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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. As such, this paper is based in detailed, direct industry observation, complemented with large-sample secondary data collection when necessary. Through such combination of industry observation and accompanying quantitative analysis, I find that this competence evolved with increasing market specificity. Such evolutionary path determined a significant part of performance heterogeneity during the technological disruption. Diversifying entrants outperformed incumbents only in the variant of the new technology that required rDNA/fermentation technology, that is, only in the variant with this particular evolutionary path. This case study supports the theoretical conclusion that incumbents do not necessarily fail to successfully execute R&D for all radically new technologies, as previously argued in studies of incumbents' structural inertia. Incumbents in the present case fail to execute the R&D of the new technology only for that variant in which they cannot foresee the applicability to their own markets. That is, incumbents as organizations are distinctively subject to structural inertia in their R&D structure, and to inertia in the structure with which they monitor the environment.

Key words: evolutionary perspective; organizational capabilities; incumbent; technological disruption; R&D; organizational change.

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 on the fate of incumbents (e.g., Henderson and Clark, 1990; Henderson, 1993). However, the study of technological change seems to lag advances in mainstream strategy research. Whereas the latter keeps moving towards the origin and evolution of capabilities, the former has concentrated attention on the straightforward comparison of capabilities present vs. newly required. Specifically, studies of technological change have focused on the impact on firm performance of differences in attributes between changes (e.g., radical vs. incremental [Henderson and Clark, 1990], disruptive vs. sustaining [Christensen, 1997], core vs. periphery [Tushman and Murmann, 1998]), overlooking entirely the impact on performance generated by differences on the process through which those changes evolve. Consequently, I look at the case of a radical technological change where the new technology comprises two variants that differ

in the evolutionary path they follow precisely because one variant makes use of a specific capability that the other variant does not require, where such capability evolved through a particular process.

Specifically, I look at the market for anti-cancer drugs and its transition from cytotoxic to targeted drugs. As a consequence of the biotechnology revolution this transition is a radical change in technological paradigms (Henderson, Orsenigo and Pisano, 1999) and is competence-destroying to the incumbent firms (Rothaermel, 2001). Among targeted (i.e., biotech-based) anti-cancer drugs, I look at two variants, namely small- vs. large-molecule drugs, which differ in their requirement of one technological capability: rDNA/fermentation techniques. Given that rDNA/fermentation techniques evolved in a very distinctive path, the presence of this capability makes the evolution of large-molecule targeted anti-cancer drugs quite contrasting in comparison to that of their small-molecule counterparts. It is in this comparison that I can distinguish two variants that are radical changes to the technological standard (i.e., cytotoxic drugs) but that differ in their evolutionary paths.

With no a priori hypotheses about neither the specific nature of the difference in evolutionary paths nor the impact of that difference on firm performance, I design this study more as a theory-building exercise than a hypothesis test. Nevertheless, my choice of combining qualitative and quantitative research requires that quantitative analyses be performed following a simple hypothesis, which I state at the start of each section.

In preliminary analyses, I show how the gradual decrease in market specificity (i.e., the gradual increase in the number of markets for which the technological capability is applicable) of one variant of the new technology led to differential timing of investment across firms. This heterogeneity in investment resulted later in performance heterogeneity in several dimensions of R&D performance among incumbents and both diversifying and de novo entrants. But more importantly, the R&D performance of incumbents was different in each variant of the new technology. Incumbents only fell behind in their R&D performance in the one variant that made use of rDNA/fermentation techniques, and such underperformance was tied to the evolutionary path followed by this set of techniques.

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 (e.g., Kim and Kogut, 1996) and of persistent within-market differences in R&D competence (e.g., Helfat, 1994) but also our understanding of incumbents' fate during technological discontinuities. Furthermore, I show that the fate of incumbents during a technological discontinuity differed across variants of the radically new technology. I argue that this difference is not the result of differences in the technologies but rather in the evolutionary paths of these technologies. Whereas the stance of the new technology as radical change generated structural inertia among incumbents, it was the specific evolutionary path of one variant of the new technology that additionally generated cognitive inertia. Only in the variant where both structural and cognitive inertia accumulated, did incumbents fall behind other firms in their R&D performance. In this case, cognitive inertia arose in spite of the change in technologies being sustaining in customer preferences, contrary to what prior studies had shown (Christensen, 1997).

More broadly, the finding that only the presence of both cognitive and structural inertia results in a lagging response from incumbents brings renewed attention to the proposition that research on organizational change requires attention to both the speed of learning mechanisms and the responsiveness of the structure to designed changes (Arrow, 1974; Hannan and Freeman, 1984; Williams and Mitchell, 2004). It is only when we pay attention to both factors that we get a full picture of environmental change and organizational adaptation.

