

Note to readers: Please do not be alarmed by the length. There is a 48 page Appendix. You may want to print only the paper itself, pp. 1- 66. We would, however, welcome reactions to the Appendix and thoughts on how and whether to present the case materials.

Chance, Necessité, et Naïveté: Ingredients to create a new organizational form*

Walter W. Powell

Kurt Sandholtz

Stanford University

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*The title comes from remarks by Genentech co-founder Herbert Boyer (2001: 95-96): “I think if we had known about all the problems we were going to encounter, we would have thought twice about starting. I once gave a little talk to a group at a Stanford Business School luncheon, and I took off on the title of a book on evolution by Jacques Monod...*Chance et Necessité*. The title of my talk was ‘Chance, Necessité, et Naïveté.’ Naïveté was the extra added ingredient in biotechnology.”

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Introduction

Where do new practices and models of organization come from? Of course, nothing is entirely new, so the obvious answer is that new things have lineages that are typically traced back through earlier incarnations and to the careers of individuals involved in their construction. Such tracing is indeed useful, but it can lead to either a frustrating, infinite regress, with scant analytical purchase, or undue attention paid to the role of inventors, without sufficient consideration of the surrounding context in which their creations occurred.

We pursue a different tack, focusing on components of new things and identifying the sources of separable parts, which can be moved, recombined, and translated by inventive humans. We want to account for how and when components are cobbled together. Sociologists of science and technology refer to this assembly process as “lash-up” (Law, 1984; Latour, 1987; Molotch, 2003), a label intended to capture how diverse elements become interactively stable. We are interested in which elements can or cannot fit together, and under what circumstances. Consider the combination of food and prayer. A mother who brings muffins to her Sunday school bible class combines breakfast and religious instruction, a combination that is commonplace. But a priest would rarely give a sermon at a formal Sunday dinner, as theology and fine dining are seldom mixed. Our goal is to ascertain which relationships and practices can crystallize into something definable and consistent.

We explore this process by examination of the creation of the earliest biotechnology companies. They were most unusual for their time, because they hewed to neither an industrial nor an academic model. They emerged out of the academy but

combined with practices from the realms of finance and industry to produce something new: a science-based firm. Through historical research, we chart the processes by which this development occurred in the late 1970s and early 1980s and identify the mechanisms that enabled it. In so doing, we show how careers, ideas, and organizational practices crossed significant boundaries and eventually congealed to produce a novel form of organization that had robust consequences.

In this chapter, we first introduce the scientific, political, and economic context in which the new industry was spawned. Then we present our ideas about processes of technological change and suggest mechanisms that explain how new models of organization develop. We follow with discussion of our data collection strategy for capturing the first wave of biotechnology companies, emphasizing that we include companies that failed as well as those that persisted. Just six of this original generation are alive in some form today, and only three are independent entities. Our analysis is aimed at characterizing the most notable organizational practices that sprang up at these early companies, whether out of necessity, inspiration, luck, or simply because the founders did not know any better. Not all of these initial ideas proved durable or productive, but out of a concatenation of alternative and novel means of organizing science, finance, and commerce, a new template for running a science-based company (i.e., a dedicated biotech firm or DBF) was assembled. We conclude with reflections on the consequences of these novel forms for the domains of science and industry.

The Invasion of the “Cloners”

Looking back today on the origins of the field of biotechnology, we might think that its growth and development was somehow ordained or predetermined. Science journalist Stephen Hall (1987: 21) captured the transformation and tumult that recombinant DNA research brought to the biological sciences: “It was like the microscope had been reinvented. Everything had to be reexamined, and the molecular biologists roared like Huns through other scientists’ turf.”

The breakthrough discoveries of the early 1970s attracted enormous attention. At the forefront of this research were scientists at Harvard, MIT, the University of Cambridge, the University of California, San Francisco (UCSF), and Stanford. The initial procedures for making recombinant DNA were developed by Stanford biochemist Paul Berg and his colleagues Peter Lobban and Dale Kaiser (Yi, 2008). At UCSF, William Rutter and his colleagues were at work isolating the gene for insulin. On the East Coast, Walter Gilbert’s Harvard lab was exploring chemical methods to identify the base sequences of RNA and DNA. In Cambridge, England, Frederick Sanger and colleagues were also determining the nucleotide sequences of genes.

Into this world of scientific fervor was introduced a cleavage between scientific recognition and legal ownership. Even though Berg, Gilbert, and Sanger would share the Nobel Prize in 1980, the legal award of invention was eventually assigned to two papers on the process for creating recombinant DNA. These seminal papers, written by Herbert Boyer of the University of California, San Francisco and Stanley Cohen of Stanford University, appeared in 1973 and 1974 (Cohen et al, 1973; Morrow et al, 1974). They were quickly followed by another path-breaking paper that laid the groundwork for

monoclonal antibody techniques, written by Georges Köhler and César Milstein (1975), at the Medical Research Council in Cambridge, England. In its consequences for economic development, the most fateful step was that the Cohen-Boyer papers were followed by patent applications, whereas the Milstein-Köhler work was not. Portending the potential impact of this research, Cohen (1975) wrote an article for *Scientific American* explaining DNA cloning techniques, and emphasizing their usefulness to basic science and commercial promise for synthesizing antibiotics, hormones, and enzymes.

Discussions of the prospects from human genetic intervention overflowed from scientific labs and conferences to the media, city councils across the nation, and to Congress. Scientists learned an alarming lesson – their own efforts to debate and regulate laboratory safety invited public scrutiny of their research. Controversies arose due to fears raised in the minds of the public as well as some scientists about the hazards of recombinant DNA research (Hall, 1987; Wright, 1994; Colyvas, 2007a). An April 18, 1977 *Time* magazine cover story entitled “The DNA Furor: Tinkering with Life” raised the prospects of great promise and considerable peril. The image of the mushroom cloud of the atomic bomb and the DNA double helix were frequently linked in the popular press. And in the late 1970s, at least 16 separate bills were introduced in Congress to regulate recombinant DNA research (Wright, 1994; Fredrickson, 2001). But even as these concerns were bandied about, recognition was growing that recombinant DNA was a scientific tool of enormous potential.

By 1980, many of the concerns about safety had been resolved or silenced, and the commercial, political, and social enthusiasm seemed boundless. The National Institutes of Health research guidelines issued in 1979 were far more permissive than the

original restrictive draft legislation of the mid-1970s. And the inviting label “biotechnology” came to replace a more ominous one of “genetic engineering.” A series of new government policies heralded a political sea change from a model of science based on the philosophy of the public domain to one championing ideas about proprietary ownership and control. These federal policies represented a deliberate Congressional strategy to alter the landscape of scientific production and innovation, and move universities out of the ivory tower and toward the market. A central component of this reconfiguration was a new alliance between industry and university. Federal policies such as the Bayh-Dole Act of 1980, the Stevenson-Wydler Technology Innovation Act of 1980, and the Economic Recovery Act of 1981 transformed university-industry relations by allowing universities to retain the property rights from innovations arising from federally funded research projects and mandating higher education’s participation in technology transfer. Empowered with new patenting capabilities, universities were assigned a central role in the capital accumulation process (Mowery et al., 2004; Rhoten and Powell, 2007).

In June 1980, the U.S. Supreme Court decision in *Diamond v. Chakrabarty* recognized for the first time the patentability of human life forms. Back in 1972, a General Electric scientist, Ananda Chakrabarty, had filed a patent on a living, altered bacterium that could consume oil, which might have proved useful to clean up oil spills. The U.S. patent office declined the application on the grounds that Congress had not passed legislation permitting products of nature to be patented (Kevles, 1994: 66). GE appealed the decision, and many years later it reached the Court. A growing backlog of more than 100 recombinant DNA patents, including the three patents associated with

Cohen and Boyer's research, awaited the outcome of the ruling. Even though this bacterium was created by conventional breeding methods and not through genetic engineering, and GE did not subsequently pursue the technology, the Supreme Court decision proved to be a landmark one. Edward Penhoet, former chair of the biochemistry department at UC – Berkeley and one of the three founders of the biotech company Chiron, reflected on the impact of the ruling: “if you couldn't protect this intellectual property, then people were not going to invest in this field” (Penhoet, 2001: 102). It was one thing to demonstrate that a new technology worked, but the Court decision now made it possible for the new ideas to be owned, traded, and licensed.

The Supreme Court ruling cleared the way for the first biotech initial public offering. On October 14, 1980, the young company Genentech had its IPO, which set a record at the time for the fastest run-up in stock price, rocketing from \$35.00 to \$89.00 in just 20 minutes. By day's end, Genentech – without a single product on the horizon – had a valuation of \$532 million, and its founders Herbert Boyer and Robert Swanson were fabulously wealthy. This spectacular success, coming in the midst of a steep recession, gave credence to the view that scientific research, infused with start-up firm spunk, could be a critical component of economic growth (Kenney, 1986a: 156-57). On the very same day, Paul Berg of Stanford received the Nobel Prize in Chemistry for his “studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA.” The other half of the prize went jointly to Walter Gilbert of Harvard and Frederick Sanger of Cambridge for “determination of base sequences in nucleic acids” (Press release, NobelPrize.org). It was a propitious day for biotechnology.

The new industry also benefited from changes in tax laws and the regulation of financial markets, which gave start-up firms wider access to equity investments. As anti-tax sentiment welled up across the country in the context of Carter-era stagflation, a bipartisan coalition in Congress cut capital gains taxes in 1978, with the hope that the wealthy would increase their investment in small business. Also in 1978, the Department of Labor issued guidelines for the re-interpretation of the Employment Retirement Income Security Act (ERISA), incorporating the insights of portfolio theory from the field of finance. Subsequently, in July 1979, the Prudent-Man Rule was applied to the entire portfolio of a pension fund, allowing institutional investors to bet a portion of their funds on the stock of high-risk, large-return ventures. This decision opened retirement funds and university and foundation endowments to the financial community for investment in new technology ventures (Berman, 2007, Ch. 4).

Clearly, then, the emergence of the biotech industry occurred in the context of a number of supportive economic and political changes. Obviously, the rapid development of the life sciences and molecular biology as academic disciplines was central, but increased federal funding for biomedical research, a more proprietary intellectual property regime, and the expansion of the pharmaceutical and healthcare industries and their particular modes of conducting industrial research were critical as well. Equally consequential was the emergence and maturation of venture capital organizations, and the growing public sense that established U.S. industries were losing ground to foreign competition, most notably the Japanese. There was widespread hope in both in the corridors of power and finance and in cities and communities throughout the country that new industries such as information technology and biotechnology would provide engines

for industrial renaissance. These broader structural forces turned over the soil for the emergence of biotech, but they did not determine the path of its development, most notably the organizational form in which this new research would be conducted or the places where such research and business activity would eventually be located.

Organizational and Technical Change

Many thoughtful analysts of this era have assumed that the economic opportunities created by biotechnology were transparent to entrepreneurs in the late 1970s and early 1980s, and that scientific advances had clearly opened up new markets for companies to exploit (Kenney, 1986b; Orsenigo, 1989; McKelvey, 1996). Seen in this neo-Schumpeterian view, the subsequent organizational transformations in both the academy and biomedical product development followed directly from this technological disruption. We want to challenge, or at least amend, this view in which technological evolution is paramount.

Without question, laboratory advances had outpaced commercial applications. Ron Cape (2006:16), a co-founder of the first bio-engineering company, Cetus, captured the pent-up feeling of the times: “It was like maybe a dam waiting to burst or an egg waiting to hatch, but the fact is, there were a lot of Nobel Prizes in molecular biology, but no practical applications”. But the process by which Nobel-quality science is translated into serviceable medicines is by no means trivial; nor does poisedness imply predictability. What retrospectively appears to have been a technologically-determined path was, we argue, the result of innumerable social and political choice points, each of which could have radically altered the field’s trajectory.

The foundational Cohen-Boyer patent, for instance, was nearly scuttled multiple times. First, consider that at Stanford University, today much celebrated for its successful technology transfer program, the Office of Technology Licensing (OTL) was established in 1968 as only a one-year pilot program; renewal was by no means guaranteed as faculty opposition to it was considerable. Second, had the OTL director, Nils Reimers, spent more time courting renowned DNA researcher Paul Berg, he would have run headfirst into Berg's opposition to patenting scientific research. Third, Reimers did not even know Prof. Cohen; instead he learned about recombinant DNA research from Stanford's news director, who had read about it in the *New York Times* (Reimers, 1987). Fourth, Cohen at first rebuffed Reimers; then he worried that his co-authors would not be included on the patent (Hughes, 2001). He was persuaded to proceed with the patenting of their gene splicing technique only once consensus was reached that any proceeds would be plowed back into research funding (Reimers, 1997; Colyvas, 2007b).¹ Finally, Stanford then had to decide whether to have an exclusive or open license for the patent. The OTL resisted the then princely offer of \$6 million from the pharmaceutical giant Merck for exclusive rights, opting instead for an open license on the principle that it was more in keeping with the standards of public science. Moving away from Stanford to the broader judicial context, the Supreme Court ruling in *Diamond v. Chakrabarty* that permitted the patenting of human life forms passed with a narrow 5-4 vote. Had any of these events (or countless others) played out differently, the biotech field may not have

¹ Cohen's initial response was: "Gee, this can't be patented. This is basic research. How can you patent basic research? And besides, it's dependent on all of these findings that have occurred in molecular biology for the past 15 to 20 years" (Chemical Heritage Foundation, 1997: 133). Herbert Boyer's immediate response when Cohen called him about Stanford's effort to patent their recombinant DNA technology was, "That's illegal" (Chemical Heritage Foundation, 1997: 126). Paul Berg also had a strong averse reaction to the patent idea: "Hey, wait a minute! I mean, where do Stanford and UC get the entitlement to this whole thing?" (Chemical Heritage Foundation, 1997: 129).

spawned a new industry; instead the scientific discoveries would have been harvested much more slowly by large multinational chemical and pharmaceutical companies.

Although the soil might have been fertile for the sprouting of biotechnology, there is little evidence to suggest that it was destined to develop in the organizational form that it did or in the specific places where it flourished. We return to the critical distinction made by Schumpeter (1939: 85) when he argued that “the making of the invention and the carrying out of the corresponding innovation are, economically and sociologically, two entirely different things.” He went on to suggest that “innovation combines components in a new way, or that it consists in carrying out New Combinations” (p. 88). A rich literature has developed in the ensuing years that analyzes how new combinations of previously existing components are forged (Henderson and Clark, 1990; Hargadon and Sutton, 1997; Fleming, 2001; Baker and Nelson, 2005). In addition, considerable work has identified how the prior affiliations of entrepreneurs shape the strategies they pursue when they move into nascent fields (Baron, Hannan, and Burton, 1999; Burton, Sorenson, and Beckman, 2002).²

We draw on these lines of work to examine the emergence of biotechnology, but depart by making a finer distinction about two types of recombination. To be sure, almost all novelty is “a recombination of conceptual and physical materials that were previously in existence” (Nelson and Winter, 1982: 130). We maintain, however, that it matters a great deal whether recombination occurs on a familiar terrain (e.g. an

² Beckman and Burton (2008: 3) document how Silicon Valley entrepreneurs “bring important experiences and make critical choices early in a firm’s history that leave a lasting imprint.” Others have focused on how the founders of spinoff companies inherit ideas and practices from their parent companies (Helfat and Lieberman, 2002; Chatterji, 2009). Klepper and Sleeper (2005) even employ a genetic metaphor, suggesting that entrepreneurs carry the organizational DNA from their parent firms into new ventures, producing offspring that, although not exact copies of the parent, still carry the same traits with some variation.

organization in the same or closely related sector or industry) or in an altogether new setting where the components are foreign. The movement of digital technology from computing to photography, or of an actor from Hollywood to Broadway, and even the current mash-up of the Internet, telephones, and video all represent innovative recombinations that import practices from one sector into a new one. The imported practices, however, remain recognizable. In contrast, some recombinations involve the movement of ideas and practices from one domain into another where they are alien and not initially recognized. We label these *transpositions*. For example, moving from the realm of science or religion into the world of commerce or vice versa represents a boundary crossing. Such leaps are much less frequent and less likely to be successful than recombinations that take place on “safer” ground. We expect, however, that even failures of this sort generate “fresh” action, which may be subsequently exploited by others.

In order to effect transpositions, individuals must violate institutional boundaries, repurposing old tools or recombining past practices in an unusual manner. Such people have been have been termed “moral entrepreneurs” or “rule creators” by sociologist Howard Becker (1963). Symbolic interactionist scholars typically refer to such rule creating activity as traffic across social worlds (Strauss, 1978; Fujimura, 1987; Clarke, 1991). Under such circumstances, participants create new social spaces and synthesize existing cultural practices in these unfamiliar circumstances, resulting in marked departures from the past (Rabinow, 1996). Yet, although such trespassings can have a revolutionary effect, transposition need not be radical in its intent. Padgett and McLean (2006), for example, show how the invention of the partnership form in Renaissance

Florence, with its unforeseeable transformative reverberations, resulted from the essentially conservative efforts of the ruling elite to retain power by coopting merchant-class bankers into local political positions.

We further suggest that the social synthesis that results from transposition is rarely deliberate, much less visionary. To be sure, such efforts entail considerable social skill (Fligstein, 2001), but they are best discussed in pragmatist terms. Hence, our theoretical ground does not come from work in strategy and entrepreneurship, but is derived from the ideas of the Carnegie school on premises and routines (March and Simon, 1958), and the microsociological insights of symbolic interactionists (Mead, 1934; Blumer, 1969; Becker, 1986) and ethnomethodologists (Sudnow, 1965; Garfinkel, 1967; Cicourel, 1968). Put simply, when the established routines for conducting everyday affairs prove limiting, people begin to search and experiment. In so doing, they draw on their stock of existing knowledge, both formal and tacit, and look around their social worlds for cues about appropriate steps. With this stock of information, they forge new tools for coping with situations without precedent.

The extant literature on organization founding tends to emphasize that entrepreneurs must work especially hard to mobilize the resources required to launch new organizations in new sectors (Stinchcombe, 1965; Freeman, Carroll, and Hannan, 1983; Aldrich and Fiol, 1994). Clearly, the resource aspect of the founding process is critical, but we depart from conventional wisdom by suggesting that the creative aspect of coming up with a new template in a new domain might be easier when the canvas has yet to be painted.³ One advantage that newcomers bring is that they are unencumbered by the

³ Brook Byers, the venture capitalist who was the early CEO of Hybritech, San Diego's first biotech company, recalled: "So we were naïve. I think if we had known everything about all the potential huge

baggage of established industry practices (Kaplan and Tripsas, 2008). This is not to say that newcomers are baggage-free, but rather that their baggage comes from their domain of origin, not the realm they are entering. Moreover, they may not even be aware of such baggage; it is taken-for-granted, an unquestioned part of their values, expectations, norms, and decision premises. But when transposed into a new domain, these ingrained *modi operandi* can afford startling possibilities for refunctionality and novelty.⁴

Of course, when identities are too diverse and diffuse, the emergence of a new collective entity is problematic (McKendrick and Carroll, 2001), and entities that span too many categories can suffer an “illegitimacy discount” (Zuckerman, 1999). Hence the conceptual puzzle: How are truly novel social forms created? As Johnson (2007) puts it, why are certain building blocks, but not others, incorporated into a new enterprise?

The people who built the commercial field of biotechnology lacked any formal blueprint for constructing a DBF, and yet each carried tacit blueprints from the domains they knew well.⁵ Scientists, financiers, and business people, drawing on their existing networks and prior skills, came together and managed to create novel organizational

competitors, we might not have even done it. One of the benefits we had, I suppose, was some combination of naïveté and ambition and this desire to do something on our own...I think there was a feeling of a green field, and that we were the first. We didn't know all the answers, but we had time to figure it out...” (Byers, 2006: 21-22).

⁴ In music, transposition means to rewrite or play a piece in a different key. When such transposition happens on the fly, as in any type of improvisational music, the musician plays a familiar piece in an unfamiliar tonal environment. This can have the effect of opening up new musical interpretations. Jazz improvisation, for example, always involves recombination. But suppose a jazz musician is asked to play “Take the A-Train” in E-flat instead of the customary key of C. Suppose further that the musician is not used to playing ‘A Train’ in E-flat, and yet she is used to playing other tunes in E-flat. This instantly opens up possibilities (consciously or not) for the crossover, melding, and exchange of musical phrases between the two previously separate domains. Licks and riffs that she tends to use in other E-flat songs are now automatically available for “A Train,” and embellishments she has made to “A-Train” in the past become available for future tunes that she plays in E-flat. The analogy is far from perfect, but it helps to illustrate the difference between recombination (within domains) and transpositions (across domains).

⁵ Brook Byers, VC backer and CEO of Hybritech further commented that: “We did not have the business model mapped out, or the ultimate value proposition, which are all things we do today in doing a start-up. We're much more sophisticated now. Back then, we didn't have any of that” (Byers, 2006: 22).

forms, obtain new sources of funding for biomedical research, and initiate pioneering work on diagnostic and therapeutic medicines. Some of the companies developed a business model that operated according to quite different principles from the traditional vertically organized corporate hierarchy. In time, a model of a science-based company was constructed, based on horizontal flows of information, porous organizational boundaries, a strong reliance on intellectual capital and collective know-how, and a strategy of pursuing innovation through collaborative ventures with other organizations, some of whom were even competitors.

No single early company had all of the elements of the eventual model; in fact, it is clear that few if any of the participants were aware that they were creating a new organizational form. Some, such as Amgen's George Rathman and Genzyme's Henri Termeer, were motivated by dissatisfaction with existing corporate constraints and practices. But most founders, such as Ron Cape and Peter Farley at Cetus, seemed determined to experiment with new conditions and rules. Others simply made it up on the fly, so to speak, inserting new tasks into the confines of existing settings until such arrangements no longer proved viable.⁶ One of the earliest firms, Genentech, which would later turn out to be a bellwether for the industry, was a virtual company for two years.⁷ Similarly, Biogen's first breakthrough came from the lab of one of its founders at

⁶ Hall (1987:9) captured this sense of excitement and ambition in his vivid account of the race to make insulin using the tools of genetic engineering. He observed that the new molecular biologists, especially the younger ones, "had the reputation of being opportunistic, of trespassing onto other scientists' intellectual turf in search of answers." They embraced the tremendous power of the new technology with "unconflicted fervor." A young West Coast biologist, Richard Scheller, commented to Hall (ibid.), "There was the thought that there were some real key questions and there were a few people who were going to answer them, and if you weren't one of them, then you were going to be left out."

