Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

How does regulatory uncertainty shape the innovation process? Evidence from the case of Nanomedicine

Seokbeom Kwon[a]*, Jan Youtie[b], Alan Porter[b,c], and Nils Newman[c]

[a]Department of Systems Management Engineering, Sungkyunkwan University, Korea

[b]School of Public Policy, Georgia Institute of Technology, USA

[c]Search Technology Inc., USA

Abstract

This study investigates the effect of regulatory uncertainty on the translation of scientific discovery on emerging research topics to technical applications in science-driven industry. Our empirical analysis using the case of the US Federal Drug and Food Administration's release of the report on the regulatory approach to nanomedicine in 2007 shows that; (1) the regulatory uncertainty decelerated the translation of nanomedicine research to technical applications, (2) this effect was particular for the nanomedicine research on emerging topics in the field. Our further analysis suggests that the effect of the regulatory uncertainty originated from the suppressed business activities in the field where the regulatory uncertainty presents. Our study elaborates on how regulatory authority actions shape the innovation process by shedding light on the impact of regulatory uncertainty on the development of technical applications of an emerging scientific area.

Keywords: regulatory uncertainty; nanomedicine; emerging technology; patent-paper citation; innovation

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

1. Introduction

Although regulatory governance over science and technology (S&T) is one of the crucial factors shaping the innovation process (Blind, 2012; Kesidou & Demirel, 2012; Konishi & Managi, 2020; Lee, Veloso, & Hounshell, 2011; Paraskevopoulou, 2012; Porter & Van der Linde, 1995; Taminiau, 2006), authorities do not always clearly establish the necessary regulatory frameworks nor practice them consistently, which results in the creation of so-called "regulatory uncertainty"(Birnbaum, 1984; Engau & Hoffmann, 2009). Anticipating the consequence of new scientific discovery and subsequent technology development in public safety or their environmental effects is challenging (Greer & Trump, 2019; Hamburg, 2012) as the developments of S&T are deeply integrated into a wide range of social systems that dynamically evolve (Dosi, 1982). The development of S&T could create new markets while reconfiguring existing ones where the introduction of a new regulation results in reconstruction of the pre-existing relationship among the market players (Breitzman & Thomas, 2015), exhibiting more difficulties in drawing on social consensus for defining and establishing the proper regulatory governance over the S&T. These difficulties induce regulatory uncertainty that is defined as "*individuals' inability to predict the future state of the regulatory environment"* (Hoffmann, Trautmann, & Hamprecht, 2009).

The regulatory uncertainty may be more prominent when it comes to emerging S&T (OECD, 2020). The ambiguity in its definition, the uncertainty of its impact on public welfare, and its fast-changing nature (Kuhlmann, Stegmaier, & Konrad, 2019; Roca, Vaishnav, Morgan, Mendonça, & Fuchs, 2017; Rotolo, Hicks, & Martin, 2015) make the existing regulatory framework quickly obsolete (Guston, 2008). Due to the inherent uncertainty but potentially prominent socio-economic impact (Martin, 1995), how to establish a proper regulatory framework for emerging S&T while promoting its diffusion has been a salient issue to the S&T policymakers and scholars (Conley, 2020; Guston, 2008, 2014; Hansson, 2020; Kuhlmann et al., 2019; Marchant, 2020). To this question, there has been broad discussion about the necessity of iterative, adaptive, and flexible regulative governance over emerging S&T (Greer & Trump, 2019; Guston, 2008, 2014; Hoffmann et al., 2009; Holdren, Sunstein, & Siddiqui, 2011; Stilgoe, Owen, & Macnaghten, 2013) along with arguments for properly incorporating top-down and bottom-up approach (Bosso, 2016; Rafols, van Zwanenberg, Morgan, Nightingale, & Smith, 2011). Yet, it has been also concerned that the emphasis on the flexibility/adaptability of the regulatory regime cause governance uncertainty (Fisher, 2019; Teeter & Sandberg, 2017), which may undermine the industrial exploitation of emerging S&T (e.g., Savolainen, 2013).

Then, how does regulatory uncertainty affect the innovation process for an emerging S&T? Although the answer can be informative for designing and implementing a governance framework over emerging

S&T with a potential contribution to elaborating on the role of regulatory authority in shaping the innovation process, studies provide somewhat mixed viewpoints.

On the one hand, the classical management studies and real-option theory (e.g., Engau & Hoffmann, 2009; Marcus, 1981) expect that, as an external uncertainty to firms, the regulatory uncertainty may slow down firms' business activities, including R&D investments. Under an external uncertainty, firms may prefer a "wait-and-see" strategy when irreversible investments are required (e.g., Bittlingmayer, 2000; Dixit, 1992; Dixit & Pindyck, 1994; Marcus, 1981). Because the R&D demands a series of irreversible investments (Czarnitzki & Toole, 2011), while regulatory uncertainty being the external uncertainty factor (Hoffmann et al., 2009), firms may postpone their R&D investment until the regulatory uncertainty is addressed.

On the other hand, strategic management scholars repeatedly find evidence showing that firms may build strategies to mitigate the uncertainty (e.g., lobbying, participating in the law-making process) (Carrera, Mesquita, Perkins, & Vassolo, 2003; Pinkse, 2007), or even take advantage of the uncertainty to create the new business opportunity. When it comes to the emerging S&T under regulatory uncertainty, firms may even increase R&D efforts as a part of coping strategies to the uncertainty (Aragón-Correa & Sharma, 2003; Ettlie, 1983; Ettlie & Bridges, 1982; Goel & Nelson, 2021; Stern, 2017). This view expects that the regulatory uncertainty does not necessarily deter firms' innovation with emerging S&T.

The present research aspires to contribute to empirically solving this puzzling question by investigating how the regulatory uncertainty affects the innovation process for emerging S&T. Our focus is to examine the way the regulatory uncertainty shapes the translation of the new scientific discovery on emerging S&T into technical application development, which is a crucial part of the innovation process in the science-driven industry.

Our empirical setting is based on the case of the U.S. Food and Drug Administration (FDA)'s release of a report on the regulatory status of nanomaterials. In June 2007, FDA's task force released a report responding to the rising concern as to whether the FDA's current regulatory framework is adequate to assess the drug products containing nanomaterials (i.e., nanomedicine) (Bawa, 2011; Miller, 2002; Nature, 2007; Paradise, 2019). This report concludes that FDA's current regulatory approach is comprehensive enough to assess nanomedicine and, thus, a new regulatory approach is unnecessary. However, the report also implicated changes in the regulatory pathway for nanomedicine, as well as its regulatory status later in time. With the release of this report, the FDA also noticed that more specific guidance for manufacturers and sponsors of nanomedicine will be provided later. Yet, the first draft guidance became available after five years, leaving the period between 2007 and 2012 uncertain in terms of the regulatory framework for nanomedicine products (Bawa, 2011). Because regulatory authority's public disclosure of its ambiguous position with the absence of the specific guidance could result in the creation of regulatory uncertainty (Hoffmann et al., 2009), our empirical setting utilizes this event as the opportunity to examine the impact of regulatory uncertainty.

By using patent citation to research paper as the paper trail of the translation of scientific discovery into technical applications, we attempt to estimate the impact of the resulting regulatory uncertainty on the change in the rate of patent citations to the nanomedicine-related research papers on emerging research topics within the field. For the empirical setting, we choose Nano-Enabled Drug Delivery (NEDD) papers as the research publications on nanomedicine because NEDD is one of the prominent subdomains of the nanomedicine research fields (De Jong & Borm, 2008). As a comparison group, we use synthetic biology (SynBio) papers for several empirical conveniences which will be illustrated in section 3. We measure the degree to which the scientific discovery in a research paper relates to emerging technological topics within the field by using the emergence score algorithm (Carley, Newman, Porter, & Garner, 2018; Porter, Garner, Carley, & Newman, 2019).

Our Difference-in-Differences (DiD) and triple DiD (DDD) analyses of the NEDD and SynBio papers published from 2003 to 2012 shows that there was a substantial drop in the number of patent citations accrued to a NEDD paper that was published after the release of the FDA's report compared to a SynBio paper. We find that the observed drop was stronger as the NEDD papers are more related to emerging research topics. Our additional investigation of the daily rate of premarket authorization submissions on nanomedicine to the FDA, beginning from one year before to one year after the release of the draft guidance in 2011, reveals that the observed drop might have originated from the suppressed business activities for nanomedicine development by the regulatory uncertainty.

The present study extends the scholarly efforts toward elucidating how firms' business decisions and innovation activities are influenced by governmental regulation by shedding new empirical light on the way the regulatory uncertainty shapes the innovation process for emerging S&T. Our study also provides implications for science policymakers and scholars. The findings that the translation of scientific discovery on emerging research topics to technical applications is decelerated by the regulatory uncertainty suggests that there may be a tradeoff between making the regulatory governance over S&T flexibly/adaptable and promoting its diffusion.

The remainder of this paper is structured as follows. Section 2 reviews two contrasting views on how external environmental uncertainty influences firms' business activities and the literature describing the characteristics of the emerging S&T. Section 3 describes the data and methods for empirical analysis.

Section 4 presents the findings, and Section 5 reports additional analyses results. Finally, section 6 discusses the contributions and implications of the present research.

2. Literature review

2.1. Uncertainty, Firm Investment, and Innovation

When uncertainty arises (e.g., political turmoil), firms seek ways to strategically respond to the uncertainty through various measures including adjustment of investment plan (Carter, 1990; Parnell, Lester, & Menefee, 2000; Teeter & Sandberg, 2017). In this section, we review two strains of literature that expect contrasting consequences of regulatory uncertainty (environmental uncertainty, more broadly) in firms' investment decisions.

On the one hand, the classical management literature anticipates that external uncertainty will deter firms from making long-term or irreversible investments. Because the external uncertainty creates difficulties in anticipating the consequence of a firm's action at the moment (Hoffmann, Trautmann, & Schneider, 2008; Milliken, 1987), the firm may prefer postponing its action until the uncertainty is addressed (Bittlingmayer, 2000; Yang, Burns, & Backhouse, 2004). This logic is formally described by the real-option theory that predicts firms will prefer a "wait-and-see" strategy when deciding for irreversible investment in the light of an external uncertainty (Dixit, 1992; Dixit & Pindyck, 1994). A firm anticipates revenue and cost streams factoring the business risk into a discount factor. The discount factor increases by the emergence of external uncertainty, which consequently reduces the net present value of business projects in question and makes the firm defer their further actions but wait for the uncertainty to be addressed (Engau & Hoffmann, 2009; Marcus, 1981).

A series of empirical studies in various contexts provides supportive evidence. For example, by analyzing the relationship between the time trend of the antitrust case filing and the real investment and GDP, Bittlingmayer (2000) argued that the uncertainty in the stringency of antitrust law enforcement in the US is associated with the decreased-level of business investment activities. The analysis of the impact of the policy shocks on firms' investment decisions by Kang, Lee, and Ratti (2014) shows that the policy uncertainty suppressed firms' investment because the uncertainty leads firms to be conservative in the investment decision. Czarnitzki and Toole (2011) analyzed the survey data on product-innovating firms in Germany. From the analysis of the firm-level panel data, they showed that the volatility of the market revenue (market uncertainty) that a firm experienced was negatively associated with its R&D investment. Rivera and Oh (2013) demonstrated that the change in the level of regulatory uncertainty affect firms' market entry decision by showing that multinational corporation market entry increases as the environmental regulatory uncertainty decreases. By using the case of Renewal Portfolio Standard policies in the U.S. electricity industry, Fabrizio (2013) finds evidence showing that firms invest less in new assets under an unstable regulatory environment. By analyzing 300 organizations of which operations were liable under Australia's clean energy act, Teeter and Sandberg (2017) showed that regulatory uncertainty created by the flexible (environmental) regulation by this act drove firms to focus on short-term investment rather than a long-term investment.

Considering that R&D is a risky endeavor requiring decisions for and irreversible R&D investments (Czarnitzki & Toole, 2011), the regulatory uncertainty may deter firms from investing in the innovation process (Fleming, 2015; Gerard & Lave, 2005; Henisz & Zelner, 2001; Jones, 2015; Marcus, 1981). Several studies explain the various mechanisms. For example, Marcus (1981) explained that regulatory uncertainty may deter firms' adoption of innovation due to the difficulty in assessing the associated risk or opportunities. Jones (2015) illustrated how the ambiguity in the regulatory pathway for technology may affect firms' investment into the development of the relevant technology by using the case of genome-edited crops. The authors argued that the absence of a clear conclusion on the regulatory status of the gene-edited crops may result in stifling firms' investment in gene-editing innovation. Fleming (2015) and Hoerr (2011) argued another pathway that regulatory uncertainty affects technology development and the innovation process. These studies suggest that the regulatory instability (i.e., uncertainty) may result in undersupply of early-stage venture capital investment that is crucial for innovation. Through the analysis of the panel data of 23 OECD countries over 20 years, Kalamova, Johnstone, and Haščič (2012) showed that the volatility in public expenditure on environmental R&D was negatively associated with the patenting activities in the environmental technology domain, supporting the argument that the policy uncertainty negatively impacts on the innovation activities. Goel (2007) theoretically examined how regulatory uncertainty impacts the research effort toward innovation. In this paper, the author specifically attempted to elucidate the theoretical relationship between two types of uncertainties associated with innovation – the scale of innovation (drastic vs. non-drastic innovation) and regulatory uncertainty (i.e., if the resulting innovation becomes the subject of regulation). The theoretical model indicated that the greater the possibility of regulation on the innovation, the less the research spending for innovation.

On the other hand, a growing number of studies found that uncertainty does not necessarily negatively impact firms' innovation. As shown in many studies, firms respond to the external uncertainty strategically by adjusting their organizational structures to minimize the influence of the uncertainty, reorganizing their business portfolio (Carrera et al., 2003), or participating in the relevant policymaking process (Engau & Hoffmann, 2009). Similarly, under regulatory uncertainty, firms may try to deploy their strategic assets to mitigate or even capitalize on the uncertainty. Thus, the impact of the regulatory uncertainty on innovation may be more complicated than one may expect. Several studies provided supportive evidence.

For instance, by analyzing the data on 54 equipment and packaging suppliers to food processing, Ettlie and Bridges (1982) and Ettlie (1983) found that firms under a greater level of external uncertainty deploy more aggressive technology policy that is believed to increase both product and process innovation. The authors interpreted this finding as firms' strategic response to cope with the external uncertainty. By analyzing the case of the German power generation industry under regulatory uncertainty imposed by the European CO2 emission trading scheme, Hoffmann et al. (2009) showed that firms facing regulatory uncertainty do not necessarily postpone their investment decisions due to the firms' strategic motivations.

Through the integration of a wide range of literature, Aragón-Correa and Sharma (2003) further suggested that managers of firms facing external uncertainty are more willing to use innovative strategies than those in environments with less uncertainty to take preventive action with anticipation of the probable external uncertainty. Recently, some scholars attempted to empirically examine whether, and to what degree firms capitalize on the regulatory uncertainty for their business.

Stern (2017) investigated if a pioneering entrant of the medical device market enjoys the first-mover advantage over the latecomers, under regulatory uncertainty. The analysis using the case of the FDA's creation of the new category of a new drug product and the resulting regulatory uncertainty found that the pioneer entrant in this new market had disadvantages compared to the latecomers in market entry. The analysis found that for the pioneer entrant, the approval of the FDA was delayed much longer than the duration until FDA's approval for the latecomer's products.

