Organizational Structure, Real Options, and the Advantage of De Novo Firms:
The Case of Gene Therapy Research

M. Lourdes Sosa
London Business School
Strategy and Entrepreneurship
Sussex Place, Regent's Park
London NW1 4SA

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Current literature demonstrates that, at least initially, incumbents invest less in the in-house development of a new technology than do entrants not only for rational reasons but also because, for incumbents, new technology requires a change in capabilities, challenges managers' mental models, disrupts customer preferences, and defies organizational identities. What has not been explored, despite its significance for strategic action, is whether (and if so, why) incumbents and entrants might invest differently across variants of a new technology once they both invest in it. This paper uses unique quantitative, archival and interview data on incumbents' versus entrants' investment choices around three variants of biotechnology—small-molecule, large-molecule, and gene therapy drugs—to demonstrate that volatility in outcomes of a new technology can explain differences in investment choices across groups of firms. When volatility in product performance generates volatility in firm-level outcomes, established firms (whether incumbent or diversifying) are most exposed, while de novo firms can avoid negative consequences by closing the enterprise. Organizational structure thus allows de novo firms to extract option value from volatility, rendering structure a possible source of competitive advantage for these firms and making established versus de novo the key groups for analysis of investment choices, not incumbent versus entrant firms. Identifying the interaction between the volatility of a technological investment and the organizational structure of de novo firms as the explanatory variable for their observed differences in investment behavior has implications for technology strategy and the competitive analysis of discontinuities.

1. Introduction

Key in the study of technological discontinuities (Abernathy and Utterback 1978, Anderson and Tushman 1990, Utterback 1994) is research on the determinants of differences in performance between incumbents and different groups of entrants. Incumbents' resistance to investing in the internal execution of research and development (R&D) based on the new technology is widely considered one of the most important differences. Current theory presents several mechanisms predicting this initial resistance while entrants advance, gaining a lead that might grant them the market. Under certain conditions, it might be rational for incumbents to resist or at least delay investment in the new technology (Kaplan and Henderson 2005, Gilbert and Newbery 1982, Henderson 1993, Reinganum 1983). But, in other cases, incumbents resist investing in new technology while entrants take the lead because the discontinuity challenges the mental models of their managers due to the emergence of a gap in capabilities (Leonard-Barton 1992, Tushman and Anderson 1986), a different revenue model (Tripsas and Gavetti 2000), a different set of product features driving value (Christensen and Bower 1996) or a different organizational identity (Tripsas 2009).

Prior literature would clearly predict the same initial differences between incumbents and entrants in the case of internal R&D investment in currently unfolding discontinuities. This, for example, is the case with the biotechnology revolution at the industry level (Kaplan, Murray and Henderson 2003, Zucker and Darby 1997). However, a clear prediction is not available regarding investment *across variants* of a new technology, that is, across technical solutions that although all based on a new technological paradigm are based on distinct aspects of it (Sutton 1998). Given that the dynamics of competition across variants in a new technology have only recently been examined (Bhaskarabhatla and Klepper 2011, Klepper and Thompson 2006), there are no specific theories to inform firms' choices across variants. However, incumbents must make investment decisions not only between old and new technologies but also among variants of the latter; thus understanding the dynamics behind investment across variants is a crucial element in the generation of strategic recommendations. In this paper, I look at the unexplored pattern of investment in internal

R&D among incumbents and entrants (diversifying and de novo) across variants of the new technology.

For this purpose, I use data on the anticancer drug market, the market with the most entry in the pharmaceutical industry, as it transitions from standard chemotherapy into biotechnology. I first use quantitative analyses of a sample of 791 firms derived from *Pharmaprojects* May 1989 – February 2005 to demonstrate that incumbent, diversifying and de novo firms do invest differently in the three main variants within biotechnology: small-molecule, large-molecule, and gene therapy drugs. In particular, I show that there are differences in investment choices across groups of firms: de novo entrants invested disproportionately more in gene therapy while established (incumbent and diversifying) firms invested in small and large-molecule biotechnology.

I next use archival data from the collection at the National Library of Medicine and interview data from 66 interviews with executives, scientists and analysts to investigate the reason behind this difference. I show that current theories of the investment behavior of incumbents versus entrants cannot explain it. Incumbent, diversifying and de novo firms did not invest differently across variants of biotechnology for rational reasons. Neither did they do so because, for incumbents, particular variants of the new technology required a change in capabilities, challenged managers' mental models, disrupted customer preferences, or defied organizational identities.

Instead, I demonstrate that the reason established and de novo firms invested differently across variants of biotechnology is that established firms had no way to avoid the possible financial and organizational liabilities associated with investing in a variant with volatile patient outcomes (in this case, gene therapy). In contrast, de novo firms could avoid firm-level losses by readily disbanding the enterprise if extreme negative patient outcomes occurred in the use of a gene therapy drug. My argument proceeds as follows: (1) for technological reasons, gene therapy has greater volatility of patient outcomes than do small and large-molecule biotech variants because gene therapy has more unexpected side effects; (2) in the pharmaceutical industry, negative patient outcomes generate firm-level financial

and organizational liabilities for the innovating firm (regardless of firm type) that can be larger than the original investment; and (3) established (incumbent and diversifying) firms cannot disband the enterprise to avoid extreme liabilities while de novo firms can.

This unique case study allows me to make two contributions to theory. First, by identifying the interaction between the volatility of a technological investment and the organizational structure of de novo firms as the explanatory variable for their observed differences in investment behavior, I highlight structure as a possible source of competitive advantage (Chandler 1973). This finding is in contrast to the emphasis on the prehistory (capabilities) of incumbent and diversifying firms in prior literature (e.g., Agarwal and Helfat 2009, Carroll et al. 1996, Klepper and Simons 2000) and informs the larger question of the conditions under which it is structure and not reusable capabilities that represents firms' key source of competitive advantage (Teece, Pisano and Shuen 1997). As a second contribution, I present a new application of options theory to the strategic analysis of R&D that, unlike prior studies emphasizing the creation of option value through the option to expand (e.g., McGrath and Nerkar 2004, Ziedonis 2007), focuses on the option to abandon. As I will explain, by focusing on capping the losses through abandonment, this application does not overlap with the predictions of path dependent search, a major criticism of prior work (Adner and Levinthal 2004a, 2004b).

Below, I first review the existing literature on the investment behavior of incumbents versus entrants and the little we know about the investment behavior of diversifying firms in comparison. I then describe my methods and use quantitative data to show that incumbent, diversifying and de novo firms do invest differently in the three main biotech variants and that it is established versus de novo, and not incumbent versus entrant firms, that are the relevant groups for analysis. I next use archival and interview data to show that current theories of investment behavior cannot explain this difference. What explains it is the interaction of the high volatility that gene therapy imposes as a technology investment and the features of organizational structure that de novo firms can use to manage volatility. I close with implications for strategy research on options theory and for technology strategy.

2. Theories of Investment Behavior through a Discontinuity

2.1 Theories of Investment Behavior of Incumbents versus Entrants

According to current literature, differences in investment in in-house R&D between incumbents and entrants competing through the R&D race that ensues during a discontinuity can be driven by five mostly independent mechanisms. The mechanisms explain the reasons for incumbents to resist investment such that, comparatively, only entrants would invest.

The first is competence destruction (Tushman and Anderson 1986). Competence destruction refers to the change in capabilities faced by incumbents given a discontinuity's shift to a new technology. Incumbents are then faced with the obsolescence of their standing capabilities and the need to replace them with new ones before entrants push them out of the market. Competence destruction can have an effect on incumbents' investment behavior through biasing managers' decision making, since a significant change in the capabilities necessary for R&D can alter the mental models and value systems under which the firm has been operating (Kaplan, Murray and Henderson 2003, Kaplan and Tripsas 2008, Leonard-Barton 1992). As a result, incumbents can be less likely than entrants to invest in a new technology that is competence destroying.

The second mechanism, changes in revenue model (Tripsas and Gavetti 2000), biases incumbent firm managers' investment decisions independently of the bias generated by competence destruction (Kaplan 2008b). The revenue model of a firm has been described as a critical component of its business model that is independent of the firm's capabilities (Amit and Zott 2001). As Tripsas and Gavetti (2000) showed, during the discontinuity that moved the camera market from analog to digital technology, managers at Polaroid found the renewal of capabilities feasible but the move away from a razor-blade revenue model insurmountable.

The third mechanism is disruption in customer preferences, that is, the new technology might create value for the consumer through product features different from those supported by the old technology (Christensen 1997, Christensen and Bower 1996, Henderson 2006, Tripsas 2008). Due to inertial forces, incumbents tend to miss the shift in customer preferences and instead offer further increases in existing features. A classic example is the

shift from 8- to 5.25-inch disk drives where consumers stopped needing ever more memory capacity and began paying attention to disk drive size and weight for portability purposes (Christensen 1997). Missing the change in customer preferences, incumbents developed new models of 8-inch disk drives with additional memory instead of investing in the development of 5.25-inch disk drives even though the latter offered more total value to consumers.

