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DECODING THE ADAPTABILITY–RIGIDITY PUZZLE: EVIDENCE FROM PHARMACEUTICAL INCUMBENTS' PURSUIT OF GENE THERAPY AND MONOCLONAL ANTIBODIES

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The emergence of radical technologies presents a significant challenge to incumbent firms. We study firms' management of radical technological change by separating their actions into upstream research (the "R" of R&D) and downstream development (the "D" of R&D). We introduce two contingencies to explain when incumbents' research investments in radical technologies translate into product development and when these upstream investments may get voided by organizational inertia downstream. First, radical technologies can differ in how they conform to incumbents' existing business models, impacting the extent to which the movement of research outputs toward development will be subject to inertial pressures. Second, incumbents can invest in a radical technology through a variety of modes (internal research, external research contracts, alliances, acquisitions). These modes represent unique combinations of who does research and who is involved in the decision for subsequent development, and, hence, differ in the extent to which they are shielded from inertial pressures. This difference helps explain why incumbents, despite responding to radical technologies, may still be unable to adapt, as well as what types of investments will be more effective in helping firms navigate technological change. Evidence from pharmaceutical incumbents' pursuit of monoclonal antibodies and gene therapy offers strong support for our arguments.

INTRODUCTION

The emergence of radical technological regimes renders obsolete the value of incumbent firms' existing competences and presents a significant challenge to their long-term sustainability (Cooper & Schendel, 1976; Hill & Rothaermel, 2003; Tushman & Anderson, 1986). Incumbents have been shown to successfully adapt if they invest in new technologies and possess complementary assets that are necessary for the technology's commercialization (e.g., Rothaermel, 2001; Tripsas, 1997). Yet, established firms such as Kodak, National Cash Register (NCR), and Polaroid, despite investing in new technologies and having access to complementary assets, faced great difficulties in managing technological change (e.g., Christensen, 2006; Rosenbloom, 2000; Taylor & Helfat, 2009; Tripsas & Gavetti, 2000). In this study, we shed light on this puzzle by explaining when incumbents' well-intended investments in a radical technological regime are likely to facilitate adaptation, and when these

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investments may get voided by the forces of organizational inertia.[1]

We explore how incumbents manage radical technological change by drawing on the important distinction between "invention" and "innovation" (Freeman & Soete, 1997; Schumpeter, 1934). This distinction helps separate firms' responses into research efforts toward creation of new knowledge (i.e., invention) and the development efforts toward commercialization of the new knowledge (i.e., innovation). We focus on the decision to initiate product development following research investments. This decision represents a significant step for established firms because the translation of research discoveries into commercial products entails substantial commitment and support from a variety of organizational actors and functions (Burgelman & Sayles, 1988; Dougherty, 1992; Katz & Allen, 1984; Rosenbloom, 2000). While research discoveries may constitute important technological advances, established firms may not move them toward development, thereby affecting the firms' ability to adapt to radical technological change. Shedding light on the "adaptability–rigidity puzzle," we introduce two contingencies that, we argue, affect the likelihood that a firm's research investment in a radical technological regime will lead to product development.

First, although all radical technological regimes require that incumbents undertake research investments, these regimes can differ in the extent to which they conform to the incumbents' existing business model in terms of how they generate revenues and appropriate profits (Abernathy & Clark, 1985; Christensen & Raynor, 2003). Some radical technological regimes may be *sustaining* and conform to the prevailing business models, whereas others may be *disruptive*. For example, monoclonal antibodies (mAbs) and gene therapy (GT) are two radical technological regimes that emerged in the pharmaceutical industry during the 1990s. MAbs represent a sustaining technological regime because they, like traditional chemistry-based alternatives, are often prescribed as long-term medical treatments and result in recurring costs for patients and insurers. In contrast, GT represents a disruptive technological regime because gene therapies are typically one-off or significantly less frequent customized treatments, resulting in major challenges in pricing and reimbursement (Wilson, 2012). We argue that this difference between radical technologies is an important but underexplored source of organizational inertia associated with incumbents' decisions to develop radical technologies following research investments.

Second, beyond the technological contingency, we consider the different organizational modes by which incumbents can invest in radical technologies. While the extant literature has tended to focus on in-house research investments (e.g., Chesbrough & Rosenbloom, 2002; Henderson & Clark, 1990; Tripsas & Gavetti, 2000), incumbents increasingly also access and build on external knowledge from entrants and research organizations (i.e., universities, dedicated research institutes) through the use of research contracts, research alliances and technology acquisitions (e.g., Nicholls-Nixon & Woo, 2003). These different modes represent unique combinations of who does the research (in-house research unit, acquired research unit, contracted research unit, joint research team) and who is involved in the decision for subsequent development (incumbents, alliance partners, acquired start-ups).

We argue that the decisions to pursue development following in-house and contract research are strongly influenced by the cognition and incentives of managers as well as the resource allocation processes within incumbent firms. While these organizational characteristics facilitate firms' development of sustaining technologies, they induce inertial pressures when the technological regime is disruptive and make it more difficult to garner resources and support for subsequent development. Hence, investments in in-house and contract research will less likely lead to development when the technological regime is disruptive than when it is sustaining. In contrast, the development decisions following research alliances and acquisitions will be shielded from inertial pressures. This is because these decisions involve outside partners or personnel from start-ups and research organizations, and tend to be structurally separated from the internal incumbent organization (Hill & Rothaermel, 2003; Schweizer, 2005; Steensma & Corley, 2000). Therefore, for disruptive technological regimes, investments in alliances and

[1] We use the terms "technological regime" and "technologies" interchangeably to refer to specific knowledge bases and/or procedures as solutions to relevant problems within a given context (Anderson & Tushman, 1990; Dosi, 1982; Nelson & Winter, 1982). Note that while "technology" may sometimes be confounded with a physical artifact (e.g., steamship, cell phone), "technological regime" provides greater generalizability and is more consistent with our empirical context (e.g., Nicholls-Nixon & Woo, 2003; Pisano, 1990).

acquisitions will more likely lead to development than will investments in contract and in-house research.

We explore our arguments in the context of the pharmaceutical industry from 1989 to 2008, when the industry witnessed two of the most promising therapeutic approaches based on genetic engineering: mAbs and GT. Incumbent firms had access to the specialized complementary assets such as capabilities in clinical development, relationships with health care service providers, and sales teams that are required for the commercialization of both mAbs and GT. Incumbents responded to the emergence of these radical technologies by investing in both technologies. These investments were directed toward their internal research units as well as toward biotechnology entrants and research organizations through research contracts, alliances, and acquisitions. While mAbs sustained the existing business model of incumbent firms, GT was disruptive. Hence, this context presents a research setting in which two radical technologies emerged around the same time and were pursued by incumbents through a variety of modes, but differed in how each conformed to the incumbents' prevailing business models.

We assembled a unique panel dataset that included information on incumbents' research investments and drug development for mAbs and GT over approximately two decades. In addition, we conducted semi-structured interviews with senior industry professionals to build an in-depth understanding of our empirical context and corroborate our findings. Consistent with our arguments, while investments in in-house and contract research resulted in incumbent firms initiating drug development for mAbs, no such effect was found for GT. In our interviews, we learnt why, as compared to drug development decisions in mAbs, those in GT were subject to greater skepticism and scrutiny by strategic decision makers, making it difficult to move in-house research discoveries toward drug development. We further learnt that, while incumbents use contract research to access external knowledge, the subsequent development decisions remain internal, explaining why investments in contract research in GT also did not readily translate into development. In contrast to investments in in-house and contract research, those in alliances and acquisitions resulted in incumbents initiating drug development for GT. Our interviewees helped to shed light on this finding. They mentioned that, unlike in contract research, development decisions in alliances are collectively made by the incumbents and their partners (typically, start-ups and universities with strong incentives to commercialize research). They also explained how, as compared to in-house research units, incumbent firms pursue a hands-off approach with acquired research units, and ensure that the scientists and managers of the acquired biotechnology start-ups remain involved in strategic decision making. This shields the acquired research units from inertial pressures faced by in-house research units.

Our findings also help clarify a frequent misconception that incumbents tend to not invest in disruptive technological regimes. As documented in several case studies (e.g., Christensen, 1997; Gilbert, 2005; Tripsas & Gavetti, 2000), incumbents often do invest in such regimes. However, as our results show, many of the initial research investments in the form of in-house and contract research may not lead to development and commercialization. This suggests that the locus of incumbents' inertia is not necessarily at the initial stage of research but rather at the later stage of development, and that research alliances and acquisitions may help firms overcome that inertia.

To our knowledge, this study is a first attempt to systematically identify the different organizational modes by which incumbents may invest in radical technologies while accounting for the possibility that, beyond competence destruction, radical technologies may also not conform to the incumbents' business models. This allows us to offer a framework that introduces new organizational and technological contingencies to explain when incumbents' investments in a radical technology are likely to facilitate adaptation and when they may succumb to the forces of organizational inertia. In so doing, the study reaffirms the value of moving beyond incumbent adaptability versus incumbent rigidity to how these organizational features are intertwined during periods of technological change.

HYPOTHESES DEVELOPMENT

The emergence of radical technological regimes presents a significant threat to the sustainability of industry incumbents. These regimes introduce novel methods and materials derived from knowledge domains that are entirely different from those of established firms (Freeman & Soete, 1997; Hill & Rothaermel, 2003). A large body of literature has examined how radical technological change impacts incumbents. Earlier studies emphasized incumbents' entrenchment in the existing technology and

their failure to invest in the emerging technology (Cooper & Schendel, 1976; Foster, 1986; Utterback, 1994). Recent studies, however, have consistently found incumbents to be more responsive to and to invest in the radical technology (e.g., Eggers & Kaplan, 2009; Rothaermel, 2001; Tripsas, 1997). Within this research stream, the adaptability of incumbents in the face of technological change has been attributed to their ability to leverage their specialized complementary assets that are necessary for the commercialization of the new technology. Therefore, investments in radical technologies, coupled with access to specialized complementary assets, are generally theorized to facilitate adaptation (Hill & Rothaermel, 2003). Contrary to this expectation, there are documented cases in which incumbents, despite investing in radical technologies and having access to complementary assets, faced great difficulties in managing technological change (Cooper & Schendel, 1976; Rosenbloom, 2000; Taylor & Helfat, 2009; Tripsas & Gavetti, 2000). Such empirical irregularities have led to doubts about the external validity of several studies and our general understanding of the impact of technological change on incumbents (e.g., Chesbrough, 2001; Christensen, 2006).

In this study, we explore how incumbent firms manage radical technological change by drawing on the important distinction between invention and innovation (Freeman & Soete, 1997; Schumpeter, 1934). Specifically, we separate incumbents' research efforts toward creation of new knowledge (invention) from their development efforts toward commercialization of new knowledge (innovation). This allows us to explicitly consider the challenges incumbents might face in translating their research investments into product innovations (Abernathy & Clark, 1985; Rosenbloom, 2000).[2] For example, John Seely Brown, chief scientist of Xerox Corporation and director of the Xerox Palo Alto Research Center, discussed the challenges Xerox faced in converting research outputs into products as follows:

> Not everything we start ends up fitting with our business later on. Many of the ideas we work on here involve a paradigm shift in order to deliver value. So sometimes we must work particularly hard to find the "architecture of the revenues." ... [H]ere at Xerox, there has been a growing appreciation for the struggle to create a value proposition for our research output, and for the fact that this struggle is as valuable as inventing the technology itself.
>
> (Chesbrough & Rosenbloom, 2002)

We focus on incumbents' product development decisions following their research investments in a radical technology. Traditionally, such decisions have been viewed through the lens of incumbents' internal research investments (e.g., Chesbrough & Rosenbloom, 2002; Henderson & Clark, 1990; Leonard-Barton, 1992; Tripsas & Gavetti, 2000). Beyond their in-house research units, however, incumbents increasingly access and build on knowledge from entrants and research organizations through the use of research contracts, research alliances, and technology acquisitions (Anand, Oriani, & Vassolo, 2010; Nicholls-Nixon & Woo, 2003; Rothaermel, 2001). In the following sections, we develop predictions regarding the extent to which these different modes of incumbents' research investments lead to subsequent product development.