Goel and Nelson (2021) found evidence showing that firms may invest more in innovation to mitigate economic or political uncertainty. Their analysis of the survey data on firms in 135 countries showed that the greater the level of external uncertainty (either economic or political uncertainty) in the country where a firm operates, the greater the likelihood the firm introduces process innovations. From these findings, the authors argued that firms may attempt to "hedge" the regulatory uncertainty through innovation.

2.2. Emerging Science and Technology for Innovation

Emerging S&T changes the ways of doing, while competing with the existing technology (and science), which expectedly imposes a prominent socio-economic impact (Martin, 1995). However, the definition of an emerging S&T is often ambiguous (Rotolo et al., 2015), and the consequence of its applications in public health and environmental effect is as uncertain (or even risky). Due to these characteristics, identifying emerging S&T and building the proper governance have been challenging quests for policymakers.

To firms, emerging S&T can be both an opportunity and a threat. On the one hand, a firm may capitalize on the emerging S&T as a new window of technological opportunities to compete over the market rivals through innovation (Hung & Chu, 2006). From the Schumpeterian perspective, this aspect implies that the emerging S&T could be a driver of the creative destruction that induces dynamic market competition and innovation by inducing active market entry and exit with the creation of the new market (Nelson, 2012).

On the other hand, because of the inherent uncertainty of emerging S&T, it often becomes the subject of various regulations by authorities, which consequently makes firms perceive the investment into innovation for emerging S&T as a risky business. The perceived regulatory risk by firms is inflated by the inherent uncertainty of emerging S&T, and as described in section 2.1, this could deter further firms from investing in innovation using the emerging S&T. When it comes to emerging S&T where scientific discovery is a crucial knowledge source for technical application development, this deterrence effect can result in decelerating the pace of translation of scientific discovery in emerging research domains into technical applications.

Utilization of the emerging S&T by downstream players and the consequential new application of emerging S&T add further difficulties to predicting the impact of the development of an emerging S&T on human health and the environment. The unpredictable evolution of emerging S&T applications leads scholars to discuss the importance of engaging stakeholders of the emerging S&T at various layers into defining proper governance. For instance, given the nature of nanotechnology that can be utilized in various ways by the downstream players (i.e. end-users), Rafols et al. (2011) argued for the necessity of expanding current discussion for governance over nanotechnology in the U.K. toward accounting for downstream uses of the nanotechnology. Based on an extensive review of the literature on nanotechnology and governance, Bosso (2016) reached a similar conclusion, showing that the scholarly discussion has advanced to the necessity of accommodating the use of nanotechnology by stakeholders in various layers of the value chain.

The complexity and difficulties of effective governance of emerging S&T also lead scholars and policymakers to emphasize the "flexible" approach so that the governance can adaptably work according to the development of the various applications of emerging S&T (Holdren et al., 2011). Yet, because excessive flexibility could result in the creation of "uncertainty" in that governance, which could undermine the utilization of emerging S&T (Fisher, 2019; Savolainen, 2013; Teeter & Sandberg, 2017), it has been also argued that flexibility and adaptability of that governance could slow its diffusion.

In sum, because emerging S&T exhibits considerable uncertainty in its definition and trajectory of development, there have been significant difficulties in establishing the proper (regulatory) governance. When firms are concerned about external uncertainty and their investment decision is slowed down by it, the inherent uncertainty of the emerging S&T may result in even more slowing of the exploitation of the emerging S&T by inflating firms perceived external uncertainty under regulatory uncertainty. In the next section, we illustrate our research design to empirically identify the impact of regulatory uncertainty on the innovation process for emerging S&T.

3. Empirical setting

3.1. Release of the FDA's report on nanomaterials in 2007

Our empirical analysis is based on the release of the FDA taskforce's report on the view of drugs containing nanomaterials in 2007 (July 23, 2007)[1]. Nanotechnology has been expected to bring transformative impact to drug product development. However, because the biological and environmental effects of the nanomaterials have not been fully assessed (De Jong & Borm, 2008), FDA has increasingly encountered concerns if its current regulatory framework is appropriate to assess drug products containing nanomaterials (hereafter, nanomedicine) (Miller, 2002; Nature, 2007; Paradise, 2019). To this challenge, in October 2006, FDA's (acting) commissioner assembled a task force to assess the adequacy of the FDA's current regulatory framework for nanomedicine and recommend appropriate regulatory approaches if necessary. On July 23, 2007, the task force published the report addressing the following three parts: (1) review of the scientific information on the biological effect of nanomaterials, (2) analysis of the science issues on nanomaterials, and (3) analysis and recommendation for regulatory policy issues.

The report stated, "*FDA's authority over products subject to premarket authorization is comprehensive and provides FDA with the ability to obtain detailed scientific information needed to assess the safety and, as applicable, the effectiveness of products, including relevant effects of nanoscale materials* (p.32)", indicating the current regulatory approach is capable of assessing nanomedicine without demanding a novel regulatory approach.

Interestingly, in the same paragraph, the report also implicated a probable change of the regulatory status of nanomedicine later in time by stating, "*the presence of nanoscale materials may change the*

[1] Available at https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-task-force-report-2007 (accessed on June 10, 2021)

regulatory status/regulatory pathway of products […]. It is important that manufacturers and sponsors be aware of the issues raised by nanoscale materials and the possible change in the regulatory status/pathway when products contain nanoscale materials (p.32)". Along with the release of this report, FDA noticed that they would provide more detailed guidance for the sponsors and manufacturers of nanomedicine later. Yet, there have been no more updates on the FDA's view on the regulatory status of nanomedicine, nor the guidance, until the release of the "*Draft Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*" in June 2011. Figure 1 summarizes the timings of these events.

[Insert Figure 1 about here]

The release of the FDA report on nanomedicine is useful to address our research question. First, this event created regulatory uncertainty to the range of stakeholders of nanomedicine development and manufacturing. Implicating the probable change in the regulatory approach and status of nanomedicine could create uncertainty in *Measures and Rules* (Hoffman et al., 2008) that the FDA may apply to nanomedicine in the future. Given that the nanomedicine field is the domain where academic research becomes the source for developing new products (Eaton, 2007), the release of this report and the absence of guidance until Mid-2011 created regulatory uncertainty (Bawa, 2011).

Second, the first version of the draft guidance became available five years after the publication of the report. As a result, what regulatory pathways the manufacturers and sponsors need to account for when developing nanomedicine has remained uncertain for at least five years. More importantly, due to the announcement of the FDA on the future release of the guidance, the manufacturers and sponsors were forced to expose to the uncertain regulatory status of nanomedicine until the guidance is provided.

Third, utilizing this event allows us to conveniently analyze the probable consequence of the regulatory uncertainty for the features of the relevant events to the FDA's release of the report. Although there has been active discussion on whether the FDA's current regulatory framework is suitable for nanomaterial-containing drug products, when and in what way FDA responds to this concern was far from predictable. Furthermore, due to the first version of the draft guidance prepared after five years by the FDA in consultation with national research institutes or FDA's research centers[2] without the participation

[2] See, the footnote in the final version of guidance available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considering-whether-fda-regulated-product-involves-application-nanotechnology

of the sponsors or manufacturers of nanomedicine, the timing of the release of the draft guidelines was also difficult to predict for the stakeholders of the nanomedicine.[3]

Note that the period after June 2011 is excluded from the period of regulatory uncertainty (See figure 1). This exclusion is to account for the mitigated regulatory uncertainty after June 2011 by the FDA's release of draft "guidance". This draft guidance contained the FDA's recommendation for the sponsors and manufacturers of nanomedicine regarding the steps that they need to follow when developing nanomedicine. Accordingly, including the period after June 2011 could result in underestimating the causal impact of regulatory uncertainty.

3.2. Overview of research design

We consider a research paper (journal articles or conference proceedings) as a container of scientific discovery. Considering that a research paper receives citations from patents when the patented inventions were built upon the discovery presented in the research paper, while a patent is granted to the invention when it is novel, not obvious, and industrially useful, we analyze the individual research paper as the unit of analysis, measuring the extent of scientific discovery as translated into technical applications with the total number of patent citations accrued to the research paper of interest.[4]

Our econometric approach aims to estimate the relative change of the patent citation counts accrued to the research papers on nanomedicine (i.e., treatment group) compared to papers in a similar research domain but not of nanomedicine (i.e., comparison group). The estimated difference implicates the impact of the regulatory uncertainty. Next, we investigate if the estimated difference is associated with the degree to which the scientific discovery in a research paper is relevant to emerging research topics within the field.

As the treatment group, we choose the research papers on Nano-Enabled Drug Delivery (NEDD). NEDD is one of the prominent subdomains of the nanomedicine research field. The bibliometric definition of NEDD has been established (Zhou, Porter, Robinson, Shim, & Guo, 2014).

[3] After the first draft guidance was released, the FDA called for comments and suggestions from the public for the final version of the guidance.

[4] Analyzing the number of nanomedicine-related patents over the period of observation can be helpful to measure the change in innovation activities and its association with regulatory uncertainty. Yet, because our research is focused on examining the impact of regulatory uncertainty on the pace of translation of scientific discovery in this field to technical applications rather than examining the level of innovation activities as a whole, the use of the simple count of the patents lends limited utility in addressing our research question— simple patent counting does not explicitly operationalize the degree to which a new scientific finding is translated to its technical application.

For a causal interpretation of the analysis result, it is essential to find a proper comparison group. The comparison group should have similar characteristics to those of the treatment group. At the same time, the comparison group should have not experienced the same or similar events as the treatment group during the period of observation. We argue that research papers of synthetic biology (SynBio) satisfy these conditions. First, like NEDD, SynBio is one of the prominent new biotechnology domains that are expected to bring transformative impact to a broad range of research fields and industries including enhancing biodiesel production or drug development process (Medema, Breitling, Bovenberg, & Takano, 2011; Weber & Fussenegger, 2009). By integrating the engineering principle into bioscience, SynBio research aims to design biological blocks that have naturally non-existing novel functions or enhance the existing ones. Second, the bibliometric definition of SynBio has been built and refined by a series of prior studies (Oldham, Hall, & Burton, 2012; Shapira, Kwon, & Youtie, 2017; Van Doren, Koenigstein, & Reiss, 2013) and is bibliometrically demarcated from the research on NEDD without overlaps in their bibliometric definitions.[5] Third, as both NEDD and SynBio either belong to or are relevant to, the biotechnology research domain, choosing SynBio as the comparison group helps to minimize the probable field-level heterogeneity. Fourth, although there were discussions and concerns regarding the adequacy of the current regulatory framework for synthetic biology, there were no notable events that could change the existing regulatory frameworks for synthetic biology in the U.S during the period between 2003 and 2012. As summarized by Carter et al. (2014), the development of synthetic biology raises two regulatory challenges. One is that synthetic biology could generate genetically engineered plants that are not subject to the USDA's Animal and Plant Health Inspection Service (APHIS), the regulatory authority over genetically engineered plants through plant pests. Another challenge is that synthetic biology enables the creation of genetically engineered microbes that could result in the Environmental Protection Agency (EPA)'s regulatory review on genetically engineered microbes. Due to the limited experience and resources of EPA in reviewing genetically engineered microbes thus far, the development of new genetically engineered microbes by synthetic biology may lead to inadequate regulatory decisions. Several policy options for APHIS and EPA were suggested to address these regulatory challenges, and yet, we could not find actual policy events that resulted in changes to the regulatory frameworks for synthetic biology, nor events generating regulatory uncertainty, for the period of observation. One exception is the APHIS's attempt to extend its authority from the "pest plant only" to the inclusion of all the noxious weeds in 2008. However, this has not been advanced and more importantly, the inclusion of the noxious weed

[5] To ensure that the SynBio and NEDD papers have no overlap, we have dropped overlapping records among the searched papers in the empirical analysis.

was not for establishing a regulatory framework for "synthetic biology-enabled" products. Also, unlike the case of Nanomedicine, APHIS has not released official documents implicating probable change in the regulatory framework for *SynBio* during the period of observation.

Although our research design lends its utility to the quantitative investigation of the causal impact of the regulatory uncertainty in question, its limitation also needs thorough discussion. Our research design does not allow one to distinguish the research papers containing scientific discoveries that are unlikely to be used for technical application development in the first place from those that are likely, but have not been translated to technical applications yet. The two groups of papers may have different natures, and thus, our research method may result in bringing excessive noise in estimating the true impact of the regulatory uncertainty on the degree to which a scientific discovery in a research paper is "translated to technical applications". This limitation could be particularly significant when the research domain in the analysis is featured with a weak linkage between science and technology (e.g., social science fields). The present research analyzes the impact of regulatory uncertainty in a research field that is well-known for the close connection between science and technology (i.e., science-driven domains). Hence, we argue that the limitation of the research design is unlikely to be significant here. However, in the case where the research field in the analysis is featured with a weak linkage between scientific research and the development of the technological application, the limitation of the present research design could be significant, which requires one to use the present research design with careful consideration of how the limitation may challenge the validity of the interpretation of the analysis results.

Our analysis begins with estimating the average impact of the FDA's release of the report in 2007 on the patent citation accrued to a NEDD paper compared to a SynBio paper by using the Difference-in-Differences (DiD) approach. To examine if the sign and size of the impact differ by the degree to which the discovery in a research paper associates with emerging technological topics, we measure the degree to which a research paper contains emerging technological terms within the field of the paper (i.e., NEDD or SynBio), by using the recently developed emerging score algorithm (Carley et al., 2018; Porter et al., 2019). By using the text data in the title and abstract of a corpus of research papers in each research domain, this algorithm allows one to extract emerging terms and quantify the extent to which each of the extracted terms represents technological emergence within the field (i.e., emergence score). We calculate the paper-level emergence score by aggregating the emergence scores of all the appeared emerging terms in the abstract and title of each research paper (Kwon, Liu, Porter, & Youtie, 2019; Kwon, Youtie, & Porter, 2020). The paper-level emergence score operationalizes the extent to which the scientific discovery addressed in the research paper is associated with emerging topics within the field where the paper belongs. We test if the impact of the regulatory uncertainty differs by the paper-level emergence score by fitting our data to the triple DiD regression model (DDD). Section 3.4 provides analytical details of our research design.

If the regulatory uncertainty decelerates (accelerates) translation of scientific discovery into a technical application, the patent citation count accrued to a NEDD paper that was published after 2007 is expected to be significantly lower (higher) than that of a NEDD paper published before 2007, compared to SynBio. If this impact was prominent for the NEDD research on emerging technological topics, the magnitude of the decline (increase) in the patent citation count after 2007 for NEDD papers is expected to be larger as the paper-level emergence score increase.

3.3. Data

We begin by retrieving metadata of NEDD and SynBio research papers that were published between 2003 and 2012 from Clarivate's Web of Science Core Collection (WoS CC). We choose this period because it allows us to observe at least five-year-long publication records before and after the event of interest, respectively. The selection of this period is also based on the way the emergence score is calculated. According to the method that will be described in detail in the next section, emerging terms are extracted from, and their emergence scores are calculated by using the text in the abstract and title of papers published for at least 10-year periods. The period between 2003 and 2012 is 10-years long. Finally, although the FDA released the first version of the draft guidance on the regulatory status of biological products containing nanomaterials in June 2011, we include the papers published in 2012 to account for the probable delay in the impact of the guidance release being presented.