⁷ In the first two years of its existence, 1976-78, Genentech had no labs or location of its own; instead it had contractual agreements with co-founder Herbert Boyer to pursue research on insulin and human growth hormone in his lab at UCSF and with City of Hope Medical Center researchers in Los Angeles to work on synthetic DNA (McKelvey, 1996: 99-107). Although some tensions arose over Boyer's starting a firm

the University of Zurich. Centocor began by licensing a patent for a monoclonal antibody developed by two of its founders at the Wistar Institute on the University of Pennsylvania campus. Genex's top scientist – a tenured professor at the University of Michigan – was finally persuaded to join the company full-time when he grew weary of constantly defending his “Frankenscience” from campus protestors. Common to all four stories is the tension created by new practices in old contexts. Goffman (1974) highlighted the process of framing, whereby individuals summarize complex situations into context-specific accounts that enable them to chart a new course of action. When then-current frames – the academic laboratory, the “garage” start-up, the industrial R&D organization – developed stress fractures from attempting to accommodate the odd contours of a fledgling biotech industry, founders had little choice but to create a frame of their own.

We are not arguing that the flatter, leaner, and more nimble biotech firms ultimately prevailed over established corporate hierarchies. Indeed they have not (Pisano, 2006). Far from streamlining the process of drug discovery and testing, many of the new firms stumbled through costly clinical trials and underestimated the challenges of scaling up for commercial production. Most DBFs ended up deriving the bulk of their financing from venture investments, public stock offerings, and partnerships with large pharmaceutical companies. Only a small number achieved profitability and successfully marketed new biomedical products on their own. Even though the array of new medicines developed with the tools of molecular biology is impressive, the number of failures has also been considerable. Instead of out-competing the industry giants, the new

inside the university, and an investigation was conducted by the faculty senate committee on rules and jurisdiction, the university administration viewed the relationship in conventional terms as an R&D contract and licensing agreement (McKelvey, 1996: 104).

biotech companies have frequently teamed with them in R&D collaborations, and many small companies had to give away their crown jewels in exchange for financial support. For the big firms, these arrangements provided options on new technologies that many were wary of developing in-house, whereas for the smaller firms the collaborations were necessary for survival. Moreover, when scientific and product development successes pushed biotech companies closer to profitability, these accomplishments often made them more visible targets for takeover by larger companies that were eager to expand their product pipelines.

Our concern here is not about the viability of specific small firms. We focus on the creation of a new organizational form, one that has become canonical with the knowledge economy. Out of necessity and naiveté, biotech's founding scientists, managers, and financiers improvised an organizational model whose principles were subsequently insinuated into the most unlikely of settings: the conservative corridors of the largest pharmaceutical corporations, and even back into the academy itself.⁸ Indeed, the recent reorganizations of biomedical research at almost every major research university have, to some degree, been spurred by the changes ushered in by DBFs (Jong, 2008). Moreover, the new biotech firms were not all commercial failures. Companies such as Amgen, Biogen, and Genentech brought important novel medicines to market, developed different means for conducting research and clinical trials, and reaped considerable gains in the process. But perhaps of greater import than such achievements was the manner in which they were organized. These firms thrived with fluid boundaries, fostering a model of basic and translational R&D that hinged on close interactions among

⁸ The changes sparked by this feedback are central to the creation of an "open elite," analyzed in Chapter 14.

university, government, and industrial scientists located throughout the world. Over time, this approach supplanted the formerly dominant model of a large, inwardly focused, hermetically sealed industrial R&D lab, as well as the entrenched disciplinary structure of traditional biomedical departments at research universities.

We are not the first to argue that biotechnology forged a recombination of scientific and commercial cultures, which led to the creation of new organizational practices and forms of discovery (see Powell, 1996; Rabinow, 1996). Our contribution is a detailed historical examination of the mechanisms by which traditional institutional boundaries and organizational barriers in both universities and large corporations were transgressed and redrawn. Biomedical research and drug development are inherently interdisciplinary; success is deeply dependent on the ability of organizations to bring together people from different academic backgrounds with those with experience in industry to conduct research and coordinate the work of science and business. The founding teams of the earliest companies embodied such cross-realm contacts, combining and mixing different academic and industrial rhythms and divergent registers of worth. The new spaces were created by trespassers, not by professional managers, university administrators, or government officials; the novel features of the DBF followed no established blueprint. We show that the critical dimensions of this organizational form were rooted in unprecedented recombinations and transpositions of conventions, practices, and bodies of knowledge of basic life-science research into the realms of venture finance and corporate management.

To be sure, the new biotechnology firms shared certain characteristics found in other high-tech industries in their ways of organizing research and development, and they

evinced parallels with consulting and professional service firms in fields as different as advertising and engineering. But none of the other available models from consulting, think tanks, or information technology encountered the types of financial and organizational challenges that biotechnology did. No industry in recent years has been as reliant on basic science for its origins and sustenance as biotech, and no other new-economy industry is subject to such extensive regulatory oversight or has such a lengthy product development cycle. As novel relations were forged between new biotechnology companies and research universities, high-profile scientists began to act as amphibious creatures, moving back and forth as consultants, advisors and as founders of university-spinoff firms. We highlight this process of trespassing, because those few who traversed the divides between university and industry science remade boundaries. Over time they received *both* federal research support and industry funding, and in so doing, not only recast the landscape of industrial research but altered the structure of scientific careers and the allocation of professional rewards.⁹

Data and Methods

Using archival and secondary materials, along with oral history interviews, speeches, autobiographical writings, and interviews, we reconstructed the founding stories of the first era of biotechnology companies. Our sample selection criteria were straightforward. First, we used notable science journalists and historical accounts of the

⁹ A number of studies have shown that many of these early amphibious creatures were “star scientists,” suggesting that their fame made it easier for them to move into these new habitats (Zucker and Darby, 1996; Owen-Smith and Powell, 2001; Stuart and Ding, 2006). Our historical research suggests that many nonetheless felt the pain of “arrows in their backs” from colleagues, experiencing scorn and innuendo from fellow academics.

origins of the industry to identify the earliest companies.¹⁰ Second, we drew on key industry analysts and government reports that followed the young industry.¹¹ Third, we reviewed a number of PhD dissertations that covered the history of biotechnology and its early participants.¹² Fourth, we consulted a database collected by Powell and colleagues to identify the firms with the earliest founding dates.¹³ Using this database, we created network maps from 1980 to 1988 of the initial collaborations among universities, pharmaceutical companies, financiers, and biotechnology firms, to ascertain which DBFs were most central.

The resulting sample is small. Only a handful of firms were created before the early 1980s; fewer still left a sufficient historical record to examine. We believe that the ones that quickly failed had little impact on the subsequent evolution of the field. Those that persisted a few years, we maintain, ultimately had outsized influence, as they provided a template for subsequent generations of biotech firms, as well as a model for new science-based firms more generally. The 11 companies that emerged from this selection process are listed below, with their founding year, location, and a short tagline capturing their *raison d'être*:

¹⁰ We found Kenney (1986a), Hall (1987), Teitelman (1989), Wright (1994), Robbins-Roth (2000), and Vettel (2006) to be particularly useful.

¹¹ For example, Burrill (2007) dates the inception of the industry to “circa 1973,” and notes the first generation companies were Alza, Cetus, Amgen, Genentech, and Biogen. Articles in the *New York Times* and the *Wall Street Journal* in the early 1980s routinely referred to the “Big Four” - - Cetus, Genentech, Genex, and Biogen. The U.S. Government Office of Technology Assessment produced a widely-cited 1984 report on the new industry, also identifying the earliest firms.

¹² For dissertations, Hybels (1994), Porter (2004), Jones (2005), Berman (2007), and Nelson (2007) were especially helpful.

¹³ These data provide the basis for the empirical analyses in Chapters 13 and 14.

COMPANY	FOUNDING YEAR	LOCATION	FOUNDING MODEL	CURRENTLY
Alza	1968	Palo Alto, CA	"A great place if it were a nonprofit think tank"	No longer in existence
Cetus	1972	Emeryville, CA	Academic playground or "Free Space"; biotech tools would be applied to a host of problems	No longer in existence
Genentech	1976	So. San Francisco, CA	"Best of both worlds": serious science and VC funding create a new model for basic research	Subsidiary of Roche
Genex	1977	Montgomery, MD	Low-cost producer: Apply biotech methods to the manufacture of industrial chemicals	No longer in existence
Biogen	1978	Geneva, Switzerland	Transatlantic network of world-class scientists	Biogen Idec
Hybritech	1978	La Jolla, CA	New diagnostic tools for the war on cancer	No longer in existence
Centocor	1979	Philadelphia, PA	Bridge between academia and commercial health care	No longer in existence
Amgen	1980	Thousand Oaks, CA	To become a FIPCO (fully-integrated pharmaceutical co.)	Independent
Chiron	1981	Emeryville, CA	"Get in or lose out": tired of losing top scientists to biotech ventures, UCSF dept chair starts his own	Subsidiary of Novartis
Genzyme	1981	Boston, MA	Niche collector: "Company of singles rather than home-runs"	Independent
Immunex	1981	Seattle, WA	Academics find a "pugnacious" entrepreneur willing to back "underdog" scientists	Subsidiary of Amgen

Conscious of the potential for survival bias in historical analysis, we find it notable that eight of the 11 firms in our sample have not survived as independent entities. Indeed, two of the earliest companies (Cetus and Genex) are portrayed in the literature as failures. Commercial success (or failure) is not central to our analysis, however. We are much more interested in the events surrounding each firm's founding, the prior experiences and contacts of the groups of founders, and the practices in which the companies engaged in. The firms exhibit considerable variation in their founding stories: from a serial entrepreneur who had just sold his packaging company and was looking for his next deal (see Genzyme in Appendix, pp. 100-105), to an all-star collection of academic scientists determined to manage their company as a transatlantic research seminar (see Biogen in Appendix, pp. 75-81), to seasoned venture capitalists assembling

an ideal venture to capitalize on the “next big thing” (see Amgen in Appendix pp. 70-75). We do not view these companies as but the lengthened shadow of a few men; our interest is in identifying the mechanisms that forged novelty.

Capturing the particularities of each company’s birth required extensive analysis of archival sources, supplemented by semi-structured interviews with company founders to fill in gaps in the historical record. Of primary interest to us were direct statements by members of each company’s founding team regarding their motives, circumstances, and organizational ideas, both pre- and post-founding. A collection of oral history interviews from the Bancroft Library at UC Berkeley was particularly fruitful; we digested more than 1,800 pages, gleaning insights from the scientists, entrepreneurs, venture capitalists and earliest employees of the first biotech ventures. We also gathered transcribed interviews with biotech founders from the Chemical Heritage Institute, the Smithsonian Institution, and the San Jose Tech Museum. Public information was sparse for three of the companies on our list. For each of these companies, we conducted interviews with at least two of the founders, thus enabling us to cross-check individual perceptions and recollections against those of at least one peer. These interviews lasted between 45 minutes and two hours; all were recorded and transcribed, generating about 150 additional pages of interview data. In all cases, the interview transcripts were reviewed, edited, and approved by the respective informants.¹⁴

¹⁴ To guard against post-hoc impression management, we triangulated accounts from the interviews with real-time archival data, such as company press releases, IPO prospectuses, newspaper and magazine articles, and numerous books written during the mid-1980s on the burgeoning biotech industry. Here again, we sought direct statements from company founders. This allowed us to corroborate their recollections in recent interviews with statements recorded during the time period in question, with the aim of minimizing retrospective bias.

Over the course of twelve months, we integrated the data from interviews, oral histories, and archival sources to create case histories of each firm's founding. Concise summaries of the founding stories for each firm are presented in the Appendix, along with a list of all sources used to generate the cases. We analyzed the founders' backgrounds, their roles in the start-up, and the unique practices each company pursued. We searched for similarities and noted salient differences (Eisenhardt and Graebner, 2007). We turn now to a discussion of these practices, but to set the stage, we note here an unexpected outcome of our multi-case analysis: With the exception of Alza – a precursor, really, of the DBF – the 10 firms in the sample divided evenly into two categories, which we label science-centered and commerce-centered variants of the DBF.¹⁵ The former represent movement of practices into an unfamiliar domain; the latter exemplify mixing of ideas from different commercial settings.

Distinctive Elements of the Earliest Firms

Our goal is to account for the origins of the dedicated biotech firm, discerning its diverse sources and explaining how the various elements crystallized. To do so, we culled from the case materials the distinctive organizational practices that characterized

¹⁵ Of the 11 companies, 10 should be considered new (or *de novo*) entrants. They were formed for the express purpose of pursuing commercial applications of biotechnology and did not rely on any preexisting corporate structure to do so. Only Alza is a lateral (or *de alio*) entrant as it moved from the pharmaceutical world of drug delivery into biotechnology. Research has examined how these two types of entrants differ with respect to performance and survival prospects. The general argument is that *de alio* firms are likely to pursue incremental innovation that builds on existing know-how, whereas *de novo* entrants are more likely to generate radical innovations (Anderson and Tushman, 1990; Henderson, 1993; Christiansen and Rosenbloom, 1995; Tripsas, 1997). On the other hand, prior experience and vastly greater resources are likely to result in *de alio* companies having a lower mortality rate than start-ups (Carroll et al, 1996; Klepper and Simons, 2000). In the biotech field, many established pharmaceutical companies initially took a wait and see approach (Gambardella, 1995), thus the number of diversifying incumbents was quite low in the early years (Wright, 1994; Zucker and Darby, 1997). Over time, once the large pharmaceutical firms no longer reacted defensively and made the choice to transform their technological identity, huge resources were mobilized to do so. (We discuss this transformation in more detail in Ch. 14). Amgen represents an interesting illustration of this contrast, as its first CEO left a large pharmaceutical firm (Abbott Labs) to join Amgen. In an effort to retain him, Abbott offered to set up a biotech subsidiary, which he declined.

each company, and sorted them according to the three domains – science, finance, and commerce – from which they were borrowed. All of the early companies combined, to differing degrees, resources, personnel, and practices from the academy, venture capital, and the established pharmaceutical and chemical industries. But they varied markedly regarding which elements they used; moreover, as the components were imported and melded in a new setting, they were transformed by their insertion into a start-up firm context and assemblage with other unfamiliar parts. We begin with a discussion of the individual elements, distilled from the case histories we have done. These distinctive features are summarized in Table 1. The companies are listed chronologically by founding date, with Alza in 1968 the first, followed by Cetus in 1972, and then a host of companies from 1976 to 1981.

[Table 1 here]

Several attributes are common to nearly all of the companies; the most universal is backing from venture capital firms. In terms of financing, this is a group of “classic” start-up firms that burst onto the scene with the support of VCs. Venture capital was still a cottage industry in the 1970s (Gompers, 1994). VC firms had become an established presence in Silicon Valley, but were very much a small circle of insiders, mostly successful past investors in electronics companies, with their headquarters on Sand Hill Road in Menlo Park, CA (Kenney and Florida, 2000). Kleiner & Perkins was the first VC firm founded by partners who came from the world of operations and management rather than pure finance; both Gene Kleiner and Tom Perkins had engineering backgrounds. It was Kleiner and Perkins who led VC investors into biotech. The first biotech IPO was Genentech’s in 1980, and soon thereafter other companies followed suit.

To be sure, many of these companies had initial public offerings out of desperation, with Amgen being perhaps the most notable as it was running low on cash with no research breakthroughs, revenues, or products in sight (see Amgen in Appendix, pp. 70-75). The success of Genentech's IPO spurred Amgen to turn to the public equity markets in hopes that they would realize "gene dreams" as well.

The marriage of venture capital and cutting-edge research in molecular biology is best typified in the long-term relationship between Kleiner Perkins and such companies as Genentech and Hybritech. In the case of Hybritech, Kleiner Perkins partner Brook Byers became the CEO of the new venture. With respect to Genentech, Perkins (2002: 24) recalls that it was "the most important deal" of his life:

What was so different about Genentech was the astonishing amount of capital required to do all of this. I know, on day one, if anyone had whispered into my ear that, "for the next twenty years you will be involved in raising literally billions of dollars for this thing," I might not have done it. But in 1979, it occurred to me that for something of this importance, that there was enough money out there for us to do whatever we needed to do. I always viewed my role - my ultimate responsibility - was to make sure that the company didn't run out of money. That was my job. [Genentech co-founder Robert] Swanson's job was to make sure the company deserved more money, at ever increasing prices. We both had a pretty clear notion of that. It worked for a long time. Hence, all the different things that we did - the private rounds, the research partnerships, the public rounds, and all the deals. It was always more capital than I anticipated. It dawned on Swanson before it dawned on me. I can't remember at what point it dawned on me that Genentech would probably be the most important deal of my life, in many terms - the returns, the social benefits, the excitement, the technical prowess, and the fun. By 1979 I was a total Genentech junkie. I was committed to making Genentech into a huge success. I had signed on for the long haul pretty early.

The second common attribute was the use of research contracts with large pharmaceutical companies, a practice used at all but two of the companies. The two exceptions - Centocor and Genzyme - pursued strategies that were less research intensive, focusing more on the commercialization of existing breakthroughs rather than the pursuit

of new ones. For most fledgling biotech companies, however, such contracts were a financial necessity. The founders quickly realized that new biotech products would take many years to bring to market, and in the meantime they desperately needed sources of cash. Cetus pioneered the use of research contracts, agreeing to deals early on with an eclectic mix of partners - oil companies, distillers, cosmetic makers, soft drink bottlers, and drug companies. Genentech, Genex, Biogen, and Amgen cast similarly wide nets initially, but subsequently aligned their portfolios of research partnerships with much clearer scientific direction. Genentech honed this practice by developing the idea of a milestone payment, which was a form of incremental financing based on money in return for demonstrated research progress.

The origins of the “research for hire” mentality are easy to trace. Ever since the post-World War II boom in government funding for basic science, successful academic scientists had grown adept at the pursuit of government grants. For the scientific founders of the early biotechs, the idea of outside funding for one’s research program was well established (Kenney, 1986). They merely substituted venture capital and corporate R&D partnerships for government grants. Genentech pioneered by treating the corporate support very much like a multi-year research grant. Indeed, for the scientists at the early companies, securing corporate funding may have involved less rigmarole than applying for federal grants. From the corporate perspective, however, this model of R&D funding did not fit tidily into traditional customer-supplier-competitor categories. Many large companies were deeply challenged in dealing with research funding for multiple start-up companies and even more befuddled by trying to establish relationships with star

scientists who had limited understanding of, and even less interest in, corporate organization.

A third widely shared attribute relates to what we earlier termed “amphibious” scientists. In six of the eleven companies, one or more of the academic founders either retained his faculty position while consulting with the new venture or temporarily moved out of the academy only to return later. Companies such as Chiron and Biogen had both types of amphibious founders. And four of the five companies without amphibious founders featured high-powered scientific advisory boards staffed by renowned academics, whose exclusive consulting arrangements and generous stock options made them semi-amphibious as well. This is not to say that straddling domains was easy. On the contrary, scientists associated with the earliest biotech firms - Donald Glaser at Cetus, Herbert Boyer at Genentech, David Jackson at Genex, Ivor Royston at Hybritech, and Wally Gilbert at Biogen - endured the frowns and skepticism of many of their academic colleagues, and some were subjected to formal university investigations of impropriety. Despite any professional discomfort, however, the fact that such accomplished scientists were associated with these new commercial ventures provided a conduit of ideas and values between unfamiliar domains, which later evolved into an accepted, indeed valued, career path for many younger scientists.¹⁶

If the amphibian image implies the ability to toggle between diverse domains, other new career paths represented more a fusion or melding of domains. Note in Table 1 that many of the founding scientists went on to become either serial entrepreneurs or

¹⁶ The fault lines between the academy and industry had long been drawn on the principles of openness and autonomy. The academy was purported to be much less constrained in the allocation of scientists’ time and attention. The new biotech firms challenged these conventions, by offering relief from the burdens of grantsmanship, committees, and teaching, as well as access to exciting new research tools (Kornberg, 1995). Cetus was described as a “playground for academic scientists” (Glaser, 2006: 105).

investors in subsequent bioscience ventures. The combination of scientific stature and start-up experience evidently proved to be both seductive and marketable; the financial independence gained from their first efforts was of course a stimulus as well.

Although clusters of companies shared particular elements, some organizational attributes were unique to individual companies. Centocor was the sole practitioner of its bridge model of business development: find an unlicensed scientific breakthrough, buy the rights to it, develop it into a diagnostic kit for use on existing diagnostic hardware in clinics and hospitals, then sell the kits through the hardware's distribution channels (see Centocor in Appendix, pp. 81-84). Genzyme's focus on orphan drugs - treatments for rare but deadly diseases - likewise attracted few imitators as other biotechs went after blockbuster drugs for major unmet medical needs (see Genzyme in Appendix, pp. 100-105). For both Centocor and Genzyme, however, their unique strategies led to predictable cash flow and even quicker profitability, but failed to find traction in a nascent industry culture bent on curing the incurable through cutting-edge science.

Among the early companies, only Genzyme and later Amgen would attempt to grow by acquiring other biotech companies. Chiron was founded by noted academics, very much in the vein of Genentech and Biogen, but with a twist. The academic heads of Chiron had been department chairs and deans at UCSF and Berkeley, and they felt that the skills of running large laboratories and managing departments could be translated to a start-up firm. In almost every other case, the professors who were founders of start-up companies did not seek the role of top manager. Chiron and Genzyme were alike in that they were initially bankrolled with the migration of a research grant from a university to the company.

Looking at the distinctive elements of each company in chronological order, we see no apparent pattern of temporal accumulation. Nor is there a pattern of regional similarity. It is not the case that West Coast companies resembled each other more but bore less resemblance to their East Coast counterparts. And though the sample is small, there is little sign of a “founder’s effect.” Companies whose founders had comparable prior experiences developed in quite divergent ways.¹⁷ Instead of a temporal, regional or biographical clustering, the attributes appear to cleave with respect to how deep the respective imprints of science and commerce were.

