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Translating Emergent Technologies into Novel Therapeutics: Tracing Complementarity and Co-evolution in the Cambridge-Boston Innovation Ecosystem

Abstract

This article traces the history of the life sciences business in the Cambridge-Boston area and explores how it became the global epicenter of the modern therapeutics industry. While business history scholarship on therapeutics is extensive, few have studied recent technological modalities – from therapeutic proteins to cell and gene therapies – or have adopted a regional ecosystem perspective. Based on archival materials and oral histories, this research bridges these works and incorporates insights from the innovation ecosystems framework. It considers how dynamic interactions between an evolving network of complementary and interdependent actors – from therapeutics firms, universities, hospitals to risk capital providers – enhanced innovative capacity. This perspective also illuminates how ecosystem strength derived from the co-evolution of actors; from universities restructuring technology transfer offices to academic scientists becoming entrepreneurs. The research further highlights the non-linearity of innovation processes. It shows how an extraordinary interplay between structural advantage, serendipitous timing, and strategic actions cultivated an unparalleled capacity to translate emergent technologies into novel therapies.

Keywords: business history, therapeutics, innovation ecosystem, biotechnology

Introduction

The Cambridge-Boston area has become a world-leading center for innovation in the life sciences business. In recent years, the area has played a disproportionate role in the commercialization of therapeutics, particularly as new technological modalities – such as cell and gene therapies – have come to market. Given its home to early biotechnology firms such as Cetus and Genentech in the 1970s, it would not have been surprising if the Golden State had become the global center for novel therapeutics. Yet, in the late 1990s, New England replaced New York as the leading regional biotechnology hub in the Eastern United States.¹ By 2021, Massachusetts surpassed California in the number of public companies, market capitalization and R&D expenditures in the biotechnology sector.² This paper explores how the Cambridge-Boston innovation ecosystem became the epicenter for translating scientific discoveries into ground-breaking therapeutic applications, pioneering the evolution of the field.

This article bridges existing business histories of therapeutics and industrial clusters. Previous scholarship has explored the history of the therapeutics sector, often on large pharmaceutical

¹ G. Steven Burrill and Kenneth B. Lee, Jr., *Biotech '97 Alignment: Ernst & Young 11th Industry Annual Report* (Palo Alto, 1996), 45, 46. This and subsequent industry reports by Ernst & Young between 1991 and 2013 were accessed in the Henri A. Termeer Papers, Baker Library Special Collections and Archives, Harvard Business School, Boston, Massachusetts.

² Ernst & Young, *Beyond Borders: EY Biotechnology Report* (London, 2022), 37.

firms,³ on themes such as intellectual property,⁴ regulation⁵ and corporate organization.⁶ While growing studies have explored the business history of biotechnology-based therapies,⁷ few have examined recent technological modalities or have studied the sector from the perspective of geographic concentration. Similarly, while prior business history scholarship has explored the rise – and decline – of industrial clusters on themes such as corporate organization,⁸ social

³ Tobias Cramer, "Building the "World's Pharmacy": The Rise of the German Pharmaceutical Industry, 1871–1914," *Business History Review* 89, no. 1 (2015): 43-73; David Schwartzman, *Innovation in the Pharmaceutical Industry* (Baltimore, 1976).

⁴ Mar Cebrián Villar and Santiago López García, "Assessing the Impact of Field-of-Use Restrictions in Patent Licensing Agreements: The Ethical Pharmaceutical Industry in the United States, 1950–1962," *Enterprise & Society* 18, no. 2 (2017): 282–323.

⁵ Judy Slinn, "Price Controls or Control through Prices? Regulating the Cost and Consumption of Prescription Pharmaceuticals in the UK, 1948–67," *Business History* 47 no. 3 (2005): 352–66.

⁶ Alfred D. Chandler Jr., *Shaping the Industrial Century: The Remarkable Story of the Evolution of the Modern Chemical and Pharmaceutical Industries* (Cambridge, 2009).

⁷ Lara V. Marks, *The Lock and Key of Medicine: Monoclonal Antibodies and the Transformation of Healthcare* (New Haven, 2015); Nicolas Rasmussen, *Gene Jockeys: Life Science and the Rise of Biotech Enterprise* (Baltimore, 2014).

⁸ William Lazonick, *Competitive Advantage on the Shop Floor* (Cambridge, 1990).

networks⁹ and industrial structure,¹⁰ many have focused on traditional manufacturing.¹¹ While some have examined high technology industries,¹² few include therapeutics.

This article extends existing business history research on regional competitive dynamics by incorporating the concept of innovation ecosystems; defined as the constellation of diverse and interdependent actors required to commercialize new ideas.¹³ With a business historical ecosystem perspective, the research reveals how an evolving network of complementary and interdependent actors – including therapeutics firms, universities, hospitals and risk capital providers – coordinated their activities to commercialize novel therapeutics. It also shows how ecosystem capabilities strengthen over time as these actors co-evolve. The article also contributes to innovation ecosystems scholarship by challenging the idea of linear development and highlighting how structural advantage, serendipitous timing, and strategic actions shape innovation trajectories.

⁹ Philip Scranton, *Endless Novelty: Specialty Production and American Industrialization, 1865–1925* (Princeton, NJ: 1997).

¹⁰ Charles Sabel and Jonathan Zeitlin. "Historical Alternatives to Mass Production: Politics, Markets and Technology in Nineteenth-Century Industrialization," *Past & Present* 108 (1985): 133-76.

¹¹ Mary Rose, ed. *The Lancashire Cotton Industry: A History since 1700* (Preston, 1996).

¹² Martin Kenney, ed. *Understanding Silicon Valley: The Anatomy of an Entrepreneurial Region* (Stanford, 2000).

¹³ Ron Adner, "Match your Innovation Strategy to your Innovation Ecosystem," *Harvard Business Review* 84, no. 4 (2006): 98-107; Ron Adner, "Ecosystem as Structure: An Actionable Construct for Strategy," *Journal of Management* 43, no. 1 (2017): 39-58.

This paper refers to the modern therapeutics sector following the biotechnology revolution in the 1970s. Groundbreaking discoveries such as recombinant DNA and monoclonal antibody technologies generated unprecedented possibilities for novel therapeutics and transformed the industry. The sector refers to both therapeutic biotechnology firms as well as conventional pharmaceutical firms. Biotechnology firms refer to firms founded from the 1970s that have taken biological approaches to drug discovery, such as Genentech and Biogen. While the distinction between the biotechnology and pharmaceutical firms have been blurring, the latter refer to the larger, established firms that long used chemistry-based approaches to drug discovery, such as Pfizer and Novartis.

This paper is based on archival sources and oral histories. The archival sources enabled an appreciation of the evolving industry context, including scientific advances, regulatory changes and key players. Archival materials included the Henri A. Termeer Papers in the Baker Library at Harvard Business School (HBS), which provided industry reports and annual reports of Genzyme and affiliated companies. The Walter Gilbert Papers at Harvard University Archives and the Phillip A. Sharp Papers at MIT Libraries' Distinctive Collections offered documentation related to the operations and founding of Biogen, respectively. At Cold Spring Harbor Laboratory Archives, internal company documents were available in the Collections of Walter Gilbert, Charles Weissman (Biogen) and Tom Maniatis (Genetics Institute). Materials consulted at the State Library of Massachusetts included historical, region-specific industry reports. Combined with newspaper and magazine articles, such as *The Boston Globe* and *Nature*, these sources provided both industry-wide perspective well as firm-specific insights into the evolving therapeutics sector.

The oral histories proved invaluable; particularly for understanding the undocumented perspectives and informal relationships between actors that were crucial to building the local ecosystem. The discussions also helped to appreciate the historical context that generated specific actions.¹⁴ The oral histories comprised of 24 semi-structured anonymous and non-anonymous interviews with a range of key figures in the local life sciences business, conducted between October 2023 and July 2024 following university ethics approval. The 19 non-anonymous interviews included (in alphabetical order): Noubar Afeyan, Robert Carpenter, Cristina Csimma, Zoltan Csimma, Walter Gilbert, Bob Higgins, Wilbur Kim, Robert Langer, Harvey Lodish, Lita Nelson, Andrew Plump, Stephen Reeders, Scott Requadt, Jack Reynolds, William Schnoor, Matt Segneri, Phillip Sharp, Josef von Rickenbach and George Whitesides. The conversations systematically explored similar themes relating to professional experience, historical industry trends, and reasons for the rise of the Cambridge-Boston area as a global epicenter of the therapeutics business.

