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Public research, innovation and R&D performance; Science funding restrictions and the corporate R&D landscape in the cell therapy field

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Abstract

We find that firms in science-intensive industries are more likely to initiate novel R&D projects and that projects that are initiated are less likely to fail when the funding outlook for public research is better. The context of our study is the development of the corporate R&D landscape in the global cell therapy industry across four periods that were distinctive in terms of the outlook for relevant public research. Analysing our unique dataset on 633 commercial product development projects in the cell therapy field from 1989 until 2011, we find lower R&D project initiation rates and higher failure rates for US firms in the aftermath of the announcement in 2001 of a federal funding moratorium on specific types human embryotic stem cell research. Our findings advance scholarship on dynamics governing R&D in science-intensive industries, in which innovation is organized in inter-organizational networks that encompass academic institutions.

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Abstract
We find that firms in science-intensive industries are more likely to initiate novel R&D projects and that projects that are initiated are less likely to fail when the funding outlook for public research is better. The context of our study is the development of the corporate R&D landscape in the global cell therapy industry across four periods that were distinctive in terms of the outlook for relevant public research. Analysing our unique dataset on 633 commercial product development projects in the cell therapy field from 1989 until 2011, we find lower R&D project initiation rates and higher failure rates for US firms in the aftermath of the announcement in 2001 of a federal funding moratorium on specific types human embryotic stem cell research. Our findings advance scholarship on dynamics governing R&D in science-intensive industries, in which innovation is organized in inter-organizational networks that encompass academic institutions.

Introduction

How do changes in the funding outlook for public research affect R&D investment decisions and technology commercialisation in industry? Organised within inter-organisational networks encompassing academic and commercial organisations, R&D in technology-intensive sectors of contemporary capitalist economies often feeds off and is intertwined with public research carried out in academic laboratories (e.g. Cohen et al. 2002; Powell et al. 2005). While existing scholarship has expanded our understanding of knowledge transfer processes between academia and industry, our appreciation of the mechanisms through which investment decisions in public research affect the allocation of corporate resources to specific R&D projects and firms' ability to successfully progress these projects along the development pipeline, remains underdeveloped.

Public funding constitutes an important source of upstream R&D investment in university-centred high-tech clusters (e.g. Saxenian, 1994; Zucker et al. 1998). Private venture capitalists in Silicon Valley, the US region with the largest amount of early stage funding for biotechnology firms, provided US$ 104 Million in seed- and start-up- funding for biotechnology firms in 2012 (PricewaterhouseCoopers 2015). In contrast, federal spending on biomedical research at the region's three research universities through the National Institutes of Health (NIH) alone was US$ 258 Million in that same year (NIH 2015). In addition, the NIH distributed an additional US$ 41 Million directly to Silicon Valley start-up firms through its Small Business Innovation Research grant scheme in 2012 (NIH 2015).

Our study will examine two aspects of the dynamics, by which science funding policies affect R&D pipelines in science-based industries. First, R&D projects in science-intensive industries such as the biotechnology industry represent major asset-specific investments and we

propose that the funding outlook for public research in an area is an important factor driving firms' willingness to make such investments. Firms tend to delay asset-specific investments in projects as uncertainties increase about costs of key inputs for these projects (e.g. Dixit and Pindyck 1994; Pindyck 1993) or critical regulations affecting their development (Fabrizio 2013; Henisz and Williamson 1999; Henisz 2000a). We propose that a similar dynamic causes deteriorations in the funding outlook for public research in a field to reduce the attractiveness of asset-specific investments in corporate R&D projects that are linked to this public research.

Second, the level of funding commitment to public research affects the progression of R&D projects along the development pipeline in science-intensive industries. Firms that pursue R&D projects in science-based industries are dependent on networks of academic and commercial partners for critical resources in progressing these projects down the development pipeline (Powell et al. 1996; 2005; Stuart et al. 2007). Reduced levels of asset-specific investments by such partners during periods when the funding outlook for public research is depressed, would make it more difficult to access critical resources within these networks. Accordingly, we propose a link between the funding outlook for public research in a field and the R&D performance of firms in terms of moving new projects down the pipeline.

We assess the outlined interdependencies in the context of the development of commercial R&D pipelines of the global cell therapy industry across four periods that were distinctive in their outlook for public research. Specifically, we examine the impact of various levels of funding restrictions on research involving new human embryonic stem cell (hESC) lines that were seen as important to the development of this industry. US policy shifts in the hESC field have proven a fruitful 'natural experiment' setting for examining the impact of changes in funding for academic research on the advancement of science (Furman et al. 2012;

Owen-Smith 2006), and on the regional mobility of scientists (Levine 2008; 2012). We use these policy shifts to examine the impact of changes in funding for public research on commercial R&D. To this end, we created a unique dataset with information about 868 worldwide university-industry deals in the cell therapy field from 1986 until 2013, and the advancement of 633 new commercial cell therapy projects initiated by life sciences companies from across the globe over the period 1989 until 2011. We use these data to analyse the impact of different funding environments for hESC research on R&D activity in the US cell therapy sector and contrast the development of this sector with that of cell therapy sectors of countries that were not directly affected by the policy interventions that shaped the funding environment for hESC research in the US.

Our findings indicate that in the immediate aftermath of the announcement of the federal funding moratorium on specific types of hESC research, the involvement of universities in commercial markets for ideas in the cell therapy field diminished, and the propensity of US firms to initiate novel cell therapy R&D projects as compared to firms elsewhere decreased. Moreover, cell therapy projects that were initiated by US firms were less successful than those initiated by non-US firms during this period. Finally, our evidence suggests that the detrimental effects for innovation in the cell therapy sector were specific to the US and were reversed as the funding outlook for public research in the hESC sub-fields that had been targeted by the federal funding moratorium improved after 2004.

