

Public Funding for Science and the Value of Corporate R&D Projects; Evidence from Project Initiation and Termination Decisions in Cell Therapy

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ABSTRACT How do firms decide which R&D projects to pursue and which ones to cast aside? We use a real options approach to advance our understanding of how firms manage uncertainties in R&D project management, in particular uncertainties linked to the external scientific environment. Our findings highlight how these uncertainties have an impact on the initiation and discontinuation of R&D projects. We examine these effects in the context of shifts in US science policy in the cell therapy field, using a dataset on 570 R&D projects in the global cell therapy sector, initiated over the period 1986–2011. We find decreased R&D project initiation rates and higher discontinuation rates for projects initiated by US firms in the aftermath of policy shifts that increased uncertainties about public funding support for US cell therapy research. We also highlight how this effect was reversed as the US public funding outlook for such research recovered.

Keywords: Cell therapy, human embryonic stem cells, R&D projects, real options, science policy, technology management

INTRODUCTION

Organised within networks encompassing both academic institutions and commercial entities, the development of R&D projects in science-intensive industries such as the biotechnology industry feeds off and is closely intertwined with publicly funded scientific research (e.g., Cohen et al., 2002; Powell et al., 2005). Accordingly, public funding plays an important role in upstream R&D in these industries. While venture capitalists in Silicon Valley, the US region with the largest amount of early stage funding for biotechnology

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Journal of Management Studies published by Society for the Advancement of Management Studies and John Wiley & Sons, Ltd.

firms, provided US\$ 104 million in seed- and start-up- funding for biotechnology firms in 2012 (PricewaterhouseCoopers, 2015), the National Institutes of Health (NIH) alone distributed US\$ 258 million for biomedical research at the region's three major research universities in that same year. Moreover, NIH provided an additional US\$ 41 million of funding to Silicon Valley firms through its Small Business Innovation Research grant scheme (National Institutes of Health, 2015a).

Given the central role of external scientific communities in corporate R&D projects, uncertainties relating to firms' ability to rely on these communities as R&D projects progress, likely shape firms' management of these projects. The challenges these uncertainties represent are substantial. Both the scientific knowhow a firm needs over the course of an R&D project, and the new scientific knowhow that will become available during that period, are often difficult to predict when a firm commits resources to a new project.

One approach to understanding the management of uncertainties in a firm's external environment emanates from the finance literature on real options. Adopting a real options approach entails conceptualising investments in R&D projects as investments in a platform, which could enable, but does not oblige a firm to bring to the market new products in a specific technological field in the future (Bowman and Hurry, 1993; Kim and Kogut, 1996; McGrath and Nerkar, 2004; Oriani and Sobrero, 2008; Trigeorgis and Reuer, 2017). However, existing real options approaches are often seen as overestimating R&D project valuations as these mostly rely on assessments of uncertainties linked to future revenue streams, and do not sufficiently take into account other important sources of uncertainty (Van Putten and MacMillan, 2004). By focusing on uncertainties about a firm's external scientific environment, we expand the focus of this literature to the role of uncertainties about critical input resources for R&D projects.

Specifically, we focus on uncertainties that are the result of changes in science policy. Those involved in policy and regulation play an important role in shaping uncertainties that a firm faces in its external environment (Fabrizio, 2013; Henisz, 2000; Henisz and Williamson, 1999). In the case of R&D project investments, firms have for example been found to strategically allocate R&D resources to minimize market uncertainties based on different types of patent protection and regulatory approval requirements (Budish et al., 2015; Olson and Yin, 2017), as well as publicly funded reimbursement schemes for new products that R&D projects result in (Krieger et al., 2018).

We posit that science policies that increase funding uncertainties for scientific research have detrimental effects for the development of corporate R&D projects. According to the real options literature, a critical challenge for firms that consider irreversible, non-transferable resource commitments to projects is to manage uncertainties about future supplies of key input resources for these projects (Dixit and Pindyck, 1994; Kogut and Kulatilaka, 2001; Pindyck, 1993). Firms tend to delay or avoid such commitments as uncertainties increase about costs of project inputs (Dixit and Pindyck, 1994; Pindyck, 1993). Building on this insight we examine two effects of increased funding uncertainties for public research, on firms' management of resource commitments to R&D projects.

First, changes in the funding outlook for public research affect considerations underlying the initiation of projects. The initiation of R&D projects in science-driven technological

fields generally requires firms to make substantial upfront resource commitments that are not transferable to other fields. To gain access to and use tacitly held scientific know-how in specific fields, firms often set up internal corporate laboratories, as well as attract researchers from, and forge collaborations with academic laboratories with expertise in those fields (Cohen and Levinthal, 1990; Fabrizio, 2009; Fleming and Sorenson, 2004; Jong, 2016; Liebeskind et al., 1996; Wong et al., 2015; Zucker et al., 1998). However, the ability to redeploy those R&D resources across different fields is limited. For example, a firm that recruits stem cell biologists from top academic laboratories to work on an R&D project involving stem cells will in most cases face significant hurdles in redeploying those scientists to projects involving small molecule- or protein- drugs. Therefore, we posit that increased funding uncertainties for public research in a field will make it less attractive for firms to make upfront resource commitments to new R&D projects in that field.

Second, changes in the funding outlook for public research in a field affect firms' ability to move R&D projects down the development pathway towards the market. Advancing R&D projects in industries such as the biotechnology industry requires firms to forge collaborations across extensive interorganisational networks encompassing R&D partners, academic institutions, professional services firms, investors, contract manufacturers, etc. (Powell et al., 2005, 1996; Stuart et al., 2007). As new technological fields emerge, organisations across these networks face trade-offs about whether or not to make resource commitments to these fields. We argue that making such commitments becomes less attractive for *all* organisations across these networks when the funding outlook for scientific research deteriorates, not only for those firms that take decisions about the initiation of new R&D projects. This creates an additional hurdle for innovator firms that do decide to commit resources to new R&D projects in a field with a negative public funding outlook. It eventually makes it more difficult for these firms to find partners willing to commit the additional resources needed to bring these projects to a successful completion.

We assess these effects in the context of the R&D landscape of the global cell therapy sector following changes in US federal policies that restricted funding for research involving human embryonic stem cells (hESC) during the first decade of the 21st century. The global cell therapy sector finds its origins in the 1980s. However, the sector was mostly focused on the commercialisation of therapies comprising of mature, specialised cells directed at a relatively small number of therapeutic application areas with limited market potential up until the dawn of the 21st century. This all changed with a series of discoveries that allowed researchers to isolate hESCs and use these cells in drug discovery during the late 1990s opening up a wider set of opportunities to develop new therapies focused on pressing disease burdens in areas such as Alzheimer's, Parkinson's, diabetes, cardiovascular-, and liver- disease. Thus, hESC research was seen as critical to the development of the cell therapy sector during the first decade of the 21st century and US federal restrictions on hESC research were seen as potentially undermining scientific programs that were key for this sector (Mason and Manzotti, 2009; National Academies of Sciences, Engineering, and Medicine, 2002).

To examine the impact of shifts in hESC funding policy on the initiation and advancement of corporate R&D projects in the cell therapy sector, we created a unique dataset. It contains information on 868 worldwide deals involving the transfer of cell

therapy technologies from universities to firms over the period 1986–2013, and 570 new commercial cell therapy projects initiated by firms from across the globe over the period 1986–2011. We use these data to examine the initiation and advancement of corporate R&D projects in the US cell therapy sector and contrast it with the initiation and advancement of projects in the cell therapy sectors of other countries across four periods, during which the funding environment for public hESC research in the US changed.

Our findings indicate a drop in the propensity of US firms to initiate novel cell therapy R&D projects as compared to firms elsewhere after the announcement of a US federal funding moratorium on specific types of hESC research in 2001. We find that the involvement of universities in commercial markets for ideas in the cell therapy field diminished as well during this period. Focusing on the discontinuation of R&D projects in the cell therapy field, our results indicate that cell therapy projects that were initiated by US firms during the period following the examined changes in US science policy had a higher propensity for failure than projects initiated by non-US firms. A further analysis of our data shows that these increases in project failure rates were concentrated among US cell therapy projects that involved human embryonic stem cells and adult stem cells. Finally, we show that the drops in R&D performance we describe were reversed as the US funding outlook for cell therapy research stabilised and recovered.

Public Research and Novel Corporate R&D Projects

The initiation of a new R&D project in an emergent scientific field usually requires firms to make significant irreversible resource commitments to gain access to and use scientific knowledge in that field. While economists used to view scientific knowledge as a public good that is free to use (Arrow, 1959; Nelson, 1959), scholars nowadays tend to argue that scientific knowledge is not free to use. Especially knowledge at the scientific knowledge frontier that generally is of the greatest commercial value, often is tacitly held by star scientists, postdocs, and PhD students at top academic laboratories (e.g., Jong, 2006; Jong, 2008; Liebeskind et al., 1996; Thursby and Thursby, 2002; Zucker et al., 1998). Searching for and assimilating this knowledge requires firms to set up internal R&D organizations (Cohen and Levinthal, 1990; Fleming and Sorenson, 2004), forge collaborations with academic laboratories (Liebeskind et al., 1996; Stuart et al., 2007; Zucker et al., 1998), and participate in open methods of knowledge exchange such as through publications in scientific journals or presentations at academic conferences (Fabrizio, 2009; Jong, 2011; Jong and Slavova, 2014). Investments firms make in this context such as those in facilities to carry out specific types of experiments, in recruiting scientists proficient in the state of the art in a field, or in relationships with thought leaders in a scientific area, often are costly to repurpose for R&D projects in other fields later on.

Firms' dependency on external scientific communities in the initiation of new R&D projects in industries such as the bio-, nano-, and ICT- technology industries is substantial. A survey published in the 1990s found that 15 per cent of new products developed by industry over the period 1986–1994 could not have been developed without recent advances in academic research (Mansfield, 1998, 1995). This number was substantially higher for new drugs and medical products, namely 31 per cent. Another 1994 survey

found that 41.4 per cent of pharmaceutical drugs R&D builds on findings from public research, 12.3 per cent of pharmaceutical drugs R&D relies on prototypes that resulted from public research, and 35.4 per cent of pharmaceutical drugs R&D relies on instruments and techniques developed through public research (Cohen et al., 2002).

