Entrepreneurship and the construction of value in biotechnology

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The entrepreneurship literature typically depicts Schumpeterian entrepreneurs – those in a quest to profit from new technologies – as individuals seeking out pre-existing opportunities and building organizations to create and capture financial profit (Shane 2000; Shane and Venkataraman 2000; Venkataraman 1997). Implicit in this view is the idea that a technology is something to discover rather than something to influence and that technology evolution is exogenous to the entrepreneurial process (as noted by Shah and Tripsas 2007). An alternative perspective argues that technologies are at least partially changeable and that the role of effective Schumpeterian entrepreneurs is to mold them to a particular (exogenously given) institutional environment (Hargadon and Douglas 2001). Either view of technical change (and of the role of entrepreneurship in it) is at odds with findings from studies of the evolution of new technologies, which describe both deeply uncertain institutional environments and contested efforts to shape what the technology becomes (for an overview, see Kaplan and Tripsas 2008). Specifically, the burgeoning literature on institutional entrepreneurship (Fligstein 2001; Garud, Hardy and Maguire 2007; Garud, Jain and Kumaraswamy 2002; Lounsbury and Glynn 2001; Munir and Phillips 2005) argues precisely that neither the technology nor the institutional environment is fixed and that multiple actors with multiple goals (not always, or not even often, the profit motive) act to shape the institutional setup that would govern activities in a particular field. From this standpoint, a technology is mutable and shaped as the field is shaped (Garud and Karnøe 2001).

Certainly, in the case of biotechnology, which we analyze in this paper, what biotechnology meant at any one point in time was up for grabs. The technology was often thought to hold huge potential but was equivocal (Weick 1990) – multiple interpretations of its potential were possible. The institutional environment was also complex and highly uncertain. In this context, a large number of Schumpeterian entrepreneurs created new organizations (such as Genentech, Amgen, Biogen, and others) to commercialize a variety of bio-technologies. It was also the case that a wide

array of institutional entrepreneurs (including city governments, federal agencies, social movement organizations, etc.) mobilized around issues of safety, efficacy, intellectual property, and economic development. Each of these actors saw the opportunities and risks of biotechnology in different ways and acted according to these understandings of the value (either positive or negative) they perceived the technology could have.

We think of these interpretations of value as economic logics that comprise the organizing principles of what is valued and valuable in the institutional setup of a field (David 2003; Friedland and Alford 1991). Central to the biotechnology case we study, and to the institutional perspective on entrepreneurship more generally, is the idea that the financial profits motivating the Schumpeterian entrepreneur are only one of many interpretations of the value of the technology that exist in the field. Other institutional entrepreneurs whose notions of value may be focused on ends other than making profits will also articulate their perspectives. What animates our enquiry is to understand the evolution of biotechnology in the marketplace and the role entrepreneurial action has in shaping this process. We find that, where there are multiple interpretations, contests between all sorts of entrepreneurs (Schumpeterian and other) about which economic logic will dominate are likely. These contests about value are highly consequential because they have implications for the shape of the field and of the evolution of technologies within it. Yet, the mechanisms for resolving these disputes about value and the entrepreneur's role in such a process are poorly understood.

Conventionalist theory – as most comprehensively articulated by Boltanski and Thévenot (2006) (and also exemplified in Beunza and Stark 2004; Callon and Muniesa 2005; Stark 2000) – provides a useful lens for unpacking these dynamics. This theory suggests that an economic logic defines what is of value in a particular context. Their insight is that there is no single economic logic and therefore no single articulation of value – multiple economic logics are possible and may often co-exist. Each economic logic is based in its own internally consistent sets of tests for

establishing value and, more importantly, the evidence that satisfy those tests. The combination of tests and evidence provide the justification or legitimization of the value for a good. A particular sphere of action – the marketplace or elsewhere – will be governed by an institutional set up which is based in a compromise across multiple possible economic logics and which sustains an is sustained by a particular constellation of justifications. One implication of this perspective is that entrepreneurs – Schumpeterian as well as institutional entrepreneurs – will engage in contests with one another to propose and stabilize the economic logic. They seek to define the tests of value and to provide evidence that satisfy these tests.

With regard to commercializing new technologies, entrepreneurs produce or draw on a wide range of evidence: courts and government agencies making decisions defining appropriability, financial markets placing value on technologies well before products materialize, scientists producing technical evidence on viability, and firms making sense of the technology and its commercial applications. The entrepreneurial task is therefore to establish or undermine different tests of value, mobilize or suppress evidence to satisfy or refute these tests, and construct a compromise across the contested values associated with a technology. Throughout this process, we argue that entrepreneurs take action to create new logics or transform existing ones, leading to a new set of opportunities. The outcome of such entrepreneurial action strongly shapes the evolution of a technology and, therefore, the organizations that exploit it.

Through our historical analysis of the evolution of biotechnology, we show that highly varied understandings of the value embodied in biotechnology existed. Across three eras (1973-1986 and 1988-2000 and 2003-present), entrepreneurs constructed different economic logics for biotechnology, often in highly contested settings against multiple entrepreneurial adversaries. We also find that an economic logic was not easily stabilized; biotechnology's evolution was arrested by moments when the stabilized constellations fell apart (in 1987-1989 and again in 2001-2002) and

new logics were constructed. We argue that such breakdowns may occur when evidence fails to meet critical tests or when different understandings of value are in conflict. These breakdowns create new opportunities for other entrepreneurs to construct alternative economic logics.

By exploring these processes of contestation, (temporary) stabilization and subsequent breakdowns, we contribute first to the entrepreneurship literature by expanding the definition of the entrepreneurial act. We find that the entrepreneur creating a new firm to commercialize a technology, while being a Schumpeterian opportunity seeker, is also acting as an institutional entrepreneur, constructing the economic logics and institutional setups as they build their organizations. Not only does this perspective redefine the role of Schumpeterian entrepreneurs, it also opens up the discussion of entrepreneurship to a whole set of different entrepreneurial actors who may not be creating firms but who are seeking to shape the economic logic and institutions which will govern the system of exchange. This full complement of entrepreneurs function like Becker's (1963) "moral entrepreneurs," each seeking to set the rules of exchange and provide evidence to support a particular institutional setup (see also Epstein 2007).

Second, we contribute to the literature on technical change by showing that entrepreneurs are central actors in this process. Their challenge is to exploit, negotiate and resolve the uncertainties created during the emergence of a new technology. They must develop an economic logic and constitute the logic in an effective organization. In doing so, they act to change the institutional setup in a process that shapes and is shaped by the evolving technology. By taking this view, we present a broader definition of the institutional arrangements that are central to technical change, placing legal institutions promulgating and defining patent law alongside government agencies establishing safety regulations together with financial market institutions validating the financial value of a startup. By examining the entire the institutional setup, we can more precisely explain patterns of technical change. We show that such change may not be smooth, but instead can

be arrested or change direction when compromises about the economic logic break down. As such, the forces shaping technology evolution are best understood as not purely technical, but also, and unavoidably, economic.

Third, while we have known since the pioneering work of Joan Woodward that different technologies require different organizational configurations (Woodward 1958), our analysis suggests that the entrepreneurial act of defining the value of a technology and creating new organizations to constitute this value actually shapes the direction that technologies evolve. Thus, it is not simply a matter of matching an organization to a technology but rather of seeing how the creation of new organizations to commercialize technologies interacts with the definition of the technology itself in the marketplace.

Economic logics and the evolution of technology

By taking conventionalist view of the evolution of biotechnology, we suggest that the process by which entrepreneurs determined what made biotechnology valuable and figured out how to organize around such an economic logic was contested. The shape that biotechnology has ultimately taken emerged from the resolution of these contests. Convention theory – as elaborated in Boltanski and Thévenot's *On Justification* (2006)[1] – argues that our economy is shaped by participants affecting the rules of economic action. While most economists would argue that the assignment of value underpins any system of exchange, conventionalists suggest that this value is not only given by the principles of optimization, but instead can be derived from many possible spheres such as civic duty, attainment of fame, proof of technologic performance, demonstration of creativity, etc. More specifically, Boltanski and Thévenot (2006: 43) claim that the establishment of a particular logic "comes about as a part of a coordinated process that relies on two supports: a

[1] This discussion of the economies of convention is also deeply influenced by David Stark's work including Stark (2000), Girard and Stark (2002) and Beunza and Stark (2004) as well as the opportunity to read the manuscript from his forthcoming book at the Princeton University Press, provisionally titled "Assets of Ambiguity."

common identification of market goods, whose exchange defines the course of action, and a common evaluation of these objects in terms of prices that make it possible to adjust various actions." Simply put, economic logics embody principles of economic coordination or conventions that guide interpretation of the technology and its value.

We use the notion of a logic as it is defined by Friedland and Alford (1991: 248-249) (and discussed in DiMaggio 1997: 277); a set of "material practices and symbolic constructions" that are the "organizing principles" of the institutional setup. An *economic* logic concerns the organizing principles that define what is of value. It underpins a "system of exchange" (Biagioli 2000: 552fn) which can be understood as being similar to Latour and Woolgar's (1979) cycles of credit that transform valued outputs into resources for further production. The guiding focus of the conventionalist perspective is in explaining how economic action is socially constructed and in analyzing how what is valuable is determined (Stark 2000). It relies on the idea that multiple values can co-exist, each being coherent within its own economic logic, and each of which entails its own metrics and standards of evidence for proving the value of any object or idea (Callon and Muniesa 2005). Each logic has its own tests for value, and actions are taken with the idea that they will or at least could be subject to tests of "justification." There are various loci where the tests can play out, such as the courts, markets, labs or government agencies. The process is one of mutual substantiation in which a particular test is determined to be a deciding factor and certain evidence is deemed to be a justification. The test and the evidence are co-produced.

While the institutional perspective has highlighted the importance of logics and their institutional setup in the evolution of new industries (Lounsbury, Ventresca and Hirsch 2003), the key insight of the Conventionalists is that what is valuable will differ in different spheres, not only the market, but also social, religious, civic and others. And, more importantly, that even within a given sphere there can be a contest over which particular economic logic will prevail. For example,

scientists engaging in research in the academic sphere may value intellectual contribution and recognition and follow the economic logic of Open Science (David 2003; Latour and Woolgar 1979; Merton 1968). However, scientists in industry may value relevance to practical problems. Likewise, technologies can be subject to different economic logics in different spheres. In the market sphere, the value of a new technology will be associated with financial profit. But, in the civic sphere, the value may be in job creation or economic development. Or, in the social sphere, the value may be negative, coming in the form of fears of toxicity.

Just as Zelizer (1983; 2005) has shown that multiple logics – social and market – can affect they ways intimate goods and services are traded in the marketplace, the conventionalist view suggests that many potential economic logics can operate in a single sphere. This has been demonstrated by Lounsbury (2007) who, in his study of the mutual fund industry, identifies the contrasting trustee and performance logics that defined the values of the Boston and New York-based funds respectively. In publishing, Thornton and Ocasio (1999) describe the yielding of the editorial logic to a market-oriented logic as firms in the industry changed hands and brought in professional managers. And, specifically in biotechnology, both academic and commercial (or venture capital) economic logics have been shown to operate, often in highly conflictual ways, within the academic sphere (Murray 2008; Powell and Owen-Smith 2002; Vallas and Lee 2008). In the context of the commercialization of a new technology, we argue that the Conventionalist perspective makes room for the potential that different definitions of an economic logic associated with technology may be part of the compromise that structures the institutional setup surrounding it and allows a system of exchange to operate. The prevailing economic logic is therefore the set – or in Latour and Woolgar's (1979) language, the "lash up" – of conventions that govern the action.

