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Translational research: from basic research to regional biomedical entrepreneurship

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Abstract This paper examines the effect of translational research on knowledge production and biomedical entrepreneurship across U.S. regions. Researchers have earlier investigated the outputs of translational research by focusing on academic publications. Little attention has been paid to linking translational research to biomedical entrepreneurship. We construct an analytical model based on the knowledge spillover theory of entrepreneurship and the entrepreneurial ecosystem approach to examine the relationship between translational research, biomedical patents, clinical trials, and biomedical entrepreneurship. We test the model across 381 U.S. metropolitan statistical areas using 10 years of panel data related to the NIH Clinical and Translational Science Awards (CTSA) program. CTSA appears to increase the number of biomedical patents and biomedical entrepreneurship as proxied by the NIH Small Business Innovation Research (SBIR) grants. However, the magnitudes of the effects are relatively small. Path analysis shows that the effect of translational research on regional biomedical entrepreneurship is not strongly conveyed through biomedical patents or clinical trials.

Plain English Summary Can programs designed to speed the transformation of research results into products/processes increase regional entrepreneurship in the biomedical sector? Translational research programs generally address the gap between basic science and clinical trials/commercialization. We examine one such program, the National Institutes of Health (NIH)'s Clinical and Translational Science Awards (CTSA) program, that has supported more than 60 U.S. universities and other institutions since 2006. We find that the program has positively affected regional biomedical entrepreneurship. Translational research also appears to increase the number of regional biomedical patents. The increased biomedical patents could not, however, be said to have "caused" the higher levels of regional biomedical entrepreneurship. Policymakers may intensify efforts to improve the utilization of knowledge produced by translational research activity by boosting efforts to enhance the entrepreneurial awareness and inclination of translational researchers.

Keywords Translational research · CTSA · Biomedical · SBIR · Entrepreneurship · Ecosystem

JEL Classification L26 · O31 · R11 · L65

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1 Introduction

Recent COVID-19 vaccine developments have demonstrated the importance of the rapid transfer of scientific knowledge to the clinical and commercial fields for public health. The first U.S. COVID-19 vaccine utilizes a novel technology, messenger RNA (mRNA), developed by a biotech firm, and reduced the development time significantly (Zimmer et al., 2021). Other COVID-19 vaccines also have been developed by rapidly transferring new technologies from labs to hospitals (The Johns Hopkins Coronavirus Resource Center, n.d.; Zimmer et al., 2021).

Rapid transfer between basic research and clinical and commercial applications has been discussed for a long time. The decreasing productivity—the average FDA approvals per R&D investment—in the pharmaceutical sector has, however, put this topic once again at the center of attention (Heller & de Melo-Martín, 2009; Juliano, 2013; Kim, 2019; Schuhmacher et al., 2016; Wegener & Rujescu, 2013). The slow transfer has been pointed out as one of the reasons for anemic performance (Institute of Medicine, 2013). Slow connection largely comes from multiple barriers including risky and expensive clinical trials, data sharing issues, and lack of experts (Coller & Califf, 2009; Heller & de Melo-Martín, 2009; Institute of Medicine, 2013).

In response to this policy concern, the National Institutes of Health's (NIH) Clinical and Translational Science Awards (CTSA) program has been providing over $500 million annually to more than 60 U.S. universities and non-profit research institutions since 2006 to help address those obstacles (Kim, 2019; Llewellyn et al., 2018). Through the improvement of translational research conditions, the CTSA program desires to increase the speed and volume of the transfer of scientific knowledge into more practical applications (NIH, 2006).

Scholars have analyzed the contribution of the CTSA program to increasing academic publications (Kim, 2019; Kim et al., 2020; Liu et al., 2016; Llewellyn et al., 2018; Schneider et al., 2017). However, the literature has yet to address whether and how this specific translational research program contributes to the biomedical business. Also, the earlier appraisals were generally restricted to the funding of recipient institutions and did not comprehensively consider other factors surrounding translational research and their interactions. As translational research aims to facilitate the transfer of basic research into more practical forms of knowledge, it is important to examine its contribution to the biomedical enterprise, beyond the publication performance of the grant recipients.

We examine the effect of translational research on biomedical knowledge production and biomedical entrepreneurship. Based on the knowledge spillover theory of entrepreneurship and entrepreneurial ecosystem approach, we construct an analytical model and test it across all 381 U.S. metropolitan statistical areas (MSAs) using 10 years of panel data. The NIH CTSA program is utilized as an approximation for translational research while the NIH Small Business Innovation Research (SBIR) program serves as an approximation for biomedical entrepreneurship.

The results indicate a positive association between CTSA funding and regional SBIR grants, but the magnitude is relatively small. CTSA funding increases biomedical patents, but it does not increase the number of clinical trials conducted regionally. Biomedical patents have a positive relationship with SBIR grants, whereas clinical trials do not. Path analysis reveals that the effect of the CTSA funding on SBIR grants is not strongly conveyed through either biomedical patents or clinical trials. We thus conclude that translational research through the CTSA program has had a limited impact on exploitable knowledge production and regional biomedical entrepreneurship.

The rest of the paper is organized as follows. Section 2 presents background on translational research, literature review, and research questions. In Section 3, we explain how we construct and operationalize the analytical model. We present results in-detail in Section 4 and discuss main findings and policy implications in the following section. The last section concludes.

2 Literature review

2.1 The context of translational research

Translational research has emerged as an important driver to facilitate conversion and increase biomedical productivity (Fishburn, 2013; Van der Laan & Boenink, 2015; Woolf, 2008; Zerhouni, 2003). Translational research is generally understood as a concerted effort to produce new products, services, or treatments from basic research in a rapid manner (Fishburn, 2013). Van der Laan and Boenink (2015)

succinctly summarize the emergence of translational research as a reflection of the desire to get more benefit from society's investment in basic research.

The conceptualization of "translational research" varies among researchers and continues to evolve (Van der Laan & Boenink, 2015). Originally, translational research was viewed as a two-phase process: the translation from basic science to human studies, and the translation of new knowledge into clinical practice and health decision-making (Sung et al., 2003). NIH (2006) has a similar definition, found in its first request for application for the Institutional CTSA program.

In the biomedical sector, researchers have recently more narrowly conceptualized the translation framework, which spans from basic science to translation to community (Blumberg et al., 2012). This more elongated framework has been reflected in the NIH's CTSA funding opportunity announcement (NIH, 2012). The core elements in the newer translational research framework are from basic science to translation to patients—processes to convert discoveries in the laboratory into clinical trials (Fishburn, 2013). Similarly, the FDA also identified this part as a "critical path" to drug development (Woodcock & Woosley, 2008, p. 4). Many biomedical researchers focused on a narrow conception that usually covered the area "between basic science…and new approaches for pre-clinical work" (Van der Laan & Boenink, 2015, p. 37).

The domain between basic research and the near-market can be recognized as a market failure because of the sub-optimal distribution of resources such as venture capital funding. Public agencies like the NIH strongly support basic research, while the private sector heavily invests in marketable products or services. However, the middle part—the so-called valley of death—is often regarded as too risky for the private sector to invest in because it requires huge investments (Butler, 2008), along with the uncertainty of getting a good return on such investments. Figure 1 illustrates the conceptualization of the valley of death along the translational continuum in the biomedical sector.

The gap between basic science and clinical science is often referred "translational gap" in the biomedical sector (Seyhan, 2019, p. 6). Crossing the gap requires not just enough funding, but also strong support to advance discoveries in the lab toward the bedside. Thus, public intervention is justified to mitigate the uncertainty and a large number of resource inputs when developing scientific knowledge, products, and services. Proper policy measures have the potential to shorten the time required for the development of biomedical products and services, thereby contributing to the greater public good.

2.2 Extant literature and research questions

Several scholars have studied the effects of translational research on academic publications, especially by analyzing the CTSA program (Kim, 2019; Kim et al., 2020; Liu et al., 2016; Llewellyn et al., 2018; Schneider et al., 2017). A strong emphasis has been paid to the number of articles published, among other outputs, resulting from the CTSA program. Investigators have shown that the CTSA program has increased

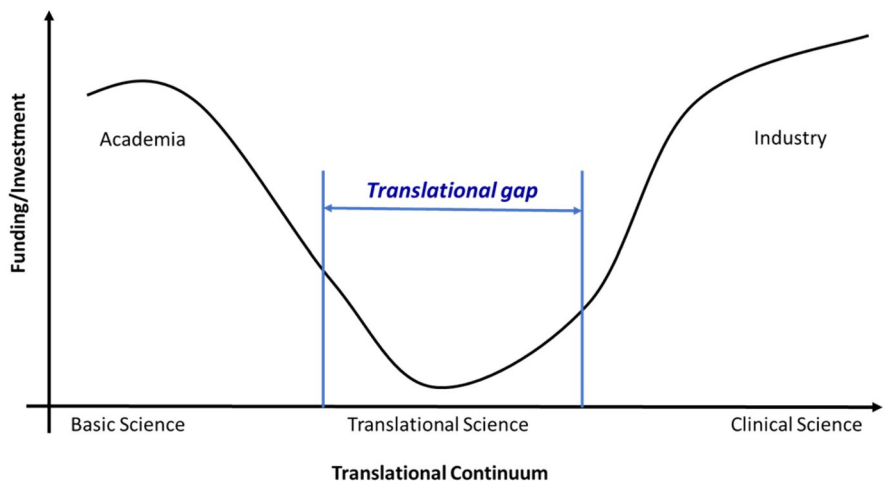

Fig. 1 Illustration of valley of death in biomedical sector. Adapted from Seyhan (2019, p.7) and Reis et al., (2008, p.10)

the recipients' numbers of publications (Kim, 2019; Liu et al., 2016; Llewellyn et al., 2018).

