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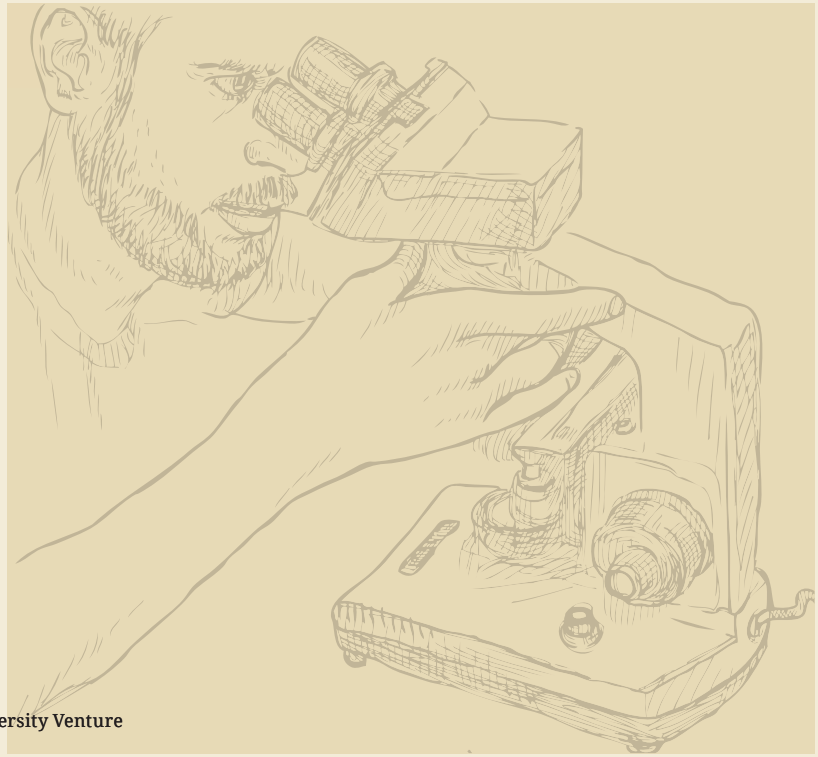
THE UNIQUENESS OF STEM CELL ECOSYSTEMS

LESSONS IN MATCHING LOCAL CULTURE: WISCONSIN, EDINBURGH, SKOLKOVO



Introduction

While Univenture ecosystems present an exciting vision for economic development, policy and practice should be grounded in reality. The truth is that a limited number of hyper-successful university spin-outs hide real challenges and mediocre economic outcomes. There is, in fact, limited evidence to support university venturing as a critical driver of technology-based economic development. Beyond outlier successes at a handful of institutions — most notably Stanford and MIT/Harvard — the link between university innovation and economic development is tenuous. In the U.S., US$65 billion of annual university R&D leads to fewer than 1,000 new companies each year. Outliers such as Google (Stanford), TomoTherapy (Wisconsin), Wolfson Microelectronics (Edinburgh), and Momenta Pharmaceuticals (MIT) overshadow the majority of university ventures that fail.

SUCCESSES BUILD CAPACITY, BUT FAILURES DRIVE MARKET-CENTRIC LEARNING AND INNOVATION

The success stories of venture and Technology Transfer Offices (TTOs) are inspirational but present a biased and potentially counterproductive lens for understanding ecosystems. Successes build capacity, but failures drive market-centric learning and innovation. To date, guidance for nurturing university venturing ecosystems has tried to avoid the hard truths about ecosystem dynamics and the value of failure. Globally, the average university TTO does not generate positive returns from licensing or spin-out activity. Spin-outs are sexy, and successful academic entrepreneurs are heroes, but big successes are rare. From 1990-2005, two spin-outs generated 80% of Stanford's returns from all of its equity licensing activity. In the long-run, building sustainable technology ecosystems at the university-industry (U-I) boundary requires a different perspective.

