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Sub-national technology policy and commerce: evaluating the impacts of the California Institute for Regenerative Medicine

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Abstract In the last 20 years, state governments have funded a large number of science-based economic development programs. Remarkably, there have been few evaluations of either their economic impact or their prospects for economic impact. The 2004 decision by California voters to issue bonds to fund $3 billion of research on human pluripotent stem cells is an ideal case study for introducing an evaluation methodology for the progress by state programs in developing and transferring research results. In the process of evaluating the California stem cell initiative, we make three methodological contributions to the study of the impacts of sub-national science-based economic development programs. First, the following data sources are introduced as indicators of the prospective economic benefits of these programs: changes in targeted federal research funding, patenting, small business investment research grants, venture capital investment, new firm formations, and clinical trials. Second, the use of regional or industrial controls is introduced. In the case study of the California stem cell initiative the regional control is the comparison of the two dominant California stem cell research and firm clusters, San Diego and the San Francisco Bay Area, to the other dominant cluster, Boston. The biotechnology industry, as a whole, is used to control for exogenous shocks such as changes in the overall interest in new life science technologies. Third, because technology transfer is predicated upon commercialization, a value chain perspective can visualize commercialization obstacles. In this study, a stylized human stem cell therapy value chain is compared to the existing biotechnology value chain and the differences suggest areas where human stem cell therapies are likely to face difficulties. The discussion and conclusion evaluates the progress of the California stem cell initiative and suggests that the evaluation methodology developed can improve the evaluation and guidance of science-based economic development programs.

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1 Introduction

The belief that university scientific and engineering research can form a linchpin for economic development has become accepted policy doctrine at nearly all levels of government. In the U.S. state and local governments have launched numerous initiatives aimed at encouraging capacity building in narrowly targeted scientific or engineering fields that are believed to have possible commercial applications (Feldman et al. 2013; Geiger and Sá 2005). This is paradoxical, for the last 20 years state governments have decreased their direct funding to local universities (SHEEO 2015), even as states have launched multiple initiatives. The justification for these investments has been that they would build capacity that would be translated into concrete commercial benefits to the state. Despite the increasing number of state initiatives and increased funding devoted to them, there have been few comprehensive assessments of their commercial impact. In fact, most assessments are based on non-commercial criteria such as papers published or relatively weak indicators of commercial value such as patents. This paper suggests that more comprehensive assessments can be undertaken through the use of multiple indicators, analysis of the commercialization value chain, and the introduction of regional and commercialization controls. Our methodology is introduced through an examination of the economic and commercial impacts of one of the largest targeted sub-national research projects in U.S. history, the California Institute of Regenerative Medicine (CIRM).

The need for a more comprehensive methodology for assessing targeted research initiatives is driven by two key factors. The first factor is the increasing number and size of such initiatives. The second factor is the concern among research policy scholars about scientists using public media to influence policy-makers' decisions regarding funding research, and the promise of such research to produce inventions that will generate economic and social benefits (Brown 2003; Geels and Smit 2000). Because of increased public policy interest in the research commercialization, media announcements are increasingly an instrument for affecting public opinion in favor of narrowly targeted research funding commitments (Cooke 2004; Lewenstein 1995).

Public investment in research, as a whole, has been remarkably cost effective and valuable to economic growth (Cohen et al. 2002; Mansfield 1991). Yet it is difficult to know ex ante whether the scientific discoveries can be transformed into an innovation and commercial success. As a generalization, the more basic the research is, the greater the uncertainty as to whether it will have commercial application and, if there is an application, how significant they will be. The most effective method of allocating research funds is a vexing question for researchers, politicians, and science policy-makers (Buxton 2011; Dietz and Rogers 2012; Feller 2013; Wallace and Rafols 2015). It is widely accepted that research funding allocations are buffeted by the vagaries of politics, emotion, hope, and hype (Strickland 1972). And yet, to be effective, policy-makers must parse reality from inflated claims in the inherently uncertain world of research and make a well-considered decision (Cohen and Noll 2002).[1]

[1] Hegde and Sampat (2015) show that in the case of orphan diseases that the influence of advocates exists but did not have a large impact on research choices.

Our case study, the CIRM, is particularly interesting because it was a long-term, sustained investment program that funded basic research, product development, labor training, and subsidization of clinical trials and corporate research. One of its express purposes was establishing California as the leading industrial cluster for stem cell (SC) commercialization. Given its size, visibility, and longevity, it is a critical case study for evaluating the results of a major subnational science funding initiative. In undertaking the evaluation of the CIRM, we make the following three contributions to technology policy evaluation methodologies:

First, we undertake a rigorous, though still preliminary, assessment of the commercial outcomes of CIRM. The data used are funding increases from the National Institutes of Health (NIH), patents, small business investment research (SBIR) grants, venture capital (VC) investment, new firm formation, and clinical trials in California. By using these multiple measures our analysis avoids the pitfall of using a single performance measure (Perkmann et al. 2015) and evaluates the CIRM using multiple measures of the path to ultimate commercialization.

Second, evaluations of research investment decisions rarely consider funding itself as a treatment, and pose the question of what the outcome might have been had a new funding program not been undertaken. In most cases, this cannot be effectively measured as there is no reasonable comparison. Fortunately, the funding by CIRM of California researchers can be seen as a treatment and compared to Boston, which is a location with a comparable concentration of biomedical research institutes and commercialization assets, but no state program. We also introduce a further control, which is the larger research-intensive biotechnology industry of which SCs are a subset. If biotechnology funding and commercialization tracks SC commercialization, then the results in the SC industrial subsector might be a reflection of larger industry developments. If they differ significantly, then it would suggest that the SC field has unique characteristics.

Third, we introduce value-chain analysis as a heuristic tool to understand the ease with which a new therapy might be commercialized. Commercialization by definition must mobilize actors to produce, distribute, and ultimately pay for the product (Hargadon and Douglas 2001; Teece 1986). We show that personalized medicine will have to develop a therapy delivery system different from the existing one for biotechnology products. In other words, translation will be more difficult, because a new value chain will have to be organized. For policy-makers considering funding new technologies that they expect to have economic and therapeutic impact, understanding the value chain will clarify the constraints to translation that research faces.

2 The historical context

Interest in biological approaches to creating body replacement parts dates back to the 1930s. By the late 1980s, the term “tissue engineering” came into use as the belief that it might be possible to produce living replacement “parts” grew (Nerem 2010: 1). The term “stem cells” has a long history, first being used in 1868 to describe the origin of multicellular organisms from a unicellular organism (Gallicano 2010). During the 1970s and 1980s, significant research progress was made in manipulating animal embryonic SCs, particularly those from mice. In 1998 University of Wisconsin researchers, funded by the California firm, Geron Corporation, used extracted and cloned human embryonic stem cells (HESCs), which in theory could be grown in vitro for any other human cell or cell mass, such as organs (Murray 2007). The promise of replacement organs or cells appeared to be within reach.