To retrieve the metadata of NEDD papers, we use the bibliometric definition of NEDD that was formulated by Zhou et al. (2014). For SynBio papers, we employed the search strategy compiled by Shapira et al. (2017). The appendix provides the bibliometric definitions of NEDD and SynBio.

In our research design, we use the number of patent citations accrued to each research paper as the dependent variable. To obtain the information on patent citations accrued to research papers, we use recently disclosed data by Marx and Fuegi (2020) (hereafter, M&F data). These data contain the information of patent-cited research papers that are indexed in Microsoft Academic Graph (MAG). By applying natural language processing and machine learning algorithm to the non-patent literature that was cited in patents, Marx and Fuegi (2020) identified papers that were cited by patents and link them to the research paper indexed in MAG.[6] By combining those data with our dataset based on the Document Object Identifier (DOI)[7], we count the patent citations that each paper received through the end of 2019. We drop the papers that have invalid bibliometric information (e.g., records without author information) and the records that are categorized as SynBio and NEDD paper together.[8] Our final sample contains 41,321 NEDD (94%) and 2,705 SynBio papers, respectively.

Our data show that the likelihood of a paper receiving patent citations is seemingly indifferent between NEDD and SynBio. According to the sample, 32% of the NEDD papers had received at least one patent citation while 34% of the SynBio papers received one or more patent citations through the end of 2019.[9]

3.4. Variables and econometric model specifications

Dependent variables. We use the number of US patent citations accrued to each research paper through the end of 2019 (*nUSPatCite*) as the dependent variable. Despite the benefits of the use of the patent citation counts, it is worthwhile highlighting that the patent citation accrued to a paper is not a flawless measurement of the degree to which scientific discovery in the paper of interest serves knowledge input for developing technical applications. Not all patents contain commercially valuable inventions nor are all commercially valuable inventions patented. For instance, in the information and communication technology domain, firms may incline to patent their inventions for strategic purposes (Hall & Ziedonis, 2001; Noel & Schankerman, 2013). In the food industry, inventions are less patented but more protected through secrecy (Cohen, Nelson, & Walsh, 2000). Nevertheless, in the context of the present research, the patent citation count can be still useful because pharmaceutical and biotechnology domains are sectors where patenting is a major instrument for protecting valuable inventions while, in this domain, a patent corresponds to a distinctive technology that has commercial value (Cohen et al., 2000). One may consider the number of patent-paper pairs as an alternative measure. Yet, we argue that it does not correctly operationalize the concept of the translation of the scientific discoveries to technical applications for two reasons. First, the inventor of the patent and researcher of the paper must be the same person for a patent-paper pair, which excludes cases where a patented invention is developed by a different person from the researcher of the scientific discovery that the invention was built upon. Thus, the use of the patent-pair measure may capture a limited portion of the entire translation of scientific

[6] This data is available at http://relianceonscience.org/
[7] Therefore, papers that have no DOI were excluded from the final dataset.
[8] In the original data, we found that 96 articles were included both in NEDD and SynBio.
[9] About 23% and 25% of the NEDD and SynBio papers received one or more US patent citations, respectively.

discovery to technical application. Second, a patent-paper pair indicates a scientific discovery that has technical application potential rather than that the discovery serves as a knowledge input for technical application *ex-post*. This implies that the use of the patent-paper pair may bring excessive noise in operationalizing the concept of the translation of scientific discovery to technical applications—exploiting an existing scientific discovery to build a technical application upon it.

In counting the patent citations, we choose to use the US patent citation to take into account not only the fact that FDA's jurisdiction is restricted to the US, but also a feature of the patent citation practice of USPTO. In the U.S., inventors are obliged to cite all the known prior art when filing patent applications (by the Inequitable Conduct Doctrine). If it is found that inventors did not cite any of the "known" prior art in the patent application, the patent can be invalidated, even after it is granted. In contrast, in EPO, the patent examiners are mostly responsible for searching prior art / adding citations and, hence, examining the patentability of the inventions. Studies have emphasized that such difference needs to be properly considered in patent citation analysis (Alcacer & Gittelman, 2006; Criscuolo & Verspagen, 2008). Our use of the citation counts originated from US patents is to mitigate the probable systematic difference arising from the different citation practices by patent authorities.[10]

Use of the accumulated patent citation count through the end of 2019 becomes subject to a truncation problem. The newer the paper is, the less chance of being cited, simply due to the shorter time to be cited. To account for this right-truncation problem, we additionally employ the fixed-window (seven-year-long, since publication) patent citation count as an alternative dependent variable (*7YrPatCite*)[11].

Independent variables. Our econometric analysis employs the standard multi-term DiD design. We generate the following three sets of variables as the independent variables. First, we create ten binary variables that respectively take the value of 1s for each of the publication years between 2003 and 2012 ($PY_k, k \in [2003, .., 2012]$). For example, if a research paper was published in 2003, the binary variable PY_{2003} takes the value 1. Second, we create a dummy variable that takes the value of 1 for NEDD papers (*NEDD*) and 0 for SynBio papers. Finally, we generate ten interaction terms between *PY*s and *NEDD* (*PY X NEDD*). The coefficients of these interaction terms are the DiD estimators. If the regulatory uncertainty decelerated (accelerated) the translation of scientific discovery in NEDD to technical application, negative (positive) and statistically significant coefficients of *PY X NEDD* after 2007 are expected.

[10] For the robustness check, we conducted additional analyses by using the total patent citation count without restriction to the US patent citation. Our analyses showed the consistent findings with our main regression results. The robustness check result is available upon request.

[11] This is because, in our data, the last year of patent citation to the papers published in 2012 is 2019. To account for the 2019 patent citation is unlikely to be complete due to the delay between patent filing and its publication, we count patent citation made until 2018 (7-year window).

To test if the impact was prominent for scientific discovery on emerging research topics within each field, we employ a paper-level emergence score algorithm that quantifies the degree to which a research paper of interest contains emerging technological terms within each field where the focal paper belongs. The paper-level emergence score proxies for the degree to which the discovery addressed in a research paper relates to emerging research topics. The higher the paper-level emergence score, the greater the extent to which the research paper contains new knowledge on emerging research topics within the research field (i.e., NEDD or SynBio in our analysis). For calculation of the paper-level emergence score, we follow the procedures described by Kwon et al. (2019) and Kwon et al. (2020). First, from each of the NEDD and SynBio datasets, we extract the emerging terms by using the algorithm as proposed by Carley et al. (2018). The emergence score algorithm generates a list of emerging terms with their "emergence score" that takes a non-negative value, by operationalizing the four characteristics of technological emergence– persistence, novelty, growth, community, and scope. The emergence score of each term is calculated by aggregating three types of the trend of the term in question appear in the corpus of papers—active trend, recent trend, and slope (see section 2.3 of the paper by Kwon et al. (2019)). Second, for each paper, we aggregate the emergence scores of the emerging terms in the paper's abstract and title. To account for the right-skewed distribution of the paper-level emergence scores that have 0 as the minimum value, we take a natural log on the paper-level emergence score with an increment of 1 (*lES*). If a paper takes the value of 0 for its *lES*, this indicates that any of the extracted emerging terms has not appeared in the abstract nor title of the paper in question. Then, we generate triple interaction terms between *lES*, *PYs*, and *NEDD* (*lES X PY X NEDD*). The coefficients of these triple interaction terms estimate the difference in the marginal impact of the regulatory uncertainty on patent citations to a paper by the extent to which the paper in question addresses emerging technological topics within the field where the paper belongs. To be more specific, if the impact of the regulatory uncertainty was more (or less) prominent for translating scientific discovery to technical application (because the paper contains more emerging terms), post-2007 triple interaction terms are expected to take negative (or positive) and statistically significant coefficients.

Control variables. To rule out probable spurious effects, we introduce several control variables that may simultaneously correlate with our dependent and independent variables.

First, we control for the research team size (*Team Size*). Studies have found that research team size is associated with research impact (including technology impact) with the growth of the size of the research team over time (Cohen & Bailey, 1997; Larivière, Gingras, Sugimoto, & Tsou, 2015; Vogel, Hall, Fiore, Klein, Bennett, Gadlin et al., 2013). Meanwhile, the average research team size differs by the field of research due to the different levels of required resources by research domain. Accordingly, the probable difference between NEDD and SynBio papers in terms of the post-2007 patent citation counts could be driven by the simultaneous correlations among the research team size growing at a different rate between NEDD and SynBio, research domain, and patent citation counts. Controlling for the number of authors of the paper of interest accounts for this confounding effect.

Second, we account for the number of cited references as the proxy for the number of prior studies to the focal research paper. Because the number of relevant prior research papers is positively associated with the academic research activity around the relevant field, it is also likely to correlate with technology development activities. Meanwhile, the number of citable references for a paper increases over time by the accumulation of published research papers. Introducing the natural log-transformed number of cited references added by 1 (*lnRef*) as a control variable helps to account for this confounding effect.

Third, we control for whether the research paper of interest originated from international collaboration. The greater the inclusion of international collaboration, the greater the visibility of the research works (Van Raan, 1998), which could positively associate with the patent citation counts (also U.S. citations for the same reason). Conversely, technologically impactful research may need the collaboration of researchers across countries. Either way, whether the research was conducted based on international collaboration may associate with the extent to which the research outcomes served as the knowledge inputs for technological application developments. Meanwhile, studies have found that international collaboration for research has steadily grown with field-level heterogeneity in its prevalence (Gazni, Sugimoto, & Didegah, 2012; Wagner, Park, & Leydesdorff, 2015). To account for this international collaboration-induced confounding effect, we introduce a binary variable that takes the value of 1 if the authors' countries are two or more, and 0 otherwise (*IntCollabo*) as a control variable in the regression analysis.

Finally, we control for whether the lead author of the research paper was located in the US by introducing a binary variable that takes the value of 1 if the first author of the paper in question was located in the US (*1stAuthorInUS*). This variable is to take into account the fact that the knowledge diffusion is localized (e.g., Jaffe, Trajtenberg, & Henderson, 1993), and the FDA's jurisdiction is limited to the U.S. Table 1 lists the key variables and their descriptions.

[Insert Table 1 about here]

Econometric model specifications: Because the dependent variable is a count variable having right-skewed distribution (i.e., overdispersion problem), we fit our data to the generalized negative binomial

(GNB) regression model that allows capturing the overdispersion parameter into the analysis.[12] To investigate the total impact of the regulatory uncertainty on the translation of scientific discovery into technological applications, we fit our data to the following regression model specification using robust standard errors.

$$nPatCite_i^* = \beta_0 + \sum_{t=2003}^{2006} \beta_{1t} \times PY_{i,t} \times NEDD_i + \sum_{t=2008}^{2012} \beta_{2t} \times PY_{i,t} \times NEDD_i + \sum_{t=2003}^{2012} \beta_{3t} \times PY_{i,t} + \beta_4 \times NEDD_i + \sum_j \gamma_j \times C_{i,j} + \epsilon_i$$

where $nPatCite_i^*$ is either *nUsPatCite* or *7YrPatCite*, $C_{i,j}$ is jth control variable of paper *i* and ϵ_i is the error term. To examine if the impact of the regulatory uncertainty was particular, we fit our data to the triple DiD model (DDD), as presented in the following formula.

$$nPatCite_i^* = \beta_0 + \sum_{t=2003}^{2006} \beta_{1t} \times PY_{i,t} \times NEDD_i \times lES_i + \sum_{t=2008}^{2012} \beta_{2t} \times PY_{i,t} \times NEDD_i \times lES_i + \sum_{t=2003}^{2012} \beta_{3t} \times PY_{i,t} \times lES_i + \sum_{t=2003}^{2012} \beta_{4t} \times PY_{i,t} \times NEDD_i + \beta_5 \times NEDD_i \times lES_i + \sum_j \gamma_j \times C_{i,j} + \epsilon_i$$

4. Results

4.1. Descriptive analyses

Table 2 presents the summary statistics of the key variables and their pairwise correlations for NEDD (upper table) and SynBio papers (lower table), respectively.[13]

[Insert Table 2 about here]

All the correlation coefficients are below 0.4, both for NEDD and SynBio papers, indicating no significant multi-collinearity issues found. The mean value of *lES* of NEDD papers (2.19) is greater than

[12] As an alternative regression model, a zero-inflated negative binomial regression model can be considered because 75% of the research papers in our sample received zero-patent citations. However, because the zero-inflation factor (the factor that makes the U.S. patent citation count always zero) is unknown, fitting our data to the zero-inflated negative binomial regression model is infeasible. As another alternative model, Veugelers and Wang (2019) used the probit regression model by employing a binary variable that takes the value of 1 if the research paper in question received at least one patent citation, as the dependent variable. Our alternative regression analysis using the same approach yielded consistent findings with the generalized negative binomial regression analyses. The probit regression results are available upon request.

[13] Because *PY*s are mutually exclusive dummy variables, we present the publication year of the paper as is in the correlation analysis.

that of SynBio (0.83). The average number of co-authors (i.e., Team Size) of a NEDD paper (5.91) is greater than that of a SynBio paper (4.87), suggesting that one more researcher collaborates for NEDD research than SynBio research. 29% of the NEDD papers in the sample had a US scientist as the lead author, whereas 40% of the SynBio papers had a US scientist as the first author. There are virtually no differences between NEDD and SynBio papers in the mean values of the rest of the variables.

4.2. Main regression results

[Insert Table *3* about here]

Table *3* reports the main regression results. In the first two columns, we present the regression results without introducing the triple interaction terms to estimate the aggregated effect of the regulatory uncertainty. In the first column, we use *nUSPatCite* as the dependent variable. The DiD estimators for pre-2007 (from *PY2003 X NEDD* to *PY2006 X NEDD*) are all statistically insignificant at the 0.1 significance level, indicating the time trend of the outcome variables of NEDD and SynBio papers in the pre-2007 period are parallel. However, from *PY2011 X NEDD*, the coefficients turn negative and statistically significant at the 0.1 significance level with an increase in size. The second column presents regression results using the *7YrPatCite* as the dependent variable. From *PY2010 X NEDD*, the coefficients are all negative and statistically significant at the 0.05 significance level. Figure 2 visualizes the estimated aggregated impact of the regulatory uncertainty.

[Insert Figure 2 about here]

From the third to fourth columns, we report the regression results including the triple interaction terms. In the third column, we report the regression results using *nUSPatCite* as the dependent variable. The coefficients of *PY2010 X NEDD X lES* and *PY2011 X NEDD X lES* are negative and statistically significant at the 0.1 significance level. In the fourth column, only the coefficient of *PY2011 X NEDD X lES* is negative and statistically significant at the 0.01 significance level. In contrast, in both columns, the coefficients of *PY2008 X NEDD* through *PY2012 X NEDD* are all insignificant at the 0.1 significance level. These results indicate that the drop in the patent citation count for a NEDD paper was particular to the papers containing at least one emerging term.

For a clearer illustration of our findings, we conduct an additional analysis by dividing our sample into the papers that have positive emergence score (*lES*>0, papers on emerging research topics) and those have 0 as the *lES*. Then, we fit these subsamples to DiD regression models separately. The fifth and sixth columns of Table 3 report the regression results using the papers with positive *lES*. The coefficients of

PY2010 X NEDD and *PY2012 X NEDD* are negative and statistically significant at 0.1 significance level minimum in both columns. In contrast, the regression results reported in the seventh and eighth columns with the papers having *lES*=0 show that any of the coefficients of the DiD estimators are statistically significant at the 0.1 significance level. Figure 3 visualizes this finding. In this analysis, we divide the sample into the three groups by the percentile of the *lES* (lES<50 percentile, 5<=lES<75 percentile, and lES>=75 percentile), and present the DiD estimators by using each sample respectively. For both dependent variables (*nUSPatCite* and *7YrUSPatCite*). The analysis results indicate that the impact of the regulatory uncertainty was more prominent for research on emerging research topics.