While publication is one critical channel to advance and spread knowledge in the biomedical sector (Llewellyn et al., 2018), the literature has yet to address whether or how the CTSA program contributes to economic activity. Economic activity matters because translational research was initiated to facilitate the conversion of basic research into clinical and commercial areas (NIH, 2006; Van der Laan & Boenink, 2015). Furthermore, the CTSA program considers collaboration with industry and other stakeholders as one of its objectives (NIH, 2006, 2017).

The expansion of the scope of current research to address the impact of translational research on the commercialization of the produced knowledge would be helpful in deepening our understanding. For instance, one can consider whether translational research increases the production of commercially exploitable knowledge, as approximated by biomedical patents and clinical trials, and the extent to which this knowledge enhances biomedical entrepreneurship.

The extant literature on translational research also lacks a general theoretical framework to analyze the effects of translational research comprehensively. Instead, investigators have narrowly restricted their analysis only to the CTSA program recipients (e.g., Kim, 2019; Liu et al., 2016; Llewellyn et al., 2018; Schneider et al., 2017). Furthermore, these examinations have not taken into account the fact that translational research is a part of the complex biomedical ecosystem. Indeed, diverse stakeholders (e.g., universities, biomedical firms, and pharmaceuticals) take part in the process that moves a product or a service from its scientific discovery to clinical and commercial fields (Fishburn, 2013; Pisano, 2006). Given that translational research covers a wide spectrum within the broader biomedical ecosystem, it is imperative to take into account how translational research interacts with other components in the system (Simons et al., 2020).

In this vein, a more systemic focus on relevant interactions could lead to a more comprehensive analysis of the effects of translational research. Additionally, we assert that a relevant conceptual framework is needed linking translational research to economic and business activities more comprehensively. We propose such an analytical model in the next section.

Knowledge is typically assumed to spill over from its original source. However, the flows of the ideas and knowledge are hampered by the so-called knowledge filter including institutional, geographical, and economic constraints (Almeida & Kogut, 1999; Carlsson et al., 2009). Audretsch and Lehmann (2005, p. 1195) define knowledge filter as "the gap between new knowledge and what Arrow (1962) referred to as economic knowledge or commercialized knowledge." The knowledge filter concept is in line with the notion of "barriers to transmission" proposed by Hayter (2013).

The literature in the field of the knowledge spillover theory of entrepreneurship (KSTE) provides a theoretical foundation for explaining knowledge production and utilization (Ghio et al., 2015). Economic agents like entrepreneurs utilize the new knowledge to open opportunities by creating new firms to exploit the unused knowledge that firms or research organizations have generated (Acs et al., 2009; Audretsch, 1995; Braunerhjelm et al., 2010; Hayter, 2013). This concept envisages entrepreneurship as an effective vehicle enabling the utilization of new knowledge. At the same time, the KSTE implies that knowledge does not flow seamlessly from the inventor to the innovator; neither is all knowledge commercially useful in its original form (Braunerhjelm et al., 2010; Hayter, 2013).

Based on the KSTE, it is expected that more knowledge production and spillover would lead to higher levels of entrepreneurship (Acs et al., 2009). By definition, translational research is expected to generate more usable forms of knowledge, such as publications, patents, and clinical trials. This, in turn, could affect entrepreneurship, since entrepreneurs can utilize converted knowledge to start a new business, for instance, in the biomedical sector. Thus, translational research activities would seem to facilitate knowledge exchange and help overcome obstacles associated with the traditional linear model of technology transfer (Hayter et al., 2020). It is in this sense that the KSTE can help us understand how translational research can affect biomedical entrepreneurship through the conversion and utilization of knowledge.

Another useful thread of research that provides insights for the current study is the entrepreneurial ecosystem approach. Explaining what makes a particular region or city achieve more than

its counterparts has been an important focus for researchers and practitioners around the globe (Brown & Mason, 2017; Feldman, 2014). The entrepreneurial ecosystem approach has emerged as a conceptual framework to explain the dynamics within a system (Brown & Mason, 2017). While there is no standard definition of an entrepreneurial ecosystem (Stam & Van de Ven, 2021), scholars proposed several working terms. For instance, an entrepreneurial ecosystem is a dynamic system with diverse stakeholders, which can include entrepreneurs, universities, government, and consumers (Audretsch & Belitski, 2017). More broadly, Stam (2015) defined the entrepreneurial ecosystem as "a set of interdependent actors and factors coordinated in such a way that they enable productive entrepreneurship" (p. 1765). While there has been some criticism (See Stam & Van den Ven, 2021), the entrepreneurial ecosystem approach has provided a compelling framework to analyze regional context (e.g., Mack & Mayer, 2016; Spigel, 2017).

The sectoral perspective of the biomedical sector should also be emphasized. Every sector has different knowledge and technology bases, as well as different types of actors, networks, and institutions (Malerba, 2004). Thus, entrepreneurial ecosystems could be formed or worked based on industry-specific characters (Mason & Brown, 2014). As Pisano (2006) described, the biotech sector has its own particular anatomy, quite distinct from other sectors like information technology. Considering that the biomedical industry is a science-based business, in this paper we define biomedical entrepreneurship as knowledge-intensive entrepreneurial activities that utilize knowledge to exploit opportunities within the biotechnology sector (Malerba & McKelvey, 2020; Pisano, 2006).

In light of the KSTE and the entrepreneurial ecosystem approach, we consider the following two research questions. First, to what extent do increased level of knowledge translate into biomedical entrepreneurship? Second, do biomedical patents and clinical trials serve as effective forms of knowledge connecting translational research to biomedical entrepreneurship? Further downstream than academic publications, we would like to explore whether these two well-known forms of knowledge are the connecting rods between basic research and biomedical entrepreneurship as described by scholars (e.g., Pisano, 2006).

3 Methodology

3.1 Empirical context

To support and facilitate the translation process, the NIH initiated a translational research program called the Clinical and Translational Science Awards (CTSA) program in 2006. Through it, the NIH provides about $500 million annually to approximately 60 universities and nonprofit institutes (Llewellyn et al., 2018; NIH, 2019). The CTSA program is designed "to transform the local, regional, and national environment for clinical and translational science, thereby increasing the efficiency and speed of clinical and translational research" (NIH, 2006). To achieve its goals, the program supports "training, research and infrastructure to help researchers engage in clinical research—and cross the valley of death" (Butler, 2008, p. 841). In particular, the funded projects and initiatives sponsor activities that influence the translation environment. For instance, SMART IRB provides a platform to help researchers and institutions researching multiple sites that require integrated collaboration. One thing to note is that unlike other NIH awards supporting projects based on diseases, specialties, and investigators, the CTSA program supports improvements specifically in the translational environment (NIH, 2006).

3.2 Model specification

We construct an analytical model for biomedical knowledge production and biomedical entrepreneurship. Considering that translational research helps facilitate the conversion of basic science into more usable forms of knowledge, we expect that a vibrant translational research activity increases more useful and commercially exploitable knowledge production. Then, entrepreneurs have a wider set of relevant knowledge stocks to draw from. In this respect, the knowledge spillover theory of entrepreneurship enables us to analyze whether translational research increases biomedical entrepreneurship.

We explore the linkage between translational research and biomedical entrepreneurship, biomedical patents, and clinical trials. Patents are regarded as an important milestone before moving toward commercialization (Reitz & Czupich, 2014).

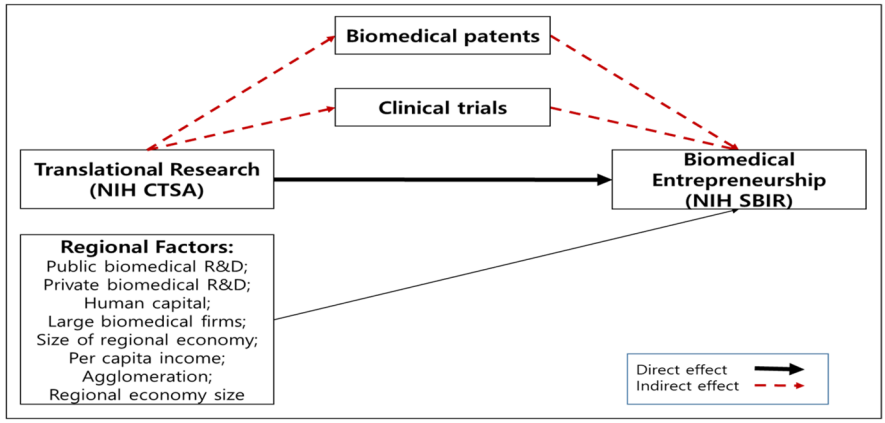

Fig. 2 A schematic description of the analytical model

Commercialization in the biomedical sector generally occurs through the licensing of intellectual property rights (Kettler, 2000; Pisano, 2006; Scherer, 2010). Each stage of clinical trials generates critical information regarding safety, efficacy, and others, and they are pre-requisite for commercialization in the biomedical sector (NIH, n.d.-a; Varmaghani et al., 2020). In sum, our model posits that by increasing such exploitable knowledge translational research endows entrepreneurs in a region with a wider set of relevant knowledge stock to utilize.