The fourth mechanism driving differences in investment behavior is the challenge to the organizational identity that a discontinuity can impose (Tripsas 2009). Some discontinuities can press incumbents to change the organizational identity they have built both internally with staff and with external audiences such as investors. In those cases, incumbents can resist investment in the new technology in an attempt to avoid both the costly process that a change in identity imposes and the risk of being perceived as illegitimate players in the market by outside stakeholders (Benner 2009). Tripsas (2009) exemplified this mechanism in the shift of an anonymous supplier of flash memory cards from an identity as a key player in digital photography to that of a memory company. Symbolic practices such as giving employees a digital camera for the holidays and adapting metrics used in analog photographic film to flash memory cards built an identity with internal and external audiences whose resistance had to be managed during the change.

The fifth and last mechanism operates through rational disincentives to invest (Arrow 1962) that are independent of cognitive issues (Kaplan and Henderson 2005). In certain discontinuities, it might be rational for incumbents to resist or at least delay investment in the new technology. Classic game theory research has modeled this concept by examining investment in preemptive actions such as patenting or internal R&D (Gilbert and Newbery 1982) and by emphasizing the contrast between "milking" the old technology and investing in the new one (Reinganum 1983). In summarizing these formal models, Henderson (1993: 250) identified two key variables. If incumbents can delay the start of the discontinuity or if they can profit from the old technology in spite of the emergence of the new (i.e., the technologies are not substitutes), incumbents will delay investment in the new technology.

I list these five mechanisms in the first column of Table 1. In the empirical section of the paper, I return to this table to offer evidence that the three variants of biotechnology I study in this paper do not differ in any of the five dimensions.

Insert Table 1

2.2 Theories of Investment Behavior of Diversifying and De Novo Entrants

The five mechanisms reviewed show that under certain conditions incumbents can resist investment in the new technology while entrants pursue it. Because in this study all established firms, incumbent and diversifying, underinvest in gene therapy in comparison to de novo firms, it becomes important to review any mechanisms that explain investment differences between diversifying and de novo entrants.

Unfortunately, research is limited in this regard. Studies have addressed within-group variance among diversifying entrants with different characteristics (e.g., Benner and Tripsas 2012) or de novo entrants with different endowments (e.g., Stuart, Hoang and Hybels 1999), outside of the scope of between-group comparisons. Nonetheless, a few comparative studies have shown that diversifying and de novo firms differ in survival rates, market shares and innovative activity, explaining those differences through differences in reusable capabilities (Carroll et al. 1996, Helfat and Lieberman 2002, Khessina and Carroll 2008, Klepper and Simons 2000). Moreover, a study comparing the three groups of firms in competition found that a sub-set of diversifying entrants outperformed incumbent, de novo and other diversifying firms in R&D performance thanks to the reuse of capabilities they acquired at a time when only they had incentives to do so (Sosa 2011). If some diversifying entrants have reusable capabilities that can grant them an advantage in one particular variant of biotechnology, foresight of that advantage could give them incentives to overinvest in that variant (and in turn underinvest in gene therapy) as compared to competitors. I evaluate this mechanism in empirical analyses.

3. Empirical Approach

This paper uses a combination of quantitative and qualitative data on the transition of the anticancer drug market from standard chemotherapy into biotechnology to explore differences in investment in in-house R&D across incumbent, diversifying and de novo firms as they face a discontinuity in which the new technology is divided into variants. To investigate if these firm groups invest differently across variants, I first use quantitative analyses of a sample of 791 firms derived from *Pharmaprojects* May 1989 – February 2005. As I will explain in further detail, I find that firm groups did invest differently in the three main variants within biotechnology: small-molecule, large-molecule, and gene therapy drugs; de novo firms invested disproportionately more in gene therapy while incumbent and diversifying firms invested on small and large-molecule drugs. I next use archival data from the collection at the National Library of Medicine and interview data from 66 interviews with executives, scientists and analysts to show that current theories of the investment behavior of these firm groups cannot explain this difference in investment. I show that a new mechanism, the interaction of volatility and organizational structure, explains this difference.

3.1 The Setting

The transition of the anticancer drug market from chemotherapy to biotechnology starts in 1983, the year interferon alpha became the first biotech drug available for cancer treatment according to the *Physicians' Desk Reference* (PDR) collection 1947-2005 (a yearly collection of directories of approved drugs and the diseases they are approved for).

A key objective of this study is the identification of separate variants within biotechnology to study the choices incumbents and different groups of entrants make across them, beyond the choice between the old and new technologies. Variants are not simply different models of the product that proliferate as a discontinuity unfolds (Abernathy and Utterback 1978, Anderson and Tushman 1990, Utterback 1994). They reflect the structure of the division of knowledge behind the new technology. For example, in the discontinuity that caused the market for electrical amplifiers to transition from vacuum tubes to transistors in the 1950s, the shift imposed a move from controlling electrical current through a vacuum to controlling it through solid-state materials (Tilton 1971). The solid-state materials used in transistors

differed, however. Silicon-based transistors were a variant different from germanium-based transistors. Although there were several models per variant and although both variants pertained to the solid-state materials technological paradigm, the two variants required different specializations for the scientists working on them and ultimately led to different outcomes (germanium-based transistors outperformed silicon-based transistors). The specialization of the knowledge behind a new technology in sub-sets creates variants as the supply-side mirror image of customer segments, and has been studied as the basis for economic irregularities in high-tech markets (Sutton 1998).[1]

In the transition of the anticancer drug market into biotechnology, three variants reached clinical trials in the period of observation: small-molecule, large-molecule, and gene therapy drugs. Although the three variants each use knowledge of molecular biology for drug discovery, they make use of different aspects of molecular biology. According to interviews and archival material, small-molecule anticancer drugs are biotech drugs that receive the name "small" because their molecular weight remains within the hundreds of Daltons (the unit of molecular mass) and thus can often be formulated as pills.[2] Large-molecule anticancer drugs are biotech drugs that receive the name "large" because their molecular weight falls in the thousands of Daltons and thus have to be formulated as injectables.[3] Lastly, gene therapy drugs are meant to replace malfunctioning genes with correct ones. The correct genes have to be encapsulated in a delivery mechanism called a vector, most frequently an engineered virus although non-viral vectors are also investigated. Gene therapy is an injectable.[4]

[1] When the supply technology displays different variants and the customers different segments, a market displays a clustering structure termed sub-market fragmentation that explains irregularities such as low market concentration in spite of high R&D intensity (Sutton 1998). If a variant evolves to service all customer segments, the clustering structure disappears (Bhaskarabhatla and Klepper 2011).
[2] To distinguish them from drugs in the same range of molecular weight developed through methods prior to biotechnology, practitioners refer to them as "targeted." For simplicity, in this paper I refer to targeted small-molecule drugs as simply small-molecule drugs.
[3] As with small-molecule drugs, I refer to targeted large-molecule drugs as simply large-molecule drugs.
[4] Although ethical concerns with some of these variants have been raised historically (see, for example, Kaplan and Murray 2010 for the case of large-molecule drugs and Friedmann 1992 for the case of gene therapy), all three had been legitimate lines of scientific research for many years prior to the start of the period of observation in this study (Ryser and Weber 1990; see Appendix 1 for a historical review).

The anticancer drug market is ideal for the present study. Among markets in the pharmaceutical industry, it contains the largest number of firms competing through the R&D race generated by the biotechnology revolution, providing a large sample size. Furthermore, the significant extent of its competence destruction is identifiable (Chabner and Roberts 2005, Rang 2006). Figure 1 shows the value chain in pharmaceuticals and identifies the portion that has been impacted by competence destruction, lending support to my choice to use introductions into Phase 1 trials (a proxy for the completion of drug discovery) as the appropriate step in incumbents' value chain to focus on.

Insert Figure 1

As shown in Figure 1, the key complementary assets (Teece 1986, Tripsas 1997) in the industry, namely the capability to execute clinical trials (Rothaermel 2001) and the capabilities involved in marketing, remain unchanged.[5] That said, entrants do not face a disincentive due to their lack of complementary assets. Because strong intellectual property protection (Levin et al. 1987) promotes the emergence of markets for technology in which intermediary outcomes of R&D are traded (Arora, Fosfuri and Gambardella 2001; Gans and Stern 2000, 2003), entrants can profit from drug discovery regardless of their lack of complementary assets. This means that downstream differences in complementary assets do not generate differences in incentives to invest upstream between incumbents and entrants.

3.2 Quantitative Data Collection

I used quantitative analysis to investigate whether different groups of firms did invest differently in the three main variants within biotechnology, and if so, in what ways. For that purpose, I started by mapping all firms competing in the anticancer drug market to then classify them and their drugs and to define control variables. I explain these measurements next. In section 4.1, I use these data to explore differences in the pattern of choice among variants made by the firm groups. Beyond descriptive statistics, I build regressions predicting

[5] The only exception is manufacturing, a secondary complementary asset that has changed for large-molecule and gene therapy drugs, but remains the same as for chemotherapy in the case of small-molecule drugs, a feature that thus would not explain the differential pattern for gene therapy.

choice between old and new technologies as well as between gene therapy and other biotech variants. Because those choices are binary, I use a Logit specification.

3.2.1 Sample. I had two starting points for the identification of the relevant sample: (1) all firms that had marketed an anticancer drug before the start of the discontinuity in 1983 according to the records listed in the PDR 1947-2005;[6] and (2) all firms that had entered an anticancer drug into clinical trials from the start of the *Pharmaprojects* database (May 1989) until February 2005.[7]

The step based on the PDR 1947-2005 allowed me to identify all eight incumbents in the market. The step based on the *Pharmaprojects* collection identified 1,259 organizations. I first identified all incumbents competing through the discontinuity (all eight did). Of the 1,251 organizations left, I discarded 451 firms because they could not be classified for lack of information;[8] 12 non-profit organizations because their objectives are different from the profit-maximization of the rest of the competitors; and 4 firms because they did not pursue in-house R&D (e.g., Epitome Pharmaceuticals brokers the acquisition and licensing of drug molecules).[9] This left a total of 783 entrants.

