Regenerative Medicine Translation: Cross-national analysis of entrepreneurial ecosystem development

Abstract

In the field of regenerative medicine, new ventures face unformed markets and inconsistent industry practices. We study two university-centric regenerative medicine ecosystems to explore the characteristics of venturing activity and ecosystem development under irreducible uncertainty. The situational analysis reveals multi-level effects. At the micro-level, entrepreneurial coping strategies are significantly affected by cultural artifacts generated by the ecosystem university. At the macro-level, entrepreneurial ecosystems may develop along different paths, generating idiosyncratic contexts for venturing activity. A model of entrepreneurial ecosystem development is presented, with implications for theories of entrepreneurial behavior as well as policy practice in developing technology sectors.

Keywords: coping, entrepreneurship, ecosystem, regenerative medicine, technology transfer

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1. Introduction

Many technology-based entrepreneurial ecosystems bridge academic institutions, industry and government. As universities have been spotlighted as potential engines for high-value economic development, these ecosystems have received significantly more research and policy attention (Etzkowitz, 2003). Entrepreneurial ecosystems are complex, often poorly defined clusters of economic activity whose participants are linked variously by field, technology, geographic proximity or parent institution. It is not surprising that the innovation and commercialization outcomes of these systems are contingent on a variety of factors, including entrepreneurial behavior, cultural norms and the context of the originating university (Walshok *et al*, 2012; Zahra and Wright, 2011).

Universities drive regional economic outcomes via basic research, teaching, knowledge transfer, policy developments, economic initiatives and other activities (Breznitz and Feldman, 2012). Although the regional economic benefits of university technology transfer are not consistent (Miner *et al*, 2001), universities clearly contribute to the formation of industry and innovation clusters (Porter, 1998). One important university activity that contributes to cluster development is the generation of *de novo* ventures.

Venture development at the university-industry (UI) boundary is difficult and uncertain. Entrepreneurs, often academics with limited business training or experience, must acquire scarce resources, capabilities and partners (Alvarez and Barney, 2005). The experiences of academic entrepreneurs are highly idiosyncratic, and the outcomes of any given university spinout is difficult to predict from either endogenous or exogenous factors (Festel, 2013; Wright *et al*, 2012a; Yosuf and Jain, 2010). At the same time, characteristic

and structural patterns suggest that the underlying venturing processes are similar across ecosystems (George and Bock, 2008).

The regenerative medicine (RM) industry provides a useful setting to study entrepreneurial behavior and ecosystem development at the UI boundary. The RM field presents unusually high levels of uncertainty associated with complex and unresolved regulatory and intellectual property (IP) frameworks (Ledford, 2008). This limits entrepreneurial planning, hinders the identification of key capabilities and prevents *ex ante* validation of stem cell-based business models (George and Bock, 2012; Heirman and Clarysse, 2004). In this context, RM ventures must simultaneously explore unfamiliar territory and acquire the knowledge resources to navigate that territory.

In robust clusters, new ventures acquire and create knowledge through spillovers and human capital (Saxenian, 1994; Zucker *et al,* 1998). Human capital, such as prior venture experience of the entrepreneur, can enable greater network ties and more diverse social networks (Mosey and Wright, 2007). Across ecosystems, specific resource assembly challenges and entrepreneurial behavior differ (Clarysse *et al*, 2011). In the RM space, valuable knowledge, capabilities and IP are extremely sophisticated, scarce and tightly contested. We use the backdrop of the complex and uncertain RM field to explore micro-level dynamics of entrepreneurial ecosystems in the context of knowledge acquisition. First, we investigate entrepreneurial attributions across apparently similar RM ecosystems. Second, we consider how entrepreneurial ecosystems develop differently, with specific emphasis on imprinting effects of the parent institution.

We report on a cross-national study of RM venturing in Edinburgh (Scotland, United Kingdom) and Madison (Wisconsin, United States) to explore entrepreneurial behavior and ecosystem development. Our findings emphasize how entrepreneurial coping strategies may be partly driven by university culture. The data shows apparently similar ecosystems at

different stages and points towards the dynamic and evolving nature of entrepreneurial ecosystems. Based on the situational context presented in the data, we propose a model of entrepreneurial ecosystem development.

This paper proceeds as follows. First, we review prior research on entrepreneurial ecosystems at the UI boundary, with particular reference to RM ecosystems. We report Methods in Section 3. Findings are presented in Section 4, highlighting ecosystem and informant role differences. We consider these differences in the Discussion section, presented in Section 5. We conclude with limitations and directions for future research.

2. Entrepreneurial ecosystems

Broadly speaking, business clusters embody the co-evolution of firms around particular innovations, technologies or markets. The industrial-organizational literature specifically defines a cluster as "a geographically proximate group of interconnected companies and associated institutions" (Porter, 2000). These firms interact cooperatively and competitively to generate new products, meet market needs and stimulate further innovations (Moore, 1993). Clustered ventures benefit from reduced transaction costs, specialized pools of labor and improved access to resources and knowledge, particularly through collaborating and competing with other cluster members (Bell *et al*, 2009).

An entrepreneurial ecosystem is a specialized type of organizational-industrial cluster, which develops over time within a specific geographic region and is replenished or expanded by new ventures (Cohen, 2006). Ecosystem participants are connected by venture formation and growth activities, potentially spanning otherwise disparate technology fields and capability sets. The ecosystem generates incentives for entrepreneurial activity, linking potentially surplus resources to extant ecosystem participants and opportunity-oriented individuals outside the system (Spilling, 1996). Participants in an entrepreneurial ecosystem

may or may not be closely connected. Spinouts from the same university laboratory may share fundamental technology capabilities and human capital. For example, Cellular Dynamics International, Inc. and Stem Cell Products, Inc., were both spun out of The University of Wisconsin-Madison based on stem cell innovations associated with research by Professor James Thomson. These firms even shared physical facilities and certain executive managers.[1] Other ecosystem participants may be connected only by formative links to the parent university or by relationships to other specialized businesses in the ecosystem, such as IP law firms.

Networks are especially important to the development and performance of these ecosystems. Network content, connections and structures affect resource assembly practices and outcomes (Hoang and Antoncic, 2003). This is especially relevant for access to resources and the creation and exchange of knowledge (Aldrich and Martinez, 2001; Ardichvili *et al*, 2002). As entrepreneurial ecosystems commonly span otherwise disparate industrial sectors, social networks play an important role in venture formation and development (Birley, 1985; Jack, 2010). These social networks are influenced by differences in human capital (Mosey and Wright, 2007). Entrepreneurs must invest in operating and managing networks for venture formation and growth (Nijkamp, 2003). Such networks enable entrepreneurs and ventures to interact (directly and indirectly) with economic and social organizations and institutions. These interactions are mediated by cultural norms within the wider ecosystem (Johannisson *et al*, 2002).