Even as the technology progressed, the use of human embryos as a source of human stem cells (HSCs) became embroiled in an ongoing controversy over abortion (e.g., Benjamin 2013). In response to the impassioned reaction of anti-abortion activists in 2001, then-President George W. Bush announced stringent limits on federal funding for research that uses human embryos. The backlash to his decision was particularly strong in states where Bush was already unpopular. In California, a coalition of HESC researchers,[2] patient advocacy groups, Hollywood actors, and investors secured a sufficient number of signatures to get a proposition, on the November 2004 ballot (Benjamin 2013). Proposition 71 authorized the formation of a California Institute for Regenerative Medicine (CIRM) with the authority to issue $3 billion in state bonds over 10 years to fund HSC and especially HESC research and develop and commercialize the results. In 2007, CIRM began to disburse grants in earnest.

The passage of Proposition 71 creates the scenario for exploring the commercial impacts of targeted research funding—effectively, a bet by California taxpayers on a specific technology—the choice of a winner. The proposition, which was passed into law, was drafted in such a way that it left little leeway to reallocate the funds. Proposition 71 was meant to "maximize the use of research funds by giving priority to SC research that has the greatest potential for therapies and cures, specifically focused on pluripotent SC and progenitor [a term for "embryonic"] cell research." The text of Proposition 71 stated that HSC research would result in a large number of therapies for various ailments as well as significant health-care savings. Most important, it claimed that the funded research would lead to the formation of an HSC industry based in California.

3 Previous economic studies

The centrality of the promises of CIRM's economic benefits included a series of consultant reports paid for by CIRM advocates. For example, in 2004 Baker and Deal (2004: 2) authored a report suggesting that over the 30 years of the bond issue total state revenues and health care cost savings would be between $6.4 billion and $12.6 billion and thereby generate a 120–236% return on the investment made in the research. The belief that CIRM would benefit California was widely held at the time. For example, the non-profit Public Policy Institute of California averred that:

> Proposition 71 will likely attract talents throughout the world to California to conduct biotech research. Given the strong VC industry and risk-taking culture in California, any commercializable research findings will soon catch the attention of venture capitalists and find their way into the industry. It is widely expected that California's biotech industry will benefit a great deal from Proposition 71 (Zhang and Patel 2005).

These optimistic estimates were disputed by Gilbert (2006) who suggested that the Baker and Deal report's estimate of state income from licensing revenues of $537-1100 million was optimistic. Robert Noll (2006) also believed that the economic predictions made by proposition supporters might be excessive (Noll 2006).

[2] For a discussion of this campaign and the decisions one of the leading stem cell scientists made to advocate and secure passage of the proposition funding the CIRM, see Goldstein (2010, 2011).

> Writing in *Nature Biotechnology*, Longaker et al. (2007: 520) wrote that
> It seems highly valuable to assess the success of the initiative at producing benefits and the return on the investment made by California. If such an evaluation is to be undertaken, it would make sense to start at the beginning, building analysis tools as the initiative itself progresses.

In one of the few evaluative studies, on the basis of interviews and observation of the development of CIRM, Adelson and Weinberg (2010: 450) concluded:

> CIRM has taken on a vigorous life of its own. It is apparent that the shift of a major focus for SC research to California will have a significant effect into the future on the geographic distribution of biological science and biotechnology infrastructure in the United States; on the location of university, biotechnology, and pharmaceutical research and start-up firms; and on the investment of venture capital (Adelson and Weinberg 2010: 450).

Despite the call from economists and others to undertake an evaluation and build tools for evaluating the benefits of Proposition 71, there have been remarkably few data-based evaluations. As important, the existing evaluations of the commercial impact of other large sub-national programs remains rudimentary despite the fact that the number and availability of databases with indicators for commercialization has improved remarkably.

3.1 Investment logic

It has been accepted, at least since Griliches (1979), that scientific research provides significant economic benefits and that government funding is necessary because of the public goods nature of research results (Jones and Williams 1998; Lichtenberg and Siegel 1991; Mansfield 1980). Of course, the outcome of each R&D investment will not be equally valuable. Further, the more basic the research, the more difficult it is to predict investment return. Future commercial outcomes from specific scientific research projects or fields are always uncertain and particularly so in the early days of a new technology—what appears promising may ultimately prove valueless and vice versa. Faced with uncertainty, the optimal investment strategy is diversification (Nelson 1959).

Uncertainty regarding the future is the essence of the concern about the government's "picking winners" too early. At the federal level, selecting research targets such as cancer and heart disease are driven by a complicated mix of politicians, business, and public interests, while the technical methods for achievement were left to peer review. In the case of the CIRM, the public chose a research methodology, rather than a research objective. The CIRM initiative is an ideal case study for examining the impacts of R&D targeting driven by political decision-making. The sheer size of the CIRM can be seen in the fact that, in 2002, the NIH allocated less than $400 million for all SC research (see also Zhang and Patel 2005: iii).

Any analysis needs to take two circumstances into account. First, firms were already commercializing SCs prior to the establishment of the CIRM. For this reason, not all the positive changes can be attributed to the CIRM. Therefore, second, the situation prior to the passage of Proposition 71 should be considered in order to determine whether the CIRM's expenditures contributed to increased commercialization.

4 Data and methodology

The data reported in this paper were assembled from a variety of sources. One of the difficulties involved is separating the various SC technologies. For most of the database searches, except where otherwise reported, we used the keywords "stem cells," rather than "human stem cells," to cast as broad a net as possible. In the case of NIH research funding data, all the data are reported verbatim by category and come from the NIH ProjectReporter website. The CIRM research funding data come from its website. The patent data was provided to us by French researchers at the Groupe de Recherche en Économie Théorique et Appliquée (GREThA) at the University of Bordeaux. They extracted all patents that included SCs in their description from the two most salient categories: "c12N 5/00 Undifferentiated human, animal or plant cells, e.g. cell lines; Tissues; Cultivation or maintenance thereof and culture media therefor; A61K 35/00 Medicinal preparations containing materials or reaction products thereof with undetermined constitution." This was compared with overall United States Patent and Trademark Office (US PTO) patent category #435: "Chemistry: Molecular biology and microbiology," the most prominent category for biotechnology products.

The SBIR data is from SBIR.gov, and again we used the search term "stem cells." Each firm was then inspected to ensure that it was an SC firm and not an input maker or a firm that used SCs only peripherally. For example, a firm may describe a non-SC product—say, a bioactive compound—but state that SCs were used in the research process; we excluded such firms. The clinical trial data were downloaded from ClinicalTrials.gov, where we searched on the keyword "stem cells." Given the large number of clinical trials and absence of detailed information, we used the raw counts. Previous research has shown that the results are likely inflated, but, as we are comparing California and Massachusetts and all trials to SC trials, this is not likely to affect the comparisons.

The VC funding data was from Thomson VentureXpert and PitchBook, which were searched using the keyword "stem cells." All firms with SC in their description were verified as SC firms. Because there is no category for SCs in VentureXpert, to calculate the annual VC funding for SC firms, the individual firm investment data was aggregated by year. Further, we searched various websites for SC firms that might have been missed. One of the complications was the proliferation of SC clinics, embryo and umbilical cord collection firms, and offices that offered various unapproved SC treatments. These firms were excluded as not research-derived. As a result, we may have missed a few VC-funded firms, if they did not identify themselves as SC firms. The value-chain diagrams were derived from the literature on how HSCs are expected to be commercialized. The information on biotechnology VC investment was also from VentureXpert.