The final sample consists of 791 firms responsible for 5,068 drugs in clinical trials (comprising 74% of the 6,851 total anticancer drugs reported in *Pharmaprojects*). Firms are from 33 countries, with 50% based in the USA. This sample is significantly more comprehensive than samples used in previous research on this market (Guedj and Scharfstein [2004] used a 175-firm sample whereas Sosa [2011] used a 165-firm sample), allowing me to distinguish the presence of gene therapy, which represents 8% of biotech drugs.

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[6] For robustness, I triangulated the records available from the Federal Drug Administration (FDA) (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, retrieved 29 May 2005), the FDA's Center for Drug Evaluation and Research (http://www.fda.gov/cder/cancer/druglistframe.htm, retrieved 29 May 2005), *Top Prescription Drugs* yearly report 1991-2002, and introduction of generics from the PDR collection.

[7] Although ideally I would have used data on clinical trials from 1983, such data is not available. Nonetheless, data from *Wiley's Journal of Gene Medicine* (described next) shows that gene therapy clinical trials started in 1989, making the dataset well suited for the comparison of activity in gene therapy versus other biotech variants.

[8] For robustness, I repeated analyses including the 451 discarded firms. Because the identification of incumbents is exhaustive, all discarded firms are entrants. I classified them as diversifying firms if founded before 1983 and as de novo firms otherwise. Conclusions remain unchanged. I also tested that firms in the sample and those discarded do not differ in firm age, number of employees, R&D expenditures or country of origin.

[9] One more firm was discarded due to a *Pharmaprojects* typographical error.

3.2.2 Dependent Variable

Chemotherapy and Biotech Drugs (Small-Molecule, Large-Molecule, and Gene Therapy). For operationalization of variants in the sample, I asked a post-doctoral fellow at a medical research cancer laboratory to analyze all anticancer drugs that entered clinical trials listed in *Pharmaprojects* 1989-2005.[10] Scientists have direct knowledge of these drugs such as the fact that drugs targeting tyrosine kinase inhibition are small-molecule drugs. Therefore, although time-consuming and knowledge-intensive, the classification of anticancer drugs into variants can be done accurately as long as the rater has significant expertise (see for example Roberts et al. 2004). Nonetheless, I repeated the creation of the gene therapy and large-molecule variables alternatively based on keywords. Conclusions remained unchanged.

For Logit regression analyses, I created two dummy variables: *Biotechnology* equal to 1 if the drug was classified as any of the three variants of biotech and 0 otherwise; and *Gene Therapy* equal to 1 if the drug was classified as gene therapy and 0 otherwise.

3.2.3 Independent Variables

Incumbent, Diversifying and De Novo Firms. I categorized firms as incumbents and entrants through the process of building the sample previously explained. I then distinguished among entrants between diversifying and de novo firms based on information in the firms' corporate histories, available from their corporate websites and *Pharmaprojects* profiles. The sample contains 8 incumbent (e.g., Bristol-Myers Squibb, GlaxoSmithKline), 192 diversifying (e.g., Novartis, Novo Nordisk, Kirin Brewery, Amgen), and 591 de novo firms (e.g., Therion Biologics). The dummy variable *Incumbent* was equal to 1 when the firm had been operating in the anticancer drug market prior to 1983 (by definition through chemotherapy drugs). The dummy variable *Diversifying* was equal to 1 when the firm had been operating in any market other than the anticancer drug market and diversified into this market after 1983. De novo firms, the firms that were born in the anticancer drug market after 1983, remained the omitted category.

[10] The data made available to the fellow included, among others: generic name and synonyms, pharmacology description, molecular target, origin of material description, molecular weight, chemical name, and molecular structure when available.

3.2.4 Control Variables. The availability of strong patent protection in this industry gives rise to markets for technology where firms transact on intermediary outcomes of drug discovery. Because I study choices of investment in in-house R&D across firm groups, exchanges made across firms could bias the pattern measured (if transactions took place across firm groups). I therefore control for the presence of these transactions through four control variables measured from the drug histories available in *Pharmaprojects*.

Drug Discovery Collaborations. A dummy variable equal to 1 whenever a collaboration (whether in a collaborative agreement or a formal joint venture) took place.

Molecule Acquired. A dummy variable equal to 1 if the molecule for the drug was acquired from another organization.

Technology Licensed. A dummy variable equal to 1 if the drug was developed with licensed access to a technological platform from another organization.

Other Licensed. A dummy variable equal to 1 if the drug was developed making use of a gene, antigen, or target from another organization, or if the firm had out-sourced preclinical work such as animal studies.

3.3 Qualitative Data Collection

Once I had determined that de novo entrants invested disproportionately more in gene therapy while established firms focused on small and large-molecule biotechnology, I used archival and interview data to determine if any current theories of investment behavior across firm groups could explain this difference and, if not, what could.

Since I was interested in understanding why de novo entrants invested disproportionately in gene therapy while established firms invested disproportionately in small and large-molecule biotechnology, I interviewed people at incumbent, diversifying and de novo firms who were involved with these investment choices. I conducted a total of 66 semi-structured interviews. These included interviews with executives from R&D strategy, safety risk management and business development from established (17 interviews comprising 11 interviews with incumbents and 6 with diversifying firms) and de novo firms (16 interviews). I interviewed as well analysts (5), oncologists (6) and scientists from academia (22). The interviews,

performed in person (except for several interviews done by phone) at the firms in Seattle, San Francisco, Boston, New Jersey, the United Kingdom, mainland Europe, and India averaged between forty-five minutes to one hour. Among interviews, 28 were recorded. Other interviews were not recorded either due to the preference of the interviewee or because the company had a policy against recordings.

I first asked questions to determine whether investment choices regarding the different variants of biotechnology were made as current theories would lead us to expect (see Table 1). I also asked questions to explore what other factors affected investment choices regarding the different variants.

I kept questions as broadly phrased as possible. For example, when trying to understand the competence destruction faced by incumbents, I started interviews with people on the business side by asking about the changes to the core competences of the firm. In cases where a question seemed too broad, I presented a more concrete question: "Have you had to replace personnel? Why couldn't you just retrain them?" I also brought schematics, such as a figure matching the value chain in pharmaceuticals to different professions from a practitioner's book (Rang 2006: 200), to ground the conversation.

I found that interviewees were able to recall appropriately details anchored in salient events (e.g., the start of their firm's involvement in biotechnology). However, without salient events, interviewees found recall difficult. For example, an interviewee who had founded his own gene therapy startup answered my inquiry about the difference between large-molecule and gene therapy drug discovery before 1997 (when both variants had no approved drugs) with simply an "I don't remember." To avoid bias due to recall among interviewees, I bolstered my interviews with significant use of archival material as done in prior research (Tripsas 2009). In the prior example, I was able to quote books published prior to 1997 in which scientists were skeptical about large-molecule drugs, a skepticism similar to that of gene therapy (Parsons and Parsons 1987, Tyle and Ram 1990).

I thus used archival data to understand the evolution of the three variants. I used the archives of the National Library of Medicine, including its physical, electronic, video and rare

books collections to investigate differences across variants in technological characteristics, time of birth of the variant, and history of ethical concerns and unexpected side effects.[11] The work of Edelstein et al. (2004, 2007) led me to the records from *Wiley's Journal of Gene Medicine* collection.[12] The *Wiley's* collection uses governmental filing to trace all gene therapy trials (without drug or firm name) in 22 countries (71% of trials are from the USA) from their start in 1989. I used this collection to understand the evolution of gene therapy in terms of clinical trials and volatility (e.g., historical use of vectors that are viral and thus increase the likelihood of unexpected side effects). I complemented archival material with searches in the journal *Nature Reviews Drug Discovery* to document prototypical cases of drugs in each variant and in *Factiva* for further background on industry cases mentioned in interviews or found in archival data.

4. Analyses and Results

4.1 The Pattern under Study

Similar to prior literature (e.g., Henderson 1993), I start by examining the choice to invest in the new technology through internal R&D by incumbents and entrants. Table 2 shows descriptive statistics for the dataset. Because all variables are dummies, I report only their counts and correlation coefficients.[13]

Insert Table 2

Figure 2a shows yearly new drug introductions into clinical trials. For visual purposes, I omit incomplete years (1989 and 2005) from the figure. As can be seen, the proportion of the gray area (incumbents' activity) in the second column to the gray area in the first column is not different from the proportion of the black area (entrants' activity) in the second column to the black area in the first column. This means that the proportion allocated to biotechnology versus chemotherapy drug discovery seems similar for incumbents and entrants.

[11] Different collections became more relevant for this project. For example, the video collection consisted of documentaries on families affected by devastating genetic disorders and their willingness to try gene therapy in their search for a cure, references that were unnecessary in the present paper.
[12] Retrieved from http://www.wiley.com/legacy/wileychi/genmed/clinical/ from January 6-19, 2010.
[13] Correlation coefficients are below 0.4, thus ruling out concerns of multicollinearity.