Two Variants of the DBF Model: Science vs. Commerce

To explore this distinction between start-up companies that fused science and finance with those that forged commerce and finance, we compare the firms in terms of important attributes that are common to two or more of the companies. Our analysis of the archival and interview materials point to a handful of widely shared features that DBFs borrowed or adapted from the academy, industry, and venture capital. These twelve attributes and their distribution across the companies are presented in Table 2.

[Table 2 here]

After sorting the companies on each of these twelve attributes, a distinctive pattern emerged. Three of the four elements on the science side cohere, most notably: a strong insistence that newly hired scientists be allowed to publish and contribute to public

¹⁷ For example, Amgen and Hybritech were very similar in founding team characteristics: a well-regarded younger stellar scientist, top-drawer venture capital backing, and an experienced pharma exec in charge. But Hybritech opted for quick growth with monoclonal antibody diagnostics and was bred for sale to big pharma, whereas Amgen swung for the fences to develop novel therapeutics and become a stand-alone company. Genex and Immunex were also alike in their respective founders’ backgrounds, but opted for completely different strategies - Genex chose a highly commercial, low-cost route of producing specialty chemicals and Immunex went for developing first-to-the-world medicines. In contrast, Biogen and Chiron were similar in having strong scientific credentials in their top leadership, and neither allowed much room for commercial input in their early years.

science, a campus-like setting near a university, and a founder who retained his university position,. The firms that displayed these attributes most clearly were Cetus, Genentech, Biogen, Chiron, and Immunex. The all-star, high-profile science advisory board was more common to the commerce-oriented firms, who flaunted such boards as a signal of their credibility but did not display the same commitment to letting scientific considerations shape the organization of their respective companies. At the other end of the spectrum, there is another group of start-ups where science features were less prevalent; instead, they all borrowed elements from the world of commerce, including having a founder with a prior business track record and choosing an experienced senior executive from the world of health care to run the company. Often, a restless senior manager was persuaded to leave a second-tier pharmaceutical company and take the risk of being the top executive at a new biotech firm.¹⁸ With this group of companies, scientific founders left their university positions and often went on to become serial entrepreneurs, starting numerous companies. Most of these companies opted initially to pursue non-therapeutic products, rather than new medicines, in order to have consistent and predictable sources of revenue. The examples here include Genex, Hybritech, Centocor, Amgen, and Genzyme.

We want to stress that we neither view these combinations as an either/or choice of models nor believe that the founders had a clear template in mind. Rather the distribution of elements in table 2 is best viewed as a continuum, ranging from the “pure”

¹⁸ Interestingly, the execs who took the leap from pharma to take the helm of an unbuilt ship did not come from industry giants such as Merck or Pfizer, but instead from Abbott and Baxter. These were second-tier companies organized into entrepreneurial divisions where general managers had considerably more autonomy than in the more hierarchical giant firms (Higgins, 2005). Abbott ended up providing a pipeline of managers to Amgen as well as a successor CEO to Biogen, and Baxter a cadre of senior managers to both Genzyme and later Biogen, replacing its scientist founders.

domain of science to the “pure” domain of commerce. Finance was blended into both, with the largest imprint on Genentech and Hybritech. We think the various combinations of elements predisposed the participants to act in different ways as a result of their prior experiences as well as pragmatic responses to new opportunities. Note, in particular, that the science cluster drew less on commercial elements than the commercial cluster built on scientific practices. Unlike in traditional technology startups, where once scientific research spawns technological applications, those technologies follow a trajectory that is largely independent of university science, the entire field of biotechnology has drawn on and collaborated with university-based research and depended on basic science for continuing input (Powell, 1996).

The commerce-driven companies were clearly more “orderly,” in contrast to the “bet the farm” blue-sky approach at the science-dominated companies. Amgen was perhaps the most planned in advance, as experienced venture capitalists set out to “do biotech right” by both recruiting a stellar scientific advisory board and putting a talented, well-regarded pharmaceutical executive in charge. Amgen went on to become the largest biotech firm. Similarly, Hybritech and Centocor had reasonably deep prior founder experience from both the pharmaceutical industry and venture capital. These firms were eventually purchased and absorbed by pharma giants Eli Lilly and Johnson & Johnson, respectively. The fit between the commerce variant and the pharmaceutical world is fairly clear; the disjuncture between the science model and the large company ethos is vividly illustrated with the case of Biogen.

Consider the contrasting portraits of Biogen co-founder and Harvard professor Wally Gilbert, given by veteran pharmaceutical executive Hugh D’Andrade and science

journalist Stephen Hall. D'Andrade was an attorney for Ciba-Geigy from 1968 to 1981; he joined New Jersey-based pharma giant Schering Plough as Senior Vice President in 1981. He served as Schering's representative on Biogen's board for six years, overseeing their joint interferon project. He described going to the Biogen scientific board meetings in Geneva:

There would be a two-day scientific board meeting before each board meeting. Two full days. They were real events....Somebody would get up and make a presentation, and then Wally Gilbert [chair of the science board] - - I don't know whether Wally tried to humiliate; I couldn't read his mind. And being a non-scientist I couldn't appreciate exactly what was going on. But it looked like the guy presenting wasn't having a lot of fun! Charles Weissman [head of the Zurich lab] is a gentler soul, but could be pretty tough. They'd have the lab scientists present...and members of the scientific board would go at them, and then go at each other. So it was very, very rigorous (D'Andrade, 2001: 8-10).

From a corporate lawyer's perspective, the science board meetings looked like the Grand Inquisition; moreover, they trumped the board of directors meetings in importance.

To a science journalist, however, Gilbert cast a different image:

To his peers, Walter Gilbert possessed a most desirable array of scientific traits: great intellectual curiosity, rigorous scientific standards, a rich imagination, and a lust for understanding the way life worked in its most microscopic and, in many respects, most intricately beautiful manifestation. "I'm driven by just an intense curiosity," he [Gilbert] would say, his very self-explanation riven by a kind of driving impatience. "I love new things, new ideas, new facts. It goes along with a tremendous impatience. It's very nice to have the old things, but a week or so later, they're all old hat, and you want something new." His was a pursuit of correctness, a kind of intellectual high ground, so focused and astute that temporal distractions - like a caviling colleague - intruded at some peril (Hall, 1987: 29-30).

Different interpretations of intellectual jousting carry over into disparate views of how laboratories should be organized. Hall is attracted by spontaneity and intensity, and

D'Andrade somewhat alarmed by disorder. Hall (1987: 36) describes Gilbert's Harvard lab in this manner:

The atmosphere in Gilbert's lab reflected the personality of the leader in two important respects: the craving for information was immense, something akin to physical need, and the tone of the place was casual, almost fiercely informal. Graduate students would drift into the lab around noon..., and often work until the wee hours of the morning or on through the next day. There would be mass excursions to the local Szechwan restaurant for meals, or sandwiches grabbed on the fly. DNA would be chopped and mixed and analyzed to the sounds of Joni Mitchell and the Rolling Stones. At about three or four a.m., the stereos would turn up very loud. People would be working madly.

In contrast, D'Andrade (2001: 10) felt that Biogen, with its amalgam of seven top-tier science labs located at elite universities, was "an organization in constant conflict and turmoil. Because the work was all being parceled out..., there was no centralized decision-making structure. There were no regular interactions, other than the scientific board, that would allow the scientists to coordinate their actions, and there was no executive authority."

These differing accounts nicely capture the "classic" competing goals of science and industry. Inside Gilbert's lab, the paramount concerns were novel information and speed, guided by both intense curiosity and skepticism about any answer. To a seasoned pharmaceutical executive, this looked like a disorderly debating team, lacking coordination and authority. As a result, resource allocation decisions and project investments were difficult to make. D'Andrade (2001: 12) clearly thought that oversight was needed, and he chafed at the operating model transposed to Biogen. "Biogen's unique organizing concept when it set itself up was that it was run by its scientists, not by the venture capitalists or the banks." He felt that Amgen beat Biogen to the release of the earliest biotech medicines because it was able to use "brute force," that is, it was

“hierarchically structured and the executives had the scientists in the lab,” not the boardroom. D’Andrade (2001: 16) recognized the promise in the Biogen model, however: “I don’t know how anybody could have spent as much time as I did with people like Wally Gilbert, Charles Weissman, and Phil Sharp, and not be convinced that they were going to be successful. They were just extraordinarily intelligent people, with more energy and drive than most corporate executives have.”¹⁹

The pharmaceutical-biotech contrast also comes through in discussions of publishing scientific results, which is perhaps the most central divide between the science model and the commerce variant. In the pharmaceutical industry, the open science model of publishing scientific findings was largely eschewed, as freely sharing research was regarded as giving away the crown jewels. Concerns about appropriability and intellectual property took precedence over open science. As a consequence, pharmaceutical scientists were career employees, typically staying with one firm throughout their lives, unless they opted to move out of the lab into management, where they might build up a track record of accomplishment that would bring them recognition and capture the attention of other companies. Even those scientists who received some recognition by having their name on a crucial patent did not have the kind of currency that would generate attention in the world outside of the large corporate R&D lab. Salaried researchers at big pharma assumed little personal risk; in return for their efforts they received well-compensated, steady employment.

¹⁹ Later in the interview, D’Andrade (2001: 21) was asked about biotechnology in New Jersey. “I associate pharmaceutical companies with New Jersey, but not biotechnology. The Biogen way of organizing things demonstrated that the people with the techniques to do this early cloning were in universities. You could have gone to every pharmaceutical company in New Jersey and you wouldn’t have found a Wally Gilbert.”

Genentech, nurtured for its first two years in Boyer's UCSF lab, broke the mold on restricting publishing, transposing the academic invisible college model into the new company as it moved into its South San Francisco headquarters. Co-founder Bob Swanson (2001: 56-57) commented that: "it was always clear that we were going to publish our results. Everybody wanted to publish in *Nature* or *Science* or another good journal, and so what we did had to be of a quality that would be published." Here science and intellectual property were put to joint use. Again, Swanson is on point: "So we said, look, let's publish the results; let's make sure we get the patents, and we'll make the patent attorneys work overtime to get them filed before you actually get the papers out. But we'll have to work together on that."

Genentech bet that they could create an alternative to both the academic world and the corporate sector, a setting with more autonomy and opportunity than both. Like industry scientists, their early hires would not have the academic concerns of writing grants. Unlike pharmaceutical or academic scientists, they had a chance to be owners of the enterprise.²⁰ They were given equity, and as the company thrived, the value of their stock went up. Such financial opportunity was quite appealing to young scientists at the

²⁰ Running through many of the interviews with scientists who moved to biotech labs is the sense that working in these companies was more fun than the academy. David Martin, a professor of medicine and biochemistry at UCSF and a prestigious Howard Hughes investigator, initially declined offers to move to Genentech but after giving a seminar there, was hooked: "There was a rather broad camaraderie. Everybody was working on the same team, rather than in a series of fiefdoms. I realized that my career opportunities at UCSF, while pretty clear-cut, were not very exciting. At Genentech, however, the opportunities to break out of the mold were tremendous" (quoted in Van Brunt, 2000: 3). Martin was cautious, worried that the move would be irreversible. He consulted with colleagues, program directors at the NIH, and even the Howard Hughes people, all of whom encouraged him to "give it a whirl," saying they'd welcome him back. He joined Genentech in 1983, and never returned to academe.

postdoc and assistant professor career stages. At the same time, publishing was a channel back into the world of university science.²¹ Swanson (2001: 57) commented that:

Boyer's philosophy, which I agreed with, was that you gain more from interaction with your academic peers than you give up by telling the competition where you are. So with interaction you can move quicker; you gain more people willing to collaborate with you. We knew then we weren't going to have all the best ideas, and we said, where do the academic scientists go when they have an idea that they think needs to be commercialized? We want them to come to Genentech first, because this is a group of scientists that are well published and that a university scientist would be proud to collaborate with, where they can get a product developed and make it available. So that was a goal from the very beginning.

In contrast to Genentech, Genex made a deliberate decision not to permit its scientists to publish, choosing to pursue more applied work. This strategy was adopted even though its scientific co-founder was an esteemed senior scientist at the University of Michigan, and co-author with Paul Berg of Stanford on a famous 1972 paper, which described a new method of generating hybrid DNA molecules using a complementary extension to form a new duplex DNA molecule that could be expressed in mammalian cells (Jackson et al., 1972). We spoke with David Jackson in August 2009, and he evinced some regret about their prohibition against publishing.

We did make a decision that was different from what Genentech made. They made a deliberate decision that they wanted their people to publish and that they were going to support them and deal with the intellectual property issues that arose, either, hopefully, proactively but if necessary reactively. And I have come to think that Genentech's way is the right

²¹ We have highlighted both chance and naïveté, but necessity also loomed large in forging these new companies. Axel Ullrich (2006: 22), one of the first-generation cloners who subsequently cloned insulin, moved from a post-doc at UCSF to Genentech with great trepidation: "How could we know what Genentech would be? Essentially, we made it what it is. And that was made out of concern. The reason Genentech became such a major power in basic research is because of people like me and Peter (Seeburg). We were worried that if we started doing commercial research we would have problems returning to academia if things wouldn't work out. We were discriminated against at that time. We thought that if we (did) all this applied stuff, we couldn't publish. It would be terrible. We would never get a job if the company failed. If it turned out that this whole thing would never work, we would be in the streets. So we had to publish."

way. I think it does help one recruit to let people who you're trying to hire know that they will be able to continue to publish. I think science is such a collaborative and communicative enterprise that you really do need to be connected to a broad, effectively world-wide, community. And the way you do that is by telling people about what you're doing that they're interested in, and you talk to them about what they're doing that you're interested in, and in the long run, everybody benefits from that.

Immunex, the Seattle-based company that spun out of the Fred Hutchinson Cancer Center, also went the science route, encouraging its scientists to publish freely and collaborate with others in the new field. In an August 2009 interview, co-founder Steve Gillis reflected to us on the relational benefits of publishing:

We encouraged scientists within the company to publish their findings and speak at meetings. We made reagents freely available to investigators who wanted to play with things that we had invented; again, we weren't totally stupid about that, we had them sign material transfer agreements. But that resulted in spreading the influence of the company, and allowed us to get collaborators who otherwise might not have been open to collaborating with us, because we had this relatively open relationship with academia.

I'd also say it was interesting that Genentech, who was obviously the pioneer biotech company of all, would publish in their annual report the number of times their articles were cited by other scientists. They would have a graph of how many times Genentech scientists were cited versus other companies. And they were proud that they were always in a leadership position. But we were always either second or third. That was something that gave us pride, and, believe it or not, in the early days, Wall Street analysts looked at that, too. Obviously, those days are long gone.

The divergent approaches to publishing scientific results underlie the distinction between the features of the science and commerce variants of the DBF model, which we summarize in Table 3. The science model is research driven, with elite scientist founders who move freely back and forth between their universities and companies. The model for these companies was the interdisciplinary biomedical research group at UCSF, assembled by William Rutter, who later became a co-founder of Chiron. As department

head, Rutter approved Herbert Boyer's early engagement with Genentech. In each of these science-based companies - Cetus, Genentech, Biogen, Chiron, and Immunex - practices of the academy were transposed to the start-up context, extending even to governance, product development, and financing.

[Table 3 here]

The commerce model builds on an alternate framework, with management in the lead role and science brought on board, though more as a passenger than driver. In these firms - Hybritech, Centocor, Genex, Amgen, and Genzyme - important science was harnessed but an academic ethos was not adopted. Publishing was not encouraged; the scientific advisory boards provided a seal of approval but did not dictate or set business strategy. Venture capital financing was tied to market and product opportunities, not to proof of principle or milestone payments as scientific progress was realized.

The commerce-centered variant of the DBF was a recombination, mixing elements of corporate division management, translational science, and traditional venture capital backing. Even though academic scientists may have had a hand in starting these companies, seasoned pharmaceutical executives soon took the reins and directed the development. The scientists-founders did not retain their academic positions; instead they moved on to start numerous subsequent biotech firms.

We are confident that the distinction between the science and commerce ends of the continuum captures distinctive combinations of attributes associated with the earliest firms. Nonetheless, we take a further step to test whether these initial differences were influential in the subsequent behavior of the two groups of firms. If science was indeed the core identity of the science-centered firms, then their record of scientific publishing

should be both more voluminous and of higher quality than their commerce-centered counterparts. To test this hypothesis, we first searched the ISI Web of Science® database for all scientific publications with at least one author who was affiliated with one of the early companies in our sample. This produced a publication count for each firm for the 10 years following its initial public offering. The IPO year, rather than founding date, is used because one could argue that firms might have published to capture Wall Street's attention, but stopped doing so after they went public. Hence this is a stricter test. The publication counts are used to generate a citation analysis for each firm, showing how many times the publications authored (or coauthored) by their scientists had been cited. The total citation frequency and "h-index"²² for each firm is reported in Table 4. We then grouped the firm-level results and conducted a one-tailed t-test to determine whether the differences in publication frequency and quality were statistically significant. In every case, the differences between the two models were significant at the $p < 0.05$ level or higher.

[Table 4 here]

Having established that there were two distinctive variants of the DBF form, and that both models left an imprint on the respective companies' orientations toward science and publishing, we turn to an examination of the dynamics by which the various attributes became joined together.

²² The h-index is a measure of publication quality and quantity, defined on the ISI Web of Science webpage accordingly: "The h-index is based on a list of publications ranked in descending order by the Times Cited. The value of h is equal to the number of papers (N) in the list that have N or more citations. This metric is useful because it discounts the disproportionate weight of highly cited papers or papers that have not yet been cited."

“Lash-up”: The Assembly of Elements from Multiple Domains

Our final step in the analysis is to ask how the various components fitted together and became a coherent assembly, and with what ramifications. Analytically, our aim is to capture both *process* – i.e., how do elements of science, commerce, and finance flow out of those domains into a new entity – and *feedback dynamics* – i.e., the manner in which practices are repurposed to define a new field, with potent reverberations back into their domains of origin. We shall see that it is important to keep these two stages analytically distinct, as the commerce model became the more common DBF form, whereas the science model had transformative effects on the world of the academy, the pharmaceutical industry, and venture capital.

Transformative feedback effects, we argue, are often associated with transpositions – or, at least, with those that survive long enough for such effects to be felt. At the heart of the transposition process is the disruption or reconfiguration of a domain’s fundamental autocatalytic process – that is, the self-sustaining flows of ideas and resources that constitute and reproduce actors and activities within that domain. When a “trespasser” enters a foreign domain, he or she carries cognitive and material resources from her domain of origin. If the trespasser is of sufficient stature to be taken seriously in the new domain, her customary uses of ideas and resources have potential to intermingle with existing flows within the new domain. This confluence of ideas and resources from previously separate domains holds great potential to generate novel social forms, or what Sewell (1992) calls “structures.” And because the novel form remains connected to both prior domains, its new arrangements of schemas and resources are transportable back into

these domains through flows of ideas and people. Hence, instances of transposition are freighted with the opportunity but not the guarantee of transformative feedback effects.

The process of “lash-up” is graphically represented in figure 1, juxtaposing a “traditional” high-tech venture with the two variants of the DBF. Technology-based startups often drew ideas from university science, as well as human capital in the form of university graduates. If the ideas were sufficiently tangible, they could be licensed as intellectual property. This exchange, however, was a one-way transfer from the academy to industry. Investors were attracted through the public equity markets, and financial analysts evaluated a company’s prospects before deciding to invest. The core activity of the firm was the conversion of knowledge into marketable products, which generated revenues, funding the development of additional products, and so on. Note that in the stylized model at the top of Figure 1, there is no overlap between the flow of funding and knowledge in the science domain and the flow of capital and return in the finance domain.

[Figure 1 here]

With the emergence of the DBF, autocatalytic flows in the formerly separate domains began to intermingle in a way that was markedly different from either the “industrial science” model of Big Pharma or the “garage startup” template of information and computer technology ventures. First, traditional pharmaceutical firms had considerable difficulty in accessing the breakthrough discoveries in molecular biology (Orsenigo, 1989; Gambardella, 1995); moreover, the insular organization of their research labs was unappealing to world-class researchers. When he was a young professor at University of Illinois, William Rutter (later of UCSF and Chiron) tried to

work with a series of pharma companies, including Abbott, Lilly, and Merck. But he was unsuccessful in attempts “to broaden their research interests,” unable to overcome the view of executives that “there would be only narrow applicability of biotechnology to the pharmaceutical industry,” and frustrated by their lack of interest in vaccine research (Rutter, 1997: 58-60). For top-flight university scientists to leave the academy to go to a company, the research opportunities had to be superior. Thus when these elite scientists “trespassed” into the worlds of commerce and finance to start their own companies, they imported (as much out of naïveté as necessity) the invisible college model, and searched for alternatives to the cycle of applying for federal grants. This move opened the autocatalytic flow of knowledge production within the science domain to new sources of funding.

The need for funding brought scientists and venture capitalists together, and their intersection triggered notable changes in both domains. The model of venture capital that had developed in the late 1970s was ill-suited for biotech. The idea that VCs would ante up start-up capital for a product prototype and increase funding as the prospect of a market opportunity led to an IPO did not map onto the tremendous cost of drug development, the lengthy process of drug discovery, or protracted stages of clinical trials and regulatory review. A handful of venture capitalists began to explore how to signal commercial progress in the absence of tangible products, and hit upon the idea that scientific accomplishment could be a marker.

The repurposing of scientific output as a criterion for investment had wide-ranging ramifications. Researchers at the science-oriented biotechs began publishing in top journals, proving that the academic coin of the realm not only retained its value in

industry but could be deployed to attract new sources of funding and talent, as young scientists increasingly gravitated to what had previously been considered a second-class career. But just as university researchers moved into industry, industry-spawned ideas also migrated to the academy. Scientists and their universities shifted from the older, traditional model of technology transfer to much more hands-on engagement through university spinoffs, equity participation, and a wide array of research partnerships between universities and companies. In time, the types of arrangements that were previously looked at with concern became deemed appropriate and endorsed with enthusiasm (Colyvas and Powell, 2006).