There are numerous policy puzzles in nurturing entrepreneurial ecosystems based on university venturing. For example, prior research shows that university spin-outs take longer to "graduate" from incubators than other technology ventures. TTO policies designed to protect intellectual property, such as tight control over licensing processes, can limit knowledge exchange and spillovers. Efforts to copy successful ecosystem policies have relatively poor track records; most university venturing ecosystems have not generated widespread economic benefits. Using the backdrop of the regenerative medicine (regenmed) sector, focused on stem cell technologies, we examine these puzzles. We propose solutions, including specific tactical choices and options available to university and government policymakers.

1. University Venturing in Regenerative Medicine

Prior studies of venture formation, funding activity, and economic impact have focused primarily on ecosystem growth factors. Here, we explore the drivers of entrepreneurial choice and behavior that explain *why* ecosystems evolve in specific ways. Focusing on regenmed, which is dominated by university-led research activity, highlights the unique circumstances of ecosystems at the U-I boundary.

To examine entrepreneurial ecosystems at the U-I boundary we studied three nascent regenmed ecosystems. The University of Wisconsin-Madison (Madison, U.S.) is a global leader in stem cell research, home to Professor James Thomson who first isolated primate and human stem cells. The University of Edinburgh (Scotland, U.K.) has regenmed research history dating to Dolly the Sheep and is a top five European medical research institution. The Skolkovo Institute of Science and Technology (Moscow, Russia) is a new model for an innovation-centric university at the heart of an entrepreneurial ecosystem, created in partnership with MIT.

Over a three-year period, we conducted dozens of in-depth interviews with regenmed entrepreneurs, stem cell company executives, academic scientists, and the managers of regional venturing support to provide rich snapshots of the real-world venturing context at the U-I boundary. We developed characteristic profiles to understand the role and influence of each university on the

THE RISE OF UNIVERSITY VENTURING IN REGENERATIVE MEDICINE

Stem cell-based regenerative medicine (regenmed) is defined as the *"process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage or congenital defects"* (NIH, 2006). Stem cells are undifferentiated cells that can be induced to become tissue or organ-specific cells. They can be categorized into three main groups: tissue stem cells, embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs).

Estimates suggest that total stem cell research and market activity will exceed US$100 billion by 2020. From 2008-2011, there were 3,134 published and 777 granted patents having WO, US, EP and GB designations. Japan was the top for published patents, with the U.S. leading in granted stem cell patents. Billions of dollars are being invested in research and development amidst shifting government policies, complex lawsuits, and uncertain regulatory requirements.

Corporate R&D in regenmed, however, is dwarfed by public sector investing. In the U.S., the NIH spends approximately US$1.5 billion/year on regenmed, primarily through university research. Not surprisingly, most stem cell innovations are linked to long-term university research programs. Entrepreneurial activity in regenmed is highly concentrated in small ecosystems centered on academic institutions. Uncertainty about commercially viable stem cell business models has focused investment in technology innovation rather than experienced teams and manufacturing scale-up. This has encouraged academic entrepreneurs to launch companies, but hints at high rates of failure for stem cell ventures. The Alliance for Regenerative Medicine (ARM) identified more than 700 regenmed companies operating around the world, most with direct ties to universities, and more than US$2 billion in private and public equity funding invested.

evolution of the broader system, and we explored the key issues, assumptions, and behavioral drivers operating within the ecosystems.

2. Solving Univenture Puzzles

We suggest a different vision for the role of TTOs and government agencies hoping to foster entrepreneurial ecosystems based on university venturing. We identify and discuss solutions to four policy "puzzles" that challenge the conventional wisdom around entrepreneurial ecosystems at the U-I boundary.

Puzzle solution 1: Support the ecosystem first, the innovation last
Universities often shelter nascent innovations and ventures, "protecting" them from market forces. Preventing premature disclosure to safeguard patent prosecution is fully justified. Shielding innovations from market feedback, however, can only

IN GENERAL, UNIVERSITY TECHNOLOGY INNOVATIONS CANNOT BE EFFECTIVELY EVALUATED FOR COMMERCIAL SUCCESS

increase the probability of a product-market mismatch. Innovations licensed from universities fail three to four times more often than innovations licensed from corporations. In general, university technology innovations cannot be effectively evaluated for commercial success because they are too early and have not been tested against customer and market needs.