When social networks facilitate knowledge acquisition, ventures are often better placed to exploit knowledge for competitive advantage (Yli-Renko *et al*, 2001). Under uncertainty, particularly in emerging or nascent markets, ventures are likely to benefit from a diverse network and the ability to form ties with a wide range of networked partners (De Vaan, 2014;

[1] The firms were, in fact, ultimately merged in 2008.

Meyskens and Carsrud, 2013). When uncertainty is high, network openness improves ecosystem performance by accepting new participants, supporting diversity and facilitating tie-formation to other ecosystems. Networks enable the spillover of knowledge, which further promotes clustering between ventures in similar industries (Audretsch and Feldman, 1996; Hayter, 2013).

There is clear evidence of the importance of context and institutional forces in ecosystem formation and development. Considering ecosystem development from a range of contextual frameworks, such as technological, institutional, social and spatial contexts, is important to gain a richer understanding of ecosystems (Autio *et al*, 2014). Networks thus play a critical role in the outcomes of individual ventures and the overall ecosystem (Eisingerich *et al*, 2010). Yet, research has not generally been directed at the impact of the central institution (university) on the participants in the ecosystem and their entrepreneurial decision-making.

2.1. University-centric ecosystems

Research universities often anchor entrepreneurial ecosystems in knowledge-intensive fields. Since many technology-intensive firms have potential high-growth profiles, special emphasis is commonly placed on the role of university spinouts in regional economic growth (Etzkowitz, 2003). Although the actual economic impact of university-based entrepreneurship is overshadowed by media focus on outlier successes, universities and technology transfer offices (TTOs) are commonly identified as important engines of economic growth (Bock, 2012; Miner *et al,* 2001).

The dynamics of entrepreneurial ecosystems at the UI boundary are poorly understood. On the one hand, universities may foster entrepreneurial activity and subsequent interaction between ecosystem participants (Swamidass, 2013). Many universities and civic-minded

entities support subject-specific research, translational resources and practices, access to seed funding and venture capital (VC), investments in human capital, and even subsidized professional services. Yet geographic, economic, socio-demographic and other factors beyond the control of the university or any ecosystem participant are also relevant. Policy differences across ecosystems result in variations in spinout activity and performance (Goldfarb and Henrekson, 2003; Mustar and Wright, 2010). Innovation and economic outcomes may derive from initial configurations and path dependencies, limiting the influence of policymakers (Zacharakis *et al*, 2003).

In particular, venture formation at the UI boundary has received a great deal of attention (c.f. Djokovic and Souitaris, 2008; O'Shea *et al*, 2004). Venturing activity is informed and influenced by institutional norms and culture. The motivation for technology transfer, and the choice of transfer instrument, are driven by ecosystem norms and university-based incentive structures (Decter *et al*, 2007; Henrekson and Rosenberg, 2001).

Venturing at the UI boundary is challenging. Academic entrepreneurs usually lack resources and commercialization expertise. Spinouts face significant uncertainties related to proving technologies, market needs and value creation potential (Doganova and Eyquem-Renault, 2009; Lehoux *et al*, 2014; Vohora *et al*, 2004). Resource access and configurations are highly dependent on exogenous factors outside the entrepreneur's control (Clarysse *et* al, 2011). New ventures generated at the UI boundary may require entirely new business models specific to the innovation (Pries and Guild, 2011).

2.2. Knowledge spillover and creation

Universities play an important role in knowledge creation within ecosystems. The spillover of knowledge from universities is important for innovation and ultimately ecosystem development and economic growth (Acs *et* al, 1994; Audretsch and Feldman,

1996). New knowledge generated within the university can spillover to the surrounding ecosystem, which is facilitated by the entrepreneurial culture at the focal university (Audretsch, 2014). External ecosystem actors are able to exploit and benefit from this spillover of knowledge (Agarwal *et al*, 2010), which is often tacit in nature (Agarwal and Shah, 2014). When there are greater levels of university-based knowledge spillovers, there are likely to be higher levels of new venture startups located around the university (Audretsch and Lehmann, 2005). The highly sophisticated, technological requirements of RM venturing indicate that new RM ventures are most likely to locate themselves around the university in order to capitalize on localized university knowledge spillovers (Acosta *et al*, 2011; Audretsch *et al*, 2005). By being in close proximity to the university, RM ventures may benefit from smoother transmission of tacit knowledge (Kolympiris and Kalaitzandonakes, 2013). Spatially, university ventures spun out to university-linked science parks, in contrast those spun out within the wider ecosystem, may be better placed to overcome resource scarcity and uncertainty (Lofsten and Lindelof, 2003).

The generation of new knowledge in ecosystems, and the subsequent spillover of this knowledge, drives entrepreneurial opportunities (Audretsch and Belitski, 2013). Exploiting these opportunities requires absorptive capacity to understand, recognize and commercialize this knowledge (Qian and Acs, 2013). Entrepreneurs must find ways to distinguish partnerships that create exploitable knowledge, rather than expropriate otherwise protected knowledge assets (Hernandez *et* al, 2014; Katila *et al*, 2008).

2.3. Regenerative medicine ecosystems: venturing under irreducible uncertainty

RM venturing is a complex and resource intensive process. Individual and institutional tensions are driven by conflicting motivations at the UI boundary, as well as business model uncertainty in the marketplace (Ledford, 2008). RM spinouts are generally capital intensive

yet capability-poor. They face field-specific challenges in manufacturing scale-up, distribution logistics and exit uncertainty. RM ventures must operate with little or no slack in their resource pool, limiting product-market and business model exploration and testing (Bock *et al*, 2012; George, 2005). This capabilities gap between university RM innovation and RM entrepreneurial activity requires new ventures to partner for critical industry knowledge and deep capabilities, in order to explore RM opportunities (George *et al*, 2008).

The development of a RM ecosystem ultimately depends heavily on the actions of individual entrepreneurs (Feldman, 2014; Wright *et al*, 2012b). The decision to become an inventing entrepreneur in the RM field may be controversial, difficult and uncertain (George and Bock, 2008). Academic scientists participating in commercialization activities will be required to modify their role-identity (Jain *et al,* 2009). Shifting from a scientific orientation to a more market-driven approach creates tensions for the individual, university and the venture. The deeply embedded culture within academic institutions preferentially focuses on research and publications at the expense of patent and commercialization activities and is, therefore, at odds with an entrepreneurial approach (Decter *et al*, 2007).

