The Evolution of a Competence's Market Specificity and the Emergence of Advantage during a Technological Disruption

I present an exploratory study to investigate the evolutionary path of a competence (rDNA/fermentation technology) during a technological discontinuity, and its impact on the performance heterogeneity across incumbents and both diversifying and de novo entrants. I find that this competence evolved with increasing market specificity, impacting later performance heterogeneity. Diversifying entrants outperformed incumbents only in the variant of the new technology that required rDNA/fermentation technology, supporting the theoretical conclusion that incumbents do not necessarily fail to successfully execute R&D for all radically new technologies, but only for those in which they cannot foresee the applicability to their own markets.

Key words: organizational capabilities; firm performance; incumbent; technological disruption; R&D; competence destruction; first mover advantage.

1. Introduction

As support has grown for the idea that heterogeneity in firm performance is not a transitory effect (Rumelt, 1991), the strategy field has looked deeper into the drivers of that performance heterogeneity. Emphasis has expanded ever more from cross-sectional research into "the longitudinal question" (Porter, 1991), that is, an evolutionary, dynamic perspective (e.g., Nelson and Winter, 1982; Kogut and Zander, 1992; Teece, Pisano and Shuen, 1997). Indeed, current strategy research is starting to unpack the process of emergence of heterogeneity in firms' endowments, a precursor of heterogeneity in firm performance (e.g., Helfat and Lieberman, 2002; Ahuja and Katila, 2004; Ethiraj, et al., 2005). To that end, research about a firm's ability to adapt to change has begun to move beyond the traditional interest in the inertial aspects of organizational structure (e.g., Hannan and Freeman, 1977). Recent research is instead now looking into the question of appropriately designing a firm's adaptability strategy depending on, for example, the characteristics of the tasks in which the firm chooses to engage (Zollo and Winter, 2002).

Mirroring the direction of mainstream strategy, the study of technological discontinuities has gradually expanded from attention to resource/competence destruction (e.g., Tushman and Anderson, 1986) to evolutionary dynamics involving, for example, the emergence and effects of organizational inertia (e.g., Henderson and Clark, 1990; Henderson, 1993). In this paper, I use current advances in mainstream strategy research to move forward the study of technological discontinuities. Consequently, I design this study more as a theory-building exercise than a hypothesis test, although my choice to mix qualitative and quantitative analyses requires that the latter be driven by simple hypotheses. I trace the evolution of a particular technological competence, rDNA/fermentation technology, where I can pinpoint its origin in the history of the biotechnology revolution. Furthermore, I can measure the resulting impact of access to it on the R&D performance of competing firms.

In preliminary analyses, I find that this competence evolved gradually increasing its market specificity, and the differences in market specificity led to differential timing of investment across firms. Heterogeneity in investment resulted later in performance heterogeneity in several dimensions of R&D execution among incumbents and both diversifying and de novo entrants. This performance heterogeneity is particularly contrasting between two variants of the new technology, precisely the two variants that differ in their use of rDNA/fermentation technology.

With this case study I aim at contributing to research in technological disruptions, and as such, to research in strategy formulation for markets with rapid change. I show in preliminary analyses how the evolution of technological trajectories informs not only our understanding of diversification dynamics (Kim and Kogut, 1996) but also our understanding of incumbents' fate during technological disruptions. Furthermore, the fact that incumbents fail to successfully execute the R&D of one variant of the radically new technology but not the other, has important theoretical implications. It implies that incumbents do not necessarily fail to successfully execute R&D for all radically new technologies, as theories based on organizational inertia had found before (Henderson, 1993). It also implies that the main source of uncertainty that affects the response of incumbents is not always related to the evolution of the technology, as previous research has also argued (Christensen, 1997). This study implies that part of the delayed response from incumbents is derived from uncertainty directly related to the market, and as previous strategy research has suggested, uncertainty related to the market might be more difficult to overcome than uncertainty in the technology per se (Freeman, 1987; Kim and Kogut, 1996).

2. The Origin of Performance Heterogeneity

As scholars grow convinced that performance heterogeneity across firms competing in a market is a stable effect (e.g., Rumelt, 1991), and that this heterogeneity is in turn explained by heterogeneity in these firms' resource endowments (e.g., Rumelt, 1984; Wernerfelt, 1984), interest moves to the source of heterogeneity in resource endowments. In other words, where do resources and capabilities/competences[1] come from? We now know differences in capabilities stem not only from heterogeneity in access to assets but also in heterogeneity in the knowledge that the firm, as a community, accumulates over time (Kogut and Zander, 1992). The quest continues in understanding in ever more detail how firms end up with differential endowments. One proposition is to think that firms exhibit differences in competitive advantage as they compete to acquire resources/competences in "strategic factor markets" (Barney, 1991). Of course, the next question is then to understand the determinants that generate differences in the competitive advantage of firms as they compete in these strategic factor markets. Recent research is beginning to unpack those determinants, with particular focus on information access (e.g., Makadok and Barney, 2001). A recent set of studies has begun looking into the origin of capabilities directly. A mix of theoretical and empirical work has grown in the strategy literature to understand precisely the origin of capabilities. Evidence is mounting in the distinction between idiosyncratic sources of heterogeneity in resource endowments and measurable patterns. Perfect examples include patters arising from the structure of the tasks themselves (e.g., Ethiraj, et al., 2005) or the evolutionary path of the competences (e.g., Kim and Kogut, 1996).

[1] I use the terms "capabilities" and "competence" interchangeably, and link resources to their resulting competences following the definitions in Amit and Schoemaker (1993).