5 Results

Given the nature of biomedical research, it is too early to calculate the ultimate benefits of the CIRM. However, it is possible to assess its progress. At present, no human pluripotent SC FDA-approved products are on the market, no health savings have been realized, no licenses have been issued to the large pharmaceutical firms, and no SC-related research is being conducted by large pharmaceutical firms in California. The vast majority of direct employment that resulted from creation of the CIRM has come from three major sources:

private philanthropy attracted by the promise of the CIRM,[3] increased federal or other research funding that leverages the CIRM, and direct expenditures of CIRM funds. The CIRM was also expected to produce employment through new firm formation and the movement of SC inventions to commercialization, but these are difficult to calculate. The California initiative only began to disburse funds in 2006 but because SC commercialization was already underway, it is possible to establish a baseline including NIH funding, patents granted, SBIR grants, VC, and new firm formation invested prior to this date and then examine whether California has experienced a positive impact versus our regional control, Boston, and our industrial control, the entire biotechnology industry.

5.1 Research funding

In science-based industries, such as biomedicine, basic research is almost exclusively the province of universities while the NIH has been the major source of US biomedical research funding. The NIH provides a baseline with which to compare the magnitude of CIRM research funding. In the first years of the program, the CIRM's impact was larger than it is today as the NIH has dramatically increased its SC funding. Given the CIRM's goals to attract researchers and the significant increases in funding, one would hypothesize that California researchers would more rapidly increase their share of NIH SC funding than would Boston. In the early years, as Table 1 indicates, the CIRM funding was larger than all NIH HSC investment to California and gave California researchers a remarkable amount of additional HSC investment.

This advantage in funding might be expected to have allowed California's share of NIH SC funding to grow more rapidly than the national average, which grew at 11.53% compound annual growth rate (CAGR) from 2008 to 2014. In fact, California's share grew at the slower CAGR of 9.07% (CAGR). In contrast, Boston's share grew at 10.59% CAGR, somewhat more rapidly than did California (NIH Reporter 2015). This suggests that the availability of CIRM funding did not make California researchers more competitive for NIH funding.

Because there is no evidence that California became more competitive in the general category of SCs, we also examined the geographical changes in NIH HESC funding data. It should be expected that the influx of CIRM investment and attraction of researchers should be greatest in this narrow field. California scientists would be expected to have a powerful advantage due to the creation of specialized assets such as space, resources, and skilled personnel. HESC funding from 2008 to 2014 in California increased 10.78% CAGR, which tracked the national average increase of 11.01%, while in Massachusetts funding increased at 16.70% CAGR—nearly 50% faster than did California or the nation as a whole. The impact of the CIRM can be understood in two ways. First, it did not have a displacement effect in that California researchers continued to compete successfully for NIH grants. However, CIRM funding did not result in California researchers becoming more competitive at winning federal grants.

5.2 Patenting

Patents are a significant indicator of whether inventors believe they have a commercially promising invention. The large influx of research funds due to the CIRM should result in an

[3] The passage of Proposition 71 led to a major burst of philanthropic funding of SC facilities in California (Walshok and Shapiro 2015).

Table 1 Total NIH and CIRM HSC funding per year, 2002–2012 in millions of dollars. *Source* http://stemcells.nih.gov/research/funding/pages/Funding.aspx and CIRM Annual Reports various years

Years	Human SCs		CIRM funding
	Embryonic	Non-embryonic	
2002	10.10	170.90	NA
2003	20.30	190.70	NA
2004	24.30	203.20	NA
2005	39.60	199.40	NA
2006	37.80	206.10	55
2007	42.10	203.50	260
2008	88.10	297.20	320
2009[a]	119.90	339.30	338
2010[a]	125.50	340.80	213
2011	123.00	394.60	194
2012	146.50	504.00	307
2013	146.10	431.00	163
2014	166.00	443.00	143

[a] This table omits American Recovery and Reinvestment Act funds

increase in the number of SC patents granted to California researchers. In total, between 2000 and 2014 2391 SC patents were granted. As Fig. 1 indicates, beginning in 2000 SC patents increased dramatically, peaking in 2006, immediately prior to CIRM beginning disbursements. There was another peak appeared in 2008, somewhat early for them to be the fruits of CIRM funding. After 2008, the number of SC patents filed nationally and in California declined even as the CIRM (and NIH) dramatically increased funding. Although California continued to be the national patenting leader, CIRM funding does not appear to have resulted in increasing numbers of patents or an increase in California's share of SC patents.

These results suggest researchers, entrepreneurs, and firms are seeing fewer commercial opportunities. There is, of course, the possibility that the decline in SC patenting is a function of changes in the general market for biotechnology patents. The results for biotechnology in Fig. 2 show that both the United States and California did not demonstrably decrease patenting in the larger patent class 435, which tracks biotechnology as a whole. Although applications for patents in class 435 slowed down beginning in 2000, after 2009 they increased again. This suggests that decline in SC patents is not part of a more general slowdown in biotechnology. Patenting in SC declined, while remaining relatively stable in biotechnology suggesting that the number of promising SC inventions has been decreasing despite the concentrated influx of research funds. One explanation of the decline is that was a patenting rush during the period of SC euphoria, but, as researchers and investors became more educated about the difficulties inherent in commercialization, they became less sanguine about the value of SC-related inventions.

5.3 Small business innovation research (SBIR) grants

For entrepreneurs, SBIRs are attractive because the funds do not dilute the equity of the firm's owners. SBIRs have been found to be particularly valuable for academic scientists forming biomedical firms (Toole and Czarnitzki 2007). Research suggests that firms receiving SBIR

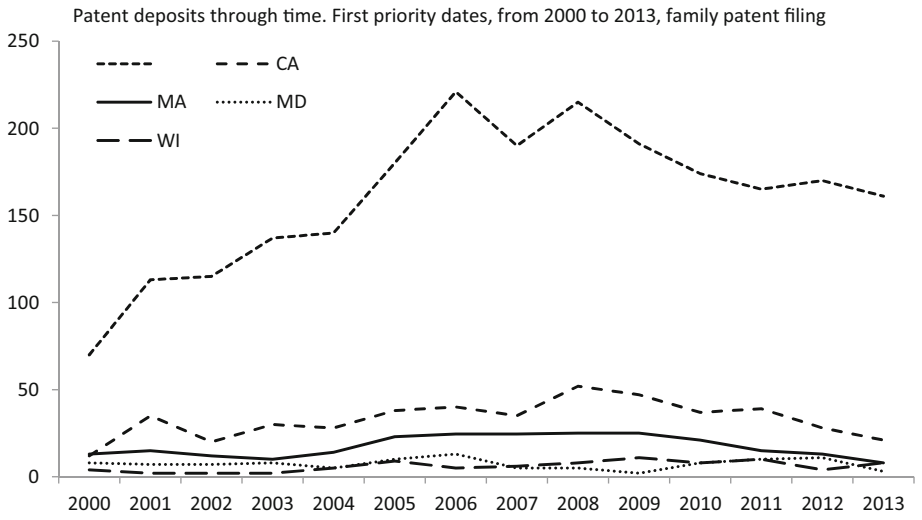

Fig. 1 SC patents, 2000–2013. *Source* Analysis by University of Bordeaux GREThA researchers, July 2015