The next section situates this research within existing scholarship and outlines the nature of the novel therapeutics industry. The article then follows the trajectory of the life sciences business in the Cambridge-Boston area. It shows how an exceptional combination of structural advantage, serendipity, and strategic actions cultivated a locus for translating emergent technologies into therapeutic applications.

Literature Review

¹⁴ Geoffrey Jones and Rachael Comunale, "Oral History and the Business History of Emerging Markets," *Enterprise & Society* 20, no. 1 (2019): 19-32; Robert Crawford, "Off the Books: Oral History and Transnational Advertising Agencies in Southeast Asia," *Enterprise & Society* 20, no. 1 (2019): 47-59.

This research builds upon two strands of business history scholarship: therapeutics and industrial clusters. The business history of therapeutics includes micro-level firm studies¹⁵ and meso-level industry studies¹⁶ around the world.¹⁷ While many have focused on chemistry-based pharmaceutical firms,¹⁸ growing works have studied biotechnology firms founded on biological sciences. Such studies have examined: founders of companies such as Biogen and Genzyme;¹⁹ firms such as Genentech and Vertex;²⁰ and new entrants who diversified into

¹⁵ Richard Davenport-Hines and Judy Slinn, *Glaxo: A History to 1962* (Cambridge, 1992); Carsten Burhop, "Pharmaceutical Research in Wilhelmine Germany: The Case of E. Merck." *Business History Review* 83, no. 3 (2009): 475–503.

¹⁶ Hans-Werner Gottinger and Celia L. Umali, "The Evolution of the Pharmaceutical-biotechnology Industry," *Business History* 50, no. 5 (2008): 583-601.

¹⁷ Laurence Monnais and Laurence Monnais-Rousselot, *The Colonial Life of Pharmaceuticals* (Cambridge, 2019); Timothy M. Yang, *A Medicated Empire: The Pharmaceutical Industry and Modern Japan* (Ithaca, 2021).

¹⁸ Jonathan M. Liebenau, "Public Health and the Production and Use of Diphtheria Antitoxin in Philadelphia" *Bulletin of the History of Medicine* 61, no. 2 (1987): 216-236; Charles C. Mann and Mark L. Plummer, *The Aspirin Wars: Money, Medicine, and 100 Years of Rampant Competition* (New York, 1991).

¹⁹ John Hawkins, *Conscience and Courage: How Visionary CEO Henry Termeer Built a Biotech Giant and Pioneered the Rare Disease Industry* (Cold Spring Harbor, 2019); Brian Dick and Mark Jones, "The Commercialization of Molecular Biology: Walter Gilbert and the Biogen Startup," *History and Technology* 33, no. 1 (2017): 126-151.

²⁰ Sally S. Hughes, *Genentech: The Beginnings of Biotech* (Chicago, 2011); Barry Werth, *The Billion-dollar Molecule: The Quest for the Perfect Drug* (New York, 1995).

biotechnology-based therapies, such as Kirin.²¹ Others have examined the role of institutional context²² or exogenous factors – such as technological²³ or regulatory change²⁴ – in reshaping the industry. Some executives have also reflected upon the industry’s evolution through their professional experience.²⁵ A recent book on Kendall Square near MIT offers textured documentation into how the district became a global innovation hub.²⁶ Augmenting existing business histories with an ecosystem-based perspective, this article considers how the alignment of structure, serendipity and strategy cultivated conditions that enabled the translation of scientific discoveries into novel therapies in the Cambridge-Boston area.

²¹ Michael J. Lynskey, "The Locus of Corporate Entrepreneurship: Kirin Brewery's Diversification into Biopharmaceuticals," *Business History Review* 80, no. 4 (2006): 689-723.

²² Luigi Orsenigo, *The Emergence of Biotechnology. Institutions and Markets in Industrial Innovation* (New York, 1989).

²³ Louis Galambos and Jeffrey L. Sturchio, "Pharmaceutical Firms and the Transition to Biotechnology: A Study in Strategic Innovation" *Business History Review* 72, no. 2 (1998): 250-278.

²⁴ James Geraghty, *Inside the Orphan Drug Revolution: The Promise of Patient-Centered Biotechnology* (Cold Spring Harbor, 2022).

²⁵ Tim Harris, *In Pursuit of Unicorns: A Journey Through 50 Years of Biotechnology* (Cold Spring Harbor, 2024).

²⁶ Robert Buderl, *Where Futures Converge: Kendall Square and the Making of a Global Innovation Hub* (Cambridge, 2022).

Business historians have long examined the importance of geographic concentration and inter-firm relations, well before the seminal work of Michael Porter and industrial clusters.²⁷ Research on industrial districts illustrated how specialized skills within a network of small firms employing flexible production methods enabled regions to maintain competitiveness.²⁸ Porter's studies discussed how factor conditions, skilled labor, infrastructure, and supporting industries determined cluster formation and success – as well as the enduring significance of local clusters amidst globalization.²⁹ Studies of industrial clusters thus focused on innovation, inter-firm relationships, supporting institutions and competitive advantage. For instance, Annalee Saxenian's work on regional advantage elaborated on how local institutions and corporate forms shaped distinct advantages for the semiconductor and computer industries in Silicon Valley compared to Route 128.³⁰ A range of business history work has examined the role of key actors in building industrial clusters, such as the state or academia in Silicon Valley.³¹ Business historians have also questioned whether institutional path dependence

²⁷ Jonathan Zeitlin, "Industrial Districts and Regional Clusters" in *Oxford Handbook of Business History*, eds. Geoffrey Jones and Jonathan Zeitlin (Oxford, 2007), 219-243.

²⁸ Scranton 1997, Sabel and Zeitlin, 1997.

²⁹ Michael Porter, *The Competitive Advantage of Nations* (New York, 1990); Michael Porter, "Location, Competition, and Economic Development: Local Clusters in a Global Economy," *Economic Development Quarterly* 14, no. 1 (2000): 15-34.

³⁰ AnnaLee Saxenian, *Regional Advantage: Culture and Competition in Silicon Valley and Route 128* (Cambridge, 1994).

³¹ Stuart W. Leslie and Robert H. Kargon, "Selling Silicon Valley: Frederick Terman's Model for Regional Advantage," *Business History Review* 70, no. 4 (1996): 435–472;

cultivates or undermines subsequent industrial development.³² For example, the knowledge, skills and networks from past industries may continue to support subsequent industries, as in the case of the UK outdoor trade around Lancashire during the second half of the twentieth century.³³ They may not be the case when complementary institutions are conducive to supporting a specific technology; small firms are acquired by larger, less innovative firms; or exogenous shocks obliterate supporting institutions. While Cleveland's decline from a center of technological innovation may be attributed to such factors,³⁴ this article suggests that the Cambridge-Boston area's industrial legacies were largely favorable to the subsequent rise of the therapeutics sector.

Stephen B Adams, "Arc of Empire: The Federal Telegraph Company, the U.S. Navy, and the Beginnings of Silicon Valley," *Business History Review* 91, no. 2 (2017): 329–359.

³² Rolv Petter Amdam and Ove Bjarnar, "Globalization and the Development of Industrial Clusters: Comparing two Norwegian Clusters, 1900–2010," *Business History Review* 89, no. 4 (2015): 693–716.

³³ Mike Parsons and Mary B. Rose, "The Neglected Legacy of Lancashire Cotton: Industrial Clusters and the UK Outdoor Trade, 1960–1990," *Enterprise & Society* 6, no. 4 (2005): 682–709.

³⁴ Naomi R. Lamoreaux, Margaret Levenstein and Kenneth L. Sokoloff, "Do Innovative Regions Inevitably Decline? Lessons from Cleveland's Experience in the 1920s," *Business and Economic History On-line* 5 (2007): 1–26, accessed 15 November 2024, <http://www.thebhc.org/publications/BEHonline/2007/lis.pdf>.