Insert Figure 2

To corroborate the pattern shown in Figure 2a, Table 3 presents a Logit regression predicting the likelihood of introducing biotech instead of chemotherapy drugs to trials, Model 1 without controls and Model 2 controlling for activity in markets for technology.

Insert Table 3

In line with Figure 2a, Table 3 Models 1 and 2 show that the proportion of biotech to chemotherapy introductions is the same for incumbent and entrant firms, with and without controls (the coefficient for *Incumbent* is no different from 1 in both models where entrants are the omitted category set to 1). Although originally late to move into biotechnology (Kaplan, Murray and Henderson 2003), six years after the start of the discontinuity in the anticancer drug market and 16 after the discovery of rDNA technology marked the birth of the biotechnology revolution, incumbents began to adapt. This pattern is in line with prior qualitative evidence at the industry level (Zucker and Darby 1997).

While differences in investment behavior in biotechnology disappeared by the early 1990s, it is still an open question whether there were differences in investment across variants of biotechnology. If there were, the strategic importance of these differences would supersede that of differences between old and new technology, the latter a short-lived choice in the current discontinuity. Figure 2b focuses on biotechnology drug introductions, distinguishing its three variants and three groups of firms. Incumbents (light gray area) seem present only among small- and large-molecule drugs but are missing in the third column, gene therapy. Table 4 presents proportions of investment across variants.

Insert Table 4

As seen in Figure 2b, incumbents are hardly present in gene therapy. Table 4a shows that the distribution of drug introductions across variants and groups of firms is disproportional

(Pearson χ^2 test is significant at $p < 0.0001$) and that the activity of de novo firms in gene therapy contrasts the limited presence of incumbents. While almost half of the activity in small- and large-molecule drug discovery came from de novo firms (47% and 45% respectively), the level of these firms' activity in gene therapy was higher (65%). As Table 4b illustrates, the disproportion is still statistically significant (Pearson χ^2 test is significant at $p < 0.0001$) even if the comparison is made only among introductions up to 1997, a comparison that rules out differences in uncertainty across variants as a possible explanation.[14] To see this consider that while the discontinuity in this market started in 1983 when interferon alpha was first listed as a cancer treatment in the PDR, the drug had a general effect on the immune system. The anticancer drug market remained without biotech drug approvals until 1997, a period of 11 years characterized by skepticism (see, for example, the uncertainty surrounding large-molecule drug discovery documented in Parsons and Parsons 1987: 225, and Tyle and Ram 1990: 3). *Rituxan*® (Biogen Idec, Weston, MA) became the first large-molecule drug approved specifically to treat cancer in 1997 (Reichert and Valge-Archer 2007), and *Gleevec*® (Novartis, Basel, Switzerland) became the first small-molecule drug approved in 2001. After 1997, the market experienced the approval of a biotech drug almost yearly within the period of observation. Therefore, all three variants were similarly uncertain in the period 1989-1997, a period during which the activity of de novo firms in gene therapy is still disproportionately high as compared to incumbent and diversifying firms.

As can be seen in Table 4a, the pattern is only partly driven by the low participation of incumbents in gene therapy (2% versus 18% in small- and 12% in large-molecule drugs). Because the proportion of incumbent activity is lower in gene therapy than in the rest of biotechnology, one would expect both diversifying and de novo firms' percentages to grow (by at least 5% each) from their non-gene therapy baseline. This is not the case. Diversifying entrants represent only 32% of gene therapy activity, versus 35% of small- and 43% of large-

[14] The disproportion is still statistically significant if I compare gene therapy to large-molecule drug discovery only, omitting small-molecule drugs. Outside of cancer, small-molecule drugs had been approved to treat cardiovascular diseases since 1981 (Lacetera, Cockburn and Henderson 2004).

molecule drugs. This means that de novo firms' higher activity in gene therapy is also partly explained by a decline in diversifying firms' participation versus their expected baseline.

The χ^2 test can only conclude that the table is disproportionate but not the pairwise comparison of different cells. Table 3, Models 3 and 4 present a Logit regression predicting the likelihood of introducing into clinical trials a gene therapy drug as opposed to a non-gene therapy biotech drug (chemotherapy drugs are dropped from the sample so that the comparison is across variants of biotechnology). Model 3 corroborates that the comparative presence of de novo firms in gene therapy as opposed to the rest of biotechnology is higher as a result of a decline in the activity not only of incumbents but also of diversifying firms (the coefficients for *Incumbent* and *Diversifying* are significantly less than 1, where *De Novo* is the omitted category set at 1). Model 4 supports this conclusion after controls.[15]

Table 3 demonstrates, first, that there is a difference in the investment behavior of the firm groups across variants of the new technology even though there is none in the choice between old and new. And second, it shows that the most relevant comparison is between established (incumbent or diversifying entrants) and de novo firms, not between incumbents and entrants.

4.2 The Possibility of Explaining the Pattern through Available Literature

4.2.1 Discarding Theories of Investment Behavior of Incumbents versus Entrants.

Explanatory mechanism(s) for this difference in investment behavior might be found in the existing literature (Table 1). Although these mechanisms refer to the comparison of the new and old technologies, a discrepancy between the difference of gene therapy versus chemotherapy and that between the other two biotech variants versus chemotherapy (a qualitative differences-in-differences approach) could explain the disproportion.

The first mechanism is competence destruction. According to archival and interview material, all three variants of biotech are competence-destroying changes from chemotherapy. To see this, consider prototypical examples of drug discovery in each variant.

[15] For robustness, I implemented this test alternatively at the firm level in two different specifications: a Logit regression predicting the likelihood that a firm had at least one gene therapy drug in its biotech portfolio vs. that it had only non-gene therapy biotech drugs; and a Tobit regression predicting the percentage of gene therapy in a firm's biotech portfolio. Conclusions remain unchanged.

A prototypical chemotherapy drug is Nitrogen Mustard (Chabner and Roberts 2005). Nitrogen mustard was derived from autopsy findings that hinted at the potential for cancer treatment of a close compound used in chemical warfare during World War I, sulphur mustard gas. Because the initial hypothesis that led to the development of Nitrogen Mustard was not based on knowledge of the biological mechanisms present but rather a "random" starting point followed by intensive use of chemistry, the process of drug discovery behind chemotherapy has often been termed "random" drug discovery. Similar processes led to the discovery of other prototypical chemotherapy drugs such as Cisplatin (*Chemical and Engineering News* 2005), Taxol and Irinotecan (Chabner and Roberts 2005).

In contrast, small-molecule, large-molecule and gene therapy drugs were discovered through a process known as "rational" drug discovery because they all took as a starting point a hypothesis derived from knowledge of the biological mechanisms present in cancer. These drug discovery processes therefore made intensive use of molecular biology. A prototypical example of a small-molecule anticancer drug is Imatinib Mesylate (*Gleevec*®, Novartis, Basel, Switzerland), which was designed on the basis that a high-incidence leukemia is characterized by a translocation of two chromosomes, a translocation that generates the BCR-ABL gene. The drug was designed to target this deregulated gene (Capdeville et al. 2002). Likewise, a prototypical example of a large-molecule anticancer drug is Bevacizumab (*Avastin*®; Genentech/Hoffmann-La Roche, Basel, Switzerland). Research on the blood supply of tumors led to the discovery of the VEGF gene, a gene around which Bevacizumab was designed (Ferrera et al. 2004). Lastly, prototypical examples of gene therapy include *Gendicine*® (SiBiono, Shenzhen, China) and Advexin (Introgen Therapeutics, Austin, Texas). Many tumors have a dysfunctional gene to make p53, a protein that prevents cancers from proliferating. Gene therapy drugs like *Gendicine*® and Advexin use a virus to insert the normal version of the gene into the tumor and restore production of p53 (Jia 2006, 2007).

The second mechanism is changes in the revenue model of incumbents. Interviewees described the three variants of biotech as using the same revenue model as chemotherapy. All three variants are traded as a high-value consumable. An interviewee who is a scientist

working in gene therapy explained that gene therapy drugs are "…not unlike IV [intravenous] delivery of antibody therapies [a type of large-molecule drug] that are not available orally." She then explained that there is a sub-set of gene therapy drugs that need to combine with a patient's bone marrow cells. After further probing, he indicated that the revenue model would be the same for this sub-set of gene therapy drugs:

> "… they [firms profiting from gene therapy] could prepare the vector that transfects the patient's cells, so they could sell vectors … to any hospital … it would come as probably a freeze dry product that would be reconstituted, or it could be a preserved product that is frozen … packaged as a product and delivered and distributed…"

Another interviewee working in the business development area of an incumbent offered a contrasting example that would change the revenue model: 3D printing of organs. In recent experiments, 3D printing has successfully grown bladders (Atala et al. 2006, Topol 2012) and a trachea (Naik 2011) and imposes a move from consumables to equipment sales.

The third mechanism is disruption in customer preferences. The key features that have driven value in anticancer drug discovery since the birth of chemotherapy in 1949 are efficacy and (low) toxicity. According to the American Cancer Society (2000, 2004), the five-year relative survival rate[16] for all cancers combined, a proxy for drug efficacy that accounts for toxicity, changed from 51% to 63% in the period of observation. With such low survival rates, efficacy and toxicity remain the primary drivers of customer value. Available patient accounts support this conclusion (Vasella and Slater 2003, Bazell 1998).