One of the most telling misconceptions about university venture ecosystems blames slow development on a lack of venture capital for early-stage and growth funding. The irony is that spin-outs that obtain venture capital are more likely to be acquired and leave the ecosystem, often drawing the ire of university and regional policymakers. Venture capitalists are often blamed for indirectly "culling" out ventures with low probability of success, even though this is precisely what keeps the ecosystem vibrant.

Table 1: Stem Cell Ecosystems

Source: Author analysis

ECOSYSTEM	MADISON (UW-MADISON)	EDINBURGH (UNIVERSITY OF EDINBURGH)	MOSCOW (SKOLKOVO)
Stage of development	Growth	Early	Embryonic
University research	US$1.2 billion	US$458 million	<US$180 million
University medical research	>US$300 million	~US$175 million	<US$25 million
TTO activity	TTO founded in 1928. 2,300 patents granted. US$57.7 million license income in 2011. Currently 380+ commercial license agreements. 280+ start-ups since founding.	TTO founded in 1969. 423 patents filed 2007-2012. US$5.6 million license income in 2011. As of Q2 2016, 160+ commercial license agreements. 171 start-ups since founding.	TTO founded in 2013. Limited activity to date.
2012 VC investment	US$25 million	US$42 million	>US$318 million
Strengths	Entrepreneurial university culture; key success stories (e.g. CDI); problem-based coping strategies; very large medical research base	Extensive government support; large medical research base; biopharma collaborations	Relationship with MIT; entrepreneurial culture designed from within; significant risk capital pool
Weaknesses	CDI acquired by Fuji; tightly controlled IP regime; somewhat limited risk capital pool; over-emphasis on supporting early-stage innovations	Limited entrepreneurial culture; few success stories; very limited risk capital pool; emotion-based coping strategy; EPIS program terminated	Overdependence on MIT policies inappropriate for embryonic ecosystem; limited dedicated infrastructure; limited biotech collaborations
Development requirements	Increased knowledge collaborations with industry; experiential entrepreneurial training	Nurture entrepreneurial university culture and ecosystem infrastructure	Customized tech transfer and venturing policies specific to Russian industry strengths

In natural ecosystems, rapid cycle rates increase the rate of adaptation. The same is true for industries: fast failure cycles increase the rate of innovation. Equally important, entity types are not equally distributed among growing and sustainable ecosystems. In a technology-based entrepreneurial ecosystem, innovations and entrepreneurs are significantly more common than ventures, collaborator firms, and financiers.

Figure 1 shows the reality of "university ventures" in the broader entrepreneurial ecosystem. In general, universities and TTOs should emphasize the role of the ecosystem in evaluating the commercial potential of innovations and facilitate market-based feedback and investment. Promoting specific innovations effectively encourages short-term, high-risk investments. Universities and policymakers should encourage and

WE OBSERVED TWO DISTINCT CATEGORIES OF ENTREPRENEUR BASED UPON COPING STRATEGIES

subsidize relationships and collaboration within and across the ecosystem. This is an investment well-aligned with the long-term mission and capability of research universities.

But even aligning university venturing ecosystem participants is no easy task. Participants, especially government entities and university administrations, may default to common ground on ecosystem inputs without clear outcome metrics or accountability. In regenmed, which combines significant infrastructure requirements and high uncertainty, it is significantly easier for participants to agree on physical rather than intangible investments.