The Conventionalist view sees the efforts to construct such "lash ups" as a way of dealing with the Knightian uncertainty (Knight 1921/1965) in the market. Indeed, "for the Conventions

School, the process of justification (rationalization) is critical to actors assuaging their concerns about an unknowable future" (Biggart and Beamish 2003: 456). Uncertainties can emanate from multiple parties or settings and threaten the stability of institutionalized conventions. There may be disruptions to the existing compromise about which logic should hold. Thus, the emergence of a new technology, for example, is a kind of *moment critique* (Boltanski and Thévenot 1999: 359); a moment of crisis forcing reflexivity and a recognition that something has to change. Ambiguity is also created simply by the existence of multiple, overlapping logics. Interpretations of the value of a thing and of the thing itself are subject to debate, and actors' preferences are unknown, unclear or multiple. Different actors may be in favor of different economic logics. When commercializing a new technology, Schumpeterian entrepreneurs may articulate and contest among themselves (and with their investors) different economic logics of what is valuable in a new technology. They may also find themselves in conflict with institutional entrepreneurs whose economic logic is dramatically different in conception. Competing parties will engage in efforts not only to bring justification of a certain definition of value but also to assure that their preferred economic logic be the one structuring the process of commercialization. Actors can challenge the validity of a test, avoid a test, or introduce a test that is valid according to a different economic logic. However, the very uncertainties that usher in disputes also make negotiation and entrepreneurial action possible and even necessary (Sewell 1992).

The entrepreneur may be seen as the actor who can break from the existing institutional setup in the market and create new economic practices (Biggart and Beamish 2003). Thus, rather than being passive recipients of new technologies, logics and institutions, it is likely that entrepreneurial actors will be active in developing the technology, creating an economic logic, and building a supporting institutional setup. In this sense, entrepreneurial actors of every type can engage in creative, strategic actions which can produce new sets of coordinated practices associated

with a new economic logic that will shape subsequent activities in the field. Their role comes about because, as they develop and promote different economic logics, they work to generate evidence within existing institutions, act to change institutions and try to change the tests associated with these institutions. They instantiate these ideas through the organizations they build to exploit the economic logic they are promoting. Through the success of their organizations, they provide evidence that their proposed economic logic is viable, just as other types of entrepreneurs seek evidence supporting alternative views.

The constellation of features characterizing conventionalist theory make it particularly well-suited to the analysis of the emergence of a new technology and the surrounding institutional setup. Because new technologies are inherently equivocal (Weick 1990), it makes sense that multiple economic logics could apply. What evidence would constitute proof of the value of such a technology would itself be inherently subject to interpretation and potentially disputed. Because future outcomes of the development of the technology cannot be predicted, entrepreneurs are those skilled and knowledgeable actors (Fligstein 2001; Giddens 1984) generating evidence, sometimes in the form of creating startup organizations, and changing institutions all in the service of establishing a particular economic logic surrounding the technology. They mobilize a wide range of evidence related to different economic logics, establish tests that match their evidence, and attempt to shape the interpretation of evidence provided by others. The outcomes of their efforts shape the direction that the technology, the organizations, the logic and its underlying institutions take.

One can see a clear connection between the conventionalist perspective on technology we propose and ideas developed in the stream of research on the social construction of technology (SCOT) (Bijker, Hughes and Pinch 1987). They share a focus on the interpretive flexibility of technologies (and other goods) and on the mechanisms for closure and stabilization of an artifact. What conventionalist theory usefully adds is the focus on the establishment of tests and the

mobilization of evidence as the underlying mechanisms for achieving some sort of compromise about the value of a technology. This highlights very naturally the role of advocacy and argumentation on the part of marketplace participants in shaping such outcomes. In doing so, the conventionalist conceptual toolkit directs us to explore the ways in which entrepreneurial actors go about constructing and stabilizing a particular economic logic to define whether and under what conditions stakeholders attach value to the new technology. In demystifying the tests and evidence that validate the tests, the conventionalist perspective also highlights the degree to which compromises are fragile (being perhaps only local and contingent) and therefore the possibility that such compromises may break down at critical moments. In the following section, we explore how these ideas help explain the evolution of biotechnology.

Constructing Biotechnology

We trace the development of biotechnology in human therapeutics[2] over a thirty year period from the first demonstration of recombinant DNA techniques in 1973 to the field characterized by a complex network of dedicated biotech firms, pharmaceutical firms, investors and academics that, by around 2003 stabilized in number, organizational form, strategy and financing (Biotechnology Industry Organization 2008). The field of biotechnology has been extensively studied by organizational scholars and its complex story has merited books and articles too numerous to count (for overviews, see Kenney 1986; Kornberg 1995; Pisano 2006; Robbins-Roth 2000). We therefore do not pretend to offer a full account of the field but rather seek to view 30 years of biotechnology through a particular lens, which we hope will shed light on some important dynamics shaping its evolution. Our analysis highlights entrepreneurial action across three eras. Each one characterized

[2] Occurring in parallel was the application of recombinant DNA and other techniques in other fields such as agriculture. Because the industry and market dynamics were quite different in these other contexts, we chose to examine the trajectory of development in human therapeutics only. This allows us to constrain our discussion to a particular set of institutions and actors.

by the stabilization of a different economic logic. However, these trajectories were arrested by moments (1987-1989; 2001-2002) when the compromise over how to define the tests and the evidence of the economic logic broke down, only to be reconstructed in a different form later.

- Era 1: 1973-1986, when biotech came to be seen as a source of novel ("large molecule") human therapeutics developed by independent start-ups in competition with the "small molecule" drugs of pharmaceutical firms.
- Era 2: 1990-2000, when biotech became a set of firms providing a range of biology-based approaches supporting an alternative drug discovery platform to the traditional chemistry-based platforms used by pharmaceutical firms.
- Era 3: 2003 onwards, when biotech emerged as a method to combine biological techniques with other disciplines such as chemistry and computer science to develop various types of therapeutics for specific diseases by both independent biotech firms and pharmaceutical firms.

Most observers date the start of biotechnology in the marketplace to 1973, when the first recombinant DNA (rDNA) techniques were demonstrated at Stanford University by Stanley Cohen, Herbert Boyer and colleagues (Cohen et al. 1973). These results showed that DNA could be introduced into a bacterium and "switched on" to make a protein (Cohen et al. 1973). A plethora of methods for manipulating, isolating and modifying DNA followed, and in their wake, the potential for an economic logic in the market place and a setting ripe for entrepreneurial action. Of course, biotechnology has a long "pre-history" in both academic research and practical applications that provided the foundations for these important experiments (Kenney 1986). Evidence of thousands of years of basic expertise in biotechnology-related techniques is found in accounts of fermentation, beer production and wine making (Legras et al. 2007). However, it was in 1953, with the elucidation of the structure of DNA (Watson and Crick 1953) that the scientific underpinnings for

the development of new techniques were developed. This defined an academic agenda for the second half of the twentieth century of which Cohen and Boyer were only a part (Judson 1979; Morange 1998). Their discovery of rDNA techniques did, however, open up the possibility for commercial applications.

In the three decades following the Cohen and Boyer breakthrough, many Schumpeterian entrepreneurs launched startups to profit from biotechnology. From 1980 (the first initial public offering for a biotechnology firm) to 2003, over 470 firms were taken public and many more funded by venture capitalists and angel investors who invested over US$22 billion in early-stage biotechnology firms in the same period (Edwards 2003; Lerner 1992; Lerner and Merges 1998). In examining their activities in the market, however, we found that they were far from pure opportunity seekers. Instead, they actively constructed and reconstructed justifications for the value of their firms by arguing for particular tests of value and mobilizing evidence to satisfy those tests. They instantiated economic logics for biotech in the organizations they built, and, in doing so, they raised millions from private investors and public markets.

The Schumpeterian entrepreneurs were not alone in their efforts to construct the value of biotechnology. Many actors, concerned with their own definitions of value, fought for different understandings of biotechnology and different definitions of the possibilities associated with it. Hence, biotechnology's economic logics were defined, contested, and stabilized (and sometimes destabilized) not only in the research labs, offices of venture capitalists and biotech startups, but also in the courts, Congressional hearings, government agencies, large pharmaceutical firms, and even in the streets (in political demonstrations).

While the discovery of rDNA techniques made biotechnology's commercial application possible and generated enthusiasm among entrepreneurs, great uncertainty governed how, exactly, these applications would evolve, and how the biotechnology opportunity would be constructed.

Research on the history, economics and sociology of technology has highlighted four domains in which the value of a technology can be established – technical, appropriability, market and ethical, legal and social dimensions. From a technical perspective, the uncertainties are about whether a technology would actually "work" (Dosi 1982). Concerns about appropriability focus on establishing ownership and rights to future market rents and provide a barrier to entry (Cockburn and Griliches 1988; Levin et al. 1987; Teece 1986). Uncertainties about the market focus on the degree to which investors and customers would pay for the technology (Gans and Stern 2000; Roberts and Berry 1985). Ethical and safety concerns also generate uncertainties (Kevles and Hood 1992; Winner 1977).

Our analysis of the evolution of biotechnology indicates that there were strong dependencies between those domains. It was not enough to show a technique worked, it was also crucial to demonstrate that the ideas could be owned, that customers or investors would be willing to pay and that the social and human health risks were not too great. As a result, entrepreneurs of all sorts needed to "lash-up" evidence across these four domains in order to achieve compromises about the economic logic. In the sections that follow, we focus on how a constellation of evidence came to support the prevailing economic logic in each era, and, when that compromise failed, how it was reconstructed. These ideas are summarized in Table 1.

– Insert Table 1 about here –

The first biotech era (1973-1986)

Biotech as new biological drugs in competition with big pharma

The Cohen and Boyer breakthrough made biotechnology techniques practicable for the first time, and many entrepreneurs founded firms in attempts to capture this potential. In the very early days, firms aimed at a wide range of applications in areas as diverse as agriculture, the environment, energy, industrial chemicals, and human health (Robbins-Roth 2000). Cetus, while founded in 1971

a few years before the Cohen and Boyer discovery, is considered by some as the first biotechnology firm as it focused on vaccines, therapeutic proteins, antibiotics and even alcohol production from fermentation; Genentech was founded in 1976 with an initial focus on industrial chemicals, animal health in addition to human health, Amgen, founded in 1980 had a similarly diverse spread of applications including diagnostic kits, oil recovery and animal health. Hybritech, founded shortly afterwards in 1978 with funds from Genentech's investors, focused on another promising new technology, monoclonal antibodies.[3] It was Genentech, however, founded by Boyer and venture capitalist Bob Swanson, which ultimately came to represent the economic logic of this era. The firm soon focused on applying rDNA techniques to develop therapeutic biological drugs – building blocks such as DNA or proteins made in genetically engineered cells – as an alternative to the big pharmaceutical firms whose drugs were small chemical entities designed and made using chemistry.