Public research and novel R&D projects in industry

Publicly research is critical in fuelling new product development in key sectors of contemporary economies (Cohen et al. 2002; Laursen and Salter 2004; Liebeskind et al. 1996; Mansfield 1998; 1991). Economists have long recognized the unique role of public research in

sustaining innovation and economic performance in technology-intensive industries (Arrow 1959; Nelson 1959). Albeit socially (and economically) valuable, risks and uncertainties associated with scientific research and difficulties to *ex ante* determine its applications are seen as preventing private business to take over the role of the state in supporting public research. Accordingly, such research is considered a critical public good that firms in knowledge-intensive sectors rely on in the development of R&D pipelines. We expect two mechanisms to play a role in determining the impact of public science funding policies on corporate R&D activity.

First, policy makers regulate flows of ideas that emerge from academic research, which firms organize novel R&D projects around, by deciding on funding levels for different fields of scholarly enquiry. Previous work highlights the importance of these flows in supporting corporate R&D pipelines. One survey published in the 1990s highlights that 15% of new products developed by industry over the period 1986-1994 could not have been developed without recent advances in academic research, and that this number was substantially higher in industries such as the life sciences industry, where 31% of new drugs and medical products were tied to recent advances in academic research (Mansfield 1996). Another 1994 survey finds that 41,4% of pharmaceutical drugs R&D builds on findings from public research, 12,3% of pharmaceutical drugs R&D relied on prototypes that were the result of public research, and 35,4% of pharmaceutical drugs R&D relied on instruments and techniques developed through public research (Cohen et al. 2002). Therefore, reduced investment levels in the development of research in specific fields will have a negative impact on the availability of ideas around which novel corporate R&D projects are formed in these fields.

Second, changes in policies governing funding levels for public research signal shifts in the commitment of policy makers to specific fields of scholarly enquiry. Firms in science-

intensive sectors do not only make R&D investment decisions based on existing ideas and knowhow that public research has generated in a field, expectations about future public support for the continued development of such ideas and knowhow also are important. Analyses in the finance literature on investment decisions in projects that require irreversible resource commitments and take time to complete, suggest that it becomes more attractive for firms to postpone investment decisions or to pursue other projects as uncertainties increase about the costs of critical input resources required for the downstream development of projects (e.g. Dixit and Pindyck 1994; Pindyck 1993). In addition, scholars have extended the transaction costs economics framework to analyze decisions by firms to make asset specific investments in sectors where industry dynamics are highly contingent on government regulation regimes (Henisz and Williamson 1999; Henisz 2000a). For example, studies on corporate investments in new telecommunications infrastructure projects (Henisz and Zelner 2001) and renewable energy generation projects (Fabrizio 2013) indicate that firms are less likely to commit to such investments when regulatory uncertainty is higher. Similar to firms that are dependent on a stable regulatory environment in making major infrastructure investments, firms that rely on public research in the development of R&D pipelines must make assessments about the future outlook for public research in fields these firms consider making asset-specific investments in. In the case of science-based industries, such assessments about future public commitments to specific lines of scholarly enquiry are important to investment decisions regarding novel R&D projects for two important reasons.

To begin with, public research contributes to the completion of existing commercialization projects in equal measure to contributing to ideas for new commercialization projects (Cohen et al. 2002). Technological challenges that firms encounter along product

development pathways and the knowhow firms need to tackle these challenges are often difficult to predict *ex ante*, especially in the development of more radically innovative projects such as those pursued in science-intensive industries. As a result, firms in these industries rely on external knowledge in product development activities (Ahuja and Lampert, 2001; Katz and Tushman, 1981; Lee and Allen, 1982; Phene et al. 2006). Scientific knowledge is a particularly important source of external knowledge for firms in science-intensive industries (Fleming and Sorensen 2004; Jong and Slavova 2014). Accordingly, we argue that decisions to redirect public funding away from specific lines of academic enquiry negatively affect expectations among R&D managers about their ability to rely on scientific knowhow in R&D projects they consider initiating. As a result, such decisions are likely to make these R&D projects less attractive investment options and undermine confidence among managers, investors, and others whose support is key for launching R&D projects.

In addition, the development of absorptive capabilities that firms require to search for and assimilate external scientific knowledge requires significant investments in internal R&D organizations (Cohen and Levinthal, 1990, Fabrizio, 2009 and Fleming and Sorenson, 2004), and collaborations with academic laboratories (Liebeskind et al. 1996; Zucker et al. 1998). An extensive literature has emerged that examines the organizational models (Chesbrough 2006; Powell and Sandholz 2012), and the institutional practices and strategies (Jong and Slavova 2014; Stern 2004; Gittelman and Kogut 2002) for interacting with academic communities that optimize these absorptive capabilities. Investments associated with the development of absorptive capabilities become more attractive as scientific fields these organizations are tied into expand, and firms are able to exploit economies of scale and scope in interactions with external academic expert groups (Katz and Martin 1997; George et al. 2002). In contrast, restrictions that siphon

away public resources from specific lines of scientific enquiry are likely to increase the perceived uncertainty about opportunities to increase the scale of corporate R&D programs that follow these lines of scientific enquiry. Thus, we expect that investments in internal R&D organizations become less attractive as the base of external public research these organizations draw on is diminished through funding restrictions.