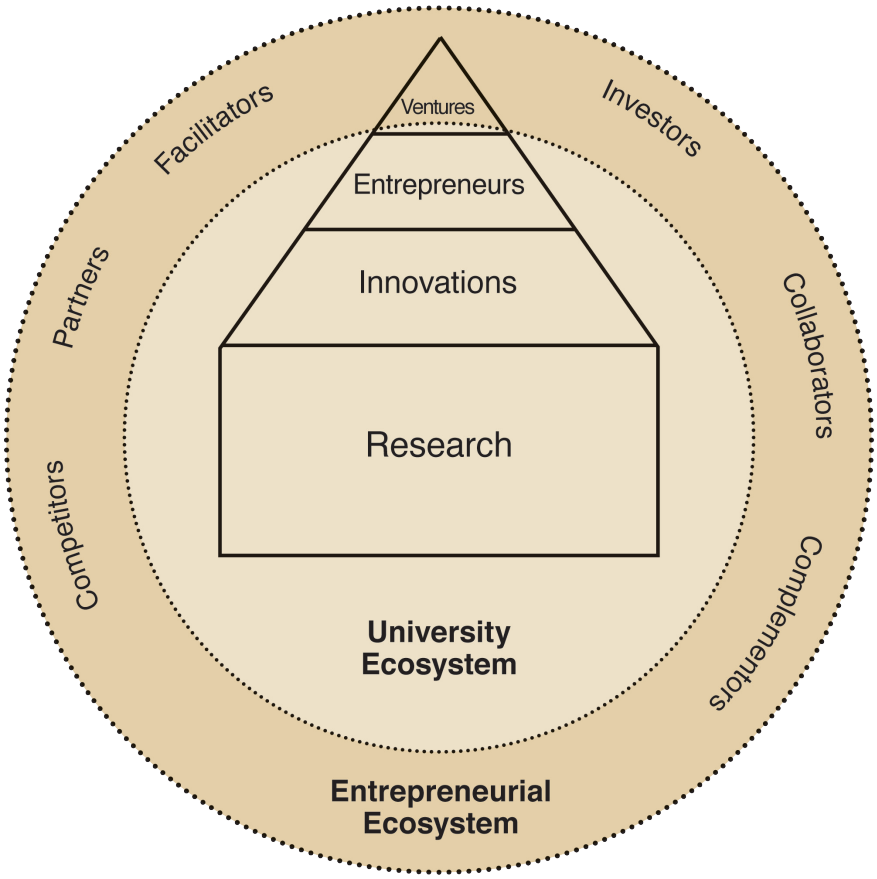
In Wisconsin, Scotland, and Moscow, collaboration between the university and government led to large investments in special-purpose stem cell research facilities, theoretically to promote translational work and reduce the time from "bench-to-bedside."

The Wisconsin Institute for Discovery, Scottish Centre for Regenerative Medicine, and Skoltech Center for Stem Cell Research all represent large-scale investments to

facilitate world-class research, advance stem cell and regenmed science, and encourage entrepreneurial activity. The value of these investments has been difficult to demonstrate, in part because the facilities have primarily served as extensions of existing research programs. Rather than help build the entrepreneurial ecosystems, these investments primarily extend the research base of their respective universities. They are a step in the right direction, but support the university more than the ecosystem.

Figure 1: University Ventures in an Entrepreneurial Ecosystem

Source: Author analysis



Puzzle solution 2: Encourage entrepreneurs — but equip them for failure

Entrepreneurs operating at the U-I boundary face the maximum of uncertainty with the minimum of resources. In regenmed, where legal and regulatory frameworks have yet to be fully standardized, this challenge is heightened. In our study, we observed two distinct categories of entrepreneur based upon coping strategies. Emotion-based entrepreneurs ignore or avoid uncertainties while problem-based entrepreneurs address uncertainties in a step-wise fashion.

An emotion-based coping strategy can be effective in the short-term because it facilitates decision-making over paralysis. Viewed through the ecosystem lens, however, it is counterproductive, because it encourages entrepreneurs to revert to personal affinities and preferences. Emotion-based entrepreneurs are more likely to lead

NEW UNIVERSITY VENTURES ARE ESPECIALLY DEPENDENT ON PARTNERSHIPS AND COLLABORATIONS

low-growth lifestyle businesses or even so-called "zombie" companies that lock up ecosystem resources rather than accept that an invention has failed in the market.

The good news is that our research highlighted the core cultural environment of the parent university to strongly influence the coping strategy of entrepreneurs operating at the U-I boundary, especially university ventures. When the university has promoted an entrepreneurial culture, spin-out founders and other ecosystem participants were more likely to use problem-based coping strategies. These entrepreneurs are both resilient and adaptive, increasing the net entrepreneurial capacity of the ecosystem.