Incumbent Inertia with Respect to Product Development: Investments in In-house and Contract Research

In-house research. Incumbents undertake significant in-house research in the face of technological change (Gambardella, 1992). As such, the literature has often theorized about and observed incumbents' pursuit of new technologies through their internal research units (e.g., Henderson, 1993; Kaplan, 2008; Tripsas & Gavetti, 2000). Internal research investments are deeply embedded within the existing organization. Once research discoveries are made by in-house scientists and engineers, managers evaluate the commercial opportunities and decide whether and how to support them through product development and commercialization initiatives. These decisions are shaped by the incentive structures of how managers are rewarded and the

[2] The distinction between "invention" and "innovation," and viewing technological advance as being initiated through a research stage that is followed by a development stage leading to product commercialization, has been the focus of many studies in management (Macher & Boerner, 2012), marketing (Chandy, Hopstaken, Narasimhan, & Prabhu, 2006), and operations (Girotra, Terwiesch, & Ulrich, 2007). Sometimes, this sequential process is also referred to as "innovation" or a "product development value chain" (Hansen & Birkinshaw, 2007; Roper, Du, & Love, 2008). We use the terms "development" and "product development" interchangeably to both capture the dichotomy between research and development and reflect that "development" typically entails the development of a product.

cognitive frames in which they view the commercial opportunities (Kaplan & Henderson, 2005). Moreover, such decisions are subject to firms' internal resource allocation processes, which are bound by resource dependencies with existing customers, investors, and suppliers (Burgelman, 1994; Christensen & Bower, 1996). Hence, having invested in in-house research, the subsequent product development is shaped by the internal incentives and the cognition of strategic decision makers, as well as the resource-allocation organizational processes.

All radical technological regimes require incumbent firms to undertake research investments to build new competences. However, these regimes may differ in the extent to which they conform to the firms' prevailing business models in terms of how they generate revenues and appropriate profits. A sustaining technological regime embraces a firm's existing model of generating revenues and profits (e.g., Christensen & Raynor, 2003).[3] For example, the emergence of wireless telephony represented a sustaining technological regime because it provided wireline telephone companies with a higher per-minute rate by building a network along the routes of their existing, most attractive, and least price-sensitive customers (Christensen, 2006: 49). In a similar vein, the emergence of monoclonal antibodies (mAbs) in the pharmaceutical industry is a case of a sustaining technological regime. MAbs-based therapies, like traditional chemistry-based therapeutic alternatives, are targeted at the mass market and prescribed as long-term treatments, resulting in recurring costs for patients and insurers. They are fairly easy to administer at home or in health care facilities. Consider that Humira, one of the best-selling mAbs drugs, is prescribed at a cost of about $20,000 to $30,000 per year per patient, can be administered at home through pre-loaded pens, and is targeted at many different major diseases, such as rheumatoid arthritis and Crohn's disease (Miller & Feldman, 2006). Recognizing the new commercial opportunities within the context of their existing business model, incumbents would have strong incentives to pursue product development following their internal research investments in sustaining technologies (Chesbrough & Rosenbloom, 2002; Christensen, 2006).

In contrast, a disruptive technological regime represents a case in which the new regime does not conform to the existing business model of how incumbents generate revenue and appropriate profits. For example, the emergence of radial technology in the U.S. tire industry offered superior performance (longer wear, better gas mileage) compared to the then existing bias-ply tires. However, longer life meant a drastic reduction in the number of tires used by an automobile over its lifetime and a corresponding decrease in the demand for tires (Sull, Tedlow, & Rosenbloom, 1997). Moreover, this reduction in demand only affected the replacement market segment, shifting the distribution of tire manufacturers' sales toward the unprofitable original equipment automobile manufacturer segment. Similarly, the emergence of gene therapy (GT) represents a case of a disruptive technological regime for pharmaceutical incumbents. Gene therapies are typically one-off or significantly less frequent customized treatments for patients with genetic disorders, and they are administered by specialized physicians. Consider an application of GT to treat hemophilia A and B. The current treatments for these illnesses are based on regularly prescribed protein replacement drugs that can be administered at home. GT treatment, predicated on a one-time injection administered by specialized physicians, not only threatens the annual $6.5 billion protein replacement market, but also presents a lack of clarity regarding how such treatments would be priced and reimbursed (Wilson, 2012). A recent example is Glybera, a GT solution commercialized by uniQure for treating lipoprotein lipase deficiency. uniQure and insurers faced significant challenges pricing this treatment for a small patient population (e.g., Brennan & Wilson, 2014).

The lack of conformance to the prevailing business model may make it difficult for in-house research discoveries to garner additional organizational resources and attention for subsequent product development. As a case in point, NCR initiated in-house research in electronics as early as 1938 to manage the transition from mechanical office equipment to electronic computing. The mechanical office equipment business was based on selling thousands of units at prices ranging from one to a few thousand dollars each. In contrast, the

[3] We note that the characterization of a new technological regime with respect to the incumbent's business model was not present in Christensen's early publications on this topic (e.g., Christensen, 1997; Christensen & Rosenbloom, 1995), but was a result of subsequent refinement (Christensen, 2006; Christensen & Raynor, 2003). Note also that this characterization has its roots in the earlier seminal paper by Abernathy and Clark (1985), who used the notion of "market transilience" to consider a similar effect.

computing business entailed selling a small number of systems for hundreds of thousands of dollars apiece. This difference made it difficult for research discoveries within the computing technology to get the necessary resources for product development, leading to substantial delays in the technology's commercialization (Rosenbloom, 2000).[4] These inertial pressures are exacerbated because product development tends to be highly routinized in incumbent firms (Dougherty, 1992; Henderson & Clark, 1990), and the development decisions following internal research investments will likely be subject to routine rigidity when the radical technology does not fit with the existing business model (Gilbert, 2005). At the same time, the presence of alternative technological solutions to those within disruptive technological regimes may require firms to make trade-offs in their resource allocation, which may further diminish the prospects for initiating product development in such technologies (Burgelman, 1994).

In summary, even though incumbent firms are often aware of the radical technology and respond to the threat by undertaking in-house research, those research investments may not easily translate to subsequent product development when the technological regime is disruptive. Therefore, firms' in-house research investments will less likely result in development when the radical technological regime is disruptive than when it is sustaining.

Hypothesis 1. In the face of radical technological change, incumbent firms' investments in internal research will less likely lead to development when the radical technological regime is disruptive than when it is sustaining.

Contract research. Beyond internal research, incumbents draw on start-ups and research organizations to access knowledge underlying new technological regimes (Pisano, 1990; Rothaermel, 2001). An increasingly common approach is the use of contract research to access external knowledge through markets (Arora, Fosfuri, & Gambardella, 2001). As compared to in-house research, in which inventions are generated internally, contract research shifts the locus of invention outside the incumbent's boundary to start-ups or research organizations that are at the leading edge of the technological advance (Nicholls-Nixon & Woo, 2003; Rothaermel, 2001).

Contract research involves an incumbent firm outsourcing a given R&D project and/or licensing a specific intellectual property (IP) with the goal of adding new knowledge to the firm (Leone & Reichstein, 2012; Markman, Gianiodis, Phan, & Balkin, 2005). Once the firm has secured access to the externally developed knowledge in exchange for money, the decisions regarding subsequent product development and commercialization lie with the incumbent firm (Dechenaux, Thursby, & Thursby, 2009). This feature of contract research makes it similar to in-house research, as, in both cases, incumbent firms are solely responsible for the product development and commercialization of inventions. Hence, as with in-house research, the development activities following contract research will be subject to incentive structures, cognition of managers, and resource allocation processes within the incumbent organization.

Accordingly, the product development decisions for disruptive technological regimes following investments in contract research will encounter similar rigidity-inducing organizational processes to those following in-house research. Moreover, upon commercialization of licensed IP obtained through contract research, firms make royalty payments to the licensor (Leone & Reichstein, 2012). This can further diminish their incentives to initiate product development for the new technology with an unproven business model. While contract research has often been proclaimed a solution for incumbents in managing radical technological change (Nicholls-Nixon & Woo, 2003; Pisano, 1990), contract research investments may be less readily translated into product development when the technological regime is disruptive than when it is sustaining.

Hypothesis 2. In the face of radical technological change, incumbent firms' investments in contract research will less likely lead to development when the radical technological regime is disruptive than when it is sustaining.

So far, we have argued that incumbent firms' translation of in-house and contract research investments into product development is subject to organizational inertia when the radical technological regime is disruptive. The inertial pressures stem from the incentive structures and cognition of firms' managers, as well as their resource allocation processes. We next consider how investments in research alliances and acquisitions might be able to overcome these inertial pressures.

[4] Taylor and Helfat (2009) offer a rich exposition of how the actions of middle managers at NCR were shaped by economic incentives, social context, organizational structure, and cognition, making NCR's transition to electronic computing very difficult.

Overcoming Incumbent Inertia: Investments in Research Alliances and Acquisitions

Research alliances. Incumbents frequently engage in bilateral research alliances, where they partner with new entrants or universities to jointly pursue research in radical technologies (Anand et al., 2010; Rothaermel, 2001). Research alliances are distinct from research contracts in several important aspects (Kale & Singh, 2009). Whereas research contracts involve transfer of IP in exchange for money, alliances involve partners jointly pooling their resources to discover new technological solutions (Hagedoorn, 2002).[5] Research alliances are typically characterized by a dedicated decision-making and governance structure that comprises technical and managerial personnel from partners (Steensma & Corley, 2000). In some cases, research alliances are carried out through a joint venture (i.e., a separate legal entity). Therefore, unlike in contract research, critical decisions regarding product development within a research alliance will be driven not only by incumbents, but also by the outside partners (i.e., start-ups or research organizations). These partners are not subject to the incumbents' cognitive constraints, and they have strong incentives to commercialize their research despite an unproven business model.

Moreover, research alliances involving incumbent firms are often governed by middle managers, who are less constrained by the existing beliefs and incentives of the top managers (Burgelman, 1994; Furr, Cavarretta, & Garg, 2012). Often, firms manage such alliances through separate organizational units (Kale & Singh, 2009). This means the decision making in an alliance is somewhat structurally separated from the mainstream incumbent organization, which reduces the inertial pressures associated with the development of disruptive technologies (Christensen & Bower, 1996; Christensen & Raynor, 2003). By being in close contact with outsiders, the incumbent firms' managers are also well informed about the commercialization opportunities underlying disruptive technologies and are more likely to question the status quo with respect to the prevailing business models (Gilbert, 2005). Finally, given that incumbents share risks and costs with external partners, they will be more likely to pursue development despite the added uncertainty with respect to the business model.

In summary, compared to contract research, the pursuit of a disruptive technology through a research alliance represents a structurally separated organization with risk sharing and outsider influence on decision making. Therefore, relative to product development decisions following investments in research contracts, those following investments in research alliances will be less subjected to incumbents' inertial pressures. Accordingly, we propose:[6]

> *Hypothesis 3. Relative to incumbent firms' investments in research contracts, those in research alliances will more likely lead to development when the radical technological regime is disruptive.*

Acquisitions. Finally, acquisitions of start-ups are another important way incumbents invest in radical technologies (Chaudhuri & Tabrizi, 1999; Nicholls-Nixon & Woo, 2003). Through acquisitions, firms can internalize and build on new knowledge developed by technology start-ups. Acquirers can benefit from such acquisitions by ensuring that the acquired research team is not severely impacted by the organizational transition and by retaining the key inventors and decision makers (Graebner, Eisenhardt, & Roundy, 2010; Puranam, Singh, & Zollo, 2006). Therefore, in their quest to continue making progress in the new technology, acquirers typically preserve the autonomy of the acquired start-ups as structurally separate units. For example, Schweizer (2005) showed that, when pharmaceutical incumbents acquire biotechnology entrants for new technological capabilities, they tend to grant a high degree of autonomy to the acquired firms. Similarly, Puranam, Singh, and Chaudhuri (2009) found that information-technology hardware firms were more likely to preserve the structural autonomy of acquired small technology-based firms with stand-alone technologies. In the case of disruptive technological regime, such a structural separation

[5] Firms in technology-based industries also form alliances that may not involve research, but only commercialization. In such a case, a research output of one firm is commercialized by drawing on the complementary assets of the partner firm. While we control for these commercialization-only alliances in our empirical analysis, these are not the focus of our theory.

