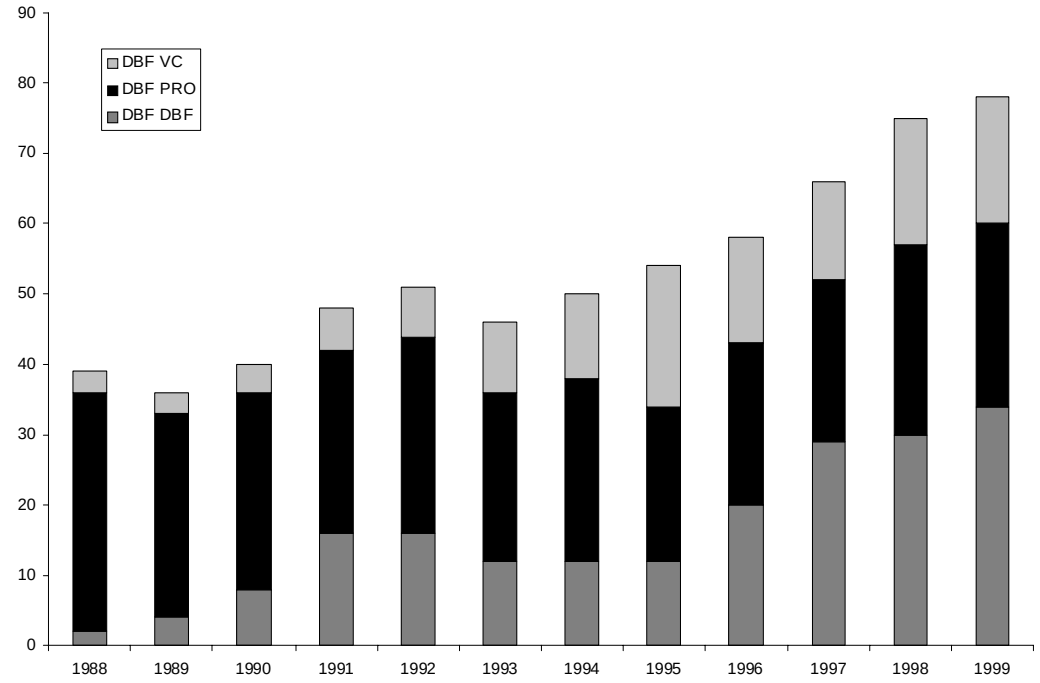

Figure 2. Bay Area Main Component ties by dyad and year, 1988-99

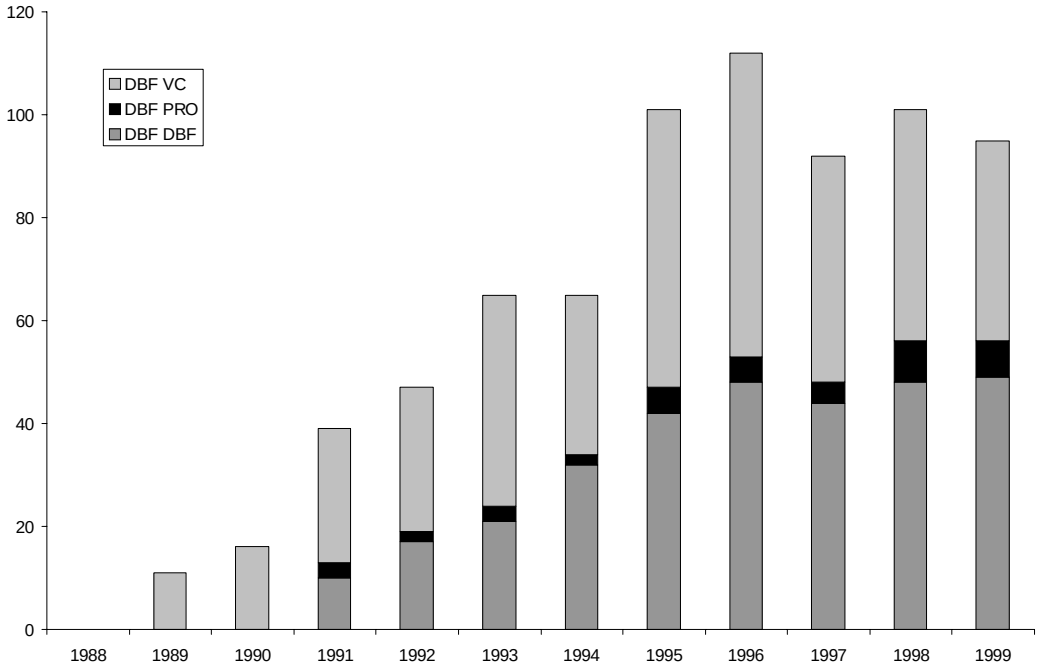

Figure 3. Boston and Bay Area Networks, 1988, 1994, 1999

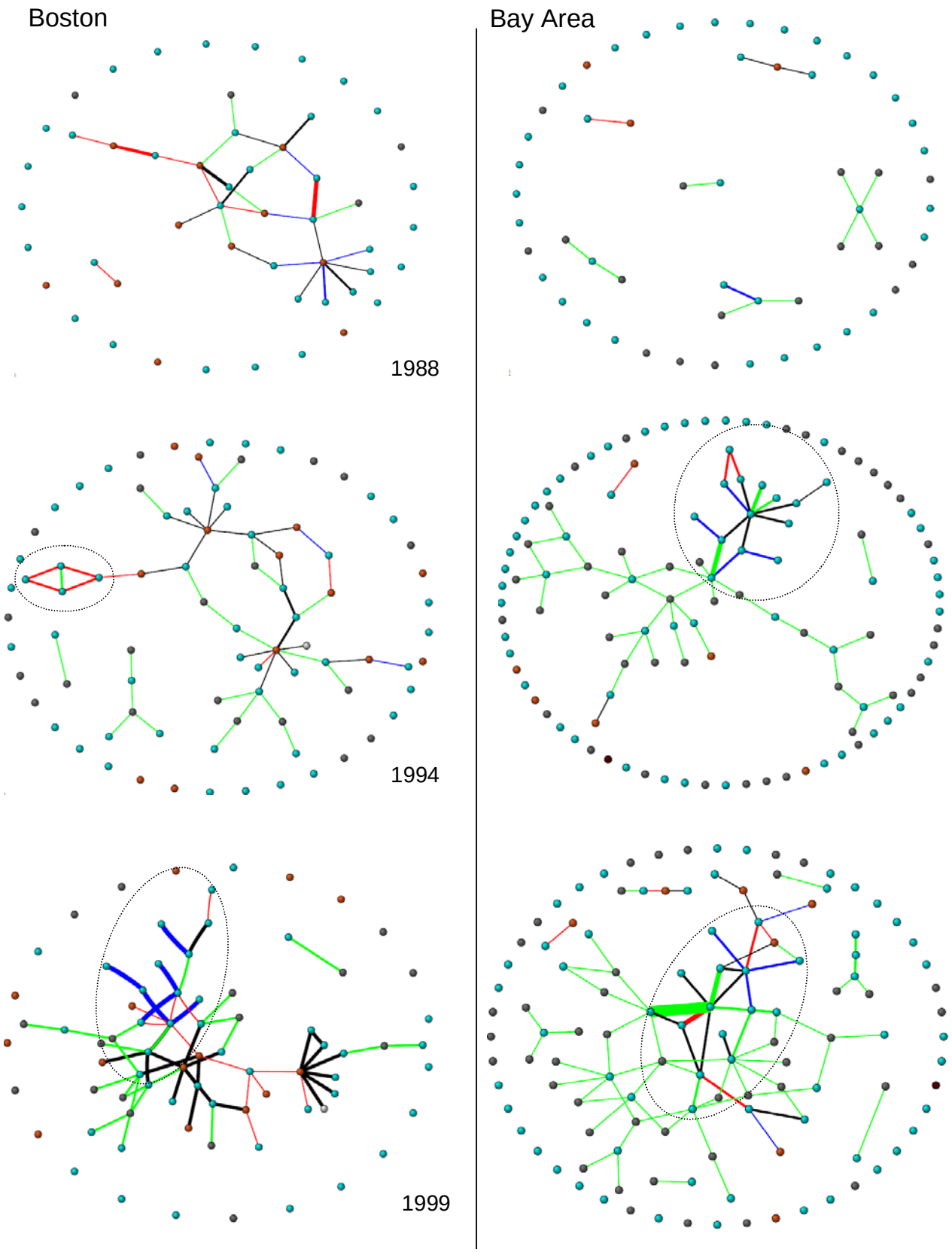

Table 1. R&D Outputs by Region, 1988-1999					
	Boston	Bay Area	Other DBFs		
# DBFs	57	82	343		
# Patents	1376	3806	4876		
Mean citations received (standardized)	1.113	0.979	0.944		
Variance	30.270	14.150	14.493		
# Citations made	12,659	41,389	43,610		
% Non-DBF cites	71%	55%	68%		
% Self Cites	12%	35%	11%		
FDA Approved Therapeutics	18	40	89		
Orphan Indications and Products	60	51	109		

Table 2. Innovation Data for Betaseron and Avonex		
	Betaseron (interferon beta -1b)	Avonex (interferon beta-1a)
FDA Approval Date (initial indication)	7/23/1993	5/17/1996
Orphan Status	Y	Y
Developer	Chiron	Biogen
Initial Patent Holder	Cetus Corporation	Biogen
Distributor	Berlex Laboratories (Schering Plough)	Biogen
Initial Indication	Remitting and Relapsing Multiple Sclerosis	Remitting and Relapsing Multiple Sclerosis
Number core patents	4	1
Number first gen citations	4	14
Number second gen citations	31	32
Number third gen citations	16	108
Total patents (original + 3 generations)	55	155
# prior art patents owned by fiduciary firms	6	0
# prior art patents from same region	2	4
# non-us prior art patents	26	61
# shared prior art patents	39	39
Notes: Both region cites for Betaseron are to other Silicon Valley DBFs (Genentech, ICN)		
The within-region cites for Avonex are to PROs (Mass Gen (1) MIT(2)) and a non-dbf firm (Ionics)		

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