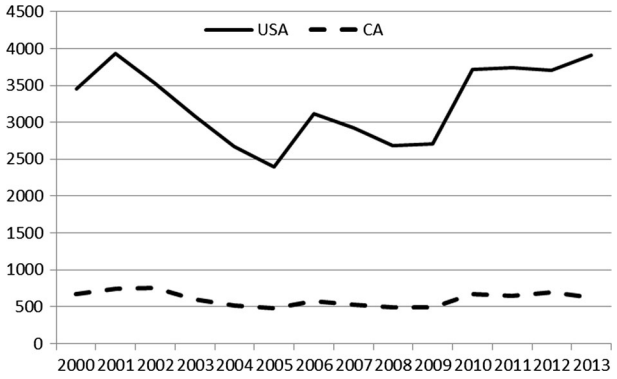

Fig. 2 US PTO patenting in class 435 chemistry: molecular biology and micro biology 2000–2013, United States and California. *Source* University of Bordeaux GREThA, July 2015

grants have better performance than control groups (Audretsch et al. 2002; Lerner 1999), thus can be an indicator of the commercial potential of inventions.

In both per capita and in absolute terms, SBIR grants are concentrated in a few cities, particularly Boston, Denver, New York, San Diego, San Francisco, and Washington, DC (Rosenbloom 2007). As Fig. 3 indicates, SC-related NIH SBIR grants over time exhibit similar spatial characteristics and are concentrated in San Francisco (41), Boston (37), and San Diego (28). From 1998 to 2014, the number of California SC firms receiving their first SBIR grant grew at 8.71% CAGR, while the national growth rate was 8.17%, and Boston lagged at 1.01%. California entrepreneurs continued to receive SC-related SBIRs, while Boston entrepreneurs were less so inclined.

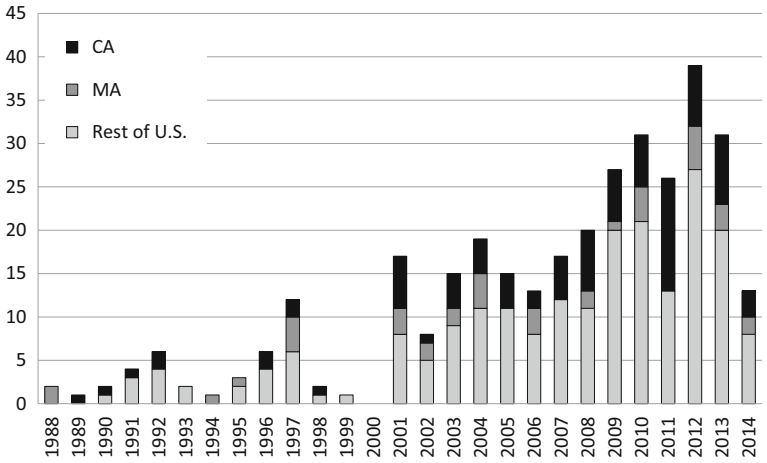

Fig. 3 SC firms receiving SBIR grants by year and location, 1988–2014. *Source* SBIR.gov, accessed March 9, 2015

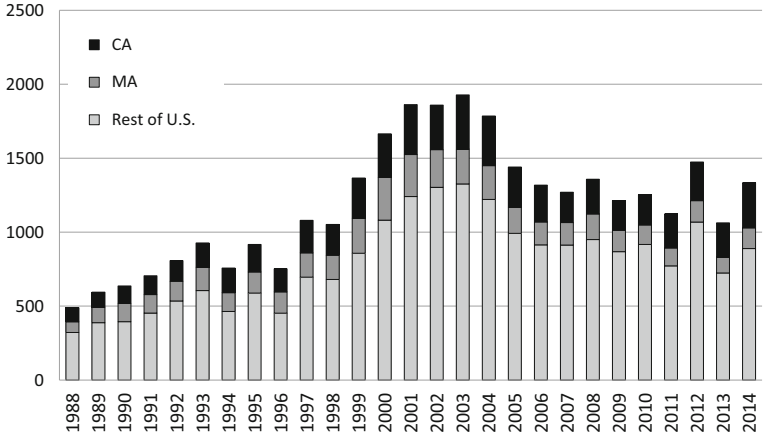

Fig. 4 HHS SBIR/STTR grant awards by year for California, Massachusetts, and rest of US, 1988–2014. *Source* SBIR.gov, accessed March 9, 2015

California was the national leader in all SBIR grants from the Department of Health and Human Service (HHS) (see Fig. 4) with an 18.7% share of the total.[4] Moreover, California's share of all HHS SBIR grants grew more rapidly than the national average, thereby increasing its national share. In comparison, because SC SBIR grants began from a very low base, in percentage terms, they increased more rapidly than the total HHS SBIR grants.

[4] Federal statistics report SBIR grants by department, and the NIH is in the Department of Health and Human Services (HHS). Fortunately, NIH funding comprises nearly all HHS research funding. The SC SBIR grant data includes individual firms only once, though many firms receive multiple grants. In the HHS data, due to the enormous number, these are simple counts not curated to include each firm only once. For this reason, the data are not strictly comparable. Due to the large number, this should have little impact on the aggregate comparisons.

The CIRM may have contributed to an increase in the knowledge base that encouraged the awarding of SC SBIR grants. The recent increase in SC SBIR grants seems promising both nationally and in California.

5.4 Venture capital financing

The ability to transfer biomedical technology from US universities through the medium of startups has been predicated upon the willingness of venture capitalists to take significant risks investing in unproven and incipient technologies (Kenney 1986; Powell et al. 2002; Thursby et al. 2001). More recently, because large pharmaceutical firms have been increasingly reluctant to invest in research and development, VC investment has become even more important (Kneller 2010; Rafols et al. 2014).

For a venture capitalist, success is measured by the returns they receive either after their portfolio firms are purchased by public investors through an initial public stock offering or another firm acquires their stake. Because the investment is by its nature temporary, they are a particularly good indicator of the promise of a technology to generate a return in the medium term (8–10 years maximum). Venture capitalists make mistakes, but fortunately these are self-correcting. If there is little return, the venture capitalists accept their losses, write off the bad investments, and discontinue investing in the unpromising area.