3. The Origin of Capabilities and Schumpeterian Capability Destruction

In contrast, the study of technological discontinuities, that is, of Schumpeterian dynamics, seems to have fallen behind. Research in this area advanced considerably through the proposition from Tushman and Anderson (1986) to interpret technological disruption to the extent that they destroy the value of the competences that incumbents had mastered in the previous state of their business. A similarly large step was taken when Henderson and Clark (1990) and Henderson (1993) argued that to explain the heterogeneous performance of incumbents and entrants during a technological discontinuity required attention not only to the competences whose value was destroyed. It in fact required attention to the ability of firms to adapt to that loss of value, and hence, to the heterogeneous presence of inertia among incumbents and entrants, as a precursor of heterogeneous performance. The literature has been fruitful in the identification of drivers of inertia (see Chesbrough, 2001, for a review). Recently, a contrasting mechanism has been brought to attention for this literature as well: the ability of one category of entrants (namely, diversifying entrants) to re-use previously acquired competences (e.g., Carroll, et al., 1996; Klepper and Simons, 2000). This step therefore brings research in technological discontinuities closer to mainstream strategy. As such, there is larger emphasis on the need for research in technological discontinuities to advance to the state of the most current studies in strategy. Clearly, strategy is beginning to shed light on the impact that the evolutionary path of competences has in resulting heterogeneity in firms' endowments, and therefore in resulting heterogeneity in firm performance. Research in technological discontinuities needs to also pay attention to how the evolutionary path of the competences necessary for the radically new technology might result in heterogeneity among incumbents and entrants (both diversifying and de novo entrants), and this is the aim of the present exploratory study.

I therefore design the present study as an exploratory endeavor, and therefore generate no a priori hypotheses. For that reason as well, I synthesize the literature to these short open-

ing sections to provide only a motivation, relegating the discussion of the implications for literature to the discussion sections, after the theory-building exercise has been presented. Still, as I explore the case I present, I move further from qualitative into quantitative methods and hence, in the later sections, I both develop and test specific, though simple, hypotheses.

4. Data

4.1 The Setting and the Technological Discontinuity

I choose as setting for this case study the biotechnology revolution and its impact on the pharmaceutical industry. This industry had many advantages, in particular, the fact that I am interested in technological competences and pharmaceuticals is the most research-intensive industry (PhRMA, 2003), where research competence and resulting drug quality is a major determinant of profitability (Lu and Comanor, 1998). Furthermore, the biotechnology revolution as the discontinuity of choice had advantages as well, including a wealth of data sources and possible interviewees currently accessible, and a mounting number of studies to characterize its impact.

Within the biotechnology revolution and its impact on pharmaceuticals, I needed to choose a particular technological competence whose evolution I would follow. According to Henderson, Orsenigo and Pisano (1999), the impact of the biotechnology revolution can be understood in two large sets: the generation of research and development (R&D) tools to discover new drugs, and the methods for drug mass-production. In fact, a cornerstone in the biotechnology revolution has been the development of recombinant DNA (rDNA) technology, a discovery that made possible for the first time the mass production of proteins, also referred to as large-molecule drugs because they outweigh common drugs by a factor of 10. The development of rDNA technology was the first on a series of innovations that have accumulated to make possible, first the mass production and later the engineered design of proteins. In fact, such innovations have been linked to the birth and growth of successful bio-

technology-based startups, such as Genentech, the original developer of rDNA technology, and Protein Design Labs, the developer of the process to "humanize" engineered proteins. I therefore chose this technological competence, the technology to manufacture large-molecule drugs, to study its evolution and, informed by recent research in the origin of capabilities (e.g., Helfat and Lieberman, 2002), search for new insights to contribute to research on technological discontinuities. I refer to this technological competence as "rDNA/fermentation technology" because the competence base spans further than just the original rDNA patented process. I actually follow the evolution of the original rDNA technology and subsequent innovations, what some strategy scholars have referred to as "technological trajectory" (Dosi, 1982; Kim and Kogut, 1996).

I organize the analysis in this study in two stages, where the first is qualitative and theory-building (i.e., exploratory), and the second is quantitative and necessarily theory-testing. The second stage is theory-testing because it aims at connecting the evolutionary dynamics documented in stage one, to differences in performance, and therefore, models are constructed to test such causal relationship.

For stage one, the qualitative portion, I collected data through 35 interviews (with 4 interviewees contacted repeatedly), and historical material collected from Walsh's (2003) report of large-molecule drug development and customized searches in the *PubMed* database. This analysis is presented next in section 5.1. I then transitioned to stage two of the study, the quantitative analysis. In section 5.2, I look into the possible impact of the technological trajectory of rDNA/fermentation technology on one specific market, the anti-cancer drug market. I needed one single market (as opposed to the entire industry) because there is wide variance in the impact that a technological competence can have on different markets even within the same industry; and because the anti-cancer drug market is the most active market in pharmaceuticals so it allowed for a larger sample. In section 5.3 then, I provide a preliminary test of the heterogeneity generated in the anti-cancer drug market in terms of one area of

R&D: process innovations. Finally, in section 5.4, I provide a preliminary test of the total R&D performance heterogeneity caused by the compounded differences in several competences, including that of generating process innovations. I place particular emphasis in section 5.4 to the comparison between two variants of the new technology: small-molecule biotech-based drugs vs. large-molecule biotech-based drugs. This comparison aids the research design because the former variant of drugs does not require rDNA/fermentation technology, whereas the latter does. Sections 5.2 to 5.4 make use of several databases, including yearly data on drugs in clinical trials from the *Pharmaprojects* database, and a customized search from the *Thomson World Patent Index*. I explain the use of these databases at the start of each of those sections.

5. Analysis and Results

5.1 The Evolution of Market Specificity in rDNA/Fermentation Technology

As mentioned, to date biotechnology has been characterized as generating technological advances on two fronts: the methods for drug design and the manufacturing systems to mass-produce drugs (Henderson, Orsenigo and Pisano, 1998). In fact, a series of innovations that comprise the technological competence I refer to as rDNA/fermentation technology, has made possible the mass-production of one variant of biotechnology-based drugs: large-molecule drugs. For instance, interferon alfa-2, the active ingredient in *Intron A*® (the newly approved, biotechnology-based anti-cancer drug), is a cytokine naturally produced in the human body in small quantities (Walsh, 2003). rDNA/fermentation technology made it possible to produce interferon alfa-2 in therapeutically and hence commercially feasible amounts. In fact, interviewees report innovations in the rDNA/fermentation technology process were first developed to mass-produce proteins (i.e., large-molecule drugs) occurring naturally in the human body. The characterization of such proteins had been performed in academic research and was publicly available. Several of the first large-molecule drugs to reach the market

were used in the treatment of enzyme deficiencies (e.g., diabetes mellitus, Goucher's disease), diseases in which not only the protein but also its therapeutic value (i.e., its connection to disease treatment) were common knowledge in the scientific community. In these initial markets, firms were competing in terms of competence in process design alone. This comprises phase I in the evolution of rDNA/fermentation technology.