[Insert Figure 3 about here]

Our additional analysis confirms that the drop in the patent citation counts accrued to a NEDD paper was specific to the NEDD papers on emerging research topics within the field.

4.3. Exploration of alternative hypotheses

We check the robustness of our main findings to several alternative hypotheses to the causal impact of regulatory uncertainty imposed by the FDA's release of the report.

First, the decline of patent citations to a NEDD paper after 2007 could have originated from the rapidly increasing number of NEDD papers over the period of observation, compared to synbio papers, and hence, a chance of a NEDD paper receiving patent citation decreases on average. To address this probable confounding effect, we build a sample that contains the same number of (exactly) matched NEDD and SynBio papers on the control variables we employed in the main regression and the year of publication. If there is more than one matched SynBio paper, we randomly select one of them. If there are no matched SynBio papers to the NEDD paper, we drop the NEDD paper from the sample. Table 4 presents the GNB regression result using the matched sample. In this analysis, we dropped all the control variables we used in the main regression because they were employed as the matching covariates. The analysis still indicates that patent citation to a NEDD paper significantly declined after 2007 compared to a matched SynBio paper. We find that the suggested hypothesis does not fully explain our findings.

[Insert Table 4 about here]

Second, it could be argued that the decline of patent citation to NEDD paper might have been confounded by the decreasing number of NEDD patents. If the release of the FDA report created regulatory uncertainty, it might have slowed the development of the technical applications of NEDD and so the number of NEDD patents decreases. However, the data on NEDD patents published worldwide from 2003 to 2012 shows no evidence of a declining number of NEDD patents after 2007.[14]

Third, we conduct a placebo test to check the specificity of our findings to the timing of the FDA's release of the report. In our test, we set the placebo year of the FDA report release to 2005 and run the regression with the papers published between 2003 and 2007. Our placebo test reported in Table 5 finds no evidence that our finding was a result of statistical coincidence.

[Insert Table 5 about here]

Finally, our findings could be explained by NEDD research becoming less impactful after 2007 for unknown reasons. We investigate the empirical validity of this explanation by examining if the research impact of NEDD declined compared to that of SynBio after 2007. For this analysis, we analyze the change in the number of paper citations accrued to a research paper as the dependent variable (*Time Cited*). By considering the number of paper citations that a focal paper received as the proxy for the focal paper's research impact, we analyze if an NEDD paper received fewer paper citations than a comparable SynBio paper after 2007.

[Insert Table *6* about here]

Table *6* reports GNB regression results. In the first column, we present the DiD regression results without triple interaction terms. The coefficients of DiD estimators are all insignificant at the 0.1 significance level. In the second column, the regression results including the triple interaction terms are presented. The coefficient of *PY2010 X NEDD X lES* is positively significant at the 0.05 significance level. The third and fourth columns show the regression result with samples of lES>0 and lES=0, respectively. All the coefficients of the DiD estimators in both columns are statistically insignificant at the 0.1 significance level. Our analysis finds no evidence of declined research impact of NEDD papers compared to SynBio published after 2007.

4.4. Endogeneity and sources of bias

Although we argue that the timing of the release of the FDA report is exogeneous to most of the stakeholders of the nanomedicine development, the probable endogeneity of the event needs a thorough discussion to ensure that our result implies a causal impact of the regulatory uncertainty of interest. In

[14] We obtained the patent data from Georgia Tech STIP group. See the method of retrieving NEDD patent data in Kwon et al., (2017)

this section, we discuss probable sources of the endogeneity of the timing of the FDA's report release and resulting regulatory uncertainty. We focus on addressing if those sources of the endogeneity are empirically valid and if the probable endogeneity challenges the validity of the causal interpretation of our analysis results.

First, the discussion and preparation of the institutional measures to address the concern over the undesirable impact of nanomedicine on public health could be a result of the active development of nanotechnology applications for drug products. Hence, the degree to which a scientific discovery in the nanomedicine research domain is translated to its technical application could trigger the FDA's consideration of a new regulatory framework for nanomedicine. This endogeneity, however, is likely to result in the opposite consequence to what we observed in our main analysis—if the FDA's action was an institutional response to increasing prominence of nanotechnology application to drug development, the degree of which a scientific discovery in NEDD research is translated to technical applications should have increased, not declined.

Second, one may argue that the impact of regulatory uncertainty could have been confounded by its probable impact on SynBio research. Some synthetic biology applications may employ nanotechnology while becoming crucial technological input for the drug development process. Hence, the regulatory uncertainty by the release of the FDA report might have impacted the translation of SynBio research to its technical application. This bias becomes the critical challenge to the validity of our causal interpretation when regulatory uncertainty did not impact the translation of NEDD research to technical applications, but *accelerated* that of SynBio research. However, the feasibility of this scenario is hard to support given the scope of the FDA's report. As discussed, the FDA's discussion and the release of the report was specific to the application of nanotechnology to drug product rather than the development of technology that is enabled by nanotechnology in general. Hence, even if the regulatory uncertainty impacts on the translation of the synbio research to technical application development might have existed, its size should have been smaller than that for NEDD.

Third, the global economic crisis in 2008 might have driven our findings. The feasibility of this alternative explanation is dependent upon the validity of the assumption that the translation of a new scientific finding in NEDD research to its technical application has been more significantly (and negatively) impacted by the economic crisis than the comparison group, SynBio. However, our data do not provide supportive empirical evidence. If the nanomedicine field has been more significantly (and negatively) impacted by the global economic recession than SynBio, it is likely to be observed that the research activities on NEDD should decline more than SynBio. However, the number of publications over the period of observation shows parallelly increasing trend.[15] In addition, if the alternative explanation is supportive, the degree to which a NEDD paper is cited by the subsequent research papers is also likely to decline more than synthetic biology (due to the suppressed research activities in the field of nanomedicine.) Yet, as our robustness check shows, we find no evidence. Therefore, we argue that the global economic recession in 2008 does not fully explain our findings.

4.5. The mechanism: Evidence from the Premarket authorization submission activities

In this section, we explore evidence on if the suppressed business activities for nanomedicine by the "uncertainty" was the main driver of our finding, as expected by real-option theory, by examining the change in the business activities for nanomedicine after the regulatory uncertainty is addressed by the release of the first draft guidance by FDA in June 2011.[16]

If the regulatory uncertainty deterred firms from investing in the R&D process and thus slowed the translation of scientific discovery into technical applications, wouldn't the mitigation of the regulatory uncertainty result in the recovery of the business activities on nanomedicine? Because empirical evidence of this expectation can be complementary to our main analysis, we conduct an analysis examining the response of organizations to the mitigated regulatory uncertainty in their business activities on nanomedicine development by FDA's release of the first draft guidance on nanomedicine development in June 2011.

Our additional analysis is based on analyzing the rate of submissions for Premarket approval (PMA) of nanomedicine before and after June 2011. There are two FDA-controlled regulatory pathways for Drug products in the U.S. The first is premarket notification (510(k)). Under this pathway, the applicant is required to demonstrate that the products (or medical devices) of interest are as safe and effective as substantially equivalent (already marketed) products (devices) in the market. The second pathway is the PMA. Under this pathway, new drug products (or medical devices) with high-risk profiles (i.e., class III[17]) are reviewed and assessed regarding safety and effectiveness. The PMA requires the applicant to provide various types of scientific information and data demonstrating the safety and effectiveness of the product

---

[15] The data is available upon request.

[16] The final version of the guidance was released in 2014 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-safety-nanomaterials-cosmetic-products). After carefully comparing the final version of the guidance and draft (https://downloads.regulations.gov/FDA-2011-D-0489-0002/attachment_1.pdf), we found that, although the final version contains more and clearer information about FDA's recommendation for the firms and sponsors of nanomedicine to follow when engaging in developing the nanomedicine products, most parts of it were maintained consistently.

[17] The FDA defines class III devices as "*those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.*" (see, https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma)

under examination (e.g., requiring both data on Non-clinical Laboratory Studies and clinical Laboratory Studies), which incurs substantial and irreversible costs of the applicant. If a product under the PMA process comes to undergo a new regulatory process due to the change of rules, the applicant's investments made until then turn to sunk costs. Meanwhile, according to the FDA's report released in 2007, it concludes that although the premarket authorization is comprehensive enough to cover the nanomedicine, the rules may change in the future. Accordingly, we argue that the response of firms and sponsors of the nanomedicine to the change in the level of regulatory uncertainty will be reflected in their submission of nanomedicine PMAs.

In this analysis, we consider the release of the first version of the draft guidance regarding the regulatory status of and approach for, nanomedicine on June 14, 2011,[18] as the event that partially mitigated the regulatory uncertainty. By the release of this draft guidance, more detailed information that the manufacturers and sponsors need to take into account regarding the FDA's regulatory stance for the business of nanomedicine, has become available. For example, it clarified that the FDA will account for (1) whether products under consideration contain nanometer-scale materials, and (2) whether the size of the materials of the product attributes to its properties including biological effects. The draft guidance also recommended for manufacturers of nanomedicine to consult with the FDA early in the product development process.

We retrieve the information of all the PMA applications from the FDA PMA database[19] and profile the daily submission numbers of PMAs on nanomedicine (nano-PMAs) from June 14, 2010, to June 14, 2012 (1-year before to 1-year after the release of the guidance). We consider the PMAs submissions as nano-PMAs if the terms matched with "nano*" appeared in the description, tradename, or generic name of the products of the application in question. We expect a surge in the number of nano-PMA submissions after June 14, 2011, if the mitigated regulatory uncertainty by the release of the first guidance induced recovery of business activities regarding the nanomedicine. Figure 4 presents our analysis result.

[Insert Figure 4 about here]

The red and gray bars present the number of submitted nano-PMA submissions and the number of all the PMA submissions during the period, respectively. The daily number of all PMA submissions (gray)

[18] "Draft Guidance for Industry; Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology "(available at https://www.federalregister.gov/documents/2011/06/14/2011-14643/draft-guidance-for-industry-considering-whether-an-fda-regulated-product-involves-the-application-of, accessed on June 10, 2021)

[19] Bulk data is available at https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals (access July 20,2021)

shows no notable difference between before and after June 14, 2011. Meanwhile, the number of nano-PMA submissions filed before June 14, 2011, was only three, while the number of nano-PMA submissions filed after that date was 15 (increase by 400%). The observed surge in the number of submissions of the nano-PMA applications suggests that the business activities related to nanomedicines recovered after the mitigation of the regulatory uncertainty by the release of the draft guideline.[20]

In sum, our additional analysis of the nano-PMA further suggests that the decelerated translation of scientific discovery in NEDD research to patented technological applications might have originated from the suppressed business activities on nanomedicine development by the regulatory uncertainty.

5. Discussion and conclusions

In the present study, we examined how regulatory uncertainty influences the translation of scientific discovery into technical applications in a science-driven industry. Our literature review stretching from the classical management studies based on real-option theory to recent works by strategic management scholars, incorporating the studies on the features of emerging S&T, revealed theoretical ambiguity of the answer. For the empirical analysis, we utilized the case of the regulatory uncertainty created by the FDA's release of the report on nanomaterials in 2007.

Our analyses using the patent citations accrued to NEDD and SynBio research papers with the recently developed emergence score algorithm found that the regulatory uncertainty of interest has decelerated the translation of new scientific discovery in nanomedicine research to technical applications. This impact was particular to the scientific discovery on emerging research topics of NEDD. Based on the literature concluding that perceived external uncertainty results in slowing down firms' investment decisions, we argue that the inherent uncertainty of emerging S&T in its definition and socio-technical impact might have inflated firm's perceived regulatory uncertainty when it comes to emerging technological topics, and thus, deter firms' investments into searching/translating scientific research on NEDD to the technical applications more in the area of emerging research areas of NEDD. Our further analysis using the data on the daily rate of nano-PMAs submissions showed that the observed effect of the regulatory uncertainty might have originated from the suppressed business activities on nanomedicine. From the findings, we conclude that in this science-driven industry, the regulatory uncertainty could decelerate the diffusion of scientific discovery on emerging research topics to technological applications development.

[20] Although comparing between nano-PMAs and SynBio-PMAs is ideal, identifying the SynBio-PMAs was bolometrically infeasible.

Does our finding imply that regulatory uncertainty "negatively" impacts innovation? Although our findings seemingly answer positively, because the diffusion of scientific discovery is a crucial part of the innovation process, it may be too early to conclude based on our findings alone. In addition to the translation of scientific discovery into technical applications, there are more processes of innovation, such as interfirm R&D collaboration, governmental R&D, venture capital investment in early-stage R&D, collaborations between universities and firms for innovation, etc. Evidence on how regulatory uncertainty affects other processes of innovation in various contexts is necessary for a comprehensive conclusion.

More importantly, our study does not allow one to draw a conclusion that regulatory uncertainty harms the public welfare. Although regulatory uncertainty may slow down a part of the innovation process in the science-driven industry as we showed, it is indispensable to avoid the probability of a negative consequence in public health, which is a crucial dimension of public welfare that the policymakers must take care of in addition to innovation diffusion.

Our finding that the slowed translation of scientific discovery into technical applications was particular to the research outcomes on emerging research topics elaborates on the conventional understanding of the tradeoff between regulation and innovation. To this understanding, our finding implies that there may be another dimension of a tradeoff when it comes to regulation and innovation—the tradeoff between seeking flexibility/adaptability in the regulatory governance over emerging S&T and promoting the diffusion of emerging S&T for innovation. Defining and formulating the adequate rule (or law) to govern emerging S&T is crucial for transforming emerging S&T into innovation. Because the way emerging S&T influences society is far from predictable, there has been growing emphasis on the necessity of engaging various stakeholders of emerging S&T into the discussion of defining adequate governance over emerging S&T (e.g., Bosso, 2016; Rafols et al., 2011), and flexibility/adaptability of the regulatory approach has been emphasized accordingly (Greer & Trump, 2019; Guston, 2008, 2014; Hoffmann et al., 2009; Holdren et al., 2011; Stilgoe et al., 2013). Although this effort is necessary given the nature of the emerging S&T, the emphasis on flexibility/adaptability may cause governance uncertainty as scholars discuss (Fisher, 2019; Teeter & Sandberg, 2017). To this discussion, our analysis indicates that the resulting regulatory uncertainty may particularly decelerate the diffusion of the emerging S&T for innovation; whereas, a prominent goal of innovation policy is to accelerate same. Therefore, we argue that when policymakers account for the consequence of regulatory uncertainty in the development of S&T, they may need to pay special attention to identifying the emerging research domains in the field of interest and devise a way of finding the balance between bearing regulatory uncertainty and pursuing the diffusion of innovation in those areas. For example, in the context of nanomedicine, releasing the report on regulatory status of nanomedicine along with the guidance for its manufacturers and sponsors at the same time could be a helpful strategy to mitigate regulatory uncertainty.