[6] It is possible that different modes of research investments may, in general, vary in their likelihood of incumbents' initiating product development. For example, investments in research alliances may be more likely to lead to development than those in research contracts or internal research. We account for this possibility in our empirical analysis by including incumbents' investments in sustaining technological regimes as a control group.

also helps ensure that product development within the acquired units is not constrained by the incentives, routines, and cognitive processes of the parent organization.[7] Hence, in contrast to in-house research units, acquired research units may be shielded from incumbents' inertial pressures associated with the development of disruptive technologies.

In addition to structural autonomy, executives from acquired firms are typically retained and continue to play influential roles in post-acquisition decision making with respect to the new technology (Chaudhuri & Tabrizi, 1999; Ranft & Lord, 2002; Schweizer, 2005). These "outsiders" are not subject to the cognitive constraints of internal managers (Furr et al., 2012). Moreover, they will have strong incentives to commercialize their unit's research output despite a lack of conformance with the incumbent's prevailing business model (Gilbert, 2005). Hence, in contrast to internal research, acquisitions typically represent the pursuit of the radical technology through structurally separated research units with decision makers who are less subjected to the cognitive and incentive constraints within the parent organization. Accordingly, we propose:

Hypothesis 4. Relative to incumbent firms' investments in internal research, those in technology acquisitions will more likely lead to development when the radical technological regime is disruptive.

RESEARCH CONTEXT

We explore our arguments in the context of the global pharmaceutical industry from 1989 to 2008. The inception of biotechnology in the 1980s has been characterized as a radical technological change from chemistry-based to biology-based therapeutic solutions. Biotechnology draws on knowledge from genetics and large molecules (proteins) in the human body to develop new types of therapies. Initially, researchers focused on recombinant DNA to develop novel drugs. The late 1980s saw the next wave of the biotechnology revolution as new therapeutic approaches drawing on genetic engineering started to emerge. We focus on the two approaches that gained the most attention during this period: mAbs and GT. MAbs and GT radically differed from the traditional chemistry-based therapeutic solutions. Both technologies required a fundamental understanding of human biology, which, according to a senior manager of a large pharmaceutical firm whom we interviewed, led to the "decline of chemists and an emergence of biologists within the drug development process of pharmaceutical firms." MAbs and GT represent distinct technological regimes, as they draw on different knowledge bases within biology and entail very different approaches to treating illnesses (Pisano, 2006).

Antibodies are produced by the human immune system in response to foreign proteins (antigens) that are the cause of illnesses and diseases. Therapies using mAbs reinforce the internal immune system and have several advantages over traditional chemistry-based treatments. For example, they are much more specific to an antigen, have a lower risk of toxicity, and can address biological mechanisms that cannot be addressed by traditional chemistry-based drugs often referred to in the industry as small molecules.

GT is targeted at inherited diseases caused by defective genes. The therapy entails inserting corrected genetic material (DNA) into human cells so as to reprogram and restore their functionality in the human body. The new genetic material is inserted through a vector, which delivers the genes to the appropriate cells. Given that the insertion of a "good" gene does not always solve the therapeutic problem, other related methods (e.g., antisense or T cells) are utilized, which may not repair a damaged gene but deter it from functioning.

The empirical context provides an ideal setting for the purpose of this study. Both mAbs and GT continued to leverage incumbent firms' key complementary assets, such as capabilities in clinical development, relationships with health care service providers, and sales teams. Both mAbs and GT required incumbents to invest in new biology-based competences, which they did by pursuing internal research as well as accessing external know-how through research contracts, alliances, and acquisitions. At the same time, mAbs and GT significantly differed in the extent to which they conformed to the incumbents' prevailing business models. As discussed earlier, mAbs sustain the industry's existing business model whereas GT is disruptive. This difference between mAbs and GT was also echoed in our interviews. For example, a business development manager of an incumbent pharmaceutical firm stated that "while mAbs have been validated

[7] Our prediction is premised on the arguments and findings in prior studies (Graebner et al., 2010; Schweizer, 2005) that acquiring firms will preserve the structural autonomy of the acquired start-ups that have knowledge and capabilities in new technologies. We confirmed that this premise continues to hold in our research setting, and we present the supporting quantitative and qualitative information after presenting our main results.

by Wall Street, understanding the business case for GT has been something that's been a moving target. And I admit the marketplace does not exactly know what it needs." Reinforcing the sustaining nature of mAbs, a scientist mentioned that mAbs resemble "a classic small molecule drug, as they are re-administered, treat a large percentage of the population, and have the opportunity to make money long term." Conversely, the disruptive nature of GT is illustrated by the quote from a report in *Fortune* magazine: "Talk about transforming an industry, Big Pharma has always been pill-based whereas gene therapy is one and done" (DuBois, 2012).

Finally, this context allows us to systematically trace incumbents' upstream research investments and downstream product development activities for the two technological regimes over a period of approximately two decades.

Data

We followed the mixed methods approach of explanatory sequential design (Creswell & Clark, 2011), in which we first conducted a quantitative analysis and followed up with a second qualitative phase to shed light on the theoretical mechanisms and explain the quantitative results in greater depth. For the quantitative analysis, we focused on the 50 largest global publicly traded pharmaceutical incumbents based on total pharmaceutical revenues in 1991 using Compustat and annual reports.[8] Limiting the sample to the leading firms ensured that we observed the vast majority of incumbents' research investments in GT and mAbs, and, at the same time, facilitated the data-collection process across multiple databases. This approach is consistent with prior research examining incumbents' management of technological change (Anand et al., 2010; Rothaermel, 2001). We excluded firms that focussed only on generics or reformulations and did not compete in the innovative pharmaceutical market segment. For each firm, we constructed a detailed history of divisions and subsidiaries using the *Directory of Corporate Affiliations*, LexisNexis, and corporate web sites. This helped ensure that the subsidiaries were accounted for within the same corporation.

We assembled a unique firm-level panel dataset that included information on incumbents' research investments and product development for both mAbs and GT from 1989 to 2008. Information on incumbents' research contracts, research alliances, and technology acquisitions was obtained from Recombinant Capital (ReCap). ReCap, a proprietary database tracking the life science industry, is one of the most comprehensive publicly available industry data sources. We used data on firms' patent grants and scientific publications as a proxy for their in-house research activities (e.g., Cockburn & Henderson, 1998; Griliches, 1990; Kaplan, 2008; Lim, 2004). Information on patents was obtained from the Derwent World Patents Index database, and the information on scientific publications was obtained from the Web of Science database. Finally, information on product development activities was obtained using Pharmaprojects and Adis R&D Insights, both of which have been used in a number of prior studies (e.g., Adegbesan & Higgins, 2011; Hess & Rothaermel, 2011; Sosa, 2014).

For the qualitative data, we interviewed 14 senior industry professionals to understand the differences between mAbs and GT and how incumbents pursue these emerging technologies. These professionals came from a variety of backgrounds (six large incumbents, three biotech start-ups, a university, and two dedicated research institutes) with direct experience in the research, development, and commercialization activities of mAbs and GT. The interviews were semi-structured based on an interview guide and lasted an average of 45 minutes. Frequently, we followed up to clarify certain details via e-mails.

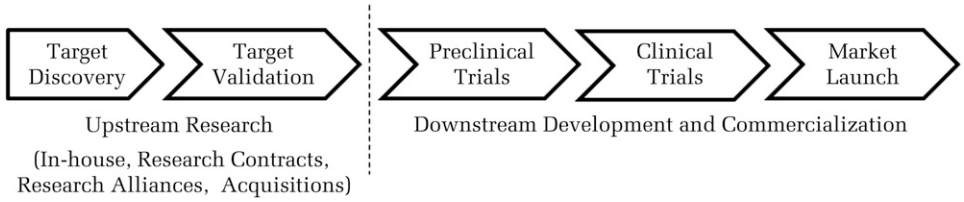
HYPOTHESES TESTING

Variables

Dependent variable. In the pharmaceutical industry, drug development is a long, uncertain process that is initiated through investments in research aimed at understanding the root cause of a given disease or illness and identifying potential therapeutic solutions. The development stage begins with the initiation of preclinical trials (often toxicology studies on animals), which is then followed by heavily regulated trials on humans. Upon approval from regulators, a drug can be commercially launched. The pharmaceutical

[8] During the period of the study, there were 14 mergers among firms in the sample (e.g., Astra AB and Zeneca forming AstraZeneca). Such cases were treated as separate firms before the merger and as a single entity after the merger. Also, among the initial sample, 5 firms merged very early on during the period of observation. We replaced these firms in the sample with large pharmaceutical firms that did not meet the initial Top 50 cutoff based on pharmaceutical sales, but which were in the Top 55.

FIGURE 1
Pharmaceutical Incumbent's Value Chain



value chain from initial research to final drug approval is illustrated in Figure 1. Because of the substantial costs associated with development, firms are very selective in channeling their potential therapeutic solutions discovered during the research stage through to the development stage (Hess & Rothaermel, 2011). Only about 2.5% of all drug candidates explored in the initial research stages enter preclinical trials (Giovannetti & Morrison, 2000).

We focused on the initiation of preclinical trials to observe incumbents' initiation of drug development (Chandy et al., 2006; Girotra et al., 2007; Macher & Boerner, 2012). In our interviews, managers and scientists confirmed the initiation of preclinical trials as an important strategic decision regarding whether the research output—referred to in the industry as a "lead drug candidate"—should be moved forward toward development and subsequent commercialization. In addition to personnel commitments, each preclinical trial entails substantial financial commitments, ranging from $1 million to $15 million. A senior manager at a large pharmaceutical incumbent explained the importance of preclinical trials in the drug development process as follows: "Preclinical trials are the gatekeeper between research and commercialization, as, at the preclinical stage, decisions take place with scientific, clinical, and commercial input."

We used Pharmaprojects to identify therapeutic solutions in preclinical trials for mAbs (categorized within Pharmaprojects' biotech classification T3) and for GT (categorized within Pharmaprojects' biotech classification T4). For each preclinical entry, in order to ensure the year for initiating the preclinical trial was accurate, two researchers independently coded the information from Pharmaprojects. We used a second database, Adis R&D Insights, to verify the year the preclinical trial was initiated and to fill in some of the missing data. If the databases differed, we used the earliest reported year. The dependent variable, *Development,* took the value of "1" if we observed a new preclinical trial initiated by the incumbent firms for mAbs or GT in a given year, and "0" otherwise.[9]

Independent variables. For all the covariates with respect to incumbents' research investments, we used a three-year window; that is, for the initiation of a preclinical trial in year *t*, we observed incumbents' research investments in the years *t*-1, *t*-2, and *t*-3. Given the complexity and uncertainty associated with the drug discovery process, it may take firms several years to translate their research investments into drug development. In our interviews, scientists who were currently conducting and/or preparing for preclinical trials indicated that it takes between two and five years for a research project to reach the preclinical stage. This timeline is consistent with the existing literature on drug development (Koehn & Carter, 2009; Rydzewski, 2008). As additional robustness checks, which we report after presenting our main results, we also used two- and four-year windows.