A case in point is insulin, the first product for which the radically new rDNA/fermentation technology processes were commercially used. Insulin's principal therapeutic value is the treatment of diabetes mellitus, a disease in which patients lack natural insulin production. The enzyme received the name "insulin" in 1909, but it was not until 1921-1922 that researchers at the University of Toronto isolated the enzyme and proved its effect in regulating sugar metabolism (Rosenfeld, 2002). By the time Genentech invested in rDNA/fermentation technology process innovations for mass-production of "artificial" insulin to be commercialized by Eli Lilly and Co. (Christensen, 1996), the enzyme had been in commercial production by semi-synthetic processes since 1923 (when Eli Lilly and Co. achieved successful yield and standardization of the first mass-production method).

It was not until later, as rDNA/fermentation technology evolved, that gradually other known enzymes for which no connection to disease treatment was known began to be researched in-depth. This is then phase II of the evolution of rDNA/fermentation technology. A case in point is that of erythropoietin, commonly referred to as Epo, an enzyme today commercially available as Amgen's best-selling large-molecule drug for anemia treatment, *Epogen*®. According to scientist J.W. Fisher's (1998) own account of his and others' breakthrough research in "the quest for erythropoietin," one of the most important academic papers confirming the existence of Epo was published in 1950, however:

> "until the gene for Epo was cloned by Lin et al. [1985] at Amgen and Jacobs et al. [1985], Epo was [erroneously] thought to be produced in the glomerular

epithelial cells. The ability to clone made it possible [to determine Epo's appropriate source and therapeutic value]" (p. 10).

As the rDNA/fermentation technology processes developed, the therapeutic potential of large-molecule drugs grew in relevance and ultimately a new product class emerged. This new product class comprises phase III in the evolution of this technological competence. The pharmaceutical industry is currently in phase III, and large-molecule drugs that enter clinical trials go beyond those naturally occurring in the human body, to include as well laboratory-designed drugs. Clearly, the development of the latter requires investment in terms of both manufacturing process and product design and includes markets with higher profitability prospects (e.g., anti-cancer drugs). A case in point in phase III is *Herceptin*®, the new biotech-based anti-cancer large-molecule drug designed by Genentech targeting Her-2 expressing aggressive breast cancers (Bazell, 1998).

Interviewees coincided in the description of the historical progression of the R&D of large-molecule drugs in the three phases described above: (I) a class of known proteins with known connections to disease treatment (e.g., insulin); (II) a class of known proteins with unknown connections to disease treatment (e.g., Epo); (III) a newly born class of engineered proteins (e.g., *Herceptin*®). In fact, interviewees classified large-molecule drugs currently available in the market into the three categories mentioned above. The resulting classification is shown in Table 1 next.

Insert Table 1

Based on this classification and the list of all large-molecule drugs approved in the USA up to 2003 as reported in Walsh (2003), I constructed Figure 1 to illustrate the evolution of the three phases.

Insert Figure 1

Notice the basic definition of market in economic theory is a set of products that are substitutes for one another. Consequently, each disease treatment is a stand alone market. What the three-phase progression of the applicability of rDNA/fermentation technology implies for our understanding of the evolution of this competence is that the competence widened its market specificity over time. This temporal difference in market specificity could have had an impact on heterogeneity in some area of firm performance, and I investigate this aspect next.

5.2 The Anti-Cancer Drug Market and the Emergence of a "Competence-Based" First Mover Advantage

The increase over time in the number of markets for which rDNA/fermentation technology was applicable could have generated heterogeneity in investment in this technological competence. In that sense, I look in this section at the question of how first mover advantages and the resource-based view (RBV) of the firm connect, a theoretical endeavor first posed by Lieberman and Montgomery (1988, 1998). Traditional economics has paid attention to first movership into a market. Yet if we are willing to accept that firms live in a dual system of markets and resources/competences (Wernerfelt, 1984) then there should be a competitive advantage to be gained through first movership into a resource/competence base. It is this latter competence-based first mover advantage that I illustrate in this section.

In order to test the impact of the evolutionary dynamics of rDNA/fermentation technology on the heterogeneous performance of firms in one market, I use data on the market for anti-cancer drugs and its transition from "chemistry-based" agents (e.g., alkylating agents, etc.) to the radically new category of "biotechnology-based" drugs (e.g., tyrosine kinase inhibitors,

etc.). This transition officially started in this market in 1983 with the use of Schering-Plough's *Intron A*® in cancer treatment.

As mentioned in section 5.1, cancer is one of the applications reached by rDNA/fermentation technology until phase III in this technological competence's evolution. To elaborate from Figure 1, where I graph drugs launched in the USA market by evolutionary phase, I repeat the exercise based this time on drugs in clinical trials (a step before market launch). Using *Pharmaprojects* as the source, I identified the 33,257 drugs that entered clinical trials in the period 1989-2004 for any indication. After discarding 10,769 drugs (32% of the total) for which no description is available in the database to classify the drug as a large- or small-molecule drug, I identified 5,474 drugs as large-molecule drugs. After discarding 351 of those drugs (6% of all large-molecule drugs) because they lack information on their dates of introduction, I ended with a sample of 5,123 large-molecule drugs that entered clinical trials in the period 1989-2004 for any indication. I then classified them as anti-cancer or not (there is not enough information for direct classification per the three categories presented in Table 1/Figure 1). The resulting pattern is shown in Figure 2 whereas the increasing proportion of large-molecule drugs in clinical trials dedicated to cancer treatment is shown in Figure 3.