The emergence score algorithm that we employed in our analysis can be used as a useful tool to identify the emerging research domains (or relevant research papers) where the impact of the regulatory uncertainty is likely to be prevalent.

The present research extends three strains of literature. First, our study contributes to studies on the relationship between governmental regulation and innovation. It has been one of the prominent research topics for environmental scientists, economists, management scholars, and public policy researchers as to whether governmental regulation positively or negatively impacts innovation (among others, "Poter's hypotheses" by Porter & Van der Linde, 1995). Since the seminal work by Porter and Van der Linde (1995), there have been myriad empirical studies showing the "stringency" of governmental regulation is associated with firms' innovation activities (e.g., Cecere & Corrocher, 2016; Johnstone, Haščič, Poirier, Hemar, & Michel, 2012; Kesidou & Demirel, 2012). In addition to these studies, our research contributes to advancing the understanding of how other aspects of the regulatory action of governmental authority other than the "stringency" affect innovation, by shedding empirical light on the way the *regulatory uncertainty* shapes the innovation process.

Second, our study contributes to the studies on the factors involved in the translation of scientific discovery into technical applications. Promoting the diffusion of scientific discovery into industrial sectors has been one of the missions of science policymakers because knowledge transfer is one of the crucial sources of technological innovation. To this end, scholars have attempted to explore various factors including scientific, technological, and organizational factors (e.g., Bercovitz, Feldman, Feller, & Burton, 2001; Caldera & Debande, 2010; González-Pernía, Kuechle, & Peña-Legazkue, 2013; Landry, Amara, & Ouimet, 2007; Shane, 2002; Veugelers & Wang, 2019) that may facilitate or hinder the translation of scientific discovery to technology and what policy instruments are worthy of consideration to maneuver those factors. Our research extends these efforts by adding the "*regulatory uncertainty*" as an institutional factor that decelerates the translation of scientific discovery into technical applications.

Third, our research contributes to extending the scholarly efforts toward elucidating the interconnection between regulatory uncertainty and technological change. On the one hand, by focusing on how regulatory uncertainty shapes the innovation "processes", we complement the prior studies that investigate the aggregated impact of the regulatory uncertainty on the level of innovation activities through the analysis of firms' patenting activities (e.g., Kalamova et al., 2012) or research investment (e.g., Goel, 2007; Jones, 2015). To this end, our study sheds empirical light on the impact of regulatory uncertainty on the translation of scientific discoveries into technical applications and its heterogeneous impact by the extent to which the discovery is relevant to emerging research topics. On the other hand, the present study helps to elucidate the presence of a bidirectional relationship between the regulatory regime and technological change. As the nanomedicine case showed, the emergence of new science and technology may result in creating regulatory uncertainty. The novel features of the new technology or science and their fast change make the existing regulatory framework quickly obsolete, which imposes a significant challenge to the regulatory authority regarding how and which part of the existing regulatory framework needs updates. This challenge is accompanied by the delay in implementing the new regulatory framework, which results in regulatory uncertainty. Conversely, as our analyses found that regulatory uncertainty slows down the development of technological application of scientific knowledge on emerging research topics, regulatory uncertainty may shape the direction of the technical change. Under the presence of regulatory uncertainty, the pace of the innovation process and resulting technical change through the translation of scientific knowledge into its application is not only slowed, but also its degree will be heterogeneous by the degree of which the underlying scientific findings are of emerging research topics in the field. All in all, our research sheds light on the way regulatory uncertainty shapes the evolutionary pathway of technological change.

The present study has several limitations that we wish future studies to address. First, as discussed, our empirical setting was based on a single event of regulatory uncertainty in the nanomedicine sector in the U.S. Because the mechanism we explained may work differently in other conditions, it is necessary to conduct more empirical analyses in various contexts for more generalizable conclusions.

Second, for the lack of data, our analysis was limited to analyzing the five-year impact of the regulatory uncertainty. In addition to the short-term effect analysis, investigating the long-term effect of the regulatory uncertainty can provide more granular insight into innovation dynamics generated by regulatory uncertainty.

Third, we measured the translation of scientific discovery into technical applications with the patent citation count accruing to research papers, which exhibits several flaws, as discussed in section 3.4. To this limitation, using the number of new nanomedicine products developed during the period of observation may be an alternative and more direct measurement, and yet, due to the lack of data, our study was limited to the patent citation analysis. We wish future studies to examine the impact of regulatory uncertainty using alternative measurements.

Fourth, given the significant field-level heterogeneity in firms' practice of R&D and difference in the innovation process by sector, readers should note that our study alone cannot generalize the impact of the regulatory uncertainty on the innovation process. Instead, we argue that our finding may be useful for understanding the way regulatory uncertainty shapes a part of innovation processes in the sector where scientific discovery serves as a crucial source for the development of technological applications (e.g., the pharmaceutical industry). How regulatory uncertainty shapes the innovation process in other sectors where scientific discovery serves as a relatively less prominent source for technological applications is an intriguing research question, which we hope future research will address.

Acknowledgment

This work is supported by the US National Science Foundation (Award #1759960 – "Indicators of Technological Emergence") and Sungkyunkwan University of Korea. The findings and observations contained herein are those of the authors and do not necessarily reflect the views of the National Science Foundation or Sungkyunkwan University. The earlier version of this paper was presented at the 82nd Academy of Management Annual Meeting.

Conflict of Interest

The authors declare that they have no conflict of interest that would affect the research or the peer review procedure.

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

FIGURES

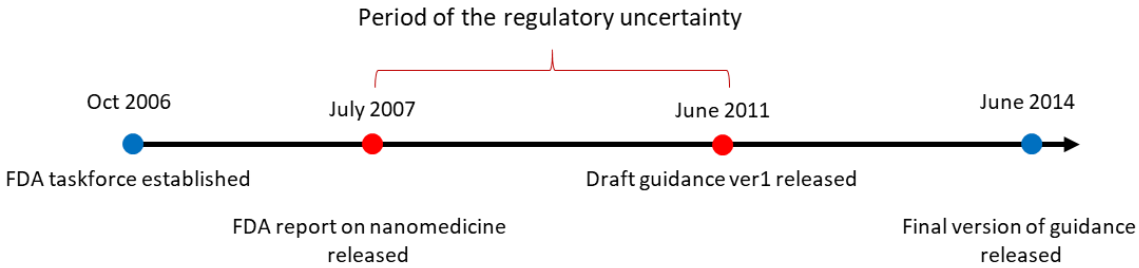
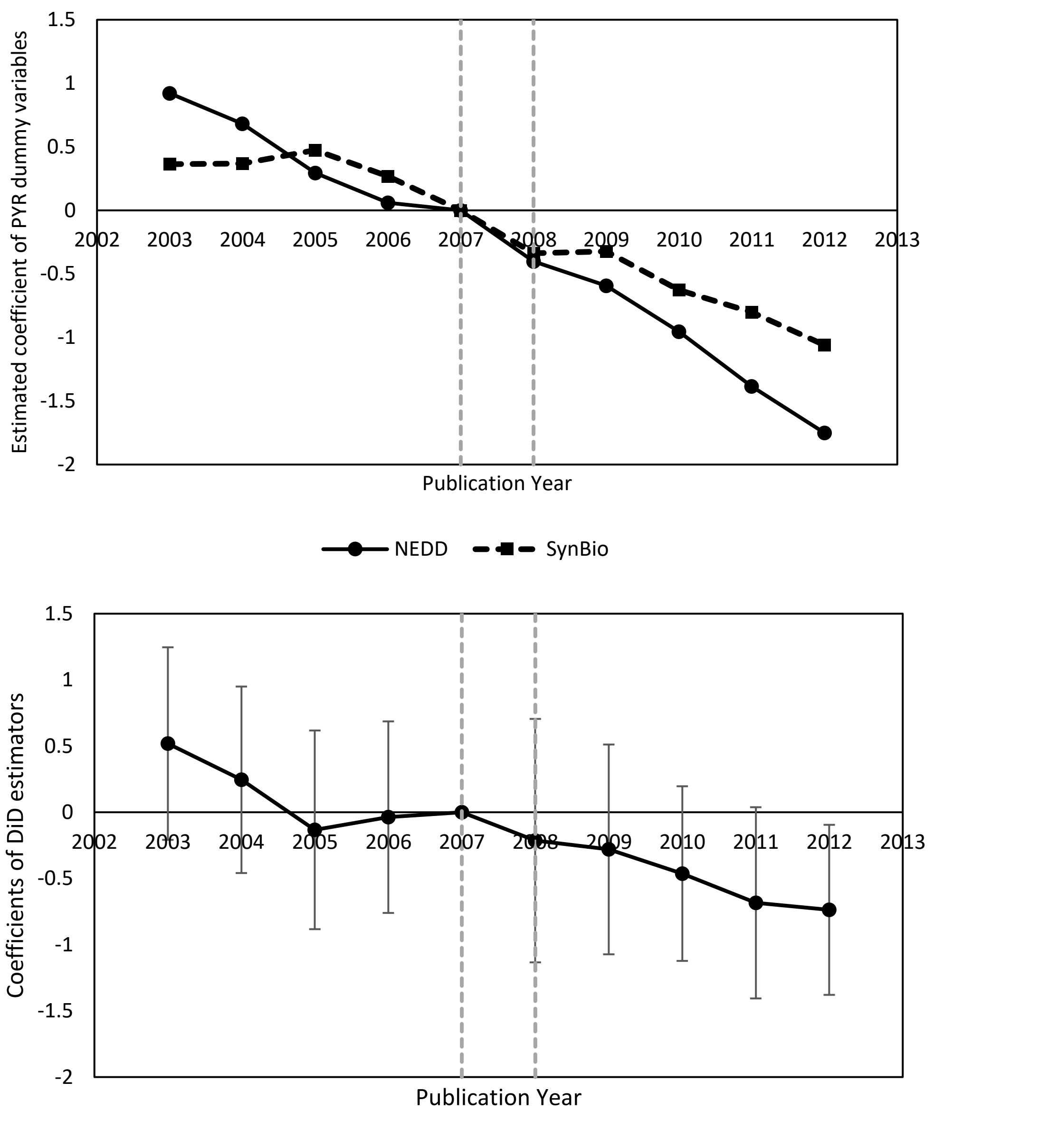


Figure 1. FDA nanomedicine-related documents release timing



Error bar: 95% confidence interval (using robust standard error)

Figure 2. Estimated regression coefficients (upper: Separate estimation, lower: DiD estimation)

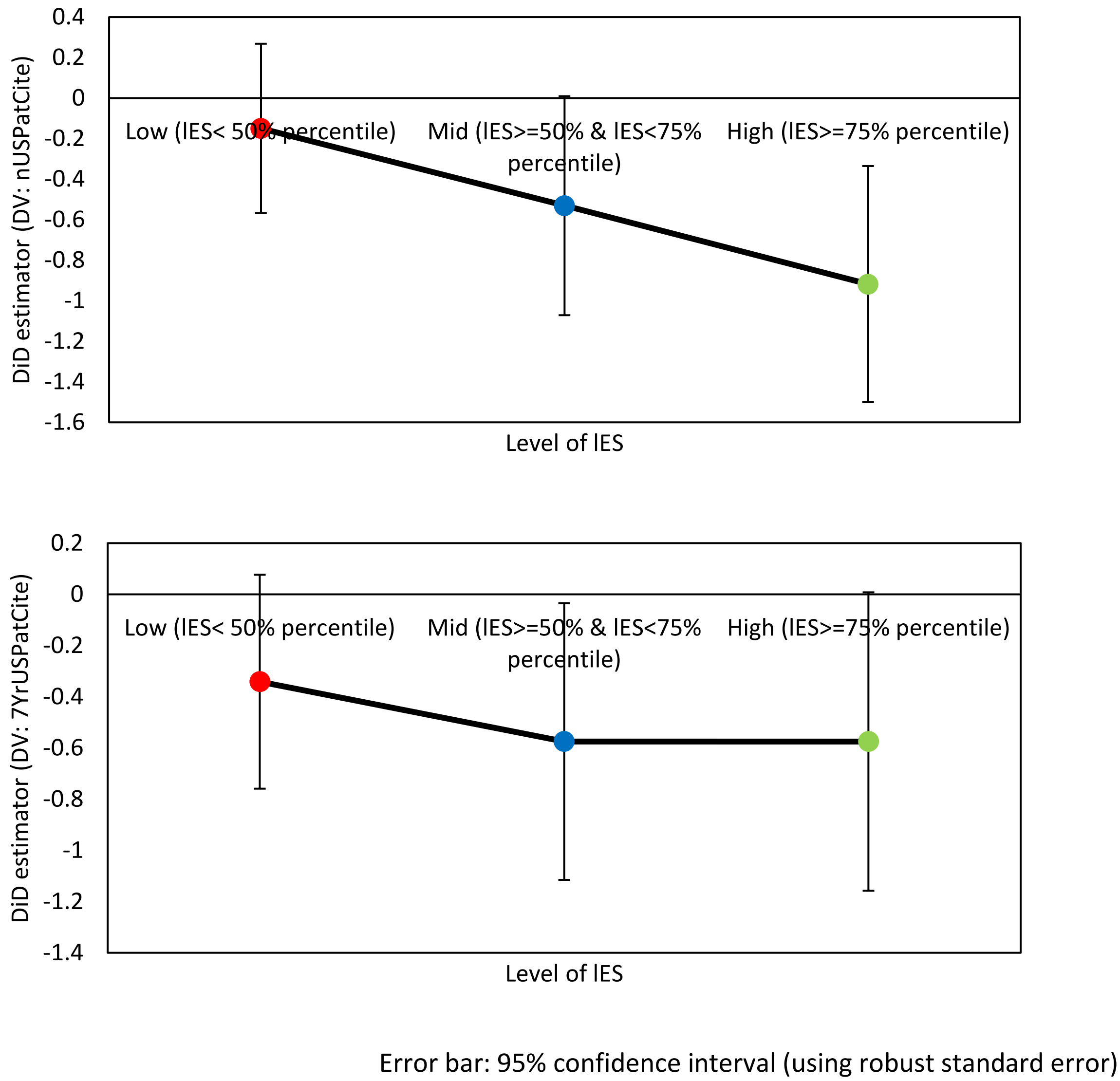


Figure 3. DiD Estimator using three subsamples (divided by the percentile of IES)