Taken together, the outlined dynamics suggest that science-funding restrictions diminish firms' propensity to make investments in new R&D projects, and we therefore propose a negative effect of funding restrictions on the number of novel R&D projects that are initiated:

Proposition 1a: *Scientific funding restrictions have a negative impact on the propensity of firms to launch new R&D projects.*

In addition, we argue that the negative impact of funding restrictions on public research is an impact that is geographically concentrated. While scholarly knowhow is a public good from many perspectives (e.g. Arrow 1959; Nelson 1959), scholarly knowhow at the scientific frontier is often held tacitly and therefore excludable by nature (e.g. Thursby and Thursby 2000; Liebeskind et al. 1996). As the transfer of such tacitly held knowledge requires personal interactions, commercial and academic R&D in science-intensive industries such as the biotechnology industry tends to be geographically co-located (e.g. Zucker et al. 1998). Thus, we expect that negative effects on firms' propensity to launch novel R&D projects as a result of deteriorations of the funding environment for public research are larger within the geographic areas where these funding restrictions are concentrated.

Proposition 1b: *The negative impact of the enactment of scientific funding restrictions on the propensity of firms to launch new R&D projects is larger for firms that are geographically located in the country where these restrictions are enacted.*

Public research and corporate R&D performance

The resource environments, in which novel R&D projects are initiated create path dependencies that shape these projects' subsequent development. For example, the literature on new technology firms, which are often constituted around new R&D projects, highlights the importance of various factors relating to the composition of founding teams for the development and success of these firms (Beckman 2006; Eesley et al. 2013; Eisenhardt and Schoonhoven 1990; Klepper 2001). Similarly, the private financing environment for new technology firms is important in determining subsequent success; 'hot' financing environments during periods when venture capital is abundant produce firms that are more innovative than firms that receive their initial venture capital investments in financing environments that are less 'hot' (Nanda and Rhodes-Kropf 2013). We argue that a resource environment within which public research support is comparatively weak will hamper the success of R&D projects that are conceived in this environment for several reasons.

First, funding restrictions undermine firms' ability to successfully move R&D projects along their development trajectories. External public research not only plays an important role in science-intensive industries at the inception stage of novel R&D projects, but also in supporting R&D processes once these projects are underway. In fact, the development of corporate R&D projects in science-intensive industries such as the biotechnology industry has been linked to the research environment at academic laboratories from which firms are spun-off and the quality of the scientific networks founders bring into firms (Jong 2006; Murray 2004; Powell and Sandholtz 2012). Moreover, academic collaborations and publishing in high-quality scientific journals have been linked to increased R&D productivity of biotechnology firms (Jong and

Slavova 2014). Accordingly, we expect the relative dearth of quality scientific resources in less favorable public research environments to undermine the success of commercial R&D projects.

Second, product innovation in science-intensive sectors is generally organized within collaboration networks that involve webs of multiple partners such as investors, contract manufacturers, and licensing partners which possess different competencies that are critical to a project's success (Powell et al. 1996; 2005; Stuart et al. 2007). As argued above, in deciding whether or not to commit resources to a field, firms that are potential development partners in a field are likely to be more inclined not to if the funding outlook for public research in that field is negative. Therefore, even if individual firms are willing to commit resources to projects if the scientific funding environment becomes less favourable, managers of these firms will likely find it more difficult to mobilise other key actors around these projects, increasing these projects' chance of failure.

Similarly, firms' ability to attract high-quality researchers might be negatively affected in a public research environment where academic career prospects are diminished as a result of reduced funding. Prospects to build up their stature in broader scientific communities is an important factor determining career decisions by researchers; This has been shown in the context of researchers pursuing careers in corporate research environments (Stern 2004) as well as in academic research environments (Anstett and Bell 2005; Levine 2006, 2008, 2012). Thus, we expect it to be more difficult for firms to assemble the teams of high-quality researchers necessary to turn R&D projects into a success in fields where public research faces restrictions.

Taken together, we posit the following regarding the propensity of R&D projects to be successful in a field where funding for public research is restricted:

Proposition 2a: *R&D projects that are initiated after the enactment of scientific funding restrictions are less likely to be successful.*

Finally, we argue that the negative impact of funding restrictions on firms' capabilities to bring R&D projects to a successful conclusion is an impact that is geographically concentrated in the country where these restrictions are enacted. Like for the effect of funding restrictions on firms' propensity to initiate novel R&D projects, we argue that the negative effect on firms' propensity to successfully complete projects is especially strong for firms that are in the same country as the public research institutions that are hit by funding cuts.

Proposition 2b: *R&D projects that are initiated in a country where scientific funding is restricted are less likely to be successful.*

Research setting - The US federal hESC research funding moratorium 2001-2009

The US federal funding moratorium covering research on specific human embryonic stem cell (hESC) lines that spanned the period 2001-2009 is a case study that provides a controlled 'experimental' research setting for us to examine the impact of changes in the funding outlook for lines of scientific enquiry on corporate R&D. The policy that enacted the moratorium was issued at a specific point in time and its scope, namely any research utilising hESC lines that were derived before 9 August 2001, was clearly delineated. Moreover, the moratorium spanned a period that offered an otherwise favourable funding environment for biomedical research; The annual NIH budget for example roughly doubled over the 1995-2005 period. Finally, the 2001-2009 moratorium on federally funded hESC research was US-specific. Accordingly, by contrasting R&D activities of US firms that build on scholarly advances in the hESC field before, during, and after the period spanning the hESC funding moratorium, as well as by contrasting these with R&D activities by firms outside the US over the same periods, we are able to control

for a range of institutional factors (other than the funding outlook for public research) that are considered instrumental in supporting innovation in science-intensive industries and change over time such as the financing environment.

We examine the impact of the hESC research moratorium on corporate R&D decision-making in the context of the development of new therapeutic products in the cell therapy sector. The cell therapy sector is organised around the development of human cells as therapies (as opposed to small molecule- or protein- drugs).[1] The first wave of cell therapy companies was formed during the late 1980s, and the sector has grown into an important sub-sector in the biotechnology industry; It is moving towards the market a number of high-profile projects, including products that regenerate human bladder, brain, and spinal cord tissues, and that trigger or act as an immune response to cancer. By the beginning of 2015, 366 cell therapy projects were under active development (Citeline 2015).