Insert Figure 2

Insert Figure 3

I now move to see if the temporal difference in investment in rDNA/fermentation technology could generate heterogeneity in some area of performance among incumbents and entrants, both diversifying and de novo. To do so, I was able to identify the first large-molecule drugs launched in the USA market and the firms involved in their R&D. I then

classified those firms by the role they play in the anti-cancer drug market (since incumbency and entry is measured at the market-level in traditional Schumpeterian research).

I used for classification the following definitions. *Incumbent* firms are firms established in one or more markets, including the focal market at the moment this market is disrupted by the radical technological change. *Diversifying entrants* are those entrants that were established in other market(s) prior to the start of the disruption in the focal market and that enter it precisely because the start of the discontinuity has lowered barriers to entry. *De novo entrants* are those entrants born in the focal market during the technological discontinuity. Figure 4 below depicts the decision tree and data sources I used to classify firms in each firm category.

Insert Figure 4

I present in Table 2 below the result of both the identification of firms pioneering investment in rDNA/fermentation technology and their corresponding profile (incumbent, diversifying or de novo entrant) in the anti-cancer drug market. Notice the extant presence of diversifying entrants among pioneers of large-molecule anti-cancer drugs, the variant of biotech-based anti-cancer drugs that makes use of rDNA/fermentation technology.

Insert Table 2

In fact, I can go back to the data used in the construction of Figures 2 and 3. I now take the sub-sample of large-molecule drugs that are generated by firms involved in the anti-cancer drug market (even if the drugs are not for cancer treatment), and separate them by the profile the firm adopts in this market. The resulting pattern is shown in Figure 5, and supports the conclusion that diversifying entrants into the anti-cancer drug market were initially

the major pioneers of large-molecule drugs (although in later years de novo firms seem to surpass them).

Insert Figure 5

5.3 Impact on Heterogeneity in Performance of one R&D Area: Process Innovations

In section 5.2 I presented preliminary evidence that differences on market specificity of rDNA/fermentation technology over time translated into temporal heterogeneity in investment in this technological competence. Furthermore, data suggested that, for the particular case of the anti-cancer drug market, it was diversifying entrants as a firm category that accrued most of this "competence-based" first mover advantage. Because rDNA/fermentation technology was born as a process technology (this is precisely what its technological trajectory showed in phase I of its evolution), the first impact that would be expected is heterogeneity in performance within one area of R&D: process innovations. This section tests precisely this hypothesis: are diversifying entrants, the pioneers in rDNA/fermentation technology, more competent in the R&D of process innovations for large-molecule drugs?

I measure competence to design processes for large-molecule drug production through a dataset comprising all patents for large-molecule drug production for a representative sample of firms competing in the market for anti-cancer drugs (the sample comprises 165 firms, the sampling method is a derivative of the decision tree displayed in Figure 4, and is explained in detail in Sosa [2006]). In order to collect only large-molecule drug process patents, I took all *Thomson Derwent* codes under the umbrella "Processes, Apparatus" and asked expert interviewees to perform the selection of relevant codes.[2] The resulting set of 4 specific *Thomson Derwent* codes paired with the 165 firms in the sample generated a dataset of 1,376

patents. I then, based on these data, analyze the rate of patenting per firm category through a Cox Model following the design used previously in the literature (Sørensen and Stuart, 2000). As a first step, I run the Cox model without controls (model 1) and with simple control variables (including firm size and age, see models 2 and 3). Table 3 offers descriptive statistics and Table 4 offers the Cox Model results (the omitted category in this analysis is diversifying entrants). As next steps, I will test the robustness of the dependent variable by taking into account forward citations (i.e., replacing patenting rate with "forward citation" rate).

Insert Table 3

Insert Table 4

Notice diversifying entrants have an advantage over all other firm categories since the hazard rates for the other two categories (incumbents and de novo firms) are less than 1 (a discount) and statistically significant. Since the dataset is built through the collection of all patents related to process design for large-molecule drugs only, this analysis implies that diversifying entrants are better at designing this radically new sub-set of processes. That is, their pioneering entry into rDNA/fermentation technology did translate into a competitive advantage in the design of processes for large-molecule drug production.

5.4 Impact on Heterogeneity in Overall R&D Performance

Lastly, the question is whether having a competitive advantage in this area of R&D, process innovations, would compound with differences in other resource endowments for the

[2] Special thanks to Samuel Ngai, for his detailed assessment of the 69 process codes under the umbrella of "Processes, Apparatus."

firm categories competing in the market (in this case, the anti-cancer drug market) and result in, as a first step, heterogeneity in total R&D performance.

Interviewees described the disruption effected by biotechnology on the anti-cancer drug market in specific detail. Whereas the availability of new drug discovery tools was advancing anti-cancer drug development into new mechanisms of action (i.e., into mechanism-driven drug design), as pointed before the availability of process innovations made the mass-production of large-molecules feasible for the first time. The comparison is illustrated in Figure 6 below.

Insert Figure 6

Traditional studies of technological disruptions usually have an old and a new technology, where incumbents are, for example, predicted to have a competitive advantage in the old technology, but a disadvantage in the new, for a variety of underlying mechanisms (see Chesbrough, 2001, for a review). In contrast, Figure 6 shows that in this study I can identify an old technology (chemistry-based anti-cancer drugs) and two variants of the new technology (small- and large-molecule biotech-based anti-cancer drugs). Both variants of biotech-based anti-cancer drugs are, by definition, a result of the biotechnology revolution and as such, require new technological platforms for their design. Both variants also make use of the same re-usable competences on the part of incumbents, mainly, the competence in executing clinical trials, and the knowledge of cancer as a disease. What these two variants of biotech-based anti-cancer drugs differ in is that only large-molecule drugs require rDNA/fermentation technology to be mass-produced. It becomes therefore informative to compare the differences in overall R&D performance across incumbents and both types of entrants, for small- vs. large-molecule drugs.