Moreover, managers must consider significant uncertainties about the future availability of critical input resources from external scientific communities when they commit resources to new R&D projects. Much scientific knowledge that firms will need in order to bring a promising idea to the market has yet to be produced when resources are committed to new R&D projects. Moreover, technological challenges along product development pathways and the knowledge firms need to tackle these challenges are often difficult to predict *ex ante*, especially in the development of projects that build on cutting-edge scientific research. Managers do know however that tackling challenges along product development pathways will most likely require access to knowledge that is external to the firm (Ahuja and Lampert, 2001; Katz and Tushman, 1981; Lee and Allen, 1982; Phene et al., 2006), with cutting-edge academic research being a particularly important source of external knowledge (Fabrizio, 2009; Fleming and Sorenson, 2004; Jong and Slavova, 2014). In fact, publicly funded scientific knowledge has been found to be an equally important input in the development phase of new R&D projects as it is in the discovery and initiation phase (Cohen et al., 2002).

This makes the management of uncertainties associated with firms' external scientific environment critical in R&D project initiation decisions. Some have analyzed the problem firms face in managing these uncertainties, using a real options logic. According to this logic, resource commitments to new R&D projects can be likened to investments in a platform (or portfolio of options), which could enable, but does not oblige a firm to further progress towards the market new products in a specific technological field at a future point in time (Bowman and Hurry, 1993; Kim and Kogut, 1996; McGrath and Nerkar, 2004; Oriani and Sobrero, 2008; Trigeorgis and Reuer, 2017). Two types of uncertainties tied to the external environment of firms have been found to shape the value of real options that R&D projects represent, namely 1) market uncertainties such as those linked to competitive dynamics in a market, market payoffs, and the opportunity scope of a project (Childs and Triantis, 1999; Huchzermeier and Loch, 2001; McGrath and Nerkar, 2004), and 2) uncertainties about how technological change shapes market structures (Tushman and Rosenkopf, 1992; Tegarden et al., 1999; Anderson and Tushman, 1990). However, existing real options approaches are often seen as overestimating R&D project valuations as these mostly rely on assessments of uncertainties linked to future revenue streams, and do not sufficiently take into account other important sources of uncertainty (Van Putten and MacMillan, 2004).

We expand existing research that uses real options approaches in examining R&D project initiation decisions by focusing on the role of uncertainties about input resources. According to real options theory, it becomes more attractive for firms to postpone these decisions or to pursue other projects as uncertainties increase about the future costs of critical input resources (e.g., Dixit and Pindyck, 1994; Kogut and Kulatilaka, 2001; Pindyck, 1993).

A central question in organizational theory is that of the coordination of resource allocations within loosely structured, networked fields, of which the biotechnology industry is an exemplar case (Owen-Smith and Powell, 2004; Powell et al., 2005, 1996; Stuart et al., 2007). The state plays a critical role in such coordination, for example by using policy and regulatory action to increase or decrease uncertainty about critical aspects of firms' environment (DiMaggio and Powell, 1983). Scholars have for example examined the impact of increased uncertainties in the regulatory environment on firms' willingness to make asset specific investments (Henisz, 2000; Henisz and Williamson, 1999). Moreover, 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. Similarly, we argue that public policy and regulation affect uncertainties about the outlook for scientific research in a field, which firms require access to for the advancement of new R&D projects. Scientific funding policies are critical in regulating the development of scientific knowledge, expertise, and skills that firms use as an input in corporate R&D projects. Changes in science policy may therefore either reinforce or undermine confidence among firms about their ability to rely on this input in the development of their projects in the future.

Restrictions and uncertainties about funding for scientific research in a particular field have already been found to be an important factor at the level of individual scientists in shaping career decisions scientists make about which fields of scientific enquiry to focus on. These decisions also involve significant upfront investments. For example, scientists spend considerable amounts of time and effort on becoming proficient in the state of the art in a particular field, for example by writing a PhD, before they are able to reap any professional, financial rewards in that field. Accordingly, expectations among researchers about their ability to attract public funding for research in a scientific field shape researchers' propensity to work on research projects in that field (Anstett and Bell 1959; Levine, 2006, 2008, 2012).

We build on this literature to argue that the public funding outlook for a scientific field is an important factor in firms' assessment about the attractiveness of R&D investment options in that field. We also argue that this is an effect that is geographically concentrated. Some have argued that laboratories in scientific fields where public science funding is restricted can mitigate some of the detrimental effects caused by these restrictions by forging collaborations with laboratories that are located in countries with more favorable funding environments (Furman et al., 2012; Vakili et al., 2015). The transfer of scientific knowledge, however, often requires personal interactions, and as a result, commercial and academic R&D in science-intensive industries tends to be geographically co-located (e.g., Zucker et al., 1998). This implies that while firms may mitigate some of the negative effects of country-level deteriorations in the scientific funding outlook by forging international collaborations, these firms remain at a comparative disadvantage in gaining access to cutting-edge scientific knowledge relative to firms in other countries. Thus, we expect that the impact of changes in the scientific funding outlook for research in a field is stronger for firms that are located in the geographical areas that are directly affected by these changes.

So what does this mean for our understanding of the effects of changes in the funding outlook for research in a scientific field on firms' propensity to launch new R&D projects? Following our reasoning we expect such changes that increase uncertainties about funding to have a negative effect on the propensity of firms to launch novel R&D projects. Moreover, we expect this negative effect to be stronger for firms that are geographically located in the regions where public research is affected by these changes. Thus, we pose the following hypothesis:

Hypothesis 1: The negative impact of deteriorations in the funding outlook for scientific research on firms' propensity to launch new R&D projects is larger for firms that are located in the geographical areas that are directly affected by these deteriorations.

Public Research and Corporate R&D Project Failure

We expect that changes in the public funding outlook for scientific research do not only affect firms' propensity to initiate new R&D projects, but also firms' propensity to move projects that are initiated down the pipeline towards the market. Resource environments, in which R&D projects are initiated, play an important role in shaping project outcomes. For example, the financing environment for new technology firms is important in shaping subsequent innovation outcomes (e.g., Jong, 2009; Nanda and Rhodes-Kropf, 2013). Firms that receive their initial venture capital investment in a 'hot' financing environments tend to be more innovative and are valued higher on the day of their initial public offering than firms that receive their initial venture capital investment in more restrictive financing environments (Nanda and Rhodes-Kropf, 2013).

We argue that a resource environment, in which the funding outlook for scientific research is poor, will produce R&D projects with a higher propensity of failure than resource environments with a better outlook for scientific research. Product innovation in science-intensive sectors is organized within collaboration networks that involve extensive webs of organizational actors possessing the wide range of competencies and resources needed for a project's advancement (Powell et al., 2005, 1996). Many of these firms (e.g., investors, contract manufacturers, clinical trials units, legal services-, and staffing- firms) actually do not directly use publicly funded scientific knowledge as an input. However, these firms do share similar trade-offs in decisions about making upfront commitments of resources to specific fields. For example, a dilemma for biopharmaceutical contract manufacturers at the time of the expansion of the cell therapy sector during the first decade of the 21st century was whether or not to invest in manufacturing facilities for cell therapies. The costs of such facilities are substantial (these can run into the hundreds of millions of dollars), and once facilities are set up and running, repurposing these for manufacturing other types of therapies (e.g., small molecule-, protein- drugs) is not feasible. Accordingly, long-term prospects for continued business in a field are an important consideration in making such investments.

Following a real options logic, we argue that science policy considerations also are an important factor for firms that do not directly use publicly funded scientific research as an input resource, in managing uncertainties in the external environment. For these

firms, science policy likely represents a useful signal about the long-term prospects for additional business opportunities beyond incidental deal opportunities that may arise in a new field. Policies that increase uncertainties about the scientific environment in a field will likely decrease the real options value of the prospects for additional business opportunities in that field. Accordingly, we expect upfront resource commitments by organizations that play a supporting role to firms that initiate and develop new science-based R&D projects in a field, to be directed away to other fields when the public funding outlook for scientific research in that field becomes more uncertain. This means that even if individual R&D firms are willing to commit resources to the initiation of novel R&D projects in a field, for which the public funding outlook is deteriorating, managers of these firms will likely find it more difficult to find other firms that are willing to commit resources to these projects, increasing these projects' chances of failure.

Finally, we argue that this effect is particularly strong for firms that are based in the geographical areas affected by deteriorations in the funding outlook. Like for the effect of funding restrictions on firms' propensity to initiate novel R&D projects, we build on the notion that knowledge that is valuable in the advancement of R&D projects in science-intensive industries is often tacitly held and benefits of the physical co-location of critical partners. Accordingly, we argue that the negative effect of scientific funding uncertainties on the propensity for failure of corporate R&D projects in a research field is larger for firms that are in the country where the funding outlook for scientific research in that field deteriorates. Accordingly, we posit the following hypothesis:

Hypothesis 2: The negative impact of science policy changes that increase scientific funding uncertainties on the propensity for failure of corporate R&D projects is larger for projects initiated by firms that are located in the geographical areas where these policy changes are enacted.

METHODOLOGY

Research Setting

We examine the impact of changes in science funding policies on corporate R&D projects in the context of the global cell therapy sector over the period 1997–2011. The cell therapy sector is an important sub-sector in the biotechnology industry and is organised around the development of cells (as opposed to small molecules or proteins) as therapies.¹ It is moving towards the market high-profile therapies, including therapies that regenerate human bladder, brain, and spinal cord tissues, and that trigger or act as an immune response to cancer. There were a total of 366 cell therapy projects under active development in 2015 (Citeline, 2015).

In this study we focus on the impact of changes in the funding outlook for human embryonic stem cells (hESC) on corporate R&D projects in the cell therapy sector. The first hESCs were isolated by the lab of James Thomson at the University of Wisconsin in 1998. The scientific advances made at Thomson's lab represented one of the important

milestones that led the journal *Science* to proclaim stem cell research as the 'Breakthrough of the Year' in 1999 (Vogel, 1999). The promise of hESCs for the cell therapy sector was derived from the unique capacity of these cells to renew themselves and to develop into the different cell types that make up the human body. Like scientific research driving corporate R&D agendas in the broader biotechnology industry (Liebeskind et al., 1996; Zucker et al., 1998), high-impact scientific research of importance to R&D in the cell therapy sector was concentrated at top universities. Furman et al. (2012) found that 24 per cent of all publications in the hESC research field had as the reprint author a researcher affiliated with a top-25 US university.