SC firms have received comparatively little VC funding. As Fig. 5 indicates, when compared to other states, California SC firms have not been particularly successful in securing VC. Moreover, after 2008, California's share of total SC VC funding decreased. The two investment peaks coincided with the greatest discussion of the promise of SCs. The first peak was in 2000, 2 years after the announcement of the first HESC cloning at the University of Wisconsin. The second peak was in 2005, immediately after the passage of Proposition 71. However, after a drop in 2006 and 2007, VC investment collapsed in 2013 and 2014. Although the SC firms receiving VC are scattered nationally, San Francisco (21), Boston (17), and San Diego (15) were home to the greatest number of VC-funded SC firms.

To see whether the decline was mirrored in biotechnology in general, we compared SC venture investment to the biotechnology total. Figure 6 indicates that there was a decline in VC financing for biotechnology nationally after 2007, though as a percentage, SC investment remained roughly the same percent of total investment. The VC data suggest that initially venture capitalists speculated on the promise of SC technology. However, in 2008 and thereafter, they retreated.

As we indicated earlier, with the exception of a strong biotechnology cluster in Boston, California is the center of the biotechnology industry and is the home to the savviest investors. And yet, as Fig. 7 indicates, in terms of total investment, California venture capitalists have been less likely to invest in stem cell startups. Moreover, after a single large investment in 2008, the reluctance to invest appears to have increased as they retrenched. This behavior is remarkable as CIRM dramatically ramped up its research investment and began a policy of funding corporate SC research and product development. Their collective decision suggests that they saw few commercial prospects.

5.5 SC startups

The US pharmaceutical industry has increasingly relied upon startups in the initial stages in the commercialization process. The relative absence of big pharmaceutical firms in the SC field reinforces their importance. Entrepreneurship, in one sense, is vibrant in the SC arena. For example, nearly every city has a number of SC clinics that are providing unapproved

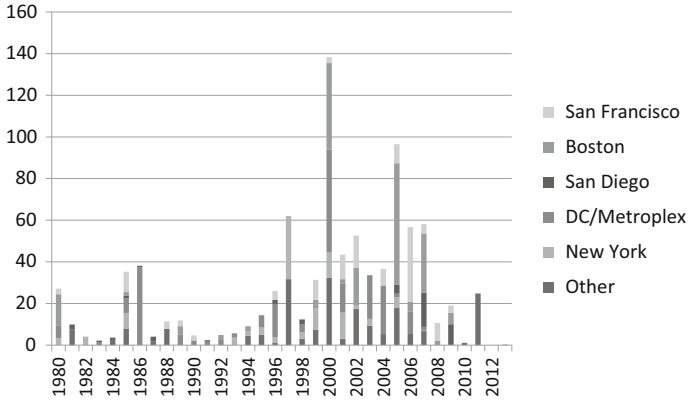

Fig. 5 US venture capital investment in SC firms 1980–2013 by region in millions of dollars. *Source* Thomson VentureXpert

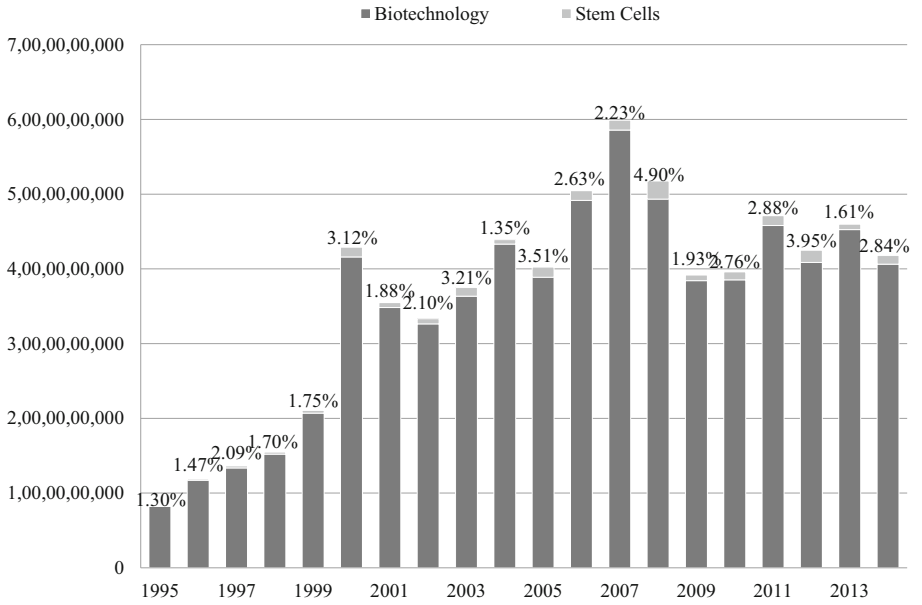

Fig. 6 Annual venture capital investment in US biotechnology and SC firms, 1995–2014. *Source* Thomson VentureXpert and authors' data

treatments to patients (Knoepfler 2015; Turner and Knoepfler 2016). In principle, these could all be considered entrepreneurial SC-related ventures, and they do create employment and economic activity—some of it likely socially unwanted from a therapeutic perspective.

Identifying science-based SC firms is not a trivial task. It is complicated because a number of the firms in our database have undergone convoluted business field and ownership changes that made identifying SC firms difficult. For example, the publicly listed Caladrius Biosciences was incorporated in 1980 as Fidelity Medical Services, but then

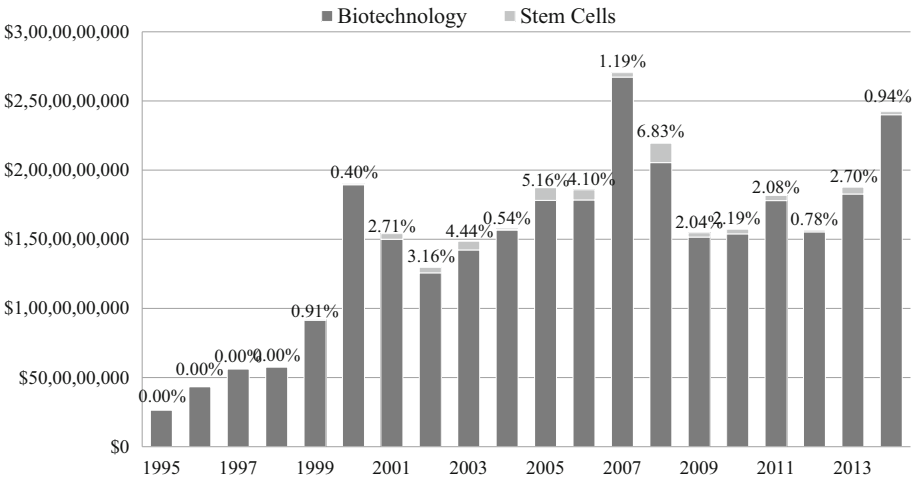

Fig. 7 Annual venture capital investment in California biotechnology and SC firms, 1995–2014. *Source* Thomson VentureXpert and authors' data

underwent a reverse merger and became a retail operation owned by the Corniche Group. This was followed by a number of business strategy changes, and in February 6, 2003, the firm became Phase III Medical. In 2004, it entered into an agreement with NeoStem. It soon came to be renamed NeoStem (2007: 1) and entered into "the business of adult SC processing, collection and banking services with the goal of making SC collection and storage widely available in 2006 offered more stock to the public." In 2015, it again changed its name to Caladrius Biosciences in conjunction with $15 million grant from the CIRM (Caladrius Biosciences 2015).[5] While Caladrius has a particularly long history of name and management changes and financial difficulties, it was by no means the only firm in this population that had a checkered past.

