Impact of regional systems of innovation on the formation of university spin-offs by biomedical star scientists

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Abstract: Scientists in research universities can play a formative role in commercialising their inventions for the benefit of society. University spin-off formation is increasing in importance as an alternative to licensing, and can be impacted by both micro and macro-level factors of the regional system of innovation. However, there is limited understanding of the ways in which these factors can interact to enable the formation of university spin-offs. In this study we examine how the productivity of two biomedical star scientists in co-founding university spin-offs can be supported or constrained by other elements of the regional system of innovation. Recommendations are made for research universities seeking to foster entrepreneurship through university spin-off formation.

Keywords: star scientists; university spin-offs; regional systems of innovation; RSI; anchor companies; technology entrepreneurship; innovation policy; science policy; academic entrepreneurship; university entrepreneurship; science commercialisation; biomedicine; lifesciences; biotechnology; technology transfer.

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1 Introduction

Scientists in research universities can play a formative role in commercialising their inventions for the benefit of society. Scientists can engage in commercialisation by licensing their inventions to large incumbent firms or by forming university spin-offs. Incumbent firms are generally not keen to license these early stage inventions as significant time and money is required for further development, the technological uncertainty is high, and incumbent organisational incentives constrain radical innovation (Maine and Seegopaul, 2016; Pisano, 2010). These incumbents prefer to wait for a small university spin-off to demonstrate the feasibility of this technology before considering sub-licensing or acquisition. Thus, research universities are increasingly choosing to embrace initiatives designed to facilitate spin-off formation.

Many research universities now support spin-off formation, though not all are equally successful. Spin-offs from MIT and Stanford have been estimated to generate US$1.9 trillion and US$2.7 trillion in annual global revenue (Roberts et al., 2015; Eesley and Miller, 2012) respectively. The regional economies surrounding these universities have also benefitted from increased job creation. 39% of all alumni founded firms are located within 60 miles of Stanford (Eesley and Miller, 2012) and the Kendall Square neighbourhood of MIT has 120 biomedical firms within a 1.5 kilometre radius (Ledford, 2015). This success is leading more universities and regions to identify ways to support university spin-off formation.

Biomedical university spin-offs emerge from academic research labs led by scientists. Some scientists choose to publish with limited or no patenting, while others may embrace commercialisation by publishing, patenting and licensing their inventions. Scientists may also be more directly involved in commercialisation as co-founders of university spin-offs (Gurdon and Samsom, 2010), generally located in close proximity to their academic institution (Zucker et al., 1998). There is a great variation in the productivity of scientists along this spectrum of invention to innovation (Stephan et al., 2007). We define star scientists as researchers who have an above average patent and publication output, and are also listed as a co-founder on a university spin-off.

In this paper, we investigate the impact of regional systems of innovation on the formation of university spin-offs by star scientists. Using two purposefully selected case studies, we demonstrate how the productivity of star scientists in co-founding university spin-offs can be supported or constrained by elements of the regional system of innovation (RSI). In Section 2, we review the literature on regional systems of innovation and star scientists with an emphasis on their role on university spin-off formation. We describe the methodology we follow in Section 3, followed by the two case studies in Section 4. We discuss our findings in Section 5 and offer conclusions in the final section.

2 Theoretical background

A RSI is defined as a system "in which firms and other organisations are systematically engaged in interactive learning through an institutional milieu characterised by embeddedness" (Cooke et al., 1998). Originating from earlier research on national systems of innovation (Lundvall, 1992; Freeman, 1995; Nelson, 1993; Edquist, 1997), the RSI concept emphasises three aspects. The first term 'interactive learning' describes the interactive processes through which knowledge is combined by different actors in the productive system. The second term 'milieu' highlights rules, standards, values, and human and material resources. The third term 'embeddedness' includes all economic and processes created within and outside firms. The increasing recognition of the RSI concept has been tempered by researchers critiquing its lack of clarity (Markusen, 2003). Others have argued that a top-down, macro-to-micro view pervades RSI analyses, which leads to insufficient attention to the micro and meso level explanations for regional innovation (Iammarino, 2005; Werker and Athreye, 2004). An integrated micro-to-macro view is needed to better understand the dynamics of RSI.