The fourth mechanism is challenges imposed to the organizational identity of incumbents. Firms in the industry invest in identity-building activities internally such as inviting patients to come explain to the staff how much the firm's drugs have helped them. Furthermore, these firms engage in identity-building activities with external audiences, as can be seen in the inclusion of patient stories in annual reports. That said, none of the three variants of

[16] The five-year relative survival rate is the survival rate observed for a group of cancer patients compared to that of a group in the general population with similar age, gender, race, and calendar year of observation, adjusting for normal life expectancy (American Cancer Society 2000: 2).

biotechnology challenges the identity of the firms in the anticancer drug market since they continue to represent treatments for cancer aligned with the identity-building activities currently in practice. An interviewee from business development gave an example of an identity-challenging change: profiting from analytics. Incumbents in this market are required by regulation to collect information about medicine use, patient demographics and biomedical characteristics, and outcomes. In theory, a firm could attempt to profit from selling that (anonymous) information. Unless the firm could make a convincing case that profiting from analytics is a contribution to cancer treatment, this would be an identity-challenging shift.

The fifth and final mechanism consists of two questions.

The first is whether the new technology is a substitute for the old. Scientists consider any biotech drug regardless of variant as a substitute for chemotherapy drugs. Their explanation is that chemotherapy for cancer treatment is based on the principle of finding a chemical entity that attacks rapidly reproducing cells in the human body. While true for cancer cells, it is also true for the cells in human hair, and more importantly, the gastrointestinal system and cardiac tissue, increasing the toxicity that accompanies drug efficacy. Biotechnology allows drug discovery to be "targeted," promising the identification of cancer cells alone, thus becoming a preferable, lower toxicity substitute.[17] The need to shift to targeted therapies does not seem contentious among interviewees. It is the choice of variant of biotechnology that is an open question.

The second question in the fifth mechanism is whether incumbents have control over the start of the discontinuity. The biotechnology revolution consists of a long list of innovations from diverse players. As a result, no organization, not even incumbents, retains control over the discontinuity for any of its variants. For example, rDNA technology, used in drug discovery for the three variants discussed, has been widely licensed by Stanford University (Feldman 2003). Several subsequent innovations have all had different origins (Kaplan and

[17] When identified in the PDR 2005 (the end of the period of observation), results in trials for biotech anticancer drugs often outperform benchmark chemotherapy treatments.

Murray 2010; for examples, see *Nature* 2007). Some R&D techniques such as hybridoma technology have even remained unpatented (Mackenzie, Cambrosio and Keating 1988).

In summary, as can be seen in Table 1, the shift from chemotherapy to each variant does not differ in any of the five mechanisms that drive differences in investment between incumbents and entrants. This means that prior literature cannot explain the differential proportion of de novo firms in gene therapy compared to the rest of biotechnology.

4.2.2 Discarding Theories of Investment Behavior of Diversifying versus De Novo Entrants. As explained in section 2.2, an important question is whether the reusable capabilities of diversifying entrants could explain their differences in investment in gene therapy as compared to de novo firms. In the particular case of the anticancer drug market, the only advantageous reusable capabilities that could incentivize diversifying entrants away from gene therapy is present in large-molecule drug discovery. Indeed, prior research has shown that a particular sub-set of diversifying entrants accrued an advantage over incumbent, de novo and other diversifying firms in this variant (Sosa 2011). Early in the history of this variant, large-molecule drugs could only treat diseases that were protein deficiencies, diseases that thus did not include cancer. The sub-set of firms profiting from treating these particular diseases invested in developing the capabilities necessary for large-molecule drug discovery earlier than any other firm. Once large-molecule drugs became applicable to cancer treatment, these firms diversified into the anticancer drug market with an advantage for that particular variant. Foresight of this advantage can give that sub-set of diversifying entrants an incentive to invest in large-molecule drugs over other variants, including gene therapy. This mechanism could explain why diversifying entrants invest in large-molecule drugs more than in the other two variants of biotechnology (43% in contrast to 35% and 32% in small-molecule and gene therapy drugs, respectively). I therefore needed to discern whether the difference in investment in gene therapy between diversifying and de novo firms is explained by the activity of the sub-set of diversifying entrants with an incentive to overinvest in large-molecule drugs (and in turn underinvest in gene therapy). To control for this alternative, I identified the large-molecule drug discovery leaders listed in Sosa (2011: 1510) in the current

data and re-ran the regressions dropping these leaders from the sample. Results are shown in Table 3, Model 5. Conclusions remained unchanged (the coefficients for *Incumbent* and *Diversifying* are significantly less than 1, where *De Novo* is the omitted category set at 1). Conclusions also remained unchanged when I re-ran the pattern in Table 4a removing all large-molecule drugs and all incumbents from the sample. Therefore, diversifying entrants' incentive to invest in the variant for which they own advantageous reusable capabilities cannot explain their observed differences in investment in gene therapy versus de novo firms.

4.3 The New Mechanism: Volatility in Outcomes and Organizational Structure as an Option to Project Abandonment

Having discarded alternative hypotheses, I present in this section a new hypothesis inductively derived from the data, as done in prior research (e.g., Cohen 2012, Fernandez-Mateo 2009, Kellogg 2009), a process that required iteration between data and theory (Eisenhardt 1989, Glaser and Strauss 1967).

I argue that the reason established (incumbent and diversifying) versus de novo firms invest differently across variants of biotechnology is that established firms are ill equipped to cope with the financial and organizational liabilities of investing in a technology with volatile patient outcomes (such as gene therapy). In contrast, de novo firms can better manage volatility by readily disbanding the enterprise if extreme liabilities are incurred. This argument has three parts: (1) for technological reasons, gene therapy has greater volatility in patient outcomes than do small and large-molecule biotech variants because gene therapy has more unexpected side effects; (2) in the pharmaceutical industry, negative patient outcomes generate firm-level financial and organizational liabilities for the innovating firm (regardless of firm type) that can be larger than the original investment; and (3) established (incumbent and diversifying) firms do not have the option to disband the enterprise to avoid extreme liabilities and de novo firms do. Table 5 summarizes these three steps in the argument, including examples of the evidence presented below from interview and archival data.

In section 5, I return to the link between this empirical case and applications of options theory to R&D strategy, to discuss this paper's contribution to theory.

4.3.1 Gene therapy has greater volatility in patient outcomes than do small- and large-molecule drugs. My archival and interview data demonstrate that gene therapy has more unexpected, serious side effects (meaning it is more volatile in patient outcomes) than do small-molecule and large-molecule drugs for two main technological reasons.

First, the side effects of gene therapy can be more uncertain than with other biotech variants because the treatment interferes with the internal dynamics of the cell. One scientist explained this by discussing a review of results from cancer Phase 1 trials published in the *Journal of the American Medical Association* (Roberts et al. 2004). In it, the same side effects were tracked in chemotherapy, small- and large-molecule drugs. As the scientist explained, for gene therapy "you haven't gotten a defined platform [of side effects to track]." Talking about the technological reasons it is more difficult to foresee the side effects of gene therapy than those of other biotech, the scientist explained: "the difficulty with gene therapy is, you got to get it into the right cells, it's got to produce and preferably only in the right tissues." Another scientist explained that in the case of gene therapy "you start interfering with that critical balance [intracellular dynamics]; it's such a risky thing." A different scientist described the higher risk in gene therapy compared to the rest of biotech as:

> "You're then doing quite a high risk interventional procedure in order to try to get an effect that is a permanent cure, and the only way you can get a permanent cure is by putting the gene into the chromosomes, into the genetic makeup of the cells … but if you do that, then you risk disrupting genetic material, so by trying to effect a permanent cure, you immediately run the risk of causing a harmful side effect, so you trade off one against the other."

Archival data state gene therapy side effects involve not only toxicity across organs (as with other variants) but also mutagenesis (the possibility of leading to other fatal diseases like leukemia), meaning these side effects are more serious than in other biotech variants (Cotrim and Baum 2008).

A second reason gene therapy is more volatile in patient outcomes than other biotech variants is that in gene therapy there are more sources of toxicity (i.e., there are more

"components" to react to). A scientist explained this point describing gene therapy experiments made to humanize pig heart valves so they could be implanted in humans without anti-rejection medication. Although the experiments worked, regulators insisted that a virus that naturally remains dormant in the pig could "wake up" as a consequence of gene therapy and cause unexpected side effects. The interviewee explained that this risk would not be present if the molecule was "inert" as is the case for small- and large-molecule drugs. Archival data highlight that with gene therapy two components, delivery device and actual gene, can trigger a toxic response (Kimmelman, 2009). According to the *Wiley's Journal of Gene Medicine* collection, the use of viral vectors, the most toxic delivery devices in gene therapy, has remained high, with an average of 75% through the period of observation and a minimum of 60% in 2003.[18]

4.3.2 Negative patient outcomes generate firm-level financial and organizational liabilities for the innovating firm beyond the original investment. My archival and interview data demonstrate that negative patient outcomes lead to firm-level losses of two kinds, namely financial and organizational liabilities, for the innovating firm regardless of whether it is an incumbent, a diversifying or a de novo firm. This is true for all kinds of technologies, not only gene therapy (as explained in section 4.3.1, it is the frequency of these catastrophes that is higher in gene therapy research).