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? 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). A competing theory argues 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). In that sense, the counterargument is evolutionary. A recent set of studies has begun looking into the origin of capabilities trying to distinguish idiosyncratic sources of heterogeneity in resource endowments from measurable patterns. Kim and Kogut (1996), for example, show how the evolutionary path that capabilities follow translates later into differences in diversification opportunities. Ahuja and Katila (2004) show how the complex interconnection of different attributes in the context in which firms compete give rise over time to differences in resources. And Ethiraj et al. (2005) show differences in the characteristics of the tasks performed by a firm give rise to differences in the evolution of particular capabilities that will impact firm performance in the future.

3. The Origin of Capabilities and Schumpeterian Capability Destruction

In contrast, the study of technological discontinuities, that is, of Schumpeterian "creative destruction," seems to have fallen behind. Research in this area advanced considerably through the proposition to characterize technological disruption based on the extent to which it destroys the value of the competences that incumbents had originally mastered (Tushman and Anderson, 1986). 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, attention needed to be paid 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 then advanced mainly on the identification of drivers of

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

inertia or the exceptions to this rule (see Chesbrough, 2001, for a review). Recently, a contrasting mechanism has been brought to attention: 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 mainstream strategy, including most current evolutionary studies. 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 a more elaborate evolutionary perspective. Creative destruction research needs to move beyond investigating the impact on heterogeneity in firm performance that the differences in the attributes across technological changes have. Creative destruction research needs to also pay attention to the impact on heterogeneity in firm performance that the differences in the evolutionary paths that technological changes follow also represents throughout a technological discontinuity. This is precisely the aim of the present study. I therefore require the comparison of two changes with the same attributes but different evolutionary paths. With this purpose in mind, I study two technological variants generated by the same radical change in technologies (therefore with the same attributes), where the variants differ in the evolutionary paths followed by the competences required to implement them. Specifically, I study the anti-cancer drug market and its transition from standard chemotherapy into targeted drug development, a transition generated by the biotechnology revolution that is radical and competence-destroying for incumbents (Henderson, Orsenigo, and Pisano, 1999; Rothaermel, 2001). Among targeted anti-cancer drugs, I differentiate between two variants: small-molecule and large-molecule drugs. These two variants differ only in that the latter makes use of a specific technological competence, rDNA/fermentation techniques. By following the evolution of rDNA/fermentation techniques, I can understand the difference in evolutionary paths between small-molecule and large-molecule targeted anti-cancer drugs, and draw conclusions about the impact on performance heterogeneity due to

differences in evolution and not only to differences in attributes for the two variants of the technological change.

With no a priori hypotheses about what the evolutionary path or its impact on firm performance would be, I design the present study as an exploratory endeavor. Nonetheless, given my choice of combining qualitative and quantitative methodologies, the latter require the statement of simple hypotheses to lead each quantitative analysis, which I provide at the start of each section, as I explain next.

4. Method

4.1 The Setting and the Technological Discontinuity

I choose as setting for this case study the market for anti-cancer drugs and its transition from cytotoxic agents (e.g., antineoplastic antibiotics, etc.) to the radically new category termed targeted drugs (e.g., tyrosine kinase inhibitors, etc.), a transition brought about by the biotechnology revolution. This setting has many advantages, as prior research has shown (Sosa, 2007a), including the advantage that its high research intensity (PhRMA, 2003) and close connection between product quality and profitability (Lu and Comanor, 1998) bring to studies of R&D performance. Furthermore, the biotechnology revolution as the discontinuity of choice had advantages as well, including a wealth of data sources and possible interviewees currently available.

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), 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. Innovations in rDNA/fermentation technology have been linked to the birth and growth of successful biotechnology-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, rDNA/fermentation techniques, for the present study. As prior research has stated, R&D competences are dynamic capabilities and not static resources (Helfat, 1994; Teece, Pisano and Shuen, 1997; Helfat and Lieberman, 2002). I therefore study rDNA/fermentation techniques, an R&D competence, as the set of innovations comprising not only the original discovery of recombinant DNA techniques (Cohen and Boyer, 1973, 1974) but also the many discoveries that followed, commonly referred to as fermentation or cell culture technology.

As described in interviews, targeted anti-cancer drug development comprises two main variants: small-molecule and large-molecule drugs. Although both variants of targeted anti-cancer drugs are radically different from standard chemotherapy in that targeted drugs are developed through a "science-driven" approach, only large-molecule targeted drugs require rDNA/fermentation techniques for their production. It is in this distinction that I can compare two variants of a technological change with the same attributes (i.e., radical and competence-destroying to incumbents) with different evolutionary paths (i.e., subjected or not to the evolutionary path of the R&D capability comprised by rDNA/fermentation techniques).

I organize the analysis in this study in two stages. Stage one is the qualitative theory-building portion, exploring what the differences in evolutionary paths were and how they mattered. Stage two is the quantitative theory-testing portion of the study, where I test whether the differences in evolutionary paths had an impact on firm performance heterogeneity. This second stage is theory-testing because it is designed to reject the null hypothesis that there exists no difference in performance given differences in evolutionary paths. I present data sources and measures for both stages of the study next.