Despite the noted research on entrepreneurial ecosystems, numerous questions require further attention. Broadly speaking, the full effects of university-based translational and commercial activity on local ecosystems and regional economies remains uncertain (Audretsch *et al*, 2014; Audretsch *et al*, 2013; Wright, 2013). More specifically, we know relatively little about the emergence of these ecosystems or the institutional characteristics that influence their development (Autio *et al*, 2014; Thomas and Autio, 2014). The impact of university policy, practice and culture on micro-level entrepreneurial cognition and behavior also requires more attention (Jennings *et al*, 2013). Specifically, there is a need for a deeper understanding of how different contexts affect entrepreneurial coping, especially under uncertainty (Autio *et al*, 2014). From a field perspective, venturing in RM has not been

rigorously studied. It presents an edge case, highly specific to university-centric entrepreneurial ecosystems, in which uncertainty limits the value of strategic planning. Venturing activity in the RM field offers clues to the emergence and dynamics of entrepreneurial ecosystems.

3. Methods

As we were primarily focused on the sensemaking and behavior of ecosystem participants, we utilized a qualitative approach to data collection (Locke, 2001). We interviewed ecosystem participants, relying on the long interview as our data collection method (McCracken, 1988). To explore entrepreneurial processes and ecosystem elements in RM venturing, we initiated a study of activity in two distinct but similar areas. We discuss the ecosystems studied and the procedures for analysis.

3.1. Entrepreneurial ecosystems under investigation

We investigated RM venturing centered on The University of Edinburgh (Edinburgh, Scotland, United Kingdom) and The University of Wisconsin-Madison (Madison, Wisconsin, United States). These ecosystems present useful and surprisingly similar contexts to explore the development of a RM ecosystem at the UI boundary.

The University of Edinburgh and The University of Wisconsin-Madison are large research institutions with long-standing RM programs. RM research at The University of Edinburgh has been popularized by media attention to Dolly the sheep. Research led by Professor Sir Ian Wilmut led to the first cloned mammal from an adult somatic stem cell. The University of Edinburgh houses The Scottish Centre for Regenerative Medicine (SCRM). This world leading research center employs more than 230 research scientists and clinicians, and was specifically commissioned to translate stem cell research to the clinic and industry.

In addition, the Scottish government has a key focus on RM translation and the development of a viable RM ecosystem.

The University of Wisconsin-Madison also has an established history of RM research, with Professor James Thomson deriving the first primate and human embryonic stem cell lines and the first human induced pluripotent stem cell lines. The Stem Cell and Regenerative Medicine Center at The University of Wisconsin-Madison is focused on being a world leader in stem cell and RM research and translation. The Wisconsin Alumni Research Foundation (WARF), the TTO for The University of Wisconsin-Madison, is generally recognized as holding the world's most foundational patent portfolio covering stem cell technology (Bergman and Graff, 2007).

Comparative information between the institutions and relative economic context is provided in Table 1 to demonstrate the surface similarities of the venturing context. The areas present strong similarities across a variety of measures. Both represent large research institutions in Tier 2 metropolitan areas. Additional similarities include the university size, socio-geographical context and relative dearth of local VC. Both ecosystems remain relatively small, providing a conducive context for investigation. The pairing is preferable to comparisons against more established and significantly larger RM ecosystems, such as San Diego (metro population 3.1 million), Boston (metro population 4.5 million), London (metro population 15 million) and Seoul (metro population 25.6 million). The similarities between the two ecosystems under investigation allowed for a more controlled exploration of variation in entrepreneurial cognition and behavior. While no two metropolitan or regional ecosystems will present enough similarity to warrant fully controlled investigation of target variables, the Scotland-Wisconsin parallel was (perhaps unusually) sufficiently similar to justify comparison over many other possible ecosystem choices.

Table 1 here

3.2. Long Interview

Target informants were purposefully selected (Morse *et al*, 2002) according to their involvement in RM commercialization. To capture full aspects of the phenomena being examined, we interviewed several categories of informants from Edinburgh and Madison. Categories included, RM entrepreneurs and firms (n=10), academic scientists (n=4) and RM/life science support entities (n=16). RM/life science support entities were defined as organizations that supported RM venturing processes. They included TTOs, agencies that supported life science innovation and governmental bodies concerned with economic development in the life sciences.

We conducted interviews in Edinburgh between November 2012 and September 2013. Interviews in Madison were conducted between March and May 2014. We adopted a narrative interview approach in which informants were asked to describe their participation in the commercialization of RM innovation. Such an approach is especially useful for theory generation within entrepreneurship studies (Fletcher, 2007; Larty and Hamilton, 2011). Beyond this initial narrative request, informants were not provided with any further direction. When appropriate, the interviewer requested additional information about specific topics of interest. Consistent with long interview practices (McCracken 1988), the interviewer encouraged the informant to discuss whatever topics, personal stories and opinions seemed relevant. Allowing informants to freely discuss areas of interest to them helps alleviate possible socially desirability bias (Podsakoff *et al*, 2003).

To limit participant bias and prejudicial preparation of information or materials, informants were not provided detailed information about the interview in advance. Interviews ranged from 14 minutes to 85 minutes in duration. Additional field notes were generated during and immediately after the interviews to support data analysis. All interviews were recorded and transcribed. We provide information on the interview informants in Table 2.

Table 2 here

3.3. Procedures

Our analysis of the narrative interviews was guided by grounded-theory building (Strauss and Corbin, 1990). The Edinburgh interviews were open-coded to generate first-order codes. This was guided by findings from an initial pilot survey. Following the open coding, we developed theoretical categories and dimensions through inductive and deductive reasoning. To ensure theoretical sensitivity and a deep understanding of the relationships between categories, we constantly shifted between the data, coding and constructs during our analysis (Charmaz, 2006; Glaser, 1965). Transcripts were reviewed at the semantic level, seeking out the meaning of phrases, sentences and short passages. All coding was performed using NVivo software.