In the construction of the model, we take into account the factors that influence biomedical entrepreneurship. Translational research is not a standalone element but an interconnected factor in the biomedical development system. We identify regional factors which may affect regional biomedical entrepreneurship, including public and private biomedical R&D investment, human capital, the presence of large biomedical firms, per capita income, population size, and the size of the regional economy. Figure 2 depicts a schematic description of the model.

In Fig. 2, the thick black arrow from translational research to biomedical entrepreneurship shows the "direct" relationship between two sides. For further exploration of the detailed relationship, we separate biomedical patents and clinical trials from other outputs, and investigate their roles in bridging translational research and biomedical entrepreneurship. Two red dashed arrows from translational research to biomedical entrepreneurship through biomedical patents and clinical trials depict the "indirect" relationships between two sides. Regional factors are included as control variables in the model.

In the following sections, we first focus on estimating the direct relationship between translational research and biomedical entrepreneurship. Subsequently, we estimate the indirect relationships in order to investigate how the indirect effects of translational research affects biomedical entrepreneurship through biomedical patents and clinical trials.

3.3 Operationalization of the model

We empirically test the analytical model across all 381 U.S. metropolitan statistical areas (MSAs[1]) with a panel dataset ranging from 2006 to 2015. The CTSA program is utilized herein as an approximation for translational research while the NIH SBIR program serves as an approximation for biomedical entrepreneurship.

First, we begin with estimating the direct effect of CTSA funding on SBIR grants. Endogeneity is one challenge in estimating the relationship between CTSA funding and SBIR grants. Institutions receiving CTSA funding are not randomly distributed, but they have been selected based on scientific competence among the applicants (NIH, 2006). In addition, the SBIR program selects small firms with "feasibility, technical merit, and commercial potential" (NIH, n.d.-b). Thus, the competitiveness in winning the CTSA funding could be related to the capability of getting the SBIR grants at the regional level.

[1] An MSA is defined as an area with "at least one urbanized area of 50,000 or more population, plus adjacent territory that has a high degree of social and economic integration with the core as measured by commuting ties (Office of Budget and Management, 2018).

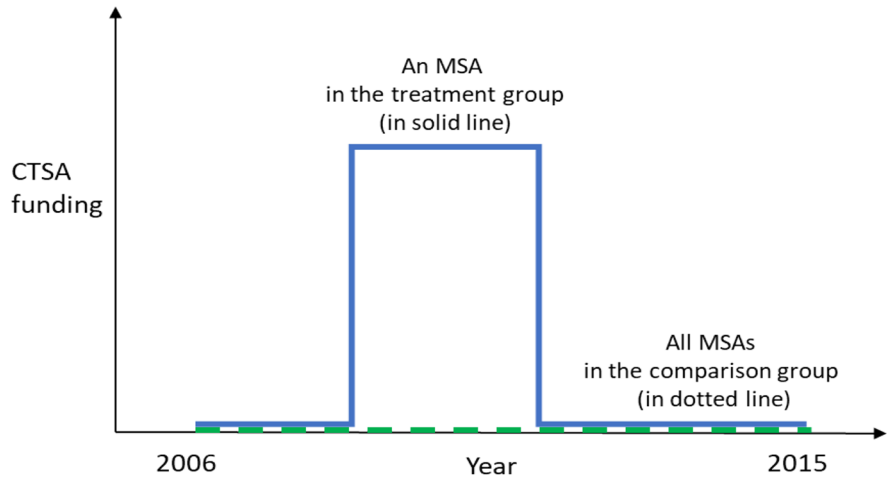

Fig. 3 Imaginary profiles of CTSA funding in the treatment and comparison groups

To address the possible endogeneity, we employ the difference-in-difference (DID) method. The treatment group is comprised of MSAs with CTSA funding, while the comparison group is MSAs with no CTSA funding. A conventional DID equation can be written as Eq. 1. The dependent variable, SBIR $_{mt}$, counts the number of SBIR grants received by small firms in an MSA $_{m}$ in year t. We use the number of grants as a proxy for entrepreneurship (Lee et al., 2004; Qian et al., 2013).

$$SBIR_{mt} = \alpha_1 + \beta_1 \bullet (Treat_m \times Post_t) + \Upsilon \bullet Treat_m + \lambda \bullet Post_t + \varepsilon_{mt1} \quad (1)$$

One thing to note is that MSAs in the treatment group receive funding in different time periods, of different durations and different funding sizes. MSAs in the comparison group have zero CTSA funding throughout the whole period. Figure 3 illustrates the difference in funding between the treatment and comparison regions. The solid line represents a profile of one MSA in the treatment group. In total, there are 46 different CTSA funding profiles, as all 46 MSAs in the treatment group have different funding sizes during different periods. The MSAs in the comparison group are represented by the dotted line in Fig. 3, which shows zero value for the whole period.

In line with previous research (Angrist & Pischke, 2008, 2014; Bertrand et al., 2004), we replace the interaction term in Eq. 1 with CTSA funding, as shown in Eq. 2. Here, the CTSA funding variable, CTSA $_{mt}$, measures the degree of treatment in MSA $_{m}$ in year $_{t}$. Accordingly, Eq. 2 includes the MSA dummy (Υ_m) and the time dummy (λ_t). X $_{mt}$ as control variables. β_2 is the coefficient of our interest. Standard errors are calculated by a robust method and clustered at the MSA. As the dependent variables are count variables that are highly right-skewed, we use the Poisson option.

$$\text{SBIR}_{mt} = \alpha_2 + \beta_2 \bullet \text{CTSA}_{mt} + \delta \bullet \text{X}_{mt} + \Upsilon_m + \lambda_t + \varepsilon_{mt2} \quad (2)$$

Second, we estimate the effects of translational research on biomedical knowledge production. Equations 3 and 4 estimate the effects of CTSA funding on biomedical patents and on clinical trials respectively. We use the same DID design as in Eq. 2.

$$Biomedical\ patent_{mt} = \alpha_3 + \beta_3 \bullet CTSA_{mt} + \delta \bullet X_{mt} + \Upsilon_m + \lambda_t + \varepsilon_{mt3} \quad (3)$$

$$\text{Clinical trials}_{mt} = \alpha_4 + \beta_4 \bullet \text{CTSA}_{mt} + \delta \bullet \text{X}_{mt} + \Upsilon_m + \lambda_t + \varepsilon_{mt4} \quad (4)$$

Third, we estimate the indirect effect of translational research on biomedical entrepreneurship through biomedical patents and clinical trials. As shown in Fig. 2, biomedical patents and clinical trials are endogenous variables. They are affected by the CTSA funding and other regional conditions. They also affect another endogenous variable, SBIR grants. In this estimation, we consider three paths between the CTSA funding and the SBIR grants: (1) indirect path 1—through biomedical patents; (2) indirect path 2—through clinical trials; (3) direct path—all other outputs except biomedical patents and clinical trials. Equation 5 describes three paths between the CTSA funding and the SBIR grants.

Table 1 Variables, measures, and data sources

Variable	Measure	Source
NIH SBIR grants	NIH SBIR (New projects in Phase I and Fast Track) grants	NIH RePORTER
Biomedical patents	Number of patents in biomedical-related technology	U.S. PTO
Clinical trials	Number of clinical trials conducted	U.S. National Library of Medicine (ClinicalTrials.Gov)
CTSA funding	Size of the CTSA funding	NIH RePORTER
Public R&D	R&D expenditure in the life science and medical field at the universities (after subtracting the CTSA funding)	NSF HERD Survey
Private R&D	R&D expenditure by publicly-traded biomedical firms	Compustat
Large biomedical firm	Number of large biomedical firms belonging to the top 25 percent in annual revenue	Compustat
Human capital	Percentage of adults (25+) holding a bachelor's degree or above	U.S. Census
Per capita income	Per capita income	U.S. BEA
Agglomeration	Population per area (i.e., square miles)	U.S. Census
Regional economy	Regional GDP	U.S. BEA

$$SBIR_{mt} = \alpha_5 + \beta_5 \bullet Biomedical\ patent_{mt} + \beta_6 \bullet Clinical\ \text{trials}_{mt} + \beta_7 \bullet CTSA_{mt} + \delta \bullet X_{mt} + \Upsilon_m + \lambda_t + \epsilon_{mt5} \quad (5)$$

We use path analysis/structural equation modeling to solve the set of simultaneous equations indicated by Eqs. 3, 4, and 5. While the negative binomial model might also be used due to the count variables with over-dispersion, the Poisson option is used here. According to Cameron and Trivedi (2010), the cluster-robust standard error can be used to address both over-dispersion and serial correlation. Standard errors are calculated by a robust method and clustered at the MSA. We also show the result with the negative binomial estimates in the following section.