From the micro perspective, star scientists in research universities have an important role in improving the innovative performance of a region (Niosi and Banik, 2005). Star scientists have been found to impact the origin and growth of the US biotechnology industry (Zucker et al., 1998). These highly productive scientists can contribute to regional innovation through tacit knowledge sharing, or through more formal mechanisms such as licensing or university spin-off formation. University spin-off formation is driven both by micro-level as well as macro-level factors. Micro-level factors include the characteristics of the inventions (Shane, 2001a), inventors psychological make-up (Roberts, 1991), and their intellectual human capital (Zucker et al., 1998). Macro-level factors such as technology regimes (Shane, 2001b), and university intellectual property policies (Kenney and Patton, 2011) can also play an important role in supporting spin-off formation. Post formation, biotech firms can grow rapidly through patenting, venture financing and strategic timing of alliances (Niosi, 2003), along with proximity to strong, relevant clusters (Maine et al., 2010).

Anchor companies have been recognised as valuable members of RSI. The presence of an anchor company may generate several positive feedback loops. Such companies, because of their extensive networks of scientific collaboration and significant R&D resources, not only provide employment, but can also act as magnets for scientific and managerial talent (Agrawal and Cockburn, 2003). Several smaller companies may often find sustenance by servicing the business needs of such larger companies. The presence of an anchor company may increase the technology transfer deal flow at local research universities and scientist-entrepreneurs may find them to be willing partners on R&D projects.

While there are significant positive impacts of the presence of large anchor companies in regional systems of innovation, not much is known about the impact of the failure of an anchor company or its decision to leave a region. This is an important question, as the impact of failure of an anchor company may vary by the breadth and depth of a RSI. A large RSI which has multiple anchor companies may be less affected by the failure/absence of one anchor company (Niosi and Zhegu, 2010). This is in contrast to the experience of a smaller RSI which may be much more dependent on the presence and continued growth of a single anchor company. The failure or absence of an anchor company may generate negative feedback loops which may impact the smaller RSI in several ways: funding from private and public sector investors may become less forthcoming for scientist-entrepreneurs in the region, there may be a flight of top-level scientific and managerial talent to other regions, and several smaller companies may lose their most significant client. Another important though less tangible impact on the smaller RSI, may be the effect of the failure of an anchor company on the collective entrepreneurial culture of a region for a number of years.

The literature also does not differentiate between an anchor company which has been established in a different region, versus an anchor company which has emerged from the same RSI. Large anchor companies with operations in multiple countries and regions, may choose to leave an RSI without having failed or becoming bankrupt. There are numerous examples of large, regional R&D centres of anchor companies being completely closed or relocated to another region. However, the failure of a local anchor company may be more severe for smaller RSIs which are dependent on their continued survival and success. In such instances, the entrepreneurial ambitions of budding and experienced scientist-entrepreneurs may be tempered by this failure, and finding investors and potential employees may become difficult. In such circumstances, university spin-off formation can become even more challenging.

Thus, the relationship between anchor companies and scientist-entrepreneurs in regional systems of innovation may be affected both by the breadth and depth of the RSI, as well as the origins of the anchor company in the RSI. Both positive and negative feedback loops can become reinforcing, success of an anchor can attract further resources and thus create potential for further success and spin-off formation, and failure may constrain the innovation potential of an RSI for multiple years, until another successful anchor company is established.

3 Methods

The biomedical star scientists selected for our study are exemplars of publishing, patenting and founding an above average number of science-based ventures. The research universities to which these star scientists belong are also recognised as leading institutions in their respective national and regional systems of innovation. We collect detailed information on the publications, patents and university spin-offs co-founded by these two star scientists in differing regional systems of innovation. We supplement this with secondary data on the research universities (MIT and UBC) and the regions (Massachusetts and British Columbia) in which these star scientists are embedded. Combining this data with interviews with the star scientists, lab members, and technology transfer personnel, we are able to link the performance of these biomedical star scientists in university spin-off formation to the university IP policies, entrepreneurial culture, and access to financing and highly qualified personnel in two biomedical regional systems of innovation in North America.

