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Scaling up in Entrepreneurial Ecosystems: A comparative study of Entrepreneurial Ecosystems in Life Science

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Keywords

Entrepreneurial Ecosystem, scale-up, high-growth firms, Life Sciences, Sweden, U.S.

JEL codes: L26 Entrepreneurship; M21 Business Economics; O33 Technological change: choices and consequences, diffusion processes

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1. Introduction

The Entrepreneurial Ecosystems (EE) literature has been evolving fast in recent years (Alvedalen and Boschma 2017; Stam and Spigel 2017). It has generated important insights with respect to favorable conditions that promote entrepreneurship, especially at the early stages of new venture development. A commonly used definition for EE is: 'a set of interdependent actors and factors coordinated in such a way that they enable productive entrepreneurship within a particular territory' (Stam and Spigel 2017 p. 1). However, the scientific literature on EE has devoted less attention to processes and factors leading to the growth of new ventures (da Rosa et al. 2017; Nadali et. al. 2018; Brush et al. 2019; Cavallo et al. 2019; Durufvé et al. 2017). Therefore, there is a need in the EE literature to go beyond the start-up stage of venture development and to increase our understanding of how firms manage, or not, to scale-up and become high-growth firms in EEs (Isenberg 2016).

This is not to say there is little understanding of how high-growth firms develop in general. It is well known that multiple supply and demand side factors can have an impact on the scale-up process, such as finance, experience in technology and management, firm strategy, hard and soft institutions, vested interests and market conditions (Wilson and Silva 2013). However, few studies have examined growth-oriented firms in an EE context. Moreover, little attention has been focused on the territorial aspects of high-growth firms in EEs (Lubik and Garnsey 2016; Alvedalen and Boschma 2017; Cowell et al. 2018). There is still little understanding of the factors enabling or constraining scale-up processes in EEs in different geographical contexts, and how regions can support scale-up capabilities of EEs.

The purpose of this study is to identify factors that support or limit high-tech firm growth in five EEs in Life Sciences (LS). Entrepreneurial firms in the LS industry face high risks and have to overcome many obstacles, because the average product development takes about 12 years. First, we address the question which factors are important for scale-ups in LS, and which can be regarded as barriers. These factors include growth ambition, technological expertise, management competence, business model alteration, funding, the role of global firms, human capital, support organizations, local growth culture, hospitals and universities. Second, we explore the differences between the scale-up factors in LS between

Entrepreneurial Ecosystems in the US and Sweden. Third, we investigate the role of actors (such as support organizations, large firms, funding organizations) in supporting scale-up processes and removing obstacles in EEs. The study has been carried out in five Entrepreneurial Ecosystems in LS, of which four are located in Sweden (Lund, Gothenburg, Stockholm, Uppsala), and one in Northeast Ohio (NEO) in the US. The data used have been derived from interviews in all five EEs and from relevant documents. We find that firm-specific and external factors and actors important for scaling-up are interconnected, and vary greatly in impact among different EEs. Other insights are that the start-up and the scale-up phases require specific mechanisms but also depend on each other, and that external factors important for scaling-up also operate at levels outside of the EE.

The remainder of the paper is structured as follows. Section 2 discusses the theoretical and empirical literature on EEs and scale-up processes, and identifies factors enabling and constraining scale-up for high-growth firms in general. Section 3 presents the data and method. Section 4 presents the main findings. Section 5 concludes and discusses future research avenues and policy implications.

2. EEs and scale-up

There is an expanding literature that looks at entrepreneurship from an EE perspective. Studies have applied a broad definition of entrepreneurship and primarily focus on start-ups in general (Alvedalen and Boschma 2017; Welter et al. 2016). This had led to key insights with respect to favorable factors that enhance entrepreneurship, in particular at the early stages of new venture development. Stam and Spigel (2017) have shown the importance of factors supporting entrepreneurs in finding the right team, resources, networks, patents and initial funding to get off the ground with their innovation. However, less attention has been devoted to factors enabling the growth of new ventures. Duruflé et al. (2017) argues that the current state of EE literature mainly discusses factors responsible for the launch of start-ups but it has given less attention to particular scaling-up processes in the EE. This is not to say that the EE literature ignored high-growth entrepreneurship. Stam and Spigel (2017) mentioned that 'productive entrepreneurship' should be the main focus of attention in EE. Likewise, Mason and Brown (2017) argued that scholars should focus on how EEs support and nourish growth of start-ups and small firms and turn them into large ones. Additionally, high-growth firms are

regarded as critical for the development of EEs themselves (Isenberg 2010; Mason and Brown 2014).