The founders were self-conscious in their desire to establish Genentech's approach as the prevailing economic logic in biotechnology. As Swanson described in an oral history (1996):

> *"We decided to raise money in our initial public offering in 1980….We did it for a number of reasons. One is that we needed more money to complete our development. There was a lot of excitement about the technology, and we wanted to be the first company out to the public market because we felt that we were doing things right. We were basically managing the business conservatively; we were focused on getting to market; and we wanted to set the right tone--the idea being, if a bunch of other biotechnology companies were out there, and they disappointed investors or they weren't doing things right, then it would be more difficult for us. So we wanted to set the standard. We had been setting the standard on the science. We wanted to set the standard as a public company."*

With a successful IPO, Genentech, its venture backers and investment bankers provided a blue print for a stable economic logic. Other firms followed, shedding their broad, multi-application orientation to focus on biological drugs ("large molecules") for human disease. From 1980 to 1986,

[3] The commercializatoin of monoclonal antibodies follows a similar path to rDNA with many of the same uncertainties. An important part of the immune system, experiments undertaken at the Medical Research Council laboratories in Cambridge, England in the mid 1970s by Kohler and Milstein (1975) were part of on-going research on the immune system that continued the academic agenda of immunology. However, like rDNA this research showed significant potential for commercial application. The first commercial step was taken in San Diego by Hybritech.

over 60 biotech firms completed IPOs. Stelios Papadopoulos (the first dedicated biotech industry analyst) noted: “In the early to mid-80s, it became clear that the only meaningful game was pharmaceuticals” (quoted in Robbins-Roth 2000: 25). However, this understanding of biotechnology, as a source of novel human therapeutics developed by independent start-ups in competition with pharmaceutical firms, could not have been reached if uncertainties across the technical, appropriability, regulatory and market domains had not been contested and resolved.

The strongest evidence of technical viability came when experiments were published and patents were filed on rDNA and genetically modified organisms. In the first seven years after its founding and until the approval if its first drug, Genentech published more than 77 peer-reviewed publications in academic journals, jointly authored with scientists including both Cohen and Boyer and also a range of others at the University of California San Francisco, Stanford, Johns Hopkins and the City of Hope Medical School. Historical accounts of the period suggest that Cohen and Boyer had limited interest in and awareness of rDNA’s commercial potential. However, an article in the New York Times (McElheny 1974) influenced Stanford’s Director of technology licensing to propose that the DNA cloning procedures be patented (Hughes 2001; Ku 1983). While Cohen was reluctant, the filing was made with only one week remaining before the U.S. limits on prior disclosure would have invalidated the patent.

The patent claimed both the process of making and the composition for biologically functional chimeras (mixes of cells from two different species) and its detailed disclosure descriptions provided additional evidence of technical viability. Two years earlier Ananda Chakrabarty, a microbiologist at General Electric’s Schenectady laboratories, had also initiated the commercial move, filing for the first patent on a genetically modified organism – a modified form of *pseudomonas* bacterium that was capable of breaking down of crude oil (Patent # 3,813,316, Chakrabarty 1974; Patent # 4,259,444, Chakrabarty 1981). In an interview, Chakrabarty described

his work: “I just shuffled the genes, changing the characteristics of a bacteria that already existed. The ‘new’ bacteria could guzzle the oil in case of oil-spills in seas or rivers, thus saving valuable marine life and preventing environmental degradation” (Chowdhury 2002). In the late 1970s, critical approaches to genetic modification in plants were also patented (see, for example, Patent # 4,459,355, Cello and Olsen 1984).

While patents were evidence of technical viability, they also assigned ownership of the intellectual property. Not everyone agreed that such ownership of living organisms was appropriate. When Chakrabarty initially submitted his patent, the patent office declined to grant it. Chakrabarty brought suit against the Commissioner of Trademarks and Patents, Sidney A. Diamond, and in 1980, the Supreme Court deliberated over the Chakrabarty patent. Many different groups provided evidence to the court, each bringing not only his own evidence but his own views about which test should be considered by the court. For the Patent Office, the test was whether or not genetically modified life forms were patentable material under the U.S. Constitution and according to patent laws passed by Congress. In contrast, executives in various biotechnology startups, whose very existence depended on the ability to own biotechnology intellectual property, expressed the view that patentability should be granted in the interests of economic development. They were joined in their view by the Pharmaceutical Manufacturers Association (who filed a separate *Amicus* brief). They felt the patent should be justified in commercial terms and hoped to gain patent rights to boost their ability to earn rents on the technologies they developed. In their *Amicus* brief to the court, Genentech’s executives summarized this perspective (Lyon and Lyon 1979: 3):

> *“In Genentech's case the patent incentive did, and doubtless elsewhere it will, prove to be an important if not indispensable factor in attracting private support for life-giving research. And where the Patent System facilitates the interposition of small but fruitful companies like Genentech in pharmaceutical and other industries traditionally dominated by major concerns, it operates to best purpose, as an essentially pro-competitive mechanism. Having delivered very substantial benefits to the public in reliance on the patent incentive, Genentech is vitally interested in continued operation of the quid pro quo principle upon which the Patent System is based.”*

The debate about the Chakrabarty patent, and by implication about biotechnology more generally, was not only about who had the right to earn rents but also about whether such technologies should be developed at all, given concerns for safety. Activists like Jeremy Rifkin, founder of the People's Business Commission, a Washington-based public interest group, saw the Supreme Court as another setting in which to bring evidence of safety concerns. In the only *Amicus* brief to the Court against the Chakrabarty patent grant, they argued that the test before the Court should relate to the possible hazards of biotech and described how genetic engineering might "irreversibly pollute the planetary gene pool in radical new ways" (quoted in Thackray 1998: 68). The judgment describes how safety activists saw what tests and evidence should be used to decide on the appropriateness of patenting biotechnology-produced organisms, pointing to:

> *"…grave risks that may be generated by research endeavors such as the respondent's. The briefs present a gruesome parade of horribles. …We are told that genetic research and related technological developments may spread pollution and disease, that it may result in a loss of genetic diversity, and that its practice may tend to depreciate the value of human life. These arguments are forcefully, even passionately, presented; they remind us that, at times, human ingenuity seems unable to control fully the forces it creates – that, as with Hamlet, it is sometimes better to bear those ills we have than fly to others that we know not of."*

It was argued that the Court should weigh these potential hazards in considering whether respondent's invention is patentable subject matter (US Supreme Court 1980).

In allowing the Chakrabarty patent (and by precedent the Cohen and Boyer patent), the judges rejected the arguments that tests of safety or commerce should be used when determining patentability. They found that questions of regulation were for the legislative process – not the courts – and that, "the grant or denial of patents on micro-organisms is not likely to put an end to genetic research or to its attendant risks." Instead, the Court determined the validity of the patent in accordance with the Constitution that anything "under the sun" should be patentable and with the Patent Act of 1952, specifically Title 35 of the U.S. Code, Section 101, describing the kinds of inventions that could be patented. While they did not give credence to the economic arguments proposed by biotechnology firms, the successful outcome of the case provided evidence for the

appropriability of invented biotech organisms, which validated the approach being pursued by Genentech. A press release for Genentech said that the Supreme Court's action had "assured this country's technology future" (Genentech 1980).

The questions of safety began to recede in the wake of the Diamond v. Chakrabarty decision. However, throughout the very early years of biotechnology, actors who defined the value of biotechnology as related to the risk of human or environmental toxicity placed limits on research and commercialization. Universities, city governments, Federal regulatory agencies, activist groups and researchers themselves worked to assure that safety concerns were factored into the approach taken to develop biotechnology.

One response to these pressures was an attempt by researchers at self-regulation. In 1974, a group of researchers – spearheaded by Paul Berg, a scientist at Stanford University who was himself conducting early experiments in recombinant DNA – requested that the National Academy of Sciences (NAS) form a committee to study the safety of conducting research biotech (Lederberg 1975). The NAS then convened the Committee on Recombinant DNA Molecules, which declared a moratorium on further research until scientists could establish guidelines for safety. The following year, more than 100 scientists, lawyers and journalists met under the auspices of the National Institutes of Health (NIH) (which took over from the NAS) at Asilomar State Beach for what has become known as the Asilomar Conference. Their goal was to set guidelines (rather than regulations) on research on rDNA that would allow scientific activity in biotechnology to continue while assuring that risks of mutant genes or toxicity were controlled (Carmen 1985; Diringer 1987). The debate dealt both with what tests for safety would be used and what the standards of evidence would be. The resulting compromise made research in biotechnology possible. The agreement was to match containment approaches to the level of risk associated with different classes of

experiments, specifying types of facilities for minimal- to high-risk situations. It also banned certain kinds of highly dangerous experiments.

Subsequent to this conference, it became possible for various Federal agencies to set regulations for conducting biotechnology research. In 1976, the NIH released its own guidelines for NIH-sponsored genetic research (41 Federal Regulation 27902). Around this time, public hearings by the Committees on Labor and Public Welfare (94th Cong., 1st Sess. 1975), Commerce, Science, and Transportation (95th Cong., 1st Sess. 1977) and Interstate and Foreign Commerce (95th Cong., 1st Sess. 1977) further codified biotech regulation. These events established a new regulatory regime that allowed researchers in academia and firms to restart biotech research that had been previously halted. By 1980, the NIH had agreed to allow private-sector firms to register their experiments voluntarily and to receive NIH certification. Large-scale production of biological products (more than 10 liters) remained unregulated and unpopular among private sector firms such as Cetus (McGarity and Bayer 1983). When developed with Federal funds it required prior approval, but privately funded projects were a gray area.

With this movement at the Federal level, local attempts to contain biotechnology research met with only partial success. For example, in Cambridge, Massachusetts – the home of the Massachusetts Institute of Technology and Harvard University as well as some of the early biotech startups – the city government initially placed its own moratorium on rDNA experiments (in response to a 1976 Harvard proposal to renovate its biology labs). The City created the Cambridge Experimentation Review Board that conducted over 75 hours of hearings during which a broad range of possible outcomes were considered. However, the Federal regulatory process, which was occurring contemporaneously, established a precedent for allowing research, and so the City ultimately decided to encode NIH guidelines into City law. This struggle for influence represented a significant turning point in the contest between regulators and for-profit constituents in influencing

a leading institution – in this case the Cambridge City government. The winners argued that the potential health benefits and the economic opportunities outweighed any risks (Wright 1986).

The net effect of these debates amongst scientists and at the local and Federal governmental levels in the late 1970s was to lay out a path for continuing research (at least in the United States) using the rDNA techniques initially proposed by Cohen and Boyer. Biological drugs for human health began to dominate biotechnology as agricultural applications had not yet achieved a stable regulatory environment. (It was not until 1986 that a Coordinated Framework for Regulation of Biotechnology in plants was announced (National Research Council (U.S.). Committee on Genetically Modified Pest-Protected Plants 2000; Office of Science and Technology Policy 1986)).

Assuring a regime for appropriability and safety paved the way for the further development of biotechnology for human therapeutics. Subsequent advances would be dependent on what kinds of research would be viable in the market and therefore receive funding. Entrepreneurial firms were often in the lead in creating market evidence. One example was the production of human insulin. Researchers at Genentech worked in 1978 with the City of Hope National Medical Center to show it was possible to produce human insulin using recombinant DNA technology. Robert Swanson, president of Genentech at the time, noted, "The development of human insulin demonstrates the viability of using recombinant DNA technology to produce products with practical application" (Genentech 1978).[4] Most of the evidence of manufacturability was generated at the small 10-liter laboratory-scale approved by the NIH, although in 1979 Genentech created a minor furor by making organisms for insulin production in batches of 100 liters. They took advantage of ambiguity in the rules to establish more dramatic evidence of rDNA's potential. The tests also allowed Genentech to show their partner – Eli Lilly – that they could meet important technical milestones in the deal that

[4] Note that these attempts to establish viability often came into conflict as Genentech also licensed out the associated patents and was found by courts in 2002 to have concealed this information. The Los Angeles Superior Court awarded the City of Hope Medical Center over $500 million to compensate for losses associated with this collaboration (Hamilton 2002).

gave Eli Lilly the right produce and distribute recombinant insulin as an alternative to Lilly's bovine insulin (Yansura 2001).