Ideally, we would have preferred to collect archival data on incumbents' internal research

[9] For more than 90% of the observation years, incumbents initiated either one or no preclinical trials for GT and mAbs; for about 5% of the observation years, incumbents initiated two preclinical trials; for the remaining observation years, incumbents initiated three to six trials. Hence, the dependent variable does not have a strong correspondence with either the Poisson or the negative binomial distributions that are typically associated with the count data. Since most of the observations take a value of "0" and "1," a binary outcome model provides a better fit to the data (Cameron & Trivedi, 2013). As an additional robustness check, we used the count of preclinical trials as the dependent variable and estimated a fixed effects negative binomial model. The results were qualitatively similar to our main results.

expenditures for specific technology regimes, but such archival data are typically not made available by firms. Instead, we used publicly available information on firms' patent grants and scientific publications to create two different proxy variables for incumbents' internal research investments in the specific technological regimes. While they are not direct measures, counts of patents and publications have been shown to be strongly correlated with research investments, especially in the pharmaceutical industry, and, hence, are useful proxies to capture differences in firms' internal research investments (Arora, Fosfuri, & Rønde, 2013; Cockburn & Henderson, 1998; Griliches, 1990; Kaplan, 2008; Lim, 2004; Narin, Noma, & Perry, 1987).

Firms' patent grant information was obtained from Derwent World Patent Index database. All patents in this database are categorized into 21 distinct technology sections, each of which is divided into several classes.[10] Section B is the primary section for pharmaceutical patents. MAbs and GT received dedicated classes in the 1990s that were labeled as monoclonal antibody, gene therapy, and gene delivery. To verify the correspondence of Derwent classes with the specific technological regime, we consulted a senior scientist with the University of Pennsylvania's School of Medicine, who confirmed their applicability for the study. Information on firms' publications was obtained from the ISI Web of Science database, an established data source for observing scientific research. Publications belonging to a focal firm were identified based on the authors' affiliation information. Publications were classified into mAbs- or GT-based research through a keyword approach. A publication was considered to be in the mAbs research domain if the phrase "monoclonal antibody" appeared in either the title, abstract, or keywords provided by the authors, or keywords created by ISI. Similarly, a publication was considered to be in the GT research domain if the phrase "gene therapy," "gene delivery," or the word "antisense" appeared in the respective fields. The two proxy variables for firms' internal research investments are *Patents* and *Publications*, which are operationalized as the count of patent grants applied for by the firm and the count of scientific publications during the three-year period within the respective technological regime.

We used the ReCap database to capture incumbents' research alliances for mAbs and GT. These arrangements are identified in ReCap as either "Co*" (collaborative agreement) and/or "JV" (joint ventures). They go beyond a simple market-based exchange of IP for money; they are based on firms sharing organizational and managerial resources (Kale & Singh, 2009).[11] Since we were interested in research investments, we considered only those agreements that were identified in ReCap as corresponding to the "discovery" stage, and not those that were formed solely for the purpose of commercialization.[12] We used the technology field in ReCap to distinguish between alliances that were specific to mAbs and those that were specific to GT. The measure, *Research Alliances*, is the count of such alliances formed by the focal incumbent firms during the three-year period within a specific technological regime.

[10] There are several advantages of using Derwent for the purpose of this study. First, given the truly global nature of the biopharmaceutical industry, Derwent provides worldwide coverage of patent grants issued to biopharmaceutical firms. Second, the database accounts for the fact that firms may seek patent protection for the same invention in multiple jurisdictions, as well as possibly having subsequent revisions to the original patent. A single patent record in the database (labeled as a patent family) often combines multiple patents related to the same invention. Third, Derwent has developed a proprietary patent technology classification system that allows for a more effective identification of patents based on the function or the application domain to which the invention corresponds.

[11] We pooled collaboration agreements and joint ventures in our analysis because our theoretical development was premised on the difference between unilateral market-based research contracts and bilateral research alliances, which is also consistent with the extant literature. For example, in their review of the literature, Kale and Singh (2009) categorized both joint R&D agreements and joint ventures as alliances, explicitly distinguishing them from market-based contracting and licensing. Note also that a very small minority of research alliances in our dataset were joint ventures (1.6%), which is consistent with the declining trend in the proportion of research-based joint ventures in recent decades (Hagedoorn, 2002).

[12] There were some cases of missing data. For those cases, we examined the corresponding press announcement to identify if the agreement was for discovery. Furthermore, we controlled for the incumbents' use of commercialization alliances in our estimations. These alliances represent collaborative arrangements in which incumbents partner with biotechnology start-ups for commercializing the start-ups' discoveries (Nicholls-Nixon & Woo, 2003).

Research contracts entail agreements wherein the firm licenses an IP or contracts its research to an external organization (typically, a biotechnology entrant or a university). Using ReCap's agreement type, we included those partnerships with either licensing (ReCap code L) or research contracting (ReCap code R), but no collaborative arrangement. As with research alliances, we considered only those research agreements that are identified in ReCap for the discovery stage. Common to these agreements is that incumbents do not share costs or collaborate with the external party. The measure, *Research Contracts*, is the count of such contracts initiated by the focal incumbent during the three-year period within a specific technological regime.

Incumbents undertook a number of technology acquisitions to invest in mAbs and GT. An acquisition was considered to be in a specific technological regime if it was classified by ReCap as either mAbs- or GT- based, if the acquired target (usually a small biotechnology startup firm) had applied for either mAbs or GT patents, or if the target had products in development in the respective technological regime. The measure, *Technology Acquisitions,* is the count of acquisitions by the incumbent firm during the three-year period within a specific technology.

Control variables. We controlled for a number of firm-level factors that may affect the likelihood of firms' initiating preclinical trials. We included the variable return on assets (*ROA*) and *Financial Slack* (measured as current ratio), which may drive the development of new technologies (Greve, 2003). We included the firm's logged *Total Assets* as a proxy for firm size, as large firms may have more resources and greater access to complementary assets. *R&D Intensity* (total R&D expenditures divided by total sales) provided a control for a firm's absorptive capacity (Cohen & Levinthal, 1990). We included *Total Pipeline* as the count of current products in U.S. Food and Drug Administration (FDA) clinical trials, which is often considered an important indicator of the firm's drug development pipeline (Girotra et al., 2007). We also controlled for the overall commitments firms have within the specific technological regimes by including the total count of projects undergoing development (preclinical and FDA trials) in a given year (*Projects in Development*) for both mAbs and GT. Given that firms may react to setbacks in a given technological regime (Greve, 2003), we also included a dichotomous variable, *Failure*, which took a value of "1" if the firm discontinued a mAbs or GT project in clinical trials within the last three years and "0" otherwise.

We included the variable *Non-Research Partnerships* to reflect the exploitative orientation of the firm with respect to either GT or mAbs (e.g., Rothaermel, 2001). This was operationalized by the number of commercialization-oriented contracts and alliances within a three-year period. Pharmaceutical incumbents' pursuit of new biology-based technologies may be constrained by their existing chemistry-based competencies (Leonard-Barton, 1992). We controlled for this effect by using the variable *Chemistry Focus*, which is the ratio of firms' chemistry-based patents to the total number of chemistry-based and biology-based patents.[13] The incumbents' pursuit of new biology-based technologies may also be affected by the cognition of their top managers (Kaplan, 2008). To control for this effect, we examined the CEO and/or chairperson's letters to shareholders in the annual reports. The measure *Cognition Biotech* is the count of biotechnology-related keywords that appear in firms' letters to shareholders in a given year (e.g., Kaplan, Murray, & Henderson, 2003).[14] All of the control variables are lagged by one year.

Model

We modeled the firm's initiation of preclinical trial in mAbs or GT using a logistic specification. We used firm-level panel data to estimate the effects of firms' research investments on the initiation of preclinical trials (*Development*). We could have tested Hypotheses 1 and 2 by pooling the data for both mAbs and GT and interacting internal research investments (*Patents* and *Publications*) and *Research Contracts* with a dummy variable that takes a value of "0" for mAbs and "1" for GT. However, this approach assumes that the unexplained variation (i.e., standard deviation of the error term) is the same across the different technological regimes (Allison, 1999); violation of this assumption can lead to false inferences regarding the differences

[13] We used patent information in the Pharmaprojects database to identify Derwent Manual Codes that refer to chemistry-based and biotechnology-based drugs respectively. The Derwent codes are available from the authors.

[14] Keywords used: biotech, biologics, cloning, gene, genome, genomics, growth factor, molecular biology, monoclonal antibody, nucleotide, protein, DNA (or rDNA), gene therapy, antisense.

between the regimes (Hoetker, 2007). We used the test developed by Allison (1999) to confirm that the unexplained variation differs across mAbs and GT. Hence, we did not pool the data, and we estimated separate models for mAbs and GT.[15]

To control for unobserved firm-level heterogeneity and unobserved changes within a technological regime over time, we included firm and year fixed effects in our analysis (estimations are performed using Stata 11's "xtlogit, fe" conditional fixed effects model procedure with year dummies).[16] Hence, we tested our predictions based on within-firm estimates for each of the two technological regimes. The fixed effects estimation led to the omission of 5 firms that did not pursue drug development for both GT and mAbs during the period of study. The final analysis is based on 591 firm-year observations for mAbs and 561 firm-year observations for GT from a total of 45 incumbent firms.[17]

Results

Table 1 provides the descriptive statistics and Table 2 shows the bivariate correlation matrix for both mAbs and GT. Multicollinearity was not a concern. Individual variance inflation factors for the independent variables are below 4.05 (mAbs) and 2.25 (GT), and below the recommended cutoff levels of 10 (Neter, Wasserman, & Kutner, 1996).

The estimates from the regression analysis are tabulated in Table 3. Models 1 and 2 are baseline models with control variables for mAbs and GT, respectively. In both models, *Failure* within the respective technological regime reduces the likelihood of a preclinical trial being initiated in the following year. Further, the size of the firm (*Total Assets*) and current *Projects in Development* increase the likelihood of a preclinical trial for mAbs, but not for GT. The coefficient for *Chemistry Focus*, as expected, is negative for both mAbs and GT, but it is significant only for GT.

In Hypothesis 1, we predicted that incumbents' investments in internal research will less likely lead to development for a disruptive technological regime (GT) than for a sustaining technological regime (mAbs). To test this hypothesis, we included the covariate *Patents* and *Publications* in Models 3 and 4. The coefficient for *Patents* is positive and significant for mAbs, but not significant for GT. Similarly, the coefficient for *Publications* is positive and significant for mAbs, but not significant for GT. Hence, consistent with our prediction, while incumbents' investments in internal research

TABLE 1
Descriptive Statistics

mAbs[a]	Mean	*SD*	Min.	Max.
Development	0.29	0.45	0.00	1.00
Internal Research (Patents)	9.72	12.74	0.00	65.00
Internal Research (Publications)	23.32	28.93	0.00	170.00
Research Contracts	0.53	1.02	0.00	6.00
Research Alliances	0.61	1.21	0.00	8.00
Technology Acquisitions	0.26	0.63	0.00	5.00
R&D Intensity	0.13	0.07	0.03	0.74
Projects in Development	3.94	5.33	0.00	19.00
Total Assets (log)	9.21	1.10	5.91	11.84
Financial Slack	2.17	0.97	1.01	4.46
ROA	0.13	0.08	−0.20	0.41
Total Pipeline (PI-III)	12.32	9.73	0.00	40.00
Chemistry Focus	0.57	0.19	0.00	1.00
Failure	0.18	0.38	0.00	1.00
Non-Research Partnerships	0.94	1.84	0.00	12.00
Cognition Biotech.	0.75	1.64	0.00	14.00
GT[b]	**Mean**	***SD***	**Min.**	**Max.**
Development	0.22	0.42	0.00	1.00
Internal Research (Patents)	10.81	18.09	0.00	91.00
Internal Research (Publications)	10.00	16.05	0.00	95.00
Research Contracts	0.26	0.48	0.00	6.00
Research Alliances	0.39	0.71	0.00	6.00
Technology Acquisitions	0.23	0.60	0.00	5.00
R&D Intensity	0.13	0.08	0.03	0.74
Projects in Development	1.71	2.86	0.00	14.00
Total Assets (log)	9.19	1.23	6.07	11.88
Financial Slack	2.17	0.94	1.01	4.46
ROA	0.13	0.08	−0.20	0.41
Total Pipeline (PI-III)	11.91	10.00	0.00	40.00
Chemistry Focus	0.56	0.18	0.02	0.87
Failure	0.11	0.31	0.00	1.00
Non-Research Partnerships	0.35	0.94	0.00	9.00
Cognition Biotech.	0.78	1.64	0.00	14.00

[a] $n = 591$.
[b] $n = 561$.