The bad news is more complicated. Propagating entrepreneurial culture throughout a large, research-based institution is an enormous challenge. Ruth Graham's Ecosystem study (see Further Resources) addresses this in powerful detail. However, the real challenge goes beyond

encouraging an entrepreneurial mindset. University and government policymakers must accept the importance of venture failure.

Failure is a necessary and valuable process. Fast rates of failure accelerate adaptation and innovation, and prevent critical resources (human, technological, and financial) from being locked up in ventures with low potential. Instilling a tolerance for failure, specifically fast failure, into the institution and the ecosystem requires at least two policy changes:

- First, TTOs and universities should openly acknowledge failed innovations and ventures rather than hide them. They should focus metrics of success on the research side of the R&D equation: disclosures, patent applications, issued patents, licenses, and spin-outs. While celebrating successful licenses and spin-outs is entirely appropriate, TTOs need to find ways to celebrate failure as well.
- Second, universities' entrepreneurial "training" programs tend to emphasize basic business skill-building rather than decision-making and coping strategies. Core business skills certainly do not hurt entrepreneurs, but are the easiest to hire from the ecosystem. By contrast, scarce capabilities include engagement with the market, decision-making under uncertainty, and coping with failure. In other words, universities should teach entrepreneurship and promote an entrepreneurial culture to enable success, but someone needs to train inventors and early-stage entrepreneurs to embrace failure. Such training must be primarily experiential rather than classroom-based.

Puzzle solution 3: Promote knowledge exchange across boundaries

Successful ecosystems rely on the ebb and flow of people, resources, and information across ecosystem boundaries. Institutions and clusters with closed boundaries risk becoming islands of ignorance, systems of self-reinforcing misinformation about market needs and scale-up requirements. New university ventures are especially dependent on partnerships and collaborations. The specialized knowledge requirements at these ventures limits internal bandwidth for market-facing activities; university ventures need reciprocal knowledge-sharing relationships to match innovation characteristics to specific customer needs.

In our study, we found that emotion-based coping strategies were associated with lower levels of knowledge exchange. This links poor entrepreneurial culture at the parent university to ineffective knowledge exchange in the ecosystem. This is a self-reinforcing cycle where tightly-held technologies and ideas do not get real-world feedback until it is too late. Academic entrepreneurs are often enamored with their innovations and unwilling to seek out, or accept, guidance on commercialization. New university ventures often avoid knowledge exchange out of fear that a collaborator could become a competitor. TTOs sometimes unintentionally inhibit knowledge exchange with restrictive licensing terms.

Knowledge exchange is the process for enabling knowledge spillovers, a key economic growth driver in the Triple Helix model linking academia, industry, and government. A broken Triple Helix

EDINBURGH'S PRE-INCUBATOR SCHEME WAS SUCCESSFUL BECAUSE IT DID NOT ATTEMPT TO FILL THE MISSING GAPS IN THE ECOSYSTEM

fails to capture the economic outcomes of innovation. TTOs should set the example by building and maintaining relationships with industry participants to vet and test innovations, creating early exposure to market needs and forces. For example, "Catalyst" groups at the Wisconsin Alumni Research Foundation (WARF) and MIT's Deshpande Center provide a mechanism for connecting inventions and inventors with experienced executives. Catalysts review patenting activity and recent inventions, providing real-time feedback to both the TTO and inventors about market trends, partnering opportunities, and nascent customer needs. Universities and local economic development entities can