Another example was the pursuit of Interferon, the first promising lead to emerge from the War on Cancer announced by President Nixon in his 1971 State of the Union Address. Its promise was to replace small-molecule chemotherapies being pursued by large pharmaceutical firms. The possible application of biotech to cancer provided entrepreneurs with compelling evidence to bolster claims of market opportunity. As a result, many of the biotechnology startups of the day, including Genentech, Amgen, Biogen and Cetus, pursued this opportunity. Indeed, much of the excitement around Genentech's IPO was due to its interferon alpha project. The appeal to the War on Cancer also helped counter continuing concerns about safety hazards. The possibility that biotech firms might develop capabilities to manufacture interferons and therefore cure cancer seems to have been a turning point that, according to at least one media analyst and observer, "swept away much of the public and governmental uneasiness over the possible dangers associated with the research" (O'Malley 1980).

The success (in the case of insulin) and the potential promise (in the case of interferon) of early biotechnology drugs was recognized by some of the large pharmaceutical firms (Kaplan, Murray and Henderson 2003). Eli Lilly had been the predominant player in insulin and therefore saw both the threat and opportunity in Genentech's work. Having bought the worldwide rights to Genetech's recombinant human insulin, the firm made significant investments in building rDNA production capabilities. In 1980, Hoffmann-La Roche bought rights to market Genentech's interferon and Schering Plough did the same for Biogen's interferon. These deals substantiated the market value of biotechnology among corporate buyers.

However, another critical market test was achieving Federal Drug Administration (FDA) approval to distribute biotechnology drugs. Initially, no guidelines for FDA tests existed and the

agency sought to incorporate the NIH Guidelines into the design of clinical trials (Federal Register 50, 134 (1978)). However with the complexity and criticism of these guidelines and their rapidly changing standards, the FDA moved to a position, supported by industry, that the 1902 Biologics Control Act could guide the tests and standards for appropriate technical evidence (McGarity and Bayer 1983). As a result, the FDA was able to being approving recombinant drugs. In 1982, the first successful approval of a recombinant drug was Genentech's human insulin, and approvals for human growth hormone (1985) and alpha interferon (1986) followed, with eventual blockbuster erythropoietin (approved for Amgen) coming a few years later in 1989.

By 1986, an apparently stable compromise about biotechnology's economic logic had emerged. Tests had been established and evidence weighed. High profile IPOs, licensing deals and drug approvals suggested there was a market for biotechnology. The IP regime had been clarified and safety concerns mitigated. Breakthroughs in the lab and in manufacturability indicated that large molecule drugs were technically viable. All signs pointed to a burgeoning industry that would yield medically efficacious products to save lives and deliver high investor returns.

Breakdown of the logic of the first biotech era (1987-1990)

If the story ended here, it would provide a rich, if simple, account of an economic logic constructed around a technology rich in entrepreneurial opportunities and institutional uncertainties. Yet, this initial "Genentech" model of biotechnology failed as a commercial project. While over $1.4 billion in funding had been raised in the public markets through IPOs, (Lerner and Merges, 1998), investors began to weary of the fading promise of biotech. By 1986, the FDA had approved only six biotechnology drugs (the three mentioned above and another form of alpha interferon, a monoclonal antibody for graft rejection and lastly Recombivax – the hepatitis B vaccine). The industry was failing tests of commercial viability. Stocks "lapsed into a near comatose languor as investors tired of waiting for all the visionary promises to be fulfilled" (Stevens 1986). The

financial markets closed to biotech firms funding only 13 IPOs between 1987 and 1990 compared to 22 in 1986 alone.

How did the compromise, crafted so carefully, fall apart? Howard Greene, former Chairman of San Diego-based biotech firm Hybritech (and a prominent venture investor) described the challenge in 1987: "All it took to form a company five or six years ago was finding a Nobel laureate from one of a dozen illustrious universities who was going to spiritually associate with the company. It was assumed that was all it took to succeed. Now people have found out that, like any business, it takes management," (Kraul 1987). However, more than simply a managerial failure on the part of biotech's early Schumpeterian entrepreneurs, the problem lay in the instability of the evidence across all domains, technical, appropriability, safety and the market.

Technical evidence suggested that one of the centerpiece drugs in biotechnology, interferon, was not as effective a cancer cure as many had hoped (Panem 1984). Numerous industry observers and scholars noted the disappointing results. An article in the New England Journal of Medicine described that the euphoria surrounding interferon as a "miracle cure for cancer was short lived and faded when it seemed that interferon's performance in large scale cancer trials had been disappointing" (1998: 1231). Interferon often produced a variety of unwanted side effects in patients (Powledge 1984). Later research would show that interferon could be incorporated into multi-drug therapeutic regimes for cancer treatment and (in different variants) for hepatitis B and C, multiple sclerosis and numerous other indications. However, the particular test chosen by these early biotech firms and scientists – single-drug trials – highlighted evidence bolstering safety concerns while failing to provided technical evidence of efficacy.

This was not limited to rDNA products. There was considerable disappointment with MABs as well, with firms confronting the rejection by the human immune system of MABs made using mouse genes. Regulatory approval procedures became so formidable that industry analysts called

for a national panel to facilitate the process. According to Steve Burrill, a high profile industry analyst, “The hurdles are placing a burden on biotech companies to the point they could make that world non-economic” (quoted in, Kraul 1987). The FDA countered that while the earliest biotech drugs were recombinant versions of widely understood drugs such as insulin, the recent new drug applications were more complex scientifically, particularly the MABs undergoing clinical trials, and the agency had limited expertise in the area (Gibbons 1991).

Legal evidence of the appropriability of biological drugs also weakened with Genentech’s 1986 announcement that the Hormone Research Foundation and its licensee, Hoffman-La Roche, were suing the firm for patent infringement in recombinant human growth hormone. Amgen entered a series of legal battles with Johnson & Johnson over its Epogen (erithropoetin) patents. This underscored the uncertainty that remained around appropriability, raised legal questions about the viability of the industry. Biotech firms also had to fight renewed challenges by safety-oriented consumer groups, in particular the Washington, D.C.- based Foundation on Economic Trends founded by Jeremy Rivkin, and by local communities. For example, in California, Advanced Genetic Sciences spent four years clearing legal hurdles and finding a community willing to host its outdoor test of frost-fighting bacteria. Even when a location was approved, opponents tried to prevent the test by destroying thousands of the experimental strawberry plants that served as the material for the bacteria tests during nighttime raids (Diringer 1987). As a result, market evidence continued to weaken – investors were concerned that there was insufficient interest among pharmaceutical firms in licensing biotech’s products (Kraul 1987).

Constructing a new logic for the second biotech era (1990-2001)

Biotech as a platform for drug discovery and other applications

In the period 1973-1990, as the biotechnology-as-large-molecule-for-human-therapy trajectory was being pursued, scientists, firms and universities added numerous tools and techniques

to biotechnology's toolkit including polymerase chain reaction to amplify DNA, DNA sequencing technologies to decode DNA, and gene chips to map the patterns of DNA in particular tissues and other samples. After the breakdown of the economic logic for biotechnology in the late 1980s, profit-seeking Schumpeterian entrepreneurs shifted from thinking of these tools and techniques as mere enablers of biotechnology to positioning them as biotechnology itself. Rather than drugs, biotechnology would be a platform for the discovery of drugs of any kind – both large-molecule and small. This approach, while connected to the prior biotechnology activities, required new scientific expertise. This "rational" (grounded in biology) drug discovery stood in stark contrast to the trial-and-error (grounded in repeated chemistry experiments) approach traditionally used by large pharmaceutical firms (Henderson, Orsenigo and Pisano 1999).

A few biotech firms – Human Genome Sciences (HGS) and Millennium – came to exemplify the new economic logic in the marketplace. HGS was founded in 1992 by Bill Haseltine, a former scientist at Harvard, and Craig Venter formerly a scientist at the NIH. Rather than focus on particular biological drugs, the company based their business on combining a diverse set of bio-technologies. This discovery platform, they argued, could be used to precisely examine the mechanisms of disease taking place in the human body and provide critical information scientists could use to design drugs to block the disease-causing mechanisms. At the core of their platform was the sequencing and collection of large amounts of genetic information, particularly for very small DNA fragments called Expressed Sequence Tags (ESTs) whose patentability would be the source of considerably controversy. When HGS successfully completed its IPO in 1993, it provided a blueprint other startups could follow. With a similar logic, a high profile group of academic scientists (including Eric Lander who was leading part of the Human Genome Project) founded Millennium Pharmaceuticals. While Millennium's specific bio-technologies focused on targeted gene sequencing and the identification of gene function, like HGS, the firm was also an important

model that other entrepreneurs followed, especially after completing an extremely successful IPO in 1996. Rather than focusing on single drugs, the new logic allowed firms to combine a collection of diverse bio-technologies to build a drug discovery "platform" – a novel combination of tools and the information essential for the new rational approach to drug discovery. By 1997, these firms captured over 30 percent of the market capitalization in biotechnology (Cohen 1997).

The first challenge for thse startups was to generate technical evidence to bolster their claims. They needed to prove that biotech-based drug discovery platforms were more effective than traditional trial-and-error discovery methods that had dominated the pharmaceutical sector. The test was not as clear as going to the FDA and arguing about the design of a clinical trial, as Genentech and others had done in the 1980s. Initially, they focused on scientific publications of results through the academic system of peer review as a source of technical evidence. In the seven years after its founding in 1991, HGS published almost one hundred peer-reviewed articles, including some in prestigious journals such as *Nature* and *Science*, co-authored with academic researchers at Johns Hopkins, Harvard and the University of Michigan. Millennium published over one hundred and fifty in its first seven years (1993-1999) again collaborating closely with academics, mainly at Harvard and the Harvard Medical School. Like their predecessors, this generation of biotech firm founders established high profile scientific advisory boards made up of well-regarded academics (Ding, Murray and Stuart 2006; Stuart and Ding 2006). However, these relationships were more likely to focus on testing out specific platform technologies and exploring newly identified drug targets than the joint development of manufacturing expertise or specific therapeutic drugs that had characterized Genentech and the other early firms.

If genetic analysis and discovery tools were to become central to biotech's newly constructed economic logic of drug discovery, evidence of appropriability would be essential. Patents on biological molecules themselves such as recombinant insulin were not enough. The new

platform companies were not constructed to discover these new molecules. Instead they provided critical knowledge that served as an input into the discovery process. The question was what evidence would convince investors that they could appropriate value? Established patent law covered some aspects of the new discovery platforms because they were new techniques to "probe" the genome – equipment, reagents, processes, etc. However, many entrepreneurs wanted to sell the information they discovered. Most of this was information about gene sequences and a complex legal debate followed over the validity of patenting the "code of life." Reminiscent of the debates in the 1970s over rDNA patents, lawyers, entrepreneurs and ethicists argued for different tests of patentability and provided different evidence to bolster their claims. Craig Venter initiated this debate while still a scientist at the NIH, when, together with NIH Director Bernadine Healy, he filed patent applications on DNA fragments discovered as part of the Human Genome Project.