The Madison data was coded using the same data structure. The researchers were sensitive to the possibility of entirely new codings in the Madison data. Although some new constructs were observed in the Madison data, we chose to emphasize consistent, comparative analysis for three reasons. First, the prevalence of novel constructs in the Madison data was low. Second, re-coding the Edinburgh data with the novel constructs would not have been possible in a tabula rasa framework. Third, the Madison dataset was

slightly smaller than the Edinburgh dataset, with a slightly different ratio of informant roles. For the sake of parsimony, we focused on the extant data structure, though we strove to remain open to novel or unexpected phenomena.

4. Findings

In this section, we report the findings from the data coding. We explore the theoretical dimensions revealed by the data and consider how these differ within and across ecosystems. We provide examples from the interview transcripts to illustrate the results of the coding analysis and emphasize key findings.

The multi-level data structure based on the interview coding is presented in Table 3 to highlight the relative prevalence of codes in each dataset (Walsh and Bartunek, 2011). The first column in the table shows the prevalence (%) of codes for a) all informants, b) informants in the Edinburgh ecosystem (ED) and c) informants in the Madison ecosystem (MSN).

Table 3 here

4.1. Ecosystem and informant role comparisons

Comparisons across ecosystems and informant role highlight several differences. These are presented in Table 4. The data presented compares normalized code frequency to account for differences in interview length and informant speaking styles. We calculate values for each ecosystem (and informant role) by dividing the total number of references for each theoretical dimension by the total number of all references across all theoretical dimensions.

Table 4 here

4.1.1. Differences across ecosystems

The data shows much higher reference to *university entrepreneurial culture* in Madison than Edinburgh. Both ecosystems highlight the conflicts faced by academic scientists looking to commercialize their stem cell innovations, since commercialization activities are at odds with traditional academic culture: *"[A]cademics are judged by their papers and their grants…Spinouts take a lot of time and a huge amount of work…group leaders find that extremely difficult because that's time that they're not doing their academic work and ultimately they will be judged with the current metrics much more on their academic work than they will on their commercialization work."* (Informant #9) Other informants placed blame on the larger academic context: *"That's the way that our scientific environment is structured. We publish papers and get proposals funded without pushing toward the edges of the spectrum…we can't have impact."* (Informant #28)

Informants from Madison highlight stronger motivation towards venture formation at the UI boundary. In Edinburgh there are perceptions that licensing, rather than spinout formation, is the preferred method of technology transfer: *"…[U]niversities don't do spinout companies, I know it sounds a bit daft, but conceptually that's not… they tend to do licensing deals and spinouts are not something they want to get involved with."* (Informant #7)

We also see a greater emphasis in Madison on the TTO policies that encourage commercialization and the resources available at the TTO to enable entrepreneurial activities.

WARF has a long history of technology commercialization. It is one of the oldest and most successful TTOs in the world and has particular expertise with RM technologies, stemming from the early seminal research and discoveries by Dr. James Thomson.

The business development capabilities of TTO personnel have been shown to influence venturing activity (Lockett and Wright, 2005). Academic scientists disclosing their innovations at The University of Wisconsin-Madison have access to a diverse team within the TTO. This includes Licensing Managers, IP Managers, Legal Counsel, and Patent and Market Intelligence Analysts. The University of Edinburgh has fewer resources allocated to this type of pre-commercialization activity.

Across ecosystems there are differences in *collaborative knowledge*, with greater emphasis on this in Madison. We see higher reference to knowledge transfer during RM venturing activities in Madison: "*So we'll be in constant communication with the inventors and communication with our outside patent counsel and work with them to build a strong patent portfolio that we can market."* (Informant #30)

The flow of knowledge within networks results in specialized knowledge being created, transferred or recombined, which results in learning (Dyer and Nobeoka, 2000). Findings from Madison highlight greater perceptions of learning taking place during the venturing process. Some emphasized lessons related to their institutional role: *"What I've learned over time is that you have to be published in peer reviewed journals."* (Informant #25) Others emphasized learning specifically about venturing: *"There were just a lot of dynamics in the process that were tremendous learning experiences."* (Informant #28)

Ecosystem comparisons illustrate a greater emphasis on *coping strategies* in Edinburgh compared to Madison. To overcome the high levels of perceived environmental uncertainty (PEU) (Milliken, 1987), the dataset highlights the implementation of coping strategies. These include collaboration and legitimacy building. Collaborations can provide access to critical

resources. Legitimacy building is especially useful when uncertainty and controversy surround a novel technology. We see support entities in Edinburgh building legitimacy in order to promote their offerings to RM ventures: "*...we've become active internationally as a mechanism of trying to demonstrate that the UK is an attractive place to do this sort of work in and then we'll partner with potential inward investors to either set up manufacturing, get clinical trials done, being the entry point into the European arena through the UK."* (Informant #15)

Findings also highlight differences in the emphasis and preference for *outcomes* between ecosystems. Edinburgh placed a greater emphasis on *outcomes* in comparison to Madison. In particular, informants in Edinburgh discussed regional economic development and innovation expectations arising from RM venturing activity: "*...make sure that the innovation coming out of Scotland is developed in Scotland, is manufactured in Scotland…that we have the economic benefit and we have the wealth gain and the health gain…it's to try and help developments stay in Scotland."* (Informant #11)

Informants in Edinburgh particularly focus on the timeframes involved in RM venturing. Some noted the conflict with policy expectations: *"...I think linked to the lack of understanding of the science, often the timescales for these end games are just not understood at all."* (Informant #1) Others noted the potential mismatch with investor expectations: *"...[the] time horizons of a VC investment just don't fit the time horizons of a development of a therapeutic…"* (Informant #10)

4.1.2. Differences between informant roles

Entrepreneurs and RM firms place a greater significance on *venture development* than academic scientists and support entities. RM venture development relies on the availability of resources and the RM business model. Findings show entrepreneurs and RM firms

extensively discussing the availability of financial resources. Informants reported that funding is accessible for RM research and development. Some funding is clearly linked to venture development: *"We've found that for this early stage activity, the Technology Strategy Board [UK government funding board] has been critical, they are a very good source of funding…the amounts of money are suitable for these early stage activities."* (Informant #16) The perception of funding accessibility may directly drive venture formation: *"And there was money available for seed funding to get started. And so that's how we ended up starting the company."* (Informant #25) Again, the link to scale-up funding, however, is less clear: "*... only large pharmaceutical companies can really afford to [bring a therapeutic to market]… it's a very expensive deal…we don't have that level and the amount of money required."* (Informant #13)

New ventures at the UI boundary require sufficient human capital. This is seen as a key driver to the growth of high-technology start-ups (Colombo *et al*, 2010). The academic founder may not possess the appropriate skills and capabilities necessary for commercialization (Venkataraman *et al*, 1992). Academics are also likely to lack the commercial experience that investors seek (Franklin *et al*, 2001), which suggests that new ventures need access to management with proven commercialization experience. However, there was strong support between informants in Madison that attracting the appropriate management team was problematic: *"…And so that is the challenge…. finding talented people to get us off the ground who are willing to take a risk…we have moved people here before and that can be harder. If they have no Midwestern ties, it's very hard to recruit to here."* (Informant #25)

Entrepreneurs and RM firms are clearly concerned with the assembly of resources in the venturing process. As a result, they place less emphasis on *university entrepreneurial culture* and *outcomes* than support entities and academic scientists. Since support entities

play an important role in establishing networks for RM venturing, they place greater emphasis on *collaborative knowledge* than RM entrepreneurs and firms and academic scientists.

