

**Division of Labor across Organizational Forms during a Technological  
Discontinuity: Evidence from Gene Therapy Research**

**M. Lourdes Sosa**  
London Business School  
Strategic and International Management  
Sussex Place, Regent's Park  
London NW1 4SA

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*Very much in progress, please do not circulate*

*(plus still in need for copy-editing, apologies!)*

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## **Division of Labor across Organizational Forms during a Technological Discontinuity: Evidence from Gene Therapy Research**

Studies in creative destruction have shown incumbents underperform entrants in the R&D of radical innovation, even if not in sales. In this paper, based on a combination of interview, historical and quantitative data on the transition of the anti-cancer drug market into biotechnology, I show that the abovementioned pattern is driven by the high R&D performance of diversifying entrants. Contrastingly, de novo entrants underperform both diversifying and incumbent firms. However, I also show that de novo entrants carry out the largest proportion of the variant of biotechnology with the highest risk: gene therapy. The explanation behind this pattern is twofold. First, in the higher-risk variant, established firms have no capabilities to re-use. Therefore, the lack of re-usable capabilities does not confer de novo firms a disadvantage in that variant. And second, projects in the higher-risk variant are less likely to starve when housed in more even-risk internal markets, a characteristic more often found in de novo firms. Therefore, their particular organizational structure confers de novo firms an advantage in that variant. It is in this sense that, through a discontinuity, established firms (whether incumbents or diversifying entrants) take advantage of their capability re-use whereas de novo firms take advantage of their organizational structure, and a division of labor arises. Overall, this paper clarifies the role of the novo firms in the industrial dynamics of radical innovation: risk bearing. I discuss implications for research in creative destruction and for the broader discussion of strategy vs. structure.

*Key words:* organizational capabilities; organizational economics; agency; innovation; incumbents; technological disruption; risk; R&D.

## 1. Introduction

At least since Schumpeter (1934, 1950) coined the term “creative destruction” to refer to the dynamics of a market disrupted by a technological discontinuity, management scholars have been interested in understanding the role that incumbents play in such dynamics (e.g., Arrow 1962; Abernathy and Utterback 1978; Utterback 1994).

Indeed, detailed research looking into the dynamics of single technological discontinuities, and that can therefore more precisely identify incumbent firms, has shown systematic trends. In particular, prior research (e.g., Henderson, 1993) has shown how incumbents underperform entering firms in the productivity of the research and development (R&D) of radical innovations. Furthermore, Tripsas (1997) has shown incumbents underperform entrants in the quantity and quality of radical innovations, even if these incumbent firms retain market leadership thanks to superior proprietary commercialization assets.

In contrast, a line of research interested in entry dynamics, hence focused on the study of newly emerging markets (markets that therefore include only entrants but no incumbents), has shown the opposite result: it is the firms in their samples that come with a pre-history that carry an advantage. In particular, when distinguishing in their samples between entrants that come with and without corporate pre-history (i.e., de alio vs. de novo entrants), these research has shown de alio entrants (i.e., diversifying firms) outperform de novo firms both in firm survival and in quantity of innovations (e.g., Mitchell 1994; Carroll et al. 1996; Klepper and Simons 2000; Khessina and Carroll 2002).

But what are the results when the three groups of firms (namely, incumbents, diversifying entrants and de novo firms) are distinguished and their R&D productivity compared? That is, what are the conclusions when the arguments in both lines of research, namely studies about incumbents vs. entrants and those about de alio vs. de novo entrants are combined?

A second look at a classic discontinuity could illustrate the abovementioned question. Indeed, a good discontinuity to revisit, given the information available about the firms in competition, is the transition from vacuum tubes to transistors in the semiconductor industry. Tilton (1971) offers a list of firms along

with the number of patents they filed in transistor technology per year and R&D investment in transistor technology for two of those years. Based on the firm names available and their corresponding corporate histories (which I culled from their websites and profiles available in *Moody's Industrial Manual* and company websites), I classified all 39 firms reported into incumbents, diversifying entrants and de novo firms. The results of this exercise, even though not statistically significant given the sample size, are illustrative. As prior research has shown (e.g., Henderson 1993), incumbents are less productive than entrants in the R&D of the radically new technology (incumbents' average productivity is 1.8 patents/MM USD lower than the average 2.3 patents/MM USD of all entrant firms). Moreover, incumbents fall behind diversifying entrants (these latter average 2.4 patents/MM USD), a difference in R&D productivity that, according to prior literature (e.g., Klepper and Simmons 2000), is rooted in the dynamics of these firms' underlying R&D capabilities. That said, incumbents are also not the least productive firms once entrants are split into those with re-usable capabilities and those without them: the least productive firms are de novo firms (de novo entrants' average productivity is 1.7 patents/MM USD).<sup>1</sup>

If this result can be confirmed in a larger sample (which allows then for statistical significance, and which constitutes the first step in this paper), an immediate question will follow: if de novo firms are the least productive group of firms in the R&D of radical innovation, then do they play a specific role within the dynamics of a technological discontinuity beyond simply increasing the number of "experiments" executed based on the new technology?

In this paper I target precisely these two questions: are de novo firms the firm category with the lowest R&D performance during a technological discontinuity? And if so, what specific role do de novo firms play through a discontinuity (and why)? To answer these questions, I analyze R&D competition in a discontinuity by looking beyond the transition from an old to a new technology, as prior research has done. I look instead at the choice that firms make across different technological variants within the new

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<sup>1</sup> In line with prior research in de alio vs. de novo firms, diversifying entrants outperform de novo entrants (at an average of 2.4 patents/MM USD and 1.8 patents/MM USD, respectively, a difference that is statistically significant at  $p < 0.05$ ).

technology.<sup>2</sup> In particular, I study the transition of the anti-cancer drug market from cytotoxic to targeted drug discovery, a transition that is a consequence of the biotechnology revolution. Furthermore, among targeted drugs, I identify separate variants: small-molecule drugs, large-molecule drugs, and gene therapy. The identification of these three variants then becomes central to the research design. Competition in the two former variants has been driven by the dynamics of the underlying capabilities of the established firms, in favor of incumbents in small-molecule drugs and of some of the entrants in large-molecule drugs (Sosa 2010). In contrast, although these are all variants of the new technology and hence all carry some level of risk, the particular characteristics of gene therapy single out this variant as the higher-risk variant among targeted anti-cancer drugs. As I will explain further, the argument of this paper is that competition in this last variant, gene therapy, is driven not by capabilities but by organizational structure favoring *de novo* firms.

Indeed, based on preliminary analyses, I find that *de novo* firms underperform in the R&D of targeted anti-cancer drugs as compared to established firms (both incumbents and diversifying entrants). That said, I also find that *de novo* firms are more likely to invest in gene therapy and less likely to discontinue any given gene therapy project. Furthermore, I find the behavior of *de novo* firms in gene therapy R&D to be significantly explained by the structure of their internal markets, more likely to be even-risk portfolios than those of established firms. Ultimately, *de novo* firms carry out the largest proportion of total gene therapy research in the anti-cancer drug market, and thus, a division of labor across organizations arises. Although throughout the discontinuity it will remain uncertain whether any technological variant(s) will dominate the market, it is only through investment on all variants that such question will be resolved. It is in that sense that a division of labor across organizations appears beneficial through a discontinuity.