We begin by searching the USPTO database for the name of the star scientist under ‘inventor’ and the institution as an ‘assignee’ until 31st December 2015. For collecting publication data, we combine the publication list on the scientist’s lab webpage and compare it with Google Scholar. This data is also taken until 31st December 2015 for consistency. Other sources like the Web of Science and PubMed may not offer complete coverage of all scientific publications and can underestimate publication output. The data on the number of university spin-offs co-founded have been compiled by the author from multiple sources such as company web pages, annual reports, press releases, SEC filings, published CEO interviews and firm media reports. The data on current lab members has been compiled from the official lab websites of the star scientists. Lab members include graduate students, postdoctoral fellows, visiting researchers and technicians while excluding managers and other associated members. University and industry association reports are used to compile the metrics for the institution and region. We use this data to examine how the productivity of two biomedical star scientists in co-founding university spin-offs can be supported or constrained by elements of the RSI. In doing so, we conduct a case study which examines not only the star scientists, but the environment to which they contribute to and draw on, for their productivity (Dana and Dana, 2005).

4 Case data and analysis

4.1 MIT, biomedical star scientist A, and the Massachusetts RSI

4.1.1 University – MIT

The Massachusetts Institute of Technology was incorporated on 10th April 1861. Its motto ‘Mens et manus’ which translates to ‘mind and hand’, encourages faculty, students and staff to develop strong ties with industry (Roberts and Eesley, 2009). This entrepreneurial culture has not detracted from the quality of science and engineering generated by the MIT community. It lists 86 Nobel laureates among its current and former members (MIT, 2016a).

The entrepreneurial ecosystem at MIT has a long history. The early emphasis on involvement with industry was further accelerated through the exigencies of the war effort in the 1940s. Research groups were reorganised and university research redirected to support the development of practical devices for winning the war. Policies permitting faculty members to engage in active consulting for about one day a week, approving faculty part-time efforts in spin-off formation, and pioneering technology entrepreneurship research legitimised the entrepreneurial culture at MIT. Other institutions such as Harvard University, Northeastern University, University of Massachusetts and Tufts University also played important roles in nurturing the technology-based community in Boston and Route 128.

Table 1a University – MIT

Metric	*Value*	*Data source*
Established (year)	1861	MIT (2016a)
University operating revenue (USD)	$3.4B	MIT (2016b)
University endowment (USD)	$13.1B	MIT (2016b)
Undergraduate students	4,527	MIT (2016a)
Postgraduate students	6,804	MIT (2016a)
Faculty	1,863	MIT (2016a)
IP ownership	MIT	MIT (2016c)
University equity share (%)	5	Wong et al. (2015)
Invention disclosures (fiscal year 2016)	800	MIT (2016a)
Industry sponsored research (USD) in 2015	$134M	MIT (2016a)
US patents issued (fiscal year 2016)	279	MIT (2016d)
Number of licenses granted (FY 2016)	110	MIT (2016d)
Companies started in fiscal year 2016	25	MIT (2016d)

Entrepreneurship support and training initiatives within MIT have now expanded significantly beyond the initial policies encouraging consulting and spin-off formation. Formal entrepreneurship training at MIT began in 1990 with the founding of the Martin Trust Center for MIT Entrepreneurship and the launch of the MIT 50K business plan competition. Widespread student and faculty participation in training and mentorship programs (such as the venture mentoring service, the MIT enterprise forum, and 63 entrepreneurship and innovation credit courses) has resulted in 40% of MIT alumni having launched two or more companies (MIT, 2015; Roberts et al., 2015; Bulovic and Murray, 2016). The MIT innovation initiative, launched by President Rafael Reif in 2013 and co-Chaired by associate deans from the faculties of engineering and management, gives strategic oversight to the development of entrepreneurship initiatives at the MIT. Seed funding is broadly available to de-risk technologies and develop prototypes (Bulovic and Murray, 2016).