4.2. Differences between informant roles across ecosystems

Comparisons of informant roles across the two ecosystems are shown in Table 5. Again, values are normalized and calculated as previously reported.

Table 5 here

Findings highlight less reference to *PEU* by entrepreneurs and RM firms in Madison than Edinburgh. Whilst funding uncertainties are highlighted in both ecosystems, Edinburgh faces particular challenges in acquiring angel and VC funding: "*We're too small for VC's but we're too big for angels."* (Informant #2)

Results show a greater reference to *university entrepreneurial culture* for entrepreneurs and RM firms in Madison. This may be explained by the discrepancy in informant roles across the datasets. Two entrepreneur informants in Madison had been academic scientists prior to starting the new venture. Academic scientists and support entities in Madison also make greater reference to *university entrepreneurial culture* in contrast to Edinburgh. Academic scientists in Madison appear to show stronger motivations towards venturing activity at the UI boundary.

We see less reference to *coping strategies* but more emphasis on *collaborative knowledge* across all informant roles in Madison than Edinburgh. In particular, findings emphasize the individual learning that has taken place: "*So, I'm kind of learning myself… My*

hope is that interacting with people like you and talking to other people that I learn something." (Informant #20)

Entrepreneurs and RM firms refer less to *venture development* in Madison than Edinburgh. In contrast, support entities and to some extent academic scientists in Madison place a greater emphasis on *venture development*. Across all informant roles in Madison, there is less discussion of *outcomes* in comparison to Edinburgh, particularly for academic scientists and support entities.

5. Discussion

Our cross-national comparative study contributes to research on entrepreneurial behavior, technology transfer and ecosystem development. We discuss these to emphasize both the key findings from our study as well as opportunities for further research.

5.1. Entrepreneurial coping strategies and institutional culture

Entrepreneurial behavior is driven by a variety of factors (Aldrich and Martinez, 2001; Alvarez and Barney, 2005). Entrepreneurs translating innovations from the university to industry experience significant changes in the role-identity profile that drives their beliefs and goals (George and Bock, 2008). The cultural context from which entrepreneurs emerge directly affects the cognitive framework and interpretation of information used to make decisions under uncertainty. The culture of the "parent" institution thus directly shapes the individual traits that drive entrepreneurial behavior (Hofstede, 1980; Mueller and Thomas, 2001).

A significant amount of university technology transfer takes place in fields with high levels of technological sophistication and correspondingly high levels of uncertainty. This is especially so for innovations in RM. Faced with irreducible uncertainty, participants in RM

entrepreneurial ecosystems must utilize coping strategies to continue to make decisions without viable risk-reward calculations. Entrepreneurial coping strategies are the behavioral patterns entrepreneurs employ to contextualize or make sense of non-resolvable venturing problems (Johnson and Bock, forthcoming).

Prior research shows that entrepreneurs utilize both problem-focused coping and emotion-focused coping responses (Carver *et al*, 1989; Lazarus and Folkman, 1984). Problem-focused coping is associated with internal locus of control and the entrepreneur's perception that further information gathering and analysis will resolve uncertainties or mitigate their impact. By contrast, emotion-focused coping is associated with external locus of control and the belief that some or all aspects of the situation are either out of the entrepreneur's control or at least not amenable to influence via the entrepreneur's efforts. This distinction is especially important in RM, where entrepreneurs often rely on collaboration and partnerships to access knowledge and develop key capabilities.

The cross-national comparison suggests that the profile of dominant coping strategies may vary across similar entrepreneurial ecosystems. Since coping strategies are driven by persistent beliefs and assumptions about the nature of the technology transfer process, the most likely driver of coping strategy profiles is the culture of the originating institution. Prior research has emphasized the critical role of context and originating culture to entrepreneurial behavior and sensemaking (e.g. Autio *et al*, 2014; Jennings *et al*, 2013). Our findings reveal differences between the dominance of originating university entrepreneurial culture and the application of coping strategies. We propose:

Proposition 1: Entrepreneurial culture at the originating institution is associated with coping strategies in the entrepreneurial ecosystem.

The ecosystem around Edinburgh presents higher levels of PEU, lower institutional entrepreneurial culture and a higher reliance on coping strategies. Participants in this ecosystem appear to rely more on emotion-focused coping than participants in the Wisconsin ecosystem. This has important implications for theories of entrepreneurial behavior at the UI boundary, including the prevalence of residual effects of institutional culture on the broader ecosystem. We further specify this relationship:

> *Proposition 1a: The level of entrepreneurial culture at the originating institution is negatively associated with the prevalence of emotion-focused coping strategies in the entrepreneurial ecosystem.*

> *Proposition 1b: The level of entrepreneurial culture at the originating institution is positively associated with the prevalence of problem-focused coping strategies in the entrepreneurial ecosystem.*

5.2. Entrepreneurial ecosystem characteristics

Ecosystem development is a multi-dimensional and idiosyncratic process. The structure and content of a given ecosystem emerges from a series of non-path-deterministic events and exogenous circumstances. Our findings suggest disparate paths for the observed ecosystems.

Distinctions between micro-level sensemaking and behavior across the ecosystems are clearly shown in Figure 1. The ecosystem around The University of Wisconsin-Madison demonstrates a stronger entrepreneurial culture associated with the university as well as an emphasis on collaborative knowledge development in the venturing process. By contrast, the ecosystem around The University of Edinburgh presents a stronger emphasis on coping strategies and venturing outcomes. These reflect important differences in underlying

dimensions of behavioral norms and translational approaches to technology commercialization and venture development.