The findings in this paper then answer the question of the specific role of *de novo* firms in the dynamics of creative destruction: even though *de novo* firms might be the least productive firms in the R&D of a

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<sup>2</sup> This would be the equivalent of re-visiting the abovementioned transition from vacuum tubes to transistors, but this time paying attention to the different variants of transistors: silicon-based transistors, germanium-based transistors, etc.

radically new technology, these firms carry the largest proportion of the sub-set of that technology with the highest risk. In other words, through a discontinuity, established firms drive R&D productivity thanks to their capability re-use whereas de novo firms drive risk bearing thanks to their organizational structure.

These findings have implications for theory beyond the role of de novo firms in the dynamics of creative destruction. On the one hand, this study separates the effect of “strategy” (capabilities) from that of “structure” (organizational design) through a discontinuity therefore contributing to the larger debate on strategy vs. structure (Chandler 1969). On the other hand, this study extends prior research showing the tradeoffs present in single- vs. multi-market firms (e.g., Argyres and Silverman, 2004), into the tradeoffs present in single- vs. multi-technology firms. As Wernerfelt (1984: 173) stated: “There is thus a nice duality... corresponding to the duality between products and resources.” Understanding both sides of the dual context in which organizations compete, namely product markets and (technological) resources, becomes indispensable to gain a full perspective on both cross-sectional and longitudinal competitive dynamics.

## **2. Organizational Capabilities and Radical Innovation**

Research in organizational capabilities is now pervasive (e.g., Teece, Pisano and Shuen 1997; Martin and Eisenhardt 2000). In the particular case of radical innovation, the concept of organizational capabilities underlies discussions both of newly emerging markets (i.e., de alio vs. de novo studies) and of existing markets disrupted by technological discontinuities (i.e., incumbent vs. entrant studies). Both of these literatures posit an advantage for one firm category over the other when valuable organizational capabilities can be re-used. In the case of de alio vs. de novo studies, classic studies have found the former group outperformed the latter in survival rates and number of innovations due to re-usable capabilities (Mitchell 1994; Carroll et al. 1996; Klepper and Simons 2000; Khessina and Carroll 2002). In the case of studies about incumbent vs. entrant firms, classic work has shown that when a discontinuity leaves some valuable capabilities for incumbents to re-use, whether within research and development (R&D) or commercialization, that might be enough to grant these firms a source of competitive advantage with which to outperform entrants (see the discussion on competence-enhancing discontinuities in

Tushman and Anderson 1986; see also Tripsas 1997; King and Tucci 2002; Sosa 2009). Indeed, recent research has shown that in discontinuities that are only partially competence-destroying to the R&D process of incumbent firms, which group of established firms outperforms the competition depends on which group owns the capabilities with the highest strategic value (Sosa 2010).<sup>3</sup>

Therefore, based on the mechanisms identified in prior literature, during a discontinuity that is at least partially competence-destroying to the R&D capabilities of incumbent firms, de novo entrants can be expected to underperform all established firms (both incumbents and diversifying entrants). This is because de novo firms are the only group of firms without capabilities to re-use at the organizational level.<sup>4</sup> Therefore, I posit the following hypothesis:

**Hypothesis 1:** In a competence-destroying discontinuity where established firms have re-usable capabilities, de novo firms will fall behind established firms (both incumbents and diversifying entrants) in R&D performance.

### **3. Organizational Design, Internal Markets and Radical Innovation**

As Gibbons (2005) explained, although mainly focused on theories about the boundary of the firm (i.e., the make vs. buy question), organizational economists have also been interested more broadly on theories of the firm (i.e., the inner workings of organizations). As a result, work has advanced in interpretations of organizations as bundles of principal-agent contracts (e.g., Holmstrom and Tirole 1989) and as instances of different forms of governance (e.g., Scharfstein, 1998; Scharfstein and Stein 2000).

Though clearly separate from the question of organizational capabilities, organizational economics has paid clear attention to differences across firms, rooted instead in organizational structure. Indeed, inter-

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<sup>3</sup> I refer to a resource/capability as having strategic value when it adds value in the value chain of the owning firm and is also inaccessible to competitors, in line with prior literature (Rumelt, 1987; Barney 1986, 1991).

<sup>4</sup> I emphasize the fact that these mechanisms involve capabilities at the organizational level given that the individuals working for de novo entrants do not have individual-level capabilities to re-use. But this is true for the personnel working in incumbent and diversifying firms as well. These are individual-level processes. Because there is no evidence at this point that these effects are disproportionately present in the personnel employed in incumbent, diversifying, or de novo firms, re-usable individual-level capabilities can currently only be assumed as randomly distributed across firm categories. As a result, individual-level re-usable capabilities cannot currently be hypothesized as explaining differences in performance across incumbents, diversifying and de novo firms.

disciplinary work in strategy has explained how differences in organizational structure can represent a source of competitive advantage (e.g., Zenger 1994).

A central idea in the study of the inner workings of organizations has been the distinction between external and internal markets. External markets are collections of single-project firms, all seeking funding independently. In contrast, an internal market is a multi-project firm. Even if an external market has funding decisions centralized, as long as the central fund-allocating “agent” remains without control rights over the projects of different single-project firms, the dynamics of external and internal markets differ. An external market with a hundred single-project firms is different from a firm with a hundred-project internal market because in the latter the resource-allocating agent has control rights over all hundred projects. Therefore, the internal market can engage in “winner picking,” that is, re-allocating resources from low-performing projects to high-performing ones (Gertner, Scharfstein and Stein 1994). Indeed, the dynamics of single-project firms can be seen as “loser sticking,” thus allocating resources to projects that would otherwise be ceased, because the managers try to avoid liquidating the entire firm (Stein 1997; Guedj and Scharfstein 2004).

The discussion above assumes projects can differ in their performance (average outcome) but not in their level of risk (variance in outcome), where a project is riskier if it has higher variance than another even if both are equal in expected value. Once projects differ in their level of risk, the dynamics of winner picking in internal markets can turn detrimental to organizations. If the resource-allocating agent in an internal market is risk-averse, so that he is sensitive to the probability distribution of success, then winner picking can turn into risk avoidance.

The conclusion should then be a parallel analogy to that found in multi-task incentive systems, where tasks with different levels of risk cannot be assigned to the same risk-averse agent, since he will underinvest his effort in the risky tasks. It becomes best to assign tasks with different levels of risk to different risk-averse agents (Holmstrom 1989).

Analogically, projects with different levels of risk should be housed in different internal markets (as long as the resource-allocating agent is risk averse). When housed within the same internal market, high-

risk projects will receive fewer resources than they would have received if they were in an external market, that is, if they were each housed in a single-project firm. This is because in an internal market, the winner picking dynamics will continue to re-allocate resources away from high-risk projects. Thus, an even-risk internal market (i.e., one that combines projects with similar levels of risk) will be less likely to re-allocate resources on the basis of risk than an uneven-risk internal market, other things equal. Consequently, high-risk projects will be funded for longer in an even-risk internal market than in an uneven-risk internal market, simply because in the former market, high-risk projects do not have to compete internally against projects with relatively lower risk. Notice as well that even-risk internal markets will continue to re-allocate resources on the basis of performance, even if not on the basis of risk, thus outperforming external markets of equally high-risk projects.