The first category of losses from side effect catastrophes is financial liabilities for the innovating firm. An executive in the safety risk management area of an established firm explained that firms in pharmaceuticals can be sued for compensation if their drug produces a side effect that was not listed in the official drug label, and thus one of the first responses to a side effect catastrophe is to set aside large financial provisions to respond to litigation.[19] Archival data shows financial losses can be significant. A prototypical case in the industry is the catastrophe surrounding *Vioxx*®, a drug for acute pain that Merck & Co. commercialized

[18] Beyond these two main reasons, archival sources argue as well that the usual sequential steps in drug discovery (e.g., animal studies) can be less informative in gene therapy than in other biotech variants, leading to higher uncertainty in side effects encountered in subsequent human use (Kimmelman 2009).
[19] An interviewee pointed out there is also a decrease in the firm's stock value after such a catastrophe.

after approval in 1999[20] (*Business Insight* 2011). After the drug was linked to an increased risk of heart attack with long-term use five years after approval, Merck & Co. voluntarily withdrew it from the market (*Merck & Co.* 2004). Given the uproar from the medical community (e.g., Horton 2004) and the public (e.g., Mathews and Martinez 2004) and the risk of further unknown side effects, Merck & Co. refused to re-launch the drug after the FDA concluded that its benefits outweighed its risks. Refusal to re-launch came with an estimated loss of yearly revenue of $2.5 billion (*Reuters* 2006) and an estimated loss of further billions in litigation (Berenson et al. 2004). By 2012, Merck & Co. had paid nearly $5B to end *Vioxx*® lawsuits (*NBC Universal* 2012). In the period 1992-2010, there were 25 drug withdrawals from the USA market due to unexpected side effects (*Business Insight* 2011: 26), many with similar consequences (see Appendix 2).

The second category of losses incurred in side effect catastrophes is negative organizational consequences. An executive in the safety risk management area of an established firm pointed out that after such a catastrophe has taken place, there is an urgent need in the firm to assign personnel to work on an immediate response in conjunction with the authorities. Moreover, there is internal turmoil finding a way to avoid such an experience in the future. "The organization can change dramatically," he explained, describing the case of an established firm that responded to a catastrophe by requiring the safety risk management group composed of physicians and scientists to report to the legal department. He described the decision as one that would make the R&D process significantly less efficient. Archival data provides other examples. A case in point is the side effect catastrophe surrounding the cardiovascular drug *Manoplax*® withdrawn by Boots in 1993, a catastrophe that forced the firm out of prescription drugs altogether (*Financial Times* 2005).

The losses described are true for side effect catastrophes from all technologies. Nonetheless, if a particular drug class comes under suspicion, subsequent approvals within that class face further scrutiny, leading to delays that lower financial gains and increase exposure to litigation costs, should they occur. This was the case with analgesics within the

[20] Retrieved from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ on December 14, 2011.

class known as Cox-2 inhibitors after the *Vioxx*® catastrophe (Jackson 2005). This was also the case with weight-loss drugs after the withdrawals of *Meridia*® and the *Pondimin*® - *Redux*® combination (Krishnan 2010), the latter a catastrophe amounting to $21B in litigation costs (Loftus 2007). In the particular case of gene therapy research, its history of malpractice is more likely to exacerbate liabilities and delay subsequent approvals. A critical incident in the history of gene therapy was the clinical trial of 18-year-old Jesse Gelsinger in 1999 at the University of Pennsylvania's Institute of Human Gene Therapy (Pearson 2009, Thompson 2000).[21] After Gelsinger died from a reaction to gene therapy treatment, the FDA and National Institutes of Health (NIH) discovered that fewer than 5% of serious adverse events from a common type of gene therapy treatment were being reported across trials in the country. In the end, the FDA and NIH tightened rules for gene therapy work (Thompson 2000). Subsequent trials have faced greater scrutiny from regulatory agencies worldwide. Trials on two types of a rare genetic disorder, X-linked SCID and ADA SCID, were performed on children in 2000 in France and in 2002 in Italy. In the ADA trial, eight out of ten patients achieved persistent improvement in their condition with no improvement in the remaining two patients. However, in the X-linked trial, although 18 of 20 patients achieved persistent improvement, five children developed a leukemia-like reaction, with one dying despite treatment. Although success rates in benchmark treatments of SCID are 50-85%, the X-linked trial's 75% success rate was interpreted negatively. Gene therapy for the treatment of only ADA SCID has received orphan-drug status by the European Medicines Agency (Kohn and Candotti 2009).

4.3.3 Established (incumbent and diversifying) firms do not have the option to disband the enterprise to avoid extreme liabilities while de novo firms do. My archival and interview data show that although all firm groups are more likely to face financial and organizational liabilities when executing gene therapy as opposed to other biotech variants, de novo firms can more readily manage this firm-level volatility. Firms in the pharmaceuticals industry do

[21] Prior to this case, another gene therapy experiment on humans, Dr. Martin Cline's work on a blood disease in two patients in 1980 at UCLA, violated practice guidelines by neglecting to get adequate permission for human experiments from UCLA's institutional review board (Beutler 2001).

not have the option to set up organizational structures under their corporate roofs that grant them the ability to limit their exposure if liabilities are incurred. Therefore, disbanding the entire firm is the only way to cap such liabilities, a significantly less costly option for de novo firms.

An interviewee in the private equity industry explained how "special purpose vehicles (SPVs)" constitute an alternative organizational structure that limits the liability of the parent company in this alternative industry, a feature termed "no recourse" to the parent. He described how he set up a fund in solar energy with each project housed in a separate SPV to manage liabilities.

In contrast, an executive in the safety risk management group of an established firm explained why this is impossible in the execution of internal R&D in the pharmaceuticals industry. In this industry, firms exposed to critical information about a drug are expected to exercise due diligence; thus, for example, even licensees can be legally liable. The liabilities are so far reaching that if a drug approved in Europe causes unexpected side effects in Africa, the firm is liable in Europe. The interviewee explained that major markets in the industry (USA, Europe and Japan) share the level of risk exposure for firms. The industry concern with exposing the firm to liabilities in order to incentivize the right behavior is so severe that by regulation firms are obliged to have a person in the role of "Qualified Person" who is individually liable for catastrophes in the entire portfolio of approved drugs of the firm, meaning the person could go to jail as part of the required response.

Aware of the difference in exposure to the financial and organizational liabilities possible in gene therapy research, established firms wait to invest in that variant disproportionately more than they do in other biotech variants, thus explaining the pattern observed in Table 4.

An anecdote from a founder of a gene therapy de novo firm attempting a partnership with a mid-size diversifying entrant demonstrates the reluctance of established firms to get directly involved in gene therapy. The de novo firm had approached the diversifying entrant to ask for a partnership in which the latter would provide a viral vector it owned while the de novo firm would do the rest of the drug discovery. The idea was for the two firms to share

revenues afterwards. The diversifying entrant replied that they would supply the viral vector for free, and the exchange would remain with no commitment. If the gene therapy drug worked, then since the drug uses their patented viral vector, a partnership would be formed to profit from the discovery. Otherwise, the diversifying entrant would remain officially uninvolved and hence not be liable, either financially or in image, for the losses.

An R&D executive at an incumbent firm analyzed the situation similarly when asked why gene therapy is executed in-house less frequently than other biotech variants:

> "I think the fact that there is a sufficiently vibrant small company community... allows this group [established firms] off the book of making the decision about whether to get into it or not... [in a report on gene therapy] our conclusion... [was] to invest in the best viral vector company... knowing that they would be automatically the alliances of choice of the therapy companies... we could latch it in to delivery"

The founder of a gene therapy de novo firm stated an analogous belief: "with gene therapy there's a lot of risk involved, and therefore big pharma was not interested until this year [2011]." Moreover, in an interview with an executive in an incumbent firm I inquired whether the firm was not present in gene therapy because, unlike small- and large-molecule drug discovery, they had lost interest in the variant. He insisted on their interest in gene therapy drug discovery: "with antisense we are saying 'oh we told you so, wouldn't work,' with gene therapy, ...we are still watching."

In August 2011 GlaxoSmithKline, an incumbent in the anticancer drug market, announced a licensing agreement with the San Raffaele Telethon Institute for Gene Therapy for the gene therapy treatment of ADA SCID (*Datamonitor* 2011). The firm had remained unattached to SCID projects and thus unaffected by the scrutiny of the deaths in the X-linked SCID trials mentioned before, but was now willing to pay for the drug that did work.

5. Discussion

With this unique case study, I have shown that the choice among variants of a new technology, a choice of significant strategic importance, is different across firm groups in

competition. After discarding existing explanations in studies of incumbent vs. entrant and diversifying vs. de novo firms, I presented a new mechanism. I showed that the interaction between the volatility in product performance of a technological investment and the organizational structure of de novo firms explains the different choices firm groups make among variants. When volatility in product performance translates to volatility in firm-level outcomes, firms less equipped to cope with the negative side of such volatility can choose to delay their investments. In the present case, gene therapy has higher volatility (more unexpected side effects) than other biotech variants. Drugs with unexpected side effects lead to financial and organizational liabilities. De novo firms' nimble structure allows them to limit liabilities by disbanding the enterprise if a catastrophe occurs, thus making them better able to manage a variant such as gene therapy. In contrast, established firms do not have an alternative organizational design that could limit their exposure.

I discuss next the two main contributions stemming from the present case.