Figure 1 here

RM venturing is disproportionately driven by individuals that are trained in academic institutions and that experience significant transitions when engaging in commercialization. While broad patterns for these transitions are consistent across institutions and ecosystems, the translational approach adopted by participants clearly varies across ecosystems. We therefore propose:

Proposition 2: The dominant translational approach of an entrepreneurial ecosystem is associated with the entrepreneurial culture of the originating institution and the utilization of collaborative knowledge development.

In the case of the RM ecosystem around The University of Wisconsin-Madison, the ecosystem combines a relatively strong entrepreneurial culture extant within the university with collaborative knowledge development. In other words, this ecosystem values a collaborative and opportunistic approach to translational activity. The ecosystem around The University of Wisconsin-Madison presents much lower levels of coping strategies and outcome emphasis. This is indicative of an improvisational approach, with less emphasis on behavioral change in the service of achieving specific goals. We propose:

Proposition 2a: Improvisational entrepreneurial ecosystems are associated with higher levels of entrepreneurial culture in the originating institution and increased utilization of collaborative knowledge development.

By contrast, the ecosystem around The University of Edinburgh is lower on entrepreneurial university culture and collaborative knowledge development. Entrepreneurs and other ecosystem participants rely on a more autonomous and focused approach to translating technologies across the UI boundary. The ecosystem around The University of Edinburgh emphasizes coping strategies and venturing outcomes. This suggests a reactive practice to addressing uncertainty.

Proposition 2b: Focused entrepreneurial ecosystems are associated with lower levels of entrepreneurial culture in the originating institution and decreased utilization of collaborative knowledge development.

5.3. The development paths of entrepreneurial ecosystems

Our study does not address performance outcomes at any level; we draw no conclusions at this time regarding whether specific translational or behavioral ecosystem profiles are correlated with the probability of success of entrepreneurs, TTOs, or ecosystems. At the same time, prior research on venturing, learning, industry and cluster development suggest implications for profile differences as well as opportunities for future research.

Generally speaking, knowledge creation and collaborative learning are associated with more rapidly developing ventures and clusters (Porter, 1998). As learning is time-dependent, a translational preference for autonomous learning may unintentionally delay the development of dynamic capabilities that underpin firm and ecosystem development (Jantunen *et al*, 2012; Teece, *et al*, 1997). Further, highly uncertain environments may necessitate trial-and-error learning in venture development (Loch *et al,* 2008; Sosna *et* al, 2010). Research on absorptive capacity also suggests that the sophisticated requirements of life science entrepreneurship make it unlikely that new ventures will possess adequate internal knowledge (Cohen and Levinthal, 1990; Zahra and George, 2002). The greater

emphasis on knowledge exchange and entrepreneurial culture within The University of Wisconsin-Madison, linked to a more improvisational and collaborative ecosystem, may suggest long-term venture growth and success.

On the behavioral side, the ecosystem around Edinburgh presents an apparently more adaptive approach to RM venturing activity. While improvisation may be effective in some entrepreneurial contexts (Moorman and Miner, 1998), especially under uncertainty, firms must implement consistent structures, routines and predictive systems to manage risks and scale value creation activities (Baker and Nelson, 2005). Greater reliance on coping strategies may be explained by the perception of greater uncertainty within the ecosystem. Although specific coping strategies differ across individuals (Carver *et al*, 1989), coping responses can be effective in reducing, acknowledging and suppressing uncertainty (Lipshitz and Strauss, 1997).

A dynamic model of ecosystem development represents an important step forward in our understanding of technology transfer and translation of innovation (Autio *et al*, 2014; Thomas and Autio, 2014). Based on the comparison of characteristics, we propose a two-dimensional model of entrepreneurial ecosystem development. Although an ecosystem may be described by a variety of characteristics, these appear to have direct relevance to venturing activity at the UI boundary. Figure 2 shows the model, incorporating Translation and Behavioral dimensions of ecosystems.

Figure 2 here

To address the dynamics of ecosystem development, we presume that an entrepreneurial ecosystem centered on a university must be initiated with a relatively autonomous approach to translation and an improvisational approach to behavior. At the very

earliest stages of university-based ecosystem formation in a sector that relies on long-term research, the innovations at the core of the nascent ecosystem originate within the university. While scientists and university or TTO administrators may be well-attuned to market factors and industry dynamics, early activities will necessarily require researchers with potentially commercializable activities to operate independently. This is because there will be little to no comparable entrepreneurial culture or activity related to that type of innovation. The entrepreneurial culture at the university must be strong enough to manifest at the departmental level (Rasmussen *et al*, 2014). Since there will be little or no extant infrastructure to support translational activities for a specific innovation type, either within or outside the university, the inventing entrepreneur's behavior is likely to be primarily improvisational. Again, either the university or the regional technology cluster may provide a context for adaptive behavior through mentoring schemes, support entities and prior success stories. At the same time, when innovations are novel and uncertainty high, identifying proven behaviors and processes becomes more difficult. This is precisely the situation in RM.

The ecosystem around Madison has developed more collaborative translational approaches, while the ecosystem around Edinburgh has developed more adaptive behavioral norms. It is important to emphasize that this picture of ecosystem development does not reflect a purely linear process or a specific rate of development. On the other hand, the relative novelty of RM research and commercialization activity (see Table 1 for the relatively low number of RM patents compared to the overall portfolio of the TTOs) reinforces that these ecosystems are still relatively early-stage.

Despite significant surface-level similarities between the industrial-geographic regions around the universities, key differences should be noted. Collaborative effects in the Wisconsin ecosystem may benefit from WARF's extensive technology transfer history and the prior experience of numerous life science spinouts with exit events (e.g.

Nimblegen/Roche, Tomotherapy/Accuray, Lunar/GE, BoneCare/Genzyme and others) in the area. Although both areas have relatively limited VC resources (compared to other life science venturing hubs), numerous life science ventures in the Madison ecosystem have obtained mid- and late-stage investments from VC firms in California and the U.S. East Coast.

Our model suggests that entrepreneurial ecosystem development at the UI boundary is a dynamic and path independent process. The development of the ecosystem is both a driver and outcome of the nature and type of entrepreneurial coping strategies prevalent within the ecosystem. Coping responses are particularly important to *de novo* ventures, especially at start-up, as they assist in resource and knowledge identification and access. Since cultural artifacts and ecosystem specific factors affect coping responses, similar ecosystems may generate significantly different behaviors for knowledge and learning. It is not sufficient to characterize an ecosystem's configuration of resources and prior history to understand how the ecosystem is likely to develop further. The interplay of the central university's entrepreneurial culture and the dominant coping strategy profile of the ecosystem will be tightly linked to the ecosystem's locus of attention and collaborative knowledge emphasis.