4.2 Data Sources and Measures

4.2.1 Qualitative Analysis

I collected data through 45 interviews (with four interviewees contacted repeatedly) ranging between 30 and 90 minutes each, with a semi-structured interview guide that kept evolving as I gathered

further insight. Interviewees included R&D managers in large and small pharmaceutical firms, industry analysts, and scientists both from industry and from academia. I complemented that data with historical material collected from Walsh's (2003) report of large-molecule drug development and customized searches in the *PubMed* database for historical background on specific drugs. I also made use of the data in PJB Publications' *Pharmaprojects* for selected information on the introduction of drugs into clinical trials over the period 1989-2004. The analysis of this stage of the study is presented in section 5.1.

4.2.2 Quantitative Analysis

For stage two of the study, presented in section 5.2, I look into the possible impact of the evolutionary path of rDNA/fermentation techniques on the performance heterogeneity of incumbents, diversifying and de novo entrants competing in the anti-cancer drug market during the biotechnology discontinuity. In order to test whether differences in evolution led to differences in R&D performance, I first tested whether differences in evolution resulted in sustainable differences in the performance of research on rDNA/fermentation techniques. After testing for these differences, I then proceeded to test whether these differences led to differences in the performance of large-molecule anti-cancer drug research and development.

Sample. To construct the sample of firms, I started by identifying all anti-cancer drugs in clinical trials in the period 1989-2004 through PJB Publications' database *Pharmaprojects* and then focused on the firms responsible for them. In order to generate a sample that included firms with a clear intention to compete in the anti-cancer drug market, I matched the firms from *Pharmaprojects* to the firms reported in all available PhRMA surveys *New Medicines in Development for Cancer* (administered in 1988 and every two years from 1989 to 2003). After excluding non-profit organizations, matching all cases to parent company names only, and adjusting for mergers and acquisitions and missing data, I identified the final sample, which comprises 165 firms (further detail of the sampling frame is given in Sosa, 2007a).

Dependent Variables. Because I performed tests on the impact of differences in evolutionary paths of the two technological variants on two separate aspects of firm performance, I have two main dependent variables.

Competence in researching rDNA/fermentation techniques. I estimated this R&D competence by measuring the rate of production of patented innovations in this area, as reported in Thomson Scientific's *Derwent World Patent Index*. I took all *Derwent* manual codes under the umbrella "Processes, Apparatus" and asked expert interviewees to perform the selection of relevant codes. The resulting set of 4 specific *Derwent* manual codes paired with the 165 firms in the sample generated a dataset of 1,375 patented innovations.[2] I then, based on these data, analyzed the rate of production of patented innovations through a Cox model following the design used previously in the literature (Sørensen and Stuart, 2000). To do this, I used the earliest date of priority filing for the patented innovation as the time where the event took place. I considered the start of the time at risk to be either January 1st of the first year in the dataset (1979) or of the year of founding for the firm, whichever was latest, in the case of the firm's first patented innovation. All subsequent cases were set starting as the day immediately after the previous event occurrence. I ran a second set of regressions taking into account the total number of forward citations that the set of patents tied to each innovation generated. I incorporated this measure in Cox regressions by using the total number of forward citations as frequency weights, that is, by duplicating records by as many forward citations they had. This implies the second set of regressions is then predicting rather the rate of production of forward citations in this area.

Competence in Targeted Anti-Cancer Drug Development. In order to test for differences in competence in the research and development of targeted anti-cancer drugs, I identified when each drug entered and exited clinical trials as reported in *Pharmaprojects*. I distinguished whether the drug was ultimately approved, discontinued or right-censored and analyzed the data through Cox regression focusing on the approval event, treating discontinuations and right-censored cases as right-censored (although alternative specifications for the discontinued records did not alter results).

Independent Variables. The principal interest was to distinguish whether performance advantages accrued to some categories of firms in particular, and whether there was a difference between the two variants of the new technology that differed on the basis of their use of rDNA/fermentation techniques. Therefore, the following binary variables were constructed.

Small- vs. Large-Molecule Targeted Drugs. I classified targeted anti-cancer drugs as large- vs. small-molecule drugs through the information in the *Pharmaprojects* database. For large-molecule drugs, this information is directly provided in the database. For small-molecule drugs, I matched the mechanism of action reported in *Pharmaprojects* to the mechanisms of action described in industry reports (e.g., Bear Sterns, 2002; Stephens Inc., 2002; UBS Warburg, 2001) as targeted (in the end, mainly comprising angiogenesis and kinase inhibitors). I then generated a dummy variable "Large-Molecule" to distinguish these two classes of drugs.