The application of the above dynamics to the dynamics of technological discontinuities can be easily seen once the new technology is broken down into technological variants. When the new technology comprises several technological variants, projects in these different variants might vary in their levels of risk. Thus, firms whose investment in the new technology involves investment in technological variants with differing levels of risk will exhibit uneven-risk internal markets. As a consequence, such firms will underinvest in projects in the higher-risk variant in favor of those in a variant(s) with relatively lower risk. Hence I posit:

**Hypothesis 2:** In a competence-destroying discontinuity, firms with uneven-risk internal markets will invest less than firms with even-risk internal markets in the higher-risk technological variant(s) of the new technology.

Indeed, an uneven-risk internal market will underinvest in the higher-risk technological variant in the new technology not only because the agent allocating resources across projects is risk-averse, but also because such risk-averse agent can engage in winner picking behavior. That means that the underinvestment in the higher-risk technological variant should be reflected not only on total underinvestment, but also on re-allocation of resources away from the higher-risk technological variant over the life of the firm. Hence I posit:

**Hypothesis 3:** In a competence-destroying discontinuity, firms with uneven-risk internal markets will be more likely than firms with even-risk internal markets to discontinue projects in the higher-risk technological variant(s) of the new technology.

#### **4. Industrial Dynamics and Radical Innovation**

The mechanism described above can be seen within the dynamics not only of technological discontinuities but also of competition across incumbents, diversifying and de novo firms. Prior literature concerning investment in the new technology through a discontinuity has paid most attention to incumbents' fear of cannibalization. That is, prior literature has paid most attention to incumbents' disincentives to invest in a new technology when that new technology will erode their previous stream of revenue. That said, once the discontinuity is competence destroying, if incumbents' R&D capabilities were the main barriers to entry into the market, those barriers to entry are gone and entry ensues. Therefore, fear of cannibalization stops deterring incumbents from investment in the new technology: their original stream of revenue will be eroded, whether it is eaten by entrants or cannibalized by themselves. Cannibalization at least allows incumbents a chance to retain the market. Put in other words, if the introduction date of the radical innovation does not depend on incumbent investment, and if the radical innovation obsoletes existing technology, then incumbents and entrants have equivalent incentives to invest (Henderson 1993: 250).

However, even though in competence-destroying discontinuities incumbents and entrants might have equal incentives to invest in the new technology, if the new technology comprises several technological variants, investment behavior across incumbents and entrants might vary. This is precisely because, as explained before, the structure of internal markets affects investment behavior. If incumbents, diversifying and de novo firms vary in the structure of their internal markets, then their investment behavior across technological variants might systematically vary as well. Although internal markets have the advantage of winner-picking dynamics over external markets, as said before they can also have their disadvantage. If internal markets are uneven-risk markets and if the agent allocating resources across projects is risk averse, then winner picking will starve higher-risk projects. The question becomes if

uneven-risk internal markets are more commonly present in incumbents, diversifying and/or de novo firms. If that is the case, the differential distribution of such organizational structure will explain some of the differences in investment behavior across groups of firms through a discontinuity.

To explore that point, it is important to consider the implications of having an even-risk internal market through a discontinuity. Within a single discontinuity, firms are more likely to have an even-risk internal market if they span fewer variants of the new technology. In the extreme, single-variant internal markets are always even-risk internal markets. Spanning fewer technological variants means the resource base of the firm is limited: only those capabilities that directly apply to the few variants considered are necessary. Furthermore, smaller, younger firms are more likely to have smaller portfolios, span fewer technological variants, and own fewer resources and capabilities. As a trend, de novo firms are more likely to be small, young firms with fewer technological variants as their initial target. Thus, de novo firms are as well more likely to have even-risk internal markets. I therefore posit the following hypothesis:

**Hypothesis 4:** In a competence-destroying discontinuity, de novo firms will be more likely to have an even-risk internal market than established firms (both incumbents and diversifying entrants).

Given the abovementioned hypotheses, there are two patterns to conclude for de novo firms within the dynamics of creative destruction. On the one hand, de novo firms concentrate in the technological variant(s) that represents the sub-set of radical innovations where there are fewest capabilities to re-use by any potential competitor. This is because such technological variant(s) represents a plain level field, where de novo firms' disadvantage versus established firms (both incumbents and diversifying entrants) disappear. Therefore, de novo firms should have a preference for investing in the higher-risk technological variant. On the other hand, as posited before, de novo firms are more likely to have even-risk internal markets, a feature in their organizational structure that spares them from re-allocating resources away from the higher-risk technological variant. Therefore, de novo firms should be less likely to discontinue projects in the higher-risk technological variant once they have been started.

Ultimately, de novo firms' behavior in the higher-risk technological variant(s) of the new technology explains their unique role within the dynamics of creative destruction (beyond simply increasing the number of total innovations carried out through the discontinuity). In contrast to established firms, which drive R&D performance in the new technology across the discontinuity, de novo firms drive risk-bearing behavior. Therefore, I posit:

**Hypothesis 5:** In a competence-destroying discontinuity, at the market level, the proportion of projects in the higher-risk technological variant(s) of the new technology carried out by de novo firms will be larger than that carried out by established firms (both incumbents and diversifying entrants).

It remains indeterminate whether the higher-risk technological variant(s) will or will not turn out to be the basis for the R&D of highest-performing products at the end of a discontinuity. Nonetheless, it seems important for the dynamics of creative destruction that some firms absorb the risk of finding that out. It is my proposition in this paper that de novo firms fulfil that particular role thanks to their lack of re-usable capabilities and the presence of their unique organizational structure.

## **5. Data and Methods**

Next I describe the setting and measurements used for hypothesis testing. Additionally, I conducted 45 interviews, each 30-90 minutes long, spanning R&D executives, industry analysts and scientists, to provide background to the study.

### **5.1 The Radical Technological Discontinuity**

I selected as setting for this study the market for anti-cancer drugs and its transition from cytotoxic to targeted drugs. This transition is a consequence of the disruption posed by the biotechnology revolution and has therefore been characterized as a competence-destroying change to the drug discovery part of incumbents' standing value chain (see the discussions of biotechnology's competence-destroying effect on the pharmaceutical industry at large [Rothaermel 2001] and on the anti-cancer drug market in particular [Sosa 2010]). Indeed, the discontinuity has also been shown as sustaining in customer preferences (Sosa 2010) since the dimensions of merit that customers value in new drugs in this modality

have not moved away from efficacy and safety since the birth of drug treatment in oncology in 1949 (Chabner and Roberts 2005).

For the purposes of the present paper, I needed to go beyond the characterization of the new technology (i.e., targeted drugs) in comparison to the old one (i.e., cytotoxic drugs) as a competence-destroying, sustaining change. I also needed to characterize the different variants within the new technology in order to identify among them the one with the highest risk. In the next sections I discuss the three major variants in existence among targeted anti-cancer drugs up to the end of the period of observation, that is, up to 2004: small-molecule drugs, large-molecule drugs, and gene therapy.