Our findings have important theoretical and practical implications. We advance theories of UI technology transfer by presenting cross-national findings on the characteristics and dynamics of entrepreneurial ecosystem development under irreducible uncertainty. We further inform institutional entrepreneurship and technology transfer literature by developing specific propositions linking originating culture to resulting characteristics of the ecosystem.

We also extend research linking entrepreneurial cognition and sensemaking to ecosystem development (Wright *et* al, 2012b). Our findings highlight individual-level coping responses to institutional culture and high levels of uncertainty. We have shown coping strategies to be important for resource and knowledge acquisition and assembly. All of these

factors are implicated in the process and outcome of new venture development at the UI boundary. These findings further emphasize the importance of the entrepreneur and entrepreneurial cognition in ecosystem development and competiveness. This is consistent with prior research (Feldman, 2014) but presents entirely new directions for further study of coping strategies and collaborative activities. In particular, our findings help identify the specific mechanisms that drive entrepreneurial decision-making in fields of high uncertainty, emphasizing that university policy and culture plays a critical role in ecosystem outcomes (Audretsch *et al*, 2014; Audretsch *et al*, 2013; Wright, 2013).

5.4. Limitations and research directions

Certain limitations in this research must be kept in mind in the interpretation of the study. First, the datasets are relatively small and may not effectively capture the situational perspective of the entire ecosystems. Second, open coding has specific limitations, including the potential for biasing effects of prior researcher knowledge. Third, the datasets were coded asynchronously. It is possible that synchronous coding of the datasets in a randomized order might have generated a slightly different data structure. Since our data is not longitudinal or time-synchronized, we cannot address potential differential rates of ecosystem development between ecosystems.

The inductive, theory-driven approach was suitable for the development of novel phenomena. At the same time, our findings should be tested empirically to identify the strength of relationships and impact in context. We have shown how cognition and behavior of ecosystem participants is important for ecosystem development with potentially long-term effects on firm and ecosystem competitiveness. We hope to see large-scale, quantitative research that tests for the cognitive and behavioral characteristics in entrepreneurial ecosystems, as well as ecosystem development processes.

Our findings report on entrepreneurial ecosystem development of two similar but distinct ecosystems. While Edinburgh and Madison present close similarity, the difference in TTO activity between these two ecosystems warrants further analysis, since this will be implicated in ecosystem development. Given that we could not control all target variables between ecosystems, additional research could extend to other similar ecosystems. It would also be interesting for future research to investigate more established ecosystems in other industries and RM ecosystems in larger and more well-resourced industrial-geographic or non-western regions, in order to reveal differences in ecosystem development.

6. Conclusion

This study presents a cross-national analysis of ecosystem development under irreducible uncertainty. We use qualitative analysis of interview data collected from distinct but similar entrepreneurial ecosystems in the RM field. The results suggest that university culture and PEU impact the characteristics and development path of entrepreneurial ecosystems. The findings point towards important new theories of entrepreneurial ecosystem development and micro-level entrepreneurial behavior at the UI boundary.

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Tables and Figures

Table 1. Institution and regional economic data

	University of Edinburgh / Edinburgh / Scotland	**University of Wisconsin-Madison / Madison / Wisconsin**
University student population	30 579	43 275
Annual research budget	$458 million	$1 billion
Metropolitan population	Edinburgh: 495 360	Madison: 240 323
City status	Capital of Scotland	Capital of Wisconsin
State/Region population	Scotland: 5 295 000	Wisconsin: 5 726 000
GDP for region	Scotland: $216 billion	Wisconsin: $261 billion
Significant local industries	Finance, insurance, health, education, agriculture, tourism, whiskey	Insurance, health, education, agriculture, tourism, machinery
VC in region	<5	<5
School/College of Medicine research and academic faculty #	2594	4447
University research income	$506 million	N/A
University research expenditures	N/A	$1.2 billion
Medical research expenditures	Estimated $175 million	$333 million
TTO activity (funding, patents)	TTO founded in 1969. 423 patents filed 2007-2012. $5.6 million license/royalty income in 2011.	TTO founded in 1928. 2300 patents granted. $57.7 million license/royalty income in 2011.
License/spinouts	Currently maintains 160+ commercial license agreements. 171 spinout/start-ups since 1969.	Currently maintains 380+ commercial license agreements. 280+ spinout start-ups since founding.
RM patents granted between 2009-2011	9	15
RM publicity	Dolly the sheep	Jamie Thomson, WARF

Note: All data for 2012-2013 unless otherwise noted.

Sources: University of Wisconsin-Madison and subsidiary School/College websites; University of Edinburgh and subsidiary School/College websites and Annual Report; Scottish and Wisconsin Government websites (including UK Intellectual Property Office); and Milwaukee Journal-Sentinel.

Table 2. Study informant and organization information

Informant #		Category	Informant role	Organization type
Edinburgh	1	SE	Executive	Provides support to the RM community. Government-backed initiative.
	2	E/RMF	Founder	Main operations are in tools/diagnostics. Also, offer services to other organizations and are actively developing in the cell therapy space.
	3	E/RMF	Manager	Involved in providing stem cell technical support and services to other organizations.
	4	E/RMF	Founder	Primarily involved in providing stem cell training and consultancy to other organizations.
	5	AS	Manager	University academic scientist (Principal Investigator).
	6	SE	Manager	Governmental organization to encourage economic growth in Edinburgh.
	7	SE	Executive	Supports academic innovation and commercialization.
	8	SE	Manager	Supports technology transfer and innovation.
	9	AS	Executive	University academic scientist (Principal Investigator).
	10	E/RMF	Founder	Operates in RM products and services.
	11	SE	Manager	Generate economic growth for Scotland through supporting a life science community.
	12	SE	Manager	Supports a healthcare community and enable innovation.
	13	E/RMF	Founder	Operates in the RM tools and diagnostics space.
	14	E/RMF	Founder	Biotechnology and stem cell services organization.
	15	SE	Executive	Establishing a cell therapy industry and community.
	16	E/RMF	Executive	Products and services organization with operations in stem cell space.
	17	SE	Manager	Supports innovation and economic development in Scotland.
	18	SE	Manager	Supports economic growth in Edinburgh and Scotland.
Madison	19	SE	Manager	Supports technology transfer and company formation.
	20	E/RMF	Founder	Operates in the RM tools space with therapeutic potential.
	21	E/RMF	Founder	Operates in the RM tools space with therapeutic potential.
	22	SE	Manager	Supports regional economic growth.
	23	SE	Executive	Supports scientific and technological innovation.
	24	SE	Executive	Supports new venture creation and growth.
	25	E/RMF	Founder	Operates in the tools and diagnostics space. Also, developing stem cell therapeutics.
	26	SE	Manager	Supports technology transfer and innovation.
	27	AS	Executive	University academic scientist (Principal Investigator).
	28	AS	Manager	University academic scientist (Principal Investigator).
	29	SE	Executive	Supports technology transfer and innovation.
	30	SE	Senior Manager	Supports company investments.