The core controversy of the 1991 filing was the possibility of patenting small pieces of DNA – DNA fragments of a gene whose function was not yet determined, having no link to a specific disease and only speculative utility. The NIH patents contained hundreds of gene fragments but disclosed only a narrow understanding of their utility; no one was sure of the ways in which these fragments could be useful and so the patents typically speculated about their use in a variety of experiments rather than in their therapeutic application (Holman and Munzer 2000). While scientists had provided evidence in favor of patenting in the earlier Diamond v. Chakrabarty case (in their *Amicus* briefs), this time scientists had a wide variety of reasons to argue against it.

Academic geneticists, who had often spent their entire careers (at the NIH and elsewhere) exploring a single gene and its role in disease, wanted the tests to be based on the impact of patents on scientific life, suggesting that DNA patents would allow corporations to control a priceless resource (Nash 2000). They also framed the argument in terms of fairness and the appropriate use of patents as a reward. Their argument was exemplified by a patent filed by HGS on a gene called

CCR5. At the time of filing, the firm had no idea of its role in disease. By the time of patent grant, Robert Gallo, a leading researcher in the field, and his team had discovered that CCR5 was critical for HIV and the HGS share price jumped 21 percent. HGS could directly benefit from the discoveries of others. In response, Gallo was quoted in *Science*: "As a society, we have to ask if it's fair to give the main commercial prize to the company that simply sequences a gene rather than to those who do the hard work of figuring out its biological function" (Marshall 2000b: 1375).

Other scientists including James Watson, who was leading the Human Genome Project, and his UK counterpart, John Sulston, argued that this type of patenting would stifle the international collaboration that characterized the Human Genome Project and lead to a patent war among research institutions (Andrews, 1991). Watson argued that the idea of patenting small gene fragments was "sheer lunacy" (cited in Kevles and Berkowitz 2001: 237; Roberts 1991: 184). Their fear was realized in June 1992 when the British government's Medical Research Council filed its own patent applications for 1,000 partial human gene sequences (Veggeberg 1992). Unlike the Diamond v. Chakrabarty case, the gene patenting debate did not play out in front of the Supreme Court as it was not framed around a single patent. Instead, the scientific press (mainly the editorial pages of *Science* and *Nature*), as well as the mass media, gave widespread coverage.

This was followed by a variety of Congressional Hearings. Public interest groups, including ethicists and activists such as Jeremy Rifkin again objected to gene patents but argued for a moral test rather than a utilitarian one: genes should be seen as a sacred code – the blueprint of life (Kevles and Berkowitz 2001). While a gene patent did not equate to the ownership of a person, the very notion of property rights on a human gene violated human dignity. Other vocal opponents included representatives of disease foundations whose funding went towards solving complex and life threatening diseases. They argued that gene patents would increase the price of genetic tests to diagnose life threatening diseases (Merz 1999). Moreover, they argued, patients with breast cancer,

Canavan disease and PXE disease whose genes formed the basis for gene patents should, they contended, have a right to the research results. These patients spoke out vocally at Congressional Hearings (Merz 1999; Nature 1996).

Biotechnology and pharmaceutical firms were divided in their view of the value of gene sequence patents. In Congressional hearings, press statements and at the National Academy of Sciences, the newer startups, such as HGS, pointed to the extensive investments in new biological drugs enabled by strong patent rights on human genes of therapeutic importance. The Association of Biotechnology Companies endorsed EST patents (Eisenberg 1992). However, the more established biotechnology firms, those that survived from the first biotechnology era, worried that strong patent claims on gene fragments would crowd the patent landscape for their research and make it more difficult for them to make money on biological drugs. Their position was represented by the Industrial Biotechnology Association which argued that while a company might be willing to pay a single licensing fee to access to a full gene for drug development, they were reluctant to sign multiple licenses on a plethora of gene fragments that happened to map to a gene that they had discovered through long and costly R&D (Henry et al. 2002).

Nevertheless, by 1997, the USPTO had issued over 400 human gene sequence patents providing evidence for appropriability of gene sequences and some DNA fragments (Jensen and Murray, 2005). Under continued pressure, the USPTO continued to seek guidance on this issue, inviting comment on its newly proposed utility guidelines for gene patenting. Corporations again expressed concern that if gene fragment patents might constitute sufficient prior art, patents on complete genes would be precluded, thus undermining their claims on certain appropriability (U.S. Patent and Trademark Office 1999). This time the USPTO changed its position and, in 2001, published new utility guidelines that required inventors to identify a specific gene target, the

biological reaction involving a specific protein and a real world use linked to a disease (Duke Law and Technology Review 2001).

The challenge for establishing the value of this new economic logic would not be the same as in the earlier biotechnology era. For one, it was not necessary to generate new regulatory evidence. Conceived as providing new ways of discovering drugs, these firms did not create any new safety concerns, nor did they have to worry about working to create new FDA approval standards. Existing tests for the safety and efficacy remained salient. Instead, entrepreneurs quickly had to contend with new questions about information privacy and the possibility of genetic discrimination. In the late 1980s, the government sought to include studies of ethical, legal and social issues (ELSI) in all areas of genetics and genetic information. Entrepreneurs such as Millennium co-founder Steve Holtzman played an active role in shaping discussions of the appropriate tests and evidence for the use of clinical genetic information in research (Office of Technology Assessment (U.S. Congress) 1991), in the criminal justice system (National Research Council 1992; Office of Technology Assessment (U.S. Congress) 1990), and in diagnostic genetic testing (Holtzman 1989).

In 1991, the Government Operations subcommittee on government information held two hearings on legislation proposed to protect the privacy of genetic information. According to Congressman Robert E. Wise (D-West Virginia), chairman of the subcommittee: “One of the most serious and most immediate concerns is that genetic information may be used to create a new genetic underclass...People may be unable to obtain jobs and insurance, or participate in other routine activities, because of the stigma of having an undesirable gene” (quoted in Breeder 1991). The privacy of genetic information was also considered by the California legislature, which passed a bill prohibiting genetic discrimination by employers or insurers (California Government Code: §§12926, 12926.1 (2001), 1998), a requirement that extended not only to genetic testing but also to

the use of family histories (Nedelcu et al. 2004). The emergence of these concerns pointed out that, even as some evidence might be stabilized, new vectors of concern could be opened (in this case privacy) and had to be confronted.

The question remained whether pharmaceutical firms, the target customer for these new platform-based biotechnology firms, would pay a substantial price for drug discovery services. It was increasingly recognized that large pharmaceutical firms were experiencing a problem with R&D productivity. The number of new drug approvals was stable while spending on drug development continued to rise (DiMasi 2001). Patent expirations on blockbuster products would leave the pharma companies searching for new product opportunities that might be filled by new biotech discovery techniques (Teitelman and Coletti 1989). This left pharmaceutical companies with underused sales capacity and declining profits.

To translate this crisis into demand for their services, new biotechnology startups had to find established pharmaceutical companies willing to pay for their drug discovery tools. Just as Genentech's deal with Eli Lilly provided critical market evidence for biotech firms in the first biotechnology era, in this era, it was a $125 million HGS deal with SmithKline Beecham to provide access to HGS's database of genetic codes that validated this new model. HGS CEO Bill Haseltine took credit for creating the market evidence needed (Edwards and Hamilton 1998):

> *"This is the deal that changed everything. It was the shot, the deal that has transformed the life sciences. Now, you see a shift away from an industry based on chemistry to an industry based on genes . . .What we did -- me personally -- I was the first one to realize the practical application of this new gene discovery."*

The deal established the value of information about genes for drug discovery. Haseltine argued that, "The value is now from the ability to work with genes" (quoted in, Edwards and Hamilton 1998). This was followed with similar deals such as Millenium's 1998 agreement with Bayer to provide access to over 200 new drug targets over a five year period. In 1997, Monsanto paid Millennium

over $200 million for access to its suite of genomic technologies. Through the joint venture, Millennium would apply their expertise to help Monsanto to apply genomics to agribusiness.

These deals, following on the heels of successful IPOs by HGS (1993) and Millennium (1996), secured vital market evidence for the economic logic of platform-based discovery. Entrepreneurs also used the achievement of milestones in alliance relationships to provide evidence that their technology was validated by thorough scientifically trained experts with full access to the scientific details. Firms publicized successes in hitting milestones. For example, in April 1996, HGS announced that it had achieved the first milestone in its collaboration with Pioneer Hi Bred and received a milestone payment. The press released noted that, "This first milestone was the successful installation and testing of HGS proprietary bioinformatics software at Pioneer. This will allow Pioneer to analyze the corn cDNA sequence information being compiled by HGS as a part of the collaboration" (Human Genome Sciences 1996). Like Swanson before, Haseltine and Millennium CEO Mark Levin were self-conscious in their desire to set a standard and gain legitimacy for their particular economic logic. Industry observers, such as the press, recognized the role of these entrepreneurs in the success and failure of commercial biotech, describing how [HGS's] "media-savvy chairman, William Haseltine, has become a poster boy for the entire genomics industry" (Red Herring 2001). AlanWalton, a venture capitalist with Oxford Bioscience Partners in Boston and a founding investor with HGS, was also clear about the role HGS and others played in shaping the logic of the entire sector: "If HGS's first drugs should fail, the public, and certainly Wall Street, will say, 'See, all this excitement about genomics has led nowhere.'" (quoted in Stipp 2001).

Breakdown and reconstruction of the biotechnology economic logic in the 2000s

Biotech firms discover drugs for specific diseases in partnership with big pharma

The constellation of evidence lashed up by various types of entrepreneurs in the 1990s did indeed begin to collapse as the high tech bubble burst in 2001-2002. Public funds for investing in all technological sectors, including biotechnology, diminished dramatically. With no foreseeable market payouts, venture capital investing also dried up. At the same time, an announcement by Britain's Prime Minister Tony Blair and U.S. President Bill Clinton on the appropriability of the human genome invalidated a critical piece of evidence supporting the economic logic of biotechnology in the 1990s. The two leaders declared that the sequence of the human genome "should be made freely available to scientists everywhere" (Berenson and Wade 2000). Many biotech firms including HGS and Incyte lost more than 20 percent of their value in one day (Marshall 2000a). Soon after, the USPTO finalized a fairly restrictive set of guidelines for gene patents. They required that a human DNA patent must be specific and must identify a gene target, specify the biological reaction involving a specific protein and have a real world use linked to a disease (Duke Law and Technology Review 2001).

These two events undermined much of the evidence for appropriability of gene sequences. On the regulatory side, patient advocates who had earlier spoken out against ownership of genes became more vocal. In his presidential address to the American College of Medical Genetics, Dr. Edward McCabe described the challenges of gene patenting and for-profit use of genetics and genomics more broadly. He cited a pending lawsuit brought by the parents of children with Canavan disease against Miami Children's Hospital. Having provided samples for the development of a diagnostic test, the families claimed the lack of access and high test price to be inappropriate. The Pseudozanthoma Elasticum (PZXE) Foundation for children with this disease took the more dramatic measure of seeking patent rights on a test developed using their samples. The value of genomics and the complex of technologies, data and samples upon which it was constructed was

again subject to debate and discussion that as the title of McCabe's address aptly described, mixed "compassion, access, science and advocacy" (McCabe 2001).