The cell therapy sector has been the main sector where companies incorporated scientific advances in hESC research in novel product development projects. Not all product development projects in the cell therapy sector incorporate insights developed by academic researchers in the academic field that was directly affected by the hESC moratorium. However, the fates of academic hESC research and the industrial cell therapy sector were considered intrinsically interlinked by external observers (e.g. Mason and Manzotti 2009), senior academic researchers in the field (Klein et al. 2009; Wolinsky 2008), investors (Brick 2001), policy makers (NIH 2015b), and leading industry executives. For example, reflecting on the impact of the hESC

[1] Boundaries and definitions used to delineate the scope of what we now refer to as the 'cell therapy' sector have evolved over time. The concept of 'cell therapy' that refers to 'human cells' (as opposed to small molecule- or protein- drugs) as therapies, encompasses other, related concepts such as 'regenerative medicine', 'stem cell', and 'tissue engineering,' that were more commonly used at various points in the past to refer to the R&D focus that is the focus of this study (Culme-Seymour and Mason 2012).

research moratorium beyond industrial R&D projects that were directly linked to this research Thomas Okarma, CEO of Geron, one of the leading stem cell companies during the 2000s, remarked:

> *'It's a disaster. The Bush [hESC federal research funding moratorium] decree cut off federal funding for research into new embryonic stem-cell lines. Investors fear the next shoe that might drop. Is Congress going to pass a law making [all cloning] illegal? How crazy is the regulatory environment going to get? In an attempt to fill the federal-funding void, a bunch of companies are trying to get funding to study adult stem cells. But investors can't discriminate, so they're sitting on the sidelines until all this controversy is sorted out.' (Bloomberg Business Week 2003).*

We focus on cell therapy R&D projects initiated during one of four time intervals that mark distinctive periods in terms of the funding environment for hESC research in the US in the development of the R&D landscape in the cell therapy field. These intervals are similar to ones used by studies that examined the impact of the hESC funding moratorium on publications and labour market mobility of US hESC researchers (Anstett and Bell 2005; Furman et al. 2012; Levine 2006, 2008, 2012; Moon and Cho 2014; Owen-Smith and McCormick 2006). Two of the intervals, the 1997-2001 and 2009-2011 periods, cover periods before and after the federal funding moratorium on hESC research. The 2001-2003 interval covers the first years of the funding moratorium when prospects to attract public funding for hESC research that fell under the moratorium were practically non-existent. The 2004-2009 interval covers the period when the funding outlook for public research on hESC lines significantly improved. While the federal funding moratorium remained in place, movements to strengthen funding support for stem cell research won important victories at both the state- and federal- levels. At the level of individual states, initiatives were enacted that sought to offset restrictions that characterised the federal funding landscape for hESC research. The most notable of these initiatives was Proposition 71,

also known as the California Stem Cell Research and Cures Act, through which California voters in 2004 approved a state bonds issue to fund US$3 billion of stem cell research.

At the federal level, a series of victories by opponents of the federal hESC research-funding moratorium made a reversal of the moratorium appear increasingly inevitable. The Stem Cell Research Enhancement Act, passed by a bipartisan majority in the US House of Representatives in 2005, and subsequently by the US Senate eventually encountered a presidential veto. Yet, by the time of this veto, even leading figures of the social conservative movement in the Republican Party, which had been an important force behind the enactment of hESC research funding restrictions, conceded that the end of the moratorium was only a matter of time.[2] Studies on the development of the hESC research field in the US highlight how aided by new funding initiatives and international collaborators, publications in this field authored by US scientists increased as well over the 2004-2008 period (Furman et al. 2012).

Finally, our unit of analysis is the cell therapy product development project. Specifically, we focus on the initiation and progression of cell therapies that enter (pre-) clinical trials. The development of new products in biopharma sub-sectors such as the cell therapy sector is costly, risky, and takes many years. In fact, by the beginning of 2015, the R&D effort of the global cell therapy sector over approximately 20 years had resulted in the commercialisation of only 32 cell therapies (Citeline 2015). The number of projects that enter (pre-) clinical trials is a good proxy to assess market entry decisions as these trials constitute by far the most resource-intensive component of the product development process in the biopharma industry (e.g. Pisano 2006).

[2] For example, the day after the Presidential veto, the New York Times quoted Gordon H. Smith, Republican Senator of Oregon, reflecting on the veto and future prospects of a repeal of the moratorium: "When there's another election, another chapter of democracy opens,'' …. "Most of the candidates who have a shot at winning are in favor of stem cell research. This represents a delay en route, but I know where we're going, and it's where the American people want to go.'' (New York Times, 20 July 2006).

Data

We collected data on firms and R&D projects in the cell therapy field from multiple sources (table 1). We used the Citeline Pharmaprojects database, a leading industry database that tracks the progress of pharmaceutical product development projects to collect data on 521 cell therapy project that was under active development in (pre)-clinical trials over the period 1986-2011. For the purpose of our analysis of the performance of R&D projects in the cell therapy industry, we identified 483 projects with starting years ranging between 1997 and 2011. We used additional sources to collect information on the firms that initiated these projects, including information on firm size measured as numbers of employees in 2012, firm location, and firm age at the time of the initiation of a new project. Finally, we collected information on 864 cell therapy deals and the organisations that were involved in these deals, over the period 1986-2011 from Thomson-Reuters' Recap database, which tracks technology deals in the bio-pharmaceutical sector.