## **5.2 Variants in Biotechnology and Capability Re-Use**

As a first step, I needed to identify whether the variants of the new technology had R&D capabilities re-usable by de novo firms' competitors (i.e., by any established firm). The list of possible de novo entrants' competitors with re-usable capabilities includes incumbent firms, since any R&D capabilities that were in use in this market and have not become obsolete due to the discontinuity, could be re-used to incumbents' advantage. That list also includes diversifying entrants, since any capabilities acquired in a firm's previous experience in another market that might be value-adding in the market under disruption, could be re-used to the advantage of these diversifying firms.

I therefore analyze in this section the three main variants of the new technology, each with reference to the presence of re-usable R&D capabilities by at least one competitor of de novo entrants. In doing so, I can then identify the variant with fewest (if any) re-usable capabilities by a competitor of de novo firms. Such variant represents the technological space in which de novo entrants could avoid the disadvantage that their lack of re-usable capabilities at the organizational level represents for them.

**Small-Molecule Drugs.** As discussed in previous research (Sosa 2009, 2010), oncology research is a capability in use in the old technology, well developed by incumbent firms in this market, and that has remained re-usable and highly valuable in anti-cancer drug discovery. Small-molecule drug discovery in this market therefore contains in oncology research a capability re-usable by incumbent firms.

**Large-Molecule Drugs.** As discussed in previous research (Sosa 2010), oncology research as a capability is also re-usable for large-molecule drug discovery. More importantly, that same research showed that biopharmaceutical technology is a capability also valuable and re-usable for large-molecule drug discovery, although this time re-usable not by incumbents but by a sub-set of diversifying entrants. Large-molecule drug discovery therefore contains in biopharmaceutical technology and oncology research two capabilities re-usable by de novo firms' competitors (diversifying entrants and incumbent firms, respectively).

**Gene Therapy Drugs.** Neither prior research nor interview material sustain that there are capabilities to re-use from another modality of drug discovery, whether prior or as part of biotechnology, or from another market (even outside pharmaceuticals) when moving into gene therapy discovery. Thus, gene therapy drug discovery ranks lowest in capability re-use, a key feature I will use in the research design for the present paper.

### **5.3 Variants in Biotechnology and Risk**

Hypotheses 2 and 3 require the identification of the variant among those comprised by the radically new technology, where the risk represented by executing its drug discovery will be highest. Based on interview-based and archival material, I categorized the type of risk reflected in drug discovery into three sets: procedural risk (comprising biohazards for workers, patients' relatives, and the general public), ethical risk (comprising ethical debates), and technological risk (comprising technological uncertainty). I discuss next for each of these three types of risk how each variant fares in comparison to the others, in order to identify which of the variants represents the highest risk (as well as to assess the nature and origin of that risk). Ultimately, given the resolution of procedural and ethical risk by the start of the period of observation (i.e., 1989), gene therapy represents the highest risk among the variants of targeted drug discovery, and that risk is constituted by technological uncertainty only.

**Procedural Risk, its Presence and its Resolution.** Stanley Cohen and Herbert Boyer reported the first experiment with recombinant DNA (rDNA) in 1973 giving birth to recombinant DNA (rDNA) technology (Ryser and Weber, 1990). rDNA technology as a technological platform is used across the

board in biotech-based drug discovery, albeit in differing degrees. In this section I briefly describe the controversy surrounding the birth of rDNA technology and its possible biohazards. Since such controversy resolved before the start of the period of observation, it does not represent a source of differences in levels of risk across the three variants of targeted drugs included in this paper.

In 1974, Paul Berg and ten other US scientists including Cohen and Boyer, called for a moratorium on experiments making use of rDNA. A concern with laboratory biohazards had grown among scientists, especially when Berg took the first steps for an experiment that would give a bacteria commonly found in the human gastrointestinal system the ability to produce potentially cancer-causing genes (Fredrickson, 2001). The consequences of an accidental spill in experiments of this nature for laboratory workers and the general public seemed incommensurable. Although in 1973 a small-scale scientific conference at the Asilomar Conference Center in Monterey, California had discussed initial guidelines, a large-scale conference of international proportions was needed. Such international conference came after the moratorium requested by Berg and colleagues. Now known as the Asilomar conference, it was held in 1975 in the same venue as the previous small meeting. Thanks to this conference and the events it promoted, the risk associated with the use of rDNA technology subsided in the years prior to 1989, the start of the period of observation in the present study. In 1975 the Recombinant DNA Advisory Committee within the US National Institutes of Health (NIHRAC) was established and generated guidelines for rDNA work, adopted internationally, in some cases immediately, such as in the United Kingdom and Germany. By 1978, the US Congress concluded that the guidelines established by the NIHRAC were sufficient to ensure the safety of rDNA work and the debate began to reach closure (Ryser and Weber, 1990). In 1984, the NIHRAC created the Human Gene Therapy Working Group (later called the Human Gene Therapy Subcommittee [HGTS]) and maintained gene therapy as a variant within the same levels of contained procedural risk as other variants of biotechnology.

Therefore, all variants of biotechnology, including all variants of targeted drug discovery for the specific application to anti-cancer drug discovery, represent an equal level of contained procedural risk within the period of observation of the present study.

**Ethical Risk, its Presence and its Resolution.** Beyond the procedural risk and ensuing debate on biohazards that involved all variants of biotechnology, most variants were not faced with a particular ethical debate. Indeed, small- and large-molecule drug discovery have faced no ethical controversy.<sup>5</sup> The same is not true of gene therapy in general and as a variant of cancer treatment in particular. In this section, I offer a summary on the conditions of birth and evolution of gene therapy that gave rise to the ethical debate that accompanied this variant of technology early in its development. I discuss as well the resolution of this risk.

The main precursory events leading to the birth of gene therapy are commonly considered as the discovery of the chemical nature of genes by Avery, McLeod and McCarty in 1944 and of the double-helix structure of DNA by Watson and Crick in 1953 (Lederberg, 1994). By the 1960s, uptake and expression of exogenous DNA in mammalian cells was successful and gene therapy as a variant began its evolution (Friedmann 1992). Indeed, the advent of rDNA technology in the 1970s would speed up the evolution of gene therapy.

At the same time, the 1960s saw the start of the debate around the ethics of gene therapy research. The ethical concern linked gene therapy (and genetic research in general) with eugenics. Eugenics was a movement started in Britain in the 1860s attempting to do for the human race what selective breeding had done to improve plant breeds: selective breeding for the betterment of the species. Eugenics as a movement exploded around the Great Depression in 1929, where beyond preliminary statistics provided by the US, a report in Britain claimed that the rate of mental deficiency in the country had doubled between 1908 and 1929. The conclusion was the need for governmental action. The eugenics movement ultimately led to the sterilization laws of the 1930s enacted in parts of the US, Scandinavian countries, and Nazi Germany (Kevles 1985).