While many of the research agendas that the isolation of hESCs had opened up still were in their early stages of development, a consensus had formed around the dawn of the 21st century that hESCs would be critical to the future of the cell therapy sector. The first cell therapy companies date back to the late 1980s, and most of these firms focused on the commercialisation of new cell therapies that do not involve stem cells. Apligraf and Dermagraft are examples of such cell therapies, consisting of mature, specialised cells, that were developed during the 1980s and 1990s (Forti and Jong, 2014). These two therapies are skin substitute products used for foot ulcer healing that produce many of the same proteins and growth factors found in healthy skin. Such therapies typically remain viable for relatively short periods (days, weeks) and then die off.

The outlined breakthroughs in hESC research, however, heralded a much broader set of opportunities to develop new therapies focused on pressing disease burdens in areas such as Alzheimer's, Parkinson's, diabetes, cardiovascular disease, and liver disease. A commission of leading basic and clinical biomedical researchers that the National Academies of Sciences convened in 2001 focused on the role of hESC research in the future development of regenerative medicine. The commission's report put forward that new hESC lines would likely be critical in the advancement of the cell therapy field, even though it was not possible to specify *ex ante* which new stem cell lines would be needed and, in which areas these stem cell lines would be most critical (National Academies of Sciences, Engineering, and Medicine, 2002). This intrinsic link between the fates of academic hESC research and the industrial cell therapy sector have continued to permeate the discourse about prospects for the cell therapy field among external observers (e.g., Mason and Manzotti, 2009), senior academic researchers involved in the field (Klein et al., 2009; Wolinsky, 2008), investors (Brick, 2001), policy makers (NIH, 2015b), and industry executives.

The changes in the public funding environment for hESC research we will focus on in this study centre on the aftermath of an executive order on federally funded hESC research that was announced in a nationally televised address by President George W Bush on 9 August 2001. While permitting NIH to provide grant funding for research on seventy-one lines of hESCs left over from in vitro fertilisation treatments from 14 laboratories prior to the instatement of the moratorium, this executive order prohibited such funding for research on any newly created hESC lines.

The aftermath of the announcement of this moratorium provided something akin to a controlled 'natural experiment' research setting to examine the impact of changes in science funding environments on academic research (Furman et al., 2012; Levine, 2012, 2008; Owen-Smith 2006; Moon and Cho, 2014; Owen-Smith and McCormick, 2006;

Vakili et al., 2015). There is a number of reasons why this setting is such a fruitful setting to examine the interplay between scientific funding decisions and the activities of those affected by these decisions.

- The funding moratorium was enacted at a specific point in time and its scope, namely any research utilising hESC lines that were derived before the announcement of the moratorium, was clearly delineated.
- The specifics of US funding policy regarding hESC research were not known up until the announcement of the moratorium by President George W. Bush on 9 August 2001. In fact, the announcement was met with considerable surprise by the media and scientists (Furman et al., 2012).
- The moratorium spanned a period that offered an otherwise favourable funding environment for biomedical research. The annual NIH budget roughly doubled over the 1995–2005 period.
- The 2001–2009 moratorium on federally funded hESC research was US-specific. Thus, by contrasting R&D activities of US and non-US firms before, during, and after the the enactment of the US federal funding moratorium on specific types of hESC research, we are able to control for a range of factors that are instrumental in supporting innovation in science-intensive industries and that change over time.

While the impact of the various funding policy shifts in the hESC field on scientific programs involving human embryonic- and other types of stem cells, has by now been well documented, this study will extend the existing literature on these shifts by focusing on their impact on corporate R&D projects.

Time Intervals

We focus our analyses on four time intervals that mark distinctive periods in terms of the funding outlook for cell therapy research in the US (see Table I). These intervals are similar to ones used by studies that examined the impact of the hESC funding moratorium on publications by and labour market mobility of US-based hESC researchers (Anstett and Bell 1959; Furman et al., 2012; Levine, 2006, 2008, 2012; Moon and Cho, 2014; Owen-Smith and McCormick, 2006; Vakili et al., 2015).

1997–2000: Initial embrace of new hESC research programs by science policy makers. The isolation of embryonic stem cells at the Thomson laboratory of the University of Wisconsin (of monkeys in 1995; of humans in 1998), was followed by an initial embrace of hESC research programs by science policy makers during the last two years of the administration of US President Bill Clinton. During this period federal funding agencies were seen as positively inclined towards funding new hESC research programs opened up by Thomson's discoveries, with NIH soliciting proposals for future research beyond existing cell lines (Furman et al., 2012). Moreover, studies on the development of hESC research indicate no significant cross-national differences in the growth rates of publications in the hESC field over this time interval (Furman et al., 2012; Moon and Cho, 2014; Vakili et al., 2015).

Table I. Milestones in development of US hESC policy (1997–2011)

1997–2000	• First hESCs isolated by lab of James Thomson, University of Wisconsin-Madison in 1998. Breakthrough followed isolation of monkey embryonic stem cells by same laboratory in 1996. • <i>Science</i> proclaims stem cell research ‘Breakthrough of the Year’ in 1999.
2001–2003	• Reports by the National Institutes of Health (2001), and National Academies of Sciences, Engineering, and Medicine (2002) emphasize importance of further research on human embryonic stem cells for future of cell therapy field. • US President George W. Bush signs executive order in August 2001 that imposes a federal funding moratorium on research on new human embryonic stem cell lines.
2004–2008	• California voters approve Proposition 71. The Act is also known as the California Stem Cell Research and Cures Act of 2004. It includes a US\$ 3 billion state bonds issue to fund stem cell research. • Stem Cell Research Enhancement Act of 2005 (H.R. 810) is passed by US Congress. The Act was supposed to pave the way for federal support for research that utilizes hESCs, but was vetoed by US President George W. Bush in 2006. • Connecticut, Illinois, Massachusetts, and New Jersey step in with state-level stem cell programs (2004–06).
2009–2011	• President Barack Obama signs executive order in 2009 that repeals Bush-era moratorium limiting federal tax dollars for embryonic stem cell research.

2001–2003: The enactment of a federal moratorium on specific types of hESC research. The 2001–2003 interval covers the first years of the funding moratorium. As federal funding traditionally represents the most important source of funding for basic biomedical research in the US, prospects to attract public funding for future hESC research were greatly diminished after the enactment of the 2001 hESC research funding moratorium. The size of the scientific effort in stem cell research was relatively small in the context of the broader basic and clinical biomedical research endeavour of the early 2000s. NIH funding for human embryonic stem cell research totalled US\$ 10.7 million in 2002, and US\$ 17 million in 2003; NIH funding for adult stem cell research totalled US\$ 170 million in 2002, and US\$ 181.5 million in 2003 (The President’s Council on Bioethics 2004). Moreover, stem cell research comprised less than 1 per cent of the total NIH budget, which was US\$ 23.6 billion in 2002, and US\$ 27.1 billion in 2003.

Several studies highlight an immediate and sizable drop in research productivity of US-based researchers as compared to researchers based elsewhere during the years after the enactment of the moratorium (Furman et al., 2012; Moon and Cho, 2014; Owen-Smith and McCormick, 2006; Scott et al., 2011). US knowledge production in the hESC field fell 35 to 40 per cent below anticipated levels, 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 career prospects in the field of hESC research in the US suddenly uncertain, increasing numbers of researchers in the field

Table II. Variables used in empirical analyses

<i>Variable names</i>	<i>Description</i>	<i>Source</i>
<i>Dependent variables</i>		
No. project initiation	Total number of new cell therapy projects that enter pre-clinical or clinical trials in a given year.	Citeline Pharmaprojects
% of non-SC project	The percentage of cell therapy projects initiated by a firm that does not involve stem cells in a given year	Citeline Pharmaprojects
% of adult SC projects	The percentage of cell therapy projects initiated by a firm that does not involve any hESCs in a given year	Citeline Pharmaprojects
% of hESC projects	The percentage of cell therapy projects initiated by a firm that involves hESCs in a given year	Citeline Pharmaprojects
Project failure	A binary variable that takes the value of 1 if a cell therapy project is discontinued by a firm AND is not taken up for development by another firm. The value is 0 if otherwise	Citeline Pharmaprojects
<i>Independent variables (firm-level)</i>		
US project	A binary variable that takes the value of 1 if a cell therapy project is initiated by a firm based in the United States. The value is 0 if otherwise.	Compustat, LexisNexis firm database
Large firms (≥ 500 employees)	A binary variable that takes the value of 1 if the firm which initiates a focal project had more than 500 employees during the year the project is initiated.	Compustat, LexisNexis firm database
Small firms (≤ 50 employees)	A binary variable that takes the value of 1 if the firm which initiates a focal project had fewer than 50 employees at the year the project is initiated. (medium-sized firms is the reference group)	Compustat, LexisNexis firm database
Company age	Difference between the project start year and the firm's founding year.	Compustat, LexisNexis firm database
No. university deals	Number of prior university deals of a firm at the time a new project is initiated.	Recap IQ Series, Deal Builder
No. deals	Number of all prior deals of a firm at the time a new project is initiated.	Recap IQ Series, Deal Builder
<i>Independent variables (project-level)</i>		
<i>Project initiation period</i>		
Post2000	A binary variable that takes the value of 1 if a cell therapy project was initiated during or after 2000. The value is 0 if otherwise.	Citeline Pharmaprojects
1997–00	A binary variable that takes the value of 1 if a cell therapy project was initiated between 1997 and 2000. The value is 0 if otherwise.	Citeline Pharmaprojects
2001–03	A binary variable that takes the value of 1 if a cell therapy project was initiated between 2001 and 2003. The value is 0 if otherwise.	Citeline Pharmaprojects

(Continued)

Table II. (*Continued*)

<i>Variable names</i>	<i>Description</i>	<i>Source</i>
2004–08	A binary variable that takes the value of 1 if a cell therapy project was initiated between 2004 and 2008. The value is 0 if otherwise.	Citeline Pharmaprojects
2009–11	A binary variable that takes the value of 1 if a cell therapy project was initiated between 2009 and 2011. The value is 0 if otherwise.	Citeline Pharmaprojects
No. patients enrolled in clinical trials	The cumulative number of patients enrolled in clinical trials for a focal project from the start of the project up until 2012.	ClinicalTrials.gov
No. clinical trials	The cumulative number of clinical trials undertaken for a focal project from the start of the project up until 2012.	ClinicalTrials.gov
Project duration	The number of years from the time a new cell therapy project enters pre-clinical or clinical trials until the therapy hits the market (or if not completed by 2012, then the duration is calculated from the start of the project up until 2012).	Citeline Pharmaprojects
Therapeutic classes	Dummy variable that classifies a cell therapy as belonging to one of the following nine therapeutic classes: alimentary metabolic, anti-infective, anti-cancer, blood clotting, cardiovascular, dermatological, musculoskeletal, neurological, and miscellaneous products	Citeline Pharmaprojects
Stem cell project	A binary variable that takes the value of 1 if a cell therapy project is a stem cell project.	Citeline Pharmaprojects
Constrained regime	A binary variable that takes the value of 1 if the cell therapy project was initiated in a country regime with a constrained regulatory regime that restricted research on hESCs during the examined period. The value is 0 if otherwise.	Vakili et al. (2015)

moved to different countries with more favourable funding environments (Anstett and Bell 1959; Levine, 2006, 2008, 2012).