[INSERT TABLE 1 HERE]

[INSERT TABLE 2 HERE]

Assessing the impact of the hESC research funding moratorium

Impact on academic research

The impact of the federal funding moratorium on hESC research has been well documented. In the short run, the moratorium led to a sizable drop in the research productivity of US-based hESC researchers as compared to researchers based elsewhere (Furman et al. 2012; Moon and Cho 2014; Owen-Smith and McCormick 2006). In fact, US knowledge production in the hESC field fell 35 to 40 per cent below anticipated levels in the aftermath of the 2001 policy, and measured in terms of forward citations to core research publications in the hESC field, US-

based hESC follow-on work declined by nearly 59 per cent relative to non-US-based research over the period 2001-2003 (Furman et al. 2012). The federal hESC research moratorium affected the career mobility of hESC researchers as well, with several studies highlighting transfers of these researchers to different countries, or states within the US, which fostered more favourable funding environments for hESC research (Anstett and Bell 2005; Levine 2006, 2008, 2012).

In the long run, the deterioration of the hESC research environment in the US was gradually reversed. Furman et al. (2012) highlight that the gap in research productivity between non-US- and US-based hESC researchers narrowed after 2004: Over the period 2004-2007 the production of US hESC follow-on papers was only 29 per cent lower than the production of non-US follow-on papers. This reversal has been attributed to three factors. First, US researchers forged collaborative ties with international research groups that operated in a less restrictive regulatory environment (Furman et al. 2012). Second, at the state level, public funding initiatives were launched to offset the funding gap in the hESC research field that had been caused policies at the federal level. Third, the federal hESC research moratorium ended in 2009, removing the barriers to hESC research that had held back US-based researchers in the first place.

Impact on technology transfer

The presence of universities in markets for intellectual property (IP) has markedly increased over the past decades (e.g. Mowery et al. 2004). Over the period 1965-1992, the number of university patents increased 15-fold, while the overall number of patents increased by less than 50% (Henderson et al. 1998). Moreover, universities have accumulated significant patent portfolios in fields such as biotechnology: Over the period 1990-1994, the proportion of biotechnology patents by universities and government entities increased from 15% to 20% (Adelman and DeAngelis 2007). Thus, the transfer of university-owned IP to industry now

constitutes a key mechanism through which publicly funded research is transferred to industry in the life sciences.

Our Recap data suggest that the drops in university output in the cell therapy field that followed the enactment of the 2001 hESC federal funding moratorium were not confined to publications; Data also show a drop in university participation in commercial IP markets for cell therapy technologies (Table 3). Firms benefit more from scientific input when technologies are more novel and radically innovative (e.g. Fleming and Sorenson 2004; Jong and Slavova 2014; Zucker et al. 1998). Consistent with this insight, we find that the prevalence of cell therapy deals involving universities as a proportion of the total number of deals in the cell therapy field was highest during the field's early history. Thirty-five per cent of 128 cell therapy deals were deals involving universities over the period 1986-1996. The prevalence of deals involving US academic institutions dropped to around 16-18 per cent during the subsequent decade, except during the period 2001-2003, which immediately followed the enactment of the federal hESC research funding moratorium. During this period, the prevalence of deals involving US academic institutions in the cell therapy field dropped to around 10 per cent, which is well below levels of involvement of US academic institutions in IP markets in the cell therapy field seen before and after this period.

Impact on market entry

Figure 1 plots over time data on the initiation by US- and non-US- firms of novel cell therapy projects that entered (pre-) clinical trials. The graphs in figure 1 highlight comparatively low numbers of product development projects launched by US firms in the immediate aftermath of the enactment of the hESC federal funding moratorium, which suggests diminished market entry by US firms in the cell therapy field during this period. Whereas in 2002, US firms

initiated twenty-six new cell therapy projects and non-US firms initiated five new cell therapy projects, this situation reversed in 2005. In that year, US firms initiated ten new cell therapy projects, as compared to twenty-four new cell therapy projects originated by non-US firms. Figure 1 also highlights a recovery of the number of cell therapy projects that US firms initiated following the launch of state initiatives aimed at providing local public funding support for stem cell research, most notably California's Proposition 71, which Californians passed in 2004. In fact, by 2006, US firms again were leading in terms of numbers of new cell therapy projects these firms moved into (pre-) clinical trials. The US cell therapy sector experienced a second significant drop in terms of the number of cell therapy project initiated in 2009, after the collapse of Lehman Brothers, and the ensuing great recession, which hit the entire economy. However, this second drop in R&D output of the the US cell therapy sector coincided with a similar drop in R&D output of the cell therapy sectors outside the US, which were also affected by the financial crisis.

[INSERT FIGURE 1 HERE]

Impact on R&D performance

Tables 4 and 5 present logit regression models that assess the propensity of cell therapy projects initiated by US-based firms to successfully progress towards the clinic across four time intervals with distinctive funding outlooks for public hESC research. Table 4 examines factors affecting *project failure* separately for our samples of US- and non-US- projects. In examining whether the fact that a US project was initiated before or after the enactment of the US hESC research funding moratorium affected *project failure*, we do not find a significant effect. We do find a significant effect of the moratorium by looking more closely at different time intervals; Using projects initiated over the period 1997-2000 as the reference group, we find that projects

launched by US firms over the period 2001-2003, were more likely to fail than those launched during the period before the enactment of these restrictions. This period covers the immediate aftermath of the announcement of hESC research funding restrictions and precedes the enactment of state initiatives that made available public funding for stem cell research, and congressional efforts to reverse the federal funding moratorium. We do not find the same effect for projects in our sample of projects initiated by firms based outside the US.

[INSERT TABLE 4 HERE]

To assess the short-term effect of hESC research funding restrictions on project failure rates and any spillover effects of these restrictions beyond the US we employ difference-in-difference techniques in analyzing our entire sample of US- and non-US- R&D projects. Table 5 presents tests on the combined sample of US- and non-US projects for region-level differences in project failure rates. Moreover, we examine the role of interaction effects between where and when a project was initiated in predicting project failure. Using projects initiated over the period of 2009 – 2011 as the reference group, model 1 is the base model and only tests the policy effects on project failure. Models 2 and 3 include additional firm- and project- level variables.