But not only university science was transformed. Leading venture capitalists were busy coming up with their own novel practices. Tom Perkins, for example, created two financial innovations (one was actually patented) in response to the special requirements of biotech. One was designed to shield a struggling biotech's balance sheet from the enormous costs of clinical trials; the other was a means to retain scientists who were being poached by second- and third-generation companies that could offer equity options as an enticement. Perkins (2002: 9-10) recalled the first of these, the "clinical R&D partnership":

There had to be a lot of financial engineering in this thing... If you looked at the profit and loss statement, there was no income, no sales. Tremendous expense, big loss. It dawned on me that that was not a viable financial model. Subsequent world events with the Internet have changed that. But in those days, a company was supposed to make earnings, or at least have reasonable prospects of making earnings fairly soon. And we had to fund clinical trials through the FDA. After all, we were making pharmaceuticals. I didn't see how we could take Genentech public and have a decent stock price if that's what our P&L was going to look like. Gallons of red ink for years. So I invented this idea of the clinical R&D partnership. We separated out the clinical trials, the largest expense in any drug development company. We set up a partnership that would fund the

clinical trials, and that funding came back to Genentech. So the profit and loss statement is transformed. At the top line, you have hundreds of millions of dollars coming in as revenue. Then the company does the clinical trial under a subcontract, and has that expense. It essentially breaks even on that whole transaction. With a stroke of a pen I was able to change the P&L from just horrific red ink to break-even... These worked very well, until some years later the Securities and Exchange Commission decided it was too aggressive.

The second innovation was a form of “junior common stock,” concocted as a means to hire and retain scientists after Genentech had its initial public offering and the financial opportunity to hold shares in a pre-public company had waned. After Genentech’s landmark IPO in 1980, Perkins (2002: 10) recalled that the retention of key employees became an issue:

We didn’t have a clue how to price the stock. We knew it was going to be a hot issue, and oversubscribed. But Swanson, the board, the management, the investment bankers – we were all caught somewhat by surprise. It came out at thirty-five, shot up to eighty-five, then drifted back down. But that spread brought world wide publicity. Everybody knew about Genentech. It established the idea that you could start a new biotechnology company, raise obscene amounts of money, hire good employees, sell stock to the public. Our competitors started doing all of that, so much so that it became an impediment for us to hire and retain employees. We started to lose employees to other biotech start-ups. Our employees had originally acquired our stock as common stock. We were able to justify a ten-to-one difference in price. So if the preferred stock was at thirty-five a share, then employees got common at three-fifty a share... But you can only do that once. Once it becomes a public stock, the preferred shares convert to common and everyone is on the same platform. So how are we going to continue to attract these people? Continue to hold these people? It was a big problem. (Perkins, 2002: 10).

Perkins created a new kind of stock that did not have voting or liquidation rights. In the event of a merger, holders of this stock would be last in line to redeem their shares.

We got an opinion from the accountants that this stock was only worth one tenth of what the regular common stock was worth, and we called it junior common stock. It would convert to ordinary common stock in case of certain events...such as: Genentech had to be earning a certain amount, or

some product had to be achieved, events they had to work towards which have a risk factor. By diddling that formula over about four years, we were able to use that form of stock to attract and hold key employees. We were the first company to ever have such a thing. My name and fingerprints were all over it. We were very careful to run these plans through the SEC. They approved it. We never had to retract any of that stock. However, the idea was stolen by all of our competitors and so grossly abused that the SEC made most of our competitors retract and eliminate those stock plans. (Perkins, 2002: 11).

In summary, the intersecting flows of ideas and resources from science and finance rebounded back into both domains. Top-tier scientists moved their research into start-up companies, unleashing new career possibilities for younger scientists. Yet, these amphibious founders retained their university affiliations – and in turn, universities became much more immersed in the commercial exploitation of basic research. In the venture capital domain, leading VCs had to rethink their investment model to accommodate the protracted and unpredictable timetable of drug discovery and development. In the early years, they converted scientific fame and later notable research papers into evidence of commercial promise. They developed the idea of milestone payments, very much like the renewal of a program project grant. And in a number of cases, the VC partners took the lead executive role, as the scientific founders were either uninterested in such duties or not disposed toward them. The result was a thorough mixing of science and finance for commercial purposes, with transformative feedback effects in each domain.

Such mixing was not without contestation, however. For example, Genentech's early existence as a "virtual" company created unprecedented tensions in the academy. The idea of a for-profit company funding and owning the research output of a university lab was not only foreign but offensive to some. Edward Penhoet, subsequently a co-

founder of Chiron, spent a sabbatical year at UCSF in 1978 and remembers the infamous day that a senior researcher placed a lock on the freezers where his reagents were stored:

While I was there, Howard Goodman put locks on all his freezers, because Axel Ullrich and Pete Seeburg had left his lab to go to Genentech. Howard was concerned that they had taken clones with them that belonged to him. . . . So that was a tumultuous time over there, with the locks on the freezers, et cetera, and with those two guys going down the street with the clones. So you couldn't be at UCSF in '78 without sensing all of this foment about what was happening in the field . . . and the controversy around the general issue of shared resources between UCSF and Genentech. (Penhoet, 2001:96-97)

Of course, secrecy and concern for ownership were not unheard of in academia; scientific recognition has long been built on being first to publish key results. Competition between labs propels scientific progress. The introduction of a direct commercial challenge, however, disrupted long-standing patterns of interaction *within* university labs, a change that was at first contested and then lamented by academic purists (Yoxen, 1984; also see chapter 15 by Colyvas and Maroulis).

The commerce model (depicted in the lower right side of figure 1) recombined existing practices, and hence produced less novel action. As discussed above, commerce-driven DBFs typically featured mid-career executives from established health care companies who took the plunge to head up new ventures in the unproven world of molecular biology. Not surprisingly, these executives sought ways to attenuate the risks (business and personal) of their unorthodox career moves. First, they focused their firms on more tangible and short-term goals – for instance, specialty chemicals (Genex) or monoclonal antibodies (Hybritech, Centocor) that did not have to go through FDA review, or orphan drugs (Genzyme) where competition was precluded. Only Amgen went after the new-to-the world medicines that the science-focused companies pursued, but it organized its laboratories and research program rather more along the lines of a

traditional pharma company. Second, they developed closer, long-lasting relationships than were typical between hired managers and venture capitalists: Hybritech's first CEO *was* its venture capitalist, Brook Byers, and Genzyme's VCs were actively involved in running the company for much of its first decade.

Science was needed in these companies too, but typically the scientific founder left the academy, limiting his connections to, and influence in, the broader community of scientists. Younger scientists who came to work in these well-paid jobs forsook the opportunity to return to the academy as publishing was much less commonplace in the commerce model. These firms also forged research and development partnerships with large pharmaceutical companies, and eventually Hybritech and Centocor were acquired by their larger partners. In contrast, the science-based companies fought to maintain their independence, viewing merger as a loss.²³ Venture capital and law firms played a critical role in negotiating the terms of partnerships with established companies, as the young, commerce influenced companies did not want to give away their most valuable assets too cheaply. Many of the relationships with big pharma turned sour, however. Hybritech was acquired by Eli Lilly in 1986; within a year all the former Hybritech employees had left. Genex built a close supply relationship with Searle, going so far as to set up a factory, only to have Searle pull the plug on the deal, sending Genex stock on a downward spiral (see Genex in Appendix, pp. 96-100). Amgen jointly developed its drug

²³ When Amgen acquired Immunex in 1991, the Seattle scientists lamented that Amgen did not encourage the publishing of research results, saying that "Amgen is big pharma," with a completely different culture (see Immunex in Appendix, pp. 106-111). In summer 2008, as Swiss giant Roche moved to buy up all of the stock of Genentech, employees of the Bay Area company took to the media to decry a loss of independence that would threaten an illustrious 33-year history of research and medical accomplishments. Now that the acquisition is complete, Roche is attempting to leave in place Genentech's research culture (Weintraub, 2009).

for kidney failure and dialysis with Ortho, a subsidiary of Johnson and Johnson, only to be embroiled in a decade of lawsuits.

In short, the commerce variant involved more of the familiar features of corporate relationships – partnerships that often led either to acquisition or litigation. But the commerce model also proved to be a route to success, as the acquisitions of Hybritech and Centocor produced a plethora of well-compensated employees, and Amgen and Genzyme grew into large firms, still independent today.

We summarize the development paths in each domain in Table 5, going through the stages and their consequences. Our takeaway from this analysis is that the transpositions that occurred in the science-based company were much more far-reaching in their novel aspects than the recombinations in the commerce model. The intersection of science and finance produced all manner of fresh action, whose consequences proved destabilizing for both the academy and industry. Nonetheless, recombinatory activities in the commerce-centered firms also had feedback consequences in the academy. For example, failures at product development reverberated in unexpected ways. Centocor was founded as a product-focused biotech, producing reagents and diagnostics rather than human therapeutics. Seduced by the sexier science-based model, however, the company shifted its focus in the mid-1980s and placed a huge bet on the success of Centoxin, a monoclonal-derived anti-sepsis treatment:

“Our [original] plan was founded as being producers of reagents. We evolved into product development and fully integrated into that side of it, using partners. Then, in the mid-1980s, we decided to take the technology platform and apply it for therapeutics to treat sepsis, septic shock. . . . From 1986 to 1992, we essentially worked on that vision and dream of being a fully independent biopharmaceutical company, essentially built around the success of Centoxin. . . . What happened was that the originating culture got fragmented. From the mid-1980s to 1992, you saw two

businesses at Centocor: there was the diagnostic business, which was pretty much of the founding culture; and there was the pharmaceutical business” (Holveck, 2001:46).

In 1992, Centoxin failed to receive FDA approval. Centocor made drastic headcount reductions and barely survived as an independent company. More far-reaching, however, was the blowback of regulatory failure into academic science. Sepsis research had been a prominent and growing area of scientific inquiry in the 1980s. But Centocor’s high-profile failure “killed sepsis research for ten years,” according to Richard Proctor, Global Director of Scientific Affairs for Infectious Diseases at Merck: “Sepsis research became a pariah – no funding, no projects. It was an enormous setback for an important line of research” (Proctor, 2009). That a commercial and regulatory setback could place such a long-lasting damper on the funding of basic research shows how intertwined the domains of commerce, finance, and science had become by the early 1990s. Although such interconnections had forged a new organizational form, they also had become a conduit for the transfer of evaluation criteria and standards of desirability between domains.

[Table 5 here]

We have emphasized the extent to which transposition uproots the status quo in multiple domains. Perhaps our point is best illuminated by a comparison of the consequences of trespassing and boundary-crossing. The latter implies translation, transporting, and brokering ideas across interfaces. In Burt’s (2009) language, this is creativity born of the export-import trade. Trespassing highlights the puncturing of boundaries, violating conventions (whether consciously or not), and thereby creating myriad opportunities for unfreezing and re-purposing. Most trespassers do not survive. And if they do, the trespassing itself has a short life. Once such movement becomes commonplace, it is no longer inappropriate. Instead it becomes an accepted path for

people and the conduit of ideas, but with unpredictable reverberations back through the now-overlapping territories. The new biotech firms ushered in a new era: Basic science advances were no longer made only in universities, and positions in science-based companies came to be viewed as rich in both financial and research opportunities. These alterations proved to have pronounced effects on both the research university and corporate enterprise.

Conclusion and Implications: Reshaping the Production of Knowledge

We began by asking: Where do new organizational practices and forms come from? We are, of course, not the first to take up this issue, but we think our answers are distinctive. Consider the contrast with Rao's (1998) excellent work on consumer watchdog organizations, and his broader line of research on the role of social movements in advancing new organizational forms (Rao, Morrill, and Zald, 2000; Rao and Kenney, 2008). The different emphases are perhaps subtle, but nonetheless consequential.

In his analysis of contestation between rival consumer movements, Rao (1998: 920) argued that a new form becomes established "only when there is a truce amongst the constituents of the organizational field about which frame is used to organize activities." The Consumers Union "strove to import characteristics of trade unions into the consumption sector" (Rao, 1998: 948). This model failed to galvanize support, and generated much opposition from legislators and the press. Foregoing the activist labor model, Consumer Union later adopted the "rational consumer" ideology of its rival – the Consumers Research Council. The truce produced a new form: the consumer watchdog organization. The analytical purchase in this strand of research comes from a focus on

“settlement” – “agreements have to be negotiated among parties before new forms can be institutionalized as codes” (Rao and Kenney, 2008: 368).

Our examination of the genesis of new organizational forms in commercial bioscience, however, begins upstream from subsequent settlements or negotiations between competing models. We have traced how career flows triggered disruption. Moving energy from one realm into another, or converting reputations and resources in one domain into motivating energy in a new arena, unlocked existing social bonds and expectations, creating space for a new form. In other words, the real action happened prior to the fashioning of any truces, in the releasing of new practices whose effects extended well beyond the handful of organizations where they began. Indeed, in a narrow sense, the commerce variant could be seen as the victor in this contest of models, as these recombinations resulted in earlier success and more examples of this model are around today. (We list the eventual “outcomes” for the first-generation companies below.) Although the commerce model may have won the battle, the science model ultimately won the war, as it proved to be more influential institutionally in multiple domains.

What happened to the first generation?

Alza	Ahead-of-his-time founder creates a prototype for future biotech firms. Acquired by Johnson & Johnson in 2001.
Cetus	First-mover advantage doesn't hold due to lack of focus; acquired in 1991 by Chiron.
Genentech	Science married to finance creates novel model that produces an enviable record of innovation. Despite resistance, became a fully-owned subsidiary of Roche in 2009.
Genex	Low-margin business model becomes unsustainable without investment by corporate partners; acquired in 1991 by Enzon.
Biogen	"World class research seminar" makes corporate governance challenging; licensing model proves robust. Merged with IDEC in 2003.
Hybritech	Entrepreneurial scientist finds world-class VC, who recruits a pharma escapee to run the show; bred for eventual sale and acquired by Eli Lilly in 1986.
Centocor	"Academic scavengers" almost lose their company due to grand aspirations to become a fully integrated pharmaceutical company. Acquired by Johnson & Johnson in 1999.
Amgen	Savvy VCs set out to "do biotech right" by recruiting stellar SAB and putting talented pharma escapee in charge; a biopharma titan is born.
Chiron	Scientist-entrepreneurs move the invisible college model to a business setting. Became a wholly-owned Novartis subsidiary in 2006.
Genzyme	Venture capital group goes shopping for a new venture; builds business around orphan drug opportunities.
Immunex	Despite stellar scientific record, business success comes late. Acquired by Amgen in 2002, resulting in the loss of local "Immunoid" culture.

By influential, we do not mean a "mere" case of one side adopting notable practices of the other, and vice versa. To be sure, there are signs of this intermingling everywhere. Industrial science today clearly recognizes the importance of intellectual capital, and builds university-like campus settings to attract the talent of the creative class. Research universities have become much more business-like as entrepreneurship is celebrated and compensation is market-based and laden with incentives. Nor are we satisfied to make the point that the formerly separate domains of science, commerce, and finance have become blurred, although university endowments drove much of the investing in the knowledge economy, and collaboration between industry and the academy has become embraced, encouraged, even evangelized by those in high positions of science policy. To be sure, these interminglings and reshaping of the boundaries of knowledge production have altered both reward systems and career paths. But we claim

that the transposition of science and commerce was even more unsettling and transformative; it recast the nature of science and industrial work itself, and altered the institutional framework for economic growth.

Scientific and corporate work were formerly organized around the twin frames of disciplines and departments. Both were steeped in deep functional expertise – in the academy, specialized knowledge accumulated in an area of scientific inquiry, and in industry, prowess at a skill relevant to a particular product or therapeutic domain was the trademark. The science-based form opened up a project-focused alternative, driven by interdisciplinary and inter-organizational collaborations and impelled by an urgent need to solve problems more quickly. This shift to more project-based work has the virtue of flexibility as well as the limitation of fragility.

In the academic realm, recall that molecular biology was championed as a revolt against traditional biology. “The Huns” were crashing in, outsiders from physics and biochemistry, even engineering (Hall, 1987: 21). Today, every major research university has a large initiative underway, linking the biomedical sciences, engineering, and the physical sciences, with grand synthetic names like “systems biology” and “Bio-X.” These programs are generating important work; they are also growing at the expense of the traditional science departments.

In both the corporate and academic domains, project-based work has become a collaborative enterprise. It transcends department and organizational boundaries, drawing together firms, universities, research institutes, and government labs in fierce research and product development races. Research is no longer a local enterprise, but a coordinated and collective affair. And many scientists prefer this collaborative model as

more engaging than an individualist approach.²⁴ Moreover, as we show in the next chapter, the ability to work across multiple organizational boundaries has had profound consequences for regional economic growth.

Finally, consider that a project also has an endpoint – something tangible is created, an idea is followed through to its resolution, sometimes in a manner that has very real consequences in the lives of ordinary people. This aspect of the remaking of research emphasizes again the effects of careers and networks. Today, many scientists and technologists are more tightly aligned with their research goals or the technology they are working on than with their employers. Viewed over the course of the last four decades, these novel organizational arrangements were generated as much by chance and necessity as by intention, as science-based organizational practices imported into a new space had profound, cascading effects back into the formerly conservative domains of the university and the corporation.

²⁴ Perhaps our early science founders were indeed transitional figures. In retaining their university positions, they may not have been risk averse, as is often thought, but still held a preference for running their own lab according to their goals, as opposed to the collectivist endeavors of their new companies, where everyone would drop his own work to join in on whichever project proved hottest.

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Table 1: Distinctive Features of Early Biotech Firms

	Alza (1968)	Cetus (1972)	Genentech (1976)	Genex (1977)	Biogen (1978)	Hybritech (1978)
SCIENCE	<ul style="list-style-type: none"> ◆ All-star science advisory board ◆ Campus-like setting near a major research university 	<ul style="list-style-type: none"> ◆ All-star science advisory board ◆ Campus-like setting near a major research university ◆ “Free space” for scientists ◆ Scientific founder stayed at university full-time, consulted with company 	<ul style="list-style-type: none"> ◆ Insisted that staff scientists publish and contribute to public science ◆ Scientific founder stayed at university, consulted with company ◆ “Virtual” start-up: all initial research conducted by contract with UCSF and City of Hope Hospital 	<ul style="list-style-type: none"> ◆ All-star science advisory board ◆ Scientific founder stayed at university initially 	<ul style="list-style-type: none"> ◆ International consortium of top academic labs (i.e., science advisory board was the company) ◆ “Virtual” start-up: all initial research conducted in founders’ labs ◆ Scientific founders stayed at their respective universities full-time 	<ul style="list-style-type: none"> ◆ Scientific founder stayed at university full-time, consulted with the company ◆ Key founding role for talented lab assistant ◆ Campus-like setting near a major research university (UCSD) and research institute (Salk)
FINANCE	<ul style="list-style-type: none"> ◆ Went public with no products, breakthroughs, or revenues ◆ Used research partnerships with big pharma to generate funds 	<ul style="list-style-type: none"> ◆ Used research partnerships with diverse array of large corporations ◆ Record-breaking IPO in 1981 	<ul style="list-style-type: none"> ◆ Meager funding until scientific “proof of concept” ◆ Invented “milestone payment” form of incremental financing ◆ First biotech IPO (1980): gene dreams for Wall Street ◆ Used research partnerships to share costs and risk 	<ul style="list-style-type: none"> ◆ Numerous research contracts with large companies 	<ul style="list-style-type: none"> ◆ Modest initial VC funding ◆ Out-licensed early breakthroughs to big pharma 	<ul style="list-style-type: none"> ◆ Venture capitalist was first CEO ◆ First company to commercialize monoclonal antibody technology for diagnostics
COMMERCE	<ul style="list-style-type: none"> ◆ Founder went on to start numerous biotech firms 	<ul style="list-style-type: none"> ◆ Wide range of commercial applications for biotech 	<ul style="list-style-type: none"> ◆ Swing for the fences – focus on blockbuster medicines 	<ul style="list-style-type: none"> ◆ Pursued low-cost, high-volume strategy (e.g., biotech production of industrial chemicals) ◆ Early investment in manufacturing plant ◆ Scientific founder went on to start additional biotech firms 	<ul style="list-style-type: none"> ◆ Targeted blockbuster medicines ◆ Scientific founders ran the company for first seven years 	<ul style="list-style-type: none"> ◆ Scientific founders became serial entrepreneurs and/or VCs ◆ Recruited senior exec from Baxter to run the company ◆ Focused on diagnostic products; avoided long clinical trials

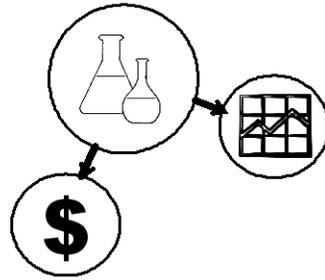
Table 1: Distinctive Features of Early Biotech Firms (cont.)