I measure overall R&D performance directly through the *Pharmaprojects* database. I use a representative sample of all anti-cancer drugs reported in *Pharmaprojects* generating a set of 2,281 drugs. I identify when each drug entered and exited clinical trials, and whether the drug was ultimately approved (or if it is still in clinical trials or was discontinued, in which cases I treat them as right-censored) in order to perform event history analysis. I use the same variables to identify the three categories of firms as I developed previously. I identify biotech-based large-molecule drugs directly from the *Pharmaprojects* database. To identify biotech-based small-molecule drugs, I look at the mechanism of action reported per drug in *Pharmaprojects* and include in this class only those drugs whose mechanism matches those described in industry reports (e.g., Bear Sterns, 2002; Stephens Inc., 2002; UBS Warburg, 2001) as "biotech-based" or "mechanism-driven" (in the end, mainly comprising angiogenesis and kinase inhibitors). Controls include differences in firm age and size; the cumulative introduction of drugs into clinical trials by firm category (variable "Cumulative"); the "novelty" of the drug (a replicate of the measure included in Guedj and Scharfstein, 2004); and the presence of an R&D Alliance (as reported in the cancer sub-section of the *Windhover's Pharmaceutical Strategic Alliances* collection 1986-2003).

Table 5 presents descriptive statistics. Table 6 presents then models for the subsample of biotech-based *small*-molecule drugs; whereas Table 7 presents models for the subsample of biotech-based *large*-molecule drugs.

Insert Table 5

Insert Table 6

Insert Table 7

Although the split samples are rather small to support statistical significance in all models (even if stratified separately), coefficients are of the expected direction (all hazard rates above 1) and many of marginal significance. Models in Table 6 support the idea that incumbents have a competitive advantage in biotech-based small-molecule anti-cancer drugs. This is particularly seen in models 3 and 4, where the "incumbent" coefficient in model 3 has a p-value of 0.12. In contrast, models in Table 7 support the idea that, in the contrasting case of large-molecule drugs, it is diversifying entrants who hold the competitive advantage. In fact, all models in Table 7 show the variable "diversifying" as significant, with a hazard rate above 1. The contrasting results for small- vs. large-molecule drugs in Tables 6 vs. 7 are precisely as would be expected for two variants of the new technology that differ only in their use of rDNA/fermentation technology (a competence in which diversifying entrants have a first mover advantage).

6. Discussion

In this paper, I have presented a theory-building study combining qualitative and quantitative methods. Motivated by recent research in the origin of capabilities as a driver of heterogeneity in firm performance, I ask whether we could better understand heterogeneity in the performance of incumbents and entrants during a technological discontinuity, if we were to explore the evolutionary dynamics of the new capabilities/competences that are necessary by the radically new technology. I look at one specific technological competence, rDNA/fermentation technology, that forms a cornerstone in the biotechnology revolution. As I explore the evolutionary path this competence followed, I find preliminary evidence to sup-

port that the market specificity of this competence increased over time. Such temporal difference in market specificity generated temporal heterogeneity in investment across firms interested in pharmaceuticals. This heterogeneous investment then cascaded into differences in market-level competition. In the one market I was able to measure, the anti-cancer drug market, I found preliminary evidence that heterogeneous timing of investment on rDNA/fermentation technology led to heterogeneous performance in the design of process innovations across incumbents and both diversifying and de novo entrants. Because diversifying entrants were first to invest in rDNA/fermentation technology, they accrued an advantage in the design of process innovations for downstream market applications, where anti-cancer drugs is one such case. Furthermore, this competitive advantage in the case of diversifying entrants resulted in their competitive advantage in the one variant of the radically new technology (namely, large-molecule biotech-based anti-cancer drugs).

With this case study I generate two main contributions.

First, I contribute to the literature on technological disruption, my original aim in this paper. I show how the "technological trajectory" that a competence follows has an impact in our understanding not only of diversification dynamics (Kim and Kogut, 1996) but also of the dynamics of technological discontinuities. Prior research had looked into the market specificity of resources and competences because higher specificity led to fewer firms having access to that resource/competence, and hence, to higher resource/competence value (Montgomery and Wernerfelt, 1988). In the present case, it was the evolution of a competence's market specificity that affected performance, precisely during a technological discontinuity. Changes in market specificity can make a difference in the investment patterns of different firms. Later, such differences in investment timing translate into competitive advantage, an advantage that can support the performance of diversifying entrants against that of incumbents, at least in some variants of the new technology. The contrasting performance of incumbents in the two variants of biotech-based drugs has important theoretical implications.

Traditional research had found that incumbents failed in the R&D of radically new technologies due to inertia (Henderson, 1993). That is, incumbents' organizational inertia prevented them from replacing the competences they had mastered with new ones, in spite of the fact that the technological disruption had destroyed the value of the old competences. A competing argument had been that it is not incumbents' inertia in adaptation that leads to their demise. It is their inability to timely recognize the need for change due to uncertainty in the technology. Christensen (1997) argued that often the evolutionary path of a radically new technology made it difficult for firms to recognize whether the technology would ever ramp up to match the performance required by customers. This paper elaborates the concept that incumbents' do not always fail because they cannot respond to the change imposed on them. However, in contrast to Christensen's (1997) original research, where the uncertainty was technological, the case I present here shows how uncertainty can also be market-related. Prior research has argued that uncertainty related to market applications is harder to overcome for organizations, than uncertainty related to the technology itself (Freeman, 1987). If that is the case, the distinction between them might prove key to incumbents' strategy formulation as they respond to a technological discontinuity.

As a second contribution, I further the theory on how first mover advantages and the resource-based view of the firm connect, a theoretical endeavor first posed by Lieberman and Montgomery (1988, 1998). Traditional economics has paid attention to first movership into a market. However, if we are willing to accept that firms live in a dual system of markets and resources (Wernerfelt, 1984) then there should be a competitive advantage to be gained through first movership into a resource/competence base, and I illustrate this point with the present case study.