[15] Testing Hypothesis 1 and 2 by using pooled data and interaction terms yielded results that supported our predictions.

[16] To check for autocorrelation in our dataset, we performed the Wooldridge (2002) test. The test could not reject the null hypothesis of no first-order autocorrelation.

[17] Among the 45 firms, 9 firms did not initiate any preclinical trial in GT and 6 firms did not initiate any preclinical trial in mAbs. These firms were dropped from the fixed effects analysis for the specific technological regimes. We ran additional robustness checks including the firms that did not initiate any preclinical trial in GT and/or mAbs using a random effects specification and only including those firms that initiated the preclinical trials for both GT and mAbs using the fixed effects specification. The pattern of coefficients was very similar to the main results.

TABLE 2
Correlation Table[a]

	mAbs[b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Development	1.00															
2	Internal Research (Patents)	0.43	1.00														
3	Internal Research (Publications)	0.27	0.47	1.00													
4	Research Contracts	0.40	0.52	0.29	1.00												
5	Research Alliances	0.43	0.53	0.29	0.51	1.00											
6	Technology Acquisitions	0.25	0.30	0.17	0.30	0.39	1.00										
7	R&D Intensity	0.20	0.40	0.29	0.21	0.25	0.11	1.00									
8	Projects in Development	0.42	0.59	0.39	0.49	0.55	0.51	0.28	1.00								
9	Financial Slack	0.07	0.07	0.07	−0.01	0.00	−0.07	0.36	−0.05	1.00							
10	ROA	0.13	0.04	0.14	0.04	0.10	0.08	−0.03	0.10	−0.17	1.00						
11	Total Assets (log)	0.24	0.33	0.26	0.31	0.38	0.33	−0.15	0.44	−0.32	0.13	1.00					
12	Total Pipeline (PI-III)	0.19	0.15	0.23	0.19	0.18	0.27	0.08	0.27	−0.08	0.19	0.40	1.00				
13	Chemistry Focus	−0.10	−0.35	−0.32	−0.14	−0.12	−0.02	−0.33	−0.16	−0.12	0.01	0.08	0.28	1.00			
14	Failure	0.12	0.29	0.20	0.27	0.25	0.25	0.07	0.44	−0.12	0.02	0.25	0.29	−0.09	1.00		
15	Non-Research Partnerships	0.29	0.46	0.33	0.40	0.44	0.29	0.26	0.62	0.02	0.05	0.23	0.20	−0.19	0.33	1.00	
16	Cognition Biotech.	0.13	0.33	0.16	0.24	0.27	0.09	0.24	0.33	0.02	0.01	0.05	−0.01	−0.30	0.11	0.30	1.00
	GT[c]																
1	Development	1.00															
2	Internal Research (Patents)	0.20	1.00														
3	Internal Research (Publications)	0.30	0.39	1.00													
4	Research Contracts	0.31	0.31	0.25	1.00												
5	Research Alliances	0.39	0.22	0.26	0.49	1.00											
6	Technology Acquisitions	0.30	0.18	0.44	0.09	0.23	1.00										
7	R&D Intensity	0.01	0.21	0.21	0.04	0.09	0.10	1.00									
8	Projects in Development	0.42	0.33	0.57	0.54	0.48	0.42	0.10	1.00								
9	Financial Slack	−0.12	0.02	−0.08	−0.17	−0.12	−0.12	0.39	−0.17	1.00							
10	ROA	0.09	−0.02	0.14	−0.01	0.06	0.14	−0.05	0.07	−0.18	1.00						
11	Total Assets (log)	0.31	0.34	0.48	0.30	0.25	0.36	−0.12	0.42	−0.34	0.16	1.00					
12	Total Pipeline (PI-III)	0.29	0.18	0.43	0.20	0.25	0.29	0.06	0.36	−0.12	0.21	0.47	1.00				
13	Chemistry Focus	−0.02	−0.27	−0.08	−0.07	−0.05	−0.01	−0.41	−0.07	−0.30	0.02	0.14	0.32	1.00			
14	Failure	0.07	0.24	0.30	0.22	0.14	0.13	0.01	0.26	−0.08	−0.09	0.25	0.02	−0.15	1.00		
15	Non-Research Partnerships	0.31	0.24	0.38	0.31	0.29	0.50	0.10	0.46	−0.15	0.05	0.32	0.29	0.07	0.03	1.00	
16	Cognition Biotech.	0.02	0.20	0.11	0.05	−0.04	0.02	0.26	−0.05	0.01	−0.02	0.01	−0.05	−0.34	0.07	0.04	1.00

[a] Values above 0.1 and below −0.1 indicate significance at $p < 0.01$.
[b] $n = 591$.
[c] $n = 561$.

TABLE 3
Conditional Fixed-Effects Logit Regression Estimates for Incumbents' Preclinical Development

Dependent Variable: Development	(1) mAbs	(2) GT	(3) mAbs	(4) GT	(5) mAbs	(6) GT	(7) mAbs	(8) GT	(9) mAbs	(10) GT	(11) mAbs	(12) GT
R&D Intensity	−1.013	−2.503	−2.175	−2.201	−1.100	−2.496	−4.306	−3.762	−1.991	−2.821	−3.538	−3.733
	(2.665)	(3.176)	(3.177)	(3.206)	(2.979)	(3.181)	(2.991)	(3.273)	(2.838)	(3.193)	(3.356)	(3.309)
Projects in Development	0.085**	0.047	0.015	0.063	0.057	0.048	0.024	0.002	0.071	0.001	−0.084	−0.035
	(0.042)	(0.054)	(0.046)	(0.056)	(0.044)	(0.057)	(0.046)	(0.057)	(0.046)	(0.057)	(0.055)	(0.066)
Total Assets (log)	0.935**	0.341	0.535	0.410	0.710	0.344	0.967**	0.508	0.943**	0.218	0.328	0.388
	(0.396)	(0.445)	(0.463)	(0.450)	(0.458)	(0.450)	(0.452)	(0.456)	(0.456)	(0.456)	(0.474)	(0.482)
Financial Slack	0.162	0.364	0.152	0.332	0.144	0.364	0.164	0.377	0.201	0.436*	0.141	0.389
	(0.214)	(0.245)	(0.224)	(0.248)	(0.223)	(0.246)	(0.222)	(0.253)	(0.220)	(0.254)	(0.230)	(0.260)
ROA	2.978	0.551	2.794	1.200	3.053	0.564	2.612	−0.462	2.814	−0.104	2.239	−0.849
	(2.162)	(2.479)	(2.263)	(2.529)	(2.295)	(2.498)	(2.213)	(2.549)	(2.193)	(2.554)	(2.336)	(2.739)
Total Pipeline (PI-III)	0.437	0.492	0.371	0.570	0.243	0.493	0.405	0.615	0.412	0.489	0.119	0.660
	(0.403)	(0.400)	(0.412)	(0.408)	(0.417)	(0.400)	(0.409)	(0.415)	(0.405)	(0.407)	(0.424)	(0.433)
Chemistry Focus	−0.420	−3.635**	0.819	−3.601*	−0.450	−3.639**	−1.208	−3.091*	−0.775	−4.409**	−0.047	−4.186**
	(1.455)	(1.832)	(1.650)	(1.962)	(1.486)	(1.834)	(1.415)	(1.856)	(1.454)	(1.889)	(1.648)	(2.096)
Failure	−0.732*	−0.984**	−0.856**	−0.937**	−1.076**	−0.983**	−0.972**	−0.993**	−0.930**	−1.228**	−1.061**	−1.191**
	(0.384)	(0.457)	(0.435)	(0.462)	(0.429)	(0.457)	(0.420)	(0.469)	(0.409)	(0.486)	(0.463)	(0.517)
Non-Research Partnerships	0.068	0.161	0.130	0.136	0.106	0.162	0.113	0.126	0.085	0.024	0.208*	−0.032
	(0.095)	(0.167)	(0.099)	(0.164)	(0.101)	(0.168)	(0.099)	(0.168)	(0.096)	(0.182)	(0.109)	(0.188)
Cognition Biotech.	−0.081	0.042	−0.059	0.036	−0.079	0.042	−0.084	0.066	−0.085	0.035	−0.065	0.050
	(0.090)	(0.090)	(0.096)	(0.090)	(0.094)	(0.090)	(0.092)	(0.090)	(0.090)	(0.091)	(0.096)	(0.091)
Internal Research:												
Patents			0.073***	0.007							0.062***	0.001
			(0.022)	(0.011)							(0.023)	(0.012)
Publications			0.015**	−0.017							0.018**	−0.012
			(0.007)	(0.014)							(0.008)	(0.016)
Research Contracts					0.681***	0.011					0.480***	0.136
					(0.171)	(0.253)					(0.175)	(0.287)
Research Alliances							0.651***	0.716***			0.522***	0.618***
							(0.170)	(0.207)			(0.182)	(0.221)
Technology Acquisitions									0.238	0.920***	0.447*	0.812***
									(0.245)	(0.300)	(0.261)	(0.302)
Firm Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Log Likelihood	−202.65	−172.35	−190.02	−171.39	−190.28	−172.35	−190.87	−165.70	−198.96	−167.14	−177.15	−161.44
Observations	591	561	591	561	591	561	591	561	591	561	591	561

* $p < 0.1$
** $p < 0.05$
*** $p < 0.01$

increase the likelihood of development for mAbs, no such effect is found for GT.

To offer further statistical support for this hypothesis, we compared the coefficients for *Patents* and *Publications* across the mAbs and GT models. Because coefficients for logit models are scaled by the unexplained variance, it was not possible to compare them directly (Allison, 1999). A solution to this problem entails identifying a common covariate that is significant and similar in magnitude in both models and comparing the ratio of coefficients across the two models (Hoetker, 2007; Train, 1998). The coefficient for *Failure* within both technology regimes is negative and similar in magnitude (−0.86 for mAbs and −0.94 for GT). Hence, we used *Failure* as a common denominator for performing the statistical comparison.[18]

The ratio of coefficients for *Patents* and *Failure* is 0.08 for mAbs and is only 0.01 for GT. Although statistical significance in the tests of differences between ratios of coefficients can be difficult to achieve (Hoetker, 2007), we find that the difference between the ratios is statistically significant (χ^2 = 4.33, $p < 0.05$), offering support for Hypothesis 1. The difference between the ratio of coefficients for *Publications* and *Failure* for mAbs and that for GT is also statistically significant (χ^2 = 3.86, $p < 0.05$), offering further support for Hypothesis 1. Our arguments underlying Hypothesis 1 were also validated in our interviews. For example, a senior scientist in one of the largest pharmaceutical firms discussed the general challenges of moving in-house research discoveries toward drug development as follows:

> Big Pharma typically is run by managers not scientists—they have unique challenges. You know some companies—they do not want to make a drug out of it unless it makes $1 billion dollars, so basically commercial people will decide if it [research discovery] goes to the next step or not.