Model 3 in Table 5 shows that projects are less likely to fail as these projects progress and complete more clinical trials, which is consistent with other data regarding failure rates along the biopharma development trajectory (e.g. Pisano 2006). The number of transactions a firm has with academic institutions in the form of technology licensing deals also reduces the log odds of failure of a firm's R&D projects. This finding is in line with insights about the importance of scientific input in the development of more radically innovative technologies such as those developed in the biotechnology industry (e.g. Fleming and Sorenson 2004). Finally, model 3 highlights a positive and significant coefficient for interaction terms *USx2001-2003*.

This confirms the increased propensity of project failure for US cell therapy projects that were initiated in the immediate aftermath of the hESC research funding moratorium in the US.

[INSERT TABLE 5 HERE]

To deal with the fact that coefficients and their significance might not represent accurate relationships in non-linear logistic models, such as logit models, we also estimated the marginal effects of the interaction terms (Ai and Norton 2003). Figure 2 illustrates our estimates of model 3 in table 5 and highlights that projects initiated by US firms had a significantly higher predicted marginal probability of failure (94%) than projects initiated by non-US firms (80%) over the 2001-2003 period. In estimating these effects, results of the difference-in-difference test are strong, both in magnitude and statistical significance. The divergence in predicted failure rates for US- and non-US projects in the immediate aftermath of the enactment of the US federal research moratorium indicates that the negative effects of this moratorium were statistically significant during the period 2001-2003 and that these negative effects were specific to the US.

[INSERT FIGURE 2 HERE]

Discussion of findings

Our results provide interesting new insights into how the interplay between public and private R&D in science-intensive industries. First, our results re-affirm the importance of public research in these industries and do not indicate that private firms are able to adapt and substitute the function of public research in driving industry innovation if funding support for public research is removed. Specifically, we find that negative effects in innovation outcomes in our data for the period 2001-2003, in the aftermath of the enactment of the hESC research funding moratorium are linked to a reduced role of universities in markets for ideas in the cell therapy field during this period. Moreover, we find that the return of the US cell therapy sector to a level

of innovative performance in the commercialization of cell therapies that was similar to that of the non-US cell therapy sector from 2004 onwards, is linked to a return of US universities to a level of involvement in markets for IP in cell therapy that was similar to the level of involvement in the pre-2001 era. Accordingly, the moratorium did not lead to a structural transformation in the cell therapy field in a way that diminished the role of public research in product innovation, for example by leading firms to adopt alternative search modes in R&D.

Second, our results offer insights into how trade-offs in industry governing the allocation of R&D resources are shaped by the funding outlook for public research. Two effects in terms of changes in R&D efforts in the cell therapy over the observed periods are especially noteworthy:

- The decisive uptake of R&D efforts activity from 2005 onwards. While the drop in R&D efforts in the cell therapy field following the enactment of the hESC research-funding moratorium is in line with existing scholarship, the swift uptake of these R&D after 2005 is not. This uptake occurred as the political movement against the moratorium, and in favor of greater state- and federal- funding support for stem cell research gained credible momentum. Accordingly, the renewed willingness to commit corporate R&D resources to the development of novel cell therapies after, initially appears to have been more driven by a renewed confidence in funding outlook for public research, than by any specific policy shifts.
- The size of the negative effects on new R&D activity in the cell therapy field over the period 2001-2003. Proponents of the 2001 hESC funding moratorium asserted that because of its limited scope (the moratorium neither completely banned hESC research, nor restricted private and state-level funding), effects on corporate R&D activities and industry competitiveness would be minor and manageable. However, our evidence suggests that this assertion did not turn out to be correct. In fact, the drop in innovation activity in the cell

therapy field in the immediate aftermath of the enactment of the federal hESC research funding moratorium was disproportionately large in relationship to the size of hESC research in the broader stem cell research field; hESC research was a nascent field in 2001 and still today represents a fraction of scholarly activities in the stem cell research field. In 2012, three years after the federal hESC research funding moratorium had been reversed by Executive order, US$146 Million of the US$1.4 Billion NIH funding for stem cell research was used for hESC research (NIH 2015a). Yet, our data show a 77% drop in the number of new cell therapy projects entering (pre-) clinical trials over the period 2002-2004 (from 26 cell therapy projects that entered (pre-) clinical trials in 2002, to 13 in 2003, to 6 in 2004).

These two effects outline how changes in industry sentiment about the outlook for public funding in the stem cell research field were an important driver in the allocation of R&D resources away from and towards specific types of R&D projects. Accordingly, we are able to extend existing scholarship on the impact of changes in the 'hotness' of the private financing environment on the type of innovation activities firms focus on (e.g. Nanda and Rhodes-Kropf 2013), by highlighting the distinctive impact of the 'hotness' of the financing environment for public research in a field on the type of innovation activity firms focus on.

Third, we highlight how changes in public support for academic research that fuel innovation in science-intensive sectors such as the cell therapy sector, affect constraints firms face in the development of corporate R&D programs. Innovation in technology-intensive sectors is often characterized as 'open' (Chesbrough 2003), 'networked' (Powell 1998), and 'democratized' (Von Hippel 2005) to denote a high dependence in R&D on organizations that are external to the firm. Our results suggest that when the funding environment for public research in a field deteriorates and firms become more hesitant to make asset-specific

investments in this field, it is also more difficult for firms that do initiate new R&D projects to bring these projects to a successful completion. Specifically, the increased log odds of project failure for cell therapy projects initiated by US firms *vis a vis* non-US firms when the funding outlook for public research on hESCs was at its worst in the US, highlights interesting interdependencies between a firm's capability to successfully progress R&D projects in science-intensive industries and the funding outlook for public research. This finding enriches our appreciation of the specific role that support for public research plays in sustaining innovation networks providing key input for firms' R&D projects.