When the concept of gene therapy arose in the 1960s, debate around eugenics ensued again. In 1963, Nobel laureate Crick opened a roundtable discussion on eugenics and genetics at a scientific gathering

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<sup>5</sup> In some cases, ethical debates have emerged regarding commercialization concerns such as the age of administration or the pricing of the resulting drugs in different countries. These ethical debates remain outside of the scope of this study, namely risk within drug discovery.

sponsored by the Ciba Foundation with a thought experiment. He asked the audience to imagine that the government could turn the population temporarily infertile and then, based on biological fit, citizens could obtain a license that would grant them permission to become fertile again and bear children. People with inheritable diseases would be allowed only one child. Others could be encouraged to bear more children. The discussion that followed aggressively debated such resurgence of eugenics, and the possible connection to the emerging fields of genetics and gene therapy (Wolstenholme 1963: 274-277). The concern with the ethics of genetic intervention increased in the 1970s (Nienhuis 2008). Ultimately, the ethical debate surrounding gene therapy resolved by separating somatic gene therapy from germline gene therapy, where the treatment achieved is not inheritable in the former yet inheritable in the latter. Indeed, somatic gene therapy, the type to which gene therapy for cancer treatment pertains, was likened in discourse to surgery, a treatment whose outcome is also not inheritable, turning therefore the variant into a legitimate area of research (Wolff and Lederberg 1994).

**Technological Risk, its Presence and its Progress so far.** It is technological risk, in other words the uncertainty surrounding the technology and its effectiveness in supporting the R&D of high-performing innovations, that has not resolved and makes gene therapy remain as the variant among targeted drugs whose discovery carries the highest risk. Indeed, even in current reports on gene therapy, this variant is described as higher-risk as compared to other variants of targeted drugs:

“As a class, cancer GT [Gene Therapy] interventions (indeed, all GT interventions) are relatively novel... For a variety of reasons, our ability to predict the properties and behavior of gene transfer agents has important limitations” (Kimmelman, 2009: 425).

The author presents a list of reasons behind the high technological uncertainty of gene therapy including: (1) the involvement of active agents that could produce novel pathogens, in contrast to the nature of other drugs as passive compositions of matter; (2) the possibility that both, the vector acting as a delivery device and the actual gene, can trigger a toxic response; (3) the high species specificity of gene therapy that turns current animal models less informative for gene therapy than for any other variant; (4) the dependence of the immunological reaction on previous exposure to the virus acting as delivery device;

(5) in some cases, gene therapy's nonlinear dose-response curves that turn the dose escalation in a traditional phase I study into a highly uncertain process. Furthermore, in the cases of gene therapy delivered through a viral vector (i.e., an engineered virus), the possibility of "bystander risk" (i.e., contagion to the volunteer's social contacts) has not been discarded even if no documented case has occurred (Kimmelman, 2009: 433). Furthermore, the side effects of gene therapy (especially its most common modality, namely viral-vector gene therapy) involve not only toxicity but mutagenesis, that is, the possibility that the gene therapy might affect the DNA of other cells, resulting, as in previously documented cases, in leukemia or other possibly fatal diseases (Cotrim and Baum, 2008). Other authors provide as well reasons to consider gene therapy as a higher risk than other variants (e.g., Flotte, 2007).

Ultimately, Kimmelman (2009) reports that the probability of moving from phase I to II for an anti-cancer drug is generally 77%, with a subsequent probability of 27% of moving from phase I all the way to approval. In contrast, the estimation is that gene therapy in cancer will move from phase I to II with a 20% probability, with a zero probability of moving into approval, at least within the major markets (USA, Europe and Japan).<sup>6</sup>

In summary, gene therapy involves additional sources of technological uncertainty that are not present in any of the other variants of targeted drug discovery. For that reason, gene therapy remains the technological variant within the new technology (targeted anti-cancer drugs) representing the highest risk.

#### **5.4 Sample and Variables**

**Sample.** To identify the set of firms competing in the anti-cancer drug market as it transitions into targeted drug discovery, I started by identifying all firms that had entered an anti-cancer drug in clinical trials in the period 1989-2004 according to PJB Publications' database *Pharmaprojects*. After excluding non-profit organizations, matching all cases to parent company names only, and adjusting for mergers and acquisitions and missing data, I identified 808 firms (of those, 777 firms have information on the specific

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<sup>6</sup> The only gene therapy drug approved, Genedicine®, is a cancer treatment and was approved in China in October, 2003 (Pearson, Jia and Kandachi 2004).

date of entry and exit in clinical trials and hence, event history analyses are based on a 777-firm sample instead).

**Dependent Variables.** In accordance to the hypotheses posited, different dependent variables are needed in each case. I describe here dependent variables for each hypothesis test in question.

Hypothesis 1 requires a measurement of R&D performance. I operationalize R&D performance in this setting in two ways, one based on the quantity and the other on the quality of innovations.

*R&D Performance based on Quantity: Introduction of Targeted Drugs into Trials.* I measured performance in drug discovery by counting the drugs that a firm entered into clinical trials (the start of clinical trials marks the end of the drug discovery phase), using the information in the *Pharmaprojects* database. Because *Pharmaprojects* provides the date when the drug started clinical trials, and because the rate of entering clinical trials might change over the 15 years of observation, I use a Cox regression model (as opposed to a Poisson or Negative Binomial specification) to analyze these data. I implemented the model with each drug representing a repeated event per firm so that it becomes a count model as done in prior research (Sørensen and Stuart 2000).

*R&D Performance based on Quality: Progression of Targeted Drugs towards Approval.* Alternatively, I also measured performance in drug discovery by tracking the advancement towards approval of the drugs that a firm entered into clinical trials, using again the information in the *Pharmaprojects* database. Because *Pharmaprojects* provides the date not only when the drug started clinical trials but also when it was either discontinued or, in few cases, approved, I use also a Cox regression specification, although this time as a single-failure specification.

Hypothesis 2 requires the differentiation of the three technological variants within targeted drugs. I operationalized this difference as follows.

*Technological Variants: Small-Molecule, Large-Molecule and Gene Therapy Targeted Anti-Cancer Drugs.* A post-doctoral fellow at the Medical Research Cancer Laboratory for Molecular Cell Biology at a University in the area assigned all drugs listed in *Pharmaprojects* for anti-cancer drugs to one of four

groups of drugs: cytotoxic, small-molecule targeted, large-molecule targeted, and gene therapy.<sup>7</sup> I then created three dummy variables, *Small-Molecule*, *Large-Molecule*, and *Gene Therapy* based on that information. Because in the end the only technological variant that had a distinguishable level of risk versus others among targeted therapies, I grouped *Small-Molecule* and *Large-Molecule Drugs* as *Targeted, not Gene therapy* in statistical analyses. I analyze the likelihood of a firm to enter one more drugs into clinical trials in gene therapy or targeted not gene therapy as a competing-risks model.

Hypothesis 3 tests the likelihood of discontinuing an R&D project in the higher-risk technological variant. I operationalized this test looking at the likelihood to discontinue a drug whose clinical trials have been started, as follows.

*Discontinuation of Gene Therapy Drugs in Trials.* As done for progression to approval, I recorded the date in which each drug started and ended clinical trials. The event in this case is discontinuation so that approval represents right-censoring, just as discontinuation represented right-censoring when the event was approval (a competing-risks model would require both events to be independent [Petersen, 1995], and approval and discontinuation are not independent events in this setting).

Hypothesis 4 requires the measurement of a firm's internal market as an even- or uneven-risk market as dependent variable (the same variable is an independent variable in the tests for hypotheses 3 and 4). I operationalize this as a continuous variable that measures the proportion of a firm's portfolio of targeted anti-cancer drugs that are gene therapy. I operationalized this dependent variable as follows.