Business histories of regional industry development can be enriched by the concept of innovation ecosystems,³⁵ defined as the configuration of relationships between an interdependent collective of multiple actors that enable the commercialization of new ideas.³⁶ Prior scholarship on industrial clusters have focused on competitive dynamics³⁷ while those on regional systems of innovation (RSI)³⁸ have emphasized governance and policy interventions within defined administrative regions. By incorporating the ecosystem framework, this article illustrates how multilateral interactions between complementary and interdependent actors were critical for translating scientific discoveries into commercial applications.

³⁵ Adner, 98-107; Adner, 39-58.

³⁶ This research incorporates the innovation ecosystem framework, rather than the proximate literature on entrepreneurial ecosystems, given its holistic focus on the network of organisations and their collaboration that enable the introduction of new products, rather than on the environment that specifically fosters the creation and growth of new firms.

³⁷ Porter, *The Competitive Advantage of Nations*; Porter, "Location, Competition, and Economic Development."

³⁸ Philip Cooke, Mikel Gomez Uranga and Goio Etxebarria, "Regional Innovation Systems: Institutional and Organisational Dimensions," *Research Policy* 26, no. 4-5 (1997): 475-491.

Existing scholarship on innovation ecosystems include longitudinal studies that consider ecosystem emergence, evolution³⁹ and the coevolution of technologies, actors and institutions.⁴⁰ This research also contributes to these works by emphasizing the role of serendipity and non-linearity in ecosystem development. Here, serendipity refers to “unanticipated, anomalous, and strategic” alignments⁴¹ – such as the timing of scientific discoveries – which are historically contingent and momentary.⁴² Non-linearity refers to the uncertain and unordered process of innovation that challenge deterministic perspectives. The research illustrates how a delicate combination of structural advantage, serendipity and deliberate interventions shape the non-linear trajectory of innovation ecosystems.

The Nature of the Industry

³⁹ Ozgur Dedehayir, Saku J. Mäkinen, and J. Roland Ortt, "Roles during Innovation Ecosystem Genesis: A Literature Review." *Technological Forecasting and Social Change* 136 (2018): 18-29.

⁴⁰ Leena Aarikka-Stenroos and Paavo Ritala, "Network Management in the Era of Ecosystems: Systematic Review and Management Framework." *Industrial Marketing Management* 67 (2017): 23-36; Gifford, Ethan, Maureen McKelvey and Rögnvaldur Saemundsson, "The Evolution of Knowledge-intensive Innovation Ecosystems: Co-evolving Entrepreneurial Activity and Innovation Policy in the West Swedish Maritime System," *Industry and Innovation* 28, no. 5 (2021): 651-676.

⁴¹ Robert K. Merton and Elinor Barber, *The Travels and Adventures of Serendipity: A Study in Sociological Semantics and the Sociology of Science* (Princeton, 2004), 197.

⁴² Saxenian, *Regional Advantage*.

The features of the modern therapeutics industry should be noted in exploring its history. Comparisons have been made between the Cambridge-Boston therapeutics sector and Silicon Valley's high technology sectors, as there are several shared features. These include: rapid technological advances; requirements for risk capital; interdisciplinary collaboration; and entrepreneurial spirit. Yet, closer inspection reveals that the two areas are not entirely comparable. The modern therapeutics sector features much longer lead times along with higher levels of uncertainty, risk, technological complexity, regulatory intervention and cost.⁴³

Even in pharmaceutical firms, where chemistry was the dominant technology until the 1980s, therapeutic R&D had been subject to much higher cost, longer lead times and significant risk of failure compared to most industries. Until outsourcing to contract research organizations (CROs) became more commonplace from the 1990s, pharmaceutical R&D was usually based in large firms and comprised of the large-scale scanning of chemical substances that might safely and effectively remedy certain symptoms of disease. The discovery of a potential therapy was therefore based on considerable serendipity. Given requirements to gain regulatory approval across several phases of clinical trials, many firms developed therapies for ailments shared across a large patient population or chronic ailments, to maximize revenue and recoup the cost of R&D. For medicines approved in the 1980s, for example, the average cost of development was estimated at \$231 million (in 1987 dollars), with a lead time of 12 years, and

⁴³ Gary P. Pisano, *Science Business: The Promise, the Reality, and the Future of Biotech* (Cambridge, 2006); Andrew Plump (President of R&D at Cambridge-based Takeda), Interview by author, 17 January 2024.

an average success rate of 23%.⁴⁴ By comparison, Moore's Law – which observed that the number of transistors on a microchip doubled biennially⁴⁵ – revealed a more rapid rate of development and significantly shorter lead times for semiconductors.

The risks involving uncertainty and cost in therapeutic development increased with advances in biotechnology. Since the early 1970s, recombinant DNA technology – developed by Paul Berg, Herbert Boyer, Stanley Cohen, and others⁴⁶ – enabled scientists to engineer genetic material to produce proteins as therapeutic agents (e.g., insulin, hormones, enzymes) in host cells (e.g., bacteria, yeast). The discovery of hybridoma technology – by Köhler and Milstein in 1975⁴⁷ – enabled scientists to create an immortal cell that could produce large amounts of

⁴⁴ Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, and Louis Lasagna, "Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10, no. 2 (1991): 107-142.

⁴⁵ Robert R. Schaller, "Moore's Law: Past, Present and Future," *IEEE Spectrum* 34, no. 6 (1997): 52-59.

⁴⁶ David A. Jackson, Robert H. Symons, and Paul Berg, "Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of Escherichia Coli," *Proceedings of the National Academy of Sciences* 69, no. 10 (October 1972): 2904-2909; Stanley N. Cohen, Annie CY Chang, Herbert W. Boyer, and Robert B. Helling, "Construction of Biologically functional Bacterial Plasmids In Vitro," *Proceedings of the National Academy of Sciences* 70, no. 11 (1973): 3240-3244.

⁴⁷ Georges Köhler and Cesar Milstein, "Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity," *Nature* 256, no. 5517 (1975): 495-497.

identical / monoclonal antibodies to interact with disease-specific proteins. Therapeutics increasingly originated in university laboratories and were developed by academic scientists who began to launch small startups, which, for example, began making human proteins in bacteria for medical treatment.⁴⁸ From the 1980s until the early 2000s, recombinant proteins and monoclonal antibodies were at the frontier of therapeutic innovation. These included recombinant human insulin by Genentech (*Humulin*, 1982), which treated diabetes; and the first-approved monoclonal antibody by Ortho Pharmaceutical (*OKT3*, 1986), which was used for transplant rejection despite substantive side effects.⁴⁹ Over time, the larger and longer clinical trials required to demonstrate incremental clinical efficacy also raised drug

⁴⁸ Walter Gilbert, "Harvard Medical School Symposium Address," 16 November 1982, Walter Gilbert Papers, Box 8, Harvard University Archives, Cambridge, Massachusetts.

⁴⁹ Arthur D. Levinson, "For Success, Focus Your Strengths," *Nature Biotechnology* 16, Supplement 1(1998): 45–46; Thomas A. Waldmann, "Immunotherapy: Past, Present and Future," *Nature Medicine* 9, no. 3 (2003): 269-277

development costs, which increased from US\$802 million (2000 dollars) in the 1990s⁵⁰ to 1.8 billion dollars by 2010,⁵¹ with a success rate of 6.8%.⁵²

As products, therapeutics depend upon strong intellectual property protection and market exclusivity for an extended period. Given its association with academic research and human health, proximity to universities – particularly those with clinical infrastructure – has also been important. Furthermore, the sector has featured cycles of hype and disappointment, due to the extraordinary risk and returns for companies and the promise of a cure for patients.⁵³ These features illuminate how the Cambridge-Boston innovation ecosystem became a premier locus for translating emergent technologies into medicines.

Location, Declining Sectors and the Imprint of Past Clusters

A remarkable combination of structural advantage and serendipity contributed to the area's rise as the global center of the therapeutics industry. One structural advantage was location.

⁵⁰ Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 151-185.

⁵¹ Steven M. Paul, Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg, and Aaron L. Schacht, "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge," *Nature Reviews Drug Discovery* 9, no. 3 (2010): 203-214.

⁵² Chi Heem Wong, Kien Wei Siah, Andrew W Lo, "Estimation of Clinical Trial Success Rates and Related Parameters," *Biostatistics*, 20, no. 2 (2019): 273–286.