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TABLES AND FIGURES

Table 1: Variables used in empirical analyses

Variable names	Description	Source
Project failure	A binary variable that takes the value of 1 if a cell therapy project was discontinued by the originator firm AND was not taken up for development by another firm. The value is 0 if otherwise	Citeline Pharmaprojects
Post2001	A binary variable that takes the value of 1 if a cell therapy project was initiated from 2001 onwards.	Citeline Pharmaprojects
1997-2000	A binary variable that takes the value of 1 if a cell therapy project was initiated between 1997 and 2000.	Citeline Pharmaprojects
2001-2003	A binary variable that takes the value of 1 if a cell therapy project was initiated between 2001 and 2003.	Citeline Pharmaprojects
2004-2008	A binary variable that takes the value of 1 if a cell therapy projects that were initiated between 2004 and 2008.	Citeline Pharmaprojects
2009-2011	A binary variable that takes the value of 1 if a cell therapy projects was initiated between 2009 and 2010.	Citeline Pharmaprojects
Large firms (>= 500 emp)	A binary variable that takes the value of 1 if the firm that initiated the focal project has more than 500 employees.	LexisNexis firm database
Small firms (<= 50 emp)	A binary variable that takes the value of 1 if the firm who initiated the focal project has fewer than 50 employees.	LexisNexis firm database
Company age	Difference between the project start year and the firm's founding year.	LexisNexis firm database
Startup	A binary variable that takes the value of 1 if a firm that initiated a project is less than 5 years at the time a project is initiated.	LexisNexis firm database
No. university deals	Number of university deals involved with the company initiated the cell-therapy project.	Recap IQ Series, Deal Builder
Autologous	A binary variable that takes the value of 1 if a cell therapy project is an autologous cell-therapy.	Citeline Pharmaprojects
No. enrollments	The total number of patients enrolled in all clinical trials for the focal project from the start of the project up until 2012.	ClinicalTrials.gov
No. clinical trials	The total number of clinical trials studies completed for the focal project from the start of the project up until 2012.	ClinicalTrials.gov
Therapeutic classes	Dummy variables that indicate the cell therapy project as one of nine therapeutic classes: alimentary metabolic, anti-infective, anti-cancer, blood clotting, cardiovascular, dermatological, musculoskeletal, neurological, and miscellaneous products	Citeline Pharmaprojects

Table 2: Descriptive statistics cell therapy projects initiated between 1997 and 2011 (N = 483)

	US	Non-US	chisq test	Total
Failed projects	164 (65.3%)	135 (58.2%)	Chisq = 2.61 P = 0.106	299 (61.9%)
Autologous	92 (36.6%)	115 (49.5%)	Chisq = 8.21 P = 0.004	207 (42.8%)
Large firm (emp >= 500)	25 (9.96%)	21 (9.05%)	Not significant	46 (9.52%)
Small firm (emp <= 50)	144 (57.4%)	131 (56.5%)	Not significant	275 (56.9%)
Begin the project during 1997 – 2000	41 (16.3%)	19 (8.2%)	Chisq (3)=20.8 P = 0.000	60 (12.4%))
Begin the project during 2001 – 2003	52 (23.5%)	27 (14.4%)		79 (16.4%)
Begin the project during 2004 – 2008	106 (42.2%)	107 (46.1%)		213 (44.1%)
Begin the project during 2009 – 2011	52 (20.7%)	79 (34.1%)		131 (27.1%)

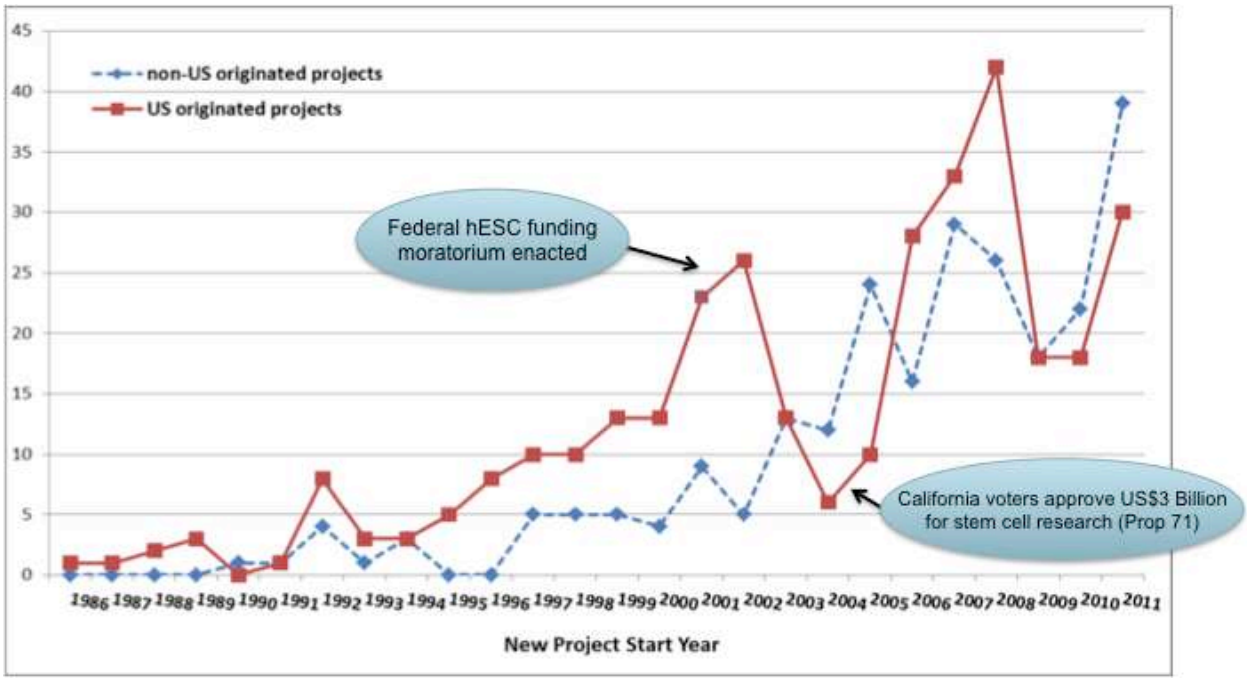
Chi-square test is used to test the significance level of the comparison of us and non-us group among the variables in our analysis: * denotes p<.05, ** denotes p <.01, and *** denotes p<.001