The MIT technology licensing office (TLO) (established 1932) has been one of the earliest organisations supporting entrepreneurship at MIT (Roberts et al., 2015). Interviews with personnel at the MIT TLO highlight some of the nuances in MIT's approach to the management of intellectual property while supporting the sharing of research in the public domain. Critically, the MIT TLO will pay for patent costs even when there is no money to be made.

> "at MIT, if it will make a difference in a small market, if it will have impact to the benefit to some cause they believe is worthy, they will file. On the flip side, could be a really important market and an enormous market, but the science is so fundamental, they don't feel they should try to establish a monopoly. They will put the technology in the public domain. We don't pursue this activity for income." (L. Foster, personal communication, January 22, 2014)

The MIT TLO also confirms that incumbent firms are generally not interested in early stage inventions, preferring to wait for start-ups and spin-offs to validate the technology (L. Foster, personal communication, January 22, 2014). Thus the TLO engages with the inventors to assess if all rights should be assigned to one start-up or if there should be field-of-use licensing. A field-of-use license grants the licensee a limited subset of uses, so that the licensor is free to work with other companies to commercialise other elements of the invention.

MIT's IP policy vests ownership to MIT for intellectual property developed by faculty, students, staff and others participating in MIT programs, including visitors, with the significant use of funds or facilities administered by MIT (MIT, 2016c). However, contrary to a large number of universities in the US, the UK and Canada, MIT takes at most a 5% equity stake in spin-outs (Wong et al., 2015; Hen, 2010). Such policies, when combined with an entrepreneurial culture, accessible financing from public and private sources, and a vast pool of skilled highly qualified personnel, can sustain university spin-off formation and lead to huge value creation.

4.1.2 Biomedical star scientist A

Even in such a munificent and supportive environment, both at MIT and in Massachusetts, founding science-based university spin-offs is not an easy task (Reif, 2015). The scientific uncertainty and regulatory hurdles inherent in the biomedical domain makes university spin-off formation a significant challenge for most scientist-entrepreneurs. In such a situation, star scientist A from MIT, has managed to co-found 32 university spin-offs based on research from his lab in collaboration with labs within MIT and other regional research institutions. These university spin-offs have gone on to raise over US$2 billion in venture financing (Thomas et al., 2016).

Table 1b Biomedical star scientist A

Metric	*Value*	*Data source*
Publications (till 31 December 2015)	1,535	MIT star scientist A's lab website and Google Scholar
Issued US patents (till 31 December 2015)	387	www.uspto.gov
University spin-offs co-founded	32	Author's compilation
Current lab members	104	MIT star scientist A's lab website

Table 1b shows the total number of scientific publications and issued US patents over a 40 year period starting in the mid-70s, with star scientist A as a co-author and a co-inventor. A core element of this extremely high level of productivity in publications and patents is the large number of graduate students, postdoctoral fellows and visiting researchers in his lab at MIT. These lab members not only contribute to the publications and patents, but some of them also engage in the co-founding of university spin-offs based on the technologies they have developed during the course of their projects (Murray, 2004). Thus, an important role of star scientist A is his ability to match lab members to interesting research projects aimed at large unmet needs. Once the project starts to deliver scientifically robust results, star scientist A and the concerned lab member collaborate with the MIT TLO to protect the invention through multiple broad, blocking patents. While the patents and publications are getting filed and granted, the star scientist also links the lab member to his broader social network in the region consisting of venture capitalists and experienced business professionals to officially launch the university spin-off. In his co-founding role, star scientist A generally joins as a member of the scientific advisory board (SAB) and as a member of the board of directors of the university spin-off. In this manner, he follows MIT policies by limiting his involvement to about one day of the week, while continuing to support the spin-off in an advisory capacity.