These events made a broad platform approach infeasible and forced firms to focus on specific disease targets. Some firms like HGS developed a portfolio of protein and MAB drug candidates which are under clinical development for use in large markets including immunology, infectious disease and oncology. Part of their approach was to promote their own internal candidates. On the other hand they also made acquisitions including buying Principia Pharamceuticals – a company whose technology for protein stability allowed HGS to develop more stable versions of existing protein drugs. Others, such as Millennium, took the significant cash reserves amassed in the technology bubble and acquired companies for their drug project portfolios. The firm acquired COR Therapeutics for over $2 billion to gain access to the revenues from their approved cardiovascular drug. They also made acquisitions in oncology. Others like Incyte, chose to continue selling genomic information but also narrowed the applications of their discovery platforms to focus on one or a few diseases. In Incyte's case, the program they selected was a small-molecule program in inflammation initiated through the acquisition of Maxia.

Because of questions about appropriability (patents would provide protection for drug molecules but not genes sequences), doing licensing or other deals in the early phases of research was no longer practicable. As a result, biotechnology firms had to acquire more expertise in the downstream analysis and testing of drugs – proteins, MABs and small molecules – (a capability they had previously relied on their large pharmaceutical firm partners to provide). While this did not replace their academic licensing, sponsored research and partnership activities, it did refocus their activities towards the clinic. This enabled deals to be struck in later phases where biotechnology startups and pharmaceutical firms could collaborate on moving drugs into clinical trials. These

drugs could then move through now well-established procedures for toxicity studies, animal tests and later clinical evidence from tests on humans.

After the downturn in 2000, the next few years were full of turmoil as firms once again sought to redefine a sustainable logic for biotech through widespread acquisitions, strategic changes, and mergers. Through the middle of 2003, the IPO market remained almost closed with only 10 percent of the industry's funding coming from public markets. Many IPOs were shelved including those of Medarex, Scios and Xoma. Overall equity into biotech dropped dramatically from almost $12 billion in the first quarter of 2000 to only $2.2 billion in the first quarter of 2001.

In the later part of 2003, the IPO window reopened. No specific event precipitated this resolution. What was distinctive, and reflective of the redefinition of value that took place well beyond the existing cash rich biotech firms, was that 33 of the 38 companies that IPO'd from September 2003 to the end of 2004 had products in clinical development compared to only 28 percent of the IPOs in the 1999-2000 "bubble" (Van Brunt 2005). This rewarded the logic of the genomics-based technology platform. By highlighting the market for unmet medical needs and focusing on drugs (of all types) to solve those needs, it seemed that biotech's economic logic was resolved again. It was clearly elaborated but flexible enough to accommodate a wide range of underlying science to discover and validate new drugs.

The model that emerged in the 2000s is one in which biotech firms, whose core technologies came either from academia or from established firms, raised substantial early-stage investment from venture capitalists. As they developed their bio-technologies in pursuit of novel drugs (proteins, MABs, small molecules and today even RNAi, gene therapy, antisense etc.), they sought partnerships with big pharma to share in the costs, risks and benefits of drug development. Conversely, big pharma relied on biotech firms to explore risky new drug discovery approaches and targets and to find the most interesting technologies emerging from universities. "Biotechnology"

has therefore come to mean a certain way of organizing drug research and development. Biotech is less about specific, narrowly defined bio-technologies *per se* and more about an organizational form and its associated economic logic. The stability of this compromise over time will depend on the degree to which the links between this set of tests and evidence are durable, uncontested and maintained over time.

Discussion & Conclusion

In our analysis of the evolution of biotechnology, we take a conventionalist lens to focus on the value associated with biotechnology in the marketplace over a thirty-year period; how it was defined, changed and stabilized. We show that what biotechnology was understood to be and how it was seen to create value changed dramatically over the course of the first 30 years of the industry. While initially hailed as an exciting but narrowly thought of as a biological technique that could be used in wide ranging applications, it was quickly defined as a means to discover and produce large molecule protein drugs, biotechnology. Only after thirty years did entrepreneurs, executives, investors, academics and even social activists come to regard biotechnology as a widely encompassing set of technologies used for more effectively discovering and developing a plethora of therapeutic drugs – large molecule and small. With this stable definition of value came a clearly delineated industrial field, constituted through a complex network of interactions between dedicated biotech firms, large pharmaceutical firms, venture capital, capital markets, universities, and lawyers.

Biotechnology's path was not inevitable; many untrodden paths might have been taken. Had uncertainties been resolved in different ways, by different actors, with different evidence of what could be of value, the trajectory biotechnology took would have been different. We contend that it is through entrepreneurial efforts by multiple actors that the particular path was constructed. Entrepreneurs mobilized a wide range of evidence, established tests that matched their evidence,

and attempted to influence the interpretation of evidence provided by others. The outcomes of their efforts shaped the direction that biotechnology took – as a technology, and as a field within the marketplace instantiated in specific organizations and institutions. The economic logic for biotechnology in the marketplace was the one that sustained a particular set of justifications for at least a period of time and ultimately came to stabilize a particular organizational form. This perspective has broad implications for our understanding of technical change and value construction and of the role of entrepreneurial actors in these processes.

The study of technical change has evolved over the years from one that portrayed technology as an exogenous shock to one that has acknowledge the social forces at play. Research has shown that the evolution of a technology is not simply the inevitable result of "normal problem solving" (Dosi 1982: 152) but rather socially and organizationally constructed (Bijker, Hughes and Pinch 1987). Further, recent models suggest that this social construction involves the interpretive processes of multiple actors in scientific, governmental, commercial and other spheres of action (Garud and Rappa 1994; Kaplan and Tripsas 2008; Lounsbury, Ventresca and Hirsch 2003). These models suggest that different actors bring different interests, different perspectives, and different experiences to the table as they interpret a technology, make choices and act. Because actors may conflict, they engage in contests to get their own interpretation to predominate. By using conventionalist theory as a lens for exploring this process, we show that the struggle over interpretations is not just about the technology itself but also about what value(s) should be attached to it. Constructing a technology thus is also about constructing the economic logic that underpins it.

This perspective also suggests that various institutions are both actors and arenas in these struggles (Kaplan and Tripsas 2008). They can be sources of uncertainty (as when regulators are unclear about standards or activist groups challenge existing rules) and also decision-makers who resolve uncertainties and in doing so provide evidence for one particular economic logic over others

(as when the Supreme Court validates a patent). Rather than privileging one type of institution, such as regulators (Schneiberg and Soule 2005) or social activists (Lounsbury and Ventresca 2002; Weber, Thomas and Rao 2006), we raise the possibility that multiple institutions play a role in technical change. In particular, we include the previously overlooked role of legal institutions in shaping technical change. Typically considered an immutable element of the institutional set-up (Teece 1986), the contestation of patent rights in the Courts and in government agencies highlights the flexibility of the legal framework and its potential to be constructed as technology is constructed (Murray and Stern 2008). This highlights the ways in which the field and its institutional setup co-evolves with the construction of the technology.

We find that, in the case of biotechnology, the entrepreneurial actor plays a critical role in this construction. From this we can make three contributions to the understanding of entrepreneurs and entrepreneurship. First, Schumpeterian entrepreneurs do not simply identify opportunities that exist "out there," start up new companies or seek venture capital (Shane 2000). Nor do they merely mold their technology to the institutional set-up (Hargadon and Douglas 2001). Entrepreneurs construct the very landscape in which they operate. This is not just the social construction of technology but also the social construction of the economic, and therefore of the organizations and institutions that instantiate a particular economic logic. As a result, Schumpeterian entrepreneurs are also institutional entrepreneurs (Fligstein 2001) who, through their actions, shape the whole set of conventions that will govern value and exchange in a particular sphere of action. They break from existing conventions with the goal of finding new ways to create and justify value.

Second, the central job for the entrepreneur, if one takes the conventionalist lens, is not only to build an organization but also to identify, establish or challenge particular tests of value and mobilize or dispute evidence that would justify value according to these tests. They can use different means to generate evidence: obtaining funding, applying for or litigating a patent,

launching product, securing favorable regulations, or establishing deal terms with partners. The organization is therefore not only the product of their efforts but also part of the process for justifying an economic logic. Success in building an organization (as validated by obtaining patents, getting FDA drug approvals, achieving milestones in alliances, doing licensing deals, or conducting a successful IPO) becomes evidence of the validity of a particular approach. It also plays a central role in establishing the categories that investors use in the evaluation of firms (Zuckerman 1999). As a result, what is of value becomes endogenized in the actual process of entrepreneurship (Garud and Karnøe 2001). As definitions of value are resolved, the categories that shape financial markets also emerge endogenously, highlighting the critical role of entrepreneurs in enabling commensuration, investment, and valuation (Espeland and Stevens 1998; Zuckerman 2004).

Third, Schumpeterian entrepreneurs are not the only entrepreneurial actors who attempt to shape the economic logic of a technology. Our analysis of the biotechnology story places many institutional entrepreneurs in sharp relief – scientists, city governments, regulatory agencies, lawyers, judges, etc. – who contributed to the establishment of justifications for particular economic logics. These other entrepreneurs operated alongside Schumpeterian entrepreneurs in influencing the evolution of a technological field. We should think of these entrepreneurial actors then, not just as the mythical heros of startup ventures but also as the executives of established firms seeking to profit from a new technology, civil servants in governmental agencies seeking to prevent risks, judges interpreting patent law, and activists giving expression to their social conscience.

From this portrayal, we conclude that constructing a technology is deeply intertwined with the construction of organizations and of the institutions that will govern their operation. Conventionalist theory provides the micro-level underpinnings to the macro-level phenomena in the field (Biggart and Beamish 2003). It gives us a conceptual apparatus for exploring the micro-level processes by which new technologies emerge and find a market and how the practices in those

markets get institutionalized (Fligstein and Dauter 2007). By suggesting that technologies are economic constructions shaped by the on-the-ground actions of entrepreneurial actors battling to get a particular economic logic to predominate, we highlight the emergent nature of coordination in markets (Latsis 2006), and we show how institutions get created and changed in addition to how they eventually become congealed (Lounsbury and Crumley 2007). Reciprocally, we show that an economic logic breaks down if it does not sustain a set of justifications. Stabilized economic logics may only be „provisional settlements“ (Girard and Stark 2002) that are specific to a certain place and time. This analysis shows that the development of technologies and organizations, as well as the institutions in which they are embedded, are intimately intertwined, and highlights the immense entrepreneurial effort required to construct the economic that shapes their emergence.

As this paper is part of a volume devoted to the impact of Joan Woodward's work, we want to point out how our conventionalist understanding of technology commercialization and valuation has its roots in her concerns with the relationship between new technologies and organizations (Woodward 1958). Woodward proposed a contingent view in which different technologies require different kinds of organizational configurations. Her work was an important advancement of a field previously based on the idea that these factors were not causally related and was foundational for contingency theory and theories about the management of technology. She left open for future scholars questions about how the match between new technologies and organizations might emerge. In our study of biotechnology, we show how entrepreneurial actors of all types construct this match as they search for economic logics that can be supported over time by particular justifications. We also show that these matches are not stable but subject to breakdowns if new sets of actors mobilize evidence to justify alternative economic logics. Thus, we argue that technologies, organizations and economic logics co-evolve as entrepreneurial actors engage in contests over what is economic about technology.

References

Becker, Howard Saul. 1963. *Outsiders; studies in the sociology of deviance*. London,: Free Press of Glencoe.

Berenson, A., and N. Wade. 2000. "A Call for Sharing of Research Causes Gene Stocks to Plunge." in *New York Times, March 15, 2000*. New York.

Beunza, Daniel, and David Stark. 2004. "Tools of the trade: the socio-technology of arbitrage in a Wall Street trading room." *Industrial and Corporate Change* 13:369-400.