*Even-Risk Internal Markets: Proportion of a Firm's Portfolio of Targeted Drugs Dedicated to Gene Therapy.* Based on the information provided in *Pharmaprojects*, I first identified the total number of targeted drugs that each of the firms in the sample had entered into clinical trials. I then calculated the percentage of those drugs that were gene therapy drugs (see the measurement of gene therapy in the independent variables section). Because this variable is a percentage, therefore bounded between 0 and 1, I analyze the data with a Tobit regression.

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<sup>7</sup> The data made available to the scientist included, among others: generic name and synonyms, pharmacology description, molecular target, origin of material description, molecular weight, chemical name, and information on the molecular structure.

Finally, hypothesis 5 changes level of analysis to look at the market as a whole and see which group of firms accounted for the largest proportion of higher-risk radical innovation. I test this hypothesis through a  $\chi^2$  test of proportions making use again of the variables identifying technological variants as described above, and the variables identifying groups of firms described next.

### **Independent Variables.**

Although many relevant independent variables for the statistical models in this paper are dependent variables in other models and hence, have been listed in the prior section, the profiles of firms are not. I describe next how these profiles were assigned.

*Firm Groups: Incumbent Firms, Diversifying and De Novo Entrants.* The major challenge was the identification of the relevant incumbent firms. These firms must have been present in the market for cytotoxic anti-cancer drugs before the era of biotechnology, which in the anti-cancer drug market started in 1983. Given the frequency of incomplete records prior to 1984, I triangulated records available from the Federal Drug Administration (FDA), the printed collection of the *Physician Desk Reference* (PDR) drug directories for the years 1947-2005, and the Med Ad News' yearly report of *Top Prescription Drugs* in the period 1991-2002 (see Sosa 2009 for further detail). Once I had separated incumbents from entrants, I categorized entrants as diversifying or de novo firms through access to their corporate histories, as described in their company websites. In the end, the 808 firms comprise 8 incumbents, 197 diversifying entrants, and 603 de novo entrants.

### **Control Variables.**

*Drug Discovery Collaboration.* The database *Pharmaprojects* also reports whether the firm responsible for each drug collaborated (whether in a collaborative agreement or a formal joint venture) with another institution(s) in the drug discovery process. Because having access to a collaborator(s) can expedite the process of drug discovery, I created a dummy variable, equal to 1 whenever a collaboration in drug discovery was in place.

*Acquisition from Markets for Technology and Other Outsourcing: Molecule Acquired, Technology Licensed, and Other Research Acquired.* The database *Pharmaprojects* also documents whether the firm

developing a drug acquired some element(s) necessary for that process from another firm or non-profit organization. Such acquisitions could also expedite the process for the developing firm and I therefore needed to build control variables for them. I constructed three dummy variables: *Molecule Acquired* equal to 1 when the molecule of the drug was acquired from another party; *Technology Licensed* equal to 1 when a technological platform was licensed from another party; and *Other Research Acquired* equal to 1 when any other part of drug discovery was acquired or licensed (such as the licensing of an antigen or gene, or the outsourcing of animal studies to another party).

*External Markets: One- or Two-Drug Portfolio.* A dummy equal to 1 if a firm had only one or two drugs in its portfolio on the year when a drug was introduced to clinical trials. This is because prior firms with one- or two-drug portfolios represent single-project firms in this setting (i.e., external markets) and hence exhibit “loser sticking” dynamics. That is, single-project firms insist on funding underperforming projects which would have been terminated in any other firm, because terminating the project implies terminating the firm (see Stein 1997 for the explanation of these dynamics, and Guedj and Scharfstein 2004 for empirical evidence in pharmaceuticals).

*Interferon (UNDER PROGRESS).* A dummy variable equal to 1 if the targeted drug was an interferon. This is because prior research (Kaplan and Murray 2008) has shown this sub-set of targeted drugs had poor results in cancer clinical trials early in its history, and therefore might have experienced fluctuations in investment that could bias analyses when all targeted drugs are included in the regression.

*Sponsor for Clinical Trial Development (UNDER PROGRESS).* A dummy variable equal to 1 if the clinical trials for the drug were sponsored by a firm or institution other than the originating firm as listed in the information available from <http://www.clinicaltrials.gov>, retrieved on March 15 2010.

*R&D Expenditures (UNDER PROGRESS).* I control for the R&D expenditure per firm per year in thousands of US dollars, as documented from *Datastream*. For missing data, I set values to the average of their firm’s firm category for the year in question.

## **6. Analysis and Results**

In this section, I present the test for the hypotheses posited.

Table 1 shows descriptive statistics and a correlation matrix for all variables in the study.

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Insert Table 1  
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Table 2 shows the comparison in R&D performance of all three firm categories. Hypothesis 1 stated that established firms (both incumbents and diversifying entrants) would outperform de novo firms in the R&D of the new technology if the nature of the discontinuity had left former firms with re-usable capabilities. Table 2, Model 1 is thus measured on the sample of targeted drugs only (firms without targeted drugs are included as at risk but right-censored to avoid selection bias). Model 1 measures R&D performance based on quantity and shows how established firms have an advantage over de novo entrants (the coefficients “incumbent” and “diversifying” are statistically significantly  $> 1$  in a model where de novo firms are the omitted category). Model 3 measures R&D performance based on quality and shows the same result: established firms outperform de novo entrants (again, the coefficients “incumbent” and “diversifying” are statistically significantly  $> 1$  in a model where de novo firms are the omitted category). Furthermore, Model 2 repeats Model 1 but now controlling for gene therapy, the variant where established firms have no re-usable capabilities, supporting the same conclusions. These models therefore lend support to hypothesis 1.

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Insert Table 2  
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Hypothesis 2 posited that firms with uneven-risk internal markets would invest less than firms with even-risk internal markets, in the higher-risk technological variant of the new technology (namely, gene therapy). Table 3, Model 1 shows the sorting of firms across the three technological variants: cytotoxic, targeted but not gene therapy, and gene therapy. Gene therapy drugs are more likely to come from more even-risk internal markets, lending support to hypothesis 2.

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Insert Table 3  
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Hypothesis 3 further stated that firms with uneven-risk internal markets would also be more likely to discontinue projects in the higher-risk variant. Table 4, Model 1 shows a Cox regression predicting the likelihood of discontinuation, using only gene therapy projects as the appropriate sample. Firms with more even-risk internal markets are less likely to discontinue any given gene therapy drug once in clinical trials (the coefficient for “proportion of a firm’s portfolio of targeted drugs dedicated to gene therapy” is statistically significantly  $< 1$ ).

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Insert Table 4  
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Hypothesis 4 then related the state of a firm’s internal market as even-risk to the fact that the firm was a de novo firm. This hypothesis stated that de novo firms would be more likely to be even-risk internal markets in part because de novo firms tend to be smaller, younger firms. Figure 1 shows the distribution of size (in number of employees) of the three firm categories as of 2004, the end of the period of observation. The horizontal axis is simply a binary variable distinguishing incumbency from entry. Within each quadrant the horizontal distance is used simply for visual purposes. As Figure 1 shows, de novo firms tend to be smaller firms. Figure 2 replicates the pattern in Figure 1 now based on organizational age. Again, de novo firms tend to be younger than their competitors.