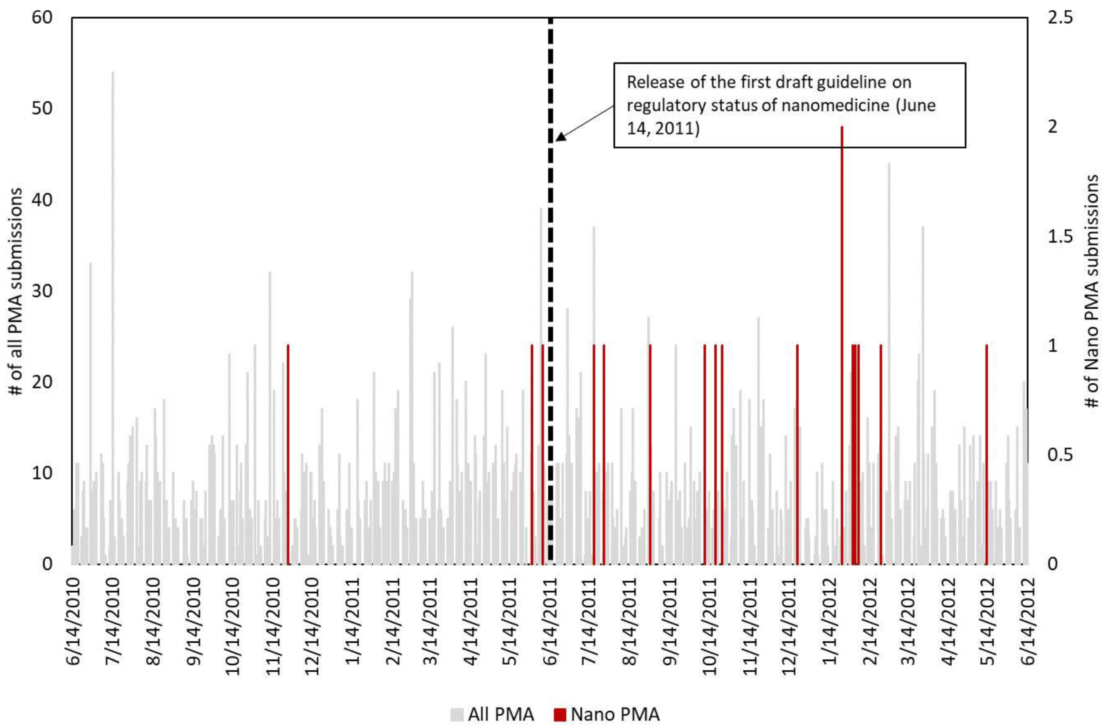


Figure 4. Premarket authorization submission (by submission date)

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

TABLES

Table 1. Descriptions of Variables

Variable	Description	Type	Source
nUSPatCite	Total number of US patent citations accrued to papers	Dependent Variable	M&F data
7YrPatCite	7-year window US patent citation accrued to papers		M&F data
PY	Publication year	Independent Variable	WoS CC
lES	Natural log transformed paper-level emergence score +1		WoS CC
Team Size	Number of authors of papers	Control Variable	WoS CC
ln(nRef+1)	Natural log transformed value of # of cited references +1		WoS CC
Int Collabo	A dummy variable takes the value of 1 if the paper in question originated from international research collaboration		WoS CC
1st author in USA	A dummy variable that takes the value of 1 if the paper in question has an US-located first author		WoS CC

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

Table 2. Pairwise correlations and summary statistics

NEDD	nUSPatCite	7YrPatCite	PY	lES	Team Size	ln(nRef+1)	Int Collabo	1st author in USA
nUSPatCite	1.00							
7YrPatCite	0.88	1.00						
PY	-0.15	-0.10	1.00					
lES	-0.04	-0.03	0.25	1.00				
Team Size	0.07	0.09	0.05	-0.10	1.00			
ln(nRef+1)	0.00	0.01	0.10	0.01	0.01	1.00		
Int Collabo	0.01	0.01	0.02	-0.03	0.22	0.06	1.00	
1st author in USA	0.11	0.12	-0.13	-0.17	-0.05	0.10	-0.05	1.00
Obs	41,321	41,321	41,321	41,321	41,321	41,321	41,321	41,321
Mean	1.36	0.89	2008.96	2.19	5.91	3.61	0.20	0.29
Std.Dev	7.10	4.30	2.60	1.63	3.14	0.48	0.40	0.45
Min	0	0	2003	0	1	0	0	0
Max	521	155	2012	5.500495	57	6.326149	1	1

SynBio	nUSPatCite	7YrPatCite	PY	lES	Team Size	ln(nRef+1)	Int Collabo	1st author in USA
nUSPatCite	1.00							
7YrPatCite	0.90	1.00						
PY	-0.13	-0.04	1.00					
lES	0.00	0.03	0.33	1.00				
Team Size	0.12	0.12	0.00	-0.07	1.00			
ln(nRef+1)	0.00	0.01	0.09	0.12	0.05	1.00		
Int Collabo	-0.04	-0.04	0.03	0.00	0.24	0.07	1.00	
1st author in USA	0.15	0.15	0.00	0.04	-0.05	0.06	-0.14	1.00
Obs	2,705	2,705	2,705	2,705	2,705	2,705	2,705	2,705
Mean	2	1	2,009	1	5	3.58	0.22	0.40
Std.Dev	6.83	4.69	2.76	1.06	3.23	0.56	0.41	0.49
Min	0	0	2003	0	1	0	0	0
Max	113	82	2012	3.84	53	5.82	1	1

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

Table 3. Estimation of Impact of the regulatory uncertainty with full sample

	DiD estimation		DDD estimation		IES>0		IES=0	
VARIABLES	nUSPatCite	7YrPatCite	nUSPatCite	7YrPatCite	nUSPatCite	7YrPatCite	nUSPatCite	7YrPatCite
PY2003XNEDDxIES			-0.281	-0.741*				
			(0.338)	(0.382)				
PY2004XNEDDxIES			-0.240	-0.477				
			(0.280)	(0.359)				
PY2005xNEDDxIES			0.0360	-0.00617				
			(0.266)	(0.260)				
PY2006xNEDDxIES			0.138	0.177				
			(0.247)	(0.266)				
PY2008xNEDDxIES			-0.0239	-0.00672				
			(0.344)	(0.351)				
PY2009xNEDDxIES			-0.0724	-0.0582				
			(0.280)	(0.286)				
PY2010xNEDDxIES			-0.303*	-0.244				
			(0.155)	(0.154)				
PY2011xNEDDxIES			-0.558***	-0.551***				
			(0.156)	(0.157)				
PY2012xNEDDxIES			-0.160	-0.166				
			(0.132)	(0.131)				
PY2003xNEDD	0.519	0.437	0.569	0.696*	0.254	-0.263	0.558	0.585
	(0.371)	(0.334)	(0.414)	(0.356)	(0.530)	(0.601)	(0.554)	(0.439)
PY2004xNEDD	0.245	0.0846	0.297	0.264	0.0150	-0.399	0.267	0.150
	(0.359)	(0.303)	(0.398)	(0.338)	(0.490)	(0.606)	(0.538)	(0.420)
PY2005xNEDD	-0.133	-0.290	-0.105	-0.254	-0.189	-0.241	0.00286	-0.275
	(0.383)	(0.333)	(0.447)	(0.401)	(0.411)	(0.416)	(0.578)	(0.477)
PY2006xNEDD	-0.0370	-0.149	-0.0750	-0.267	0.168	0.140	0.00630	-0.280
	(0.369)	(0.318)	(0.434)	(0.395)	(0.375)	(0.411)	(0.563)	(0.464)
PY2008xNEDD	-0.214	-0.436	-0.144	-0.406	-0.0771	-0.167	-0.124	-0.522
	(0.469)	(0.422)	(0.611)	(0.570)	(0.477)	(0.488)	(0.719)	(0.630)
PY2009xNEDD	-0.281	-0.409	-0.0397	-0.197	-0.318	-0.317	-0.0382	-0.316
	(0.404)	(0.359)	(0.540)	(0.518)	(0.365)	(0.351)	(0.650)	(0.571)
PY2010xNEDD	-0.463	-0.568**	0.0244	-0.139	-0.623*	-0.566*	-0.0373	-0.307
	(0.336)	(0.270)	(0.406)	(0.346)	(0.335)	(0.333)	(0.559)	(0.445)
PY2011xNEDD	-0.684*	-0.834***	0.311	0.156	-1.139***	-1.171***	0.894	0.637
	(0.368)	(0.308)	(0.424)	(0.366)	(0.369)	(0.367)	(0.562)	(0.449)
PY2012xNEDD	-0.737**	-0.894***	-0.249	-0.389	-0.712**	-0.758**	-0.391	-0.642
	(0.328)	(0.258)	(0.390)	(0.325)	(0.321)	(0.317)	(0.543)	(0.422)
PY2003xIES			0.312	0.752**				
			(0.336)	(0.380)				
PY2004xIES			0.232	0.416				
			(0.280)	(0.359)				
PY2005xIES			-0.0731	-0.0347				
			(0.265)	(0.261)				
PY2006xIES			-0.170	-0.179				
			(0.249)	(0.267)				
PY2008xIES			-0.0317	-0.0410				
			(0.346)	(0.352)				
PY2009xIES			-0.0749	-0.0870				
			(0.282)	(0.289)				
PY2010xIES			0.169	0.0918				
			(0.158)	(0.157)				
PY2011xIES			0.341**	0.319**				
			(0.158)	(0.159)				
PY2012xIES			-0.0750	-0.0869				
			(0.135)	(0.134)				

PY2003	0.403	0.0732	0.393	-0.103	0.753	0.833	0.530	0.102
	(0.353)	(0.310)	(0.390)	(0.311)	(0.510)	(0.581)	(0.526)	(0.390)
PY2004	0.435	0.200	0.460	0.192	0.719	0.681	0.532	0.324
	(0.342)	(0.281)	(0.375)	(0.297)	(0.470)	(0.591)	(0.511)	(0.373)
PY2005	0.424	0.243	0.506	0.333	0.453	0.186	0.506	0.408
	(0.366)	(0.315)	(0.419)	(0.369)	(0.392)	(0.399)	(0.546)	(0.438)
PY2006	0.0946	0.0964	0.216	0.243	-0.159	-0.203	0.235	0.312
	(0.355)	(0.300)	(0.410)	(0.354)	(0.358)	(0.395)	(0.533)	(0.415)
PY2008	-0.190	0.122	-0.149	0.185	-0.415	-0.206	-0.0620	0.342
	(0.459)	(0.411)	(0.598)	(0.552)	(0.464)	(0.476)	(0.699)	(0.603)
PY2009	-0.313	0.0326	-0.245	0.126	-0.392	-0.158	-0.284	0.150
	(0.392)	(0.345)	(0.524)	(0.499)	(0.346)	(0.331)	(0.626)	(0.545)
PY2010	-0.492	-0.0604	-0.697*	-0.165	-0.471	-0.209	-0.566	0.0419
	(0.322)	(0.251)	(0.381)	(0.310)	(0.317)	(0.316)	(0.527)	(0.401)
PY2011	-0.704**	-0.183	-1.219***	-0.660**	-0.510	-0.105	-1.575***	-0.962**
	(0.356)	(0.293)	(0.401)	(0.334)	(0.354)	(0.351)	(0.529)	(0.404)
PY2012	-1.018***	-0.481**	-0.970***	-0.410	-1.210***	-0.784***	-0.926*	-0.301
	(0.312)	(0.238)	(0.362)	(0.284)	(0.300)	(0.297)	(0.508)	(0.372)
NEDD	-0.0460	0.0942	-0.184	-0.0533	-0.119	-0.0955	-0.210	0.0335
	(0.286)	(0.202)	(0.305)	(0.217)	(0.245)	(0.240)	(0.475)	(0.331)
lES			0.115**	0.131***				
			(0.0486)	(0.0501)				
Team Size	0.102***	0.0998***	0.0996***	0.0982***	0.106***	0.105***	0.0947***	0.0925***
	(0.00740)	(0.00753)	(0.00691)	(0.00705)	(0.00869)	(0.00880)	(0.0113)	(0.0116)
ln(nRef+1)	0.185***	0.181***	0.179***	0.173***	0.293***	0.296***	0.00802	-0.0132
	(0.0569)	(0.0585)	(0.0603)	(0.0629)	(0.0551)	(0.0551)	(0.106)	(0.110)
Int Collabo	0.0896	0.0656	0.0889	0.0672	0.0805	0.0519	0.127	0.110
	(0.0617)	(0.0627)	(0.0606)	(0.0620)	(0.0749)	(0.0752)	(0.107)	(0.112)
1stAuthorInUS	1.051***	1.030***	1.042***	1.021***	1.155***	1.133***	0.859***	0.837***
	(0.0446)	(0.0450)	(0.0443)	(0.0449)	(0.0529)	(0.0531)	(0.0768)	(0.0792)
Constant	-0.986***	-1.497***	-1.047***	-1.583***	-1.213***	-1.640***	-0.430	-0.974*
	(0.348)	(0.288)	(0.384)	(0.324)	(0.303)	(0.299)	(0.617)	(0.521)
Lnalpha	2.076***	2.084***	2.068***	2.074***	2.013***	2.014***	2.160***	2.180***
	(0.0185)	(0.0206)	(0.0185)	(0.0208)	(0.0238)	(0.0261)	(0.0291)	(0.0337)
Observations	44,026	44,026	44,026	44,026	30,606	30,606	13,420	13,420
Model	GNBREG	GNBREG	GNBREG	GNBREG	GNBREG	GNBREG	GNBREG	GNBREG
Sample	All	All	All	All	lES>0	ES>0	lES=0	ES=0
Pseudo R2	0.0424	0.0316	0.0434	0.0329	0.0502	0.0390	0.0292	0.0211

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

Table 4. Estimation of Impact of the regulatory uncertainty with matched sample

	DiD estimation		DDD estimation	
VARIABLES	nUSPatCite	7YrPatCite	nUSPatCite	7YrPatCite
PY2003XNEDDxIES			0.0282	-0.431
			(0.422)	(0.429)
PY2004XNEDDxIES			-0.437	-0.346
			(0.350)	(0.289)
PY2005xNEDDxIES			-0.155	-0.181
			(0.402)	(0.387)
PY2006xNEDDxIES			0.0295	0.130
			(0.297)	(0.302)
PY2008xNEDDxIES			-0.262	-0.308
			(0.381)	(0.378)
PY2009xNEDDxIES			-0.466	-0.372
			(0.337)	(0.325)
PY2010xNEDDxIES			-0.177	-0.132
			(0.242)	(0.239)
PY2011xNEDDxIES			**-0.706****	**-0.696****
			(0.305)	**(0.306)**
PY2012xNEDDxIES			**-0.487*****	**-0.487*****
			(0.174)	**(0.174)**
PY2003xNEDD	-0.0770	0.293	-0.786	-0.271
	(0.594)	(0.624)	(0.614)	(0.600)
PY2004xNEDD	-0.507	-0.425	-0.674	-0.735
	(0.537)	(0.502)	(0.653)	(0.634)
PY2005xNEDD	0.0716	0.0641	0.143	0.122
	(0.545)	(0.541)	(0.702)	(0.668)
PY2006xNEDD	0.104	0.269	-0.200	-0.164
	(0.521)	(0.502)	(0.672)	(0.659)
PY2008xNEDD	-0.846	**-0.981***	-0.870	-0.828
	(0.570)	**(0.533)**	(0.773)	(0.732)
PY2009xNEDD	-0.642	-0.559	0.0339	0.0291
	(0.518)	(0.485)	(0.716)	(0.708)
PY2010xNEDD	-0.701	-0.590	-0.369	-0.250
	(0.487)	(0.465)	(0.646)	(0.631)
PY2011xNEDD	-0.517	-0.461	0.721	0.798
	(0.568)	(0.547)	(0.834)	(0.827)
PY2012xNEDD	**-1.156****	**-1.123****	-0.126	-0.0541
	(0.469)	**(0.442)**	(0.624)	(0.610)
PY2003xIES			0.473	0.948**
			(0.394)	(0.393)
PY2004xIES			0.554	0.489*
			(0.338)	(0.271)
PY2005xIES			0.129	0.150
			(0.389)	(0.375)
PY2006xIES			0.140	0.0469
			(0.294)	(0.299)
PY2008xIES			0.374	0.319
			(0.366)	(0.371)
PY2009xIES			0.228	0.125
			(0.333)	(0.322)
PY2010xIES			0.0316	-0.0734
			(0.241)	(0.241)
PY2011xIES			0.413**	0.360*
			(0.192)	(0.193)
PY2012xIES			0.0642	0.0166
			(0.169)	(0.171)
PY2003	0.445	-0.0800	0.347	-0.403