Regarding the decision rule of statistical analysis, we use the threshold of 0.1 and report the precise *p* value. Amrhein et al., (2019, p.306) suggested that researchers need to discuss the meaning of the estimates more explicitly, as well as provide a precise number for the *p* value if reported, rather an overly relying on "dichotomous" decision rules, like using *p* values. Following their recommendations, we report the precise *p* values of the main results and then discuss the implications in-depth.

3.4 Data and variables

Table 1 lists the variables, measures, and data sources. The NIH SBIR grant data were obtained from the NIH RePORTER (NIH, n.d.-d). We include only new SBIR projects in Phase I and Fast Track,[2] which means that renewed, supplemental, or extension projects have been excluded. Projects in Phase II also are excluded because they are only available to successful Phase I projects, which are influenced by diverse factors (e.g., firms' management). The CTSA funding data were likewise obtained from the NIH RePORTER (NIH, n.d.-d). We use the funding opportunity announcements (FOAs)[3] of the CTSA program to identify relevant projects (Liu et al., 2016).

Biomedical patent data were obtained from the U.S. Patent and Trademark Office (n.d.). Following Cortright and Mayer (2002), we include three biomedical-related technology classes: Class 424-Drug, Bio-Affecting, and Body Treating Compositions (includes Class 514); Class 435-Chemistry: Molecular Biology and Microbiology; and Class 800-Multicellular Living Organisms and Unmodified Parts Thereof and Related Processes. The patent data include the granted utility patents to an MSA

[2] Fast Track allows the submission of both Phase I and Phase II together to reduce the funding gap between phases. A Fast Track submission is recognized the same as a "new" project, just like new Phase I projects in the NIH RePORTER system (NIH, n.d.-e).

[3] The FOA numbers used in this research: RFA-RM-06-002, RFA-RM-07-007, RFA-RM-07-002, RFA-RM-07-006, RFA-RM-08-002, RFA-RM-09-004, RFA-RM-09-019, RFA-RM-10-001, RFA-RM-10-020, RFA-RR-10-007, RFA-RR-11-004, RFA-TR-12-006, RFA-TR-14-009.

from 2006 to 2015, which is the most recent year categorized at the MSA level by the U.S. Patent and Trademark Office.

We obtained clinical trial data from the U.S. National Library of Medicine's ClinicalTrials.gov website. According to the U.S. law enacted in 1997 and 2007, and the decision by the International Committee of Medical Journal Editors in 2005, all clinical studies should be registered to the ClinicalTrials.gov registry (Califf et al., 2012). We downloaded 180,926 clinical studies based on the first study submission date between 2004 and 2015. Some clinical studies were conducted at multiple sites, also including in foreign countries. We removed those that had study locations outside the U.S. After this cleaning process, we were left with 523,341 U.S. clinical trial locations.

Variables representing regional conditions are added as control variables. First, regional public R&D spending in the life science and medical research field is added to represent the strength of scientific knowledge. As there is no aggregated public R&D spending data in life science and medical fields at the MSA level, we collected university R&D expenditures from the Higher Education Research and Development (HERD) Survey (National Science Foundation, 2011, 2015, 2018). The R&D spending data has been aggregated at the MSA level. As the HERD data may include the CTSA funding, we subtracted CTSA funding from them to construct the final dataset.

Second, we measure the R&D spending of biomedical firms to control the effect of private R&D in that sector. Firm data is obtained from Compustat, a collection of financial information of publicly traded companies. Biomedical firms are selected based on North American Industry Classification System (NAICS) codes,[4] defined by DeVol et al. (2004).

Third, we approximate the regional human capital by the percentage of adults (above 25) holding at least a bachelor's degree or above (Florida, 2002; Qian et al., 2013). The data is collected from the U.S. Census (n.d.-a).

Fourth, the number of large biomedical firms is added to proxy the role of the established firms in the biomedical ecosystem as suggested by the anchor tenant theory (Agrawal & Cockburn, 2003; Feldman, 2003). Firm data is obtained from Compustat. We counted biomedical firms belonging to the top 25 percent (i.e., 75th percentile) in terms of annual revenue to include relatively large firms.

Fifth, we add per capita income to represent the individual's ability to start and support a new business. Wallsten (2001) uses this variable in estimating the probability of winning the SBIR grant at the MSA level. The data is obtained from the U.S. Bureau of Economic Analysis (BEA) (n.d.-a).

Sixth, following Qian et al. (2013), we use regional population density since agglomeration can facilitate knowledge sharing through close and frequent interactions. The population and area data were obtained from the U.S. Census (n.d.-b, n.d.-c). Populations between 2006 and 2010 are calculated by interpolating the population in 2000 and 2010 due to the lack of data at the MSA level.

Seventh, the size of the regional economy is added to the list of controls. Access to finance is an important element in expanding venture business and further growth (Isenberg, 2011). It is more critical in the biomedical sector because of large resource input needs and a high level of uncertainty (DiMasi et al., 2016; Pisano, 2006; Sacks et al., 2014). We utilize regional GDP to approximate the size of the regional economy and the strength of venture capital financing. The GDP data was obtained from the U.S. Bureau of Economic Analysis (n.d.-b).

We used the zip code-MSA code conversion file provided by the U.S. Department of Housing and Urban Development (n.d.) to aggregate the data at the MSA level. With the data introduced, we constructed a panel data set of 10 years from 2006 to 2015.

4 Findings

4.1 Descriptive statistics

Summary statistics and the correlation matrix of key variables are presented in Tables 2 and 3, respectively.

4.2 Parallel trends

With a DID design, the treatment and comparison groups need to have common trends before the treatment. We examine whether the two groups have common trends in our dependent variables—SBIR grants, biomedical patents, and clinical trials—respectively.

[4] NAICS (2017 version) codes used in this research: 325,411, 325,412, 325,413, 325,414, 339,111, 339,112, 339,113, 339,114, 339,115, 339,116, 335,410, 335,417, and 541,714.

Figure 4 presents the trend for the SBIR grants. As this study is not an ordinary pre- and post-treatment setting, there is no shared variable to indicate the treatment point. The treatment years are centered on the first CTSA funding years of each treated MSA. The comparison group is normalized in 2006, the first CTSA program funding year. The y-axis is the mean SBIR count. The top line represents the treatment group, and the bottom line is the comparison group. The dotted line represents the mean SBIR counts for all the MSAs (entire group).

For the five years prior to the treatment, all three lines declined: the treatment group by 7.4%; the comparison group by 14.8%; and the entire group by 9.4%. This indicates that the two groups had very similar declining trends before the treatment. The overall declining trends are consistent with other NIH SBIR award data, presented in Fig. 5, which continued to decline over our research period (NIH, n.d.-e).

After the treatment, the slopes are quite different: the treatment group declines only by 5.7%; the comparison group declines by 29.8%; and the entire group declines by 27.9%. The comparison group seems to follow the general declining trend of the SBIR grants, whereas the treatment group shows a slight upward trajectory with some fluctuations. Thus, the data indicate that the two groups have common trends before the funding and changed courses afterwards.

To examine the data further, Fig. 6 presents each group's ratio to the entire group's mean SBIR grants. Each group's line in Fig. 6 was calculated by dividing the mean of the SBIR grants of each group by the mean of the SBIR grants of the entire group. For instance, the treatment group's mean SBIR grants are six times larger than the mean SBIR grants of the entire group of MSAs. Before the treatment, the two groups have similar parallel trends, but after the treatment, the treated line increases slightly and steadily, whereas the comparison line declines.

Similarly, we also review the trends of biomedical patents and clinical trials. Before the treatment (funding), the two groups' trends in biomedical patents show similar, parallel trends. After the treatment, the treated line climbs rapidly, whereas the untreated line goes flat (See Figs. 7 and 8). Thus, we conclude that two groups suffice parallel trend conditions for the DID design.

However, we found that clinical trials of these two groups have different trends before the treatment: the treatment group rose by 24% and the comparison group rose by 88% (See Figs. 9 and 10). This limits the ability to make a causal claim when estimating the effect of CTSA funding on clinical trials.

4.3 Results

4.3.1 Direct relationship between CTSA funding on the SBIR grants

We first estimate the effect of CTSA funding on the SBIR grants (Eq. 2). Panel A in Table 4 presents the results. Column 3 is the model with the year and MSA fixed effects. The CTSA coefficient is 0.00725 and statistically significant at the 0.05 level (p value: 0.047). The result indicates that a 1% increase in the CTSA funding is expected to increase the number of SBIR grants in an MSA by 0.00725%.[5] With the fixed effect negative binomial estimate, we have virtually the same coefficient, but a slightly larger standard error (p value: 0.086). Considering that we cannot get the clustered-robust standard error using negative binomial model and the over-dispersion can be addressed by the Poisson model (Cameron & Trivedi, 2010), the estimate with the Poisson holds. Given that the average of SBIR grant counts in the treatment group is 5.95, doubling the CTSA funding size may change the received SBIR grants by 0.043 (=5.95*0.00725). In sum, we found that CTSA funding increases the number of SBIR grants, but the effect size seems relatively small.