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Insert Figure 1  
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Insert Figure 2  
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Furthermore, I constructed a statistical test for hypothesis 4. As discussed in section 5.3, the only variant of targeted drugs with higher risk is gene therapy. Hence, by definition, firms that house

portfolios of only targeted, not gene therapy drugs are even-risk internal markets. The question becomes what happens when the firm chooses to also invest in gene therapy: does it house gene therapy drugs in portfolios comprising large proportions of other variants of targeted drugs? Therefore, to test hypothesis 4, I took the sample of firms investing in gene therapy drugs and tested whether in those cases, de novo firms were more likely than either of their established firm counterparts (incumbents and diversifying firms) to house gene therapy drugs within portfolios heavily dedicated to gene therapy. Table 5, Model 1 supports this pattern. Established firms have smaller portions of their portfolios of targeted drugs dedicated to gene therapy, when they invest in gene therapy, as compared to the omitted category, which is de novo firms (the coefficients for “incumbent” and “diversifying” are both negative and significant).

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Insert Table 5  
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Indeed, when replacing the proxy for even-risk internal market with measures of the firm categories in previous models, the relationships hold. That is the case for Table 3, Model 2 (in support of hypothesis 2) and Table 4, Model 2 (in support of hypothesis 3).

Lastly, hypothesis 5 posited that, in the dynamics of the market as a whole, de novo firms would carry out the largest proportion of the higher-risk projects in the new technology. Table 6 shows a test of proportions at the market level, lending support to hypothesis 5: de novo firms do carry out the largest proportion of gene therapy in the anti-cancer drug market, disproportionately so when compared to the proportion of targeted, not gene therapy drugs carried out by the same groups of firms.

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Insert Table 6  
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## **7. Discussion**

I started this paper with one main research question: what role do de novo firms play in the dynamics of creative destruction? I showed how de novo firms seemed the lowest performing in the R&D of radical innovation when compared to the average performance of incumbents and of diversifying entrants

through a discontinuity. I then proceeded to investigate what the role of de novo firms could be at the market level, if it is not as drivers of R&D performance. I found evidence in this paper to support the proposition that de novo firms, although least productive in radical innovation, carry out the largest proportion of the sub-set of radical innovations with the highest risk. This latter then turns out to be the role that these firms play in the dynamics of creative destruction. Established firms (incumbents and diversifying entrants) drive performance in the R&D of radical innovation thanks to their re-use of organizational capabilities. In contrast, de novo firms bear the most risk in the R&D of radical innovation in part thanks to their unique organizational structure. Such particular roles for established and de novo firms give rise to a division of labor through a discontinuity.

Putting forth an answer to the question of what the unique role of de novo firms is in the dynamics of creative destruction has implications for strategy and innovation policy. As recent research has shown, increasingly, de novo firms are becoming both partners (e.g., Lerner and Merges 1998) and technology suppliers (e.g., Arora, Fosfuri and Gambardella 2004) of established firms (whether incumbent or diversifying entrants). Characterizing the sources of competitive advantage and disadvantage for de novo firms and their established counterparts can help both sides engage in more effective formal and informal contractual arrangements. Likewise, characterizing the patterns of activity that are most successful for de novo firms can help develop more appropriate governmental and non-profit programs to support these firms' establishment and growth.

Beyond the immediate implications of the findings in this paper for strategy and innovation policy, these findings have broader implications for research on organizational structure regarding internal vs. external markets. By analyzing the contrast between firms dedicated to one vs. multiple technological variants during a technological discontinuity, I have presented the resource analog to the dynamics argued for single- vs. multi-market firms (e.g., Argyres and Silverman 2004). Understanding the advantages and disadvantages of multi-market firm structure aids optimal value creation across markets at a given point in time. Complementary to it, the same understanding in the case of firms dedicated to single- vs. multi-variant technological development during a discontinuity can aid optimal value creation across

technological discontinuities and hence, over time. Both perspectives together can advance therefore research in strategy formulation into a fuller view that takes cross-sectional and longitudinal issues into account.

In the end, the research presented in this paper takes one more step into our understanding of the separate though intertwined effect of strategy and structure (Chandler 1969) on heterogeneity in firm performance.

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## Tables

**Table 1**  
**Descriptive Statistics and Correlation Matrix**

	count	mean	std. dev.	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
(1) Small-Molecule Targeted Anti-Cancer Drug	2,068			1											
(2) Large-Molecule Targeted Anti-Cancer Drug	1,408			-0.51	1										
(3) Gene Therapy Targeted Anti-Cancer Drug	270			0.06	0.03	1									
(4) Proportion of a Firm's Portfolio of Targeted Drugs Dedicated to Gene Therapy		0.05	0.19	0.08	0.04	0.84	1								
(5) Incumbent Firm	769			0.03	-0.07	-0.08	-0.10	1							
(6) Diversifying Entrant	2,016			-0.09	0.04	-0.04	-0.06	-0.34	1						
(7) De Novo Entrant	2,335			0.06	0.01	0.10	0.13	-0.38	-0.74	1					
(8) Drug Discovery Collaboration	644			-0.04	0.04	0.03	0.01	-0.03	-0.02	0.04	1				
(9) Molecule Acquired	403			-0.00	-0.01	-0.03	-0.02	-0.07	-0.04	0.09	-0.02	1			
(10) Technology Licensed	108			0.00	0.03	0.07	0.07	-0.05	-0.05	0.09	-0.02	0.01	1		
(11) Other Research Acquired	46			0.03	-0.01	0.01	0.00	-0.02	-0.03	0.04	0.04	0.15	0.01	1	
(12) One- or Two-Drug Portfolio	551			-0.04	0.02	0.01	0.02	-0.15	-0.15	0.25	-0.02	0.04	-0.01	-0.01	1

**Table 2**  
**R&D Performance**  
**Cox Model Analysis**  
All Coefficients in *Hazard Rates*  
Targeted Drugs Only

	<i>Event: Enter Drug in Clinical Trials Repeated Events Per Firm (Count Model)</i>		<i>Event: Approval at End of Clinical Trials Single-Failure Analysis</i>
	<b>Model 1</b>	<b>Model 2</b>	<b>Model 3</b>
Incumbent	6.90*** (1.57)	7.15*** (1.65)	2.90*** (0.90)
Diversifying	2.11*** (0.25)	2.17*** (0.26)	2.44*** (0.62)
Drug Discovery Collaboration	1.15+ (0.10)	1.16+ (0.10)	1.04 (0.31)
Molecule Acquired	1.26* (0.14)	1.28* (0.14)	1.28 (0.40)
Technology Licensed	1.20 (0.16)	1.18 (0.16)	1.34 (0.65)
Other Research Acquired	1.32 (0.30)	1.33 (0.29)	0.82 (0.60)
One- or Two-Drug Portfolio	0.18*** (0.01)	0.18*** (0.01)	1.22 (0.70)
Gene Therapy		1.32* (0.18)	
Incumbent X Gene Therapy		0.48** (0.14)	
Diversifying X Gene Therapy		0.78 (0.19)	
Spells	3,086	3,086	2,944
Events	2,944	2,944	82
Subjects	777	777	
Log Likelihood	-16,895	-16,889	-486