4.1.3 RSI – Massachusetts

Positive feedback loops continue to play a decisive role in the development of an entrepreneurial culture at MIT and in the surrounding regions. Successful entrepreneurship efforts by early role models led to greater involvement in entrepreneurship by faculty peers. High technology companies and venture capitalists began to locate in close proximity to the research institutions, and are now deeply embedded in the Greater Kendall Square neighbourhood of MIT (Sharp, 2014). With over 120 biomedical firms within a 1.5 kilometre radius, this cluster is one of the largest and densest biomedical clusters in the world (Ledford, 2015).

Table 1c RSI – Massachusetts (USA)

Metric	*Value*	*Data source*
VC investment in biotech (USD) 2015	\$2.1B	MassBio, 2016
IPOs (2015)	13	MassBio, 2016
Biomedical companies with over 500 employees	18	MassBio, 2016
Employees in largest Biopharma company	5,000	MassBio, 2016

Local anchor biopharmaceutical companies such as Genzyme (now Sanofi Genzyme) and Biogen, each employing several thousand researchers, were co-founded by MIT professors. Large multinational pharmaceutical companies such as Eli Lilly and Merck chose to have significant research presence in Boston. With four of the top five NIH funded independent hospitals in Massachusetts, extensive public and private (VC) investment is available to faculty, students and staff at research institutions in this region (MassBio, 2016). As shown in Table 1c, the Boston biomedical cluster is very strong, with 18 biomedical firms larger than 500 employees, over \$2 Bn of Biotech VC investment in 2015, and 13 IPOs.

4.2 UBC, biomedical star scientist B, and the British Columbia RSI

4.2.1 University – UBC

The University of British Columbia was established in 1908 as public research university. It has over 61,000 students in three campuses, Vancouver (Point Grey and Robson Square), and Okanagan. It is consistently ranked among the top 20 public universities in the world and has seven Nobel Laureates among current or former faculty and alumni (UBC, 2016a). The economic impact of UBC has been measured at C\$12.5 billion and over 180 companies have been spun-off from UBC research (UBC, 2016). Among research universities in Canada, it has one of the highest numbers of patents applied for and issued per year, and the highest income from licensed intellectual property (Toope, 2013; AUTM, 2015).

Table 2a University – UBC

Metric	*Value*	*Data source*
Established (year)	1908	UBC, 2016a
University revenue (CAD)	$2.3B	UBC, 2016a
University endowment (CAD)	$1.4B	UBC, 2016b
Undergraduate students	50,654	UBC, 2016a
Postgraduate students	10,459	UBC, 2016a
Faculty	5,334	UBC, 2016a
IP ownership	UBC	https://uilo.ubc.ca/
University share of net revenue	50%	UBC, 2013
Invention disclosures	133	UBC, 2016c
Industry sponsored research (CAD) in 2015	$53.2M	UBC, 2016c
US patents issued (2015)	22	AUTM, 2015
Number of licenses granted (2015/16)	39	UBC, 2016c
Companies started in 2015	13	UBC, 2016c

There are several entrepreneurship initiatives at UBC which provide seed funding, office space, mentoring and accelerator and incubator services. The UBC intellectual property policy states that the university owns all university research products with the creators getting a non-exclusive license for non-commercial mobilisation (UBC, 2013). This policy also states that 50% of the net revenue will be retained by the university. For most biomedical ventures, this would not be in the interest of inventors nor future investors and may constrain university spin-off formation.

4.2.2 Biomedical star scientist B

Like star scientist A, star scientist B is a prolific 'Pasteur scientist' (Baba et al., 2009) meaning that he conducts breakthrough research relevant to known problems. Over a prolific 40 year career, also starting in the mid-1970s, star scientist B has co-authored 325 scientific publications, co-invented 60 issued US patents, and co-founded 11 university spin-offs (Table 2b). These ventures have successfully commercialised three FDA approved drugs, novel drug delivery methods, and a range of instrumentation. He has also played key leadership roles in both the university and the RSI.