Contemporary accounts indicate that the 2001 moratorium also affected commercial R&D. These accounts suggest that the sudden policy changes and political turmoil around the topic, dampened the willingness of investors to commit resources to cell therapy companies. Reflecting on the impact of the 2001 hESC research moratorium Thomas Okarma, CEO of Geron, one of the leading stem cell companies during the 2000s for example 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)

In line with these remarks, studies have highlighted that the effects of the funding moratorium that was enacted in 2001, extended beyond the specific hESC programs the moratorium targeted. The restrictions and uncertainty the moratorium created also affected other interlinked research programs across the cell therapy field that do not involve hESCs. These for example included research programs on induced pluripotent stem cells (iPSCs). 40 per cent of scientists working on iPSCs reported negative effects of the hESC funding moratorium in their research (Levine, 2011). Moreover, Scott et al. (2011) found that the hESC research moratorium and the ensuing uncertainty about the general funding environment for cell therapy research, significantly held back research in the iPSC field.

2004–2008; Funding prospects for different types of stem cell research improve. The funding outlook for scientific research on stem cells significantly improved during the period 2004–2008. While the federal funding moratorium remained in place, movements to strengthen funding support for stem cell research won important victories at state- and federal- levels. At the state level, initiatives sought to offset federal funding restrictions in 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 US\$ 3 billion state bonds issue to fund stem cell research. Other states that by 2006 had stepped in with local stem cell research programs were Connecticut, Illinois, Massachusetts, and New Jersey (Vakili et al., 2015).

At the federal level, a series of victories by opponents of the federal hESC research-funding moratorium made a reversal of the moratorium appear 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 After 2004, the deterioration of the hESC research environment in the US was gradually reversed, and uncertainties about future funding support for hESC research diminished. Furman et al. (2012) highlight that the gap in research productivity between non-US- and US-based hESC researchers grew smaller after 2004 so that the production of US hESC follow-on papers was only 29 per cent lower than the production of non-US follow-on papers. Apart from a changing funding outlook for hESC research in the US at state and federal levels, Furman et al. (2012) attribute this reversal to US researchers who forged collaborative ties with international research groups operating in less restrictive funding environments.

2009–2011: Bush era moratorium is reversed. The election and inauguration of Barack Obama sealed the fate of the Bush era moratorium in the hESC field. Ending funding limits on hESC research imposed by the moratorium had been an important campaign promise during the presidential election. President Obama fulfilled his campaign promise and ended the Bush era moratorium using an executive order in March 2009. This period also coincided with the height of the financial crisis that followed the collapse of Lehman Brothers in 2008, which led to a general deterioration of the private funding environment for R&D-intensive companies.

Data Analysis

Project initiation. Hypothesis 1 relates to the impact of deteriorations in the outlook for scientific research in a field on the initiation of corporate R&D projects. To test this hypothesis, we implement a difference in differences analysis to estimate the impact of the 2001 policy intervention on the initiation of corporate cell therapy projects. Difference in differences is a commonly used econometric technique that estimates the effect of a specific (policy) intervention or (medical) treatment by comparing changes in outcomes before and after the intervention between a control and a treatment group. The advantage of a difference in differences analysis is to obtain the treatment effect while accounting for unobserved variables that are assumed to be fixed over time (Angrist and Pischke, 2008, Zhou et al., 2016). We implement this technique to capture differences in project trajectories before and after policy events that changed the outlook for cell therapy research in the US.

Specifically, we focus on changes in the numbers of cell therapies that enter preclinical or clinical trials in the US and outside the US, before and after the enactment of the US federal hESC research funding moratorium. The number of projects that enter preclinical or clinical studies is a good proxy to assess resource commitment decisions related to market entry in the life sciences industry (e.g., Pisano 2006). The commercialisation of new medicines is governed by a strict regulatory framework, within which firms are required to collect and report to regulators data on the safety and efficacy of these medicines. Data are collected in preclinical studies, and subsequently in phase 1, 2, and 3 human subject studies that typically escalate in scale, complexity, and costs as these studies progress to the next stage. Investments in clinical trials constitute the most resource-intensive part of the biopharmaceutical R&D process; A 2006 study estimates clinical trials costs for new drugs that are developed by major biopharmaceutical companies to run between US\$ 500 million and in excess of US\$ 2 billion (Adams and Brantner, 2006). Therefore, investment decisions by firms linked to the initiation of (pre-) clinical trials constitute a useful indicator of R&D priorities firms set across disease areas.

Project failure. Hypothesis 2 focuses on the impact of changes in the outlook for public research in a field on the propensity for failure of corporate R&D projects initiated by companies in that field. To test this hypothesis we focus on discontinuation rates of cell therapy projects initiated by US- and non-US- firms before and after the enactment of the US federal hESC research funding moratorium. As the biopharmaceutical product

development process is so costly, risky, and protracted over time, traditional markers of R&D success such as sales or even products on the market are problematic. For example, by 2015, the global R&D effort of the cell therapy sector of the preceding 20 years had yielded no more than 32 cell therapies on the market (Citeline, 2015). Accordingly, industry practitioners and observers use alternative proxies for R&D performance and value creation, with the progression of projects along the different stages of the preclinical and clinical testing trajectory being the most widely used. Firms realize a significant amount of value during the clinical trials process, well before any product hits the market. For example, in its acquisition of Pharmasset that was announced at the end of 2011, Gilead Sciences in essence paid US\$ 11 billion for a hepatitis C drug that was in clinical trials phase 2 of the drug development path (Grocer, 2011).

Data sources. We collected data on the development of the corporate R&D landscape in cell therapy from multiple sources.

Project-level variables. We used the Citeline Pharmaprojects database to collect information on cell therapy projects that were under active development at any time over the period 1986–2011. The Citeline Pharmaprojects database is a leading industry database that has tracked clinical trials in the global biopharma industry since the mid-1980s. Citeline Pharmaprojects data is compiled by an editorial team from a range of public sources (e.g., clinicaltrials.gov, press releases, news coverage, international conferences) as well as through direct communication with companies. Because of the scale and scope of the coverage of the database as well as because it is public, Citeline Pharmaprojects is both widely used for market research and scientific studies using pharmaceutical industry product development data (e.g., Aggarwal and Hsu, 2014; Bierly and Charkrabarti, 1996; Cardinal, 2001; Sosa, 2011). Despite its good coverage of the biopharmaceutical R&D landscape, Citeline Pharmaprojects does not cover projects that companies do not disclose. While firms might be less likely to disclose projects that are at earlier stages of the development process, there is no reason to suspect that there is a systematic difference in underreporting for different types of projects.

Citeline Pharmaproject's editorial team categorizes each project that is in the database according to the source material for the project – the most important distinction being between protein-, small molecule-, and cell therapy- projects. Accordingly, we were able to identify all the projects in the Citeline Pharmaprojects database that are cell therapies. In total, we extracted information on 592 cell therapy projects that entered development from 1986 until June 2012. For the purpose of our analyses, we only use projects initiated from 1997 until the end of 2011. Accordingly, we ended up with a total of 538 projects for our analyses.

From the Citeline Pharmaprojects dataset, we collected project-level data, including data on the project initiation year, and the status of the cell therapy project in 2014. The Citeline Pharmaprojects dataset indicates the status of a project, classifying it as discontinued, suspended, licensed out, taken up for development by another firm, or active. We categorize failed projects as those listed as suspended or terminated. Using information from ClinicalTrials.gov, we found that of the 538 cell therapies, 71 per cent were

undergoing preclinical trials, 12.4 per cent were in phase 1 studies, 10.4 per cent were in phase 2 studies, and 6.2 per cent were in phase 3 studies. For discontinued projects ($N = 355$), we found that 80 per cent had failed in preclinical trials and 20 per cent had failed in clinical trials.

Based on the Citeline Pharmaprojects project descriptions for the cell therapy projects in our sample, we categorized all projects in our sample (both active and discontinued projects) based on whether these were stem cell therapy projects ($N = 264$) or non-stem cell therapy projects ($N = 274$). Of the 264 stem cell projects, only 9 per cent ($N = 23$) were hESC projects.³ Due to the small number of cases of hESC projects, this study is not able to test the effect of changes in the funding outlook on the initiation and failure of hESC R&D projects only; instead we focus in our analyses on the broader set of interlinked research programs that make up the cell therapy field. As highlighted, the examined policy changes reverberated across this entire field.

We used other sources to construct several project-level measures. From the ClinicalTrials.gov database website, we obtained information on numbers of clinical trials and patient enrollments for each project. To account for different national hESC policy environments, we adopted Vakili et al.'s (2015) categorization of countries based on whether countries where projects were initiated, offered a regulatory environment that was 'constrained' (i.e., restrictive) for research on hESCs (e.g., Austria, France, Germany, Italy, Japan, Norway, Poland), or a regulatory environment that was 'flexible' (i.e., permissive) for research on hESCs (e.g., UK, China, Israel, South Korea, Taiwan). About one-third of non-US projects were projects initiated in countries with a 'constrained' regulatory environment, and 72 per cent of non-US projects were projects initiated in countries with a 'flexible' regulatory environment.