Table 3: Share of university deals in cell therapy and overall biotechnology fields

	No. cell therapy deals (N = 864)	Percentage of cell therapy deals that are with universities	Percentage of cell therapy deals that are with US universities	Number of university-industry deals in biotechnology (# deals/per year)
1986-96	128	35%	34%	1308 (130.8)
1997-00	63	17.4%	15.8%	860 (215)
2001-03	107	10.3%	10.3%	766 (255.3)
2004-08	365	23.0 %	17.8%	2187 (437.4)
2009-11	201	18.4%	11.4%	1641 (547)

Source: Compiled from Recap IQ Series (2014).

Figure 1: Number of cell therapy projects entering clinical trials by originator country



Source: Compiled from Citeline Pharmaprojects database (2012)

Table 4: Results of logistic regression models to predict failures of projects initiated by US firms and projects initiated by non-US firms (1997-2011)

	Logit regression DV = Project failure					
		US			Non-US	
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Post 2001	-0.647 (.453)			-0.451 (.645)		
2001-2003		1.135* (.648)	1.337* (.714)		1.078 (.751)	1.065 (.829)
2004-2008		-0.532 (.465)	-0.592 (.564)		0.218 (.620)	0.884 (.637)
2009-2011		-2.526*** (.570)	-2.865*** (.657)		-2.068*** (.601)	-1.898*** (.618)
Large firms (>= 500 emp)	-0.714 (.466)	-1.331** (.598)	-0.987 (.655)	-0.513 (.648)	0.002 (.749)	0.404 (730)
Small firms (<= 50 emp)	-1.007** (.466)	-1.090** (.472)	-1.333** (.569)	-0.246 (.451)	0.147 (.487)	-0.331 (.526)
Company age	0.0078 (.006)	0.019 (.0057)	0.019*** (.007)	0.0023 (.003)	-0.0008 (.0036)	-0.0065 (.004)
Startup	0.474 (.368)	0.119 (.368)	0.338 (.450)	0.0008 (.425)	-0.437 (.433)	-0.472 (.497)
No. university deals	-0.144 (.121)	-0.197* (.122)	-0.201* (.138)	-0.291 (.338)	-0.381 (.309)	-0.709** (.320)
Autologous			-0.296 (.392)			-0.650 (.431)
No. enrollments			-0.0027** (.0012)			0.0007*** (.0002)
No. clinical trials			-0.218 (.143)			-1.436*** (.386)
Constant	1.814 (.589)	2.097*** (.607)	2.742*** (.930)	0.707 (1.136)	0.894 (.744)	1.549** (.818)
Therapeutic class fixed effects	No	No	Yes	No	No	Yes
Observations	237	237	235	218	218	218
Pseudo R^2	0.049	0.217	0.306	0.006	0.204	0.378
Log likelihood	-144.69	-119.15	-104.63	-147.61	-118.57	-92.67

To account for the heterogeneity of firms, organizational_id cluster standard errors are calculated in parentheses; * significant at 10%; ** significant at 5%; *** significant at 1%

Table 5: Results of logistic regression models (Full sample)

	Logit regression DV = Project failure		
	Model 1	Model 2	Model 3
USprojects	0.151 (.480)	0.392 (.476)	0.229 (.515)
1997-2001	1.923*** (.511)	1.881** (.618)	3.863*** (.844)
2001-2003	2.899*** (.586)	2.931*** (.582)	3.547*** (.628)
2004-2008	2.236*** (.413)	2.198*** (.431)	3.049*** (.443)
US x Before 2001	0.206 (.716)	0.409 (.778)	0.580 (1.054)
US x 2001-2003	.584 (.886)	0.563 (.889)	1.558* (.968)
US x 2004 – 2008	-0.530 (.550)	-0.433 (.565)	-0.422 (.549)
Large firms (>= 500 emp)		-0.568 (.476)	-0.558 (.664)
Small firms (<= 50 emp)		-0.384 (.352)	-0.391 (.360)
Firm age		0.005 (.0048)	0.0067 (.0055)
Startup		-0.135 (.283)	-0.145 (.317)
No. university deals		-0.156 (.122)	-0.114 (.163)
Project duration			-0.306*** (.067)
Autologous			-0.364 (.283)
No. clinical trials			-0.442** (.178)
No. enrollments			-0.00010 (.00017)
Constant	-1.149*** (.322)	-0.963** (.450)	0.212 (.403)
Therapeutic class fixed effects	No	No	Yes
Observations	483	455	453
Pseudo R^2	0.185	0.199	0.307
Log likelihood	-261.61	-242.73	-208.94

To account for the heterogeneity of firms, organizational_id cluster standard errors are calculated in parentheses; * denotes significant level at 10%, ** denotes significant level at 5%, and *** denotes significant level at 1%

Figure 2: Predicted failure rates for projects initiated by US and non-US firms (Based on Model 3 in Table 6)