Firm Categories. I distinguished among incumbents, diversifying and de novo entrants based on whether a firm had been present in the anti-cancer drug market prior to the start of the biotechnology revolution in that market (i.e., 1983), and if not, whether it had been operating in any market prior to its incursion into anti-cancer drug development. The decision tree and data sources used to classify all firms in anti-cancer drug market incumbents, diversifying or de novo entrants are presented in Figure 1. Further detail is available in Sosa (2007a).

rDNA Pioneers. As will be shown in section 5.1, the evolutionary path of rDNA/fermentation techniques did lead to differences in timing of investment across firms. Because the anti-cancer drug market is one of the last markets to be reached by rDNA/fermentation techniques and their resulting large-molecule drugs (due to the complexity of this R&D capability), I took the date that large-molecule drugs entered clinical trials with a clear anti-cancer application, namely 1995 (as reported in Colwell, 2002) as the cut-off date to identify rDNA pioneers. I then used Walsh's (2003) report to identify all large-molecule drugs approved up to 1994 irrespective of market application, and then combined that information with information on *Pharmaprojects* to pinpoint the developing firms for those drugs. I classi-

[2] *Derwent World Patent Index* is constructed around innovations, and not patents. Therefore, each record represents

fied as an rDNA pioneer a firm that had a large-molecule drug approved in 1994 or before, irrespective of market application, and that was the first one in its active ingredient. The identification of these rDNA pioneering firms is shown in Table 1.

Insert Table 1

Control Variables. In all analyses using Cox regression, I control for the cumulative introduction (of patented innovations or drugs in clinical trials, for the different sets of regressions). In analyses of drug approval, I controlled for the novelty of the drug through the variable "drug novelty," defined as the natural logarithm of the inverse of the chronological place of introduction that the drug holds on the list of drugs within the same mechanism of action (a replica of the measure included in Guedj and Scharfstein, 2004). In analyses of drug approval, I also controlled for the presence of an R&D alliance through a dummy variable with value 1 if the drug had an R&D alliance associated with it reported in the cancer sub-section of the *Windhover's Pharmaceutical Strategic Alliances* collection 1986-2003.[3] Because prior research (Sosa, 2007a) has shown that in this market the cross-firm category acquisition of drugs is extremely low and more frequently present in de novo firms than either diversifying entrants or incumbents, the lack of acquisition controls is not a concern. Lastly, in analyses of drug approval I also distinguished diversifying entrants that had prior oncology research from those who did not in accordance to prior research in this market (Sosa, 2007b). In Cox regressions for rate of production of patented innovations weighted by forward citations I also controlled for the number of different patents applied for per innovation, since this number could artificially increase the number of forward citations.

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a unique innovation that matches to several patents, depending on the behavior of the patenting firm.

[3] Although projects could also be outsourced, at least in their clinical trial component, in pharmaceuticals, the level of outsourcing in cancer is extremely low, second-to-last after ophthalmology, with a mean outsourcing level of 10.3% in the period 1995-1999, and even lower levels in the years preceding 1995 (Azoulay, 2004).

5. Analysis and Results

5.1 The Evolution of rDNA/Fermentation Techniques

As mentioned, rDNA/fermentation techniques have made possible the mass-production of one variant of biotechnology-based drugs: large-molecule drugs. For instance, interferon alpha-2, the active ingredient in *Intron A*® (the newly approved, large-molecule targeted anti-cancer drug), is a cytokine naturally produced in the human body in small quantities (Walsh, 2003). rDNA/fermentation techniques made it possible to produce interferon alpha-2 in therapeutically and hence commercially feasible amounts. In fact, interviewees report innovations in rDNA/fermentation techniques evolved through a series of phases, that as I will argue in this section, decreased in market specificity (i.e., increased in the scope of markets to which they were applicable [Montgomery and Wernerfelt, 1988]).

rDNA/fermentation innovations 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), 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 pro-

duction 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 techniques 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 techniques. 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 techniques 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 targeted 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, large-

molecule drugs currently available in the market can be classified into the three categories mentioned above. The resulting three broad classes are shown in Table 2.

Insert Table 2

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 2 to illustrate the evolution of the three phases.

Insert Figure 2

The basic definition of a market in economic theory is a set of products that are substitutes for one another. Consequently, each disease treatment is, in rough terms, a stand-alone market. What the three-phase progression of the applicability of rDNA/fermentation techniques 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 Impact of Differences in Evolutionary Path on Differences in Firm Performance

5.2.1 The Emergence of a "Competence-Based" First Mover Advantage

The increase over time in the number of markets for which rDNA/fermentation techniques were applicable could have generated heterogeneity in investment in this technological competence, which would then lead to differences in the competence to research further rDNA/fermentation techniques. This is therefore the hypothesis to test in this section: whether rDNA pioneers had a sustained advantage in the competence to research rDNA/fermentation techniques. Table 3 offers descriptive statistics and Table 4

offers the Cox model results for regressions predicting the rate of production of patented innovations in the rDNA/fermentation area in the period 1979-2004.

Insert Table 3

Insert Table 4

Notice rDNA pioneers have an advantage (model 3) and their advantage is larger than that of incumbents (test of coefficients being equal is rejected at $p < 0.03$). The baseline in models 1 and 2 is diversifying entrants (the omitted category) and in both cases de novo firms incur a disadvantage in comparison (their hazard rates are < 1 in both models). In model 3, the baseline (the omitted category in this case) is diversifying entrants that are not rDNA pioneers and de novo firms are still at a significant disadvantage (their hazard rate is still < 1). This analysis implies that pioneers in the area of rDNA/fermentation techniques accrued an advantage in that R&D capability that persisted until at least 2004, the year of end of observation.