⁵³ Pisano, 25-29.

Boston was a port city that had prospered as a center of trade; through its harbor for centuries, and its public transportation networks since the 19th century. The area had evolved as a regional center of various industries; from textile and shoes in the 19th century to defense and electronics in the mid-20th century.⁵⁴ The institutional and organizational legacies following the decline of earlier industries – whether from overseas competition or technological advances⁵⁵ – facilitated the rise of subsequent industries.

[Insert Figure 1 here]

[Insert Figure 2 here]

The legacy of past industries was not inconsequential. The decline of local manufacturing – from textiles in the broader region to soap in Cambridge (e.g., Lever Brothers, Figure 1) – left behind skilled workers and physical infrastructure.⁵⁶ There was low-cost real estate that provided invaluable access to leading universities nearby. Furthermore, the clearing of 29 acres around Kendall Square area in 1964 to create NASA’s Electronic Research Center

⁵⁴ David Koistinen, *Confronting Decline: The Political Economy of Deindustrialization in Twentieth-Century New England* (Gainesville, 2013). Barry Bluestone and Bennett Harrison, *Deindustrialization in America: Plant Closings, Community Abandonment, and the Dismantling of Basic Industry* (New York, 1982).

⁵⁵ Edward L. Glaeser, “Reinventing Boston: 1630–2003,” *Journal of Economic Geography* 5, no. 2 (2005): 119-153.

⁵⁶ Ian Menzies, “New England’s Industry is Enjoying a Rebirth because it has ... the Greatest Brains in the World,” *The Boston Globe* 5 July 1959, B3-B4.

(Figure 2), not only displaced many businesses, but NASA's 1970 withdrawal also left large space available for use.⁵⁷ Such space enabled the concentrated construction of new facilities associated with biotechnology. These included, for example, the Whitehead Institute, a biomedical research organization specializing in genomics, known for its contributions to the Human Genome Project. As co-founder and MIT professor Harvey Lodish stated, "The fact that there was land that was cleared, old industrial land, made a huge difference ... There was a place to put all of this, and that is not often noticed." Moreover, local officials at both state and municipal levels (e.g., state governors, Cambridge Redevelopment Authority) collaborated with academics and private investors to support urban redevelopment. "The fact that everybody is on the same page working together makes a huge difference,"⁵⁸ he added.

Coincidentally, the institutions supportive of past industries were compatible with those of the oncoming sector. The emergent cluster benefitted from the structural advantages of world-class universities such as Harvard and MIT as a source of human capital and repository of knowledge, along with networks of collaboration between academia and industry. MIT had particularly close relationships with industry as an engineering school emphasizing the practical application of knowledge. In the shadow of industrial legacies, entrepreneurial initiative as well as a professional community — from venture capitalists, lawyers to consultants — supported startups in the nascent biotechnology sector.

⁵⁷ Urban Land Institute, "Appendix: Background of the Kendall Square Renewal Area," in *Cambridge Center: An Evaluation of the Redevelopment Potential of Cambridge Center in the Kendall Square Renewal Area for the Cambridge Redevelopment Authority, Cambridge, Massachusetts, 15-19 November 1976: A Panel Service Report* (Washington, DC, 1977).

⁵⁸ Harvey Lodish, Interview by author, 21 December 2024.

From National to Local Institutional Change

The biotechnology revolution prompted regulatory change at both national and local levels. As a heavily regulated industry, major legal changes at the national level, from the *Diamond v. Chakrabarty* ruling to the Orphan Drug Act, altered the rules of the game. The co-occurrence of local industrial decline with concurrent institutional change was remarkably well-timed.

One landmark change was the *Diamond v. Chakrabarty* ruling in 1980, which clarified that genetically modified organisms could be patented – if they were novel, original and non-obvious.⁵⁹ While the biotechnology revolution offered the possibility of creating medicines with genetically modified organisms, it remained unclear whether organisms created out of human genetic manipulation could be patented. While prevailing US regulation indicated that living organisms could not be patented, the ruling clarified and expanded the scope of patentability, catalyzing the commercialization of biotechnology-based drugs.⁶⁰ Another turning point was the passage of the Bayh-Dole Act in the same year, which had a profound impact on the commercialization of federally – often National Institutes of Health (NIH) –

⁵⁹ *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

⁶⁰ Stacy V. Jones, “Patents; Creating Life Forms in the Lab,” *The New York Times*, 4 April 1981, 38.

funded life sciences research. Indeed, university patenting in life sciences increased substantially after Bayh-Dole.⁶¹

Other significant regulatory changes at the national level included the Orphan Drug Act introduced in 1983. A result of patient advocacy, the Act created incentives for firms to conduct R&D in therapeutics for rare diseases, defined as ailments affecting less than 200,000 patients in the United States.⁶² By granting a period of market exclusivity, tax incentives, and waiver of certain FDA fees, the Act reoriented the model of therapeutic development away from blockbuster drugs and toward smaller patient populations – facilitating the rise of academic startups.⁶³ Furthermore, the Economic Recovery Tax Act of 1981 not only introduced R&D tax credits but also reduced capital gains tax, which encouraged greater investments into startups.⁶⁴

⁶¹ Bayh-Dole Act of 1980, 35 U.S.C. § 200-212; Rebecca S. Eisenberg, “Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research,” *Virginia Law Review* 82 (1996): 1663-1727.

⁶² Orphan Drug Act of 1983, 21 U.S.C. § 360aa-360ff.

⁶³ Geraghty, *Orphan Drug Revolution*.

⁶⁴ Economic Recovery Tax Act of 1981, Pub. L. 97-34. Consideration of the 1981 Tax Act noted in Genetics Institute, “Meeting of Directors,” 12 November 1981, Box 1, Folder 2, Tom Maniatis Collection, Cold Spring Harbor Laboratory Archives, Cold Spring Harbor, New York.

While national regulations – concerning safety and efficacy for marketing approval – were influential, local regulations – from planning to research permissions – were also impactful in shaping the sector. In fact, local restrictions introduced in the city of Cambridge delayed industry activity in the short-term but supported local growth in the long-term. In the 1970s, public health concerns over the safety of recombinant DNA research conducted at Harvard had prompted the city of Cambridge to impose a moratorium on recombinant research. Between July 1976 and February 1977, the municipal Cambridge Experimental Review Board held public hearings with experts from Harvard, MIT, and NIH over concerns that new organisms could cause unknown diseases. While some actors expressed frustration that the Cambridge City Council delayed research activities, the eventual vote for regulations more stringent than NIH guidelines⁶⁵ enabled local actors to operate under clear and predictable rules.⁶⁶ One reason that a leading biotechnology company, Biogen, decided to locate its operations in Cambridge was for this reason.⁶⁷ Institutional changes at both national and local levels altered drug development models and transformed the competitive environment.

Structural Transformations and Eastward Shifts in Therapeutic Innovation

⁶⁵ Cambridge City Council, Correspondence, June 1976 to April 1977, Massachusetts Institute of Technology, Oral History Program, Oral History Collection on the Recombinant DNA Controversy, accessed 15 November 2024, <https://hdl.handle.net/1721.3/200724>.

⁶⁶ Laura L. Lindsey and Massachusetts, *Recombinant DNA and the Cambridge City Council*. Boston: Science Resource Office, Massachusetts General Court, 1976, accessed 15 November 2024, <https://www.biodiversitylibrary.org/page/41433399>; Peter Feinstein Inc., *An Assessment of the Massachusetts Biotechnology Industry* (Cambridge 1990), 14.

⁶⁷ Phillip Sharp, Interview by author, 18 July 2024. Philip Sharp was a co-founder of Biogen.

While the early therapeutic biotechnology firms were often represented by West Coast firms such as Cetus (1971) and Genentech (1976), a sequence of serendipitous timings shifted the center of therapeutic innovation toward the East Coast in the 1990s. First, was the decline of large pharmaceutical firms. Second, was the rise of biopharmaceutical services, such as contract research organizations (CROs). Third, was the rise of lean biotechnology firms.