E/RMF -- entrepreneur and regenerative medicine firm
AS -- academic scientist
SE -- support entity

Table 3. Data Structure

Prevalence in study sample (%)*			First-Order Codes	Theoretical Categories	Theoretical Dimensions
Total	**ED**	**MSN**			
57	61	50	Risk	Types of uncertainty	**Perceived environmental uncertainty (PEU)**
77	67	92	Funding issues		
30	44	8	Manufacturing, scale-up and distribution uncertainty		
47	44	50	Regulatory uncertainty		
30	28	33	Scientific uncertainty		
27	28	25	Ethics		
13	17	8	Reimbursement uncertainty		
33	28	42	Academic conflicts	Inventing entrepreneurs	**University entrepreneurial culture**
40	28	58	Academic motivations		
23	22	25	Academic metrics		
30	17	50	TTO business models and processes	TTO business models and processes	
73	89	50	Collaborations with industry	Collaborative partners	**Coping strategies**
63	72	50	Collaborations with academia		
30	44	8	Collaborations with hospitals		
37	44	25	Collaborations with support entities		
33	44	17	Collaboration for sharing of resources	Collaborative outcomes	
20	28	8	Collaboration for process improvement		
13	11	17	Collaboration for funding purposes		
7	11	0	Collaboration costs		
3	6	0	Collaboration for legitimacy building		
47	56	33	Legitimacy building	Legitimacy building	
60	56	67	Knowledge transfer	Resource exchange mechanisms	**Collaborative knowledge**
63	61	67	Communication		
33	22	50	Learning		
23	28	17	Language differences		
60	61	58	RM and scientific communities	Networks	
73	89	50	Governmental funding	Funding sources	**Venture development**
47	44	50	Angel/VC funding		
23	28	17	"Big pharma" funding		
60	67	50	Spinout venture formation	Spinout venture formation	
47	33	33	Business models	Business models	
87	78	100	Resources	Existing resources	
17	28	0	Innovation	Economic development	**Outcomes**
27	28	25	Regional investment and growth		
67	83	42	Commercialization timeframes	Future scenarios	
10	11	8	Potential industry structure		

***** Does not account for multiple occurrences within a single interview

Table 4. Ecosystem and informant role comparisons

	ED	MSN	Entrepreneurs/ RM firms	Academic scientists	Support entities
PEU	18%	15%	19%	19%	14%
University entrepreneurial culture	5%	18%	4%	15%	12%
Coping strategies	21%	14%	20%	19%	18%
Collaborative knowledge	13%	19%	9%	13%	21%
Venture development	32%	29%	43%	23%	25%
Outcomes	11%	5%	5%	11%	10%
Total (%)	**100**	**100**	**100**	**100**	**100**

Table 5. Informant role across ecosystem comparisons

	Entrepreneurs / RM firms		Academic scientists		Support entities	
	Ed	**Msn**	**Ed**	**Msn**	**Ed**	**Msn**
PEU	21%	14%	19%	20%	15%	13%
University entrepreneurial culture	0%	19%	10%	20%	9%	17%
Coping strategies	21%	18%	23%	16%	21%	12%
Collaborative knowledge	7%	16%	10%	16%	20%	22%
Venture development	46%	31%	23%	24%	21%	30%
Outcomes	5%	2%	15%	4%	14%	6%
Total (%)	**100**	**100**	**100**	**100**	**100**	**100**

Figure 1. Comparison of micro-level factors across ecosystems

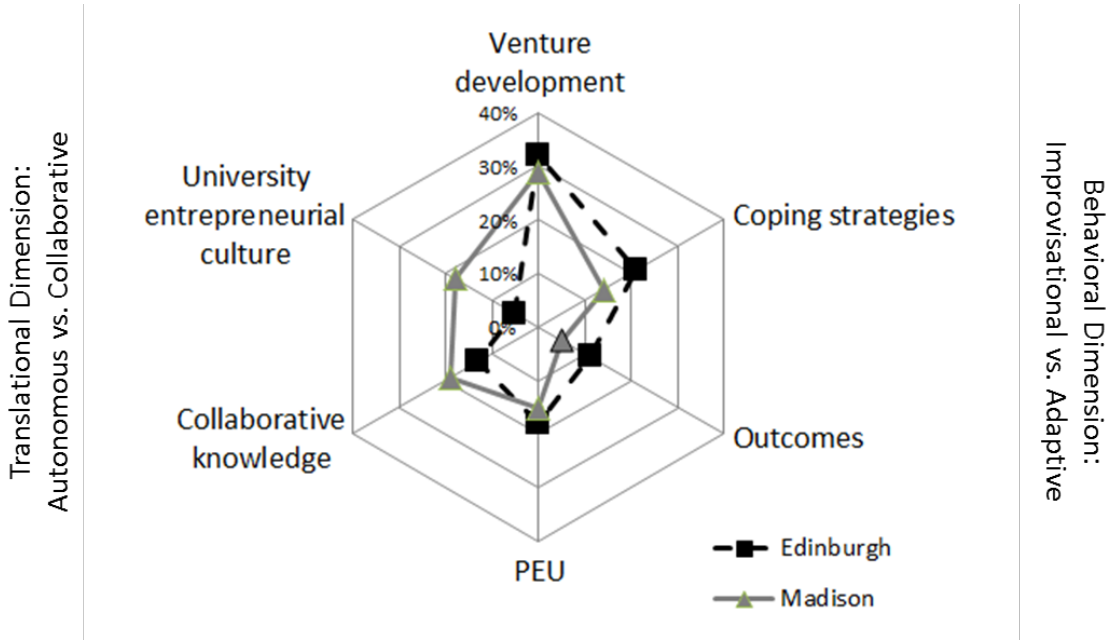

Figure 2. Model of regenerative medicine venturing ecosystem development