Because not all innovations are of equal importance, I try to control for such differences by creating frequency weights based on the forward citations of the patents tied to each innovation. Table 5 presents descriptive statistics whereas Table 6 presents results of the Cox regressions with frequency weights. Prior conclusions do not change: rDNA pioneers accrued a sustained advantage in the performance of research in rDNA/fermentation techniques.

Insert Table 5

Insert Table 6

5.2.2 Impact on Heterogeneity in R&D Performance

So far, I have offered evidence supporting the result that the evolution of rDNA/fermentation techniques with its gradual decrease on market specificity translated into temporal heterogeneity in investment in this technological competence, and more importantly, into a sustained advantage in the performance of subsequent research in rDNA/fermentation techniques. In this section, I look for evidence that the sustained advantage in the research of rDNA/fermentation techniques tested in section 5.2.1 resulted in an advantage on the research and development of large-molecule targeted anti-cancer drugs, but not on that of small-molecule targeted anti-cancer drugs. Whereas prior research found incumbents had an absolute advantage in the research and development of all targeted anti-cancer drugs, in this section I hypothesize that for the sub-set of targeted anti-cancer drugs that are large molecules, rDNA pioneers would have the largest advantage. I perform this test using Cox regressions predicting whether and when the approval of a drug takes place. In order to gain statistical power, I split the sample of targeted anti-cancer drugs into the sub-sample of small-molecule and that of large-molecule drugs. Tables 7 and 8 present descriptive statistics and correlation matrices for small-molecule and large-molecule targeted anti-cancer drugs, respectively, whereas Tables 9 and 10 present their corresponding Cox models, in the same order.

Insert Table 7

Insert Table 8

Insert Table 9

Insert Table 10

Although the small-molecule drug sub-sample is rather small to support statistical significance in any of its models (even though the stratification in this case adds statistical power), coefficients are of the expected direction: incumbents' coefficient is > 1 and larger than that of rDNA pioneers.

More importantly, the sample for large-molecule drugs does achieve statistical significance. Model 3 in Table 10 shows rDNA pioneers have a significant, > 1 hazard rate, outperforming incumbents and indeed other firm categories. In model 4, Table 10, I try to control for the presence of prior oncology research, a variable shown in previous research (Sosa, 2007b) to determine competence in preclinical design of anti-cancer drugs, a preceding step to the launch of an anti-cancer drug in clinical trials, but the sample is too small to distinguish the effects. As seen in Table 10, firms that either had prior oncology research, or were rDNA pioneers, or both, all had an advantage in the research of large-molecule targeted anti-cancer drugs, but the relative magnitudes of their comparative advantages cannot be assessed (the pair-wise comparison of the three coefficients all fail to reject the null hypotheses).

6. Discussion

In this paper, motivated by recent research in the origin of capabilities as a driver of performance heterogeneity, I asked whether we could better understand performance heterogeneity during a technological discontinuity, if we were to explore not only the new competences required by the radically new technology but also the evolutionary path followed by those capabilities. I looked at one technological competence, rDNA/fermentation techniques. As I explored its evolutionary path, I found preliminary evidence that the market specificity of this competence decreased over time (i.e., its market coverage increased). 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 downstream market I measured, the anti-cancer drug market, I found preliminary evidence that diversifying entrants pioneers in rDNA/fermentation techniques accrued a competitive advantage. They outperformed in the generation of subsequent rDNA/fermentation innova-

tions and in the overall R&D performance of the one variant of the radically new technology that made use of rDNA/fermentation techniques (namely, large-molecule targeted anti-cancer drugs).

Although the question can be raised as to whether incumbents rationally waited to invest late in rDNA/fermentation techniques, as opposed to their delay representing a lagged response, the disadvantage that these firms are incurring in R&D performance suggests otherwise. Indeed, in interviews with R&D managers in incumbent firms, they recognized they were unintentionally late in investing in rDNA/fermentation techniques and were later forced to catch up. Accounts in the public press support as well this statement (e.g., Drews, 1993).

With this case study, I hope to contribute to the literature on technological disruption. 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. In the present case, changes in market specificity made a difference in the investment patterns of different firms, and differences in investment patterns in turn translated in downstream performance heterogeneity. A main takeaway of this paper is to distinguish how incumbents were not generally underperforming in the R&D of the new technology as the traditional literature had predicted based on structural inertia arguments (e.g., Henderson, 1993). Incumbents only fell behind in the variant of the radically new technology for which it was unclear initially whether the application of the additional technological competences would affect the market where the incumbents held the leadership. That is, incumbents only fell behind in the variant of the new technology where both cognitive and structural inertia were combined. Furthermore, the process that led to lack of foresight for incumbents in this case did not involve a change in customer tastes as has been argued before in the literature (Christensen, 1997; Tripsas, 2006). In this case, the change is radical in technologies but sustaining in customer tastes, and incumbents still lacked foresight due to the particular evolutionary path that the one technological variant followed.