As the millennium neared, large pharmaceutical firms began to outsource their R&D. To begin with, there were pressures to generate new therapies. By the 1990s, many drugs were still generating significant revenue, but their patent life was nearing end. There was a sense that, unless firms outsourced the development process, they would be operating inefficiently by peak-loading staff. As firm performance was cyclical, dependent on the success of a given discovery, companies opted to outsource; to adjust employment and utilize labor more effectively.⁶⁸ Pharmaceutical firms were also becoming increasingly sensitive to short-term returns amidst growing financialization in America.

These pressures to enhance efficiency accelerated the rise of CROs. Since the 1980s, entrepreneurs had launched firms that offered a range of research and development services on a contract basis, such as pre-clinical research and clinical trials management. In 1982, HBS graduate Josef von Rickenbach and organic chemist Anne Sayigh established Parexel, which grew into a leading local CRO, rivalling contemporaries such as Quintiles and Pharmaco. CROs catered to the demands of clinical trials, which, with increasingly complex data requirements, were distinct from academic research. Rickenbach, who led Parexel for

⁶⁸ William Schnoor, Interview by author, 6 December 2023.

over two decades explained, “To run a big clinical trial is like a small business. I mean, it is a huge undertaking. You have probably dedicated, several hundred people who work on that trial for multiple years, in highly complex, highly dynamic environments.”⁶⁹ By exposing the respective activities across the value chain to market forces, the growth of biopharmaceutical service companies such as CROs enhanced the dynamism of the local innovation ecosystem and altered the competitive landscape. They did so by enabling established firms to achieve greater efficiencies and enabling less established and foreign firms to build their foothold in the market.

Pressures to enhance efficiency also encouraged pharmaceutical firms to connect with and acquire biotechnology firms with promising therapies that would secure robust returns. Biotechnology companies were gaining prominence as drugs were becoming more difficult to administer or treated complex diseases that pharmaceutical firms could not develop on their own. Academic startups emerged in the 1980s, such as Genetics Institute (Harvard), Repligen (MIT) and Alkermes (Harvard Medical School).⁷⁰ As pharmaceutical firms became less interested in conducting their own research and considered academic science too early stage and risky for commitment, biotechnology companies became the carrier that would bring academic science into the real world.

⁶⁹ Josef von Rickenbach, Interview by author, 25 June 2024.

⁷⁰ Growing actors in the local ecosystem can be identified in Massachusetts Office of International Trade and Investment, *Massachusetts International Biomed Directory* (Boston, 1990).

Biotechnology entrepreneurship was also unfolding amidst a backdrop of changes in American corporate culture. While workers in large American companies expected a job for life in the 1960s, many American workers had experienced a layoff at least once in their career by the 1990s. This shift altered employer-employee relations and made entrepreneurship in America feel less risky.⁷¹

Coincidentally, many of the world-leading pharmaceutical companies in the 1980s and 1990s were situated in the Northeastern United States. In 1985 and 1990, for example, most of the top 10 prescription drug companies in the world by sales were headquartered in the Northeast. These included: Merck & Co (New Jersey), American Home Products (New York), Pfizer (New York), SmithKline Beckman (Pennsylvania), Bristol-Myers (New York), and Johnson & Johnson (New Jersey).⁷² Geographically, the leading centers of the US biotechnology industry were in three locations (Table 1). For example, in 1991, New York, the San Francisco Bay Area, and Boston accounted for 17, 14 and 13 of public companies, or 12%, 14% and 10% of all companies, respectively.⁷³ As East Coast pharmaceutical companies realized the possibility of biologicals, they sought strategic alliances with biotechnology companies nearby.

[Insert Table 1 here]

⁷¹ Lita Nelson, Interview by author, 9 January 2024.

⁷² Scrip, *Yearbook* (Richmond, 1986), 36; Scrip, *Pharmaceutical Company League Tables* (Richmond, 1991), 2.

⁷³ G. Steven Burrill and Kenneth B. Lee, Jr. *Biotech '92: Promise to Reality: An Industry Annual Report* (San Francisco, 1991), 46.

The co-location and alliances between biotechnology and pharmaceutical firms eventuated in a more durable Eastward shift of the life sciences sector. As the East Coast was closer to Europe than the West Coast, European pharmaceutical firms also began to establish their global R&D headquarters in the area. Novartis' 2002 establishment of its primary research arm – the Novartis Institutes for BioMedical Research – in Cambridge marked the area as a central location for therapeutic R&D.⁷⁴

With the new technological modalities, drug development evolved toward a collaborative model across interdependent actors. Biotechnology firms often developed scientific discoveries from academic laboratories into “proof of concept,” or a potential therapeutic product for pharmaceutical firms, which could be integrated into their pipeline. As innovative activity moved from pharmaceutical companies to university laboratories and biotechnology firms, the locus of innovation gravitated toward world-leading universities in the Cambridge-Boston area.

The Universities and the Powering of Scientific and Entrepreneurial Talent

The Cambridge-Boston universities were deeply entwined with the development of the local therapeutics sector and were core to its strength. The universities were not only the source of a highly skilled pool of human capital. They were also the source of world-leading scientific research, star scientists and early academic entrepreneurship.

⁷⁴ Paul Smaglik, “Boston: A Magnetic Hub,” *Nature* 417 (2002): 4–5.

The local universities supplied vital human capital for emerging firms, particularly by producing graduates with advanced degrees in biology who eagerly sought opportunities in industry. After the biotechnology revolution, biochemists and molecular biologists suddenly found job opportunities – beyond teaching and academic research – that had not existed before. As former Harvard professor and Biogen CEO Walter Gilbert explained of such graduates, “If you have another turn of mind, you want something immediate in terms of human good ... creating drugs that are going to influence somebody in your lifetime ... Everybody with that sort of mind suddenly finds ... there are jobs available and even well-paying jobs ...”⁷⁵ The local biotechnology sector capitalized not only upon a strong pool of human capital, but also upon university (e.g., HBS)⁷⁶ and company (e.g., Genetics Institute, Genzyme)⁷⁷ alumni networks that facilitated talent mobility and entrepreneurship.⁷⁸

Local universities had also been at the forefront of scientific research; providing an exceptional source of scientific knowledge with a high concentration of star scientists. The latter refer to highly research productive scientists who have delivered significant social impact – through research collaborations and the commercialization of academic discoveries

⁷⁵ Walter Gilbert, Interview by author, 19 July 2024.

⁷⁶ Robert Carpenter, Interview by author, 16 July 2024

⁷⁷ Monica C. Higgins, *Career Imprints: Creating Leaders across an Industry* (San Francisco, 2005); Scott Requadt, Interview by author, 8 December 2023. Robert Weisman, “How Genzyme became a Source of Biotech Executives,” *The Boston Globe*, 11 July 2015.

⁷⁸ Zoltan Csimma, Interview by author, 15 December 2023. Zoltan Csimma, former chief human resources officer at Genzyme observed that the collaborative nature of developing therapeutics also facilitated enduring relationships.

via entrepreneurship.⁷⁹ MIT scientists' founding of the defense contractor Raytheon and computer company Digital Equipment Corporation illustrated the historical significance of universities and MIT's strengths in the application of research.

Indeed, MIT played a pioneering role in the commercialization of academic science.⁸⁰ Not only did its scientists have statutory privileges to engage in consulting activities one day of the week, but substantial reforms to the facilitate technology transfers were also made at the university, particularly after Bayh-Dole.

More specifically, the MIT technology licensing office (TLO) began to re-organize its office from a largely legal, administrative office staffed by patent attorneys to a more technology- and marketing-savvy office oriented to business. In the 1980s, MIT invited colleagues such as Neils Reimers from Stanford's TLO to: facilitate the translation of academic science into the market; allow faculty to bring their science into the real world as consultants or entrepreneurs; and support government aims to bring federally funded scientific research into public use. By the late 1990s, MIT's TLO advised start-ups and connected them to local venture capitalists, earning a reputation for speaking the language of both industry and academia.⁸¹

⁷⁹ Alexander Oettl, "Reconceptualizing Stars: Scientist Helpfulness and Peer Performance," *Management Science* 58, no. 6 (2012): 1122-1140.

⁸⁰ Noted by numerous interviewees.

⁸¹ Lita Nelson led MIT's TLO between 1986 and 2016. Nelson, Interview by author.