For the 538 cell therapy projects in our sample, we identified 221 companies as initiators of projects. Of these 221 firms, approximately half are US-based firms (56 per cent). 16 per cent of firms are large firms with more than 500 employees and 56 per cent are small firms with fewer than 50 employees. The average number of cell therapy projects per firm is 2.5 over the research period of our paper, with a standard deviation of 2.4, a median of 1, and a mode number of 1. The descriptive statistics show that 55 per cent of firms in our sample introduced only a single project. The 75th percentile is three projects.

We assembled firm-level data from a range of business intelligence sources on the 221 firms that initiated the development of the cell therapies in our sample (e.g., Compustat-Capital IQ, Factiva, Hoover's, Google, and Bloomberg.com). These data help us ascertain that observed differences in R&D project initiation and failure rates inside and outside the US were not the result of firm heterogeneity.

Finally, we collected data from the Thomson-Reuters' Recap database on the involvement of companies in technology transfer deals in the cell therapy field, including those with academic institutions, and the years when these deals were announced. The Thomson-Reuters' Recap database is one of the leading international databases on technology licensing deals in the biopharmaceutical industry. The Thomson-Reuters' editorial team specifies for each deal whether it involves cell therapies. Accordingly,

we were able to use the Recap database to identify a total of 864 technology transfer deals in the cell therapy field between 1986 and 2011. To account for a company's R&D experience and capability, we later used these data to construct two additional firm-level measures to quantify 1) a firm's total number of prior collaborations with outside organizations, and 2) a firm's total number of prior collaborations with academic institutions. Table II contains an overview of the variables and data sources we used in our analyses.

Descriptive Statistics

Table III presents descriptive statistics for cell therapy projects in our sample. Characteristics of US and non-US projects are roughly similar in terms of project duration, the number of clinical trials that are associated with a project, and the size of patient enrollments in clinical trials. T-tests are statistically insignificant between the two groups. Failure rates are slightly higher for US projects than for non-US projects (69.3% vs. 61.6%, $\chi^2 = 3.43$, $p = 0.064$). We find that non-US projects are more likely to be launched by larger, older firms, with fewer prior licensing deals. As mentioned before, we identified 264 stem cell therapy projects, including 23 projects involving human embryonic stem cells in our sample. Both half of the US- and half of the non-US projects are stem cell therapy projects, with the t-test being insignificant between the two groups. There were very few hESC projects initiated in the US (5.2%) and outside the US (3.0%, $\chi^2 = 1.58$, $p = 0.209$), with the t-test being insignificant. This suggests a similar distribution of stem cell and non-stem cell therapy projects for the US- and non-US- samples. Finally, we also provide a correlation matrix to check for the collinearity between the continuous variables (See Table IV).

Figure 1 plots over time data on the initiation of US and non-US cell therapy projects that entered preclinical or clinical trials. Figure 1 highlights comparatively low numbers of product development projects launched by US firms in the immediate aftermath of the enactment of the hESC federal funding moratorium. 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 initiated by non-US firms. Figure 1 also highlights a rebound in the number of cell therapy projects that US firms initiated following the launch of state initiatives aimed at providing funding support for stem cell research, most notably California's Proposition 71 that Californians passed in 2004. In fact, figure 1 illustrates that US firms again were leading in annual numbers of cell therapy projects that were initiated by 2006. It is notable that the US cell therapy sector experienced a second significant drop in annual project initiations in 2009, after the collapse of Lehman Brothers and the ensuing great recession that hit the entire economy. However, this second drop in R&D output of the US cell therapy sector coincided with a similar drop in R&D activity of the cell therapy sectors outside the US, which were also affected by the financial crisis. Moreover, we start to again see an increase in the number of cell therapy projects from 2011 onwards as the recovery of the great recession sets in.

Table III. Descriptive statistics for cell therapy projects initiated between 1997 and 2011

<i>Variables</i>	<i>US projects</i>		<i>Non-US projects</i>		<i>All projects</i>	
	<i>(N = 306)</i>		<i>(N = 232)</i>		<i>(N = 538)</i>	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
DV: Project discontinuation (D)	69.3%	0.46	61.6%	0.48	65.8%	0.46
IV: Project-level variables						
(1) Project initiation period:						
1997–00 (D)	19.2%	0.39	8.2%	0.27	14.5%	0.35
2001–03 (D)	20.2%	0.40	11.6%	0.32	16.5%	0.37
2004–08 (D)	38.9%	0.49	46.1%	0.50	42.0%	0.49
2009–11 (D)	21.5%	0.41	34.0%	0.47	26.9%	0.44
(2) Stem cell project (D)	50.0%	0.50	48.0%	0.50	49.1%	0.50
(3) hESC project (D)	5.2%	0.22	3.0%	0.17	4.3%	0.20
(2) Project duration (years)	4.5	2.8	4.1	2.4	4.3	2.7
(3) No. patients enrolled in clinical trials	91.3	433.1	88.2	778.9	89.9	607.1
(4) Number of clinical trials	0.66	1.5	0.53	1.0	0.60	1.4
IV: Firm-level variables						
(1) Firm size:						
Large firm (≥ 500 employees) (D)	10.1%	0.30	15.5%	0.36	12.4%	0.33
Medium-sized firm (51–499 employees) (D)	32.3%	0.46	35.7%	0.49	34.8%	0.47
Small firm (≤ 50 employees) (D)	57.5%	0.49	48.7%	0.50	53.7%	0.49
(2) Firm age	10.3	19.0	18.6	38.3	13.8	29.0
(3) No. prior university deals	0.68	1.26	0.09	0.29	0.42	1.01
(4) No. prior deals	3.12	5.3	0.81	1.5	2.12	4.3
(5) No. prior cell therapy projects	2.37	2.05	2.35	2.37	2.36	2.20

Note: (1) D denotes binary variables; (2) The numbers in the US versus non-US columns indicate the average proportion of occurring cases for each variable between US-projects and non-US projects. For example, 69 per cent of US-projects and 61.6 per cent of non-US projects failed during the examined period.

Table IV. Correlation matrix for continuous variables

<i>Variables</i>	<i>(1)</i>	<i>(2)</i>	<i>(3)</i>	<i>(4)</i>	<i>(5)</i>	<i>(6)</i>	<i>(7)</i>	<i>(8)</i>	<i>(9)</i>
(1) Project discontinuation (D)	1								
(2) Project duration	0.086	1							
(3) Number of enrollments	-0.004	0.003	1						
(4) Number of clinical trials	-0.184*	0.197*	0.421*	1					
(5) Firm age	0.048	0.085	-0.025	-0.014	1				
(6) No. prior university deals	-0.011	0.042	-0.030	0.026	-0.023	1			
(7) No. prior deals	-0.030	-0.018	-0.034	0.013	-0.005	0.860*	1		
(8) No. prior cell therapy projects	-0.013	-0.107	-0.014	-0.025	0.086	0.307*	0.396*	1	
(9) US projects (D)	0.129	0.073	0.003	0.052	-0.142*	0.287*	0.265*	0.004	1
(10) SC therapy project (D)	-0.167	-0.036	-0.076	0.019	-0.049	0.225*	0.253*	0.029	0.034

Note: (1) D stands for dummy variable; (2) * denotes significantly different from zero at the 1 percent probability threshold; (3) Pearson correlation coefficients (for two continuous variables) / Point biserial coefficient (for one continuous variable and one dummy variable) / Tetrachoric correlation (for two dummy variables).

Table V. Share of university deals in cell therapy and overall biotechnology fields

	<i>Number of cell therapy deals (N = 864)</i>	<i>Percentage of cell therapy deals that are with universities</i>	<i>Percentage of cell therapy deals that are with US universities</i>	<i>Average number of university-industry deals in biotechnology per year (N = 6762)</i>
1986–96	128	35%	34%	130.8
1997–00	63	17.4%	15.8%	215
2001–03	107	10.3%	10.3%	255.3
2004–08	365	23.0 %	17.8%	437.4
2009–11	201	18.4%	11.4%	547

Source: Compiled from Recap IQ Series (2014).

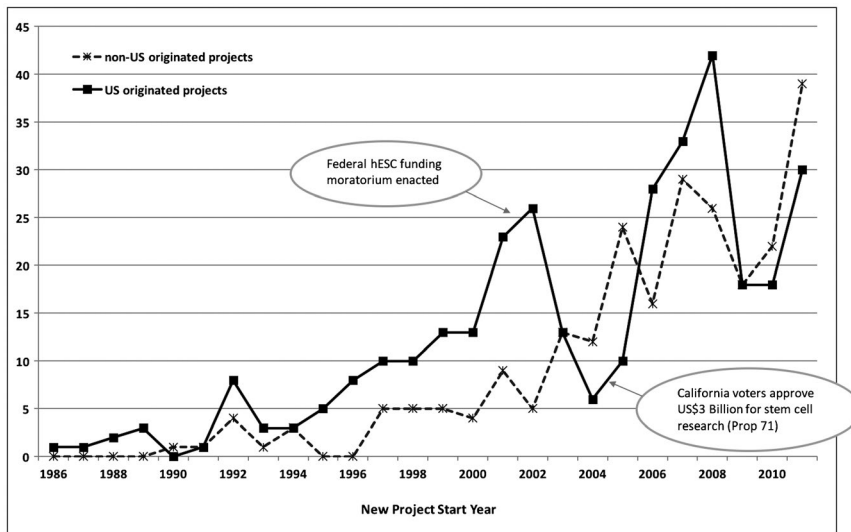


Figure 1. Number of cell therapy projects entering (pre-)clinical trials by originator country (N = 570)
 Source: Compiled from Citeline Pharamaprojects database (June 2012).

Table IV provides an overview of information we collected from the Thomson-Reuters Recap database on technology transfer deals in cell therapy. Our 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 markets for cell therapy technologies. Firms benefit more from scientific input when technologies are more novel and radically innovative (e.g., Fleming and Sorenson, 2004; 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 cell therapy 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 subsequently dropped and was around twenty-one per cent for most of the period 1997–2011, with the exception of 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 10.3 per cent. Notably, the unusual drop of university-industry deals over the period 2001–2003 appears to have been a non-trivial phenomenon that was specific to the cell therapy field. Table IV – column (4) highlights that university-industry deals in the biotechnology industry as a whole actually increased to 255 deals per year over the 2001–2003 period compared to 215 deals per year over the preceding period, and the overall trend continued to be upward afterwards.