	Centocor (1979)	Amgen (1980)	Chiron (1981)	Genzyme (1981)	Immunex (1981)
SCIENCE	<ul style="list-style-type: none"> ◆ Aggressive in-licensing of research from public science ◆ Initially located in a business incubator on Univ. of Pennsylvania campus ◆ Close relationship with research institute (Wistar) 	<ul style="list-style-type: none"> ◆ All-star science advisory board 	<ul style="list-style-type: none"> ◆ Founders stayed at universities initially ◆ Skills of academic administration applied to business ◆ Insisted that scientists publish and make contributions to public science ◆ Transfer of founder's existing research grant from university (UCSF) to company ◆ Used research partnerships with pharma and universities as a mode of exploration 	<ul style="list-style-type: none"> ◆ Transfer of founder's existing research grant from university (Tufts) to company ◆ Key founding role for talented lab assistant ◆ Hired science advisory board intact (i.e., Bio-Information Associates, a consulting firm of MIT and Harvard profs) 	<ul style="list-style-type: none"> ◆ Insisted that scientists publish and make contributions to public science ◆ Founding scientists resigned from academic jobs to avoid conflict of interest ◆ Campus-like setting near a major research university (U. of Washington) and research institute (Hutchinson Cancer Center)
FINANCE		<ul style="list-style-type: none"> ◆ IPO as salvation, despite no products, or patented breakthroughs. 		<ul style="list-style-type: none"> ◆ Used tracking stocks to compartmentalize risk ◆ Grew through numerous small acquisitions 	<ul style="list-style-type: none"> ◆ Out-licensed early patents to large pharma, then later reacquired them
COMMERCE	<ul style="list-style-type: none"> ◆ Bridge between academic labs and big-pharma manufacturing/marketing ◆ Recruited senior exec from Corning's medical products business to run the company ◆ Focused on diagnostic products 	<ul style="list-style-type: none"> ◆ Recruited senior exec from Abbott's diagnostics division to run the company ◆ Novel decision-making process for allocating resources to projects 	<ul style="list-style-type: none"> ◆ Focused on large potential market underserved by big pharma: vaccines ◆ Scientific founders ran the company 	<ul style="list-style-type: none"> ◆ Founder was serial entrepreneur from the packaging industry ◆ Focus on niche markets and orphan drugs ◆ Recruited senior exec from Baxter to run the company 	<ul style="list-style-type: none"> ◆ One of founders was a proven executive and turn-around artist

Table 2: Science vs. Commerce” A Continuum

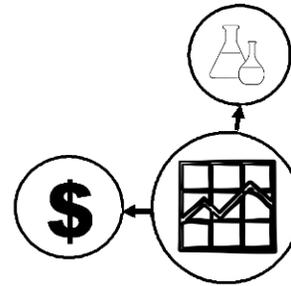
DOMAIN	Cetus 1971	Genen- tech 1976	Biogen 1978	Chiron 1981	Immu- nex 1981	ALZA 1968	Genex 1977	Hybri- tech 1978	Centocor 1979	Amgen 1980	Gen- zyme 1981
SCIENCE											
Insistence that scientists publish their findings	X	X	X	X	X	X					
Campus-like setting near a major research university	X	X		X	X	X		X	X		
Founder(s) continued at or returned to university or institute	X	X	X	X				X	X		
All-star science advisory board	X		X			X	X			X	X
FINANCE											
Research contracts with large corporations	X	X	X	X	X	X	X	X		X	
Scientific founder(s) <i>became</i> VCs or angel investors		X		X	X		X	X			
Active VC involvement in early management		X						X			X
IPO with no products and no predictable revenue stream	X					X				X	
COMMERCE											
Founder(s) already had entrepreneurial track record	X			X			X		X	X	X
Early hiring of senior exec from health care or pharma						X		X	X	X	X
Scientific founder(s) <i>became</i> serial entrepreneur (s)					X	X	X	X	X		
Initial emphasis on non-therapeutic applications	X					X	X	X	X		

Table 3: Two Variants of a New Form



A Science-Centered Variant

- Science takes the lead, with VC and management support
- Renowned scientist-founders straddle domains, often occupying key executive and academic roles simultaneously
- Science Advisory Board (SAB) used for peer review
- Strong commitment to publishing research results
- VCs invest “scientifically” – minimal funding of initial experiment (proof of principle), followed by increasing investments
- Investors place bets on proven scientific accomplishments
- Academic headwaters: William Rutter’s interdisciplinary lab at UCSF.
- Commercial headwaters: ALZA Corp.
- Exemplars: Genentech, Biogen, Chiron, Immunex
- Failed attempt: Cetus (lacked strong scientific leader)
- Mechanism of genesis: *transposition*



A Commerce-Centered Variant

- Management takes the lead, supported by funding and science
- Scientifically-trained business leaders play crucial early roles
- Science Advisory Board (SAB) is signal of approval
- Publishing not encouraged
- VCs invest traditionally – focus on markets, products, etc.
- Commercial headwaters: entrepreneurial divisions of health care or pharma companies (i.e., Baxter, Abbott, Corning)
- Exemplars: Hybritech, Centocor, Amgen, Genzyme
- Failed attempt: Genex (lacked strong commercial leader)
- Mechanism of genesis: *recombination*

Table 4: Publication and Citation Counts for 10 year period post-IPO

COMPANY	YEAR OF IPO	TOTAL PUBS	AVG PUBS/YR	TOTAL CITATIONS	AVG CITES/PUB	H-INDEX ¹
Alza	1969	116	11.6	2,608	22.48	26
COMMERCE						
<i>Genex</i>	1982	163	16.3	12,262	75.23	51
<i>Hybritech</i>	1981	272	27.2	5,678	20.88	36
<i>Centocor</i>	1982	250	25	15,677	62.71	61
<i>Amgen</i>	1983	798	79.8	55,950	70.11	122
<i>Genzyme</i>	1986	235	23.5	15,064	64.10	59
SCIENCE						
Cetus	1981	1,000	100	107,469	107.47	146
Genentech	1980	1,656	165.6	198,608	119.93	218
Biogen	1983	623	62.3	54,272	87.11	115
Chiron	1983	905	90.5	86,453	95.53	141
Immunex	1983	710	71	61,616	86.78	133
t-test (1-tail)		0.009		0.009	0.004	0.003

¹The h-index is a measure of publication quality and quantity. To derive *h*, each company's publications are listed in descending order by times cited. The value of *h* equals the number of papers (*N*) in the list that have *N* or more citations. Source: ISI Web of Science®.

Figure 1: The Intersection of Science, Finance, and Commerce – Three Models

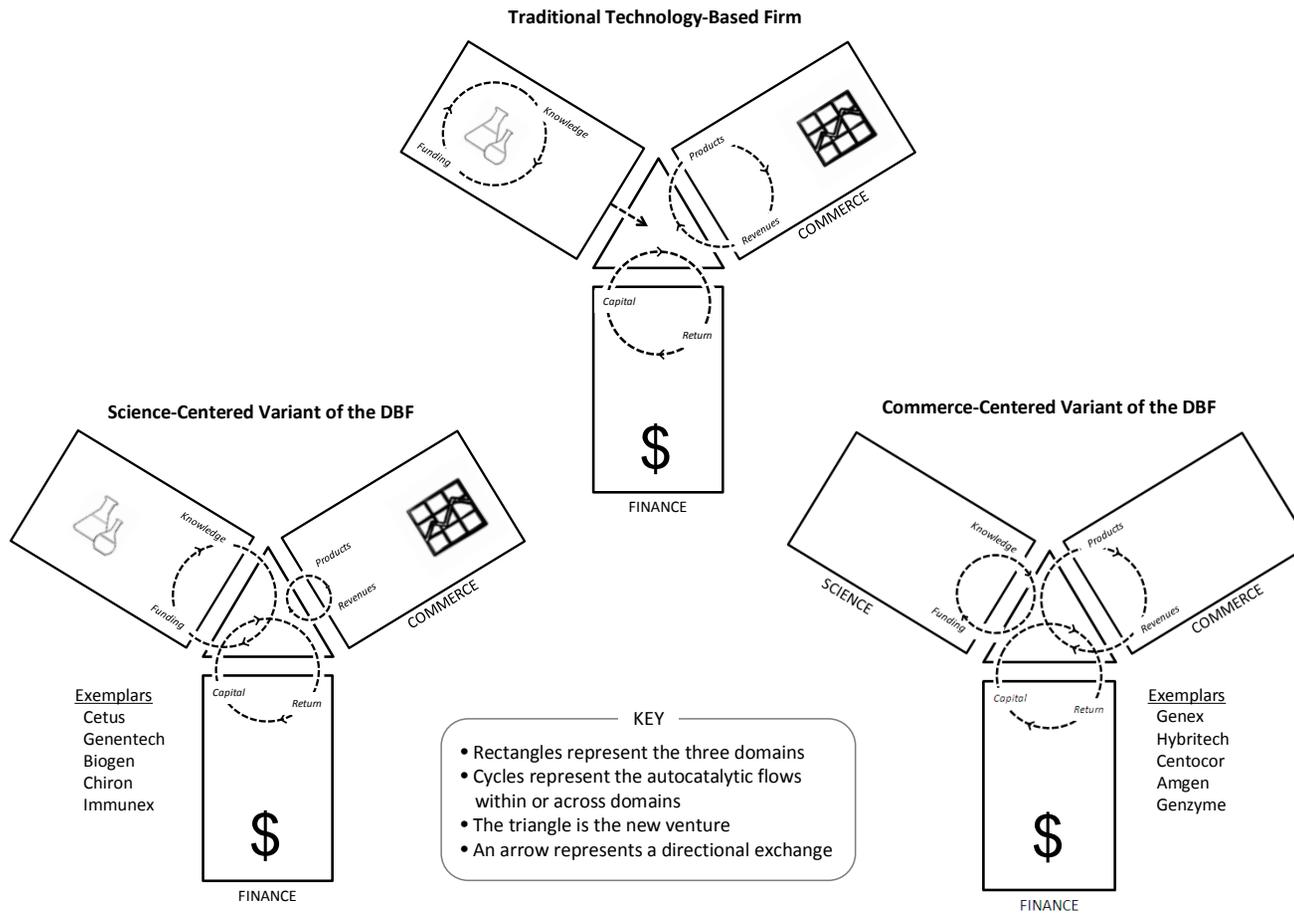


Table 5: The Creation of Novelty, Step-by-Step

	SCIENCE	FINANCE	COMMERCE
<i>Established routines prove lacking . . .</i>	Traditional corporate R&D model is too insular and proprietary for biotech's purposes; in addition, top-flight researchers are unwilling to leave the academy unless the <i>research</i> (not just economic) opportunities are comparable.	Existing VC approach (i.e., provide small amount of start-up capital, increasing as product goes to market, followed by IPO) is ill-suited to the funding needs (in quantity and duration) of biotech development.	Barriers to entry in the pharma business are formidable: clinical trials, FDA approval, creation of distribution channels, scaling up manufacturing. Traditional "bootstrap" model (i.e., start small and channel early revenues into growth) was not feasible. There is no such thing as a credible "low-budget" clinical trial, and cutting-edge life-science production processes cannot be easily outsourced to contract manufacturers.
<i>. . . so founders draw on existing knowledge . . .</i>	Scientific founders import the invisible college into a corporate setting, minus the grant-chasing and tenure dynamics.	VCs realize that the crucial issue is how to signal commercial progress in the absence of products. Without such signals, the biotech ventures will fail to attract continued investment.	Biotech founders import a proven commercialization model from the world of academia: technology transfer. ¹ In this setting, the transfer will be between two for-profit entities, but the resource asymmetries are similar: biotechs have crucial knowledge that big pharma lacks, whereas big pharma has commercialization capabilities.
<i>. . . and scan their social worlds for cues . . .</i>	Top scientists look to each other for validation of commercial involvement, and judge the legitimacy of a new model using their customary criteria: quality of scientific output (i.e., publishing in top journals). At the same time, they scan the "new" world of commerce for cues, and realize the importance of patenting before publication.	At the intersection of academic science and commercial drug development, VCs see two novel opportunities for demonstrating a biotech venture's worthiness for additional investment: (a) research partnerships with big pharma (validating the eventual product potential of the venture's core science) and (b) the sheer scientific performance of the venture (including stature of founders and/or SAB, and publication record of scientific staff). ²	To remain viable as commercial entities, however, fledgling biotechs must aggressively negotiate the terms of such technology transfers. Access to legal counsel (typically via their VC's network) becomes crucial, as biotechs learn to "sell" their scientific advances to pharma partners without jeopardizing their future independence.
<i>... forging unique elements of a science-based organizational form.</i>	R&D becomes a porous, networked endeavor whose results are published in the top journals. New career paths are established for academic life scientists.	This results in a flowering of inventive financing mechanisms: milestone agreements; research partnerships; initial, second, and third public offerings without any commercial products; tracking stocks; etc.	As a result, a wide variety of partnerships are created between small, science-rich biotechs and large, wealthy product-driven pharmaceutical companies. Many of these bargains prove Faustian, as biotechs forfeit ownership and control in exchange for resources.

¹ In commerce-driven firms, founders from large pharma drew on existing knowledge and realized the quickest way to make money was to avoid human therapeutics altogether. This was the path taken by Hybritech, Genex, and (initially) Centocor.

² Note how mechanisms for dealing with uncertainty get transposed from one domain to another. In science, uncertainty is reduced by reliance on a broader scientific community via publication and peer review. This mechanism gets imported into the commercial domain in two ways: (a) the organization of R&D as an invisible college (i.e., not knowing what the rest of the world is up to is a bigger risk than sharing what you're up to – a fundamentally different approach to uncertainty reduction from the corporate R&D model); and (b) more strikingly, the use of scientific accomplishment as a way to reduce *investor* uncertainty.

Appendix: Profiles of first-generation companies

1.) *ALZA: A DBF prototype*

Some might question why ALZA, founded in 1968, belongs among the earliest biotech companies. Like Cetus, it was founded a few years before publication of the breakthrough discoveries of gene splicing (1973) and monoclonal antibodies (1975). But ALZA merits inclusion, first, because it is an unusual example of a *de alio* biotech entrant; its origins were in the pharmaceutical industry, but its interest in novel drug delivery mechanisms moved it into bioengineering. Second, ALZA pioneered many business practices that became common in the new bioscience companies, such as an IPO before it had any marketable products, lucrative (but equity-draining) partnership arrangements with established pharma companies, and reliance on a prestigious board of scientific advisors. And third, its founder, Alejandro Zaffaroni, was deeply connected to the world of academic science and went on to found numerous biotech ventures.

If Zaffaroni had been able to persuade his then-employer, Syntex, to support basic research on novel drug delivery techniques, launching ALZA would have been unnecessary. Zaffaroni spent 17 years with Syntex, joining in 1951 after completing a PhD and post-doc in biochemistry and endocrinology at the University of Rochester. An immigrant from Uruguay, Zaffaroni was at home in the fast-paced, free-wheeling environment of Syntex's Mexico City labs. He joined the company in the thick of its race against world-famous teams from Harvard and Merck to synthesize cortisone. Under the guidance of renowned chemists George Rosencranz and Carl Djerassi, underdog Syntex won. Most unusual for the time, Rosencranz insisted that Syntex scientists publish their findings in scientific journals; Syntex's publication and research record earned it the label

“The University of Steroids” from eminent Harvard chemist Louis Fieser (Kornberg, 1995:66).

By 1960, Zaffaroni had become president and CEO of Syntex Laboratories. He pressed his board for a U.S. office. Instead of locating in the New York–New Jersey pharmaceutical corridor, Zaffaroni proposed the Stanford Industrial Park for its climate, ambiance, proximity to Djerassi (who had moved to Stanford), and direct flights to both Mexico City and New York. The first Syntex research unit established at the new location was called the Institute of Molecular Biology. It was staffed by 15 scientists and guided by Djerassi and Joshua Lederberg (another Syntex advisor at Stanford). Prompted by his earlier research on gland function, Zaffaroni began asking fundamental questions about drug delivery:

These small glands have a tremendously important function. They deliver very small amounts of materials that have tremendous impact. . . . How is it possible that these very potent agents are released under highly controlled conditions, and then in medicine we bring the same agents into the body by giving a tablet at a time or an injection at a time? It seemed to me quite evident that the way in which we administer the agents to the body is wrong, and if it is wrong for the hormones, why is it not also wrong for every compound that we throw all at once into the body? (Zaffaroni, 1997)

By the mid-1960s, Syntex had capitalized on its patents in steroid chemistry to create two market-leading products: cortisone skin cream and the birth control pill. Rich but risk averse, the company was unwilling to sponsor Zaffaroni’s foray into drug delivery. So in 1968, Zaffaroni resigned from Syntex, sold his considerable holdings of company stock, and used half of the proceeds to found ALZA, an acronym of the first two letters of his first and last names. Sadly, Syntex abolished the Institute of Molecular Biology after Zaffaroni left, only a few years before the discoveries of recombinant DNA and the sequencing and cloning of DNA catapulted molecular biology to prominence.

Had the early vision of the Institute been preserved, these new technologies almost certainly would have put Syntex years ahead of Genentech and others in the genetic engineering race.

ALZA was not an instant success. One of its first product concepts was a thin polymeric film that could be put on the eye to treat glaucoma. The usual medications had to be put in several times a day, causing blurred vision for the ensuing hour. ALZA's technology would allow the film to release the medication constantly at small enough doses to avoid side effects. Another proposed innovation was the prevention of pregnancy by the release of progesterone from a small T-shaped device placed in the uterus. The essential principle of each product was to diffuse drug molecules through membranes and release them at a controlled rate over an extended period.

These technological advances did not translate into market success, however. Disgruntled analysts began to argue that ALZA's academic culture blinded it to commercial opportunities; it did not help that ALZA had a prestigious scientific advisory board and was close to a university campus. As one critic observed, "ALZA was a university masquerading as a company. You'd go to analyst meetings and [one-time CEO] Marty Gerstel would say, 'We have 2000 patents, hallelujah! We have this technology and we have that technology'" (Longman,1996:47).

Early in its history, however, ALZA stumbled into a financing innovation. As part of the original separation agreement between Zaffaroni and Syntex, Syntex was granted 25% of ALZA's stock. As it became clear in 1969 that ALZA was developing a birth-control product that would compete directly with Syntex's pill, the two companies agreed that Syntex would distribute all of its ALZA shares to existing Syntex shareholders. The

Securities and Exchange Commission, initially resistant, eventually approved the plan. In effect, ALZA instantly became a publicly traded company with an army of shareholders and market capitalization close to \$100 million—all without a single product or any assurance that it would ever have any sales, much less profits. The company consisted of only a handful of employees and Zaffaroni's vision for revolutionizing drug delivery. For ALZA to go public at such an early stage established a precedent followed by many fledgling biotech companies in subsequent years (Kornberg, 1995:80).

ALZA also found it critical to partner with large pharmaceutical and nascent biotech companies when it ran into financial trouble. ALZA's transdermal technology was well-suited to delivering the large-molecule peptides and proteins that resulted from biotech advances, which had previously been injectable-only products. After proving the utility of such drug delivery methods in more prosaic settings (such as smoking cessation and motion sickness applications), ALZA was acquired by Johnson & Johnson in March 2001 for \$10.5 billion. Over time, ALZA's importance to Johnson & Johnson waned, and in 2005 its operations were closed. By that time, the eponymous Zaffaroni had launched six biotech firms: DNAX (1980), Affymax (1988), Affymetrix (1991), Symyx Technologies (1994), Maxygen (1997), and Alexza (2000).

2.) Amgen: Science-based, but business-led

At the end of the 1970s, Silicon Valley venture capitalist Bill Bowes saw great investment potential in the life sciences. Having served on the board of directors of Cetus from 1972 to 1978 and been privy to the founding of Genentech in 1978, Bowes set out with a handful of fellow investors to assemble a biotech venture that would avoid the

missteps of the first companies. His efforts were spectacularly successful on one level: of all the early biotechs that survived, Amgen ranks highest on most commercial measures of success (growth rate, total sales, market capitalization, etc.) and is “only the second fully integrated pharmaceutical company (after Syntex) built from scratch in the post–World War II period” (Kornberg, 1995:206-207). Curiously, despite its success, Amgen did not spawn a strong regional cluster of subsequent biotech activity (see chapter 14).

The seeds of this paradox can be seen in a sequence of early decisions and historical accidents that established Amgen’s trajectory. Bowes had been investing in new ventures since the mid-1950s, when he joined Blyth & Co. in San Francisco after earning a Harvard MBA. Following the semiconductor and computer boom of the 1960s, investors were looking for the “next big thing” (Duncan, 2005:16). From his experience on the board at Cetus, Bowes borrowed the idea of an all-star scientific advisory board. He first asked Stanford geneticist Robert Schimke to join the venture and assemble the advisory board. For personal reasons (Schimke’s father was seriously ill at the time), Schimke declined, suggesting instead UCLA molecular biologist Winston Salser.

Salser was an entrepreneurial academic who had found a clever way of funding his lab. He bought radioactive tracers in bulk and then sold them to smaller labs in small quantities at much higher prices. He was well known among West Coast academics, though perhaps less well regarded. He assembled an impressive scientific board by assuring each scientist that the others had already agreed to join, when in fact they had not (Rathmann, 2004:21-22). The board Salser had recruited ended up requesting that he be replaced—an unpleasant task that fell to another of Salser’s recruits, George Rathmann.

Rathmann had earned a PhD in chemistry at Princeton in 1952 and spent the first 20 years of his career at 3M. After a two-year detour managing a failing division at Litton Industries (1973-1975), he joined Abbott Laboratories as vice president of R&D for the diagnostics division, which he built into a market leader. Rathmann's success, however, was accompanied by restlessness; he had been frustrated by the power of the marketing department at 3M and picayune attention to detail at Abbott (Rathmann, 2004:5, 20). He became interested in the potential of biotechnology to create synthetic antigens and requested a six-month sabbatical from Abbott to explore the idea. On the advice of an Abbott colleague who was a former student of Salser, Rathmann intended to spend the sabbatical in Salser's lab at UCLA. But Salser was on leave, involved in starting Amgen. So instead of a research apprenticeship, Rathmann ended up with an offer to be the new venture's first employee and founding CEO. Accepting the offer was not easy. Abbott tried to hold on to Rathmann by offering him the opportunity to start a biotech division within the large corporation. In addition, Moshe Alafi (an investor in both Amgen and Biogen and one of the founders of Cetus), tried to recruit Rathmann to run the U.S. operations of Biogen. In the end, Rathmann opted for the freedom and control offered by Amgen. As part of the negotiation, he insisted that the high-powered scientific advisory board report directly to him: "I thought, no way am I going to have a scientific advisory board report to the board of directors and tell them what a crappy job I'm doing. So I said, 'No, if they report to me, that's fine. Otherwise, I'm not going to do this'" (Rathmann, 2004:21). Unforeseeably, this put Rathmann in the position of having to fire the person who had brought him into the venture, Winston Salser.

Salser's influence on Amgen extends beyond its illustrious scientific board and charismatic CEO. Its location was Salser's choice. He determined that Thousand Oaks, California, was roughly equidistant from three universities from which he drew heavily for Amgen's scientific advisory board: Cal Tech, UCLA, and UC Santa Barbara, and the town offered cheap housing and smog-free air (Duncan, 2005:31). This geographical isolation is certainly one cause and consequence of Amgen's development as a sort of scientific island, manifest not only in its singular achievement of FIPCO status, but also in its aggressive (and on the whole, successful) legal battles to protect its core patents.