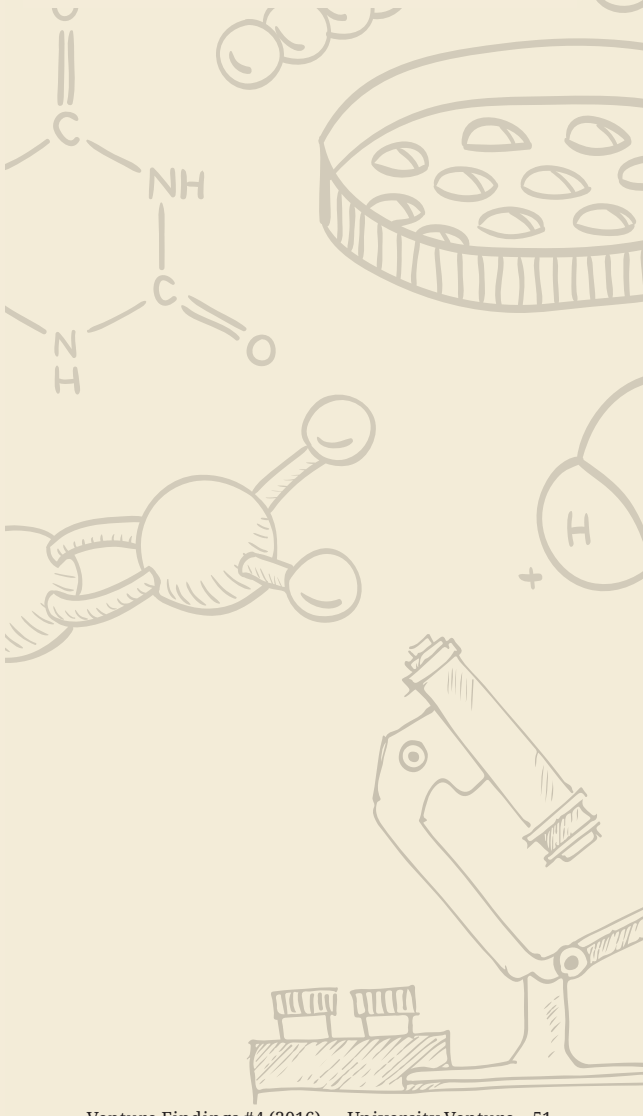
encourage knowledge exchange through a variety of activities, including events that bring together disparate participants in the ecosystem.

Puzzle solution 4: Customize and align rather than copy

Perhaps the greatest challenge in nurturing nascent entrepreneurial ecosystems is avoiding the pressure to copy practices from mature ecosystems. "Best practices" in ecosystem analysis is a misnomer because ecosystems are not, at the core, directly comparable. While policymakers have encouraged successful entrepreneurial ecosystems to be copied, our research suggests that this strategy is fundamentally flawed. Suggesting, for example, that the entrepreneurial regenmed ecosystem in Madison, Wisconsin, is simply at an earlier stage than the ecosystem around Stanford misses the point. There is probably no reasonable scenario in which the Madison ecosystem "evolves" into the Stanford ecosystem because of the vast differences between their respective industrial, geographic, and economic contexts.

The Edinburgh-Stanford Link provided clear evidence for this. The effort, funded by the Scottish government, attempted to replicate Stanford's entrepreneurial culture and technology venturing activity. Numerous Silicon Valley ecosystem participants were brought to the University of Edinburgh to "transplant" the Stanford ecosystem to Edinburgh, one of the top computer science programs in Europe. But the Edinburgh ecosystem was incomplete: it possessed few professional managers in the information technology sector, extremely limited growth capital, and few extant collaborator firms or acquirers. When the funding ended, the program had few tangible outcomes.

By contrast, the Edinburgh Pre-Incubator Scheme (EPIS) was well-suited to the nascent nature of the University of Edinburgh venture ecosystem. At the time, Edinburgh's ecosystem had few sophisticated resources for entrepreneurs, a very limited population of managers with technology-based growth ventures expertise, and very limited venture capital. EPIS was successful because it did not attempt to fill the missing gaps in the ecosystem. The program provided more than 300 "assists" — consultations to potential entrepreneurs — but only supported the launch of 50 actual ventures. EPIS did not try to select "winning" innovations or provide unmanaged venture capital. The program provided interest-free loans that resulted in self-selection by committed entrepreneurs. The nascent ventures had a limited time frame to hit specific product development or sales milestones. EPIS resources were focused on linking the entrepreneurs directly to customers or industry experts. Rather than protect the innovations and ventures, EPIS encouraged knowledge-sharing across the ecosystem boundary, forcing the projects and ventures to develop, or fail, quickly. This allowed resources from "failed" projects to be recycled within the ecosystem, which is particularly important for the development of entrepreneurial ecosystems.