In that sense, we return to the question of what determines the ability of organizations to adapt to environmental changes. Hannan and Freeman (1989) highlighted the need to understand both the speed of learning mechanisms and the responsiveness of the organizational structure to designed changes. It is

only when both, cognitive and structural inertia are considered that we can understand the adaptation ability of incumbents to a technological change and to organizations in general.

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Tables

Table 1
Pre-1995 USA Approvals of rDNA/Fermentation Technology-based Products and their Developing Firms

Year*	Brand Name*	Active Ingredient	Indication (Market)*	Commercializing Firm*	Developing Firm**	rDNA Pioneer
1982	Humulin	Insulin	Diabetes mellitus	Eli Lilly	Genentech	✓
1985	Protropin	Human growth hormone (hGH)	hGH deficiency in children	Genentech	Genentech	✓
1986	Intron A	Interferon alpha 2	Cancer, genital warts, hepatitis	Schering Plough	Biogen	✓
1986	Roferon A	Interferon alpha 2	Hairy cell leukemia	Hoffman-La Roche	Genentech	✓
1986	Recombivax	Hepatitis B virus surface antigen	Hepatitis B vaccine	Merck		
1986	Orthoclone OKT3	Muromomab CD3	Reversal of acute kidney transplant rejection	Ortho Biotech (Johnson & Johnson)	Ortho Biotech (Johnson & Johnson)	✓
1987	Activase	Tissue plasminogen activator (tPA)	Acute myocardial infarction	Genentech	Genentech	✓
1987	Humatrope	hGH	hGH deficiency in children	Eli Lilly	Eli Lilly	
1989	Epogen	Epoetin alpha	Anemia	Amgen	Amgen	✓
1990	Procrit	Epoetin alpha	Cancer-related anemia	Ortho Biotech (Johnson & Johnson)	Amgen	
1990	Actimmune	Interferon gamma 1	Chronic granulomatous disease	Genentech	Genentech	✓
1991	Novolin	Insulin	Diabetes mellitus	Novo Nordisk	Novo Nordisk	
1991	Leukine	Granulocyte macrophage colony-stimulating factor (GM-CSF)	Autologous bone marrow transplantation	Amgen and Schering AG	Immunex[1]	✓
1991	Neupogen	Filgrastim	Chemotherapy-induced neutropenia	Amgen	Amgen	✓
1992	Recombinate	Factor VIII	Hemophilia A	Baxter / Wyeth	Genetics Institute[2]	✓
1992	Proleukin	Interleukin 2	Renal cell carcinoma	Chiron	Chiron	✓
1992	OncoScint CR/OV	Satumomab pendetide	Detection/staging, colorectal and ovarian cancers	Cytogen	Cytogen	
1993	Bioclate	Factor VIII	Hemophilia A	Centeon	Genetics Institute	
1993	Kogenate	Factor VIII, 2nd generation	Hemophilia A	Bayer	Bayer	
1993	Betaseron	Interferon beta 1	Relapsing multiple sclerosis	Berlex laboratories and Chiron	Chiron	✓
1993	Pulmozyme	Dornase alpha	Cystic fibrosis	Genentech	Genentech	✓
1994	Nutropin	hGH, 2nd generation	hGH deficiency in children	Genentech	Genentech	
1994	ReoPro	Abciximab	Prevention of blood clots	Centocor	State University, NY	
1994	Cerezyme	Beta glucocerebrosidase	Gaucher's disease	Genzyme	Genzyme	✓

Sources:
* Walsh (2003)
** *Pharmaprojects*
*** Analysis in this study

Notes:
[1] Wyeth acquired a majority interest in Genetics Institute in 1992, fully acquiring the firm in 1995 (http://www.wyeth.com/aboutwyeth/history visited on June 5, 2007).
[2] Amgen acquired Immunex in 2002 (http://www.amgen.com/about/acquisitions.html visited on June 6, 2007).

Table 2
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 3
Competence in rDNA/Fermentation Technology
Descriptive Statistics and Correlation Matrix for Patenting Rate Analysis
(1,452 Spells, 1,375 Events)

	Count	Mean	Std.Dev.	Min.	Max.
(1) Incumbent	329				
(2) De Novo	252				
(3) rDNA Pioneer	450				
(4) De Novo, no rDNA Pioneer	245				
(5) Cumulative		319	247	0	846

	(1)	(2)	(3)	(4)	(5)
(1) Incumbent	1				
(2) De Novo	-0.25	1			
(3) rDNA Pioneer	-0.36	-0.28	1		
(4) De Novo, no rDNA Pioneer	-0.24	0.98	-0.30	1	
(4) Cumulative	-0.34	-0.37	0.15	-0.36	1

Table 4
Competence in rDNA/Fermentation Technology
Cox Model Analysis of Patenting Rate
(1,452 Spells, 1,375 Events)
All Coefficients in *Hazard Rates*