The founding model for Amgen, then, was the audacious vision of a bioscience-based pharmaceutical firm. Dennis Fenton, an early recruit, recalls his first visit to Amgen in 1981: "There was a window in Building 1 and all you could see was just brown California dirt. George said, 'We're going to build a pharmaceutical company as big as Pfizer.' And I looked at him and thought, 'This guy is out of his mind'" (Duncan, 2005:54). Turning that California dirt into an independent biopharmaceutical corporation required a strong managerial hand (and more than a little luck). Having seen the cost of weak management at Cetus, Bowes insisted on experienced business leadership for his own start-up. Rathmann recruited a strong team of savvy managers, many of them from his former employer, Abbott Laboratories. Recalls Gordon Binder, Amgen's first CFO and second CEO,

Much of Amgen's success in raising capital can be attributed to the fact that every one of our senior managers had worked for large corporations. As a result, we had the organizational discipline of a far bigger company, with salary grades, annual performance reviews, monthly reports, and budgets that were taken seriously. All the things that the start-ups rarely do, we did; to us, it was second nature." (Binder and Bashe, 2008:48-49)

In contrast, Amgen's scientific hires (unlike its science advisory board) were predominantly early-career PhDs. The message was clear: Amgen was to be science-based, but not science-led. That the business managers were running the show was never in question, as seen in subsequent CEO succession: Rathmann was followed by Binder, a Harvard MBA with an emphasis in finance, who passed the baton to Kevin Sharer, another Harvard MBA with a strong sales and marketing history. In contrast to many other biotech firms, no academic scientist has ever led Amgen.

Still, a large measure of research freedom and "bootleg" spirit, imprinted on Rathmann at 3M, was cultivated at Amgen. The most celebrated example (with overtones of the development of 3M's Post-It note) is Fu-Kuen Lin's dogged quest to clone and express erythropoietin. Despite opposition from management, he succeeded in late 1983, leading to the first bioengineered blockbuster drug (Epogen) and a novel research-management policy: exploratory projects needed approval from only one of three research-related senior executives in order to continue (Berkley and Nohria, 1992:6).

Amgen might not have survived long enough for Lin's breakthrough were it not for a successful, though unusual, financing ploy. Early in 1983, Rathmann calculated that the company would run out of money by September. Binder ran the numbers and figured that, with significant layoffs, Amgen might last through the end of the year. Recalls Rathmann (2004:37), "I looked at that and I thought, Jeez, I just put this team together. To start to send people home, that would just have a devastating effect on the company." Unable to attract additional research partnerships, and with current investors unwilling to pony up additional funds for a company that had so far produced nothing, Binder and Rathmann realized that their only option might be to go public. The board of directors'

reaction was predictable: “They said, ‘You want to go be a public company? Why, we think you’re smoking dope!’” (ibid.). Binder and Rathmann moved quickly, however, and by June had prepared the offering, with the help of VC Bill Bowes’s connections at various investment banks. Thus Amgen pioneered a new use for an IPO: a last-ditch effort to save the company. But investors who bought and held those shaky 1983 shares have been handsomely rewarded.

3.) *Biogen: A company run by its scientists*

Starting in 1977, Walter Gilbert began to receive unsolicited (and unwelcome) overtures from investors and entrepreneurs who tried to recruit him to bioscience ventures. A physicist-turned-molecular-biologist at Harvard, Gilbert was instrumental in devising a new technique for the rapid sequencing of DNA—work that would earn a share of the 1980 Nobel Prize in chemistry. To his peers, and students, Wally Gilbert was an inspiration, a scientist’s scientist who combined brilliance and style (Hall, 1987:29-39). He initially rebuffed all commercial propositions. Relationships with industry were not yet the norm in the biosciences, particularly at Harvard, with its tradition of academic purity. But in late 1977, Gilbert agreed to meet with a pair of venture capitalists in Boston. Still insisting that he was not interested, Gilbert nonetheless remained in their sights.

The VCs were Ray Schaefer and Dan Adams, affiliated with the investment arm of Canadian mining firm Inco Ltd. The two had been searching for new investment opportunities and, in 1976, had met Moshe Alafi, one of the founders of Cetus and at the time its chairman. Alafi persuaded Schaefer that Inco should make a small investment in Cetus. Inco’s shares in Cetus were purchased from VC Tom Perkins, who was involved

in funding Genentech; Schaefer also took a 15% stake in Genentech on behalf of Inco (Elkington, 1985:61).

Infected by the biotechnology bug, Schaefer and Adams hatched an ambitious scheme to persuade the formidable Gilbert to join them in a start-up of their own. They would recruit an international team of renowned life scientists and ask Gilbert to lead it. Targeting heads of molecular biology departments at leading U.S. and European universities, Schaefer and Adams met with little initial success. Like Gilbert, most academics were wary of commercial endeavors. A turning point came when Schaefer contacted Phillip Sharp, a highly respected molecular biologist at MIT, who in 1977 had been a scientific consultant to Inco on their investment in Genentech. With Sharp along, Schaefer could persuade Gilbert to meet for dinner early in 1978. An evening of coaxing resulted in Gilbert agreeing to attend an exploratory meeting, scheduled for March in Geneva. At a subsequent preparatory meeting with Sharp and Gilbert, the venture capitalists presented their list of the European scientists they were targeting. Essentially a who's who of molecular biologists in Europe, the list impressed Sharp and Gilbert, who suggested a few additional names. Gilbert also agreed to chair the Geneva meeting.

Schaefer was able attract the other eminent scientists by mentioning, "Wally Gilbert will be coming and chairing the scientific meetings" (Hall,1987:194), a technique not unlike Winston Salser's in assembling Amgen's scientific advisory board. On March 1, ten top scientists—three from the U.S., the rest Europeans—assembled at Geneva's Hotel Le Richemond to discuss forming a company. Unfamiliar with commercial structures and wary of the investors' motives, the scientists drafted a preliminary charter to ensure that critical aspects of control would rest with the company's scientific board. Hugh

D'Andrade, a Schering-Plough senior executive and early member of Biogen's board of directors, remembers:

Biogen's unique organizing concept . . . was that it was run by its scientists, not by venture capitalists, or the banks. . . . The scientific board had the right to elect to the Biogen board quite a few of the scientists. When they went to the scientists, they said, 'Look, you don't have to quit your lab and go to work for Biogen like you're working for Genentech, and you don't have to have somebody from some company telling you what to do. The scientists are going to run this company.' (D'Andrade, 2001:12)

The Geneva meeting ended with no commitments, and a second meeting was scheduled for three weeks later at a hotel near the Paris airport. The once-reluctant Gilbert assumed the role of go-between: "In a sense, I became a spokesman for the scientists. I also had, in some ways, the greatest sympathy or affinity for the way in which the business side was structured" (Hall, 1987:195). On March 25, the group of scientific luminaries reconvened for two days, with Schaefer and another venture capitalist (Kevin Landry of T.A. Associates) discussing the ins and outs of the potential venture. Recalled Schaefer, "Everything had to be explained in minute detail—every line, every sentence—because they thought there was something hidden there" (Hall, 1987:209).

Before the second meeting, in Gilbert's Harvard lab, researchers had successfully cloned and expressed human insulin, an achievement with unmistakable commercial potential. During a break in the meeting, Sharp recalls taking a walk with Gilbert: "He started telling me about his experiments with insulin. . . . I was excited when I heard about it and congratulated him on the achievement, and then I asked him if he was going to patent it. . . . There was a rhythm, a nonspoken feeling, that people were going to try this" (Hall, 1987: 210). Near the end of the meeting, Gilbert asked the investors to leave

the room. For two hours, Schaefer and Landry waited outside, fearing the venture was doomed. To their surprise, Gilbert emerged with news that all ten scientists had agreed to join the company. Schaefer came up with the name Biogen. He shortly convened a third meeting in Zurich to iron out financial details and officially incorporate as a European firm to take advantage of the speedier drug approval processes there. Joining Inco and T.A. Associates in the \$750,000 initial investment were Moshe Alafi and a number of European concerns.

Two unique characteristics of the fledgling company are manifest in this story of its birth. First, although the investors may have brought them together, the scientists were going to call the shots. “This is the only company in the world where scientists have their hands on the company’s jugular vein,” observed Alafi in 1980 (Bylinsky, 1980). Two years later, when Alafi tried to recruit George Rathmann to run Biogen’s U.S. operations, Rathmann declined, partly because “the so-called scientific advisory board” was “all-powerful” (Rathmann, 2004:20).

Second, with such meager start-up capital, the company had little choice but to be “virtual” at first. Even after a headquarters lab in Geneva and a research center in Cambridge, MA, were established, most of Biogen’s research was conducted in the university labs of its founders. Indeed, the founding scientists were expected to advocate and sponsor their own particular projects and were promised shares in proportion to their projects’ impact over time (Higgins, 2005). Gilbert’s leadership style, imported from the world of elite science, turned scientific board meetings into intensely rigorous research seminars. Thus Biogen’s global “mini-academy” model created the potential for scientific excellence but some coordination costs as well.

In its first three head-to-head races to bring products to market, Biogen lost out to biotech competitors: Genentech was first to make human insulin, Centocor moved more quickly on hepatitis diagnostics, and Amgen cloned erythropoietin well before Biogen. Trying to gain greater focus, Biogen began shedding its early, Cetus-like pursuit of projects in a wide range of industries (from microbial metal-leaching to biofuels) in preparation for its 1983 IPO. Said Gilbert, “The most productive use of the current technology is in the pharmaceutical field. We now concentrate our efforts there because we see it as the new field in which the technology will be the most commercially rewarding over the next ten to fifteen years” (Elkington, 1985:70). Biogen continued to swing for the fences, however. Continued Gilbert, “Unlike a contract research company, our goal is not to make a ten percent return on our research effort. Our goal is quite different. We view our research as an investment on which we want to make a ten- or hundred-fold return” (ibid.).

Under the hydra-headed leadership of its eminent scientific founders, Biogen did not achieve predictable financial returns. Its IPO was underwhelming, and by 1985, the company was on the brink of bankruptcy. Its groundbreaking work in interferons, licensed to Schering Plough, brought limited royalty revenues. At this point, Gilbert resigned from his post as CEO and returned full-time to Harvard, where he remains (although he has been involved in subsequent biotech ventures). Biogen’s board recruited a seasoned pharmaceutical captain to run the ship in a different way: James Vincent, a Wharton MBA (’63) who had built Abbott Laboratories’ diagnostics business into an industry powerhouse (where he had been George Rathmann’s boss).

Vincent inherited the challenging task of wresting control away from the scientists and focusing the company on commercial products. In his first year at the company, Vincent cancelled dozens of research projects, sold Biogen Geneva to Glaxo and its Belgian operations to Roche, closed a lab in Zurich, and laid off 275 of the company's 500 employees (Fisher, 1997). "The perception had been that everything else would take care of itself if we had good science," said Vincent (Feder, 1992). And indeed, the company had excellent science. "It was deep, broad, and sound; it had just been misguided," Vincent maintained (Fisher, 1997). Over the next four years, he replaced the senior management team and focused Biogen's product development efforts on its original scientific breakthrough, alpha interferon. By renegotiating many of Biogen's license agreements with big pharma partners, Vincent engineered a financial recovery that by the late 1980s had the company poised to take advantage of numerous promising scientific milestones.

The early 1990s saw two more of Biogen's founding scientists receive worldwide recognition. MIT's Phillip Sharp received the 1993 Nobel Prize in Medicine. (Sharp never relinquished his faculty post at MIT. He remains a member of Biogen's board of directors today.) Also in 1993, Kenneth Murray of the University of Edinburgh was knighted in England. In 1996, the FDA approved Biogen's Avonex (interferon beta-1a), for the treatment of multiple sclerosis. By 2002, Avonex had reached worldwide sales of \$1.1 billion (Biogen IDEC, 2003:6). Biogen had its first blockbuster drug.

Today, Biogen is one of only three early biotech firms that have not been acquired. Maintaining its independence required a 2003 merger with San Diego-based IDEC Pharmaceutical Corp. It is emblematic of the interwoven nature of the biotech

industry that IDEC had been the encore for Hybritech's founders—Brook Byers, Ivor Royston, and Howard Birndorf—after its acquisition by Eli Lilly in 1985. IDEC also jointly developed with Genentech a blockbuster of its own, the anti-cancer drug Rituxan.

4.) *Centocor: A bridge between the academy and commercial healthcare*

In August 1979, a seasoned entrepreneur/executive and a trio of researchers formed Centocor in Philadelphia, to commercialize monoclonal antibody technology. Michael Wall, the entrepreneur, had graduated in electrical engineering from MIT in the 1950s and worked in a series of electronics start-ups. In the mid-1960s, he shifted his focus to healthcare, founding Flow Laboratories, a medical products firm that he and his partners sold in 1969 for \$3 million. Wall continued as a senior executive at Flow until the founding of Centocor. One of the scientists was a friend of Wall's: Hilary Koprowski, director of the Wistar Institute and pioneer in the development of improved polio and rabies vaccines. Joining Koprowski was Carlo Croce, a researcher at Wistar and a co-holder of a 1979 Wistar patent on a specific monoclonal antibody, and Vincent Zurawski Jr., at the time a post-doctoral fellow in immunochemistry at Harvard Medical School and Massachusetts General Hospital.

As Wistar director, Koprowski had actively courted Boehringer-Ingelheim, a large German chemical and pharmaceutical company, to license the patent, offering a 10-year license in exchange for funding Wistar research to the tune of \$500,000 per year. "They dragged the thing out for six or eight months," Koprowski recalls. "Finally their chief of marketing said he saw no future in monoclonal antibodies" (Vaughan, 2000:179). Koprowski turned to Michael Wall, who definitely saw a future in the technology.

Koprowski came up with the name Centocor: *cento*, for a literary or a musical composition formed by selections from different authors, and *cor*, the Latin root meaning “heart,” reflecting the intent to collaborate with research institutions and established healthcare companies to bring monoclonal products to market. The company was initially housed in the University City Science Center, an incubator on the University of Pennsylvania campus near Wistar.

As influential as the original founders was the firm’s first executive hire in February 1980: Hubert Schoemaker, an energetic Dutchman with a PhD in biochemistry from MIT. Schoemaker had pursued business rather than research as a career, turning down a post-doctoral position in Stanley Cohen’s storied lab at Stanford to work in a friend’s low-tech manufacturing company. After absorbing the ins and outs of daily business operations, Schoemaker took a job with Corning Medical, eventually working his way up to head of R&D. Michael Wall at Flow Laboratories had been one of his customers. Schoemaker, in a way, was a mixture of the other founders (Shaw, 1997). Like Wall, Schoemaker had ample business and managerial experience; like Koprowski and Zurawski, he had extensive training from an elite institution in a discipline relevant to the new venture’s scientific goals.

Centocor’s self-proclaimed business model was to be “the bridge from the academic research laboratory to the established health care supplier” (Centocor, 1982:12). Its first license, Koprowski’s and Croce’s patent for a monoclonal antibody, was not without controversy, however. In granting Centocor an exclusive license to the Wistar patent, Koprowski—at the time, still Wistar’s director—incurred accusations of conflict of interest from Wistar’s board. The issue came to a head in 1982, just before

Centocor's planned IPO. With legal action threatening to scuttle the stock offering, Koprowski settled with Wistar. He agreed that he and Croce would resign from Centocor's board of directors and grant the institute 150,000 shares of Centocor stock (Vaughan, 2000:185).

Despite this setback, Centocor's strategy of licensing breakthroughs from academic and nonprofit labs continued. As Schoemaker recalled, "The visionary license agreement with Wistar set the tone. We realized it was a lot cheaper to roam academe and pay a royalty back for what we developed than start our own research facilities. Collaboration was the best way to be competitive" (Vaughan, 2000:186). As Wall commented in 1985, "You can have a garage full of PhDs working on a project, and nine times out of ten some guy across the street is going to come up with the discovery that beats them all" (Teitelman, 1985:80). Because Centocor focused on producing diagnostics rather than therapeutic drugs, the company could develop assays that would run on equipment manufactured by such healthcare giants as Abbott Laboratories and Warner-Lambert, avoiding the hassle and expense of its own manufacturing and sales arms.

As Schoemaker transitioned into the CEO role in the mid-1980s, Centocor broadened its focus from diagnostics to therapeutics. Eventually, Schoemaker bet the company on FDA approval of Centocor's first drug, Centoxin, making costly investments in proprietary manufacturing and sales capabilities. When the FDA denied Centoxin's application in 1992, Centocor barely survived. Michael Wall, then in semiretirement, came back as chairman and helped Schoemaker cut two-thirds of the company's workforce, regrouping around a pair of promising therapeutics. This

marked a return to the “bridge” model of drug development. In 1997, Schoemaker reflected, “Every drug that Centocor has developed has come out of an academic collaboration” (Shaw, 1997). After the two drugs (ReoPro and Remicade) received FDA approval, Centocor was acquired by Johnson & Johnson in 1999 for \$4.9 billion.

5.) *Cetus: An academic “free space”*

Incorporated in 1972, in Berkeley, California, Cetus was arguably the first company founded with the intent of commercializing advances in molecular biology and genetics. Its four-person founding team included two would-be entrepreneurs, a Nobel laureate in physics, and a successful Bay Area financier.

Ronald Cape, one of the two entrepreneurs, had just finished a three-year post-doc in molecular biology at UC Berkeley’s Virus Laboratory. He could sense the pregnant condition of the life sciences: “It was like maybe a dam waiting to burst or an egg waiting to hatch, but the fact is, there were a lot of Nobel Prizes in molecular biology, but no practical applications” (Cape, 2006:16). Cape’s background included a Harvard MBA, followed by a stint managing a family drugstore business in Montreal, during which time he earned a PhD in biochemistry at McGill University to escape the boredom of the job. Upon finishing his post-doc at Berkeley, he had no desire to return to the cold winters of Montreal or the confines of his family’s business. He also realized he was more interested in the business of science than in science itself. He met his eventual co-entrepreneur, Peter Farley, in a venture capitalist’s office in San Francisco. Farley was an MD who had served as a medic in Vietnam; after the war, he earned an MBA at Stanford. Like Cape, Farley was serving

as a consultant and advisor to VCs on medical-oriented ventures, biding his time until he could launch his own. Cape and Farley immediately recognized their common interests and formed a partnership.

Donald Glaser, a third founder, was a professor of molecular biology at UC Berkeley. He had earned the 1960 Nobel Prize in physics for his invention of the bubble chamber, then taught himself molecular biology. He was applying his physical science savvy to the automation of basic biological research. Having recently lost NIH funding for his project—and with a daughter headed for medical school—he saw Cetus as an opportunity to fund his work and generate some extra income. Glaser’s prestige added credibility to the venture, though his expertise in the biological sciences was not deep enough to give him direct influence over Cetus’s technical direction: “My job, really, was to interview and hire real molecular biologists who knew how to do genetic engineering” (Glaser, 2006:96). He remained a professor at Berkeley, never spending more than a day a week at Cetus.

The fourth founder, Moshe Alafi, was already a successful investor in the Bay Area and a social acquaintance of Glaser’s. Cape (2006:67) describes Alafi’s role: “Moshe Alafi was the chairman of the company, and he had experience in venture capital, had friends in the venture-capital industry. . . . It’s hard to say that he was operationally involved, but he was involved in much of the decision-making and we consulted him constantly.” Alafi gained crucial (if painful) experience from his involvement with Cetus, going on to fund two subsequent early biotech ventures, Biogen and Amgen.

An old adage asserts that true pioneers are easy to distinguish: they are the ones with the arrows in their backs. As the earliest self-proclaimed biotech company, Cetus certainly absorbed multiple attacks, many of which centered on its lack of focus. Investors became frustrated by its “wide ranging, apparently indiscriminate eclecticism” (Vettel, 2006:202), with projects ranging from genetically engineered bacteria for alcohol and fructose production, bioremediation, vaccines, antibiotics, and new approaches to fermenting microbes (Rabinow, 1996:32-33). Cape (2006:21) describes the company’s earliest approach in colorful terms: “The genetic code had been decoded. The field was preparing for something. I mean, it hadn’t been exploited *at all*. And we presented ourselves as ‘there’s got to be a pony in there someplace.’” To “find the pony,” Cetus recruited a star advisory board (which in time included six Nobel laureates, Francis Crick among them) and smart scientists, equipped them with state-of-the-art laboratories, then turned them loose to see what they came up with. This “free space” was initially exciting enough to generate a fair amount of hype and garner generous financial support; Cetus’s 1981 IPO raised \$108 million, then a record. But as time wore on, the charm wore off. As Glaser (2006:105) expresses it, “We were roundly criticized in some quarters as being a playground for academic scientists. . . . The direction was not very stringent.”

The playground allowed such free spirits as Kary Mullis to pursue his work on polymerase chain reaction (PCR), a technique that proved foundational to subsequent research in the biosciences. PCR earned Mullis the Nobel Prize in Chemistry in 1993—still the only Nobel Prize awarded so far for work conducted

solely in a biotechnology company.²⁵ Cetus later overcorrected for its lack of focus, investing heavily in Interleukin-2, an immune-system booster. When the FDA failed to approve the drug in 1990, Cetus could no longer support its operations and sold off its PCR franchise to Roche Bio. Its remaining operations were absorbed by its smaller neighbor, Chiron, in 1992. It is notable, however, that three people who played founding roles in subsequent early biotech ventures—Bob Swanson (Genentech), Moshe Alafi (Biogen), and Bill Bowes (Amgen)—were associated with Cetus as investors and learned from its early mistakes.

6.) Chiron: “Get in or lose out”

Chiron came close to never existing. Its main founder, the distinguished scientist and UCSF research director William Rutter, was one of the early members of Amgen’s scientific advisory board. Amgen’s founders had initially offered Rutter the CEO post, which he declined (Kornberg, 1995:204). After they had hired George Rathmann as CEO, he moved quickly to keep Rutter in the Amgen fold, proposing that Rutter open an “Amgen North” lab in the Bay Area, staffed with scientists of Rutter’s choosing (Rathmann, 2004:34-35). At about the same time, Rathmann (at Rutter’s suggestion) had been talking to two of Rutter’s former students about joining Amgen. One was Ed

²⁵ Mullis joined Cetus in 1979 after obtaining his Berkeley PhD in biochemistry and doing post-doc stints at University of Kansas and UCSF. During his seven years at Cetus, he did work on nucleic acid chemistry and invented PCR. His opinions about science and business, and the extent to which scientists are usually directed by those who do not understand their work, are pointed and acerbic: “I have never encountered a business person with any true interest in science. Why should he be interested? He had the choice, and he chose business. It is only through good fortune that money ends up in the hands of scientists, who know how to use it for anything other than making money, and it is a sorry situation indeed, since much scientific research is not cheap. Government grants, although offering, in theory, a preferable alternative, have the similar problem of being often administered by scientific incompetents who are after power and personal security, instead of widely useful knowledge. Good scientists don’t like administrative jobs, which leaves us exactly where we are. Science is generally directed by non-scientists.” (www.karymullis.com/pcr.shtml).