5.1 Contributions to the Application of Options Theory to Strategy Research

In innovation models within information economics, volatility is an avoidable feature if managers are risk averse or an indifferent one if managers are risk neutral (e.g., Holmstrom 1989). Conversely, options theory emphasizes the creation of value from volatility precisely due to the diversity of options that variance provides (e.g., McGrath 1997). In options theory, the options held by managers to modify projects are known as real options and can usefully be grouped into four classes (Brealy, Myers and Allen 2011: 281): (1) the option to expand (or growth options), (2) the option to abandon, (3) production options (e.g., flexible manufacturing methods), and (4) timing options.

In applications of options theory to strategy research, significant attention has been given to options to expand (Faulkner 1996). Based on a sample of firm decisions to license inventions from the University of California from 1979 to 1998, Ziedonis (2007) showed firms are more likely to purchase option contracts for more uncertain technologies. McGrath and Nerkar (2004) showed firms in the pharmaceutical industry are more likely to expand on an option (as proxied by a second patent in the same class) when there is larger scope of opportunity in

the area. Based on a sample of manufacturing joint ventures, Kogut (1991) showed that such partnerships represent an option to expand when changes in product shipments in the market offer additional information over time.

However, little attention has been given to the creation of option value through the option to abandon a project, and in particular to organizational structure as the instrument conferring such option value in R&D strategy. This is precisely what the finding in the present case study represents and the reason it has important implications for investment decisions across variants of a new technology. Furthermore, by considering the option to abandon, this case study documents an application of options theory that does not overlap with the predictions of path dependent search theories, the greatest criticism of prior work on options theory within strategy (Adner and Levinthal 2004a, 2004b).[22] To my knowledge, the only other study of organizational structure creating option value through the option to abandon is Vassolo, Anand and Folta's (2004) study of alliance divestiture. However, the authors linked the likelihood of alliance divestiture to industry uncertainty (as proxied by the standard deviation of the stock index of public companies), not to a characteristic of the technology that can inform investment decisions across technological variants.

To see how structure creates option value in the current case study, consider that the common characteristic of real options is the generation of option value from volatility through capping the losses (whether through delayed expansion or abandonment or something else) but remaining fully exposed to the gains. This feature is termed "asymmetric reward structure" and is widely accepted even in the strategy literature as a common feature of options (McGrath, Ferrier and Mendelow 2004). The creation of option value through asymmetric reward structures is clearest in the basic design of a put option. In the simplest put option, volatility in stock prices over a fixed period of time is used to offer value to the owner of the option. A put option caps the lowest price at which the owner of the option sells stock in exchange for a fixed fee. The owner has the right but not the obligation to exercise

[22] Because R&D investment is seen in path dependent search theories as granting the option not to be locked out of a technology later in time (Cohen and Levinthal 1990: 136), these theories already define any investment in R&D as an option to expand.

the option; thus if higher stock prices become available in the market within the contracted period, the owner can seize the opportunity of selling at these prices instead. As a result, a put option offers the owner the probability of significant gain beyond the cost of the initial fee while capping the losses (e.g., Brealey, Myers and Allen 2010). In doing so, the structure of the put option confers option value to its owner that other sellers of the same stock would not have. Analogically, although all firms face the same level of volatility in gene therapy, de novo firms extract option value from investing in gene therapy because their structure caps the possible losses. In contrast, established firms are exposed to the full volatility of the variant. Because competitors do not have an alternative design with equivalent functionality to that of de novo firms' structure, organizational structure becomes a possible source of competitive advantage for de novo firms.

5.2 Contributions to our Understanding of Competitive Analysis of Discontinuities

In the end, the present case study shifts attention not only toward the choice among variants of a new technology, but also toward the contrast between established and de novo firms, not incumbents versus entrants.

Current literature emphasizes the contrast of different sets of capabilities reusable by established firms as they compete against one another through a discontinuity (e.g., Agarwal and Helfat 2009, Benner and Tripsas 2012, Carroll et al. 1996, Sosa 2011). By emphasizing the comparison between established and de novo firms, the present case study shifts focus to the contrast between strategy (capabilities) and structure (Chandler 1962) illustrated by the race between competitors with firm-level prehistory (established) and those without it (de novo).

The implication is that the study of discontinuities can inform the larger question of the conditions under which it is the structure and not the reusable capabilities of the firm that represents its key source of competitive advantage (Teece, Pisano and Shuen 1997). One such condition is when technological choices differ in volatility (as opposed to when uncertainty is merely present, as prior research has argued). Further competitive analysis between established and de novo firms should yield additional insight into this line of inquiry.

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Figures

Figure 1. Competence Destruction in Anticancer Drug Discovery

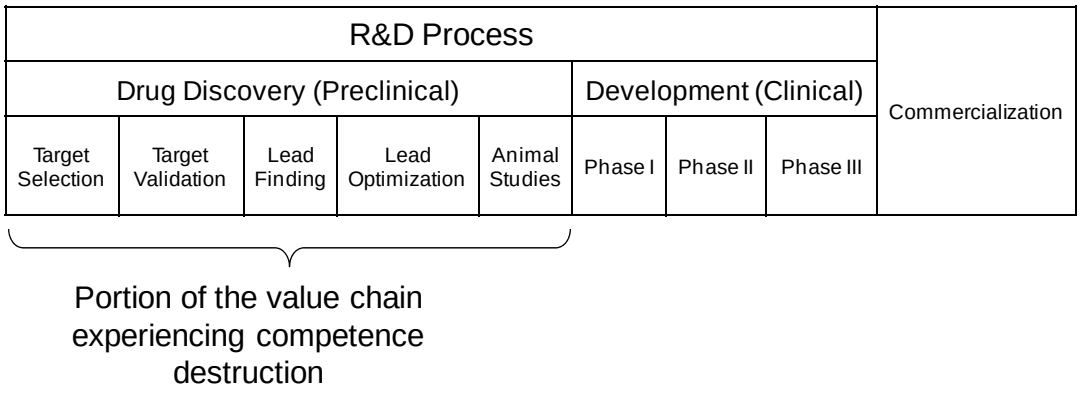
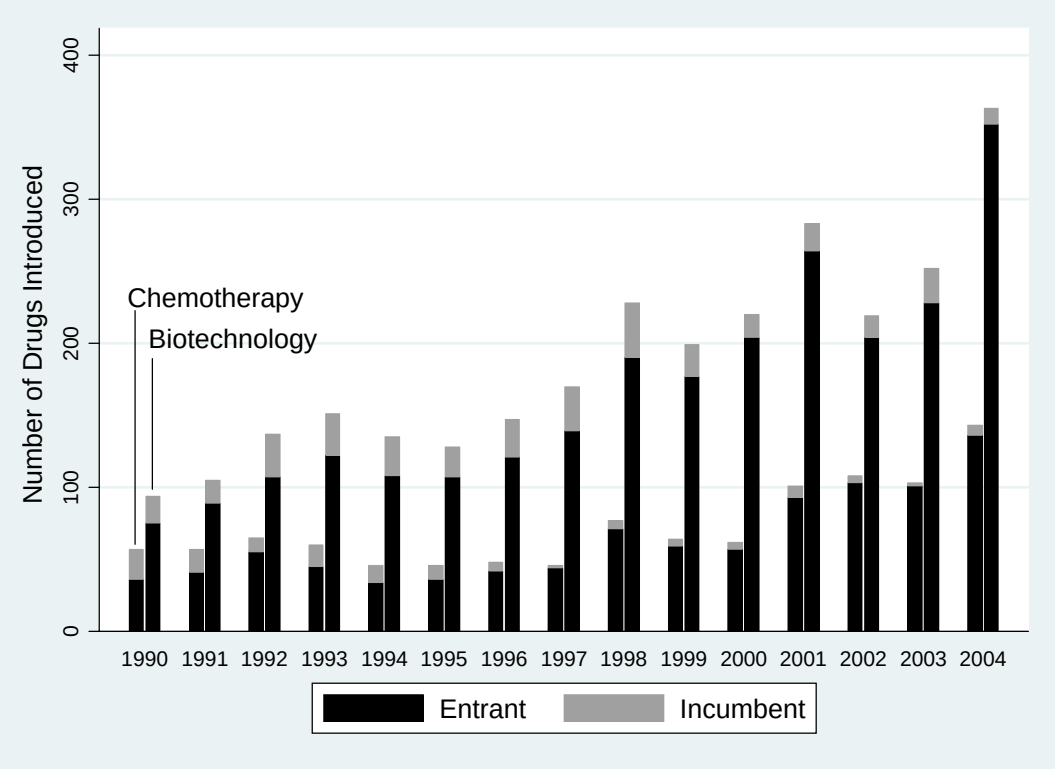
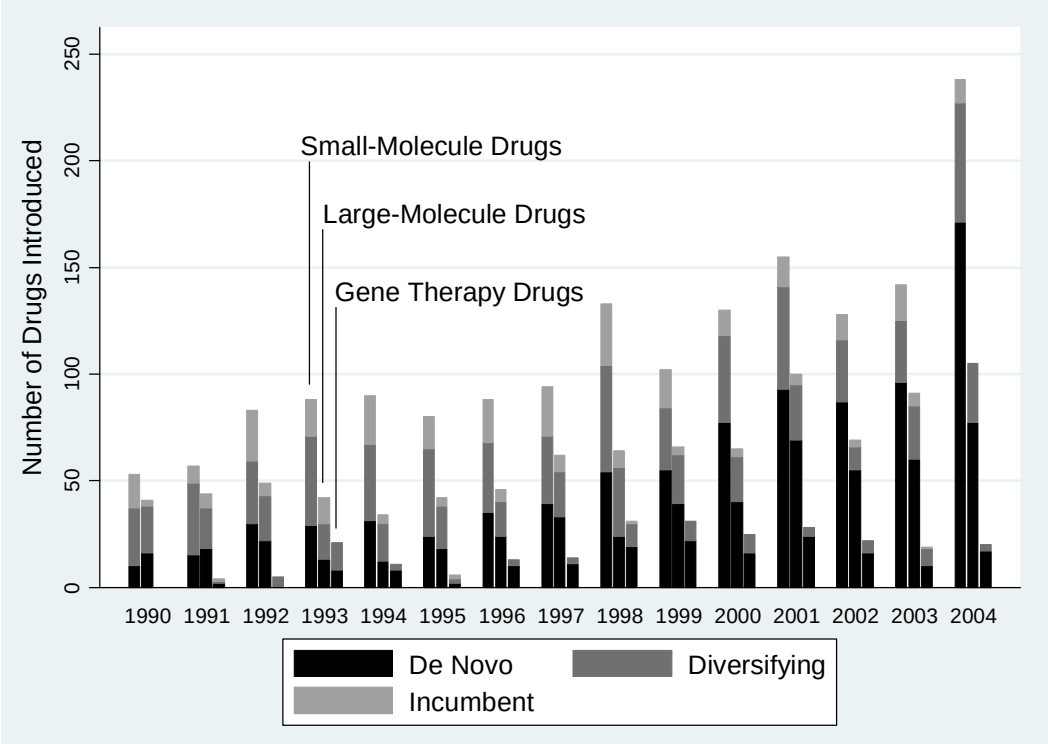