RESULTS

Changes in the Corporate R&D Landscape in Cell Therapy – Project Initiations

We construct a panel dataset with data on the 221 firms that initiated new cell therapy projects between 1992 and 2011 to examine the trend illustrated in Figure 1 more closely.⁴ We use this dataset to assess the deterioration in the funding outlook for cell therapy research caused by the impact of the 2001 federal funding moratorium on the propensity of non-US and US companies to initiate novel cell therapy projects.

We estimate the basic equation as follows:

$$\#projects_{it} = f(\gamma_i + \delta_{t-firm_{estyr}} + \alpha_0 US_i * (t \geq 2001) + \alpha_1 x_{1i} + \varepsilon_{it}) \quad (1)$$

where i indicates the firm and t the year, while γ_i is a fixed effect for each firm and $\delta_{t-firm_{estyr}}$ indicates the age of the firm. α_0 is the coefficient for the interaction term of $US_i * (t \geq 2001)$, identifying the difference in project initiation rates between US firms and non-US firms. α_1 captures the effect of a firm's prior involvement and experience in markets for technology in the cell therapy sector in year t .

We further test equation (2) and (3) to assess the impact of government funding restrictions across different periods.

$$\begin{aligned} \#projects_{it} = & f(\gamma_i + \delta_{t-firm_{estyr}} + \alpha_0 US_i * (2001 - 2003) + \alpha_1 US_i * (2004 - 2008) \\ & + \alpha_2 US_i * (2009 - 2011) + \alpha_3 x_{1i} + \varepsilon_{it}) \end{aligned} \quad (2)$$

and

$$\begin{aligned} \#projects_{it} = & f(\gamma_i + \delta_{t-firm_{estyr}} + \alpha_0 US_i * (t = 2000) + \alpha_1 US_i * (t = 2001) \\ & + \alpha_2 US_i * (2002 - 2003) + \alpha_3 US_i * (2004 - 2006) \\ & + \alpha_4 US_i * (2007 - 2008) + \alpha_5 US_i * (2009 - 2011) + \alpha_6 x_{1i} + \varepsilon_{it}) \end{aligned} \quad (3)$$

The first four models in Table VI outline a series of difference in differences results of our regression analysis that uses a conditional fixed effects negative binomial method to estimate the dependent variable $\#projects_{it}$. OLS is not appropriate for count models as our number of projects measure is highly skewed and over-dispersed. We use conditional fixed effect negative binomial models to address the overdispersion problem of the data – the conditional variance is larger than the conditional mean suggested by Hausman et al. (1984) and Allison and Waterman (2002). Model 5–1 tests the impact of the enactment of the moratorium on specific types of hESC research after 2001. The coefficient of the variable $USxPost2001$ describes the average difference in the number of projects initiated by US- and non-US- firms over the years 2001–2011, controlling for firm age, prior university deals, and firm-fixed effects. This coefficient is negative and significant, suggesting that relative to non-US firms, project initiations by US firms declined after 2001. Specifically, incidence-rate ratios, which refer to the percentage change compared to the reference group, indicate that projects initiated by US firms fell by about 60 per cent during this period.

Table VI. Predicting numbers of cell therapy projects – US originators vs. rest of world (1997 – 2011)

	Conditional fixed effects negative binominal models DV = Number of new projects initiated Estimated coefficients (Robust standard errors in parentheses) [IRR in brackets]			Fractional regression models with fixed effects Estimated coefficients (Robust standard errors) $DV = \% \text{ of } hESC \text{ projects}$		
	<i>Model 5-1</i>			<i>Model 5-5</i>		
	<i>Model 5-2</i>			<i>Model 5-6</i>		
	<i>Model 5-3</i>	<i>Model 5-4</i>	<i>Model 5-7</i>	<i>Model 5-8</i>	<i>Model 5-9</i>	<i>Model 5-10</i>
US project	0.747 (0.352)** [2.112]	1.060 (0.400)** [2.887]	1.163 (0.437) [3.200]	0.724 (0.449)* [2.063]	1.64 (0.63)**	0.600 (0.557)
Post2001	1.465 (0.223)*** [4.327]					
US x Post2001	-0.846 (0.268)*** [0.429]					
2001–2003		1.085 (0.334)*** [2.962]		0.945 (0.402)** [2.573]	2.606 (0.949)*	0.614 (0.774)
2004–2008		1.583 (0.290)*** [4.871]		1.694 (0.336)*** [5.441]	-0.311 (1.591)	-3.032 (1.441)**
2009–2011		1.932 (0.293)*** [6.903]		2.049 (0.339)*** [7.765]	6.604 (2.54)**	-2.435 (2.199)
US x 2001–2003		-0.623 (0.399) [0.536]		-0.482 (0.458) [0.617]	-2.791 (2.072)	-1.758 (1.768)
US x 2004–2008		-1.018 (0.345)** [0.361]		-1.125 (0.385)** [0.324]	-2.920 (2.174)	-4.463 (1.862)**

(Continued)

Table VI. (Continued)

	Conditional fixed effects negative binomial models DV = Number of new projects initiated Estimated coefficients (Robust standard errors in parentheses) [IRR in brackets]		Fractional regression models with fixed effects Estimated coefficients (Robust standard errors)			
			DV = % of non-SC projects		DV = % of adult SC projects	
			Model 5-4		Model 5-5	
	Model 5-1	Model 5-2	Model 5-3	Model 5-4	Model 5-5	Model 5-6
US x 2009-2011		-1.396 (0.362)*** [0.247]		US vs. flexible countries projects -1.503 (0.398)*** [0.222]	-2.533 (3.318)	-1.671 (.3.341)
2000			0.588 (0.583) [1.801]			
2001			1.158 (0.483)** [3.184]			
2002-2003			1.237 (0.396)** [3.447]			
2004-2006			1.517 (0.354)*** [4.559]			
2007-2008			1.958 (0.355) [7.091]			
2009-2011			2.059 (0.332) [7.840]			
US x 2000			-0.310 (0.683) [0.733]			0.533 (0.442)

(Continued)

Table VI. (Continued)

	Conditional fixed effects negative binomial models DV = Number of new projects initiated Estimated coefficients (Robust standard errors in parentheses) [IRR in brackets]			Fractional regression models with fixed effects Estimated coefficients (Robust standard errors)		
	Model 5-1	Model 5-2	Model 5-3	Model 5-4 US vs. flexible countries		
				US projects	Model 5-5 non-SC projects	Model 5-6 projects
US x 2001			-0.556 (0.579) [0.573]			
US x 2002-2003			-0.766 (0.470)+ [0.464]			
US x 2004-2006			-1.230 (0.428)** [0.292]			
US x 2007-2008			-0.979 (0.422)** [0.375]			
US x 2009-2011			-1.449 (0.401)*** [0.234]			
Observations	3757	3757	3757	3281	3757	3757
# of firms	221	221	221	221	221	221
Log Likelihood	-1184.8	-1015.8	-1009.3	-910.5		

Note: (1) (2) Models include unreported constant numbers of prior university deals, firm age at year t, and organization (firm_id) fixed effect. *Significant at 10 percent; **significant at 5 percent; ***significant at 1 per cent. (3) For model 5-1 to model 5-4, we use a conditional fixed effect negative binomial model to address the overdispersion problem of the data. (4) The reference group of the project initiation period dummies is 1997-2000. (5) Model 5-2 to model 5-7 are a series of difference-in-difference tests. In particular, model 5-4 represents a robustness check that compares the US projects with the projects based in flexible regulation countries. And model 5-5, 5-6, and 5-7 are robustness checks for predicting the initiation of new projects of different cell therapy projects.

Model 5–2 examines project initiation rates for different policy periods. The coefficients for *US*Year* indicate gaps between the project initiation rates of non-US and US firms for different periods. We see a negative impact of funding restrictions on US-initiated projects compared with the baseline 1997–2000 period. The first policy-shock interval (2001–2003) has a negative but not significant impact on project initiations by US firms. For the second policy interval (2004–2008), the negative impact on project initiations by US firms is stronger, suggesting that there might be a lag between deteriorations in the funding outlook and the lower propensity of firms to initiate new R&D projects in a field. To test this, we ran an additional model by breaking down the policy intervals into smaller year-intervals (see results in model 5–3). Based on the result, we still do not find a negative difference between US- and non-US- firms in project initiation rates in year 2000 and year 2001, but we do find a large and significant difference from 2003 onwards.

Because of the heterogeneity in regulatory environments governing hESC research outside the US (with policies in some countries rivaling those in the US in terms of the restrictions imposed on hESC research), we might be underestimating the effects of US funding restrictions. Using Vakili et al.'s (2015) categorization of countries based on whether these offered a constrained policy environment that was restrictive for research on hESCs, or an hESC flexible policy environment that was permissive for research on hESCs, we also run additional analyses for robustness checks. We excluded non-US cell therapy projects initiated by firms in hESC-constrained policy environments from our sample. Results of model 5–4 are consistent with model 5–2 except for the stronger coefficients. Thus, findings from model 5–2 and 5–3 highlight a delayed reduction in the propensity of US firms to initiate novel cell therapy projects following the deterioration in the funding outlook for the field in 2001. Our results show this delay to be approximately 1–2 years long (the policy change was announced and enacted during the second half of 2001).