Geron Corporation, another firm funded by CIRM also has a complicated past. Geron is not in our database because it was established to commercialize teleromes. However, in a strategy shift, in 2001 it signed a contract with the University of Wisconsin, Madison, to commercialize HESCs (Jain and George 2007). In 2013, Geron sold its SC research to the San Francisco firm BioTime (Garde 2013), and that research firm was immediately funded by the CIRM. BioTime is included in our database, while Geron is not, as it was never dedicated to SC research.

Proper firm identification was also made more difficult, as a variety of firms identified themselves as making products that could be used in the SC industry. For example, the Santa Barbara firm, OWL Biomedical, was established in 2011 to "develop microchip-based disposable cell sorting technology for cell purification applications. The company's technology is also used for basic SC and cancer cell research applications and SC sorting for cosmetic and aesthetic markets." While the firm builds products used in the SC industry, its products are not confined to SC production, so it was omitted. Such biomedical production input firms are often included in lists of SC firms. We excluded such firms, as they would artificially inflate the number of SC firms. If a firm appeared to be exclusively or largely focused on inputs to the SC industry, it was included.

[5] Oddly enough, the CIRM gave the grant to Caladrius, although it was a New York firm that had opened a branch in Irvine, CA (Caladrius Biosciences 2015).

This methodological discussion is included here because it indicates the complicated nature of the SC field and evaluating the impact on SC technology transfer through startup firms. Ultimately, we identified 102 SC firms. The oldest was founded in 1970. To evaluate the CIRM's impact in terms of startups, we compared the two most prolific California SC startup regions with Massachusetts and the United States as a whole before and after 2006. With the exception of San Francisco, as a whole, California, controlling for its far greater importance, did not appear to significantly outperform the nation or Massachusetts (see Table 2). To further test the importance of the CIRM, we collected the names of all the firm founders in our population. This list allowed us to identify which founders were employed by a university at the time the firm was founded. The results were quite surprising in that only in San Francisco did over 50% of the firms have at least one university founder. At least, with regard to our population, SC firms appear to be far less dependent upon university founders than mainstream biotechnology startups.

San Diego is interesting because it had substantially fewer university founders than other locations and the United States as a whole, thereby agreeing with Casper's (2014) findings that San Diego firms were far less university-centric than San Francisco firms. As was the case in the biotechnology industry, San Francisco has been the home to the largest number of SC firms that gave their early investors significant returns.

Startup firms are the primary vehicle for commercializing new biotechnologies. In the United States, biotechnology startups and the R&D they undertake to commercialize new technology have been funded by the private sector. Through the CIRM, firms including BioTime, Caladrius, Geron, and Viacyte have had their research funded directly by taxpayers. Effectively, the CIRM absorbed the risk that professional venture capitalists accept in return for the significant capital gains that can accrue with success. This decision has been made because, for the most part, venture capitalists have eschewed funding SC firms (with exceptions, e.g., Stemcentrx), while they continue to fund biotechnology. The results suggest that CIRM has not had a significant impact on startup formations.

5.6 Clinical trials

Clinical trials are a vital intermediate step in commercialization. Successful clinical trials can signal to investors or possible acquirers that a firm has a potentially valuable product. Studies have been conducted on the geography of SC clinical trials (Li et al. 2014). From 1988 to 2015, ClinicalTrials.gov included 2815 US SC clinical trials and their inception

Table 2 SC startups by location, date of establishment, and whether at least one University founder, 1970–2015

	Number	Prior to 2006	2006 and after	University involvement
California*	34	19	14	12
San Francisco	12	4	8	6
San Diego*	13	6	6	3
Massachusetts	12	6	6	4
United States*	102	62	37	31

Data includes all firms with SC in their descriptions from Thomson VentureXpert, PitchBook, and internet searches

* Missing date of establishment for three firms, one in San Diego and two in the rest of the US

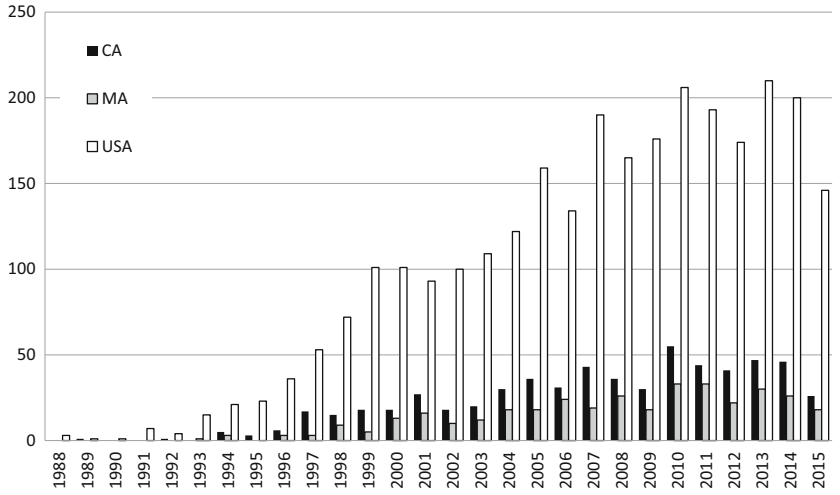

Fig. 8 Stem cell clinical trials in the United States, California, and Massachusetts, 1988–2015. *Source* U.S. Clinical Trial Registry

dates, of which 614 were conducted in California and 360 in Massachusetts. Two other SC clinical trial leaders were Texas (563) and New York (524). As Fig. 8 demonstrates, prior to the late 1990s, there were few trials. The number then increased, leveled off in the early 2000s, and then began increasing again after 2004. More recently, the number has stabilized. From 1998 to 2014, the CAGR was 6.59% in the country as a whole, 7.25% in California, and 4.43% in Massachusetts. The CIRM also funded 25 clinical trials, but that was less than 1% of the total number of SC-related clinical trials and only about 4% of California's total. In the period in which the CIRM was active (2006–2014), we find that the SC clinical trial CAGR for the country was 5.13%, while for California it was 5.06%, and for Massachusetts it was only 1.01%.

Because our data are aggregated and not curated, they should be treated cautiously. Yet our results agree with more carefully curated studies. For example, research by Bubela et al. (2012) found that, as of 2012, SC clinical trials were in their early stages. The trials they studied showed significant industry involvement, but they concluded that setbacks had caused a number of firms to discontinue their trials. In a more recent study, Li et al. (2014: 35–36) concluded that "while there are promising advances, routine clinical use of SC therapy for neurological conditions is still optimistically many decades away" and concluded that there is "as of now, limited evidence of efficacy for novel SC therapeutic applications".