We also tested the time lag effects for the CTSA and SBIR association by lagging the CTSA funding. The CTSA coefficient increases to 0.00952 which is statistically significant at the 0.01 level (p value: 0.001) at the length of 5 years. The coefficient is slightly reduced to 0.00822 (p value: 0.062) at the length of 6 years, but it is still larger than the original coefficient. The CTSA coefficients are small and insignificant with other time lags.

To check the robustness of the results, we utilize the number of CTSA institutions as the main predictor instead of CTSA funding. We draw on the anchor tenant hypothesis, which posits that large firms provide supports for regional innovation activities (Agrawal & Cockburn, 2003; Feldman, 2003). Given that CTSA institutions are generally large universities with

[5] The Poisson regression has the exponential form: $E(y|x) = \exp(x\beta)$.

Table 2 Summary statistics

Variables	CTSA-funded MSAs					Non-CTSA-funded MSAs				
	Obs	Mean	SD	Min	Max	Obs	Mean	SD	Min	Max
SBIR grants (count)	460	5.95	6.85	0	42.00	3,350	0.28	0.75	0	7.00
Biomedical patents (count)	460	114.81	173.22	0	996	3,350	5.06	12.83	0	190
Biomedical patents (count, log)	460	3.89	1.32	0	6.90	3,350	0.93	1.14	0	5.25
Clinical trials (count)	460	656.41	547.94	80	3,204	3,350	66.09	131.64	0	1,821
Clinical trials (count, log)	460	6.20	0.77	4.39	8.07	3,350	3.25	1.41	0	7.51
CTSA funding ($M)	460	12.48	13.84	0	99.46	3,350	0	0	0	0.00
CTSA funding ($, log)	460	12.73	6.79	0	18.42	3,350	0	0	0	0.00
CTSA funding (count: institution)	460	1.02	0.93	0	6	3,350	0	0	0	0
Public R&D ($M)	460	496.03	429.20	0	2434.69	3,350	16.03	46.30	0	531.79
Public R&D ($, log)	460	19.15	3.32	0	21.61	3,350	7.72	7.79	0	20.09
Private R&D($M)	460	1488.64	5445.69	0	45,727.91	3,350	17.49	212.26	0	4789.50
Private R&D ($, log)	460	15.09	7.41	0	24.55	3,350	2.37	5.78	0	22.29
Human capital (%)	460	34.46	6.22	24.00	55.20	3,173	24.80	7.58	10.0	60.60
Human capital (log)	460	3.52	0.17	3.18	4.01	3,173	3.17	0.30	2.30	4.10
Large biomedical firms (count)	460	3.87	7.69	0	44.00	3,350	0.12	0.46	0	6.00
Large biomedical firms (count, log)	460	0.87	1.06	0	3.80	3,350	0.07	0.25	0	1.95
Per capita income ($T)	460	45.55	8.18	31.96	85.01	3,350	37.37	7.96	18.73	117.15
Per capita income ($, log)	460	10.71	0.17	10.37	11.35	3,350	10.51	0.18	9.84	11.67
Agglomeration (count: Thousands)	460	0.66	0.60	0.09	2.99	3,350	0.28	0.76	0.01	13.18
Agglomeration (count, log)	460	6.16	0.81	4.49	8.00	3,350	5.11	0.91	1.92	9.49
Regional economy ($M)	460	182,264.6	245,309.5	6,455.3	1,618,366	3,350	16,890.3	28,227.6	1477.2	315,623.5
Regional economy ($, log)	460	25.27	1.17	22.59	28.11	3,350	22.98	0.93	21.11	26.48

The panel data set has a research period from 2006 to 2016 (10 years) and 381 MSAs. 177 missing values in the human capital variable due to the changes in MSAs. 'log' indicates a natural log. $M indicates a million dollars and $T for a thousand dollars. '0' in Min. in the line of CTSA funding (Count: Institution) is due to the periods before the treatment group got the CTSA institution between 2006 and 2015

Table 3 Correlation matrix

Variables	1	2	3	4	5	6	7	8	9	10	11
1. SBIR grants (count)	1										
2. Biomedical patents (log)	0.639***	1									
3. Clinical trials (log)	0.489***	0.695***	1								
4. CTSA funding (log)	0.579***	0.608***	0.528***	1							
5. Public R&D (log)	0.370***	0.609***	0.584***	0.391***	1						
6. Private R&D (log)	0.537***	0.675***	0.591***	0.517***	0.419***	1					
7. Human capital (log)	0.378***	0.654***	0.511***	0.361***	0.583***	0.436***	1				
8. Large biomedical firms (log)	0.800***	0.638***	0.505***	0.507***	0.359***	0.676***	0.353***	1			
9. Per capita income (log)	0.393***	0.523***	0.415***	0.347***	0.247***	0.384***	0.592***	0.379***	1		
10. Agglomeration (log)	0.417***	0.524***	0.510***	0.340***	0.337***	0.461***	0.271***	0.424***	0.323***	1	
11. Regional economy (log)	0.599***	0.763***	0.826***	0.566***	0.614***	0.681***	0.465***	0.639***	0.523***	0.615***	1

"log" indicates a natural log

*** $p < 0.001$

hospitals and substantial research capabilities in the region, one can assume that they work like large established organizations facilitating innovation. The NIH calls CTSA-funded institutions "hubs," and emphasizes collaboration with regional biomedical networks (NIH, 2012, 2016; Obeid et al., 2014). Even though there might be some variations in the scope of their roles in the MSA, it is reasonable to assume that CTSA institutions have similar functionality in facilitating translational research in a particular region. The results are presented in column 4, panel B of Table 4. The CTSA institution coefficient is highly significant (p value: 0.007). It indicates that additional CTSA institutions in an MSA increase the number of SBIR grants by 6.3%.

As a second robustness check, we utilize the aggregated monetary value of the SBIR grants as a dependent variable instead of using the SBIR grant counts. Column 5, panel B of Table 4 shows the results of the ordinary least squares (OLS). The dependent variable is SBIR funding in log form. We found that the CTSA funding coefficient is significant at the 0.1 level (p value: 0.096), and the results show that a 1% increase in CTSA funding increases the SBIR funding by 0.045%. Thus, the robustness checks using the number of CTSA institutions as the main independent variable and the monetary value of SBIR grants as the dependent variable support the main findings in panel A in Table 4.

4.3.2 The effect of CTSA funding on biomedical knowledge production

In this section, we estimate the effect of the CTSA funding on biomedical patents and clinical trials. To do so, we estimate Eqs. 3 and 4. Table 5 shows the results. The first column in panel A presents the relationship between CTSA funding and biomedical patents. The coefficient is significant at around 0.05 level (p value: 0.053). The estimate indicates that a 1% increase in CTSA funding increases the number of biomedical patents by 0.0518%. As the mean of biomedical patents in the CTSA-funded MSAs is 114.8, doubling the CTSA funding can change the number of biomedical patents by 0.6 (=114.8*0.0052) on average.

A reasonable question is whether the CTSA funding affects patents in different industries or technology fields. In other words, is the relationship presented in column 1 of Table 5 specific to patents in the biomedical field? To examine this question, we collected patent data in two different technology fields: Class 361-Electricity:

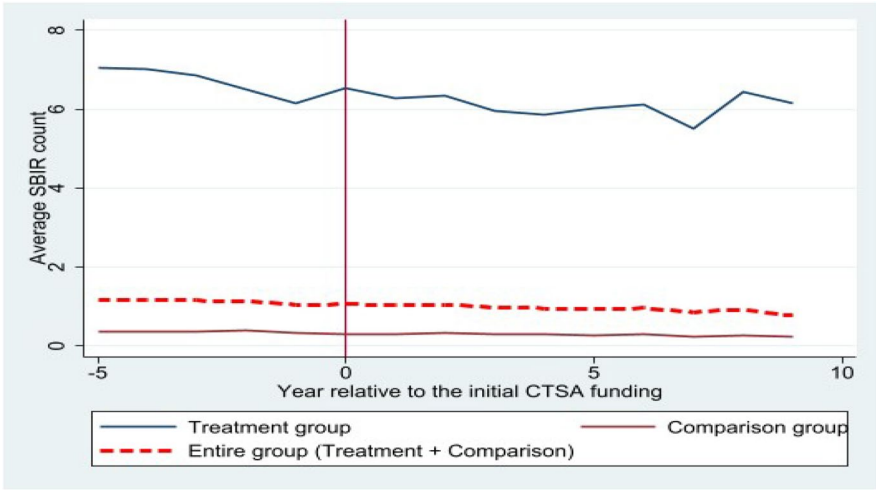

Fig. 4 The trends of the NIH SBIR grant. Treatment group (top line), comparison group (bottom line), entire group (middle line)