Penhoet, an associate professor of biochemistry at UC Berkeley; the other was Pablo Valenzuela, who was working in Rutter's lab at UCSF. When the "Amgen North" idea derailed, the three researchers realized they could found their own company instead.

Penhoet (2001: 102-104) recalls:

We continued to say to each other: we don't have to do Amgen. Other companies were being formed, and there was a lot of activity in the field at that time. . . . to a point where we said, 'Well, if we're going to do this . . . we can get some money, and we have reasonable enough management skills, having managed big labs and people.'

Rutter's experience and relationships were the key to the venture. A scientist of broad interests and training—including long-term consulting ties to pharma giants Abbott, Eli Lilly, and Merck—Rutter was the academic equivalent of a turn-around artist. Heavily recruited by the UCSF medical school to take over as department chair of biochemistry, he turned down the offer at least three times before finally agreeing:

At that time, UCSF was unpopular and considered a mediocre institution. All my friends were saying, 'Why leave a great place (Univ. of Washington) to go to a medical school?' . . . Gradually, we consolidated the department to nearly twenty open positions. It was the only significant place in the United States where they had that many open positions. . . . I realized this was a great opportunity. . . . I had gotten all steamed about making a concerted onslaught on human biology. The best way was to bring together people with complementary talents and common interests. (Rutter, 1998:16)

Granted tremendous freedom, Rutter hired a diverse group of top-notch scientists, fought for contiguous space, and transformed the department into an academic powerhouse—a seedbed for numerous scientific breakthroughs and biotech ventures. In fact, it was the poaching of his hand-picked team of scientists by upstart biotechs in the late 1970s and early 1980s that eventually convinced him to start his own commercial venture: "The best people in my lab were being recruited by other companies. It became obvious that I had to get in or lose out" (Gannes, 1987:9). Penhoet (2001:100) corroborates his motivation:

“At some point, Bill concluded that he couldn’t continue to be competitive on several projects that he was pursuing [at UCSF] . . . because all of the people who worked for him . . . were being offered compelling positions in the budding industry.”

Over Easter weekend in 1981, Rutter and Penhoet drafted a preliminary business plan for Chiron and began meeting with venture capitalists in earnest. Rutter had founded and sold a small company earlier in a deal that involved Charlie Crocker (of the Crocker Bank family); Penhoet’s wife was a social acquaintance of the Crocker family. Crocker assured Rutter, Penhoet, and other scientists who were considering job offers from Amgen that “he would help raise the money for this new company, and it would be fine” (Penhoet, 2001:107). Such assurances were crucial; two thirds of the company’s first 20 scientific hires were from UCSF, and the remaining third from UC Berkeley. By June 1, the founders had lined up enough initial funding to launch the company (based in part on a complex deal to bring a Merck-funded project from Rutter’s UCSF lab into Chiron; see Green, 2008:20). Rutter became chairman, Penhoet president, and Valenzuela R&D director. Only Valenzuela left his day job, however; Rutter remained chairman of the department of biochemistry and biophysics at UCSF, and Penhoet stayed on half-time at UC Berkeley (Penhoet, 2001: 109).

Rutter’s 12 years as chair of a growing, dynamic, interdisciplinary university department had prepared him for some of the executive duties he assumed at Chiron:

[The UCSF Biochemistry and Biophysics department] was a little bit like a company, a little bit like Chiron is today. One of the reasons why it’s been so easy for me to move to Chiron full time is that we have the flexibility [in the department] to make our own decisions and carry them out with no artificial bureaucratic barriers—tremendously important in a competitive scientific environment. (Rutter, 1998:74)

Penhoet, too, had commercial experience, having moonlighted throughout the 1970s in his wife's family's Mercedes-Benz auto leasing businesses (Koberstein, 1994:41). Rutter would remain chairman of the company until 1999, and Penhoet continued as its president and CEO for 17 years, both remarkably long tenures for scientist-founders.

Chiron's expertise was in vaccines. Indeed, Rutter's belief in the healthcare benefits and commercial potential of vaccines was what he called a "secondary reason" for founding the company: "I'd gathered that the pharmaceutical industry itself was not interested in protection from disease. . . . Most all the companies began to essentially withdraw from vaccine development. . . . I felt that, in the future, . . . prevention and vaccinology would be a tremendous boon to health care" (Rutter, 1997:65). In addition to its focus on vaccines, the creativity and broad scientific vision of its founders led Chiron to successful products in diagnostics and therapeutics.

William Green (2008:33), Chiron's General Counsel from its founding until 2004, noted that Chiron was more successful than others in partnering with larger pharmaceutical companies and universities:

Chiron prided itself in having and managing dramatically more collaborative arrangements, both with commercial entities and also with universities, than its peer companies. . . . Chiron's principal advantage was in having a very deep, early-stage research competence, and a view of having this sense of urgency and speed, and being able to move a concept through the very earliest stage of research to create a compound of some sort that would be interesting. Chiron didn't have the downstream skills to move that compound through development process or through pre-clinical or clinical testing . . . so it depended upon its collaborators to execute the more traditional parts of pharmaceutical development processes.

Like Centocor, Chiron partnered with larger pharmaceutical companies to market and distribute its products; unlike Centocor, however, Chiron's own staff of scientists developed most of the company's breakthroughs. Also, like its cross-Bay comrade

Genentech, Chiron had a “a very high order of belief in academic freedom, and . . . a very low level of concern about loss of trade secrets,” which translated into a “very aggressive desire to encourage people to publish” (Green, 2008:28). Chiron’s expansive strategy of early-stage collaborations with university researchers, which served as initial probes into new areas of medical research, made it one of the most highly connected of all the early biotech firms (Powell, Koput, and Smith-Doerr, 1996). Like Genentech, Chiron imported an “invisible college” academic model into its business strategy.

Among Chiron’s notable achievements were an IPO in 1983 (a few weeks after Amgen’s), the discovery of the hepatitis-C virus, and the bold acquisition in 1992 of biotech pioneer Cetus. Chiron was subsequently acquired by one of its big pharma partners, Novartis, in April 2006.

7.) *Genentech: The best of both worlds?*

Genentech was neither the first nor the most commercially successful of the early biotech firms, yet arguably it has exerted the greatest influence on what ultimately became the canonical DBF form. Such central practices as boundary-blurring contracts with academic scientists, simultaneous patenting and publishing, milestone payments from pharmaceutical firms, and “proof of principle” research evolved from origins that were as simple as they were novel. In the words of founder Herb Boyer (2001:87), “We tried to set up an atmosphere which would take the best from industry and the best from the academic community, and put them together.”

The scope of Genentech’s influence would have been impossible to predict in 1976, when the firm was inauspiciously founded by an unemployed would-be

entrepreneur and a celebrated molecular biologist on the verge of promotion to full professor. The entrepreneur, 28-year-old Robert Swanson, had graduated from MIT with a BS in chemistry and an MS in management, then spent five years working as an analyst for Citibank's venture investment group (1970-1974) and Kleiner & Perkins (1974-1975). When Kleiner & Perkins let him go, Swanson started an active job search. He planned to gain operational experience with an established company, then strike out on his own. But job offers were not forthcoming; among the firms that turned him down was biotech pioneer Cetus. Swanson's \$410 monthly unemployment check was stretched thin: "My half of an apartment in Pacific Heights was \$250, my lease payment on the Datsun 240Z was \$110, and the rest was peanut butter sandwiches and an occasional movie" (Swanson, 2001:21). (It is a testament to Genentech's subsequent success that nearly every account of its founding describes Swanson as a venture capitalist.)

Along with the job interviews, Swanson had been reading scientific journals, searching for commercializable ideas. He was intrigued by the burgeoning research on recombinant DNA. More out of desperation than visionary foresight, Swanson began cold-calling academics who had attended the famous Asilomar conference on patenting life forms, to explore the possibility of forming a bioscience venture: "So what triggered this [idea of starting a company] was, I needed to get a job. . . . I probably had three [job] interviews a day for three or four months. This was a pretty scary period" (Swanson, 2001:10). The first scientist who actually agreed to meet with Swanson was Herb Boyer at UCSF.

Boyer's academic career was established by the time he met Swanson in January 1976. As co-author with Stanford's Stanley Cohen on the 1973 papers detailing the

methods for recombinant DNA, Boyer was about to be promoted to full professor and made director of UCSF's newly created graduate program in genetics. Perhaps such security allowed him to risk founding a commercial venture; up to that time, distinguished bioscientists had limited their industrial involvement to advisory and consulting roles. In fact, Cohen (who was on Cetus's advisory board) tried to protect Boyer from a career misstep: "Stanley took me to lunch to talk me out of [founding Genentech]. He said, 'I've heard that Swanson's just a gofer anyway'" (Boyer, 2001:82). Boyer stuck with the "gofer," though his initial expectations were very modest: "I thought it would be a good way to fund some post-docs and some work in my laboratory" (Boyer, 2001:71).

The combination of a renowned and somewhat laid-back scientist with a high-energy, low-experience entrepreneur was oddly powerful. Boyer knew who was doing the best science; he guided Swanson to set up a contract with the City of Hope National Medical Center in Southern California, where Art Riggs and Keichi Itakura had just been denied NIH funding for their work to produce a human protein (somatostatin) in *E. coli* bacteria: "The [NIH] reviewers . . . said the proposal lacked scientific merit and that it could not be completed in the several years for which funding had been sought" (Kiley, 2002:11). With Genentech's funding and help from Genentech-funded post-docs in Boyer's lab at UCSF, Riggs and Itakura produced the protein in nine months. This "proof of concept" research showed that the technology worked. With evidence in hand, Genentech leased its own space, equipped a lab, and hired its first scientists: David Goeddel and Dennis Kleid from SRI in Palo Alto.

Swanson's decision to remain a virtual company until the technology had been demonstrated was heavily influenced by venture capitalist Tom Perkins, Swanson's former boss (Perkins, 2002:4-6). A second financial innovation stems from the same root: arranging milestone payments from large pharmaceutical partners in exchange for showing progress toward agreed goals, thus obtaining funding without diluting the company's equity (Boyer, 2001:88). Genentech also eschewed prevailing practice and did not set up a scientific advisory board of distinguished (and expensive) biomedical luminaries. Instead, Swanson relied on the opinions of the young scientists he recruited, guided from a distance by Boyer, who never left his full-time academic post at UCSF. As David Goeddel (2003:21) recalls:

The stories of some of the other people at that time with other companies were that they [the scientific founders] tried to still be the big-shot professor and tell the companies how to run. . . . I don't think Herb came as often as Bob wanted him there. But when he would come, Herb would come around and say, "Do you have problems or issues? What are you working on?" And he'd try to give advice. Other things he would say, "That's up to you. I can't help you on that. You're better at that than I am." He said, "This is your project; you're going to get credit." He wasn't putting his name on the papers. I think his approach of letting the young scientists do the work really paid off well.

Nobel laureate and Stanford professor Arthur Kornberg (1995:200), a consultant to Alza and scientific founder of the biotech company DNAX, noted the uniqueness of Genentech's approach: "Unlike other biotech ventures, with a seasoned scientist or a distinguished board of scientific advisors for guidance, Genentech relied on its 'Young Turks,' unheralded but talented, industrious, and highly motivated to succeed".

These talented young scientists thrived under another of Genentech's maxims: its insistence that they continue to publish their work in top-tier scientific

journals. Traditional pharmaceutical companies shrouded their R&D efforts in secrecy; even biotech pioneer Cetus had adopted a similar approach early on (Rabinow, 1996:32). In contrast, Boyer championed publication, and Swanson ensured that lawyers were ready to file the necessary patents just preceding the submission of the papers. The orientations of the two founders complemented each other, according to Goeddel (2003:24): “Bob was always a little more worried than Herb about publications and other people knowing what we were doing. There was probably a healthy tension—Bob at one end, Herb at the other. And somewhere in the middle was how the company worked.”

As a result, Genentech established a stellar scientific reputation. From 1980 to 2001, Genentech published more highly-cited bioscience papers than any other institution except MIT (Levinson, 2001). As Kornberg (1995:201) observed, “The impact of Genentech’s success in the ensuing years was felt both in academic and industrial circles. The excellent quality (and large volume) of papers published promptly in the leading journals helped to erase the stigma attached to research careers in an industrial environment.” Boyer certainly endured the stigma early on, suffering accusations of impropriety and profiteering from his academic colleagues (Yoxen, 1983:51). Boyer (2001:98) recalls, “I had a lot of anxieties and bouts of depression associated with this. . . The way the attacks went, I felt like I was just a criminal. But I always felt that what I was doing was right.”

Right or wrong, Boyer’s stature and Genentech’s rapid ascendance as a premier scientific lab left a lasting legacy for subsequent biotech firms. Boyer, the academic, knew how top-flight science operated; Swanson, the rookie entrepreneur,

was unencumbered by any dominant commercial model, but tightly linked to the VC network of Kleiner & Perkins. Both founders shared values around what motivates people (freedom, ownership) and how companies succeed (focus, fiscal conservatism). Perhaps most crucially, they were unbiased by the conventions of commercial science: “We were so naive we never thought it couldn’t be done. . . . I always maintain that the best attribute we had was our naiveté” (Boyer, 2001:96). They were able to create an entirely new hybrid: a world-class research lab funded by commercial means, and focused on producing human therapeutic agents.

8.) *Genex: Biology as manufacturing*

In April 1977, an employment ad in *Science* magazine sought applicants for the position of CEO of a new genetic engineering venture. The ad was placed by Robert Johnston, a Princeton-based investor who had founded his own firm (Johnston Associates) in 1968 after a career with notable New York investment banks. Among those who responded was Leslie Glick, a 37-year-old scientist who, at this relatively early point in his career, had earned a PhD in zoology from Columbia, done a post-doc at Princeton, left a department chairmanship at SUNY-Buffalo to start and manage a profitable tissue-culture company (Associated Biomedic Systems Inc.), moved to Washington, DC, to found a nonprofit institute for scientific accountability, and was consulting with companies large and small on life sciences issues. Thinking that the job posting might provide entrée to a consulting engagement, he called Johnston: “I was curious. I was wondering where did this guy get the capital to set up something like this? Because at that point, there were only two such companies that existed” (Glick, 2009).

Johnston told him that the goal was to create new medicines from recombinant DNA, and that, in fact, he had not yet lined up the capital to back the venture.

Glick's next phone call was to David Jackson, an associate professor at the University of Michigan whom Glick had met at a conference two years earlier. Jackson's PhD was in molecular biology from Stanford; he was first author on Paul Berg's 1972 paper on recombinant DNA (Jackson, Symons, and Berg, 1972). Preceding his PhD, Jackson had spent a summer internship in Eli Lilly's research labs in Indianapolis—enough to convince him that he did not want a career in industry. Still, Jackson found Glick's idea intriguing, although both Glick and Jackson believed human therapeutics to be a difficult and distant target. They reasoned that the technology could yield quicker payoff in the manufacture of industrial chemicals:

I told him [Jackson] my concerns about trying to do this to develop drugs, and he said, 'Right. The way to go is to do what you can do right now. We know enough about bacteria we could develop them to become more efficient at making chemicals and industrial products.' That resonated with me. And he gave me some examples, like amino acids. (Glick, 2009)

Glick called Johnston back with the idea of focusing the company on biological manufacturing processes. Johnston wanted to know more, so Glick started digging into it:

I spent two months in the Library of Congress looking into the fermentation industry in Japan. . . . I found out how large the market was for amino acids, and I saw some other chemicals that could be derived from amino acids. I saw there was an opportunity there. So, two months later, I said to Bob Johnston: 'Let's do it.' (Glick, 2009)

The new venture was incorporated in June of 1977 and christened Genex (pronounced "gene-x"), with Johnston and Glick contributing \$1,500 each, and Jackson earning founder's shares for assembling a scientific advisory board. Jackson was not ready to leave the university, though recent events had undermined his faith in academia. In the

early debates over the safety and ethics of bioengineering research, Jackson had been put through the wringer:

There was this long, drawn-out, dragged-out, convoluted, politicized process that went on for a year-and-a-half to two years at the University of Michigan with teach-ins, meetings of the faculty senate, meetings of the Ann Arbor City Council, the Board of Regents, I mean, it just went on and on about all of this. And I was sort of a central focus in all of this, and had to participate in it, had to defend myself. (Jackson, 2009)

Glick and Johnston put together a business plan, and the three founders began visiting VCs. At first, no one was interested; the technology was too new, and the business opportunity too unproven. At the time, only one recombinant DNA firm, Genentech, had been funded by venture capital. (Cetus was founded before rDNA's invention.) Glick rewrote the business plan and, in early 1978, InnoVen, a New Jersey-based VC backed by Monsanto and Emerson Electric, decided to invest. Genex officially opened its doors in Rockville, MD, in May.

Jackson had been involved in pitching the company to VCs and assembling the scientific advisory board; he also consulted for the company one day per week. He remained in academia until 1980, when he left Michigan to join Genex as its vice president and scientific director. Unlike Genentech's Boyer, who had co-founded the company but remained at the university, here a noted scientist resigned his tenured academic post in favor of a commercial venture. Other scientists took notice (Kenney, 1986:96). Jackson's decision boiled down to a critical question: where could he do better science? "Even though it was just this incredibly counter-cultural thing to do at that point, [I thought] that if I were at Genex with some significant money available to do R&D, I could actually do more science and have more fun than I was having at the University of Michigan" (Jackson, 2009). Jackson never looked back. His subsequent career includes

two additional biotech start-ups, 10 years in research management at DuPont and a DuPont-Merck joint venture, and subsequent consulting and angel investing. The scientific advisory board he assembled for Genex was illustrious, but its role was chiefly symbolic: “Probably the most important role of the SAB was to give the company scientific credibility when it was seeking investment capital” (Glick, 2009). Jackson nonetheless worked hard to involve the SAB in identifying and attracting promising young recruits, and in advising on the scientific feasibility of Genex’s research contracts. Publishing in scientific journals was never encouraged: “It takes a lot of time to publish stuff, and we were always under enormous time pressure to meet various milestones. And there was a concern about disclosing stuff prematurely, before we’d really had a chance to capitalize on it” (Jackson, 2009).

Genex’s founding vision—to harness biological processes for manufacturing industrial and commercial chemicals—became a reality in the 1980s and propelled the company to rapid growth. The lion’s share of the company’s revenues came from a contract with G.D. Searle to manufacture L-phenylalanine (one of two vital ingredients of the artificial sweetener aspartame) using a process developed at Genex, but Genex also did contract research (ironically, most of it for pharmaceutical companies) and even developed a patented enzyme formulation that it tried to market as a drain unclogger (Elkington, 1985:198). To fulfill the Searle contract, Genex had purchased and extensively modified a manufacturing plant in Paducah, KY, becoming for a time the world’s largest supplier of L-phenylalanine. When Searle unexpectedly pulled out of the agreement, Genex was forced to lay off 40% of its workers and scramble for new

business. Genex's revenues declined more than 80% between 1985 and 1986 (*New York Times*, 1987).

By the time Genex was acquired by Enzon Inc. in 1991, it had slipped into obscurity (Feder, 1991). But each of its founders was involved in subsequent biotech ventures. Johnston described one of the lessons he had learned from starting Genex : "You have got to go out there with a rifle, not a shotgun." He said he would never again "dream of starting a company as broad as Genex" (Elkington, 1985:43). Johnston's subsequent biotech ventures included Cytogen, Ecogen, Sepracor, i-STAT, Envirogen, and Praelux (JAI, 2009). Glick was instrumental in organizing the first biotech industry association, the Industrial Biotechnology Association, founded in 1981.

9.) *Genzyme: A niche collector*

What happens when a successful entrepreneur asks a venture capitalist to find him his next new venture? The unlikely answer is Genzyme. The entrepreneur was Sheridan Snyder, a 1958 graduate in French from the University of Virginia, where he had been the school's top tennis player. Channeling his competitive energies into business, Snyder founded a company in 1964 that manufactured envelope-stuffing equipment and was eventually sold to Pitney-Bowes. His next success was Instapak, a company that pioneered the use of packaging foam for shipping sensitive equipment. Instapak was backed by Ed Glassmeyer, managing partner at Sprout Capital Group at Donaldson, Lufkin & Jenrette. In 1974, Glassmeyer and an associate (Stewart Greenfield) left Sprout with the idea of starting their own fund, Oak Investment Partners. In 1980 Snyder contacted Glassmeyer with an unusual proposition, "I'd like you to help me find a new

venture, and as an inducement, I'll pay you a retainer" (Glassmeyer, 2009). Ginger More, an associate at Oak, ended up leading the effort.

In their search, Oak and Snyder were referred to the New England Enzyme Center at Tufts Medical School by 3M (an Oak limited partner). There they met Dr. Stanley Charm, a professor of physiology and director of the center. Charm's research on the detection of penicillin in cow's milk looked promising, but interpersonal differences got in the way of a deal. Instead, More and Snyder convinced another researcher in the Enzyme Center to join them: Henry Blair, an enzymologist, who brought with him a grant from the National Institutes of Health to develop a drug for Gaucher's disease, a rare but debilitating enzyme deficiency. On June 8, 1981, Genzyme was officially launched with Snyder as CEO, Blair as chief scientist, and More as Oak's representative on the board.