	Model 1	**Model 2**	**Model 3**	
Incumbent	0.99 (0.05)	1.16* (0.08)	1.79*** (0.15)	≠ coefficients p < 0.03
De Novo	0.40*** (0.03)	0.47*** (0.04)		
rDNA Pioneer			2.13*** (0.17)	
De Novo, no rDNA Pioneer			0.71*** (0.07)	
Cumulative		1.00*** (0.00)	1.00*** (0.00)	
Log Likelihood	-8,660	-8,648	-8,595	

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

Table 5
Competence in rDNA/Fermentation Technology
Descriptive Statistics and Correlation Matrix for Weighted Patenting Rate Analysis
(4,947 Spells, 4,870 Events)

	Count	Mean	Std.Dev.	Min.	Max.
(1) Incumbent	1,411				
(2) De Novo	955				
(3) rDNA Pioneer	1,323				
(4) De Novo, no rDNA Pioneer	903				
(5) Cumulative		764	514	0	1,710
(6) Number of Patents per Innovation		9.3	8.3	0	60

	(1)	(2)	(3)	(4)	(5)	(6)
(1) Incumbent	1					
(2) De Novo	-0.31	1				
(3) rDNA Pioneer	-0.38	-0.24	1			
(4) De Novo, no rDNA Pioneer	-0.30	0.97	-0.29	1		
(5) Cumulative	-0.22	-0.34	0.28	-0.33	1	
(6) Number of Patents per Innovation	0.19	-0.05	0.01	-0.11	-0.38	1

Table 6
Competence in rDNA/Fermentation Technology
Cox Model Analysis of Patenting Rate with FW Citations as Frequency Weights
(Rate of FW Citation Production)
(4,947 Spells, 4,870 Events)
All Coefficients in *Hazard Rates*

	Model 1	Model 2	Model 3	
Incumbent	0.90**	1.36***	2.04***	≠ coefficients p < 0.07
	(0.03)	(1.01)	(0.10)	
De Novo	0.60***	1.00		
	(0.02)	(0.04)		
rDNA Pioneer			2.21***	
			(0.11)	
De Novo, no rDNA Pioneer			1.58***	
			(0.08)	
Cumulative		1.00***	1.00***	
		(0.00)	(0.00)	
Number of Patents per Innovation			0.99**	
			(0.00)	
Log Likelihood	-36,684	-36,016	-35,827	

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

Table 7
Overall R&D Competence
Descriptive Statistics and Correlation Matrix
Only Targeted Small-Molecule Drugs
(N = 353)

	Count	Mean	Std.Dev.	Min.	Max.
(1) Incumbent	115				
(2) Diversifying	142				
(3) rDNA Pioneer	31				
(4) Diversifying, no rDNA Pioneer	112				
(5) Cumulative		467	237	5	918
(6) Drug Novelty		-1.68	1.16	-4.16	0
(7) R&D Alliance	2				

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
(1) Incumbent	1						
(2) Diversifying	-0.57	1					
(3) rDNA Pioneer	-0.22	0.36	1				
(4) Diversifying, no rDNA Pioneer	-0.47	0.83	-0.21	1			
(5) Cumulative	-0.47	0.25	0.17	0.16	1		
(6) Drug Novelty	-0.06	-0.06	-0.00	-0.07	0.56	1	
(7) R&D Alliance	-0.05	-0.06	-0.02	-0.05	-0.09	-0.01	1

Table 8
Overall R&D Competence
Descriptive Statistics and Correlation Matrix
Only Targeted Large-Molecule Drugs
(N = 638)

	Count	Mean	Std.Dev.	Min.	Max.
(1) Incumbent	47				
(2) Diversifying	212				
(3) rDNA Pioneer	73				
(4) Diversifying, no rDNA Pioneer	152				
(5) Cumulative		476	238	6	914
(6) Drug Novelty		-2.55	1.71	-5.3	0
(7) R&D Alliance	14				

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
(1) Incumbent	1						
(2) Diversifying	-0.20	1					
(3) rDNA Pioneer	-0.10	0.37	1				
(4) Diversifying, no rDNA Pioneer	-0.16	0.79	-0.20	1			
(5) Cumulative	-0.22	0.11	0.02	0.11	1		
(6) Drug Novelty	0.10	0.12	0.09	0.08	0.14	1	
(7) R&D Alliance	-0.00	-0.04	-0.05	-0.01	-0.10	-0.02	1

Table 9
Overall R&D Competence
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**
Incumbent	3.74 (4.26)	4.31 (4.68)	4.37 (4.69)
Diversifying	3.60 (4.01)	3.00 (3.87)	
rDNA Pioneer			0.00 (0.00)
Diversifying, no rDNA Pioneer			3.44 (4.38)
Cumulative Introduction		1.00 (0.00)	1.00 (0.00)
Drug Novelty		1.43 (0.47)	1.41 (0.48)
R&D Alliance		0.00 (0.00)	0.00 (0.00)
Log Likelihood	-28.7	-27.7	-27.3