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

**Table 3**  
**Sorting across Technological Variants**  
**Multinomial Logit Regression**

Base Outcome is *Targeted, Not Gene Therapy Drugs*  
 Std. Errors Clustered by Firm

	Model 1		Model 2	
	Cytotoxic Drugs	Gene Therapy Drugs	Cytotoxic Drugs	Gene Therapy Drugs
Constant	-0.63*** (0.07)	-4.51*** (0.27)	-0.92*** (0.08)	-2.17*** (0.21)
Proportion of a Firm's Portfolio of Targeted Drugs Dedicated to Gene Therapy	-594.69*** (18.69)	9.84*** (0.62)		
Incumbent			0.31+ (0.20)	-2.27*** (0.48)
Diversifying			0.32** (0.12)	-0.54+ (0.30)
Drug Discovery Collaboration	0.01 (0.11)	0.77** (0.28)	0.03 (0.11)	0.30+ (0.17)
Molecule Acquired	0.06 (0.13)	-2.17** (0.76)	0.12 (0.13)	-0.91** (0.32)
Technology Licensed	-0.41 (0.26)	1.27** (0.41)	-0.34 (0.27)	1.01*** (0.30)
Other Research Acquired	-0.48 (0.37)	1.17* (0.56)	-0.44 (0.36)	0.50 (0.52)
One- or Two-Drug Portfolio	0.04 (0.12)	-1.16* (0.59)	0.25* (0.12)	-0.05 (0.27)
Interferon Sponsor for Clinical Trials				
R&D Expenditures				
N	5,120		5,120	
Firms	808		808	
Pseudo-R <sup>2</sup>	0.20		0.02	

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

**Table 4**  
**Discontinuation of Gene Therapy Drugs**  
**Cox Model Analysis**  
**Event: Discontinuation from Clinical Trials**  
**Single-Failure Analysis**  
All Coefficients in *Hazard Rates*  
Gene Therapy Drugs Only

	Model 1	Model 2
Proportion of a Firm's Portfolio of Targeted Drugs Dedicated to Gene Therapy	0.36*** (0.08)	
Incumbent		2.40* (1.02)
Diversifying		1.37+ (0.23)
Drug Discovery Collaboration	1.13 (0.21)	1.01 (0.20)
Molecule Acquired	0.54 (0.23)	0.49+ (0.20)
Technology Licensed	0.74 (0.22)	0.75 (0.22)
Other Research Acquired	0.43 (0.23)	0.62 (0.33)
One- or Two-Drug Portfolio	1.61+ (0.45)	1.30 (0.34)
Interferon		
Sponsor for Clinical Trials		
R&D Expenditures		
Spells	260	260
Events	181	181
Log Likelihood	-859	-836

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

**Table 5**  
**Proportion of a Firm's Portfolio of Targeted Drugs**  
**Dedicated to Gene Therapy**  
**Tobit Regression**  
 Robust Standard Errors

	<b>All Targeted</b>
	<b>Model 1</b>
Incumbent	-0.56*** (0.06)
Diversifying	-0.28*** (0.09)
One- or Two-Drug Portfolio	3.23 (--)
N	110
Pseudo-R <sup>2</sup>	0.37

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

**Table 6**  
**Proportions of Total Gene Therapy in the Market Carried Out by**  
**Firm Group**  
 $\chi^2$  Test of Proportions

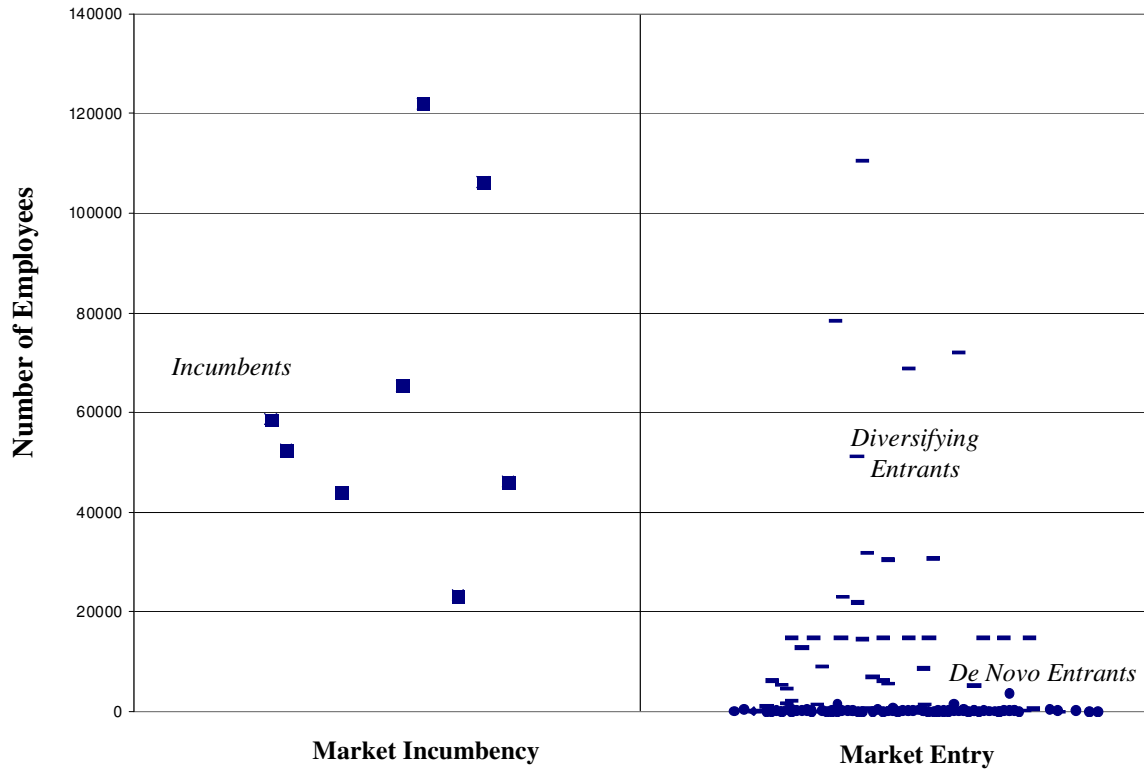
	<b>Cytotoxic</b>	<b>Targeted, Not Gene Therapy</b>	<b>Gene Therapy</b>
<b>Incumbent</b>	270 (17%)	493 (15%)	6 (2%)
<b>Diversifying</b>	695 (43%)	1,237 (38%)	84 (31%)
<b>De Novo</b>	639 (40%)	1,516 (47%)	180 (67%)
<b>Total</b>	1,604 (100%)	3,246 (100%)	270 (100%)

Pearson  $\chi^2(4) = 84.2, p < 0.0001$

Figures

**Figure 1**  
**Distribution of Firms Competing in Targeted Anti-Cancer Drugs**  
**by Firm Group and Size as of Year 2004 (End of Period of Observation)**

(■ incumbent, — diversifying entrant, • de novo entrant)



**Figure 2**  
**Distribution of Firms Competing in Targeted Anti-Cancer Drugs**  
**by Firm Group and Age as of Year 2004 (End of Period of Observation)**

(■ incumbent, — diversifying entrant, ● de novo entrant)