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Tables

Table 1
Classes of Large-Molecule Drugs
that Evolved Chronologically into a New Product Class

Phase I *protein and connection to disease known*	**Phase II** *only protein known*	**Phase III** *new product class*
Insulin	Epo	Monoclonal-Antibody-based products
Factor VIII	Interferons	
Human Growth Hormone	Interleukins	
Glucocerebrosidase		

Table 2
Pioneer rDNA/fermentation Technology Process Innovators
and their later Firm Profile in the Market for Anti-Cancer Drugs

Year (Approval in USA)*	**Brand Name**	**Commercializing Firm**	**Original Developer**	**Firm Profile of Original Developer when Competing in Biotech-Based Anti-Cancer Drugs**
1982	Humulin	Eli Lilly	Genentech	Diversifying entrant
1985	Protropin	Genentech	Genentech	Diversifying entrant
1986	Intron A	Schering Plough	Schering Plough	Diversifying entrant
1986	Roferon A	Hoffman-La Roche	Genentech	Diversifying entrant
1986	Orthoclone OKT3	Ortho Biotech (Johnson & Johnson)	Ortho Biotech (Johnson & Johnson)	Diversifying entrant
1987	Activase	Genentech	Genentech	Diversifying entrant
1987	Humatrope	Eli Lilly	Eli Lilly	Incumbent
1989	Epogen	Amgen	Amgen	Diversifying entrant
1990	Procrit	Ortho Biotech (Johnson & Johnson)	Ortho Biotech (Johnson & Johnson)	Diversifying entrant
1990	Actimmune	Genentech	Genentech	Diversifying entrant
1991	Novolin	Novo Nordisk	Novo Nordisk	Other
1991	Leukine	Immunex (Amgen)	Amgen	Diversifying entrant
1991	Neupogen	Amgen	Amgen	Diversifying entrant
1992	Recombinate	Baxter / Wyeth	Baxter / Wyeth	Diversifying entrant / Incumbent
1992	Proleukin	Chiron	Chiron	Diversifying entrant
1992	OncoScint CR/OV	Cytogen	Cytogen	De Novo entrant

* as reported in Walsh (2003)

Table 3
Process Design, Descriptive Statistics and Correlation Matrix
(1,322 Spells, 1,251 Events)

	Count	Mean	Std.Dev.	Min.	Max.
(1) Incumbent	304				
(2) De Novo	230				
(3) Firm Age		68.8	61.02	7	246
(4) Firm Size		21,518	29,391	14	122,000
(5) Incumbent X Firm Age		27.5	52.5	0	155
(6) Cumulative		298	232	0	807

	(1)	(2)	(3)	(4)	(5)	(6)
(1) Incumbent	1					
(2) De Novo	-0.22	1				
(3) Firm Age	0.47	-0.38	1			
(4) Firm Size	0.67	-0.30	0.64	1		
(5) Incumbent X Firm Age	0.97	-0.22	0.50	0.67	1	
(6) Cumulative	-0.35	-0.36	-0.10	-0.19	-0.34	1

Table 4
Process Design Competence
Cox Model Analysis of Patent Application Rate
(1322 Spells, 1251 Events)
All Coefficients in *Hazard Rates*

	Model 1	**Model 2**	**Model 3**
Incumbent	0.87*	0.32***	0.42***
	(0.05)	(0.08)	(0.11)
De Novo	0.40***	0.29***	0.50***
	(0.03)	(0.06)	(0.04)
Firm Age		0.99***	0.99***
		(0.00)	(0.00)
Firm Size		0.99**	0.99*
		(0.00)	(0.00)
Incumbent X Firm Age		1.01***	1.01***
		(0.00)	(0.00)
Cumulative			1.00***
			(0.00)
Log Likelihood	-7,803	-7,768	-7,612

+ p < 0.1, * p < .05, ** p < .01, *** p < .001 Standard errors in parentheses.

Table 5
Preclinical Drug Design and Clinical Trial Execution,
Descriptive Statistics and Correlation Matrix
Only Targeted Drugs
(N = 991)

	Count	Mean	Std.Dev.	Min.	Max.
(1) Incumbent	162				
(2) Diversifying	354				
(3) Large Molecule	638				
(4) Firm Age		58.8	64.8	4	246
(5) Firm Size		24,357	37,534	10	122,000
(6) Cumulative		473	237	5	918
(7) Drug Novelty		-2.2	1.5	-5.3	0
(8) R&D Alliance	16				

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
(1) Incumbent	1							
(2) Diversifying	-0.32	1						
(3) Targeted Large Molecule	-0.32	-0.06	1					
(4) Firm Age	0.44	0.33	-0.36	1				
(5) Firm Size	0.65	0.13	-0.39	0.82	1			
(6) Cumulative	-0.31	0.15	0.01	-0.19	-0.21	1		
(7) Drug Novelty	0.11	0.08	-0.25	0.07	0.10	0.24	1	
(8) R&D Alliance	-0.03	-0.04	0.06	-0.07	-0.06	-0.09	-0.03	1

Table 6
Preclinical Drug Design and Clinical Trial Execution
Cox Model Analysis of Drug Approval (353 Spells, 7 Events)
Only Targeted Small Molecules
All Coefficients in *Hazard Rates*

	Model 1	**Model 2**	**Model 3**	**Model 4**
Incumbent	1.70	3.73	4.31	5.60
	(1.31)	(4.26)	(4.68)	(8.10)
Diversifying		3.60	3.00	4.07
		(4.01)	(3.87)	(5.80)
Firm Age				0.99
				(0.01)
Firm Size				1.00
				(0.00)
Cumulative Introduction			1.00	1.00
			(0.00)	(0.00)
Drug Novelty			1.43	1.38
			(0.47)	(0.49)
R&D Alliance			0.00	0.00
			(0.00)	(0.00)
Log Likelihood	-29	-28	-27.7	-27.6

+ p < 0.1, * p < .05, ** p < .01, *** p < .001 Standard errors in parentheses.