Biagioli, M. 2000. "Replication or monopoly? The economies of invention and discovery in Galileo's observations of 1610." *Science in Context* 13:547-590.

Biggart, N. W., and T. D. Beamish. 2003. "The economic sociology of conventions: Habit, custom, practice, and routine in market order." *Annual Review of Sociology* 29:443-464.

Bijker, Wiebe E., Thomas Parke Hughes, and T. J. Pinch. 1987. *The Social construction of technological systems: new directions in the sociology and history of technology*. Cambridge, Mass.: MIT Press.

Biotechnology Industry Organization. 2008. "Biotechnology Industry Facts." http://www.bio.org/speeches/pubs/er/statistics.asp.

Boltanski, Luc, and Laurent Thévenot. 1999. "The sociology of critical capacity." *European Journal of Social theory* 2:359-377.

—. 2006. *On justification : economies of worth*. Princeton: Princeton University Press (Published in 1991 in French as "De la justification: les economies de la grandeur," Paris: Gallimard).

Breeder, David C. 1991. "Congress tudies issue of genetic privacy." in *The Omaha World-Herald Sunrise*.

Callon, M, and F Muniesa. 2005. "Economic markets as calculative collective devices." *Organization Studies* 26:1229-1250.

Carmen, Ira H. 1985. *Cloning and the Constitution : an inquiry into governmental policymaking and genetic experimentation*. Madison: University of Wisconsin Press.

Cello, L. M., and W. L. Olsen. 1984. "Method for transforming plant cells, US Patent Number 4459355-A." Int Paper Co.

Chakrabarty, Ananda M. 1974. "Microorganisms having multiple compatible degradative energy-generation plasmids and preparations thereof, US Patent number 3813316." General Electric Company.

—. 1981. "Microorganisms having multiple compatible degradative energy-generating plasmids and preparation thereof, US patent number 4259444." General Electric Co.

Chowdhury, Souvick. 2002. "Engineering life." in *The Hindu*.

Cockburn, Iain, and Zvi Griliches. 1988. "Industry Effects And Appropriability Measures In The Stock Market's Valuation of R&D and Patents." *The American Economic Review*:419.

Cohen, J. 1997. "The genomics gamble." *Science* 275:767-772.

Cohen, S., A. Chang, H. Boyer, and R. Helling. 1973. "Construction of biologically functional bacterial plasmids in vitro." Pp. 3240-3244 in *National Academy of Sciences*.

David, Paul A. 2003. "The economic logic of "open science" and the balance between private property rights and the public domain in scientific data and information: a primer." in *The role of the public domain in scientific and technical data and information*. Washington D.C.: National Academies Press.

DiMaggio, Paul J. 1997. "Culture and cognition." *Annual Review of Sociology* 23:263-287.

DiMasi, J. A. 2001. "Risks in new drug development: Approval success rates for investigational drugs." *Clinical Pharmacology & Therapeutics* 69:297-307.

Ding, W. W., F. Murray, and T. E. Stuart. 2006. "Gender differences in patenting in the academic life sciences." *Science* 313:665-667.
Diringer, Elliot. 1987. "Scientific optimism vs. a skeptical public." in *The San Francisco Chronicle*.
Dosi, Giovanni. 1982. "Technological Paradigms and Technological Trajectories: A Suggested Interpretation of the Determinants and Directions of Technical Change." *Research Policy* 11:147-162.
Duke Law and Technology Review. 2001. "The fate of gene patents under the new utility guidelines." *008*.
Edwards, Mark. 2003. "The year of the bear." in *Signals Magazine*.
Edwards, Mark, and J. O'C. Hamilton. 1998. "Ten deals that changes biotech." in *Signals Magazine*.
Eisenberg, R. S. 1992. "Genes, Patents, and Product Development." *Science* 257:903-908.
Epstein, Steven. 2007. *Inclusion : the politics of difference in medical research*. Chicago: University of Chicago Press.
Espeland, WN, and ML Stevens. 1998. "Commensuration as a social process." *Annual Review of Sociology* 24:313-343.
Fligstein, N., and L. Dauter. 2007. "The sociology of markets." *Annual Review of Sociology* 33:105-128.
Fligstein, Neil. 2001. "Social skill and the theory of fields." *Sociological Theory* 19:105-125.
Friedland, Roger, and Robert R. Alford. 1991. "Bringing Society Back in: Symbols, Practices, and Institutional Contradictions." Pp. 232-266 in *The New institutionalism in organizational analysis*, edited by Walter W. Powell and Paul DiMaggio. Chicago: University of Chicago Press.
Gans, Joshua S., and Scott Stern. 2000. "Incumbency and R&D Incentives: Licensing the Gale of Creative Destruction." *Journal of Economics and Management Strategy* 9:485-511.
Garud, R., C. Hardy, and S. Maguire. 2007. "Institutional entrepreneurship as embedded agency: An introduction to the special issue." *Organization Studies* 28:957-969.
Garud, Raghu, Sanjay Jain, and Arun Kumaraswamy. 2002. "Institutional entrepreneurship in the sponsorship of common technological standards: The case of Sun Microsystems and Java." *Academy of Management Journal*:196-214.
Garud, Raghu, and Peter Karnøe. 2001. "Path Creation as a Process of Mindful Deviation." Pp. 1-38 in *Path dependence and creation*, edited by Raghu Garud and Peter Karnøe. Mahwah, N.J.: Lawrence Erlbaum Associates.
Garud, Raghu, and Michael A. Rappa. 1994. "A socio-cognitive model of technology evolution: The case of cochlear implants." *Organization Science* 5:344-362.
Genentech. 1978. "First Successful Laboratory Production of Human Insulin Announced." *Company press release, September 6, 1978*.
—. 1980. "Supreme court decision will spur genetics industry." *Company press release, January 1, 1980*.
Gibbons, A. 1991. "Biotech Pipeline - Bottleneck Ahead." *Science* 254:369-370.
Giddens, Anthony. 1984. *The constitution of society : outline of the theory of structuration*. Berkeley: University of California Press.
Girard, M., and D. Stark. 2002. "Distributing intelligence and organizing diversity in new-media projects." *Environment and Planning A* 34:1927-1949.
Hamilton, David P. 2002. "Genentech Faces $500 Million Charge After Large Punitive-Damage Award." in *Wall Street Journal, January 24, 2002*.
Hargadon, Andrew B, and Yellowlees Douglas. 2001. "When innovations meet institutions: Edison and the design of the electric light." *Administrative Science Quarterly*:476-501.

Henderson, Rebecca M., Luigi Orsenigo, and Gary Pisano. 1999. "The pharmaceutical industry and the revolution in molecular biology: Interactions among scientific, institutional and organizational change." Pp. 267-311 in *Sources of Industrial Leadership: Studies in Seven Industries*, edited by D.C. Mowery and R.R. Nelson. Cambridge: Cambridge University Press.

Henry, M. R., M. K. Cho, M. A. Weaver, and J. F. Merz. 2002. "Genetics: DNA patenting and licensing." *Science* 297:1279-1279.

Holman, M. A., and S. R. Munzer. 2000. "Intellectual property rights in genes and gene fragments: A registration solution for expressed sequence tags." *Iowa Law Review* 85:735-848.

Holtzman, Neil A. 1989. *Proceed with caution : predicting genetic risks in the recombinant DNA era*. Baltimore: Johns Hopkins University Press.

Hughes, S. S. 2001. "Making dollars out of DNA - The first major patent in biotechnology and the commercialization of molecular biology, 1974-1980." *Isis* 92:541-575.

Human Genome Sciences. 1996. "Human Genome Sciences Achieves Milestone in Pioneer Hi-bred Collaboration." *Company Press Release, April 9, 1996.*

Judson, Horace Freeland. 1979. *The eighth day of creation : makers of the revolution in biology*. New York: Simon and Schuster.

Kaplan, Sarah, Fiona Murray, and Rebecca M. Henderson. 2003. "Discontinuities and Senior Management: Assessing the Role of Recognition in Pharmaceutical Firm Response to Biotechnology." *Industrial and Corporate Change* 12:203-233.

Kaplan, Sarah, and Mary Tripsas. 2008. "Thinking about technology: applying a cognitive lens to technical change." *Research Policy* 37:790-805.

Kenney, Martin. 1986. *Biotechnology: the university-industrial complex*. New Haven: Yale University Press.

Kevles, Danial, and Ari Berkowitz. 2001. "The Gene Patenting Controversy." *Brooklyn Law Review* 67:233-248.

Kevles, Daniel J., and Leroy E. Hood. 1992. *The Code of codes : scientific and social issues in the Human Genome Project*. Cambridge, Mass.: Harvard University Press.

Knight, Frank Hyneman. 1921/1965. *Risk, uncertainty and profit*. New York: Harper & Row, Publishers (first published in 1921 Hart, Schaffner & Marx).

Kohler, G., and C. Milstein. 1975. "Continuous cultures of fused cells secreting antibody of predefined specificity." *Nature* 256:495-497.

Kornberg, Arthur. 1995. *The golden helix : inside biotech ventures*. Sausalito, Calif.: University Science Books.

Kraul, Chris. 1987. "Biotech companies seeking capital have roller coaster year." in *The San Diego Union-Tribune*.

Ku, Katherine. 1983. "Licensing DNA cloning technology." *Les Nouvelles* XVIII:112-115.

Latour, Bruno, and Steve Woolgar. 1979. *Laboratory life: the construction of scientific facts*. Princeton, N.J.: Princeton University Press.

Latsis, J. 2006. "Convention and intersubjectivity: New developments in French economics." *Journal for the Theory of Social Behaviour* 36:255-+.

Lederberg, J. 1975. "DNA Splicing: Will Fear Rob Us of Its Benefits?" *Prism* 3:33-37.

Legras, J. L., D. Merdinoglu, J. M. Cornuet, and F. Karst. 2007. "Bread, beer and wine: Saccharomyces cerevisiae diversity reflects human history." *Molecular Ecology* 16:2091-2102.