Table 2b Biomedical star scientist B

Metric	*Value*	*Data source*
Publications (till 31 December 2015)	325	UBC website and Google Scholar
Issued US patents (till 31 December 2015)	60	USPTO
University spin-offs co-founded	11	Interview data
Current lab members	11	UBC lab website

Star scientist B took an active role in the leadership of his university spin-offs, reducing his academic commitments to half-time after becoming a full professor. His motivation for founding ventures was both to commercialise inventions from his lab and to provide jobs for PhD students who graduated from his lab. Star scientist B understood many of the constraints to science entrepreneurship in the BC RSI and has been effective in leading initiatives and influencing stakeholders to help move inventions further towards commercial viability. Once star scientist B returned to a full-time academic role (after more than two decades spanning the worlds of academia and entrepreneurship), he confined his role in the ventures to the membership of SABs. Graduates from his research lab and those of his collaborators generally lead his university spin-offs.

4.2.3 RSI – British Columbia

British Columbia (B.C.) is a leading province on the west coast of Canada and is home to a significant life sciences cluster of which UBC is arguably the most important player (Salazar et al., 2008). B.C. received C$450 million in venture capital investment in 2015, as shown in Table 2c. Nearly 84% of the firms in B.C.'s life sciences sector have less than ten employees (PwC, 2015).

Table 2c RSI – British Columbia (Canada)

Metric	*Value*	*Data source*
VC investment (CAD) 2015	$450 M	CVCA, 2016
IPOs (2015)	1	LifeSciences BC, 2016
Companies with over 500 employees	1	LifeSciences BC, 2016
Employees in largest Biopharma company	515	LifeSciences BC, 2016

Access to capital and highly qualified personnel is a significant challenge for life sciences start-ups and university spin-offs (PwC, 2015). Even in such an environment, UBC has continued to form several spin-offs each year with most of them belonging to the life sciences. Despite some initial success, only one biomedical spin-off, QLT, had reached the threshold of 500 employees by 2005. We briefly describe the formation, growth and reversal of UBC's first life sciences university spin-off QLT Inc. and another B.C. biomedical venture which in-licensed technology from UBC.

QLT was formed in 1981 by Dr. Julia Levy, along with other co-founders, around photodynamic therapy technology spun out of UBC. Developing their initial product, Photofrin, in collaboration with Johnson & Johnson, QLT needed early risk capital, and went public on the Vancouver Stock Exchange in 1986, raising C$3 million in its IPO. When Johnson & Johnson planned to shut down development work on QLT's technology, Levy and company raised more money, partially through an alliance partnership with American Cyanamid, to acquire all rights to Photofrin (GCS Research Society, 2001), and conducted expensive clinical trials, reaching FDA approval for the use of Photofrin in treating a range of cancers in 1995. Concurrently, QLT was also developing a drug for wet age-related macular degeneration (AMD) called Visudyne, based on technology exclusively licensed out of UBC in 1988, which achieved FDA approval in 2000. By this time, Photofrin was providing steady revenues, and was sold off profitably, with QLT making its bet on '2nd generation' technology Visudyne (Collett and Mann, 2005). Sales of Visudyne spread to more than 50 countries, making QLT one of only 14 profitable publicly traded biotechnology companies (Pederson, 2005). However, competition from Genentech and completely unexpected prescription behaviour by retinal specialists who started prescribing Avastin off-label for AMD, led to a rapid drop in Visudyne sales (Jacobs, 2006). This was followed by problems with other drug candidates after which QLT declined further. After a 2016 merger with Massachusetts pharmaceutical company Aegerion, QLT continues to survive in Vancouver as Novelion (Shore, 2016), developing innovative ocular products, but at a small fraction of its former size.