Table 7
Preclinical Drug Design and Clinical Trial Execution
Cox Model Analysis of Drug Approval (638 Spells, 15 Events)
Only Targeted Large Molecules
All Coefficients in *Hazard Rates*

	Model 1	**Model 2**	**Model 3**
Incumbent	3.05 (3.34)	2.26 (2.37)	2.29 (3.13)
Diversifying	3.91* (2.22)	4.01* (2.50)	4.70* (3.11)
Firm Age			0.99 (0.01)
Firm Size			1.00 (0.00)
Cumulative Introduction		0.99 (0.00)	0.99 (0.00)
Drug Novelty		1.27+ (0.16)	1.26+ (0.15)
R&D Alliance		2.69 (2.96)	2.63 (2.97)
Log Likelihood	-64	-62.8	-62.5

+ p < 0.1, * p < .05, ** p < .01, *** p < .001 Standard errors in parentheses.

Figures

Figure 1
The Three Phases of Evolution of Large-Molecule Drugs in the Biotechnology Revolution

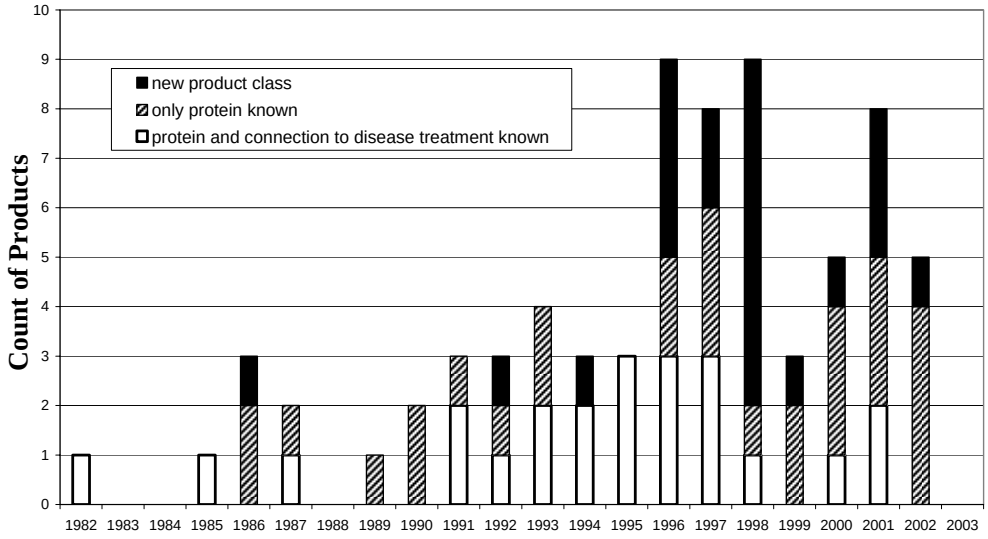


Figure 2
Increasing Presence of Large-Molecule Drugs in Clinical Trials,
And among them, of those for Cancer Treatment

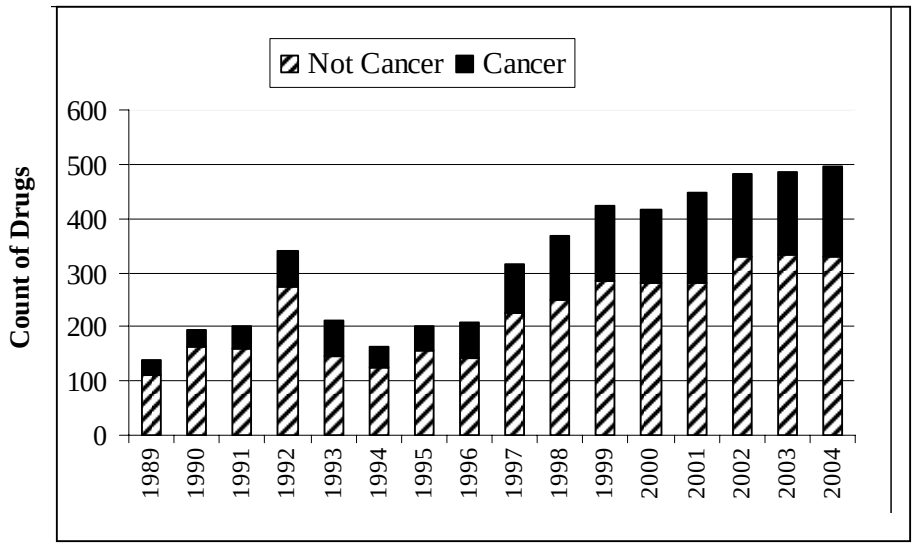


Figure 3
Increasing Proportion of Large-Molecule Drugs in Clinical Trials Dedicated to Cancer Treatment