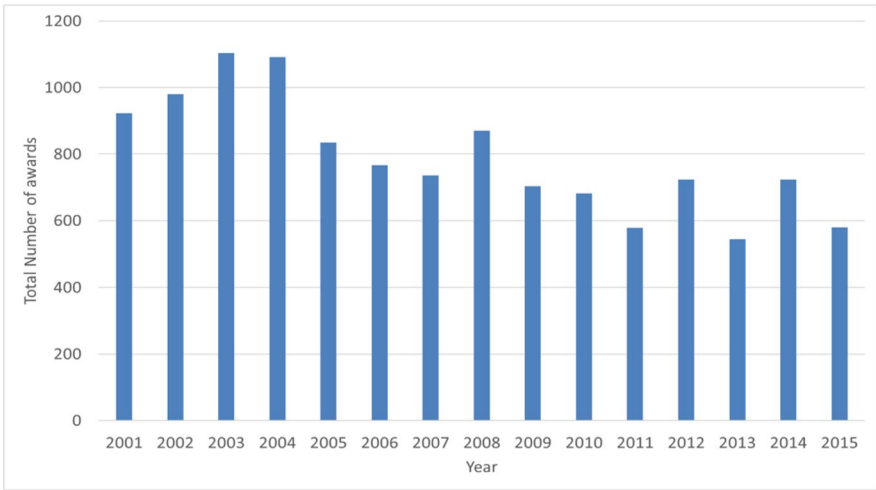

Fig. 5 The trend of the NIH SBIR awards (Phase I and Fast Track). Source: Authors, based on the NIH Data Handbook. National Institutes of Health (n.d.-e)

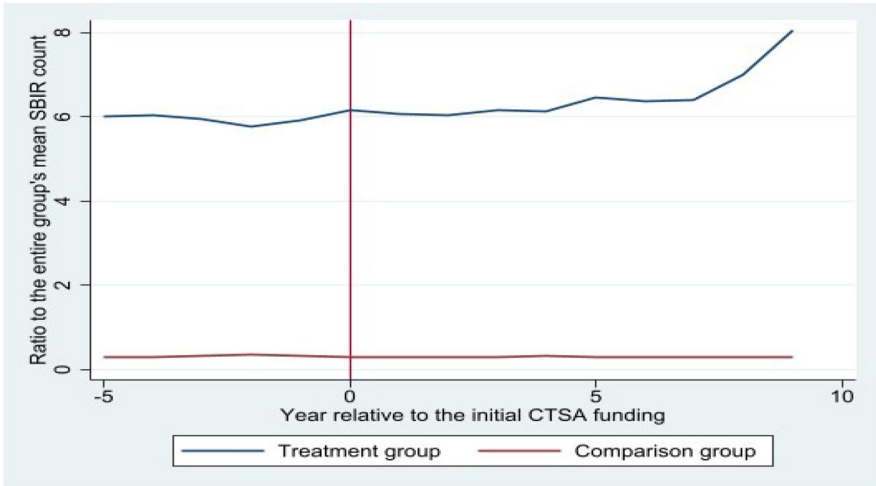

Fig. 6 The trends of the NIH SBIR grant ratio. Treatment group (top line), comparison group (bottom line)

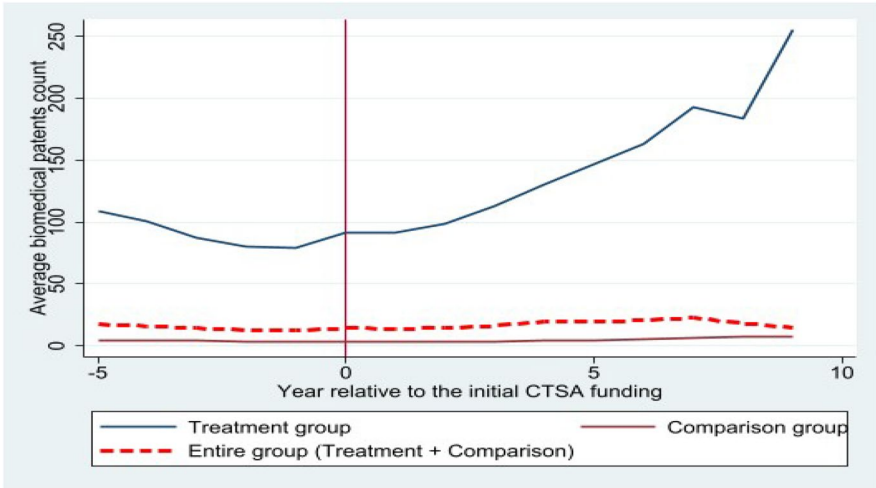

Fig. 7 The trends of biomedical patents. Treatment group (top line), comparison group (bottom line), entire group (middle line)

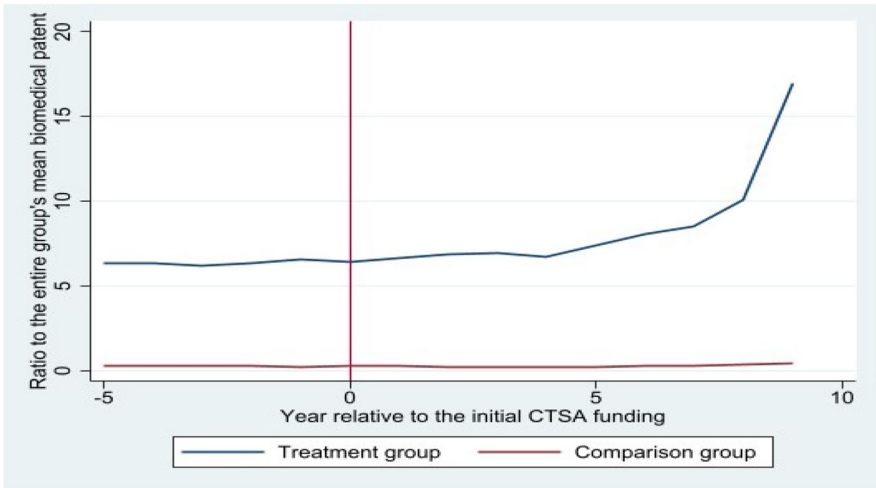

Fig. 8 The trends of biomedical patent ratio. Treatment group (top line), comparison group (bottom line)

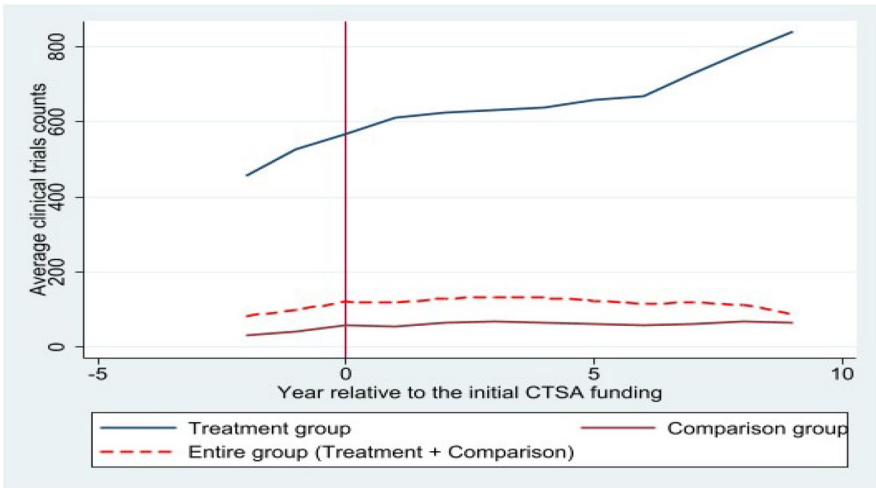

Fig. 9 The trends of clinical trials. Treatment group (top line), comparison group (bottom line), entire group (middle line)

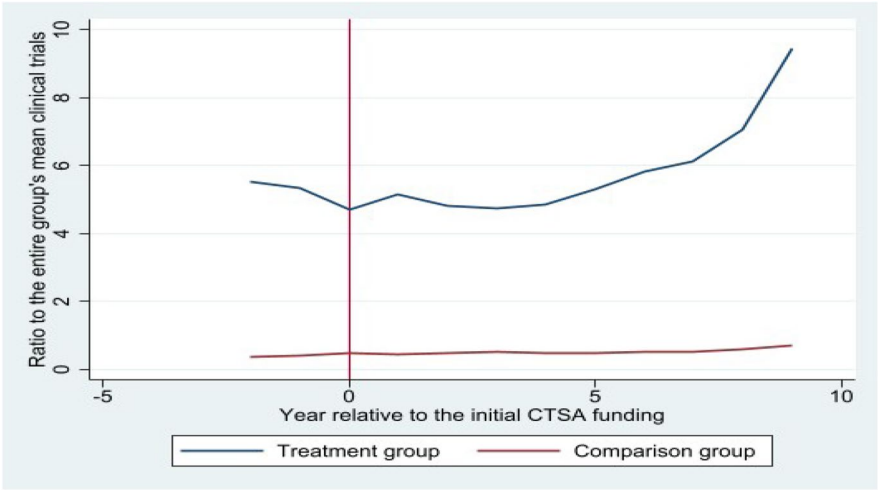

Fig. 10 The trends of clinical trials ratio. Treatment group (top line), comparison group (bottom line)

Electrical Systems and Devices; and Class 726-Information Security. We estimate the effect using the same model specification (i.e., Eq. 3). As shown in columns 4 and 6 of Table 6, all CTSA funding coefficients are statistically insignificant leading to a conclusion that the effect of CTSA funding on patents seems to be biomedical field-specific. Notably, we test only two different classes here; one should be cautious about making overly broad generalizations to other fields.