Angiotech also experienced rapid growth in the mid-2000s. It had developed a drug-eluting stent called Taxus with technology in-licensed from UBC. With a sale of C$1.4 billion in its first nine months on the US market, Angiotech rapidly grew to into a $2 billion plus market capital company (Hon, 2011). However, this growth rapidly declined as Angiotech's partner, Boston Scientific, reported in a study that patients implanted with Taxus stents had a slightly higher but statistically significant risk of developing late stent thrombosis. With declining revenues and interest payments from a loan taken to acquire a medical device manufacturer, Angiotech also started facing tough times. In both these examples, life sciences companies emerged from the B.C. RSI based on highly innovative research but were unable to sustain profitability over the long-term.

Following the financial crisis of 2008, the life sciences industry in B.C. was left without a large, profitable anchor company. This environment is slowly improving with 6 life sciences IPOs in B.C. in 2014 and renewed interest from public and private funding sources. The one surviving anchor company today, STEMCELL Technologies, had a conservative path to success, after spinning out of the BC Cancer Agency and UBC in 1993, it only surpassed 500 employees in 2014. STEMCELL Technologies, is privately held by the founders, scientists Dr. Allan Eaves and Dr. Connie Eaves, and has purposefully accepted no VC financing. Thus BC's biomedical RSI is recovering with the development of a new anchor company, but this needs to be compared to 18 large incumbent companies in Massachusetts with over 500 employees (Tables 1 and 2). The total VC investment in these small life sciences companies in B.C. is a fraction of the funding available in Massachusetts and the rest of the USA.

5 Discussion

Scientific inventions at universities have the potential to address many of the world's most pressing challenges, and university leadership is increasingly acknowledging both their opportunity and their responsibility to facilitate science entrepreneurship (Leih and Teece, 2016; Reif, 2015). There is also the potential for financial value creation, at the scientist, university, firm, regional and national levels (Zucker et al., 2002; Booth and Salehizadeh, 2011; Christini, 2012; Maine and Seeegopaul, 2016). New industries can be created by scientific inventions (Schumpeter 1942; Nelson and Winter, 1982; Utterback, 1994; Maine et al., 2014a, 2014b), and knowledge-based economies built around them (Freeman, 1982; Lundvall, 1992; Nelson, 1993; Agrawal et al., 2014). Despite the social and economic benefits of science-based university spin-off formation, the challenges inherent in commercialising science can be daunting for scientists, universities and regional systems of innovation (Langford et al, 2006; Pisano, 2010; Sen, 2014; Maine et al., 2015; Maine and Seegopaul, 2016).

In this study we adopt an integrated micro-to-macro view of RSI and analyse the productivity of two biomedical star scientists in the formation of university spin-offs. Collecting data at the level of the research lab, the university and the region, we compare and contrast two differing biomedical regional systems of innovation, at the levels of the star scientist, the university, and the RSI. This case study comparison contributes to the academic entrepreneurship, science entrepreneurship, and science policy literatures, through a more integrated examination of science-based entrepreneurship. Our case study analysis demonstrates how successful science-based entrepreneurship can lead to positive feedback loops which can lead to job creation and further spin-off formation. The constraining and supporting roles of university policies and regional innovation policy are also discussed. Our study responds to the call for more attention to micro and meso level explanations for regional innovation to complement the more pervasive macro explanations (Iammarino, 2005; Werker and Athreye, 2004).

Case study A demonstrates a positive feedback loop between the star scientist, the university, and the RSI. The high levels of productivity in patents and publications of star scientist A can be explained in part by the large number of lab members in his research lab. In addition, with patent filing a significant expense for scientists and/or research universities, MIT's policy of filing a patent if they feel the technology is valuable and based on research using university funds and facilities, also contributes substantially to the number of US patents issued to star scientist A. A large number of broad, blocking patents also play an important role in spin-off formation as patents can act as a signalling mechanism to venture and angel investors (Hsu and Ziedonis, 2006; Maine and Thomas, 2017). Venture capitalists are also far more likely to fund spin-offs in which the university has taken a smaller equity stake, such as the 5% stake typically retained by MIT, and when the TLO is motivated to get the technology out into society. The long-time head of the MIT TLO, Lita Nelsen, explained the TLO's criteria for patenting, licensing, and equity share determination:

> "We protect the intellectual property – mostly through patents, so as to provide a good 'dowry' to incentivize entrepreneurs to start companies. Then, we emphasize 'getting the deal done fairly' rather than 'getting the best deal'. We can do this because we have excellent support and understanding from MIT's senior administration. Together we understand: 'Impact, not income': It's not about the money. Sure, we like it when our ships come in, but the primary focus is getting the deal done so that the technology gets developed." Chandler (2014)

The entrepreneurial culture of Massachusetts, and the greater Kendall square cluster in particular, is the result of several decades of university leadership, entrepreneurial experience and innovation policies. With early entrepreneurial successes at MIT leading to a virtuous cycle of experimentation, learning and innovation, star scientist A has found (and contributed to developing) a fertile arena with access to financing and personnel from multiple sources. This enables him to contribute to the regional economy through tacit knowledge sharing, mentoring, licensing and spin-off formation. In the longer term, both the university and the RSI benefit from their early stage support of the star scientist in his patenting and formation of spin-off ventures.

In contrast, case study B has not yet developed a positive feedback loop between the star scientist, the university, and the RSI. Indeed, the publications, patents and spin-offs generated by star scientist B are even more impressive for having been in an environment with limited university resources supporting technology transfer (for instance, compare total US patents issued at each institution, as shown in Tables 1a and 2a), comparatively low levels of venture capital (for instance, compare life sciences VC investment in each RIS, as shown in Tables 1c and 2c), and without the alliance partnerships, anchor companies, and range and depth of highly qualified personnel of a more developed RSI.

The RSI has been negatively affected by the failure of two biotechnology anchor companies, which rose to great heights only to fall in rapid succession in the mid-2000s. These examples highlight the fact that regional systems of innovation are equally susceptible to negative feedback loops particularly in regions with limited resources.

Innovation policymakers and university leadership can play active roles in creating the conditions for positive feedback loops between star scientists, research universities, university spin-offs, and the RSI. Innovation policy at the national and regional levels should support the formation and growth of university spin-offs (Thomas et al., 2016), the interaction between large and small science-based firms with university research labs and each other (Agrawal et al, 2014), the development of highly qualified personnel, and access to early stage financing (Jenkins, 2011). University leadership can reconsider their technology transfer practices (Bubela and Caulfied, 2010), support entrepreneurial culture through such initiatives as entrepreneurship training to scientists and university-wide business plan competitions (Roberts et al, 2015; Maine, 2013; Leih and Teece, 2016), incentivising faculty members to form spin-offs by awarding targeted commercialisation funding, taking a relatively small share of equity from university spin-offs (such as the 5% equity claimed by MIT), and by building research partnerships with anchor companies. This will better align the longer term incentives of the star scientist with that of the university and the RSI.

6 Conclusions

We have analysed the impact of the regional systems of innovation on the university spin-offs co-founded by two biomedical star scientists, one from MIT in Boston, Massachusetts, and the other from the University of British Columbia in Vancouver, British Columbia. We show that elements of the RSI, such as the entrepreneurial culture, university IP policy, availability of financing and trained personnel, and the surrounding innovation intermediaries play an important role in sustained university spin-off formation. The productivity of star scientists and the formation of university spin-offs are thus, dependent upon the context in which they are embedded (Dana and Dumez, 2015). The relationship between star scientists and the formation and concentration of biomedical spin-offs in a region is iterative and multi-faceted. Universities desirous of fostering entrepreneurship in regions with limited resources can take the following steps:

1. focus on developing technology transfer and IP policies which support inventors and which align the longer term interests of the scientist-entrepreneur, the university and the RSI
2. provide targeted funding for faculty and student research with commercial potential
3. build research partnerships with local anchor companies to generate positive feedback loops
4. encourage an entrepreneurial mindset among STEM students through entrepreneurship training and business plan competitions.

Developing an entrepreneurial culture within universities can contribute not just to university spin-off formation but can fuel growth in the regional, national and global economy.

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