Interviewees commented upon the office's efficiency and speed.

Area universities also began to launch entrepreneurship education and interdisciplinary research centers that would help translate scientific discoveries into therapeutic applications. For instance, MIT professor Edward Roberts, who founded the university's Entrepreneurship Center (1990) and related programs, was credited for cultivating the university's entrepreneurial culture.⁸² As MIT attracted family foundations who established research centers supportive of commercialization, such as the Broad Institute (2004) and the Koch Center for Integrative Cancer Research (2007), similar centers were established at Harvard, such as the Harvard Stem Cell Institute (2004) and the Paglucia Life Lab (2016).

These universities had a high concentration of star scientists whose role expanded over the years: from conducting groundbreaking research; establishing startups; to wider industry engagement. Early star scientists such as Walter Gilbert (Harvard), Phillip Sharp (MIT), Mark Ptashne (Harvard) and Tom Maniatis (Harvard) were world-renowned scientists who established companies such as Biogen and Genetics Institute based on university research; situated these firms near their universities; and spearheaded the academic-industry collaboration model at a time of significant skepticism toward academic entrepreneurship.⁸³ The second generation of star scientists, such as Robert Langer (MIT) and George Church

⁸² Edward B. Roberts, Interview by Infinite MIT. Available at:

<https://infinite.mit.edu/video/edward-b-roberts-58-sm-58-sm-60-phd-62> (accessed on 6 November 2024).

⁸³ Biogen N.V., "Private Placing Memorandum," 28 September 1981, 3, Walter Gilbert Papers, Box 8, Harvard University Archives, Cambridge, Massachusetts; Deliberation between scientists and Harvard administration on patent use are noted, for example, in Genetics Institute, "Meeting of Directors."

(Harvard), were esteemed scholars with considerable publications and research grants who solidified the academia-industry collaboration model. They not only worked with companies,⁸⁴ but also established multiple companies – often based on a platform technology – with strong patent protection.⁸⁵ Furthermore, star scientists attracted star students and star postdocs and trained the next generation of academic entrepreneurs. Local universities – and affiliated hospitals – helped establish the area as the center of the therapeutics industry, creating a self-reinforcing ecosystem that attracted more firms. As MIT institute professor and entrepreneur Robert Langer explained:

If I thought the number one thing that was critical was ... that you have two of the greatest universities in the world, two miles from each other in Cambridge: MIT and Harvard. You have Harvard Medical School, all the great hospitals here ... and you have a lot of other colleges that are excellent, too, like BU, BC, Tufts, Brandeis. I think that to me, and then you had some companies that got started like Biogen and Repligen and then more just kept coming and coming...⁸⁶

The Clinical Infrastructure

The prominence of the Cambridge-Boston area as a center for novel therapeutics also owed much to the local clinical infrastructure, such as that of the Longwood area. Harvard Medical School moved closer to its affiliated teaching hospitals in the early 20th century, and these

⁸⁴ Carolyn Y. Johnson, “Building a Better Bacteria,” *The Boston Globe*, 29 August 2011.

⁸⁵ Carolyn Y. Johnson, “MIT Bioengineer to Share Medical Prize,” *The Boston Globe*, 15 September 2011.

⁸⁶ Robert Langer, Interview by author, 17 July 2024.

hospitals were leaders in education, research and clinical delivery. Over the years, the proximity of these specialist hospitals –from the Boston Children’s Hospital to the Dana-Farber Cancer Institute – facilitated the training of clinicians across specialisms as well as interdisciplinary and translational research.

[Insert Figure 3 here]

The hospitals’ research focus was evidenced as major recipients of NIH funding, which placed Boston – over San Francisco (Figure 3) – as the highest recipient city of NIH funds since 1992.⁸⁷ Four were also among the seven largest recipients of industry-sponsored hospital research in the mid-1990s.⁸⁸ As MIT institute professor and Biogen co-founder Phillip Sharp elaborated, the working relationships between hospitals, firms and universities were significant:

One of the things – there were many things that made Cambridge and Boston so powerful in biotech – one is there are great universities here ... the other thing that's really striking is there are great hospitals and medical schools in nearby Boston ... and we have had relationships with them, working relationships for over 50 years

⁸⁷ Boston Planning & Development Agency, Research Division, *Boston: Most NIH Funds for 24 Consecutive Years* (Boston, 2019).

⁸⁸ Association of University Technology Managers, “AUTM Licensing Survey,” in Biotechnology Industry Organisation, *Economic Importance of Technology, Medical Research and Improved Healthcare: Forum of the Task Force on Science, Healthcare and the Economy*, 23 June 1998. Henri A. Termeer Papers, Box 69, Folder 22, Baker Library Special Collections and Archives, Harvard Business School, Boston, Massachusetts.

before recombinant DNA, where we collaborate, individual faculty collaborated to take technology, radiology, other technologies into medical care. So, this whole engagement with the expertise of clinical medicine, working with the basic scientists, working with the private sector was important. We understood each other. We understood who to talk to ... and this includes a whole generation of MD PhD students and others, who can talk both languages, have experience in medical care, clinical medicine and laboratories ...⁸⁹

The area's strengths in collaborative R&D drew from the complementary capacities of local universities and clinical infrastructure. For example, many MIT scientists had expertise in platform technologies – from drug delivery systems, tissue engineering to genome editing – that had a wide range of applications, rather than therapeutic compounds per se. Such technologies were often essential to developing therapies involving new technological modalities.⁹⁰ As MIT did not have a medical school, its academics often developed close collaborations with Harvard Medical School and affiliated hospitals.⁹¹ These networks facilitated knowledge exchange and the translation of fundamental discoveries from bench to bedside.

Venture Capitalists, Foundations, and Alternative Forms of Funding

⁸⁹ Phillip Sharp, Interview by author.

⁹⁰ Robert Langer, "New Methods of Drug Delivery," *Science* 249, no. 4976 (1990): 1527-1533.

⁹¹ Robert Langer and Judah Folkman, "Polymers for the Sustained Release of Proteins and Other Macromolecules," *Nature* 263, no. 5580 (1976): 797-800.

If universities and the clinical infrastructure were the engine, risk capital was the fuel that propelled growth of the life sciences business. Yet in the 1970s, there was limited venture capital and few biotechnology startups. Most investors would realize the potential gains from biotechnology following Genentech's initial public offering (IPO) in 1980.⁹² Indeed, from a sector-wide perspective, venture capital funding increased from roughly \$50 million in 1984 to over \$300 million in 1988.⁹³

Risk Capital for Biotechnology Firms in the 1970s and 1980s

The area's early biotechnology firms attracted venture capital financing from within and outside of Massachusetts, such as Kleiner Perkins (California) and Venrock Associates (New York); the venture arm of established companies; and private investors. For example, Biogen, founded by a collective of scientists, was financed by the local venture capital firm TA Associates; the venture arm of the Canadian nickel mining company Inco; the US pharmaceutical firm Schering Plough; the agricultural biotechnology company Monsanto, and private investors such as Moshe Alafi.⁹⁴ Funding amounts in those years were modest compared to later decades. For instance, Genetics Institute, founded by Harvard scientists Mark Ptashne and Tom Maniatis, to develop therapeutic proteins, was initially offered six million dollars by a venture capital consortium. The group comprised of the local Greylock,

⁹² Karen Arenson, "A 'Hot' Offering Retrospective," *The New York Times*, 30 December 1980, 1.

⁹³ Burrill and Lee, *Biotech '92*.

⁹⁴ Letter to Shareholders of Biogen N.V., May 20, 1980, Series 2: Board of Director Documents, Box 18, Charles Weissmann Collection, Cold Spring Harbor Laboratory Archives, Cold Spring Harbor, New York.