The second column in panel A of Table 5 shows the relationship between CTSA funding and the number of clinical trials conducted. The results indicate that CTSA funding is not associated with the clinical trials conducted in a region. The CTSA coefficient in the second column of Table 5 is not statistically significant at all. The results rather indicate that the number of clinical trials is affected by human capital and population. We discuss this later in Section 5.

Considering the estimates presented in panel A of Table 5 combined, one may conclude that the effects of CTSA funding on biomedical knowledge production vary depending on the types of knowledge.

4.3.3 Three paths from CTSA funding to SBIR grants

We now present the regression results of Eq. 5, which estimate the effects of CTSA funding, biomedical patents, and clinical trials on SBIR grants. The third column, panel B of Table 5 shows the results. The CTSA funding and biomedical patents coefficients are shown to be significant at the 0.1 level (p values are 0.06 and 0.039, respectively). The CTSA coefficient on the SBIR grants, 0.00663, is slightly smaller than that obtained earlier in the direct relationship between them (Table 4). We conjecture that this result is because the effect of CTSA funding is divided into three paths from CTSA funding to SBIR grants.

The biomedical patent coefficient on the SBIR grants is 0.127 as shown in the third column, panel B of Table 5, which means that a 1% increase in the number of biomedical patents in a region is associated with increases numbers of SBIR grants. Even though the magnitude is quite small, this result supports the knowledge spillover theory of entrepreneurship (KSTE), which links new knowledge production and entrepreneurial activity (Acs et al., 2009). This result provides one more piece of evidence that KSTE holds in a sectoral context like the biomedical sector.

The effect of clinical trials on the SBIR grants is negative and not significant as shown in the third column, panel B of Table 5. In conjunction with the statistically significant relationship between biomedical patents and SBIR grants, we may conclude that the effect of biomedical knowledge on SBIR grants depends on the type of knowledge as well.

4.3.4 Path analysis

Using path analysis, we estimate the indirect effects of the CTSA funding on the SBIR grants through biomedical patents and clinical trials. Figure 11 summarizes the path results, showing the main relationships between CTSA funding, biomedical patents, clinical trials, and SBIR grants. The path coefficients from the structural equation modeling are those obtained from the regressions presented in Table 5.

Table 4 Poisson regression: CTSA funding to SBIR grants

Variables	Panel A			Panel B	
	(1)	(2)	(3)	(4)	(5)
	Poisson			Poisson	OLS
	SBIR grants (Count)			SBIR grants (Count)	SBIR grants ($, log)
CTSA funding (log)	0.00715*	0.00729**	0.00725**		0.004463*
	(0.00366)	(0.00368)	(0.00365)		(0.02671)
CTSA institution (count)				0.06297***	
				(0.02343)	
Public R&D (log)		−0.00146	−0.00234	−0.00262	0.00539
		(0.01309)	(0.01320)	(0.01315)	(0.02495)
Private R&D (log)		−0.00555	−0.00533	−0.00562	0.01867
		(0.00657)	(0.00679)	(0.00701)	(0.03907)
Human capital (log)		−0.69000	−0.76102	−0.76688	−0.52955
		(0.62904)	(0.63107)	(0.62288)	(0.79447)
Large biomedical firms (log)		−0.11340	−0.11183	−0.09766	0.42355
		(0.08407)	(0.08231)	(0.08084)	(0.58331)
Per capita income (log)			0.62325	0.54059	3.01921
			(0.83169)	(0.84510)	(2.26751)
Agglomeration (log)			0.19679	0.31258	0.74944
			(0.63845)	(0.63674)	(0.67024)
Regional economy (log)			0.23878	0.23534	−0.18227
			(0.59313)	(0.59122)	(1.39347)
Constant					−25.95169
					(22.47628)
Year/MSA fixed effect	Yes	Yes	Yes	Yes	Yes
Observations	1810	1759	1759	1759	3633
Number of MSA	181	178	178	178	381

Robust standard errors are adjusted for MSAs and in parentheses: *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. 'log' indicates a natural log. Due to the missing data in the human capital variable, 177 observations were dropped in (2), (3), (4), and (5). 200 groups (2,000 obs.) in (1) and 203 groups (1874 obs.) in (2), (3), and (4) were dropped because of all zero outcomes

Following the discussion in Section 3, we estimate two indirect paths between CTSA funding and SBIR grants: (1) indirect path 1—through biomedical patents and (2) indirect path 2—through clinical trials.

Indirect path 1 from CTSA funding to SBIR grants through biomedical patents is small and insignificant. The coefficient for the indirect path 1 is 0.00066, and the p value is 0.145. The coefficient is around one tenth of the direct path (i.e., 0.00663) as shown in Fig. 11. This result is contrary to our expectation that the increased biomedical patents by CTSA funding increase SBIR grants. Indirect path 2 from CTSA funding to SBIR grants through clinical trials is also small and insignificant. The coefficient is −0.0000011, and the p value is 0.994.

These small coefficients and high p values of the indirect paths indicate that CTSA funding has a limited effect on SBIR grants through either biomedical patents or clinical trials. On the other hand, the direct path of CTSA funding on SBIR grants was found to be larger and significant. The coefficient of the direct effect is 0.00663 and significant at the 0.1 level (p value: 0.06). As discussed earlier, the direct path includes the effects of all outputs other than biomedical patents and clinical trials. Thus, the large differences could indicate that the indirect paths through biomedical patents or clinical trials are not the main channels between CTSA funding and SBIR grants. With the reference to the recent literature (e.g., Kim, 2019; Llewellyn et al., 2018),

Table 5 Poisson regression: CTSA funding, biomedical patents, clinical trials, SBIR grants

Variables	Panel A		Panel B
	(1)	(2)	(3)
	Poisson		Poisson
	Biomedical patents (Count)	Clinical trials (Count)	SBIR grants (Count)
CTSA funding (log)	0.00518*	0.00140	0.00663*
	(0.00268)	(0.00196)	(0.00352)
Biomedical patents (log)			0.12744**
			(0.06173)
Clinical trials (log)			−0.00078
			(0.10110)
Public R&D (log)	−0.00198	0.00605	−0.00216
	(0.00448)	(0.00441)	(0.01336)
Private R&D (log)	−0.00390	0.00088	−0.00450
	(0.00420)	(0.00175)	(0.00686)
Human capital (log)	0.28140	0.28561**	−0.79167
	(0.36227)	(0.13402)	(0.62189)
Large biomedical firms (log)	0.02555	0.01575	−0.11516
	(0.03348)	(0.02422)	(0.08209)
Per capita income (log)	−0.66308	−0.64215**	0.69396
	(0.47406)	(0.27643)	(0.82894)
Agglomeration (log)	0.01178	0.40153**	0.19827
	(0.40512)	(0.15615)	(0.65063)
Regional economy (log)	0.00214	−0.08568	0.23510
	(0.42701)	(0.17859)	(0.59408)
Year/MSA fixed effect	Yes	Yes	Yes
Observations	3121	3627	1759
Number of MSA	313	379	178

Robust standard errors are adjusted for MSAs and in parentheses: *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. 'log' indicates a natural log. Due to the missing data in the human capital variable, 177 observations were dropped in (1), (2), and (3). 68 groups (512 obs.) in (1), 1 group (3 obs.) in (2), and 203 groups (1874 obs.) in (3) were dropped because of all zero outcomes

one might think that items like scientific publications could be the potential connector between public funding for translational research and biomedical entrepreneurship. Unfortunately, we could not test this due to the lack of relevant publication data at the MSA level.

5 Discussion and policy implications

A core finding of this analysis is that publicly funded translational research does contribute to regional biomedical entrepreneurship. As described, translational research aims to facilitate the transformation of basic science into more usable forms of knowledge. Thus, this result supports the knowledge spillover theory of entrepreneurship (KSTE), that posits that more knowledge leads to higher entrepreneurship (Acs et al., 2009). This is also consistent with the widespread belief in the policy community that a region would benefit from vibrant translational research activity in promoting biomedical business. It is notable that academic centers in the biomedical field observe the growth of vibrant activities at the local level and appreciate entrepreneurship (Kimberly & Berglund, 2022).