CONTRASTING NATIONAL MODELS OF ECOSYSTEM DEVELOPMENT

International comparisons of regenmed activity are not obvious, because of significant disparities in funding mechanisms, regulatory frameworks, and national policies. The U.S., China, South Korea, Germany, and the U.K. are generally considered global leaders by total research, investment, and publication activity. Although wide variation exists across these countries, all rely on varying mixes of government support funnelled primarily through university research projects.

Most ecosystems in the U.S. and European Union (EU) have formed around research universities with significant federal and state funding for stem cell studies. Significant differences exist across those ecosystems. While venture capital has driven venture development in the U.S., government support has primarily played this role in the U.K. and Germany. China's unique economic structures and relatively lax regulatory frameworks have enabled extensive clinical trial activity and, more recently, development partnering with Western biopharma. South Korea has advanced stem cell research programs and arguably has the best-specified regulatory process, with three approved treatments on the market.

Japanese multinationals, fuelled by government support, are acquiring their way to a leading-edge ecosystem. Fuji purchased Cellular Dynamics International (CDI), a world-leading stem cell venture spun out of the University of Wisconsin-Madison, for US$307 million. Astellas Pharma recently purchased U.S.-based stem cell company Ocata Therapeutics in a deal valued at US$379 million. Takara purchased Cellectis (Sweden) and Clontech (U.S.) to bolster stem cell-related tools and development. ReproCELL acquired Stemgent's iPS business (U.S.), Biopta (U.K.), Reinnervate (U.K.), and BioServe (U.S.).

An interesting contrast with Japan is found in Israel. Despite limited government support and modest university research programs, Israel has strong representation at international conferences and is fifth in the world for clinical trials. In 2014, the California Institute for Regenerative Medicine and MATIMOP (the Israel Industry Center for R&D) signed a collaborative research agreement specifically focusing on early clinical trials. Gamida Cell recently signed a US$35 million investment deal with Novartis while Kadimastem signed a collaborative agreement with Merck Serono to advance research into neurodegenerative diseases.

Conclusion: Culturing Healthy University Venturing Ecosystems

Should university venture entrepreneurial ecosystems strive for the level of success observed at MIT and Stanford? Absolutely. But ecosystem evolution takes time, and simply copying "best practices" ignores critical differences in culture and entrepreneurial context. University and government policymakers need to build customized programs, systems, and policies to support those ecosystems, based on local strengths and stage of development. The hard truth is that copying elements from outlier successes is a bit like using a few specific ingredients from a complex recipe and hoping to cook the same dish.

It is useful to note the high-level perspective from one of the most successful institutions. Jon Sandelin, of Stanford's Office of Technology Licensing, specifically noted in 2005: "Fourteen percent of the companies in which Stanford has taken equity have failed... Two [successful] companies generated more than 80% of the total amount of cashed-in equity... As is true for licensing in general, when licensing and supporting spin-outs, *the focus should not be on how much income can be generated, but on the value flowing from a new partnering relationship... and on the public benefits from the products and services the spin-out may produce.*"

OUR RESEARCH STRONGLY SUPPORTS THIS ECOSYSTEM-ORIENTED PERSPECTIVE

Our research strongly supports this ecosystem-oriented perspective. Healthy entrepreneurial ecosystems at the U-I boundary depend on the university adopting a market-facing approach to venturing activity. A culture that encourages entrepreneurship but accepts failure provides the best context for knowledge collaboration across ecosystem boundaries. Policies that support the health of the ecosystem, rather than the success of specific innovations, are the most likely to generate long-term benefits.

FURTHER RESOURCES

Bock, A.J. & Johnson, D. (2015) Entrepreneurial ecosystems: Fixing the triple helix. *The European Business Review*. Nov/Dec: 70-74.

Graham, R. (2014) Creating university-based entrepreneurial ecosystems: *Evidence from emerging world leaders.* MIT-Skoltech Initiative.

Krattiger, A. et al. (2007). *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices.*

Stem cell therapy developed: #HOV8125 *in CIV's History of Venture database*