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

Table 10
Overall R&D Competence
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	Model 4
Incumbent	3.05 (3.34)	2.26 (2.37)	4.37 (4.94)	4.41 (5.04)
Diversifying	3.91* (2.22)	4.01* (2.50)		
rDNA Pioneers			14.47*** (9.54)	
rDNA Pioneers, With prior oncology research				8.60+ (10.72)
rDNA Pioneers, No prior oncology research				16.40*** (10.87)
Diversifying, no rDNA Pioneer			3.57 (3.02)	
Diversifying, No rDNA Pioneer, With prior oncology research				7.78* (7.43)
Diversifying, No rDNA Pioneer, No prior oncology research				1.64 (1.86)
Cumulative Introduction		0.99 (0.00)	1.00 (0.00)	1.00 (0.00)
Drug Novelty		1.28+ (0.16)	1.11 (0.15)	1.12 (0.16)
R&D Alliance		2.69 (2.96)	4.23 (4.98)	4.86 (5.84)
Log Likelihood	-64	-62	-57	-56.7

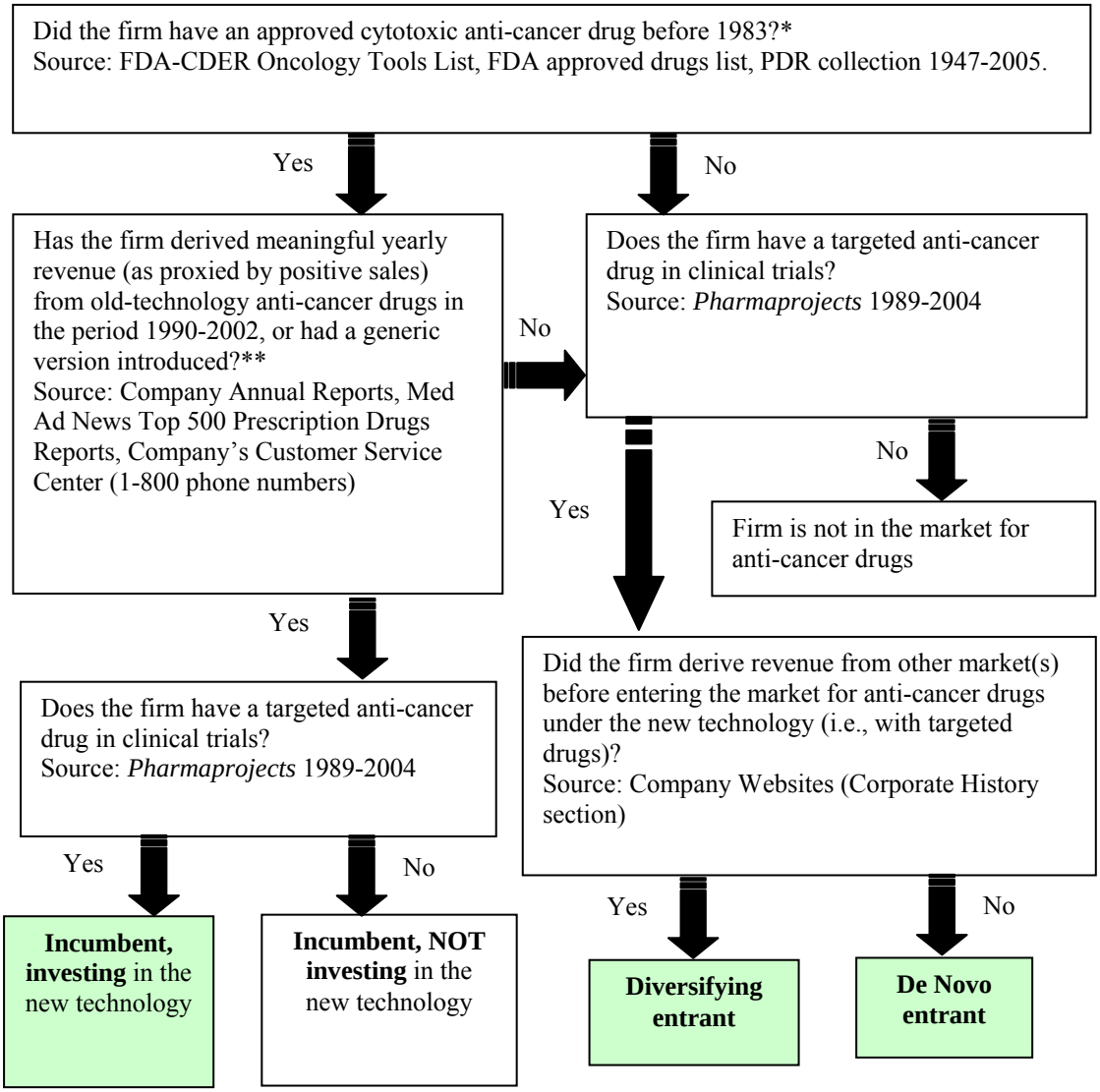
≠ coeff. $p < 0.6$
≠ coeff. $p < 0.4$
≠ coeff. $p < 0.9$

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

Figures

Figure 1

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 2
The Three Phases of Evolution of Large-Molecule Drugs in the Biotechnology Revolution