	(0.363)	(0.356)	(0.433)	(0.372)
PY2004	0.599*	0.201	0.525	0.186
	(0.351)	(0.310)	(0.411)	(0.360)
PY2005	0.175	-0.00346	0.160	0.00708
	(0.369)	(0.354)	(0.444)	(0.428)
PY2006	-0.180	-0.276	-0.231	-0.242
	(0.321)	(0.307)	(0.396)	(0.383)
PY2008	-0.232	0.0378	-0.542	-0.207
	(0.423)	(0.406)	(0.524)	(0.496)
PY2009	-0.447	-0.159	-0.616	-0.223
	(0.355)	(0.331)	(0.480)	(0.470)
PY2010	-0.450	-0.0828	-0.480	-0.000768
	(0.332)	(0.320)	(0.446)	(0.425)
PY2011	-0.832***	-0.389	-1.418***	-0.912***
	(0.297)	(0.274)	(0.376)	(0.349)
PY2012	-0.948***	-0.480*	-1.052***	-0.529
	(0.282)	(0.259)	(0.359)	(0.329)
NEDD	0.0151	-0.0316	-0.0461	-0.135
	(0.378)	(0.343)	(0.420)	(0.399)
lES			0.0621	0.113
			(0.119)	(0.121)
Constant	0.941***	0.464**	0.881***	0.345
	(0.226)	(0.195)	(0.273)	(0.231)
lnalpha	2.217***	2.238***	2.187***	2.202***
	(0.0467)	(0.0501)	(0.0472)	(0.0509)
Observations	3,836	3,836	3,836	3,836
Model	GNBREG	GNBREG	GNBREG	GNBREG
Sample	Matched	Matched	Matched	Matched
Pseudo R2	0.0185	0.00993	0.0228	0.0151

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

Table 5. Placebo Test

VARIABLES	(1) nUSPatCite	(2) 7YrUSPatCite	(3) nUSPatCite	(4) 7YrUSPatCite
PY2003XNEDDxIES			-0.340	-0.758**
			(0.354)	(0.352)
PY2004XNEDDxIES			-0.290	-0.450*
			(0.298)	(0.265)
PY2006xNEDDxIES			-0.109	0.0125
			(0.239)	(0.239)
PY2007xNEDDxIES			-0.180	-0.251
			(0.199)	(0.177)
PY2003xNEDD	0.552	0.622*	0.348	0.737*
	(0.345)	(0.355)	(0.429)	(0.420)
PY2004xNEDD	0.327	0.315	0.0918	0.254
	(0.329)	(0.330)	(0.370)	(0.350)
PY2006xNEDD	0.113	0.159	0.291	0.216
	(0.328)	(0.336)	(0.344)	(0.356)
PY2007xNEDD	0.0963	0.209	0.0779	0.215
	(0.358)	(0.315)	(0.394)	(0.360)
PY2003xIES			0.367	0.768**
			(0.354)	(0.350)
PY2004xIES			0.342	0.463*
			(0.297)	(0.263)
PY2006xIES			0.0958	0.00886
			(0.238)	(0.237)
PY2007xIES			0.229	0.297*
			(0.199)	(0.177)
PY2003	0.0476	-0.0922	0.206	-0.202
	(0.326)	(0.335)	(0.401)	(0.384)
PY2004	0.0582	0.000674	0.221	0.0347
	(0.307)	(0.311)	(0.335)	(0.317)
PY2006	-0.324	-0.147	-0.420	-0.207
	(0.312)	(0.320)	(0.304)	(0.312)
PY2007	-0.412	-0.195	-0.541	-0.360
	(0.343)	(0.299)	(0.368)	(0.330)
NEDD	-0.151	-0.157	-0.133	-0.186
	(0.246)	(0.250)	(0.239)	(0.241)
IES			0.0280	0.0468
			(0.0438)	(0.0429)
TeamSize	0.0587***	0.0510***		
	(0.00999)	(0.0109)		
ln(nRef+1)	0.0407	0.0368		
	(0.0870)	(0.0903)		
Int Collabo	0.0937	0.105		
	(0.0830)	(0.0892)		
1stAuthorInUS	0.866***	0.818***		
	(0.0650)	(0.0648)		
Constant	0.225	-0.437	1.092***	0.361
	(0.392)	(0.403)	(0.217)	(0.221)
lnalpha	1.868***	1.860***	1.936***	1.928***
	(0.0229)	(0.0272)	(0.0230)	(0.0272)
Observations	12,446	12,446	12,446	12,446
Model	GNBREG	GNBREG	GNBREG	GNBREG
Sample	All	All	All	All
Pseudo R2	0.0146	0.0125	0.00487	0.00273

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

Table 6. Testing Research Impact Change

VARIABLES	(1) TimesCited	(2) TimesCited	(3) TimesCited	(4) TimesCited
PY2003XNEDDxIES		0.197		
		(0.187)		
PY2004XNEDDxIES		0.155		
		(0.212)		
PY2005xNEDDxIES		-0.157		
		(0.104)		
PY2006xNEDDxIES		0.00813		
		(0.119)		
PY2008xNEDDxIES		0.0469		
		(0.0948)		
PY2009xNEDDxIES		-0.131		
		(0.0978)		
PY2010xNEDDxIES		**0.156****		
		(0.0655)		
PY2011xNEDDxIES		0.0107		
		(0.0534)		
PY2012xNEDDxIES		0.0256		
		(0.0558)		
PY2003xNEDD	0.147	0.115	0.494	0.0277
	(0.162)	(0.174)	(0.331)	(0.187)
PY2004xNEDD	0.252	0.153	0.510	0.0934
	(0.171)	(0.179)	(0.354)	(0.193)
PY2005xNEDD	0.121	0.178	-0.0656	0.0903
	(0.141)	(0.145)	(0.248)	(0.161)
PY2006xNEDD	0.0668	0.00732	0.231	-0.114
	(0.148)	(0.154)	(0.259)	(0.169)
PY2008xNEDD	0.0428	0.00780	0.179	-0.0991
	(0.136)	(0.141)	(0.231)	(0.158)
PY2009xNEDD	-0.201	-0.0840	-0.294	-0.133
	(0.143)	(0.154)	(0.221)	(0.171)
PY2010xNEDD	-0.0346	-0.209	0.151	-0.246
	(0.132)	(0.150)	(0.199)	(0.169)
PY2011xNEDD	-0.0823	-0.0557	0.0399	-0.184
	(0.120)	(0.138)	(0.178)	(0.158)
PY2012xNEDD	-0.0243	0.0110	0.0814	-0.0680
	(0.122)	(0.156)	(0.176)	(0.181)
PY2003xIES		-0.184		
		(0.185)		
PY2004xIES		-0.124		
		(0.211)		
PY2005xIES		0.166		
		(0.103)		
PY2006xIES		0.0128		
		(0.119)		
PY2008xIES		-0.0722		
		(0.0948)		
PY2009xIES		0.0944		
		(0.0983)		
PY2010xIES		-0.168**		
		(0.0658)		
PY2011xIES		-0.0528		
		(0.0543)		
PY2012xIES		-0.0863		
		(0.0567)		
PY2003	0.215	0.350**	-0.0170	0.432**

	(0.152)	(0.158)	(0.322)	(0.171)
PY2004	0.0735	0.205	-0.0986	0.290
	(0.164)	(0.170)	(0.348)	(0.182)
PY2005	0.0945	0.0825	0.344	0.155
	(0.134)	(0.134)	(0.243)	(0.148)
PY2006	0.0623	0.102	-0.0526	0.192
	(0.142)	(0.147)	(0.254)	(0.160)
PY2008	-0.125	-0.0569	-0.289	0.0377
	(0.131)	(0.132)	(0.227)	(0.146)
PY2009	-0.0107	-0.0839	0.0357	-0.0454
	(0.140)	(0.148)	(0.218)	(0.162)
PY2010	-0.261**	-0.129	-0.495**	-0.0871
	(0.128)	(0.142)	(0.195)	(0.157)
PY2011	-0.387***	-0.389***	-0.583***	-0.266*
	(0.116)	(0.130)	(0.175)	(0.149)
PY2012	-0.668***	-0.638***	-0.865***	-0.552***
	(0.118)	(0.149)	(0.173)	(0.170)
NEDD	0.147	-0.0694	0.0231	0.0217
	(0.102)	(0.101)	(0.158)	(0.123)
lES		0.168***		
		(0.0149)		
Team Size	0.0541***	0.0649***	0.0523***	0.0744***
	(0.00227)	(0.00228)	(0.00286)	(0.00367)
ln(nRef+1)	0.495***	0.481***	0.541***	0.376***
	(0.0184)	(0.0179)	(0.0214)	(0.0330)
Int Collabo	0.0513***	0.0725***	0.0247	0.151***
	(0.0167)	(0.0167)	(0.0195)	(0.0307)
1stAuthorInUS	0.343***	0.406***	0.363***	0.429***
	(0.0172)	(0.0168)	(0.0209)	(0.0278)
Constant	1.595***	1.418***	1.702***	1.626***
	(0.119)	(0.117)	(0.173)	(0.169)
Lnalpha	0.0456***	0.00399	0.000654	0.0445***
	(0.00897)	(0.00915)	(0.0109)	(0.0157)
Observations	44,026	44,026	30,606	13,420
Model	GNBREG	GNBREG	GNBREG	GNBREG
Sample	All	All	lES>0	lES=0
Pseudo R2	0.0177	0.0227	0.0200	0.0236

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

REFERENCES

Alcacer, J. & Gittelman, M. 2006. Patent citations as a measure of knowledge flows: The influence of examiner citations. ***The Review of Economics and Statistics***, 88(4): 774-779.

Aragón-Correa, J. A. & Sharma, S. 2003. A contingent resource-based view of proactive corporate environmental strategy. ***Academy of Management Review***, 28(1): 71-88.

Bawa, R. 2011. Regulating nanomedicine-can the FDA handle it? ***Current Drug Delivery***, 8(3): 227-234.

Bercovitz, J., Feldman, M., Feller, I., & Burton, R. 2001. Organizational structure as a determinant of academic patent and licensing behavior: An exploratory study of Duke, Johns Hopkins, and Pennsylvania State Universities. ***The Journal of Technology Transfer***, 26(1): 21-35.

Birnbaum, P. H. 1984. The choice of strategic alternatives under increasing regulation in high technology companies. ***Academy of Management Journal***, 27(3): 489-510.

Bittlingmayer, G. 2000. Regulatory uncertainty and investment: evidence from antitrust enforcement. ***Cato Journal***, 20(3): 295-325.

Blind, K. 2012. The influence of regulations on innovation: A quantitative assessment for OECD countries. ***Research Policy***, 41(2): 391-400.

Bosso, C. 2016. Settling into the midstream? Lessons for governance from the decade of nanotechnology. ***Journal of Nanoparticle Research***, 18(6): 1-15.

Breitzman, A. & Thomas, P. 2015. The Emerging Clusters Model: A tool for identifying emerging technologies across multiple patent systems. ***Research Policy***, 44(1): 195-205.

Caldera, A. & Debande, O. 2010. Performance of Spanish universities in technology transfer: An empirical analysis. ***Research Policy***, 39(9): 1160-1173.

Carley, S. F., Newman, N. C., Porter, A. L., & Garner, J. G. 2018. An indicator of technical emergence. ***Scientometrics***, 115(1): 35-49.

Carrera, A., Mesquita, L., Perkins, G., & Vassolo, R. 2003. Business groups and their corporate strategies on the Argentine roller coaster of competitive and anti-competitive shocks. ***Academy of Management Perspectives***, 17(3): 32-44.

Carter, N. M. 1990. Small firm adaptation: Responses of physicians' organizations to regulatory and competitive uncertainty. ***Academy of Management Journal***, 33(2): 307-333.

Cecere, G. & Corrocher, N. 2016. Stringency of regulation and innovation in waste management: an empirical analysis on EU countries. ***Industry and Innovation***, 23(7): 625-646.

Cohen, S. G. & Bailey, D. E. 1997. What makes teams work: Group effectiveness research from the shop floor to the executive suite. ***Journal of Management***, 23(3): 239-290.

Cohen, W. M., Nelson, R., & Walsh, J. P. 2000. Protecting their intellectual assets: Appropriability conditions and why US manufacturing firms patent (or not): National Bureau of Economic Research Cambridge, Mass., USA.

Conley, S. N. 2020. Who gets to be born? The anticipatory governance of pre-implantation genetic diagnosis technology in the United Kingdom from 1978–2001. ***Journal of Responsible Innovation***, 7(3): 507-527.

Criscuolo, P. & Verspagen, B. 2008. Does it matter where patent citations come from? Inventor vs. examiner citations in European patents. ***Research Policy***, 37(10): 1892-1908.

Czarnitzki, D. & Toole, A. A. 2011. Patent protection, market uncertainty, and R&D investment. ***The Review of Economics and Statistics***, 93(1): 147-159.

De Jong, W. H. & Borm, P. J. 2008. Drug delivery and nanoparticles: applications and hazards. ***International Journal of Nanomedicine***, 3(2): 133.

Dixit, A. 1992. Investment and hysteresis. ***Journal of Economic Perspectives***, 6(1): 107-132.

Dixit, A. & Pindyck, R. 1994. Investment under Uncertainty: Princeton University Press.

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

Dosi, G. 1982. Technological paradigms and technological trajectories: a suggested interpretation of the determinants and directions of technical change. ***Research Policy***, 11(3): 147-162.

Eaton, M. 2007. Nanomedicine: industry-wise research. ***Nature Materials***, 6(4): 251-253.

Engau, C. & Hoffmann, V. H. 2009. Effects of regulatory uncertainty on corporate strategy—an analysis of firms' responses to uncertainty about post-Kyoto policy. ***Environmental Science & Policy***, 12(7): 766-777.

Ettlie, J. E. & Bridges, W. P. 1982. Environmental uncertainty and organizational technology policy. ***IEEE Transactions on Engineering Management***, 29(1): 2-10.

Ettlie, J. E. 1983. Organizational policy and innovation among suppliers to the food processing sector. ***Academy of Management Journal***, 26(1): 27-44.

Fabrizio, K. R. 2013. The effect of regulatory uncertainty on investment: evidence from renewable energy generation. ***The Journal of Law, Economics, & Organization***, 29(4): 765-798.

Fisher, E. 2019. Governing with ambivalence: The tentative origins of socio-technical integration. ***Research Policy***, 48(5): 1138-1149.

Fleming, J. J. 2015. The decline of venture capital investment in early-stage life sciences poses a challenge to continued innovation. ***Health Affairs***, 34(2): 271-276.

Gazni, A., Sugimoto, C. R., & Didegah, F. 2012. Mapping world scientific collaboration: Authors, institutions, and countries. ***Journal of the American Society for Information Science and Technology***, 63(2): 323-335.

Gerard, D. & Lave, L. B. 2005. Implementing technology-forcing policies: The 1970 Clean Air Act Amendments and the introduction of advanced automotive emissions controls in the United States. ***Technological Forecasting and Social Change***, 72(7): 761-778.

Goel, R. K. 2007. Research spending under regulatory uncertainty. ***The Journal of Technology Transfer***, 32(6): 593-604.