New York-based Venrock and J.H. Whitney, the private investor William Paley, founder of the television company CBS, and firms such as Baxter and Pfizer. Despite its origins in university laboratories and initial support from the Harvard Management Group, which managed university endowments, the Group withdrew following faculty opposition.⁹⁵ Concerned over potential conflicts of interest, Harvard remained ambivalent toward academic entrepreneurship.⁹⁶

In the 1970s and 1980s, venture capital firms in the Boston area were generalists with limited funding.⁹⁷ When Cambridge-based Highland Capital Partners was established in 1988, it was the first among specialist venture firms that developed deep industry-specific expertise; focused on early-stage companies; and invested substantial capital with smaller syndicates.⁹⁸ As co-founder Bob Higgins reflected, “We thought focusing by technology sector would be

⁹⁵ Gabriel Schmergel interview by Arnold Thackray, Cassandra Stokes and Mark Jones, 15 December 2011, accessed 5 November 2024, <https://digital.sciencehistory.org/works/lutrzki>; Genetics Institute, Inc. Annual Report 1983, Tom Maniatis Collection, Box 1, Folder 1, Cold Spring Harbor Laboratory Archives, Cold Spring Harbor, New York.

⁹⁶ Harvard President’s Report to the Members of the Board of Overseers 3 September 1981, Tom Maniatis Collection, Box 1, Folder 9, Cold Spring Harbor Laboratory Archives, Cold Spring Harbor, New York.

⁹⁷ “Venture Capital in Boston, 1971-1974,” Patrick R. Liles papers, Box 6, Folder 7, Baker Library Special Collections and Archives, Harvard Business School, Boston, Massachusetts.

⁹⁸ Bob Higgins, interviewed by Amy Blitz, July 2001, HBS Entrepreneurs Oral History Collection, Baker Library Special Collections, Harvard Business School, Boston, Massachusetts.

an interesting idea ... we chose software, medical and telecom as our ... three foci... It doesn't sound like it's a focus, but at the time it was considered unusual, if not radical.”⁹⁹

The large investment banks such as Goldman Sachs and JP Morgan were not interested in life sciences for much of the 1990s. Life science investments were covered by four boutique banks; three in the West Coast. These were: Robertson Stephens, Hambrecht & Quist, Montgomery Securities (all San Francisco) and Alex Brown (Baltimore).¹⁰⁰ Hambrecht & Quist, for example, was an underwriter for the IPOs of Genentech and Cetus in 1980 and 1981, respectively.¹⁰¹ Following successful IPOs and therapy launches, along with advisory experience of mergers and acquisitions between pharmaceutical and biotechnology firms, larger investment banks came to form dedicated healthcare and biotechnology divisions.

Growing Interest among Local Venture Firms

As biotechnology companies from Biogen to Genzyme achieved considerable success – completing public offerings and developing effective therapies – further venture capital firms such as Morgenthaler opened offices in Boston. Existing firms such as Schroder Ventures and Atlas Ventures also became more interested in biotechnology, just as specialist firms such as Polaris Partners (1996) and Flagship Pioneering (1999) were founded. Local venture

⁹⁹ Bob Higgins, Interview by author, 15 July 2024.

¹⁰⁰ Schnoor, Interview by author; Arthur Klausner, “Demand Increasing for Biotech Analysts on Wall Street,” *Bio/Technology*, 1, no. 9 (1983): 740 – 741.

¹⁰¹ Genentech, Inc., " New Issue: 1,000,000 Shares Common Stock," [Announcement], *The Economist*, 1 November 1980, 25; Susie Gharib, “The Folks Who Brought You Apple,” *Fortune*, 12 January 1981.

companies began to take a heightened interest in biotechnology just as West Coast contemporaries began to doubt its potential.

Doubts among West Coast investors intensified in the 1990s with several high-profile failures of antibody drugs. The first monoclonal antibody drug, OKT3, encountered clinical complications, while the therapies of Xoma and Centocor – monoclonal antibody drug companies – struggled to gain FDA approval. These failures led to a decline in investment, despite strong intellectual property.¹⁰² Contemporary West Coast venture firms opted to invest in thriving tech companies with shorter lead times, clearer paths to market, and significant returns from IPOs – such as those of Yahoo (1995) Amazon (1997) and eBay (1998).

Diversification of Funding Sources

Venture capital in the biotechnology industry grew significantly after the millennium (Table 2), supporting early-stage biotechnology companies. Startups benefitted from local venture capitalists who considered companies in their earliest stages as a local business, where the ability to walk the halls of universities and understand ongoing activities was crucial.¹⁰³ Moreover, pulling a company together required conversations that were difficult to conduct at a distance.

¹⁰² Lara Marks, "The Birth Pangs of Monoclonal Antibody Therapeutics: The Failure and Legacy of Centoxin," *Mabs* 4, no. 3 (2012): 403-412; Lawrence M. Fisher, "Market Place; Price of Failure in Biotechnology," *The New York Times*, 17 April 1992; Stephen Reeder, Interview by author, MVM Partners, 22 December 2024.

¹⁰³ Stephen Reeder, Interview by author.

[Insert Table 2 here]

Meanwhile, funding sources diversified, particularly for companies in later stages of development. Corporate investment became important as pharmaceutical companies turned to biotechnology firms for the seeds of discovery and created venture arms, such as Novartis Venture Fund (1996) and Pfizer Ventures (2004). Investment banks also became more interested in the life sciences business, as reflected by JP Morgan's sponsorship of the industry's premier conference: the JP Morgan Healthcare Conference. Additionally, patient organizations became funders for firms focused on rare diseases. For example, in 2000, the Cystic Fibrosis Foundation offered Vertex a \$150 million investment in exchange for future therapy revenues.¹⁰⁴ As Vertex launched cystic fibrosis drugs, the Foundation's venture philanthropy model spread to other organizations such as CureDuchenne, which funded area firms including Sarepta Therapeutics.¹⁰⁵

Boston's long association with multi-generational wealth was also an important source of capital. While New York was regarded as a transaction city that was short-term and deal-focused, Boston was regarded as an investment city with more patient, relationship-based capital conducive to building biotechnology companies.¹⁰⁶ As biotechnology attracted

¹⁰⁴ Werth, *Billion-dollar Molecule*.

¹⁰⁵ CureDuchenne, CureDuchenne Ventures, accessed 15 November 2024, <https://cureduchenne.org/ventures/>.

¹⁰⁶ Bob Higgins, Interview by author.

attention from the wider investment community, family offices such as the local Kraft Group further supported biotechnology firms.¹⁰⁷

Over time, the Cambridge-Boston area attracted a community of investors who could identify and fund emerging opportunities with significant potential. As limited partners of venture capital firms were often universities, venture firms were also familiar with promising technologies from academic laboratories. Financing sources also came to involve sophisticated combinations, including venture capital, corporate investment, patient organizations, family offices, and public markets.¹⁰⁸

The Global Origins of Local Talent

Finally, the greater Boston area benefitted from a foreign-born population above the national average, which increased in the last decades of the twentieth century— from 13.1% in 1970 to 25.8% in 2000.¹⁰⁹ The relocation of Novartis' R&D headquarters to Cambridge in 2002 also

¹⁰⁷ Melanie Senior, "Family Offices Bolster Early-stage Financing," *Nature Biotechnology* 31 (2013) 473–474; Jessica Bartlett, "Kraft Group Participates in \$30m Funding for Cambridge Biotech," *Boston Business Journal*, 9 June 2015. It was noted that family offices that engage in such investments tend to be those that have billions or tens of billions, rather than hundreds of million or a billion dollars. Jack Reynolds, Interview by author, 7 December 2023.

¹⁰⁸ See also, Dennis Ford and Barbara Nelsen, "The View Beyond Venture Capital," *Nature Biotechnology* 32 (2014): 15–23.

¹⁰⁹ U.S. Census Bureau 2010-22 American Community Surveys (ACS), and 1970, 1990, and 2000 decennial census; and Campbell J. Gibson and Emily Lennon, "Historical Census

signaled the increasing presence of international pharmaceutical firms in the region – with foreign personnel. This influx of human capital featuring diverse ideas, perspectives and connections supported the growth of the sector.

The Cambridge-Boston universities had long attracted global talent. By the 1980s, this trend led Gabriel Schmergel, then CEO of Genetics Institute, to remark that access to international talent, along with foreign capital and markets, were key to the strengths of the field.¹¹⁰ The inflow of international students and researchers at flagship universities (Table 3) enhanced research caliber, cultivated an international workforce, and seeded immigrant entrepreneurs.