So to what extent did the effects of the hESC moratorium enacted by the Bush administration extend across the cell therapy field? And to what extent did firms curtail the initiation of cell therapy projects that were linked to scientific programs that were not directly linked to hESC research? To answer this question, we construct three new measures for each company per year, namely 1) the percentage of cell therapy projects initiated by a firm that do not involve any stem cells, 2) the percentage of cell therapy projects initiated by a firm that do not involve any hESCs, and 3) the percentage of cell therapy projects initiated by a firm that involve hESCs. Because all our three dependent variables are between 0 and 1, we run fractional probit regression models with organizational fixed effects for panel data to investigate shifts in firms' propensity to commit resources to R&D projects linked to different types of cell therapies. Models 5–5, 5–6, and 5–7 highlight the results. In model 5–5, we do not find evidence for a relative decrease in the propensity of US firms to initiate cell therapy projects that do not involve stem cells after the 2001 policy change. Our results do indicate a comparative drop in the percentage of cell therapy projects that were initiated by US firms and were hESC research projects over the 2001–2003 period (model 5–7), and a similar drop in the percentage of cell therapy therapy projects that were initiated by US firms and were adult

Table VII. Results of logistic regression models: predicting project discontinuation

<i>DV = Project discontinuation</i> <i>Estimated coefficients (Robust standard errors in parentheses)</i>					
	<i>Logit</i>	<i>Logit</i>	<i>Logit</i>	<i>Logit</i>	<i>Heckprobit selection</i> <i>US vs. flexible countries</i>
	<i>Model 6-1</i>	<i>Model 6-2</i>	<i>Model 6-3</i>	<i>Model 6-4</i>	<i>Model 6-5a</i> <i>First-stage</i>
US Project	0.229 (0.274)	0.061 (0.758)	-0.103 (0.309)	-0.289 (0.504)	0.055 (0.251)
Post2001	-1.615*** (0.381)	-1.744** (0.648)			
US x Post2001		0.176 (0.798)			
1997-2000			5.257*** (0.818)	4.978*** (0.820)	2.290** (0.758)
2001-2003			4.595*** (0.585)	3.418*** (0.633)	1.633** (0.521)
2004-2008			3.177*** (0.312)	3.288*** (0.442)	1.528*** (0.381)
US x 1997-2000				0.614 (0.842)	0.482 (0.635)
US x 2001-2003				1.961** (0.932)	0.779 (0.664)
US x 2004-2008				-0.052 (0.572)	-0.359 (0.328)

(Continued)

Table VII. (Continued)

<i>DV = Project discontinuation</i> <i>Estimated coefficients (Robust standard errors in parentheses)</i>				
	<i>Logit</i>	<i>Logit</i>	<i>Logit</i>	<i>Heckprobit selection</i> <i>US vs. flexible countries</i>
	<i>Model 6-1</i>	<i>Model 6-2</i>	<i>Model 6-3</i>	<i>Model 6-4</i>
				<i>Model 6-5a</i> <i>First-stage</i>
				<i>Model 6-5b</i>
Project duration			-0.257*** (0.068)	-0.271*** (0.074)
# clinical trials			-0.798*** (0.204)	-0.845*** (0.213)
# clinical trials^2			0.060** (0.029)	0.062** (0.030)
# patient enrollments			0.000028 (0.00014)	0.00009 (0.00014)
No. prior university deals			0.122 (0.272)	0.133 (0.278)
No. prior deals			-0.025 (0.064)	-0.027 (0.065)
SC therapy project			-0.301 (0.312)	-0.288 (0.309)
Firm age			0.014** (0.005)	0.0014** (0.005)
Autologous project				0.006 (0.004)
				-0.411*** (0.121)

(Continued)

Table VII. (Continued)

<i>DV = Project discontinuation</i> <i>Estimated coefficients (Robust standard errors in parentheses)</i>				
	<i>Logit</i>	<i>Logit</i>	<i>Logit</i>	<i>Hackprobit selection</i> <i>US vs. flexible countries</i>
	<i>Model 6-1</i>	<i>Model 6-2</i>	<i>Model 6-3</i>	<i>Model 6-4</i>
				<i>Model 6-5a</i> <i>First-stage</i>
				<i>Model 6-5b</i>
No. prior patents filed				0.183* (0.094)
rho				-0.898 (0.134) Yes
Therapeutic class fixed effects	Yes	Yes	Yes	Yes
Observations	538	538	525	470
Pseudo R ²	0.061	0.061	0.354	0.362
LR Test of (rho = 0)				Prob > $\chi^2 = 0.03$

Note: (1) To account for the heterogeneity of firms, organization_id cluster robust standard errors are calculated in parentheses; (2) * denotes significant level at 10 per cent, ** denotes significant level at 5 per cent, and *** denotes significant level at 1 per cent; (3) The reference group of the project initiation interval for model 6-3, 6-4, and 6-5 is the period 2009-2011. (4) For the heckprobit model, the first stage model predicts the likelihood of being a stem cell project conditioned on firm and project-level characteristic variables including firm size, firm age, project material, and the number of patents registered with the project. Model 6-5a reports significant coefficients. We manually calculate the inverse Mills ratio and run again a regression model for the second stage including the inverse Mills ratio as an independent variable. The coefficient of IMR (lambda) is significant (p < 0.05), proving the existence of a selection bias. This is consistent with the LR test result.

stem cell projects over the period 2004–08 (model 5–6). Thus, while the negative impact on hESC project initiations by US firms that was brought about by the federal funding moratorium on specific types of hESC research in the US was immediate, the impact on initiations of cell therapy projects tied to interlinked scientific programs in the adult stem cell research fields followed a lag period of several years.

Changes in the Corporate R&D Landscape in Cell Therapy – R&D Performance

Next, we move to Hypotheses 2. Table VI presents logit regression models that assess firms' propensity to discontinue cell therapy projects across four time intervals with distinctive funding outlooks for cell therapy research. To assess the short-term effect of the hESC research funding restrictions on project discontinuations and any spillover effects of these restrictions beyond the US, we employ difference in differences techniques in analyzing our entire sample of US- and non-US- R&D projects. We examine interaction effects between where and when a project was initiated in predicting project failure. Using projects initiated before 2001 as the reference group, model 6–1 is the base model and only includes the policy variable on project failure. The coefficient *Post2001* indicates that projects initiated after 2001 are expected to have lower odds of failure than those started before the moratorium was put in place. The marginal effects at the mean for *Post2001* is estimated to be -0.267 , which tells us that the predicted probability of failure is 0.267 lower for projects initiated after 2001 than for those initiated before 2001. In addition, we do not find a significant difference in terms of odds of project failure between US-projects and non-US-projects in the post-2001 period (see model 6–2). We do find a significant effect following the enactment of hESC US funding restrictions by dividing up the post-policy period into different time intervals. Model 6–3 uses projects initiated over the period 2009–2011 as the reference group and highlights that projects launched before 2009 were more likely to fail, controlling for firm- and project- level variables, as well as organizational fixed effects. Project duration and number of clinical trials are negatively associated with project failure. Not only are the coefficients statistically significant, results of the marginal effects at the mean suggest that a project that lasts a year longer, has a 5 per cent decrease in the probability of failure holding other variables at their mean. Moreover, one additional clinical trial will lead to a 15 per cent decrease in the project's probability of failure.

Model 6–4 includes *US*Year* interactions to compare failure rates of projects initiated by US firms versus those by non-US firms during different periods. Results show that projects are less likely to fail as these projects progress towards the market, which is consistent with existing research on product attrition rates along different stages of the clinical trials process (e.g., Pisano 2006). The results of model 6–4 highlight a positive and significant coefficient for interaction terms *USx2001–2003*, suggesting that projects initiated over the period 2001–03 by US firms were more likely to fail than those initiated by non-US firms. The coefficient for interaction terms *USx2004–2008* turns negative and not significant compared with non-US projects launched during the same period. This result also suggests that the propensity for project failure of cell therapy projects initiated by US firms dropped and was no different than those initiated by non-US firms

during the period 2004–08. Based on results of model 6–4, among all the cell therapy projects initiated during 2009 and 2011, there was no difference between failure rates between US and non-US projects.⁵ Considering the possible lagged effect of policy or strategic behavior speeding up or slowing down projects, we exclude the 2001 cohort because of potential endogeneity problems and the results of the econometric model (unreported) remain similar to results of model 6–4. We also exclude projects in countries outside the US documented as having ‘constrained’ (i.e., restrictive) policies towards the development of hESC research (Vakili et al., 2015). The results are similar to the results of our baseline model, but with a stronger significance level for our key policy variable. This indicates that US-projects initiated during the period 2001–2003 were more likely to fail compared to non-US projects from the same cohort.

To deal with the fact that coefficients and their significance levels might not represent accurate relationships in non-linear logistic models such as logit models, we also estimate the marginal effects of the interaction terms (Ai and Norton, 2003; Karaca-Mandic et al., 2012) to calculate the predicted probability of project failure. Figure 2 illustrates our estimates of model 6–4 and highlights that projects initiated by US firms had a significantly higher predicted probability of failure (94 per cent) than projects initiated by non-US firms (78 per cent) over the 2001–2003 period based on a 95 per cent confidence interval, indicating a marginal effect of around 16 per cent ($p < 0.05$). Our marginal effect results also indicate that compared with the pre-2001 era, the difference in differences probability of failure between pre-2001 (1997–2000) and post-2001 (2001–2003) projects is about 14.5 per cent. Moreover, we observe that predicted probabilities of project failure between the two groups again become similar after 2004.

Model 6–5 examines further possible selection issues. Our descriptive results do not indicate that certain type of cell therapy projects are less likely to fail than others. However, this does not preclude that companies select projects that are less likely to fail. As highlighted, models 5–6 and 5–7 in Table VI indicate that changes in the funding outlook for cell therapy research appear to have altered trade-offs firms faced in selecting the type of cell therapy projects to pursue. Specifically, our data highlight shifts in the type of cell therapy projects US firms initiated away from hESC projects (2001–03) and adult stem cell projects (2004–08). As highlighted, while the outlined US policy changes were seen as undermining the scientific basis underpinning growth of the entire cell therapy sector, the outlook was especially bleak for those R&D projects involving stem cells. Accordingly, companies appear to have particularly shied away from those types of projects. To correct for the resulting selection bias favoring the selection of certain cell therapy projects over others, we ran a Heckman selection model for probit models.⁶

We first predict the likelihood of being a stem cell project versus a non-stem cell project conditioned on firm- and project-level characteristics (including firm size, firm age, project material, and the number of patents registered with the project). We used the estimated result to predict project discontinuation rates. The choice of the endogenous selection variable is shown to be significantly valid based on the likelihood ratio test, suggesting the selection model is better than the probit models. Model 6–5 presents the

results of this analysis and shows that the policy effect becomes not significant when we exclude the selection effect of picking the stem cell projects. This result confirms that firms with capabilities in the cell therapy field appear to have been strategic in selecting types of cell therapy projects to minimize exposure to deteriorations in the external scientific environment caused by policy changes.