The CIRM has a policy of encouraging SC clinical trials in California, so we examined whether the number of SC clinical trials in California increased more rapidly than the total number of all clinical trials. Remarkably, the total number of all clinical trials increased more rapidly than did the number of SC clinical trials and California's growth in terms of total clinical trials exceeded its growth in SC clinical trials (0.66 versus 1.22%). Moreover, from 2007 to 2014, the period during which the CIRM was funding SC research, California's share of SC clinical trials grew at 5.06%, while the national average grew at 5.13%. In conclusion, while California is the leader in SC trials, California's SC accounted for less than 3% of all trials, and its number was growing more slowly than the total number of trials. As confirmed by Bubela et al. (2012) and Li et al. (2014), our results

suggest that the CIRM has had no measurable impact on SC clinical trials beyond those it subsidized.

6 The biotechnology versus SC value chain

The translation of research results into therapies is a commercialization process that first requires testing and approval by the Food and Drug Administration (FDA). After approval, the therapy must be manufactured, distributed, prescribed, and sold to the final consumer. This entire process can be understood through value chain analysis (see, e.g., Gereffi et al. 2005). In capitalist systems, each of the firms in the process must perceive the economic benefit to them for undertaking the particular step in the value chain. In this chain, there are also government actors that must act to approve the therapy. For any new product or service, one of the critical questions is whether its characteristics are such that the product can be serviced by an existing value chain. If a value chain already exists and into which it can be inserted then commercialization is likely to more rapid and less costly, as a new value chain will not need to be organized.

To illustrate, in the late 1970s the new biotechnology industry based on university spinoffs that commercialized recombinant DNA and monoclonal antibodies contracted with the existing pharmaceutical firms that had complementary assets to secure government approval, manufacture, and market the products of their research (Teece 1986). Effectively, these university spinoffs segmented an already existing value chain as the small research-intensive spinoff would develop a candidate drug sufficiently to either attract acquisition by a large established pharmaceutical firm or offer stock to public investors (see, e.g., Kenney 1986; Rothaermel and Deeds 2004). By the mid-1980s, the research-intensive spinoff had become a distinct node in the pharmaceutical industry value chain (Padgett and Powell 2012). This particular configuration of the value chain for the existing biotechnology industry is depicted in the upper panel in Fig. 9.

When potential SC products fit within the existing pharmaceutical (drug) value chain commercialization is likely to be relatively straightforward. However, when HSC therapies are personalized or include living cells re-injected into patients, the value chain is likely to be more complicated. These complications are illustrated in the lower panel of Fig. 9. A value chain perspective can illuminate of the difficulties face by firms planning to commercialize personalized medicine. The most significant obstacles can be grouped into three categories illustrated in boldface in Fig. 9. Most important, these obstacles interact in ways that make assembling an entire value chain more difficult.

The first difficulty is the lengthy development period that applies to all pharmaceuticals including HSC. This compels private investors to demand outsize returns to cover failures. Although hype and excitement do affect investors' decision-making processes, over the long term, investors must receive visible returns, if they are to continue investing.

The second difficulty is that medical products must be approved by regulators. The obstacles for innovative products that require entirely new value chain with new manufacturing and administrative procedures are great because of the absence of protocols and formulas, and thus regulators are biased to caution. The fact that the HSC regulatory process has not been normalized creates an additional layer of uncertainty for investors. Consider the conundrum: without candidates entering the regulatory process, approval protocols and procedures cannot be normalized, but the lack of protocols discourages investors (Dodson and Levine 2015; Heathman et al. 2015; Rao 2011).

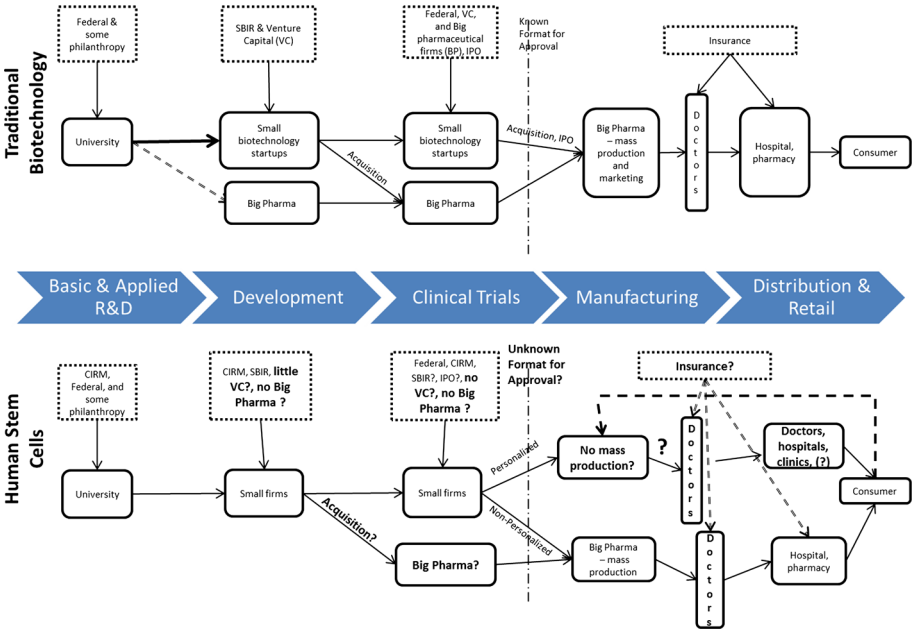

Fig. 9 Traditional biotechnology and stem cell product development/value chain model

The third difficulty for the success of an HSC therapy is that it must be produced at a price that the market will accept. Because it is a new technology, at least, initially or until it becomes standardized, just producing it under acceptable pharmaceutical practices is likely to be difficult. Personalized medicine is different from the current medical model, which is predicated upon the production of large quantities of standardized products and dosages (Dodson and Levine 2015). Because the HSC therapies are likely to be specific to individuals, mass production, by definition, is difficult. Moreover, the technical challenges of growing living HSCs for application to human beings are significant and thus likely to be costly, as each individual's cells are different, and complications or failures could be catastrophic. As these living organisms will have to be transported from the patient to the factory and then back again, the production logistics are likely to be challenging. Alternatively the production could be at the treatment site, but then the advantages of centralization, economies of scale, and specialization may be lost.

The greatest obstacle ultimately may be cost (Heathman et al. 2015). Extracting and reproducing an individual's cells is almost certain to be expensive, as it is by nature a unique process, more akin to purchasing a handmade suit than to buying one off the shelf. Personalized medicine, by definition, will be costly even if a standardized process can be developed (Kapoor and Klueter 2015). Success may depend upon the willingness of insurers to reimburse the cost sufficiently for the firm to recover development expenses and the fixed and variable cost of the therapy. Another possibility is that therapies will be available only to those able to pay sufficiently high insurance premiums or able to bear the out-of-pocket costs. Unfortunately, this would negate one of the main premises of Proposition 71 that of saving on health care costs.

Even if promising therapies are discovered in the laboratory, the HSC value chain has a number of missing and unstable segments, namely, the regulatory, manufacturing, and

reimbursement functions. Downstream uncertainties affect upstream segments. When large pharmaceutical firms are uncertain about the ultimate market they will fund fewer upstream activities at universities and show less interest in startups trying to develop HSC products. The result is less interest and investment by venture investors and less progress because of the lack of a clear pathway to profitability (Dodson and Levine 2015).