Nevertheless, few studies on EE analyze scale-up processes. In their latest literature review on the subject, Da Rosa et al. (2017) mention a lack of studies on scale-up in EEs and Duruflé et al. 2017 agrees that there is not much explicit discussion of factors that support or limit firm growth in EEs. Nadali et al. (2018) argued in a similar way that there is a need to study how EEs support firms in different development phases from start-up to scale-up. Brush et al. (2019) state that research should focus on how EEs support or hinder start-up, growth and sustainability of ventures. Cavallo et al. (2019) ask for studies on how EE's growth is nurtured, what is the relationship between growth of new firms and EE, and what is the role of different agents at different growth phases of firms. Furthermore, Duruflé et al. (2017) claim studies need to investigate the causes of scale-up and its geographical and temporal variation.

Outside the EE domain, high-growth firms have attracted a lot of attention. High-growth firms are associated with new job creation (Birch 1987; Henrekson and Johansson 2010), growth in productivity (Mason et al. 2009), high levels of innovation (Coad 2009; Mason et al. 2009) and global connections and export (Parsley and Halabisky 2008; Mason and Brown 2010). Barriers to post-entry growth have been identified as one of the key problems that need to be tackled by policy, for instance, in the EU (Coad et al. 2016).
While there is consensus on the economic importance of high-growth firms, there is less consensus on their definition (Mason and Brown 2013; Coad et al. 2014; Daunfeldt et al. 2014; Lee 2014; Anyadike-Danes et al. 2015). A popular definition of high-growth firms is the one proposed by OECD (2010), also referred to as gazelles: "enterprises with average annualized growth greater than 20% per annum, over a three-year period, and with ten or more employees at the beginning of the observation period. Growth is thus measured by the number of employees and by turnover" (p. 16). Isenberg and Onyemah (2016) define a scale-up as 'a company that grows consistently and significantly': it follows the OECD definition but adds a minimum of $1 million in revenues. Sometimes the definition of the scale-ups limits age of firms to 5 years – the cut off age for increased new firm survival (Anyadike-Danes and Hart 2014; Coad et al. 2016). Scale-ups are also associated with the aspiration to reach OECD's definition: they are entrepreneurial firms that have worked through the exploratory phase of development, found their product or service and market segment, and

now enter a growth phase with aspiration for a significant increase in sales (Duruflé et al. 2017). Nadali et al. (2018) defines a scale-up as a development stage firm that aims to grow in terms of market access, revenues and employees, and that has the goal to reward its investors by exit via acquisition or an IPO (Onetti 2014).

Studies on high-growth firms often based on cross section of all sectors have identified factors that influence the scaling-up process. These may be split into two groups: factors specific to the firm, and factors external to the firm. According to Mason and Brown (2013), firm-specific factors that support high growth of firms in a region are: (i) strong market orientation of the firms, (ii) marketing and sales support, (iii) support for business internationalization to link with global customers, (iv) experienced entrepreneurial leadership from peers and board of directors, (v) experienced entrepreneurs with track record of success, (vi) relational – ongoing – rather than transactional support with strategic relationships among private and public organizations. Nadali et al. (2018) outlined eight risk factors that can hinder a scale-up process in an EE if neglected, based on Picken (2017): "1. Setting a direction and maintaining focus; 2. Positioning products/services in an expanded market; 3. Maintaining customer/market responsiveness; 4. Building an organization and management team; 5. Developing effective processes and infrastructures; 6. Building financial capability; 7. Developing an appropriate culture; 8. Managing risks and vulnerabilities" (p. 589).
Setti (2020) identified the following firm-specific factors, based on a systematic literature review on science-based firms: (1) human capital, including scientific and market/business knowledge and diversity in the management team; (2) innovation capabilities, including an ability to link R&D to product development; (3) firm strategy and leadership; (4) ability to adjust to increasing complexity.