Discussion of Findings

Our contribution to this special issue used the science commercialization context to advance a number of theoretical- and practitioner- debates about the management of R&D projects. In terms of advancing theory, our study sheds a novel light on critical factors affecting decisions about the initiation and advancement of corporate R&D projects. We accomplish this by building on and extending contributions on the use of real options theory in business decision making around R&D projects. Real options theory provides insights into how firms manage uncertainties that factor into such decision making. Moreover, existing real options approaches that are used in the valuation of R&D projects primarily rely on assessments of uncertainties linked to markets (Childs and Triantis, 1999; Huchzermeier and Loch, 2001; McGrath and Nerkar, 2004), and technological changes that (re)shape market structures (Anderson and Tushman, 1990; Tushman and Rosenkopf, 1992; Tegarden et al., 1999). However, because existing real options approaches do not consider uncertainties beyond those linked to revenues, these approaches are often seen as overestimating valuations (Van Putten and MacMillan, 2004). Our research extends the focus of the existing literature by looking into the important role of uncertainties linked to input resources in R&D project management. Specifically, we zoomed in on the firm's external scientific environment as an important source of input resources. Using the aftermath of policy changes that led to a deterioration of the public funding outlook for cell therapy research in the US as a case study, our contribution highlights several ways, through which firms managed uncertainties relating to this environment.

First, we highlight how increased uncertainties affect the initiation of new corporate R&D projects. We find that higher levels of uncertainty about the future outlook for scientific research in a field, decrease firms' propensity to commit resources and initiate novel R&D projects in that field. Moreover, we find that this is an effect that is geographically concentrated. Our data show a diminished propensity for US firms *vis a vis* non-US firms to initiate new cell therapy projects after a number of policy changes diminished the outlook for scientific research in cell therapy in the US. Also, we find this effect to be stronger for the specific scientific subfields, for which the effects of these policy changes were more pronounced. We disentangled the effects of changes in the outlook for scientific research in the cell therapy field on the initiation of different types of cell therapy projects by US firms. Specifically, we analyzed differential effects on the initiation of cell therapy projects involving hESCs, adult stem cells, and of projects not involving stem cells. Our analyses highlight that US firms especially steered away from the types of cell therapy projects that were most directly affected by the examined policy shocks, namely those projects involving stem cells.

Second, we find an effect on project failure that is also geographically concentrated. Our analyses highlight increased log odds of project failure for cell therapy projects initiated by US firms *vis a vis* non-US firms during the aftermath of the policy changes with regards to hESC research in the US. This finding indicates that increased uncertainties about the availability of scientific input resources create an additional hurdle for innovator firms that do decide to commit resources to new R&D projects in a field with a negative outlook for scientific research. These uncertainties appear to make it more difficult for these firms to find partners willing to commit the additional resources needed to bring these projects to a successful completion. This finding expands existing research that examines interdependencies in the orchestration of resources necessary to advance R&D projects in so-called ‘networked’ industries such as the biotechnology industry (Powell et al., 2005, 1996; Stuart et al., 2007). Moreover, it helps us expand existing research on how the development of technology projects is shaped by the external environment for critical input resources, in which these projects are conceived beyond the realm of firms’ financing environment (e.g., Nanda and Rhodes-Kropf, 2013).

Our findings also provide important insights into the role of policy makers and regulation in shaping corporate R&D project management. Recent studies that examine which R&D project opportunities firms pursue and which R&D projects firms cast aside, highlight the important role of the regulatory environment (e.g., patent system, reimbursement rules) in shaping market uncertainties (Budish et al., 2015; Krieger et al., 2018; Olson and Yin, 2017). Our findings emphasize the central role of those involved in policy making as well. Specifically, (political) debates about policies can affect uncertainties driving R&D resource allocation decisions in industry in meaningful ways, even in the absence of actual changes in the policies that are in place. In fact, some of the effects we observed appear to have been the result of firms’ efforts to anticipate changes in policy or to respond to changes in the likelihood of such changes. Thus, shifting expectations about funding priorities rather than any meaningful changes in actual funding levels for scientific research can be the most important factor shaping corporate R&D project management. For example, we find a decisive uptake of corporate R&D projects in the US cell therapy sector from 2005 onwards. 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 momentum, but *before* most of this support had actually materialized. Accordingly, the greater propensity of US firms to commit R&D resources to cell therapy projects from 2005 onwards appears initially to have been mostly driven by a reversal of the funding outlook for public stem cell research, rather than by actual increases in funding.

Our findings also illustrate how shifts in policy that affect the outlook for scientific research may cause (negative) externalities and spillovers that are unintended. For example, the magnitude of the effects of policy changes that we find for project initiation- and discontinuation- rates stand out. 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 limited in size. However, this assertion did not account for the unintended consequences our findings highlight. In fact, the drop

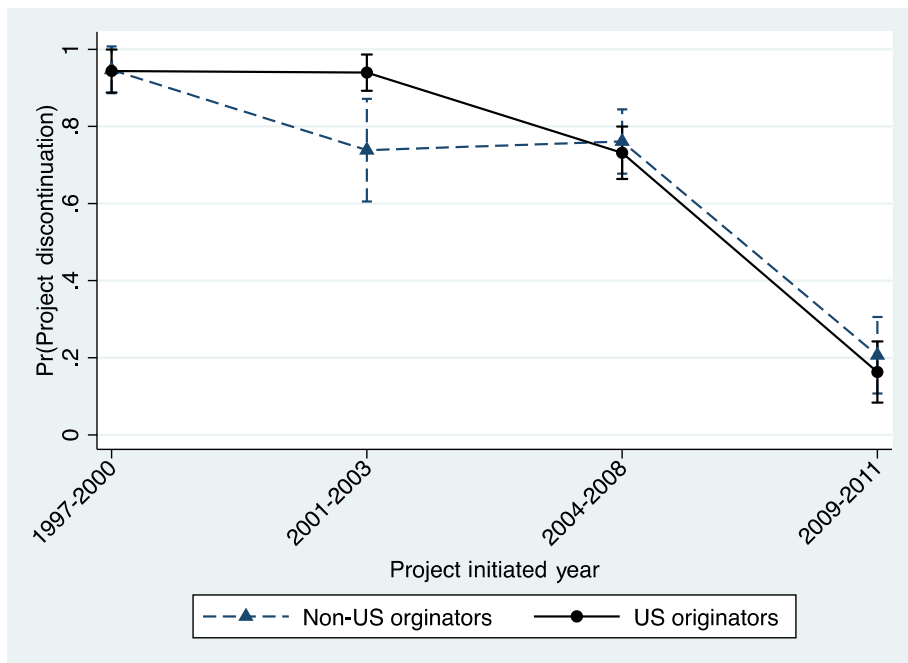


Figure 2. Predicted failure rates for projects initiated by US and non-US firms. The above figure illustrates the comparison of predicted probability of project failure between US-projects and Non-US projects at different year-interval based on the results of model 6–4. This plot indicates the 95 per cent confidence interval [Colour figure can be viewed at wileyonlinelibrary.com]

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 per cent 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, and to 6 in 2004). Thus, the restrictions on hESC research that were enacted in 2001 appear to have led to negative externalities and spill-over effects affecting the entire cell therapy field. Specifically, our analyses highlight that the increased funding uncertainty for the entire cell therapy field that was brought about by these restrictions suppressed corporate R&D activity well beyond the research fields targeted by the federal funding restrictions.

Finally, our findings open up promising avenues for further research. While the specific research setting of this study offers a unique lens on the mechanisms, through which uncertainties about critical input resources affect the development of corporate R&D projects, the scope of this study – namely the imposition (and reversal) of a funding

moratorium that causes a deterioration of the outlook for scientific research within a comparatively narrow set of scientific programs – is a limited one. Accordingly, further research will be needed to develop a more fine-grained understanding of the many other ways, in which those involved in policy and regulation affect the uncertainties firms face about critical input resources. Such policies may for example include policies aimed at funding scientific infrastructures that can also be used by industry, and the use of positive funding incentives to redirect scientific R&D efforts to specific R&D fields. In addition, science policies are only one of a series of levers those involved in policy have at their disposal in shaping the environment for critical input resources firms rely on. For example, policies and laws governing the mobility of (international) workers, and financing also represent promising avenues to better understand the external environment that shapes' firms engagement with R&D projects in different fields.

ACKNOWLEDGEMENTS

We would like to thank the editors of this special issue as well as three anonymous reviewers for their constructive and valuable feedback during the review process. Financial support of Innovate UK is gratefully acknowledged. Previous versions of this paper were presented at AOM, DRUID, 4S, SASE, OECD/EUIPO, and INFORMS conferences, as well as at the Organization, Economics, and Policy of Scientific Research workshop at the Collegio Carlo Alberto in Turin.

NOTES

- [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 of the sector we examine in this study (Culme-Seymour and Mason 1990).
- [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).
- [3] See Table A1 in the Appendix for information on hESC projects in our dataset.
- [4] We exclude data points before 1992 and after 2011 so that we can compare the project initiations between the ten years before the announcement of the 2001 funding moratorium and the ten years in the post-policy era. For comparison purposes, the four time intervals are in ranges of years that are similar.
- [5] We manually checked the status of all the cell therapy projects we collected data on using Pharmaprojects and FDA decisions to trace the performance of each project in December 2014.
- [6] The Heckman correction is a two-stage method that allows the researcher to correct regression estimators, which might suffer from sample selection bias. We use the heckprobit command in STATA because our dependent variable is dichotomous.

APPENDIX

Table A1. Numbers of hESC projects in our data by originator country, firm size, and policy period

		1997–2000	2001–2003	2004–2008	2009–2011
US projects	Big firms	0	0	0	0
	SMEs	1	0	8	8
Non-US projects	Big firms	0	0	2	0
	SMEs	0	3	2	0
total		1	3	12	8

Table A2. Example of project details extracted from the PharmaProjects database

<i>Drug name</i>	<i>NGN-9076 autologous neural stem cells</i>
Drug description	NGN-9076 is a stem cell therapy, under development by NeuroGeneration for the treatment of Parkinson's disease (PD). It works by transplanting autologous human neural stem cells, derived from dopaminergic cells, into the affected striatal structures of PD patients (BIO 2007 (Boston); Company Web Page, NeuroGeneration, 4 Mar 2008 & 23 Nov 2010, http://www.neurogeneration.com/clinical/ourp.html).
Global Status	Suspended
Originator	NeuroGeneration
Key Event Dates and History	28 Mar 2008 New Product 28 Mar 2008 Suspended Products
Development details	Phase II Clinical Trial
Therapeutic Class	Stem cell therapy Antiparkinsonian

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