7 Discussion

The CIRM was a product of significant scientific excitement and even hype. As far as we can ascertain, this is the first comprehensive study that attempts to measure the economic impact of such a large subnational technology development initiative. By definition, it is impossible to predict research outcomes. For these reasons this discussion and summary are limited to data currently available and, with this proviso, this assessment of the commercial impact of the CIRM is provisional. And yet, the most remarkable result is that on every commercialization measure, beginning with patents, the evidence suggests that the CIRM has had little economic impact beyond the direct spending of CIRM's funds. Little commercial activity can be expected in the medium term and there is no evidence that the investment has had any impact on improving California's competitive position versus Boston.

The lack of commercial impact contrasts with the finding that the number of research publications by scientists in states with increased funding does increase (Alberta et al. 2015; Casper 2015). Our research revealed there was no evidence that enhanced the ability of California researchers to secure NIH SC funding. Those arguing that CIRM would increase California scientists' ability to compete with other states will be disappointed. Conversely, it does not appear that CIRM funding led to California researchers deciding not to compete for federal funds. In this respect, it did not have a negative effect.

Patents are an indicator of commercial interest in a line of research. Despite the funding increase by the CIRM and the NIH, the number of SC patents decreased nationally and in Boston and California, even as biotechnology patents increased. This suggests that the flow of commercially valuable knowledge decreased over time. Whether this is an indicator of decreasing returns to R&D investment, an evaluation by knowledgeable parties that the research results did not have significant commercial value, or some other factor; the results do not show any increase in patents despite the enormous increase in research funding.

Small startup firms play a central role in commercializing biomedical advances. For these reasons, we measured two funding mechanisms, SBIR grants and VC funding. Though the overall number was quite small, 25.7% of SC-related SBIR grants were awarded in California—far more than were received in Boston. California had an even greater concentration (37%) of VC-funded SC firms. Not surprisingly, in terms of both SBIR grants and VC financing, Massachusetts continued to be the closest rival to the two California clusters. More puzzling, VC investment in SC firms has declined nationally but particularly in Boston and California. In effect, in the two markets with the most sophisticated venture capitalists, investment decreased the most.

In terms of startups, the database indicates that SC research appears to be generating few startups. Moreover, only one-third of the firms in the database had a university-related founder—a surprisingly low number. While CIRM may have had an impact, as it directly funded some SC firms, the overall effect was remarkably limited. Most important, the largest California clusters in San Francisco and San Diego have not outperformed the

closest comparator, Boston. Of greater concern is that the lack of SC startups was not mirrored in the biotechnology industry, which boomed without any assistance from California government funding.

The final commercialization indicator examined was clinical trials, and confirming previous research, CIRM's investments appear to have had little impact on increasing clinical trials in California as opposed to Boston or in comparison to the growth in overall clinical trials. In fact, even though the CIRM itself was supporting clinical trials, the number of SC clinical trials grew more slowly than that of all clinical trials. This combined with evidence from other studies of SC clinical trials suggests that indicators of commercialization are not improving and might be declining.

The final result suggests that for all science policy targeting commercialization, understanding the value chain context should be a part of any planning process. If the technology fits in an existing value chain, then it is more likely that commercialization will be predictable and rapid. If a new value chain must be organized, then costs will normally be higher and the rate of adoption is likely to be lower and slower. Therefore commercialization of therapies, if they are developed, will take longer and require more capital to be realized. Depending upon the obstacles, commercialization may be precluded not only for venture capitalists, but also for big pharmaceutical firms.

Given the unproven value chain for SC products it is not surprising that the now nearly $2 billion expended by the CIRM has not, and may never have, any discernable commercial impact. Of course, the long-term future is unknowable. The CIRM continues to fund SC research and increasingly is responding to the market's lack of interest by funding activities closer to commercialization—activities that are normally undertaken by the private sector. As a result, the CIRM must make progressively larger investments, thereby taking greater risks. From a policy perspective, moving further down the value chain means the CIRM's financial risks are growing.

8 Conclusion

Subnational scientific research investments, often sparked by claims of the newest scientific discoveries and justified by promises of significant economic benefits, have proliferated during the last two decades (Feldman et al. 2013). This paper is one of the first comprehensive examinations of the commercial progress of one such large subnational program. What we have shown is that, regardless of the ultimate outcome, the goals of the program advocates will likely take far longer to be realized than initially projected. In contrast to policy-making for basic research, for R&D initiatives that promise commercial benefits, policy-making could be improved by treating the claims of future benefits in the same way as an investor evaluates a high-risk business opportunity and undertakes due diligence. These initiatives can learn from venture capitalists that stage their investments, so if the initial promise from a certain research direction fades funds could be redirected in more promising directions. Further, as our research has shown, such initiatives can be monitored in real-time to further ensure wise allocation of research funds. If effective due diligence is not possible, then a broad portfolio approach is a more reasonable strategy that, at a minimum, creates ample flexibility for redirecting funding toward more promising technologies as they emerge (Wallace and Rafols 2015).

Our results suggest that making a wager on a specific technology in its uncertain early days is risky. This is particularly true in this case as initially CIRM focused almost entirely upon HESC

technology even though other SCs are showing signs of having therapeutic and commercial value. Because the proposition was written to support a narrow research field, a more diversified research investment strategy with the possibility of significant course correction was precluded.

Large subnational funding projects also have other drawbacks. Rapid funding increases such as is the case with CIRM can lead to the creation of significant concentrations of specialized human capital. Moreover, the CIRM, in particular, had an active strategy of recruiting scientists into HSC research. It invested significant resources into training programs and many other outreach activities to make HSCs an attractive research area. It had a strategy of creating HSC research-specific assets in terms of specialized researchers and facilities. If the influx of funding ends, and there is no new source of funding to absorb these trained personnel and other specialized assets, then their value is likely to decline.

Economic-development promises were used to convince many that public investment in the CIRM would lead to lower health-care costs, increased economic activity, and result in California becoming the center of a new industry. In an environment in which universities and scientists must be certain that they retain the public trust, promising commercial benefits that may never be fulfilled, tests the trust and goodwill that university researchers have accumulated. Therefore, while narrow benefits accruing to individual researchers may be welcomed, the cost to the scientific community may be far greater.

Sector-specific initiatives can be enormously productive. However, decisions to fund such initiatives should be as objective, comprehensive, and detailed as possible. Policy-makers and voters should consider the basicness of the research, the size of the investment, the specificity of the scientific targets, the sustainability of the research direction after the cessation of funding, the probability of research and commercial success, and the difficulties of actually introducing the therapy to the market—these form a matrix in which each dimension could be considered part of the public investment decision. As subnational governments increasingly are investing in research with economic goals, cultivating both a better understanding of the relevant commercialization processes, and developing methodologies for collecting data for ongoing monitoring of research and commercial performance can contribute to improved public decision making.

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