[Insert Table 3 here]

International talent had been integral to building the leading local biotechnology firms, such as Biogen (1978) and Genzyme (1981).¹¹¹ Admittedly, there was still limited entrepreneurship in the 1980s and much less so by immigrants. While the 1990 introduction of the H1-B visa program facilitated the hiring of foreign skilled workers who might become company founders, most entrepreneurs were mid-career, middle-aged white men who had

Statistics on the Foreign-Born Population of the United States: 1850 to 1990" (Working Paper no. 29, U.S. Census Bureau, Washington, DC, 1999), Table 23.

¹¹⁰ Gabriel Schmergel, "Technology Transfer: Biotechnology Industry Perspectives."

Technology and Society 8 (1986): 233–236.

¹¹¹ Inco Europe Limited, Report of Proceedings at the European Microbiology Conference II," March 25, 1978, Phillip A. Sharp Papers, Box 3, MIT Libraries Distinctive Collections, Cambridge, Massachusetts.

experience of senior-level management in large, established companies. As biotechnology firms came to play an integral role in therapeutic development, foreign-born managers and entrepreneurs assumed an increasingly prominent role in the sector, fueled by ideas, ambitions and tolerance for risk.¹¹² Noubar Afeyan, co-founder and CEO of Flagship Pioneering (established 1999), suggested that immigrants were more inclined toward innovation and entrepreneurship, as it constitutes “intellectual immigration.”¹¹³ Just as immigrant entrepreneurs made an outsized contribution to Silicon Valley high technology firms in the 1980s and 1990s,¹¹⁴ by 2006, 25.7% of founders in Massachusetts biotechnology firms were foreign-born, producing over \$7.6 billion dollars and employing over 4,000 people.¹¹⁵

Immigrant entrepreneurs not only founded firms, but also founded enduring institutions that reshaped the local innovation ecosystem. Genzyme’s Henri Termeer, for example, pioneered

¹¹² Cristina Csimma, Interview by author, 16 January 2024.

¹¹³ Don Seiffert, “Immigrant Entrepreneurs: They Get the Job Done,” *Boston Business Journal* 2 December 2016.

¹¹⁴ AnnaLee Saxenian, “Silicon Valley’s New Immigrant High-growth Entrepreneurs,” *Economic Development Quarterly* 16, no. 1 (2002): 20-31.

¹¹⁵ Immigrant Learning Center, *Immigrant Entrepreneurs in the Massachusetts Biotechnology Industry* (Malden 2007). The 2005-2007 American Community Survey indicated that the foreign-born population of Massachusetts was 14.2%. Alan Clayton-Matthews, John McCormack and Paul Watanabe, *Massachusetts Immigrants by the Numbers: Demographic Characteristics and Economic Footprint* (Malden, 2019).

the business model for orphan drug development during his decades at the firm's helm.¹¹⁶ Flagship's Noubar Afeyan introduced a business model of "institutional professional entrepreneuring," engaging in parallel – as compared to serial – entrepreneurship, based on platform technologies. Flagship also cultivated a "network insurgency"; a network architecture of interconnected companies that share novel biotechnology platforms, provide access to capital and talent, and have pushed the technological frontier.¹¹⁷ While the industry workforce remained less diverse than that of higher education into the late 2010s,¹¹⁸ diversity was regarded as a driver of strength in the local therapeutics business.¹¹⁹

Concluding Notes

This research traces how the Cambridge-Boston area evolved as the global center of the therapeutics industry. Adopting insights from the innovation ecosystem perspective, it examines how dynamic, multilateral interactions between complementary and co-evolving actors enhanced innovative capacity. This approach also illuminates how an extraordinary confluence of structural advantage, serendipitous timing, and strategic actions fostered an exceptional capacity to translate emergent technologies into novel therapies.

¹¹⁶ Annual reports such as Genzyme Corporation, *Annual Report*, Cambridge, 1995.

¹¹⁷ Noubar Afeyan, Interview by author, 4 January 2024.

¹¹⁸ Brady Huggett, "Biotech's Pale Shadow," *Nature Biotechnology* 36, no. 1 (2018): 20-30.

¹¹⁹ Jeremy M. Levin, Steven H. Holtzman, John Maraganore, Paul J. Hastings, Ron Cohen, Bassil Dahiyat, Julian Adams et al., "US Immigration Order Strikes against Biotech," *Nature Biotechnology* 35, no. 3 (2017): 204-206.

In fact, the rise of the Cambridge-Boston ecosystem often occurred at the intersection of such structural, temporal and strategic dynamics. For instance, the local therapeutics sector was built upon the institutional legacies of past innovation ecosystems, partly due to ongoing industrial decline over the 20th century. These legacies included the resources of world-leading universities as well as networks of collaboration (e.g., alumni, industry-academia). Local biotechnology firms were also proximate to pharmaceutical headquarters on the East Coast and Europe. Cambridge-Boston firms also benefitted from the cross-fertilization of knowledge arising from social and professional interactions or changing jobs within a contained geographical location.

Fortuitously, scientific breakthroughs, institutional change, and the development of risk capital unfolded in parallel. For instance, the biotechnology revolution unfolded as regulatory reforms were introduced in the 1980s, from the *Diamond v. Chakrabarty* ruling, the Bayh-Dole Act, the 1981 tax cuts, to the Orphan Drug Act. Such changes took effect alongside the emergence of research services firms and specialized and alternative forms of risk capital.

The convergence of structural advantages, historical serendipity and strategic actions generated a talent pool of globally-sourced, highly-skilled human capital as well as star scientists. The area had a high concentration of star scientists, who not only secured large grants, authored many publications, and pushed the technological frontier in interdisciplinary areas, but also founded multiple companies and mentored the next generation of star scientists.

The ecosystem perspective helped illustrate how therapeutic innovation resulted from complementary and co-evolving actors. Biotechnology firms not only altered the structure of

the therapeutics industry, but also created new networks of academic-industry collaboration. Universities enhanced technology transfer activities by restructuring TLOs. MIT's commercial orientation led academics to capitalize upon long-standing ties to industry or engage in entrepreneurship as well as form complementary collaborations with local universities and hospitals in pursuing the application of new technologies. Providers of risk capital also diversified over the years, comprising a community of specialist venture capital firms, pharmaceutical firms, patient organizations and family offices.

While the Cambridge-Boston area became an epicenter for novel therapeutics, business historians have shown that location-specific industrial prowess is impermanent and subject to change – whether from newer technologies, market shifts, or policy changes. Future research may consider how social challenges – from socio-economic inequalities to the displacement of long-standing residents and businesses – generated by ecosystem development may recursively reshape their evolution. Such studies could be enriched by cross-sectoral and comparative approaches.

The adoption of the innovation ecosystem framework helped deepen a system-level appreciation of industry development. Additional micro-level studies may provide further insights. The ecosystem perspective also helped illustrate the coevolution of actors' capabilities: of universities restructuring TLOs; of venture capital developing sector-specific specializations; or of academic scientists becoming entrepreneurs. Expanded archival work could advance insights into the co-evolution of technologies, actors and institutions.

Future research may engage in debates on the state's role in fostering innovation and knowledge-intensive industries.¹²⁰ Ecosystem actors regarded federal government as significant for basic research and approving therapeutics while they considered local government as important for enhancing livability – improving public infrastructure, from transportation to education. They did not regard government as central to commercialization, despite state funding initiatives or municipal research restrictions – as with recombinant DNA – that had affected business. Massachusetts, after all, was more an enabler of organic collaboration between geographically proximate actors: therapeutics firms, universities, hospitals, and risk capital providers. While California was similar, collaborative innovation centered less around hospitals, which were fewer and more geographically dispersed. Actors often indicated that other states – such as North Carolina or Texas – intervened more actively to foster industry development by creating research parks or generous incentives to attract companies via tax breaks, grants and business-friendly regulation. Yet, governments cannot forecast or orchestrate the development of emergent technologies, such as safe and effective cell or gene therapies. Future research may also consider how the relative significance of different levels of government, from sub-national, national, to supranational (e.g., European Union), have evolved in shaping the history of the therapeutic sector.

¹²⁰ Marianna Mazzucato, *The Entrepreneurial State: Debunking Public vs. Private Sector Myths* (London, 2013); Deirdre McCloskey, Nansen and Alberto Mingardi, *The Myth of the Entrepreneurial State* (Great Barrington, Massachusetts, 2021).