Goel, R. K. & Nelson, M. A. 2021. How do firms use innovations to hedge against economic and political uncertainty? Evidence from a large sample of nations. ***The Journal of Technology Transfer***, 46(2): 407-430.

González-Pernía, J. L., Kuechle, G., & Peña-Legazkue, I. 2013. An assessment of the determinants of university technology transfer. ***Economic Development Quarterly***, 27(1): 6-17.

Greer, S. L. & Trump, B. 2019. Regulation and regime: the comparative politics of adaptive regulation in synthetic biology. ***Policy Sciences***, 52(4): 505-524.

Guston, D. H. 2008. Innovation policy: not just a jumbo shrimp. ***Nature***, 454(7207): 940-941.

Guston, D. H. 2014. Understanding 'anticipatory governance'. ***Social Studies of Science***, 44(2): 218-242.

Hall, B. H. & Ziedonis, R. H. 2001. The patent paradox revisited: an empirical study of patenting in the US semiconductor industry, 1979-1995. ***The RAND Journal of Economics***, 32(1): 101-128.

Hamburg, M. A. 2012. FDA's approach to regulation of products of nanotechnology. ***Science***, 336(6079): 299-300.

Hansson, L. 2020. Regulatory governance in emerging technologies: The case of autonomous vehicles in Sweden and Norway. ***Research in Transportation Economics***, 83: 100967.

Henisz, W. J. & Zelner, B. A. 2001. The institutional environment for telecommunications investment. ***Journal of Economics & Management Strategy***, 10(1): 123-147.

Hoerr, R. A. 2011. Regulatory uncertainty and the associated business risk for emerging technologies. ***Journal of Nanoparticle Research***, 13(4): 1513-1520.

Hoffmann, V. H., Trautmann, T., & Schneider, M. 2008. A taxonomy for regulatory uncertainty—application to the European Emission Trading Scheme. ***Environmental Science & Policy***, 11(8): 712-722.

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

Hoffmann, V. H., Trautmann, T., & Hamprecht, J. 2009. Regulatory uncertainty: A reason to postpone investments? Not necessarily. ***Journal of Management Studies***, 46(7): 1227-1253.

Holdren, J. P., Sunstein, C. R., & Siddiqui, I. A. 2011. Policy principles for the US decision-making concerning regulation and oversight of applications of nanotechnology and nanomaterials. ***Executive Office of the President***: 4-5.

Hung, S.-C. & Chu, Y.-Y. 2006. Stimulating new industries from emerging technologies: challenges for the public sector. ***Technovation***, 26(1): 104-110.

Jaffe, A. B., Trajtenberg, M., & Henderson, R. 1993. Geographic localization of knowledge spillovers as evidenced by patent citations. ***The Quarterly journal of Economics***, 108(3): 577-598.

Johnstone, N., Haščič, I., Poirier, J., Hemar, M., & Michel, C. 2012. Environmental policy stringency and technological innovation: evidence from survey data and patent counts. ***Applied Economics***, 44(17): 2157-2170.

Jones, H. D. 2015. Regulatory uncertainty over genome editing. ***Nature Plants***, 1(1): 1-3.

Kalamova, M., Johnstone, N., & Haščič, I. 2012. Implications of policy uncertainty for innovation in environmental technologies: the case of public R&D budgets, ***The Dynamics of Environmental and Economic Systems***: 99-116: Springer.

Kang, W., Lee, K., & Ratti, R. A. 2014. Economic policy uncertainty and firm-level investment. ***Journal of Macroeconomics***, 39: 42-53.

Kesidou, E. & Demirel, P. 2012. On the drivers of eco-innovations: Empirical evidence from the UK. ***Research Policy***, 41(5): 862-870.

Konishi, Y. & Managi, S. 2020. Do regulatory loopholes distort technical change? Evidence from new vehicle launches under the Japanese fuel economy regulation. ***Journal of Environmental Economics and Management***, 104: 102377.

Kuhlmann, S., Stegmaier, P., & Konrad, K. 2019. The tentative governance of emerging science and technology—A conceptual introduction. ***Research Policy***, 48(5): 1091-1097.

Kwon, S., Liu, X., Porter, A. L., & Youtie, J. 2019. Research addressing emerging technological ideas has greater scientific impact. ***Research Policy***, 48(9): 103834.

Kwon, S., Youtie, J., & Porter, A. L. 2020. Interdisciplinary knowledge combinations and emerging technological topics: Implications for reducing uncertainties in research evaluation. ***Research Evaluation***, rvaa029: 1-14.

Landry, R., Amara, N., & Ouimet, M. 2007. Determinants of knowledge transfer: evidence from Canadian university researchers in natural sciences and engineering. ***The Journal of Technology Transfer***, 32(6): 561-592.

Larivière, V., Gingras, Y., Sugimoto, C. R., & Tsou, A. 2015. Team size matters: Collaboration and scientific impact since 1900. ***Journal of the Association for Information Science and Technology***, 66(7): 1323-1332.

Lee, J., Veloso, F. M., & Hounshell, D. A. 2011. Linking induced technological change, and environmental regulation: Evidence from patenting in the US auto industry. ***Research Policy***, 40(9): 1240-1252.

Marchant, G. E. 2020. Governance of Emerging Technologies as a wicked problem. ***Vanderbilt Law Review***, 73: 1861.

Marcus, A. A. 1981. Policy uncertainty and technological innovation. ***Academy of Management Review***, 6(3): 443-448.

Martin, B. R. 1995. Foresight in science and technology. ***Technology Analysis & Strategic Management***, 7(2): 139-168.

Marx, M. & Fuegi, A. 2020. Reliance on science: Worldwide front‐page patent citations to scientific articles. ***Strategic Management Journal***, 41(9): 1572-1594.

Medema, M. H., Breitling, R., Bovenberg, R., & Takano, E. 2011. Exploiting plug-and-play synthetic biology for drug discovery and production in microorganisms. ***Nature Reviews Microbiology***, 9(2): 131-137.

Miller, J. 2002. Beyond biotechnology: FDA regulation of nanomedicine. ***Columbia Science and Technology Law Review***, 4: 1.

Milliken, F. J. 1987. Three types of perceived uncertainty about the environment: State, effect, and response uncertainty. ***Academy of Management Review***, 12(1): 133-143.

Nature. 2007. Regulating nanomedicine. ***Nature Materials***, 6(4): 249-249.

Nelson, R. R. 2012. Why Schumpeter has had so little influence on today's main line economics, and why this may be changing. ***Journal of Evolutionary Economics***, 22(5): 901-916.

Noel, M. & Schankerman, M. 2013. Strategic patenting and software innovation. ***The Journal of Industrial Economics***, 61(3): 481-520.

OECD. 2020. Shaping the Future of Regulators: The Impact of Emerging Technologies on Economic Regulators, ***The Governance of Regulators***. Paris, France: OECD Publishing.

Oldham, P., Hall, S., & Burton, G. 2012. Synthetic biology: mapping the scientific landscape. ***PLoS One***, 7(4): e34368.

Paradise, J. 2019. Regulating nanomedicine at the food and drug administration. ***AMA Journal of Ethics***, 21(4): 347-355.

Paraskevopoulou, E. 2012. Non-technological regulatory effects: Implications for innovation and innovation policy. ***Research Policy***, 41(6): 1058-1071.

Parnell, J. A., Lester, D. L., & Menefee, M. L. 2000. Strategy as a response to organizational uncertainty: an alternative perspective on the strategy ‐ performance relationship. ***Management Decision***, 38(5): 520-530.

Pinkse, J. 2007. Corporate intentions to participate in emission trading. ***Business Strategy and the Environment***, 16(1): 12-25.

Porter, A. L., Garner, J., Carley, S. F., & Newman, N. C. 2019. Emergence scoring to identify frontier R&D topics and key players. ***Technological Forecasting and Social Change***, 146: 628-643.

Porter, M. E. & Van der Linde, C. 1995. Toward a new conception of the environment-competitiveness relationship. ***Journal of Economic Perspectives***, 9(4): 97-118.

Rafols, I., van Zwanenberg, P., Morgan, M., Nightingale, P., & Smith, A. 2011. Missing links in nanomaterials governance: bringing industrial dynamics and downstream policies into view. ***The Journal of Technology Transfer***, 36(6): 624-639.

Rivera, J. & Oh, C. H. 2013. Environmental regulations and multinational corporations' foreign market entry investments. ***Policy Studies Journal***, 41(2): 243-272.

Roca, J. B., Vaishnav, P., Morgan, M. G., Mendonça, J., & Fuchs, E. 2017. When risks cannot be seen: Regulating uncertainty in emerging technologies. ***Research Policy***, 46(7): 1215-1233.

Rotolo, D., Hicks, D., & Martin, B. R. 2015. What is an emerging technology? ***Research Policy***, 44(10): 1827-1843.

Savolainen, K. 2013. ***Nanosafety in Europe 2015-2025: Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations***: Finnish Institute of Occupational Health.

Shane, S. 2002. Selling university technology: Patterns from MIT. ***Management Science***, 48(1): 122-137.

Shapira, P., Kwon, S., & Youtie, J. 2017. Tracking the emergence of synthetic biology. ***Scientometrics***, 112(3): 1439-1469.

Stern, A. D. 2017. Innovation under regulatory uncertainty: Evidence from medical technology. ***Journal of Public Economics***, 145: 181-200.

Stilgoe, J., Owen, R., & Macnaghten, P. 2013. Developing a framework for responsible innovation. ***Research Policy***, 42(9): 1568-1580.

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

Taminiau, Y. 2006. Beyond known uncertainties: Interventions at the fuel–engine interface. ***Research Policy***, 35(2): 247-265.

Teeter, P. & Sandberg, J. 2017. Constraining or enabling green capability development? How policy uncertainty affects organizational responses to flexible environmental regulations. ***British Journal of Management***, 28(4): 649-665.

Van Doren, D., Koenigstein, S., & Reiss, T. 2013. The development of synthetic biology: a patent analysis. ***Systems and Synthetic Biology***, 7(4): 209-220.

Van Raan, A. 1998. The influence of international collaboration on the impact of research results: Some simple mathematical considerations concerning the role of self-citations. ***Scientometrics***, 42(3): 423-428.

Veugelers, R. & Wang, J. 2019. Scientific novelty and technological impact. ***Research Policy***, 48(6): 1362-1372.

Vogel, A. L., Hall, K. L., Fiore, S. M., Klein, J. T., Bennett, L. M., Gadlin, H., Stokols, D., Nebeling, L. C., Wuchty, S., & Patrick, K. 2013. The team science toolkit: enhancing research collaboration through online knowledge sharing. ***American Journal of Preventive Medicine***, 45(6): 787-789.

Wagner, C. S., Park, H. W., & Leydesdorff, L. 2015. The continuing growth of global cooperation networks in research: A conundrum for national governments. ***PloS One***, 10(7): e0131816.

Weber, W. & Fussenegger, M. 2009. The impact of synthetic biology on drug discovery. ***Drug Discovery Today***, 14(19-20): 956-963.

Yang, B., Burns, N. D., & Backhouse, C. J. 2004. Management of uncertainty through postponement. ***International Journal of Production Research***, 42(6): 1049-1064.

Zhou, X., Porter, A. L., Robinson, D. K., Shim, M. S., & Guo, Y. 2014. Nano-enabled drug delivery: A research profile. ***Nanomedicine: Nanotechnology, Biology and Medicine***, 10(5): e889-e896.

Kwon, S., Youtie, J., Porter, A., & Newman, N. (2022). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *The Journal of Technology Transfer*, 1-41.

Appendix. Search strategy of NEDD and SynBio papers in WoS

1. Nano-Enabled Drug Delivery (NEDD) (Zhou et al., 2014)

Search terms	Search with related nano modules[a]	Search in full WOS/Medline/DII[b]
TS=((deliver* or vehicle* or carrier* or vector* or "control* releas*") Near/4 (Drug* or pharmac))	Yes	No
TS=((deliver* or vehicle* or carrier* or vector* or "control* releas*" or transduct* or transfect* or transport* or translocat*) Near/4 agent*)	Yes	No
TS=((deliver* or vehicle* or carrier* or vector* or "control* releas*" or transfect*) Near/4 formulation*)	Yes	No
TS=((deliver* or vehicle* or carrier* or vector* or treat* or therap* or "control* releas*" or transduct* or transfect* or transport* or translocat*) Near/4 (siRNA or "short interfering RNA"))	No	Yes
TS = (deliver* or vehicle* or carrier* or vector* or treat* or therap* or "control* releas*" or transduct* or transfect* or transport* or translocat*) Near/4 (DNA or gene)	Yes	No
TS = (deliver* or vehicle* or carrier* or vector* or treat* or therap* or "control* releas*" or transduct* or transfect* or transport* or translocat*) Near/4 (Dox or Doxorubicin*)	No	Yes
TS=((deliver* or vehicle* or carrier* or vector* or treat* or therap* or "control* releas*"or transfect*) Near/4 ("RNA interference" or RNAi))	No	Yes

[a]: Georgia Tech constructed Nano publication (WoS), [b]: DII (Derwent Innovation Index)

2. Synthetic Biology (Shapira et al., 2017)

WoS Keyword-based Search Strategy
((TS = (“synthetic biolog*” OR “synthetic dna” OR “synthetic genom*” OR “synthetic *nucleotide” OR “synthetic promoter” OR “synthetic gene* cluster”) NOT TS = (“photosynthe*”)) OR (TS = (“synthetic mammalian gene*” AND “mammalian cell”) NOT TS = “photosynthe*”) OR (TS = “synthetic gene*” NOT TS = (“synthetic gener*” OR “photosynthe*”)) OR (TS = (“artificial gene* network” OR (“artificial gene* circuit*” AND “biological system”)) NOT TS = “gener*”) OR (TS = (“artificial cell”) NOT TS = (“cell* telephone” OR “cell* phone” OR “cell* culture” OR “logic cell*” or “fuel cell*” or “battery cell*” or “load-cell*” or “geo-synthetic cell*” or “memory cell*” or “cellular network” or “ram cell*” or “rom cell*” or “maximum cell*” OR “electrochemical cell*” OR “solar cell*”)) OR (TS = (“synthetic cell”) NOT TS = (“cell* telephone” OR “cell* phone” OR “cell* culture” OR “logic cell*” or “fuel cell*” or “battery cell*” or “load-cell*” or “geo-synthetic cell*” or “memory cell*” or “cellular network” or “ram cell*” or “rom cell*” or “maximum cell*” OR “electrochemical cell*” OR “solar cell*” OR “photosynthe*”)) OR (TS = (“artificial nucleic acid*” OR “artificial *nucleotide”)) OR (TS = (“bio brick” or “biobrick” or “bio-brick”)))
Journal Based Search Strategy

PLOSONE curated synthetic biology articles from http://collections.plos.org/s/synbio
ACS Synthetic Biology
Trends in Biotechnology volume 33(2)
ACM Journal on Emerging Technologies in Computing Systems volume 11(3)
Biochimica et Biophysica Acta-Gene Regulatory Mechanisms volume 1839(10)
Biochimica et Biophysica Acta-Bioenergetics volume 1837(9)
Natural Computing volume 12(4)
Chemical Engineering Science volume 103
FEBS Letters volume 586(15)
Acta Biotheoretica volume 58(4)
Where applicable, journal issue number is in parenthesis