When asked specifically about the difference between mAbs and GT, two senior business development executives at incumbent firms expressed their skepticism about GT, and commented as follows on greater business scrutiny for in-house GT-based research:

> Compared to monoclonal antibodies . . . gene therapy is driven by personal health and niche applications . . . for a small set of patients, you will command a very high price . . . the business case [for GT] is hard to establish.

> The idea that, in gene therapy, the technology in-house struggles to move forward in commercialization is not surprising . . . because again—this is the square peg round hole. We have it—does not look like an antibody, does not look like a small molecule—we are struggling [to justify the economic opportunity].

Hence, while incumbents invested in mAbs and GT through in-house research, the disruptive nature of GT made it more difficult for in-house research investments to result in drug development.

We tested Hypothesis 2 by including *Research Contracts* in Models 5 and 6. The coefficient for *Research Contracts* is positive and significant for mAbs, but not for GT. Consistent with our prediction, while incumbents' investments in contract research increased the likelihood of them initiating drug development for mAbs, no such effect is found for GT. Therefore, even though incumbents accessed external knowledge underlying disruptive technologies through contract research, the subsequent development still seems to be subject to similar inertial pressures as was the case with in-house research. To offer statistical support for the hypothesis, we used the same approach based on the comparison of ratio of coefficients as in Hypothesis 1. The ratio of coefficients for *Research Contracts* and *Failure* is 0.63 for mAbs and is only 0.09 for GT. The difference between ratio of coefficients is statistically significant (χ^2 = 6.16, $p < 0.05$), offering support for Hypothesis 2. In our interviews, a senior executive, responsible for managing a leading U.S. university's research activities with the pharmaceutical industry, highlighted the similarity in the incumbents' decision making following contract research and that following in-house research: "Contract research and in-house research are both managed by the organization, so there is no real difference regarding the commercialization decisions."

This helps explain why contract research investments in GT, as with-house research investments,

[18] Specifically, the test helps reject the null hypothesis of $\left(\frac{\beta_{Patents}}{\beta_{Failure}}\right)_{mAbs} = \left(\frac{\beta_{Patents}}{\beta_{Failure}}\right)_{GT}$ for *Patents* and null hypothesis of $\left(\frac{\beta_{Publications}}{\beta_{Failure}}\right)_{mAbs} = \left(\frac{\beta_{Publications}}{\beta_{Failure}}\right)_{GT}$ for *Publications*. The betas (βs) refer to the estimated coefficients. If $\beta_{Failure}$ is similar for mAbs and GT and if the difference between the ratio of coefficients between mAbs and GT is statistically significant, it could be inferred that the difference between $\beta_{Patents}$ coefficient for mAbs and that for GT is statistically significant.

did not readily translate into drug development. Further, the decisions regarding the subsequent development and commercialization of IP obtained through contract research is also subject to additional economic considerations because of royalty payments. This consideration was voiced by a senior executive at an incumbent firm responsible for managing research contracts and partnerships, and may have also contributed to the observed noneffect between incumbents' contract research investments and development for GT: "With contract research, Big Pharma firms are even more concerned about IP issues and royalty payments, which raises the bar for the business justification."

To test Hypothesis 3 and 4, we included the variables *Research Alliances* and *Technology Acquisitions* in the regression models. Models 7–10 are partial models in which we include one variable at a time, and Models 11 and 12 are fully specified models with all variables. The coefficient estimate for *Research Alliances* is positive and significant for both mAbs and GT. Similarly, the coefficient estimates for *Technology Acquisitions* are positive and significant for mAbs (Model 12) and GT (Models 10 and 12).[19]

In Hypothesis 3, we predicted that, when the radical technological regime is disruptive, relative to incumbents' investments in research contracts, investments in research alliances will more likely lead to product development. It is possible that investments through research alliances may systematically be more likely to result in development than investments through research contracts. Hence, simply testing for the difference between coefficients for *Research Alliances* and *Research Contracts* for GT may create false inferences. Our results from mAbs helped overcome this problem by providing a control group for GT (i.e., both are radical technologies that are pursued by incumbents through research contracts and research alliances). Instead of simply comparing the coefficients for *Research Alliances* and *Research Contracts* for GT, we compared the ratio of coefficients for *Research Alliances* and *Research Contracts* between GT and mAbs. This ratio captures the impact of research alliances relative to research contracts on the likelihood of development. A higher ratio for GT would imply that, for disruptive technological regimes, incumbents' investments in research alliances will more likely lead to development than will investments in research contracts.[20] The coefficient for external *Research Alliances* is 0.52 for mAbs in Model 11 and 0.62 for GT in Model 12. The coefficient for *Research Contracts* is 0.48 for mAbs and 0.14 for GT. The ratio of *Research Alliances* to *Research Contracts* is greater for GT (4.44) than for mAbs (1.08), and this difference is statistically significant ($\chi^2 = 3.10$, $p < 0.1$), supporting Hypothesis 3.

Why is it that, within a disruptive technological regime, investments through research alliances are more likely to lead to the initiation of drug development than investments in contract research? Our interviewees offered several insights that shed light on this interesting finding. For example, a business manager commented on the difference between external relationships created through research contracts and those created through research alliances: "Collaboration in research has an external partner, whereas contract research has an external contractor. This is a major difference regarding who drives the research agenda and how critical decisions regarding the research are being made."

Many of the managers in incumbent pharmaceutical firms discussed at length why alliances offered an organizational context that is separate from their internal organization and in which decisions and risks were jointly shared by their firms and the partners (start-ups or universities). For example, an interviewee commented that: "To add the biology expertise [from research partners], you need to come up with a joint governance model. I have never seen such deals without the mutual efforts of both us [the incumbent] and our partners."

We also learned that incumbents' research partners have strong incentives to undertake drug development, despite an unproven business model. For example, a head of strategy at a large pharmaceutical firm stressed that: "[External research partners] have to push their research to survive, as they do not have other chances compared to a large pharma firm pursuing many projects at once."

Finally, an executive discussed the benefits of research alliances in developing disruptive innovations: "Disruptive innovations are better managed through collaboration between Big Pharma companies and universities or start-ups because of sharing of risks and knowledge as well as collective decision making."

[19] The coefficient for *Technology Acquisitions* is insignificant for mAbs in the partial Model 9 ($p = 0.29$).

[20] Specifically, the test helps to reject the null hypothesis of $\left(\frac{\beta_{Research\ \ Alliances}}{\beta_{Research\ \ Contracts}}\right)_{mAbs} = \left(\frac{\beta_{Research\ \ Alliances}}{\beta_{Research\ \ Contracts}}\right)_{GT}$.

In Hypothesis 4, we predicted that relative to investments in internal research, those in technology acquisitions are more likely to lead to development in disruptive technological regimes. Again, we used the sustaining technology regime of mAbs as a control group. The ratio of *Technology Acquisition* to *Patents* is much lower for mAbs (7.20) than for GT (812.00). The ratio of *Technology Acquisition* to *Publications* is 24.88 for mAbs, whereas it is 67.66 for GT. We tested the difference between ratios and found the difference to be statistically significant ($\chi^2 = 5.24$ using *Patents*, $p < 0.05$; $\chi^2 = 3.31$ using *Publications*, $p < 0.10$), offering support for Hypothesis 4.[21]

In our interviews, managers of pharmaceutical incumbents offered several insights that were consistent with our arguments and help explain the effectiveness of acquisitions for developing disruptive technologies. We learned that acquirers work hard to retain and incentivize key employees of the acquired firms, who, according to the head of strategy in one incumbent firm, "have the magic." Interviewees explained the continued involvement of scientists and managers of the start-ups in the strategic decision making and the virtues of structural separation of acquired biotechnology start-ups:

> While firms get integrated, the acquirer always tries to retain and incentivize key scientists and decision makers of the acquired firm to be part of the decision making as you cannot afford to lose them . . . A lot of thought is given to this [structural autonomy vs. integration]. We would love to incentivize them on their own . . . most of the things follow a technical project lifetime. In a few years remaining you pretty much know [if they are successful as an autonomous unit].

> We try to build a very much hands-off approach, as we want to learn from the acquired entities.

In a separate supplemental analysis, we explored the extent to which pharmaceutical incumbents in our sample preserved the structural autonomy of acquired firms. We checked as to whether scientists of acquired start-ups continued to have the name of their start-ups as their affiliated organizations on publications at least three years after the acquisition. We found that 84% of these acquired firms were still being mentioned as the scientists' affiliated organizations. Hence, similar to Schweizer (2005), we found strong support for the premise that pharmaceutical incumbents tend to preserve the structural autonomy of the acquired biotechnology start-ups.

Robustness Checks

We conducted several additional checks to establish the robustness of our findings. These include assessing the sensitivity of our results to the different ways of measuring research investments and to the different periods of a technology's emergence (Table 4), as well as using an instrumental variable model as an alternative estimation approach (Tables 5a and 5b). First, instead of using count variables, we operationalized the independent variables as dichotomous variables that capture whether an incumbent invested in internal research, research contracts, research alliances, and technology-based acquisitions (Models 13 and 14).[22] In our main results, we used a three-year observational window for the independent variables. To ensure that our results were not sensitive to the choice of this window, we used windows of two and four years respectively (Models 15–18). Results in all these models are very similar to our main results.

Despite using year fixed effects, it is possible that firms may pursue different strategies during different periods of the emergence of mAbs and GT. We identified three distinct periods in which such strategic change may have occurred. First, we observed a relative decline in the patenting and research contracting for GT after 2002. One concern could be that this decline might be correlated with a systematic reduction in the incumbents' incentives toward commercializing GT (e.g., due to setbacks in clinical trials). To address this concern, we limited our analysis to the pre-2003

[21] Our theoretical development compares research alliances with research contracts, and acquisitions with in-house research. These comparisons are theoretically consistent in that, in both research contracts and research alliances, the source of knowledge is an external entity, whereas, in both in-house research and acquisitions, the source of knowledge is fully internalized. In a supplementary analysis, we tested for other possible comparisons (e.g., research alliances with in-house research, acquisitions with research contracts), and found the ratio for GT to be greater than that for mAbs.

[22] Internal research takes a value of "1" if the incumbent firm had applied for at least 5 patent grants or 12 publications within a technological regime during a three-year period, and "0" otherwise. The thresholds of 5 patents or 12 publications represent median values in the dataset. For other modes, the threshold was simply 1.