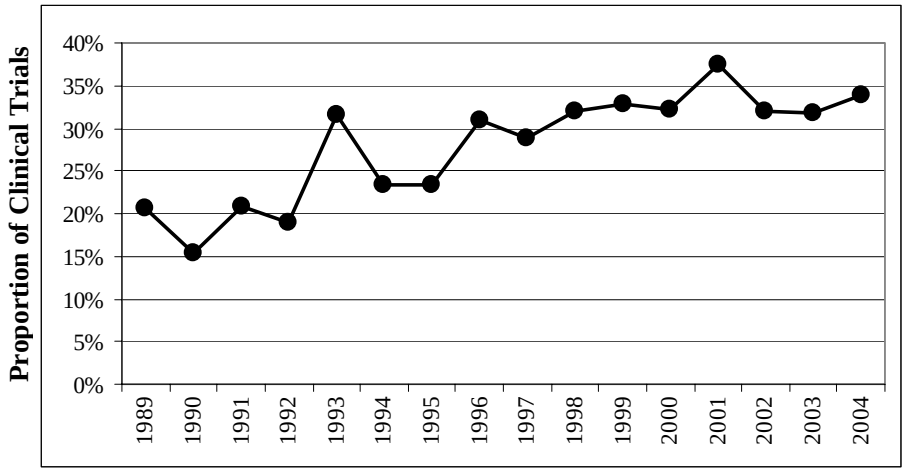
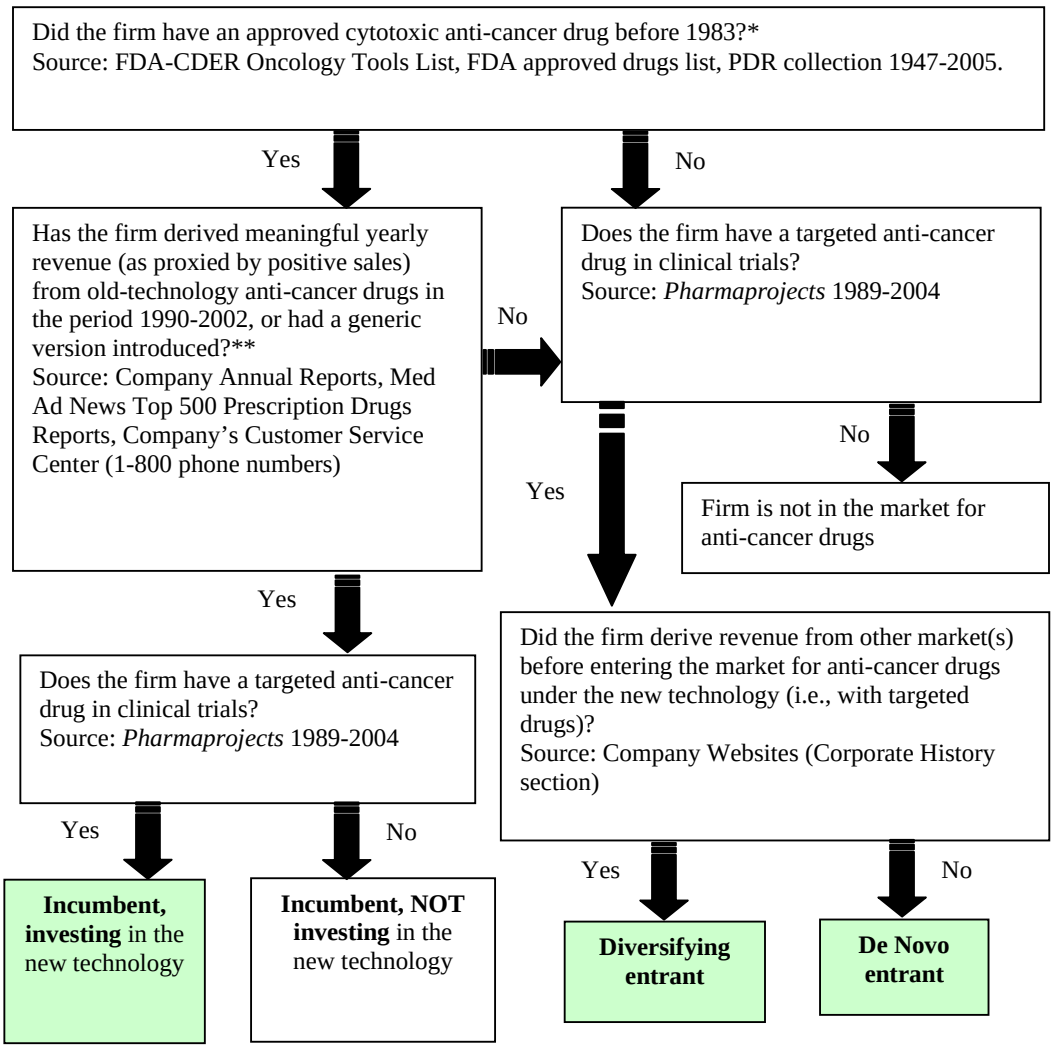


Figure 4

Decision Tree to Categorize Firms



* This requirement ensures that the firm was an incumbent to the market prior to its investment in new-technology anti-cancer drugs (as opposed to just deciding to enter the market investing in both old and new technologies in parallel). The year 1983 was when the first Targeted Anti-Cancer Drug was launched on the market, and I therefore use it as a milestone.

** This requirement ensures that the firm did not leave the market and come back to it because of the new technology's effect on lowering barriers to entry. If a firm exits a market before the transition due to the radical technological change starts, then that firm is not in the market at the time of the radical change and therefore is not an incumbent. If it stays away from the market, then it is out of the scope of relevance for this study. If it comes back after several years, investing in the new technology, then it is a diversifying entrant.

Figure 5
Proportion of Large-Molecule Drugs in Clinical Trials Generated by Each of the Three Firm Categories Competing in the Anti-Cancer Drug Market

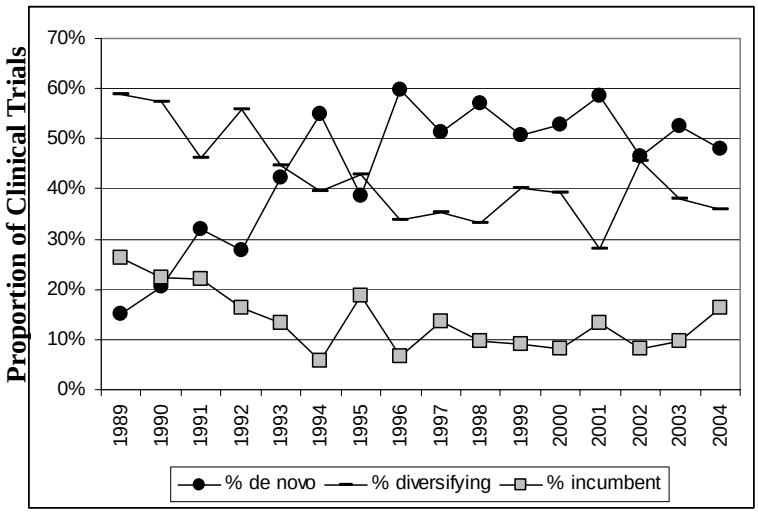


Figure 6
The Effect of the Biotechnology Disruption on Anti-Cancer Drug Development

		Mechanisms	
		Chemistry-Based (cytotoxic)	**Biotech-Based** (targeted or mechanism-driven)
Molecule Size	**Small Molecules**	Old Technology	New Technology
	Large Molecules		New Technology