Lerner, J. 1992. "ImmuLogic Pharmaceutical Corporation." *Harvard Business School Case Study* #9-293-066 through 9-293-071

Lerner, J., and R. P. Merges. 1998. "The control of technology alliances: An empirical analysis of the biotechnology industry." *Journal of Industrial Economics* 46:125-156.
Levin, Richard C., Alvin K. Klevorick, Richard R. Nelson, and Sidney G. Winter. 1987. "Appropriating the Returns from Industrial Research and Development; Comments and Discussion." *Brookings Papers on Economic Activity* 3:783-831.
Lounsbury, M. 2007. "A tale of two cities: Competing logics and practice variation in the professionalizing of mutual funds." *Academy of Management Journal* 50:289-307.
Lounsbury, M., and E. T. Crumley. 2007. "New practice creation: An institutional perspective on innovation." *Organization Studies* 28:993-1012.
Lounsbury, Michael, and Mary Ann Glynn. 2001. "Cultural entreprenuership: Stories, legitimacy, and the acquisitions of resources." *Strategic Management Journal* 22:545-564.
Lounsbury, Michael, and Marc J Ventresca. 2002. "Social structure and organizations revisited." *Research in the Sociology of Organizations* 19:3-36.
Lounsbury, Michael, Marc J. Ventresca, and Paul M. Hirsch. 2003. "Social movements, field frames and industry emergence: a cultural-political perspective on US recycling." *Socio-Economic Review* 1:71-104.
Lyon, and Lyon. 1979. "Amicus Brief in Diamond v. Chakrabarty 79-136 on Behalf of Genentech, Inc., Amicus Curiae Counsel to Amicus Curiae Genentech, Inc."
Marshall, E. 2000a. "Clinton Backs Rapid Release of Genome Data." *ScienceNOW daily news* March 14, 2000.
—. 2000b. "Gene patents - Patent on HIV receptor provokes an outcry." *Science* 287:1375-1377.
McCabe, E. R. B. 2001. "Clinical genetics: Compassion, access, science, and advocacy." *Genetics in Medicine* 3:426-429.
McElheny, V. 1974. "Gene transplants seen helping farmers and doctors." Pp. 61 in *New York Times*.
McGarity, T. O., and K. O. Bayer. 1983. "Federal-Regulation of Emerging Genetic Technologies." *Vanderbilt Law Review* 36:461-540.
Merton, Robert King. 1968. *Social theory and social structure*. New York,: Free Press.
Merz, J. F. 1999. "Disease gene patents: Overcoming unethical constraints on clinical laboratory medicine." *Clinical Chemistry* 45:324-330.
Morange, Michel. 1998. *A history of molecular biology*. Cambridge, Mass.: Harvard University Press.
Munir, KA, and N Phillips. 2005. "The birth of the 'Kodak moment': Institutional entrepreneurship and the adoption of new technologies." *Organization Studies* 26:1665-1687.
Murray, F., and S. Stern. 2008. "Learning to Live with Patents: Acquiescence & adaptation to the law by the life sciences community." *MIT Sloan Working Paper*.
Murray, Fiona. 2008. "The Oncomouse that Roared: Hybrid Exchange Strategies as a Source Of Productive Tension At The Boundary Of Overlapping Institutions." in *MIT Sloan School of Management Working Paper*. Cambridge, MA.
Nash, M. 2000. "Who owns the genome." in *CNN*.
National Research Council. 1992. *DNA technology in forensic science*. Washington, D.C.: National Academy Press.
National Research Council (U.S.). Committee on Genetically Modified Pest-Protected Plants. 2000. *Genetically modified pest-protected plants : science and regulation*. Washington, D.C.: National Academy Press.
Nature. 1996. "US coalition counters breast gene patents." *Nature* 381:265.
Nedelcu, R., K. R. Blazer, B. U. Schwerin, P. Gambol, P. Mantha, G. C. Uman, and J. N. Weitzel. 2004. "Genetic discrimination: the clinician perspective." *Clinical Genetics* 66:311-317.

O'Malley, Becky. 1980. "Money in the genes." *Multinational Monitor* 1.
Office of Science and Technology Policy. 1986. *Coordinated framework for regulation of biotechnology*. Washington DC.: U.S. Government Printing Office.
Office of Technology Assessment (U.S. Congress). 1990. *Genetic Witness: Forensic Uses of DNA Tests*. Washington, DC: U.S. Government Printing Office.
—. 1991. *Biotechnology in the Global Economy*. Washington, DC: U.S. Government Printing Office.
Panem, Sandra. 1984. *The interferon crusade*. Washington, D.C.: Brookings Institution.
Pieters, T. 1998. "Marketing medicines through randomised controlled trials: the case of interferon." *British Medical Journal* 317:1231-1233.
Pisano, Gary P. 2006. *Science business : the promise, the reality, and the future of biotech*. Boston, Mass.: Harvard Business School Press.
Powell, W. W., and J. Owen-Smith. 2002. "The new world of knowledge production in the life sciences." Pp. 107-132 in *The future of the city of intellect : the changing American university*, edited by Steven G. Brint. Stanford, Calif.: Stanford University Press.
Powledge, T. M. 1984. "Interferon on Trial." *Bio-Technology* 2:214-&.
Red Herring. 2001. "These fashionable genes are too expensive." *September 14, 2001*.
Robbins-Roth, Cynthia. 2000. *From alchemy to IPO : the business of biotechnology*. Cambridge, MA: Perseus Pub.
Roberts, Edward B., and Charles A. Berry. 1985. "Entering New Businesses: Selecting Strategies for Success." *Sloan Management Review*:3.
Roberts, L. 1991. "Genome Patent Fight Erupts." *Science* 254:184-186.
Schneiberg, Marc, and Sarah Anne Soule. 2005. "Institutionalization as a Contested, Multi-level Process: Politics, Social Movements and Rate Regulation in American Fire Insurance." Pp. 122-160 in *Social movements and organization theory*, edited by Gerald F. Davis, Doug McAdam, W. Richard Scott, and Mayer N Zald. Cambridge; New York: Cambridge University Press.
Sewell, William H. 1992. "A Theory of Structure: Duality, Agency, and Transformation." *The American Journal of Sociology* 98:1-29.
Shah, Sonali K., and Mary Tripsas. 2007. "The Accidental Entrepreneur: The Emergent and Collective Process of User Entrepreneurship." *Strategic Entrepreneurship Journal* 1:123-140.
Shane, S. 2000. "Prior knowledge and the discovery of entrepreneurial opportunities." *Organization Science* 11:448-469.
Shane, Scott, and S Venkataraman. 2000. "The promise of entrepreneurship as a field of research." *Academy of Management Review* 25:217-226.
Stark, David. 2000. "For a sociology of worth." in *Keynote address for the Meetings of the European Association of Evolutionary Political Economy*. November 2-4, 2000, Berlin.
Stevens, Catherine. 1986. "Biotechnology up close." in *Financial World*.
Stipp, David. 2001. "He's brilliant. He's swaggering. And he may soon be genomics' first billionaire." in *Fortune*.
Stuart, T. E., and W. W. Ding. 2006. "When do scientists become entrepreneurs? The social structural antecedents of commercial activity in the academic life sciences." *American Journal of Sociology* 112:97-144.
Swanson, Robert. 1996. "Interview with Robert Swanson, Co-Founder, CEO, and Chairman of Genentech, Inc., 1976-1996." *University of California Berkeley, Regional Oral History Office. The Program in the History of the Biological Sciences and Biotechnology.*

Teece, David J. 1986. "Profiting from Technological Innovation: Implications for Integration, Collaboration, Licensing and Public Policy." *Research Policy* 15:285-305.
Teitelman, Robert, and Richard Coletti. 1989. "Financial World Global Report: Pharmaceuticals." Pp. 54 in *Financial World*.
Thackray, Arnold. 1998. *Private science : biotechnology and the rise of the molecular sciences*. Philadelphia: University of Pennsylvania Press.
Thornton, P. H., and W. Ocasio. 1999. "Institutional logics and the historical contingency of power in organizations: Executive succession in the higher education publishing industry, 1958-1990." *American Journal of Sociology* 105:801-843.
U.S. Patent and Trademark Office. 1999. *Revised Utility Examination Guidelines. Request for Comments, 64, Federal Register 71440, Dec 1999.* .
US Supreme Court. 1980. "Diamond v. Chakrabarty." 447 U.S. 303, 309.
Vallas, S. P., and D.L. Lee. 2008. "Contradiction, convergence and the knowledge economy: the confluence of academic and commercial biotechnology." *Socioeconomic Review* 6:283-311.
Van Brunt, Jennifer. 2005. "Investors Fuel Biotech's Future." *Signals Magazine*
Veggeberg, S. 1992. "Controversy Mounts over Gene Patenting Policy - Scientists in Industry and Academia Foresee Trouble as NIH Persists in Claiming Ownership over Partial Sequences." *Scientist* 6:1-&.
Venkataraman, S. 1997. "The distinctive domain of entrepreneurship research: An editor's perspective." Pp. 119-138 in *Advances in entrepreneurship, firm emergence, and growth*, edited by J. Katz and R. Brockhaus. Greenwich, CT: JAI Press.
Watson, J. D., and F. H. C. Crick. 1953. "Molecular Structure of Nucleic Acids - a Structure for Deoxyribose Nucleic Acid." *Nature* 171:737-738.
Weber, Klaus, LG Thomas, and Hayagreeva Rao. 2006. "From Streets to Suites: How the Anti-Biotech Movement Affected German Pharmaceutical Firms." *Working Paper*.
Weick, Karl E. 1990. "Technology as equivoque." Pp. 1-44 in *Technology and Organizations*, edited by Paul Goodman and Lee Sproull. San Francisco: Jossey-Bass.
Winner, Langdon. 1977. *Autonomous technology : technics-out-of-control as a theme in political thought*. Cambridge, Mass.: MIT Press.
Woodward, Joan. 1958. *Management and technology*. London, UK: H. M. Stationery Office.
Wright, S. 1986. "Molecular-Biology or Molecular Politics - the Production of Scientific Consensus on the Hazards of Recombinant-DNA Technology." *Social Studies of Science* 16:593-620.
Yansura, Daniel G. 2001. "Interview with Daniel G. Yansura, Senior Scientist at Genentech." *University of California, Berkeley. Program in the History of the Biological Sciences and Biotechnology. An Interview Conducted by Sally Smith Hughes, Ph. D. in 2001 and 2002*.
Zelizer, Viviana A. Rotman. 1983. *Morals and markets : the development of life insurance in the United States*. New Brunswick, U.S.A.: Transaction Books.
—. 2005. *The purchase of intimacy*. Princeton, N.J.: Princeton University Press.
Zuckerman, E. W. 2004. "Structural incoherence and stock market activity." *American Sociological Review* 69:405-432.
Zuckerman, Ezra W. 1999. "The categorical imperative: Securities analysts and the illegitimacy discount." *American Journal of Sociology* 104:1398-1438.

Table 1: Sources of evidence in each biotechnology era

Eras	Technical evidence	Appropriability/ legal evidence	Regulatory evidence – safety, ethics etc.	Market evidence
Era 1 *1973-1986*	Publications & patents FDA approval for different clinical phases & approval for recombinant Insulin (1982) FDA approval for large-scale manufacturing	Chakrabarty patent Diamond v. Chakrabarty final Supreme Court decision (1980) Granting of Cohen & Boyer Patent (1980)	NAS Committee on Biohazards of rDNA Asilomar Conference on rDNA safety NIH Regulations on rDNA Congressional Hearings	War on Cancer – market for interferons. Pharma market for new products via licensing deals e.g., Genentech & Eli Lily, Genentech & Hoffman
De-construction 1987	Failure of interferon in single drug trials for cancer. Limited success in drug approval compared to investment in biotech R&D.	Genentech vs. Hoffman patent suit Amgen Epogen patent dispute	California disputes over genetically modified strawberries. Rise of activist groups organizing against genetics	Slow down in big pharma partnerships
Era 2 *1988-2000*	Public funding for Human Genome Project and associated scientific promise Completed milestones from discovery service agreements with big pharma	Over 1000 gene-sequence patents filed and granted.	Limited regulatory requirements for platform approach Privacy of genetic information resolved through State and Federal regulation	Large-scale partnerships for biotech & big pharma to solve discovery crisis: HGS - Smith-Kline Beecham; Millennium - Bayer.
De-construction 2001-2002	Limited technical success from biotech's discovery platforms Limited number of novel targets and drugs	USPTO utility guidelines for gene sequence patents – high hurdle for patentability. Clinton-Blair say genome placed in public domain	Patient groups debate ethics of high charges for gene testing.	Overall stock market crash
Era 3 *2003 onwards*	Publications and patents on new targets & approaches Deal milestones FDA milestones	Patent portfolios of large & small molecules robust to patent disputes	No change	Unmet needs for disease. Pharma alliances for joint development of single molecules or small programs