Figure 2. Number of Drugs Introduced into Clinical Trials over Time

2a. Chemotherapy and Biotechnology by Incumbent and Entrant Firms



2b. Small-, Large-Molecule and Gene Therapy Drugs by Incumbent, Diversifying and De Novo Firms



Tables

Table 1. Mechanisms Driving Differences in Investment Behavior between Incumbents and Entrants in the Literature on Technological Discontinuities

Mechanism	From Chemotherapy to Small-Molecule Drugs	From Chemotherapy to Large-Molecule Drugs	From Chemotherapy to Gene Therapy
1. Competence Destruction (changes in capabilities)	yes	yes	yes
2. Changes in Revenue Model	no	no	no
3. Disruption in customer preferences (changes in product features driving value)	no	no	no
4. Changes Imposed on Organizational Identity	no	no	no
5a. Substitute for the old technology	yes	yes	yes
5b. Control over the Start of the Discontinuity by Incumbents	no	no	no

Table 2. Descriptive Statistics

	Count	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Biotechnology	3,477	1.00							
Gene Therapy	260	0.16	1.00						
Incumbent	769	-0.03	-0.08	1.00					
Diversifying	2,008	-0.06	-0.04	-0.34	1.00				
Collaboration in Drug Discovery	632	0.01	0.04	-0.03	-0.02	1.00			
Molecule Acquired	399	-0.01	-0.03	-0.07	-0.05	-0.07	1.00		
Technology Licensed	107	0.04	0.08	-0.05	-0.05	-0.02	0.01	1.00	
Other Licensed	91	0.04	0.10	-0.03	-0.05	0.01	0.13	0.04	1.00

Table 3. Logit Regression on Choice across Technologies

Coefficients in Odds Ratios

Std. Errors Clustered by Firm

	Biotechnology (vs. Chemotherapy)		**Gene Therapy (vs. the rest of Biotechnology)**		
	All Firms		**All Firms**		**All Firms Except Large-Molecule Drug Leaders**
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Incumbent	0.82	0.83	0.11***	0.11***	0.11***
	(0.16)	(0.16)	(0.05)	(0.05)	(0.05)
Diversifying			0.60+	0.64+	0.64+
			(0.17)	(0.18)	(0.19)
Collaboration in Drug Discovery		1.02		1.47*	1.42*
		(0.12)		(0.26)	(0.25)
Molecule Acquired		0.84		0.38**	0.35**
		(0.11)		(0.13)	(0.12)
Technology Licensed		1.82*		2.58**	2.60**
		(0.48)		(0.79)	(0.83)
Other Licensed		2.38**		4.48***	4.30***
		(0.70)		(1.33)	(1.30)
N	5,068	5,068	3,477	3,477	3,320
Log Likelihood	-3,151	-3,141	-894	-871	-837

+ p < 0.1, * p < .05, ** p < .01, *** p < .001

Standard errors in parentheses

Table 4. Proportions of Drugs Introduced per Group of Firms and Technological Variant

4a. Proportions across Firm Groups and Variants

(Pearson $\chi^2(4) = 82.6$, $p < 0.0001$)

	Biotechnology			
	Small Molecule	**Large Molecule**	**Gene Therapy**	
Incumbent	338 *(18%)*	155 *(12%)*	6 *(2%)*	499
Diversifying	665 *(35%)*	565 *(43%)*	84 *(32%)*	1,314
De Novo	906 *(47%)*	588 *(45%)*	170 *(65%)*	1,664
	1,909 *(100%)*	1,308 *(100%)*	260 *(100%)*	3,477

4b. Proportions of Activity in Gene Therapy versus other Variants of Biotechnology among Firm Groups up to 1997

(Pearson $\chi^2(2) = 17.07$, $p < 0.0001$)

	Biotechnology		
	Small- and Large-Molecule	**Gene Therapy**	
Incumbent	215 *(20%)*	3 *(4%)*	218
Diversifying	474 *(44%)*	30 *(41%)*	504
De Novo	379 *(36%)*	41 *(55%)*	420
	1,068 *(100%)*	74 *(100%)*	1,142

Table 5: Exemplary Evidence for the Interaction between Volatility and Organizational Structure to Create Option Value

	Examples of Interview Data	Examples of Archival Data
1. Gene Therapy has Greater Volatility in Patient Outcomes than do Small-Molecule and Large-Molecule Drugs		
• Gene therapy interferes with the internal dynamics of the cell	• A scientist explained that unlike with small- and large-molecule drugs, in gene therapy "you haven't gotten a defined platform [of side effects to track]" • A scientist described that with gene therapy "you start interfering with that critical balance [intracellular dynamics]; it's such a risky thing"	• Cotrim and Baum (2008)
• Gene therapy has more sources of toxicity	• A scientist explained that in gene therapy experiments to humanize a pig heart valve for transplantation, the issue was the uncertainty of having "awaken" a dormant virus in the pig tissue that could hurt the tissue recipient, an issue that would not take place among "inert" variants such as small- and large-molecule drugs	• Kimmelman (2009)
2. Negative Patient Outcomes Generate Firm-Level Financial and Organizational Liabilities for Innovating Firms (regardless of type) beyond the Original Investment		
• Side effect catastrophes lead to significant financial liabilities	• An established firm safety risk manager explained firms can be sued for unexpected (not on label) side effects. One of the first responses to a side effect catastrophe is to set aside large financial provisions to respond to litigation	• Case of Merck's withdrawal of *Vioxx*® after it was linked to increased risk of heart attack o Uproar from medical community and public and risk of further unknown side effects led Merck not to re-launch despite estimated loss of $2.5B annual revenue (*Reuters* 2006) o By 2012, Merck & Co. had paid nearly $5B to end *Vioxx*® lawsuits (*NBC Universal* 2012)

• Side effect catastrophes lead to negative organizational consequences	• An established firm safety risk manager explained that after a side effect catastrophe, organizations assign personnel to work with authorities. Firms also redesign the structure to try to avoid such an experience in the future: "the organization can change dramatically."	• Case of Boots' withdrawal of *Manoplax*® after it was linked to increased mortality, leading the firm to exit prescription drugs altogether (*Financial Times* 2005)
• A history of malpractice exacerbates financial and organizational liabilities in gene therapy research	• The founder of a gene therapy de novo firm described the issue of public concern in gene therapy given its history of malpractice: "There is definitely a perceived public concern that increases if you go from small-molecule medicines … [to] drugs which are generated by genetic modification."	• After the tightening of rules for gene therapy by the FDA and NIH in the aftermath of the Gelsinger case in 1999, there was a negative interpretation of the X-linked SCID gene therapy trial's 75% success rate. Only ADA SCID gene therapy receives orphan-drug status by the European Medicines Agency (Thompson 2000, Kohn and Candotti 2009)
3. Established Firms Do Not Have the Option to Disband the Enterprise to Avoid Extreme Liabilities while De Novo Firms Do		
• There is no organizational structure available to established firms that allows them to cap the losses stemming from a side effect catastrophe. In contrast, de novo firms can cap the losses by disbanding the enterprise	• An established firm safety risk manager explained that the liabilities are so far-reaching that even licensees are liable, and if a drug approved in Europe causes unexpected side effects in Africa, the firm is liable in Europe.	
• Hence established firms prefer to wait to become officially involved in gene therapy research until outcomes have been proven	• The founder of a de novo gene therapy firm explained they had approached a diversifying entrant to form a partnership for access to their viral vector. The diversifying entrant supplied the viral vector for free, remaining officially unattached until the gene therapy drug works.	• In 2011, incumbent GlaxoSmithKline announced a licensing agreement with the San Raffaele Telethon Institute for their current ADA SCID gene therapy drug (*Datamonitor* 2011). Glaxo had remained unattached to SCID projects and thus unaffected by the scrutiny of the deaths in the X-linked SCID trials in 2002.