However, the estimated magnitude appears relatively small. We offer three potential reasons. First, we only analyzed the first 10 years of the CTSA program, thus the effect of the program might not have been fully exerted on the regional biomedical ecosystem for the years reviewed in this study. Considering the long-time span involved in biomedical development processes (DiMasi et al., 2003; Pisano, 2006), it

Table 6 Poisson regression: CTSA funding, different patent classes

Variables	(1) Poisson	(2)	(3)	(4)	(5)	(6)
	Biomedical patents (Count)		Class 361 patents (Count)		Class 762 patents (Count)	
CTSA funding (log)	0.00512*	0.00518*	0.00562	0.00643	0.00724	0.00541
	(0.00280)	(0.00268)	(0.00444)	(0.00451)	(0.00754)	(0.00712)
Public R&D (log)		−0.00198		−0.00882		−0.00060
		(0.00448)		(0.00863)		(0.01027)
Private R&D (log)		−0.00390		0.00815		0.00029
		(0.00420)		(0.00816)		(0.00953)
Human capital (log)		0.28140		0.36519		−0.91471
		(0.36227)		(0.73272)		(0.88861)
Large biomedical firms (log)		0.02555		0.08916		0.08800
		(0.03348)		(0.07086)		(0.06978)
Per capita income (log)		−0.66308		2.04252**		0.95887
		(0.47406)		(0.89937)		(1.19784)
Agglomeration (log)		0.01178		0.48248		−1.37949
		(0.40512)		(0.55665)		(1.56983)
Regional economy (log)		0.00214		−0.78395		−0.50014
		(0.42701)		(0.63131)		(0.88726)
Year/MSA fixed effect	Yes	Yes	Yes	Yes	Yes	Yes
Observations	3130	3121	2310	2303	1910	1907
Number of MSA	313	313	231	231	191	191

Robust standard errors are adjusted for MSAs and in parentheses: ***$p<0.01$, **$p<0.05$, *$p<0.1$. "log" indicates a natural log. Due to the missing data in the human capital variable, 177 observations were dropped in columns 2, 4, and 6. Sixty-eight groups (680 obs.), 68 groups (512 obs.), 149 groups (1490 obs.), 149 groups (1320 obs.), 190 groups (1900 obs.), and 190 groups (1726 obs.) were dropped in each column because of all zero outcomes

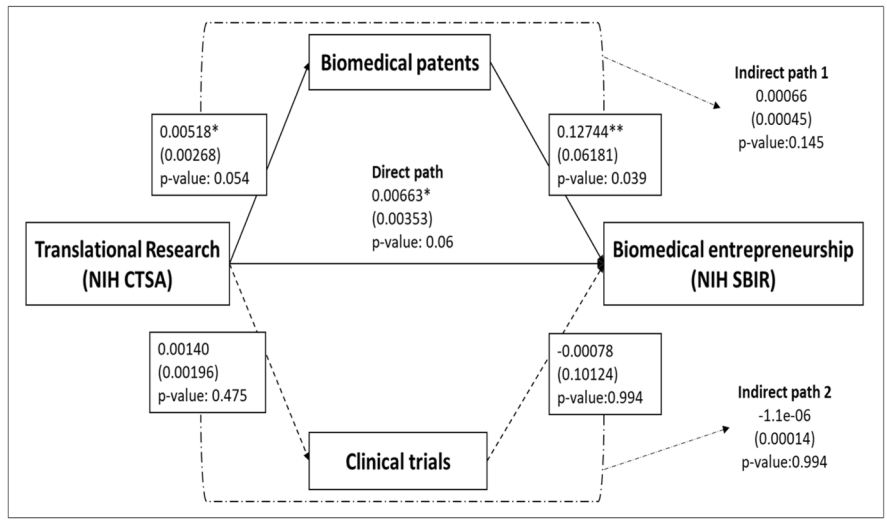

Fig. 11 Path analysis result. Poisson option and year/MSA fixed effects used in Stata. $N=3633$ due to missing values in the human capital variable. The robust standard errors are adjusted for 381 MSAs and are in parentheses: ***$p<0.01$, **$p<0.05$, *$p<0.1$. The solid lines indicate statistically significant relationships, while the dotted lines indicate insignificant ones at the 0.1 level

is conceivable that it might require a longer period to observe this relationship more accurately. Second, we could have underestimated the effect by including only SBIR grants received by regional entrepreneurs while

excluding other biomedical activities in a region. As noted earlier in the paper, NIH SBIR recipients account for only about 20% of all NIH SBIR applicants (NIH, n.d.-c). If the selected and the unselected applicants used the CTSA-related outputs with the same frequency, our measurement could have underestimated the true value. Furthermore, NIH SBIR grants are only a small fraction of total financing sources for biomedical firms. Thus, those entrepreneurs who did not apply might have absorbed the effect of the CTSA program on the SBIR grants, in which case, the CTSA coefficient would again be underestimated. Third, the CTSA funding is relatively small compared to other public and private biomedical research funding. The annual CTSA funding for over 60 institutions is equal to about 500 million dollars which compares to the total annual budget of NIH amounting to 39.1 billion dollars in 2019 (Kaiser, 2018).

Path analysis indicates that the effect of CTSA funding is not transmitted through biomedical patents. One conceivable reason is the mismatch between the patent production and utilization time, and between the patent production and utilization location. It could be the case that entrepreneurs are not limited to using knowledge produced in their particular regions, but rather, they search for knowledge more globally. For instance, entrepreneurs might have used biomedical patents produced outside their regions from years prior.

Similarly, the effect of CTSA funding on SBIR grants through clinical trials is also weak. We consider three potential explanations. First, some clinical trials are just participating sites that are not influenced by the CTSA activities in a region. According to our data from ClinicaTrials.gov, 13.8% of clinical studies were conducted on more than 10 sites worldwide and 27 clinical studies had more than 1000 sites worldwide. Thus, the large number of participating sites could have attenuated the strength of the relationship between the CTSA and clinical trials. Second, clinical trial site selection is heavily influenced by diverse factors such as recruitment-related factors (Dombernowsky et al., 2019; Hurtado-Chong et al., 2017; Silva, 2018). As shown in Table 5, the number of clinical trials is strongly associated with population density and income per capita. Thus, these factors might have influenced the clinical trials variable more heavily than other factors, such as CTSA funding. Third, when viewed from the perspective of entrepreneurs, there might be a mismatch between needed knowledge and produced knowledge. Some entrepreneurs require case-specific information for their technological developments and businesses, but the clinical trials conducted in their specific regions might not be directly relevant to their entrepreneurial activities.

Policymakers should intensify efforts to improve the utilization of knowledge produced by translational research activity. The CTSA program could, for instance, expand its educational program for young researchers regarding entrepreneurship. Policymakers can borrow key elements from the I-Corps program of the National Science Foundation supporting the commercialization of basic research. Such an expansion of the CTSA program can provide young researchers with relevant business education and allow them to get more involved in commercialization field. Local governments can also enhance their role in facilitating knowledge utilization by regional biomedical entrepreneurs. They may establish information sharing and connecting organizations adjacent to research-intensive areas to improve the flow of new knowledge between inventors and entrepreneurs. Local governments may also provide more sophisticated support to biomedical entrepreneurs beyond the current SBIR-related support, as surveyed by Lanahan and Feldman (2015). For instance, state governments may help the establishment of wet-labs for early-stage start-ups like LabCentral in Cambridge, MA, partly supported by the state government (LabCentral, n.d.).

6 Conclusion

In this paper, we investigated the effects of translational research on biomedical knowledge production and entrepreneurship. We constructed an analytical model, positing that translational research increases biomedical entrepreneurship by increasing knowledge, namely biomedical patents and clinical trials, available to regional entrepreneurs.

The results show that CTSA funding has increased regional SBIR grants, but the impact is relatively small. CTSA funding also increases regional biomedical patents, but it does not seem to increase clinical trials conducted regionally. Biomedical patents have a positive relationship with regional SBIR grants, but clinical trials do not. Path analysis indicates that the effect of the CTSA program on regional SBIR grants is not strongly conveyed through biomedical patents

or clinical trials. Based on these results, we conclude that translational research through the CTSA program has a fairly limited incremental impact on exploitable knowledge production and regional biomedical entrepreneurship. However, we will be quick to add the caveats in Section 5.

This research contributes to the literature on the intersection of translational research and entrepreneurship by explicitly linking translational research to regional biomedical business activity. We broadened the scope of analysis in two respects: (1) from the program-recipient level to the regional level, and (2) from specific outputs to broader socioeconomic impacts (e.g., biomedical entrepreneurship). In relation to the first point, we used the metropolitan statistical area (MSA) as a unit of observation to capture regional economic activities as used by Anselin et al. (1997), Florida and Mellander (2010), and Qian and Jung (2017). We also provided empirical evidence that translational research contributes to biomedical knowledge production in a region, but the knowledge production depends on the type of knowledge. Finally, we added empirical evidence that the knowledge spillover theory of entrepreneurship (Acs et al., 2009) holds at the sectoral level like the biomedical field.

As a final note for future research, it should be stressed that the CTSA funding does not represent all translational research activities and that the NIH SBIR grants proxy a small fraction of biomedical business in a region. Obtaining additional data, including a wider spectrum of translational research and biomedical entrepreneurship activities, should improve the accuracy of the results. In addition, upon getting the relevant publication data at the MSA level, researchers can consider additional indirect paths from the CTSA funding to biomedical entrepreneurship.

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