None of Genzyme's founding team had expertise in biotechnology. Oak was known for "office of the future" ventures (computers and communications), and Snyder had been successful in commercializing packaging technologies. Blair was a competent researcher but not at the forefront; his work at Tufts was an extension of the research of Dr. Roscoe Brady, an NIH scientist who had been pursuing Gaucher's treatment for more than a decade. Acknowledging Brady's foundational (though not founding) role, Sheridan Snyder recalls, "Dr. Brady is the true father of Genzyme. It was all of his research, scientifically and clinically, which resulted in the Ceradase product for Genzyme" (Snyder, 2009). To add scientific depth, Genzyme entered in 1983 into an exclusive agreement with BioInformation Associates (BIA), a group of eight tenured Harvard and MIT professors from the departments of chemical engineering, biology, biomaterials, and

chemistry (Genzyme, 1986:22). In exchange for a 10% stake of the company and annual retainers, BIA would provide scientific guidance and opinions, and Genzyme would enjoy exclusive rights to BIA's expertise without the payment of further royalties or consulting fees. "They gave us credibility with all the stellar scientists and they brought us the carbohydrate side of our chemistry," recalls Ginger More (2009). One of the original BIA partners—Charles Cooney, a professor of chemical and biochemical engineering at MIT—remains a member of Genzyme's board to this day.

In 1983, More initiated a search for a seasoned healthcare executive to help the company grow. Through Oak's network, they found Henri Termeer, a Dutchman and pharmaceutical veteran from Baxter Travenol. He joined as president, became CEO in 1985, and remains CEO today. Termeer had been head of the blood fractionating group at Baxter, looking for new ways to produce proteins and limit reliance on human donors. Also in 1983, the Orphan Drug Act was passed. Genzyme ultimately became well-known as one of the early orphan drug success stories, thanks to its development of Ceredase, a naturally derived enzyme replacement therapy for Gaucher's disease, and a follow-on recombinantly produced version of the enzyme, Cerezyme. Under Termeer's leadership, Genzyme developed orphan drugs for at least four other rare diseases.

Termeer took a significant risk in joining Genzyme. At the time, the company was a far cry from big pharma, where Termeer had built a successful and comfortable career. Genzyme's headquarters were in a cramped old building on the edge of Boston's seedy "Combat Zone," and Termeer's starting salary was half of what he had been earning at Baxter. But Termeer remembers telling himself, "Biotechnology is going to have an enormous impact on medicine, industry, and the economy. Being in at the beginning is an

opportunity that comes just once” (Wilke, 1987). Over time, he recruited a number of Baxter alumni to join Genzyme.

At Baxter, Termeer had seen the practical aspects of developing drugs for niche markets. In addition to rare diseases, Genzyme also worked on technologies that would improve the manufacturing of biotechnology drugs. Even before Termeer’s arrival, Snyder and More had purchased Whatman Chemicals, a small specialty chemical maker in the U.K., knowing that eventually Genzyme would need the ability to manufacture its own products. From BIA, Genzyme acquired expertise in glycoprotein remodeling, a process that snips away at the large protein chains that constitute most new biotech drugs. It changes their shape and the way they act in the body, potentially reducing side effects, affording a renewed patent position for an improved remodeled compound (Wilke, 1987). These and other moves made manufacturing a core value for Genzyme. As one Genzyme alumnus described it, “Henri loves producing stuff. Manufacturing is Genzyme’s strategic competitive advantage, not research, which may rub some people the wrong way—but not Henri. Manufacturing has always given Genzyme the upper hand in negotiations because they know how to produce stuff and that’s unusual. It’s a business, not a research institution” (Higgins, 2005:244).

Termeer and More also inculcated a strong sense of fiscal conservatism at Genzyme. The choice of niche markets reflected a risky bet, but it was very conservatively managed. “Ginger and Henri were a great team,” recalls Glassmeyer. “Neither was bet-the-ranch oriented, so they weren’t constantly battling over what the strategy should be” (Glassmeyer, 2009). Perfecting the enzyme replacement therapy to treat Gaucher’s was hugely expensive, and the price of treatment extremely high. The

scientific advisory board and other senior managers felt that this focus would bankrupt the company and voted against it. But Termeer saw the advantage of the government's orphan drug category, which gave exclusive rights for seven years. One NIH member was quoted as saying, "I would like to ask Henri how he had the guts to make that decision." Higgins (2005) asserts that Termeer's fortitude stemmed from his deep commitment to maintain the company's independence. Rather than overextend the company or rely on funds from big pharma or other partners, Termeer ensured that Genzyme internally generated most of its R&D funding. That strategy resulted in Genzyme being labeled a small-growth company in an environment where its biotech peers were swinging for the fences. As one analyst put it, "Genzyme is a company of singles rather than home-runs" (Senior, 2007:8). Focusing on hard-to-produce products for tiny (but low-competition) markets has allowed Genzyme to survive as one of the few remaining independent biotech entities. A less successful Termeer innovation was its tracking stocks, intended to raise money for Genzyme's highly autonomous (and often high-risk) divisions without diluting the parent company's stock price. In the end, the ploy was rejected as financial window dressing.

In executing his strategies, Termeer played the role of a portfolio manager, providing financial rather than scientific leadership. Scientific research was never a preeminent value at Genzyme. More (2009) recalls that academic excellence was not a big part of the company's founding culture, and she cannot remember much encouragement for staff scientists to publish their findings: "We weren't out publishing papers. Henry [Blair] . . . was not a scientist who was well-known, not the type who would try to get ahead by publishing a lot of papers. He was just trying to cure

Gaucher's." As Jim Vincent, the CEO of Cambridge rival Biogen, explained, "Genzyme is entrepreneurial and fast on their feet. They followed an entrepreneurial technology model, not a deep internal scientific discovery drug model" (Higgins, 2005:249).

Another area in which Genzyme stands apart from most other biotech pioneers is its history of growth through acquisition. Since 1991, Genzyme has acquired 29 companies, compared to a single merger by Genentech, four by Biogen, and eight by Amgen (although Amgen's mergers vastly exceed Genzyme's in total market capitalization). Acquiring companies distinguishes Genzyme, and in 2006 it broke a biotech taboo in successfully completing a hostile takeover of AnorMed, outbidding Millenium Pharmaceuticals, the preferred suitor.

Genzyme has become known for its niche focus on narrow markets, independence from big pharmaceutical companies, emphasis on process development and manufacturing, and decentralized business units—all of which belie the company's roots. In the words of Genzyme's venture capitalist, "This was not a team of blood brothers who met around a round table two or three times a day and pledged allegiance to one another. It was an ad hoc collection of academics (BIA), a project leader (Blair), a founding entrepreneur (Snyder), and a manager (Termeer), who together realized the potential of Genzyme" (Glassmeyer, 2009).

10.) *Hybritech: Built for Success or Biotech at the Beach?*

The oft-told story of Hybritech's founding revolves around a 1978 meeting in the San Diego Airport between UCSD researcher Ivor Royston, his lab assistant Howard Birndorf, and venture capitalists Kleiner, Perkins, Caufield & Byers. When asked how

much money they needed to create monoclonal antibodies in a commercially funded lab, Royston and Birndorf are reported to have pulled the number \$200,000 out of the air, only to have Perkins reply, “No, I’ll give you \$300,000. I am sure you underestimated” (Royston, 2006). Although he ran out of gas on the way back from the airport meeting, Birndorf located commercial lab space in La Jolla two days later. Within six months, he and Royston had successfully produced monoclonal antibodies. Hybritech was off and running.

Beneath this charming founding story, however, lies a more complex account of overlapping networks and unique founders’ backgrounds. Royston, for example, was neither a typical academic nor a traditional entrepreneur. Born in England in 1945, he emigrated to the U.S. in 1954. A high school friend recalls, “Ivor wanted to cure cancer when he was five years old” (Gibbons, 1989:2). Along with his drive, Royston exhibited a penchant for risk taking. In high school he joined with 16 classmates to invest their life savings in commercial real estate; they lost all of their money (ibid.). Undaunted, Royston purchased and operated an ice cream truck to finance his studies, earning a bachelor’s in human biology (1967) and an MD from Johns Hopkins (1970). He chose Stanford for his internship and residency, followed by two years studying immunology and virology at the NIH. He returned to Stanford for an oncology fellowship from 1975 to 1977.

Royston was in a position to observe the Bay Area biotech scene during its formative era:

While I [was] at Stanford . . . I saw Cetus develop, I saw Genentech develop, and my own professor, John Daniels, in the division of oncology at Stanford, was the founder of a company called Collagen—they were the first company to make injectable collagen for smoothing out wrinkles in skin (Royston, 2006:6).

Royston's fellowship at Stanford introduced him to people and ideas that would become crucial. His favorite lab technician was Howard Birndorf, who would follow him to UCSD and then to Hybritech. He also met his future wife, Colette, a nurse at Stanford Hospital who had previously dated another central player in the Hybritech story, venture capitalist Brook Byers (Robbins-Roth, 2000:50). While Royston was at Stanford, Kohler and Milstein's work on monoclonal antibodies was first published. "I read that paper and said, 'Gee, this looks pretty straightforward. . . . This could lead to an entirely new approach for generating highly specific, highly selective antibodies for treating cancer'" (Royston, 2006). Kohler and Milstein's work had direct impact on Birndorf as well. Dr. Leonard Herzenberg, a genetics professor at Stanford, had spent a sabbatical in Milstein's lab in England, where he had learned how to make hybridomas. "Len came back and taught the technique to a woman in his lab, who taught me," recalls Birndorf. "I started talking with Ivor about how to apply this technique to myeloma [a cancer of the white blood cells]" (Robbins-Roth, 2000:49).

When his Stanford post-doc ended in 1977, Royston accepted a position as an assistant professor of hematology and oncology at rapidly expanding UC San Diego. He recruited Birndorf to run his lab. Birndorf had spent three years in a biochemistry doctoral program at Wayne State University, but it had been a consolation prize after failing to get into medical school, and he lacked the motivation to finish his degree. Instead, he had moved west and was doing lab work to pay the bills: "I wasn't making a lot as a lab tech—around \$15,000—and there was nowhere for me to go without a doctorate. I was trying to figure out whether I should go back to school, or if there was another way to make more money" (Powell, 1999).

Birndorf's poverty and Royston's drive to cure cancer combined to form a novel business concept: a company that would produce monoclonal antibodies as superior reagents for medical researchers. "All I cared about was I needed these antibodies so I could develop a treatment program at UCSD," remembers Royston (2006). "It was never the idea that I wanted to start a business, make a lot of money and leave the university." In early 1978, Birndorf bought a book entitled *How to Start Your Own Business* and wrote a crude five-page business plan. The two would-be entrepreneurs began the hunt for funding. Royston's efforts to interest established antibody-producing companies met with disbelief: "I was talking about making antibodies in the test tube and they said 'No, antibodies—you must bleed sheep and rabbits and goats,' and it was impossible to communicate with them" (Royston, 2006). Birndorf's futile attempts included talking to friends who were commodities traders in Chicago, and making the rounds of his parents' wealthy friends in Michigan.

The fundraising breakthrough came from Colette (Royston's girlfriend at the time, subsequently his wife): she set up an appointment with her one-time beau, Brook Byers. Byers had shared an apartment with Bob Swanson before Swanson founded Genentech; the two were close friends. Having recently joined Kleiner & Perkins (investors in Cetus and Genentech), Byers was attuned to the possibilities of life-science-based ventures. Byers did the requisite due diligence (including confirmation that the Kohler and Milstein work had never been patented) and hired an attorney to iron out with UCSD the specifics of Royston's involvement. Not coincidentally, the attorney was Tom Kiley, who had done the legal work for Genentech and had been recommended by Swanson. Byers (2006:18) also sought Swanson's overall approval of the venture:

“[Swanson] thought it was a good idea, and not competitive with Genentech.” All of this set the stage for the fateful airport meeting.

Byers’s involvement in the new venture went above and beyond that of an active investor. He was Hybritech’s first president and CEO—a rare role for a VC at the time:

People who go into venture capital, for the most part, do it because they love to coach and advise and be an active board member, perhaps, but not to manage something. . . . I had no experience in managing anyone, but perhaps my best qualification for the job was that I didn’t want it long term. My first assignment was to go find a president (Byers, 2006:19).

Byers’s search took five months. Before he could recruit an executive of the requisite caliber, Byers felt the fledgling company needed to prove that the technology was practical. He had given Royston and Birndorf a goal to produce monoclonal hepatitis antibodies within six months; they accomplished the “proof of principle” within three months. With these results, Byers was able to persuade Ted Greene from Baxter to join Hybritech as president and CEO in March 1979.

At the time, Greene was looking for a new challenge, having spent five years in various executive positions with Baxter Travenol’s diagnostics business (Hybritech, 1981:22). Greene, who had worked for seven years at McKinsey & Co. after earning a Harvard MBA, was intrigued by the commercial potential of monoclonal antibodies and was seriously considering joining a start-up in Orange County. As part of his own due diligence, Greene contacted Byers to quiz the venture capitalist on the feasibility of the technology, unaware that Byers was involved in a similar start-up. Instead of advice, Greene wound up with a job offer (Fikes,1999:3). As Byers (2006:25) explains, “It was perfect timing because he [Greene] wanted to leave Baxter and start a company and run it himself. He was what I was looking for. He had a good knowledge of the science, he had

worked at the Hyland division of Baxter, which made reagents and components.” Greene’s business savvy was instrumental in steering Hybritech away from direct competition with Abbott in hepatitis diagnostics, instead focusing on such areas as prostate cancer detection.

Royston remained at the university, which had always been his goal. “[Royston] wanted to stay at UCSD and we respected that,” observed Byers (2006:19). “[He] saw as his role model Herb Boyer at UCSF, who stayed at that institution and was a consultant to Genentech.” Like Boyer, Royston endured criticisms and accusations of impropriety from his scientific colleagues. The furor escalated to the point that Royston was formally investigated by the NIH for conflict of interest; he was cleared of any wrongdoing. Unlike Boyer, Royston knew he could be fired for his extracurricular activities: “I had only been there [at UCSD] a year. I wasn’t even tenured. I thought it might jeopardize my career, but I also had a gut feeling that this was the right thing to do” (Gibbons, 1989:1).

Hybritech had a successful IPO in 1981 and was sold to Eli Lilly in 1985 for nearly \$400 million—the first biotech company to be sold at a premium to an established pharmaceutical company (Robbins-Roth, 2000). The acquisition turned out to be a commercial failure, but an overwhelming institutional success: disaffected with corporate life but wealthy, Hybritech’s founding executives and scientists went on to found dozens of biotech ventures and establish San Diego as one of the three dominant hubs of biotech activity in the U.S. (See Chapter 13 in this volume.)

11.) *Immunex: The biotech underdogs*

In 1981, Steve Gillis was a 28-year-old investigator at the Fred Hutchinson Cancer Research Center in Seattle, WA (known locally as “The Hutch”). He worked in

the lab of Christopher Henney, a 40-year old professor with a growing reputation in immunology. The two were doing novel work on Interleukin-2 (IL-2) and other immune system hormones, and they wondered about patenting their work. Gillis leafed through the phone book, found an attorney who specialized in patents, and gave him a call. The attorney he sought was out of the office; instead he reached Jim Uhlir, a partner with expertise in patents and business. Uhlir's response was, "Have you thought of forming a company?"

Henney and Gillis had, in fact, considered a start-up but didn't know where to begin. Uhlir arranged a meeting with Bruce Pym, an attorney at another firm who brought one of his clients with him: Steve Duzan, a 40-year-old executive who was looking for a new challenge. A University of Washington graduate, Duzan had spent a year in law school but left it for business. He advanced up the ranks at various companies, and in 1975 he assembled a group of Seattle investors to acquire Cello Bag Inc. Duzan ran the company for five years, then arranged its sale to Atlantic Richfield. He stayed on for another six months, enough time to realize he did not want to pursue a career within ARCO. Instead, Duzan was contemplating buying a company of his own to run: "I thought that I would like to start a company, and . . . while I didn't have any idea what it would be, I hoped it would be in some way related to science because I liked that kind of thing" (Duzan, 2009).

The meeting in Pym's office on April 6, 1981, was Duzan's first introduction to Henney and Gillis, who also introduced him to interleukin-2 (a family of molecules known as cytokines and cytokine receptors) and to their vision for its therapeutic possibilities. The three plus Uhlir formally incorporated on August 1, 1981, with Henney

and Gillis in charge of the science. Duzan would manage the business and lead the fundraising; and Uhlir would cover the legal aspects and receive founder's shares, though he continued full-time in his law practice. Uhlir and Gillis came up with the name Immunex, a play on Esso's recent rebranding as Exxon (Gillis, 2009).

The company's first challenge was to extricate Henney and Gillis from their academic commitments (Wilson and Heath, 2001). Recalls Gillis:

Most of our competitors who were involved in starting companies at the time were . . . staying in academia. We thought that might be a real conflict of interest. We wanted to make a clean break. So in exchange for the intellectual property that we had at the time, the arrangement with the Hutchinson Center was that we would give them some stock in the company, and we transferred our grants to other investigators at the Center, so that the Center would not lose that revenue (Gillis, 2009).

Various faculty colleagues tried to talk the two researchers out of starting a company, warning that they would become pariahs. Gillis remembers going back and forth with Henney on which of them should sever ties with the Cancer Center:

Chris would come into my office and say, 'Look, you're young, you can afford to make a mistake. If you go and do this thing and it doesn't work out, you can always get a job in academia.' The next week I would go into his office and say, 'You know, you're ten years older, you have a more established career than I do. Why don't I be the consultant and you go full time? If this turns out to be a mistake you can always get a job back in academia' (Gillis, 2009).

In the end, the two decided they were in it together. Duzan, too, had to take care of other obligations before joining Immunex full-time. But by July 1982, all three were working at Immunex in a lab installed in an old waterfront industrial building, and Duzan had lined up a group of investors led by Seattle-based venture capitalists Cable & Howse to provide a modest \$1 million in start-up money.

Henney focused on recruiting scientists while Gillis headed up the work in the labs. Like Genentech and Chiron, Immunex had no scientific advisory board, relying

instead on the expertise of its own young scientists. In the early 1980s, Seattle was not the technology hub it is today, and an underdog culture developed among the scientific staff. Recalls Duzan (2009):

We were stuck up in Seattle at a time when Seattle was far less well known in terms of technology of any kind except airplanes. It was us against them. We continuously found as we went around trying to raise money, trying to recruit scientists, trying to do all kinds of things, that we were going to have to be the Avis of this business and try harder and work harder. We were able to foster a culture around that, and everybody who worked there eventually began to call themselves ‘Immunoids.’

Gillis led a work-hard, play-hard culture, epitomizing an informal jeans-and-t-shirt approach to serious science. The research group, an international collection of immunologists, biochemists and molecular biologists, became known as “Immunex University,” and Gillis instituted a “Pons & Fleischmann Award” for lab mishaps, named after the researchers who thought they had discovered cold fusion, which was presented at weekly Friday beer busts (Timmerman, 2001). Most of the recruits were young: “In those days, trying to convince established researchers to do what we were doing would have been pretty tough” (Gillis, 2009).

Despite the high jinks, the young research team discovered and cloned a series of genes to produce immune-system proteins that could potentially fight cancer, heal wounds, and counter auto-immune diseases. Gillis and Henney strongly encouraged scientists to publish their findings, give talks at scientific meetings, and even share the reagents they created with outside researchers. Genentech led all biotech companies in the number of citations of its scientists’ papers, but Immunex “was always second or third,” recalls Gillis. Not only was their publication record a source of Immunoid pride,

but in the early days Wall Street analysts also paid attention to citation counts as a proxy for commercial potential.

Despite additional rounds of funding and an IPO in 1983, Immunex did not have enough money to support expensive clinical trials and bring promising drugs to market. Instead, it continued to fund its research activities by selling its technologies to established pharmaceutical companies for development. Investors worried that Immunex was becoming a research boutique, unable to convert technical breakthroughs into marketable products. “It was a very productive time for science,” recalled David Urdal, one of the early biochemists. “I’m not really sure when the connection hit on Immunex becoming a business” (Timmerman, 2001). In 1989, Henney left the company to join George Rathmann (Amgen’s first CEO) in a new Seattle-based biotech start-up, Icos. Henney has since been involved in founding two more biotech firms.

In 1991, Immunex received FDA approval for its first product: Leukine, a white-blood-cell growth stimulator approved for bone-marrow transplant patients. But a few months earlier, Amgen had introduced Neupogen, a similar product approved for much broader applications. Sales of Leukine were disappointing, and in 1993 Immunex merged with Lederle Oncology, a unit of American Cyanamid, to form a new independent, publicly traded company still called Immunex. American Cyanamid held a majority interest in the new company, but was limited to three board seats. Duzan chose to step down as CEO within six months of the merger: “The entrepreneurial phase of Immunex was largely completed with this deal and, frankly, I was a bit burned out” (Duzan, 2009). He became an angel investor in five subsequent biotech ventures. Gillis (who had been head of research) served as interim CEO for a few months, then was replaced by Ed

Fritzky, an American Cyanamid executive with marketing experience. Although he made significant changes to Immunex, Fritzky was careful not to tamper with the culture of the research center. But American Cyanamid was bought by American Home Products (AHP) in mid-1994, and Gillis left Immunex to found another biotech venture, Corixa.

Immunex achieved its hoped-for blockbuster drug with Enbrel, an anti-inflammatory approved by the FDA in 1998 for rheumatoid arthritis. Backed by the manufacturing and sales capability of AHP's Wyeth-Ayerst division, sales of Enbrel skyrocketed, Immunex's stock split multiple times in 1999, and the company began ambitious expansion plans with facilities in Bothell, WA, a plant in Rhode Island, and an architecturally striking research center in Seattle. Immunex had arrived.

Success, however, spelled the end of Immunex as an independent entity. Demand for Enbrel grew spectacularly (Immunex, 2001), but it outstripped manufacturing capability. Larger firms also were attracted by Immunex's promising research pipeline, and in December 2001, Immunex was acquired by fellow biotech pioneer Amgen for \$16 billion (Fletcher, 2002). It is curious to note the reaction among Immunex scientists to the acquisition. One senior-level scientist lamented the fact that he was no longer encouraged to publish his findings: "Amgen sees it [publishing] as giving away the company silver" (Dietrich, 2003). Another observer commented, "Morale has been impacted because people finally realized that it's a takeover, they can't keep everybody, and it's not all fun and games. Amgen is big pharma, and their culture is so different than Immunex" (ibid.). Mike Widmer, a former Immunex researcher, stated, "A lot of us have concluded there will never be another place like Immunex. It was a magical place" (Timmerman, 2004).

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