TABLE 4
Robustness Checks: Conditional Fixed-Effects Logit Regression Estimates for Incumbents' Preclinical Development

Dependent Variable: Development	(13) mAbs	(14) GT	(15) mAbs	(16) GT	(17) mAbs	(18) GT	(19) mAbs	(20) GT	(21) mAbs	(22) GT	(23) mAbs	(24) GT
R&D Intensity	−3.793	−4.083	−3.203	−3.451	−2.419	−4.484	−1.458	−4.248	−2.545	−4.725	−4.567	−6.173
	(3.039)	(3.321)	(3.411)	(3.291)	(3.401)	(3.538)	(7.053)	(4.693)	(3.450)	(4.270)	(3.979)	(4.970)
Projects in Development	−0.015	−0.006	−0.050	−0.034	−0.052	−0.057	−0.052	−0.063	−0.068	−0.086	−0.171**	−0.083
	(0.048)	(0.062)	(0.052)	(0.062)	(0.056)	(0.065)	(0.101)	(0.091)	(0.069)	(0.101)	(0.073)	(0.099)
Total Assets (log)	0.731	0.338	0.379	0.467	0.400	0.306	0.331	−0.618	0.594	−0.142	0.567	0.046
	(0.466)	(0.465)	(0.469)	(0.471)	(0.468)	(0.478)	(0.767)	(0.876)	(0.567)	(0.567)	(0.815)	(0.660)
Financial Slack	−0.005	0.447*	0.100	0.330	0.108	0.405	0.481	0.163	0.068	0.775**	−0.013	−0.375
	(0.230)	(0.256)	(0.228)	(0.261)	(0.228)	(0.269)	(0.359)	(0.357)	(0.268)	(0.350)	(0.393)	(0.358)
ROA	2.681	−0.907	2.032	0.114	2.634	−1.080	1.013	−5.262	2.251	−1.854	5.130	−1.172
	(2.293)	(2.705)	(2.338)	(2.632)	(2.368)	(2.717)	(3.723)	(3.938)	(3.037)	(3.755)	(3.321)	(3.346)
Total Pipeline (PI-III)	0.489	0.517	0.193	0.724*	0.121	0.687	0.082	0.286	0.296	0.644	0.418	0.067
	(0.435)	(0.417)	(0.425)	(0.439)	(0.424)	(0.439)	(0.513)	(0.617)	(0.539)	(0.572)	(0.800)	(0.566)
Chemistry Focus	0.334	−3.523*	−0.303	−4.391**	0.043	−4.164**	0.726	−4.358	−2.275	−3.420	4.856	−6.678**
	(1.623)	(1.920)	(1.600)	(2.020)	(1.641)	(2.089)	(2.476)	(3.327)	(2.292)	(3.042)	(3.365)	(2.809)
Failure	−0.848**	−1.106**	−0.925**	−0.989**	−1.198**	−1.299**	−0.873	−1.720**	−0.928	−1.358*	−1.619**	−1.409**
	(0.429)	(0.490)	(0.456)	(0.498)	(0.467)	(0.518)	(0.668)	(0.824)	(0.570)	(0.695)	(0.674)	(0.638)
Non-Research Partnerships	0.149	0.033	0.166	0.053	0.176	0.004	0.142	−0.409	0.142	0.098	0.181	−0.123
	(0.101)	(0.176)	(0.107)	(0.186)	(0.108)	(0.190)	(0.193)	(0.328)	(0.142)	(0.274)	(0.130)	(0.219)
Cognition Biotech.	−0.084	0.072	−0.090	0.036	−0.038	0.055	0.123	−0.068	−0.018	0.059	−0.152	0.021
	(0.096)	(0.091)	(0.101)	(0.091)	(0.096)	(0.092)	(0.165)	(0.159)	(0.106)	(0.106)	(0.122)	(0.110)
Internal Research:												
Patents	1.004**	0.137	0.096***	−0.005	0.040**	−0.003	0.109**	0.013	0.059**	0.007	0.060	0.005
	(0.395)	(0.418)	(0.030)	(0.016)	(0.019)	(0.008)	(0.044)	(0.016)	(0.029)	(0.017)	(0.038)	(0.019)
Publications	1.005**	−0.282	0.016*	−0.007	0.010**	−0.003	0.019*	−0.026	0.024**	−0.007	0.011	−0.016
	(0.432)	(0.501)	(0.009)	(0.007)	(0.004)	(0.004)	(0.010)	(0.024)	(0.010)	(0.020)	(0.015)	(0.029)
Research Contracts	0.980***	−0.236	0.601***	0.126	0.516***	0.160	0.547*	0.297	0.398**	0.274	0.461**	0.050
	(0.292)	(0.369)	(0.192)	(0.307)	(0.162)	(0.268)	(0.287)	(0.351)	(0.200)	(0.399)	(0.211)	(0.419)
Research Alliances	0.728**	0.934***	0.453**	0.643***	0.317*	0.547***	0.522*	0.446	0.680***	0.650**	0.385*	0.554
	(0.318)	(0.322)	(0.183)	(0.237)	(0.163)	(0.197)	(0.314)	(0.274)	(0.220)	(0.292)	(0.221)	(0.356)
Technology Acquisitions	0.276	0.962**	0.636**	0.796**	0.132	0.704**	0.595	0.655	0.621*	1.264***	0.421	0.889**
	(0.398)	(0.381)	(0.308)	(0.330)	(0.238)	(0.293)	(0.456)	(0.523)	(0.331)	(0.470)	(0.317)	(0.369)
Firm Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Log Likelihood	−181.29	−162.43	−179.73	−163.30	−179.96	−162.90	−100.22	−95.93	−118.79	−91.69	−88.05	−91.08
Observations	591	561	591	561	591	561	338	276	395	327	307	300

* $p < 0.1$
** $p < 0.05$
*** $p < 0.01$

TABLE 5A
Robustness Checks: IV 2SLS Regression (Second Stage)

Dependent Variable: Development	(25) mAbs	(26) GT	(27) mAbs	(28) GT	(29) mAbs	(30) GT	(31) mAbs	(32) GT	(33) mAbs	(34) GT
R&D Intensity	−1.413**	0.103	−0.197	−0.344	0.450	−0.692	−0.519	−0.911*	−0.327	−0.249
	(0.715)	(0.775)	(0.461)	(0.390)	(0.561)	(0.568)	(0.464)	(0.493)	(0.456)	(0.409)
Projects in Development	−0.036	0.016	0.016**	0.009	−0.011	−0.021	−0.011	−0.011	−0.003	−0.009
	(0.026)	(0.010)	(0.007)	(0.009)	(0.016)	(0.034)	(0.016)	(0.014)	(0.013)	(0.014)
Total Assets (log)	−0.051	−0.002	−0.114	0.041	−0.003	−0.045	0.040	0.114*	−0.025	0.007
	(0.074)	(0.097)	(0.080)	(0.052)	(0.064)	(0.111)	(0.059)	(0.062)	(0.063)	(0.058)
Financial Slack	0.037	0.055	0.044	0.054	0.023	0.037	0.053	0.032	0.070*	0.055
	(0.040)	(0.040)	(0.036)	(0.034)	(0.040)	(0.039)	(0.035)	(0.038)	(0.037)	(0.035)
ROA	0.389	0.233	−0.326	−0.034	0.414	−0.327	−0.058	−0.255	0.026	−0.064
	(0.394)	(0.414)	(0.395)	(0.331)	(0.380)	(0.535)	(0.353)	(0.392)	(0.350)	(0.348)
Total Pipeline (PI-III)	0.002	0.046	0.018	0.047	−0.130	0.094	0.066	0.061	0.011	0.046
	(0.070)	(0.060)	(0.062)	(0.052)	(0.100)	(0.064)	(0.059)	(0.057)	(0.062)	(0.053)
Chemistry Focus	0.529	0.026	0.496	−0.371	−0.156	−0.447	−0.235	−0.316	−0.317	−0.851***
	(0.349)	(0.708)	(0.304)	(0.247)	(0.254)	(0.288)	(0.249)	(0.278)	(0.266)	(0.321)
Failure	−0.013	−0.205*	−0.099*	−0.170**	−0.225***	−0.109	−0.122**	−0.068	−0.142**	−0.230***
	(0.087)	(0.116)	(0.060)	(0.067)	(0.075)	(0.080)	(0.057)	(0.075)	(0.059)	(0.079)
Non-Research Partnerships	0.037	0.020	0.016	0.030	0.017	0.019	0.003	0.006	0.024	−0.066
	(0.022)	(0.033)	(0.016)	(0.023)	(0.017)	(0.032)	(0.014)	(0.029)	(0.018)	(0.054)
Cognition Biotech.	−0.001	0.005	−0.007	0.006	−0.002	−0.009	−0.027*	0.016	−0.016	0.006
	(0.016)	(0.013)	(0.014)	(0.012)	(0.015)	(0.019)	(0.014)	(0.015)	(0.013)	(0.013)
Internal Research:										
Patents	0.057**	0.011								
	(0.025)	(0.016)								
Publications			0.014***	0.005						
			(0.005)	(0.004)						
Research Contracts					0.462**	0.406				
					(0.195)	(0.582)				
Research Alliances							0.256**	0.450**		
							(0.113)	(0.211)		
Technology Acquisitions									0.364**	0.461**
									(0.155)	(0.213)
Year and Firm FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Log Likelihood	−359.59	−230.89	−306.87	−215.40	−331.85	−303.13	−287.56	−276.05	−298.35	−237.56
Observations	591	561	591	561	591	561	591	561	591	561
Anderson Statistic	10.333***	4.490	33.625***	20.721***	11.699***	3.868	20.294***	19.889***	34.700***	19.895***
Sargan Statistic	1.533	1.196	0.696	0.894	0.618	2.701	2.13	2.765	1.43	1.352

* $p < 0.1$
** $p < 0.05$
*** $p < 0.01$

TABLE 5B
Robustness Checks: IV 2SLS Regression (First Stage)

Dependent Variable	(25) mAbs Patents	(26) GT Patents	(27) mAbs Publications	(28) GT Publications	(29) mAbs Contracts	(30) GT Contracts	(31) mAbs Alliances	(32) GT Alliances	(33) mAbs Acquisitions	(34) GT Acquisitions
R&D Intensity	20.350***	−38.839***	−11.248	−1.572	−1.914**	0.573	0.274	0.821	−0.185	−0.229
	(6.498)	(11.624)	(15.727)	(7.587)	(0.749)	(0.417)	(0.889)	(0.620)	(0.507)	(0.442)
Projects in Development	0.964***	−0.310	0.262	0.463***	0.069***	0.053***	0.124***	0.045***	0.067***	0.043***
	(0.098)	(0.266)	(0.238)	(0.174)	(0.011)	(0.009)	(0.013)	(0.014)	(0.007)	(0.010)
Total Assets (log)	0.687	4.057**	7.384***	−1.551	−0.016	0.144***	−0.197*	−0.216**	0.032	0.039
	(0.880)	(1.578)	(2.117)	(1.030)	(0.100)	(0.056)	(0.118)	(0.083)	(0.068)	(0.059)
Financial Slack	0.184	−1.392	0.554	−2.742***	0.091	0.016	0.029	0.006	−0.018	−0.012
	(0.510)	(0.974)	(1.232)	(0.636)	(0.059)	(0.035)	(0.070)	(0.053)	(0.040)	(0.037)
ROA	−3.734	−14.098	31.201***	15.700**	−0.806	0.598*	0.292	0.528	0.044	0.267
	(4.927)	(9.652)	(11.932)	(6.308)	(0.566)	(0.346)	(0.671)	(0.514)	(0.383)	(0.367)
Total Pipeline (PI-III)	0.244	1.298	0.480	2.074**	0.329***	−0.066	−0.118	0.034	0.047	0.002
	(0.875)	(1.503)	(2.101)	(0.984)	(0.099)	(0.054)	(0.118)	(0.080)	(0.067)	(0.057)
Chemistry Focus	−8.382**	−39.351***	−26.966***	−0.375	0.403	0.074	0.922**	−0.385	0.843***	0.824***
	(3.413)	(7.355)	(8.222)	(4.794)	(0.378)	(0.259)	(0.448)	(0.385)	(0.256)	(0.274)
Failure	−1.665**	5.582***	−2.067	3.865***	0.235**	−0.059	0.022	−0.152	0.045	0.175**
	(0.833)	(1.888)	(2.009)	(1.239)	(0.094)	(0.067)	(0.112)	(0.100)	(0.064)	(0.071)
Non-Research Partnerships	−0.459**	1.181*	−0.560	−0.464	−0.051**	0.022	−0.036	0.057	−0.075***	0.212***
	(0.215)	(0.704)	(0.516)	(0.462)	(0.024)	(0.024)	(0.029)	(0.036)	(0.016)	(0.026)
Cognition Biotech.	−0.272	−0.014	−0.549	−0.127	−0.020	0.024*	0.055**	−0.033*	0.009	−0.003
	(0.189)	(0.367)	(0.457)	(0.240)	(0.022)	(0.013)	(0.026)	(0.019)	(0.015)	(0.014)
Total Patents	0.002**	0.002	0.002	0.001						
	(0.001)	(0.002)	(0.002)	(0.001)						
Total Publications	0.002*	0.003	0.014***	0.019***						
	(0.001)	(0.002)	(0.002)	(0.001)						
External Research Intensity					0.009***	0.003	0.013***	0.007**	0.008***	0.007***
					(0.003)	(0.002)	(0.003)	(0.003)	(0.002)	(0.002)
Alliance Ratio					−0.161	−0.121	0.439**	0.459***	0.090	−0.011
					(0.106)	(0.104)	(0.215)	(0.155)	(0.123)	(0.110)
Acquisition Ratio					−0.134	−0.131	0.351	0.379	1.028***	0.581**
					(0.418)	(0.230)	(0.496)	(0.341)	(0.283)	(0.242)
Year and Firm FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Log Likelihood	−1853.03	−2061.30	−2374.03	−1827.90	−564.89	−226.70	−665.68	−443.31	−334.16	−255.44
N	591	561	591	561	591	561	591	561	591	561

* $p < 0.1$
** $p < 0.05$
*** $p < 0.01$

period (Models 19 and 20). Separately, to ensure that our results were not impacted by unobserved differences in incumbents' strategies during the Human Genome Project, we excluded the years 1998–2002 from the analysis (Models 21 and 22). We also limited our analysis to the post-1997 period to exclude the initial emergence period of the new technological regime, as incumbents may be somewhat less likely to pursue development during this nascent stage (Models 23 and 24). The estimates in these models confirm that the patterns we have observed are not being driven by a specific time period.

While we used within-firm estimates across the two different technological regimes to test our predictions and we checked for the possibility of changes in firms' strategies over time, we further checked for any potential firm-level time-variant endogeneity bias in our estimates. Specifically, we used an instrumental variable (IV) two-stage least squares (2SLS) regression model and perform fixed-effects estimations on our panel data. This was done using Stata's "xtivreg2" procedure (Bascle, 2008).

We identified two different instruments that are likely correlated with firms' patents and publications within a given technological regime, but uncorrelated with the firms' initiation of preclinical trials in that regime for reasons beyond their effect on the endogenous regressor (Angrist & Pischke, 2008). These are the total number of firms' patents and the total number of firms' publications that are not in the research domain of either mAbs or GT, within a three-year period. The instruments capture firms' general intensity of in-house research but they do not directly affect the initiation of the preclinical trial in either mAbs or GT. We used three different instruments that are likely correlated with firms' investments through research contracts, alliances and acquisitions within a given technological regime, but do not directly impact firms' initiation of preclinical trials in that regime. The first instrument is the total count of research contracts, alliances, and acquisitions that a firm pursues that are not targeted toward the specific technological regime. This is reflective of the firm's general intensity to draw on external sources of knowledge. The other two instruments capture the preference of a firm to use a specific mode. These are the ratio of the number of alliances (or acquisitions) to the total number of research contracts, alliances, and acquisitions.

Because we had a common set of instruments for the different regressors, we instrumented each regressor separately. We ran tests to ensure that our IVs were relevant and valid (Bascle, 2008). The results are reported in Tables 5a and 5b, and the estimates of the second-stage model exhibit patterns very similar to our main results. Note that, while we used fixed-effects IV analysis to ensure that the statistical significance of our estimates was not driven by firm-specific time-variant endogeneity bias, this approach faces some challenges regarding the specific testing of our predictions. Testing of our hypotheses requires that we have multiple endogenous regressors in the same model. This raises identification problems and requires that we have at least one unique instrument as a source of exogenous variation for each of the endogenous regressors (Angrist & Pischke, 2008). Given that all of our independent variables represent some form of research investments in radical technologies, it is difficult to find strong unrelated instruments. Having weak instruments undermines the value of instrumental variable analysis (Wooldridge, 2002). Moreover, statistical comparison of coefficients across mAbs and GT models is not possible with the IV approach, which is a prerequisite for testing our predictions. Finally, we are not aware of any IV logit models for panel data, and, hence, are unable to resolve the challenges associated with the modeling of a binary dependent variable using a 2SLS panel model (e.g., Angrist & Pischke, 2008).

We conducted a number of additional robustness checks.[23] For some observations in our dataset, firms did not invest in either mAbs or GT (i.e., the value of all of the independent variables was "0" for a given observational year). It is possible that these observations represent periods when firms may either have had no interest in these emerging technological regimes or may have changed their strategy. The results are robust to the exclusion of these observations from the analysis. We also used a threshold approach to identify incumbents' investments that may be merely symbolic but insufficient to translate into product development. Specifically, we performed our analysis by coding all observations as "0" for those in which incumbents' patent and publication counts were below the median value, and for which they only had a single research contract. Finally, to account for the possibility that some firms may focus their development efforts in only one technological regime, we ran an analysis excluding those firms that initiated the

[23] These results are available from the authors. They are not included here because of space constraints.

preclinical development for only one of the two technological regimes during the study period. The results for all these additional checks were qualitatively similar to our main results, giving us additional confidence in our findings.

DISCUSSION AND CONCLUSION

The innovation literature has long focused on the challenges that incumbents face in managing radical technological change. We contribute to this inquiry by exploring the extent to which incumbent firms' research investments in radical technological regimes lead to subsequent product development. In so doing, we offer a framework that helps explain when incumbents' well-intended investments are likely to yield successful adaptation and when they may be voided by the forces of inertia.

At the core of our investigation is the possibility that, beyond competence destruction, radical technological regimes may not conform to the incumbents' prevailing business model in terms of how they generate revenues and appropriate profits (Abernathy & Clark, 1985; Christensen & Raynor, 2003). We demonstrate that this is an important but underexplored source of organizational inertia associated with incumbents' decisions to develop radical technologies following their research investments. We further consider the different ways incumbents may choose to pursue radical technologies. These include the often-emphasized investments in their in-house research units, but also investments channeled toward entrants and research organizations through the use of research contracts, research alliances, and acquisitions (e.g., Nicholls-Nixon & Woo, 2003). These modes differ with respect to who does the research and who is involved in the decision for subsequent development.

The context for the study, the global pharmaceutical industry, witnessed the emergence of two revolutionary therapeutic approaches based on genetic engineering in the late 1980s: mAbs and GT. Both drew on incumbent firms' specialized complementary assets; however, they differed in the extent to which they conformed to the incumbents' existing business models. Whereas mAbs conformed to the existing business model of incumbent firms, GT was disruptive. Firms responded to these emerging technologies by undertaking internal research investments as well as drawing on external sources of knowledge through the use of research contracts, alliances, and acquisitions. However, the extent to which these research investments translated to drug development differed between mAbs and GT. Firms' investments in internal research and contract research resulted in them initiating drug development for mAbs (the sustaining technological regime) but not for GT (the disruptive technological regime). In contrast to investments in contract research and internal research, those in research alliances and acquisitions had a significant effect on the initiation of drug development for GT.

In our interviews, industry participants offered several insights that provided additional support for our arguments and findings. We learned why, as compared to in-house research discoveries in mAbs, those in GT were subject to greater skepticism and scrutiny by strategic decision makers within the incumbent organization. We also learned that, while incumbents may undertake investments in contract research to access new knowledge beyond their boundaries, the organizational processes underlying subsequent development and commercialization are no different from those involving investments in internal research. Hence, incumbents' investments in contract research toward GT tended to suffer from similar organizational constraints as those in internal research. Finally, we were able to uncover why, in contrast to investments in internal and contract research, those in alliances and acquisitions had a significant impact on the development for GT. Both alliances and acquisitions represented research investments that were structurally separated from the parent organization and involved outsiders (typically, scientists and managers from start-ups) in the decision-making processes. This created an organizational context that motivated the pursuit of opportunities within GT and was isolated from the demands and constraints associated with the incumbents' prevailing business models.

Taken together, these findings illustrate that our understanding of how radical technological change impacts firms is incomplete without an explicit consideration of how the change interacts with the incumbents' business models and what organizational modes are used by incumbents to invest in the radical technologies. Hence, we are able to offer a new set of organizational and technological contingencies to the question of how technological change impacts firms.

The study also sheds light on a frequent misconception regarding disruptive technologies that incumbents fail to invest in such technologies. As documented in several case studies, incumbents

often do invest in such technologies (Christensen & Bower, 1996; Gilbert, 2005; Sull et al., 1997; Tripsas & Gavetti, 2000). However, as our results illustrate, many of the initial research investments in disruptive technologies may not lead to subsequent product development and commercialization. This suggests that the locus of incumbent inertia is not necessarily at the point of initial research investment, but, rather, during the later stages of development and commercialization. Investments channeled toward technology start-ups and research organizations through collaborative alliances and acquisitions may offer incumbents with a means to overcome that inertia.

Further, the difference in the impact between investments in research contracts and those in research alliances for GT offers an important distinction between incumbents' actions and decisions during periods of technological change. While incumbents may act to draw on knowledge of entrants and research organizations through research contracts and alliances, these arrangements vary in the extent to which product development decisions are externalized. The locus of decision making remains internal to the incumbent firms in the case of unilateral market-based research contracts, while development decisions are jointly carried out by incumbents' and their alliance partners (i.e., start-ups or research organizations) in the case of bilateral research alliances. As we learned during our interviews, this is an important reason why, relative to investments in research contracts, those in research alliances are more likely to lead to product development and commercialization for disruptive technologies.

Finally, by disaggregating the biotechnology field into specific technological regimes, we are also able to shed light on the somewhat unexpected findings of earlier studies (Nicholls-Nixon & Woo, 2003; Rothaermel, 2001). For example, despite arguing that pharmaceutical firms' research investments in biotechnology would result in greater levels of product development, Nicholls-Nixon and Woo (2003) did not find support for such a relationship. Our findings suggest that this could be a result of aggregating distinct technological regimes such as mAbs and GT, which may interact very differently with the incumbents' organizational and strategic context.

This study has a number of limitations, which should provide ample opportunities for future research. First, it was conducted in the context of a single industry, and the generalizability of our findings and their boundary conditions need to be validated through explorations in other empirical contexts. Second, while our focus on mAbs and GT provided us with a unique opportunity to study two distinct types of radical biology-based technological regimes that emerged around the same time in the pharmaceutical industry, the newness of these regimes and the long development cycles in the industry did not allow us to observe the final commercialization outcomes (product approval and market share). Consistent with our theory that focuses on the incumbents' decisions about product development following their research investments, we observed the incumbents' initiation of drug development through preclinical trials. Industry participants confirmed the decision to initiate preclinical trials is an important strategic decision that incumbents make in moving newly discovered therapeutic solutions toward development. However, we are unable to draw inferences regarding final commercialization outcomes, such as product sales or firms' profits (e.g., Polidoro & Toh, 2011). Third, ideally, we would have preferred to observe the final outcomes for each research project that pharmaceutical incumbents pursued for mAbs and GT. However, such archival data for early-stage research projects are not publicly available. While our approach is consistent with prior studies (Hess & Rothaermel, 2011; Nicholls-Nixon & Woo, 2003), it would be valuable to undertake in-depth explorations of specific research projects that incumbents pursue through a variety of organizational modes. Finally, while we performed a number of robustness checks with respect to model estimations and the operationalization of variables, we were unable to fully resolve issues related to potential measurement errors. For example, we were able to draw on established categorization schema with respect to mAbs and GT to identify incumbents' investments in in-house research, contract research, and research alliances, but we were somewhat limited in our ability to precisely identify acquisitions as pertaining to mAbs and GT. Some acquired targets were start-ups that pursued both the technological regimes, and, hence, our inferences with respect to acquisitions as a means to invest in a specific technological regime may not hold in all cases.

Despite these and other limitations, the study offers an important contribution to our understanding of how radical technological change impacts firms. While incumbents often respond to and invest in new technologies, we show that their

subsequent development efforts may still be subject to organizational inertia. In contrast to investments in internal and contract research, those in research alliances and acquisitions offer a means to overcome such inertial forces and help incumbents navigate the changing technology landscape. We hope that the insights that have emerged from our study contribute to the theoretical agenda of moving beyond "adaptability versus rigidity" to developing a richer understanding of the ways in which these organizational features interact and shape the behavior of firms in the face of technological change.

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