In the EE literature, most attention has been drawn to external factors to the firm in general, with few studies referring to the scale-up process in particular. High-growth literature, on the other hand, have studied numerous factors relevant to the growth of firms. Sleuwaegen and Ramboer (2020) state that a well-developed pool of workers in a region is a factor contributing to the development of high-growth firms. Spigel and Vinodrai (2020) showed that former skilled employees of Blackberry after its collapse gave a boost to local scale-up firms in an EE in Waterloo, Ontario. Access to funding has often been described as a key constraint for the growth process of innovative firms (Colombo and Grilli 2007; Schneider and Veugelers 2010; Lee 2014; Miozzo and DiVito 2016; Cavallo et al. 2019). Scale-up

stages require ‘venture equity’ investors like (later-stage) venture capitalists and corporate investors, growth equity funds, private equity funds, hedge funds, cross-over funds, family offices, sovereign wealth funds, and institutional investors that invest directly (Duruflé et al. 2017). Cowell et al. (2018) found that local supply of angel, venture and scale-up capital was important for high-growth firms in an EE in Virginia. Brown and Mason (2017) state that ‘funding escalator’ support is critical for the scale-up process in an EE. It helps firms to transition between different types of funding sources (North et al. 2013; Schreiber and Pinelli 2013). Furthermore, local dealmakers mediate relationships and links to business angels and other actors (Feldman and Zoller 2012; Senor and Singer 2009; Napier and Hansen 2011; Kemeny et al. 2015), entrepreneurs and financial firms, and large pools of sources of funding with “smart money” for scale-up process (Mason et. al 2009). Network links to universities (Lawton Smith and Ho 2006; Wang and Shapira 2012; Lubik and Garnsey 2016) and large firms (Clarysse et al. 2011) have been pointed out as especially valuable for early firm growth, particularly for science-based firms (Scholten et al. 2015). Supporting organizations like TTOs (Ziaee Bigdeli et al. 2016), Incubators (Meyer 2003) and Targeted R&D programs (Vincett 2010) have been shown to have impact on growth of science-based firms (Setti 2020). Henrekson and Johansson (2009) highlight the importance of institutions, such as tax and labor market regulations and contestability of markets. Gamidullaeva et al. (2020) found institutional obstacles to high growth of firms in EEs in a study on 81 regions in the Russian Federation, such as shadow economy and corruption, and instability in the political field. Isenberg and Onyemah (2016) discussed actors that have been important in the scale-up EEs in Colombia and U.S. including policymakers and public leaders, financial actors, culture impactors, support organizations and event organizers, educators and developers of human capital and corporations.

In sum, the literature on EE has yet devoted little attention to the scaling-up phase specifically and to the importance of factors enabling the growth of new ventures in EEs. Studies on high-growth firms have identified factors specific and external to the firm that influence the scaling-up process. The empirical study investigates which factors limit or enable the growth of new LS firms, and how they are connected. In addition, we compare five EEs to examine whether these factors differ between different EEs in LS.

3. Methodology and data

The design for data collection and analysis has been inductive. This enables us to understand a phenomenon that has yet not been studied at length. It is an open and explorative approach in which the data generate results that are used to describe the phenomenon in a rich way and define a framework that can be tested on future cases (Eisenhardt 1989, Eisenhardt et al., 2016, Yin 1989). Comparing cases across countries and regions with different institutional conditions and other features reveal similarities and contrasts of the scale-up process in different EEs (Miles and Huberman 1994).

Focus is on the Life Science industry that includes three diverse sectors: Pharmaceuticals (Pharma), Medical Technology (MedTech) and Biotechnology (BioTech). Firms were selected to cover all three sectors. We included firms that provide services or develop products. It is important to distinguish between service and product firms because the nature of the scaling process differs (Brännback et al. 2009). In service firms, sales can be started in the same year after investments in laboratories, office spaces and administrative tasks. Product firms develop drugs and medical devices through a number of development phases that include discovery, development, production, distribution and marketing. Firm growth happens in stages and it is not linear (Kazanjian 1988; Churchill and Lewis 1983). It takes product firms on average ca 12 years to finish development. Life Science industry is known to be a high risk activity (80% of R&D projects don't recapture their R&D investments), highly dynamic and requiring heavy financial resources, long product lead times and involvement of many actors at the global scale (Batiz-Lazo and Holland 2004; Brännback et al. 2009). The scale-up process for new LS firms would typically occur at the development stage, after the discovery stage and after patents have been approved and IP rights established. In general, development encompasses formulation, toxicology and clinical trial work (phases I-III) that is needed to meet regulation requirements to be able to start selling the product (Batiz-Lazo and Holland 2004). The development process has the objective of reaching a marketable product that is produced, distributed and sold at a large scale. Where service firms would have revenue early on, product firms need to make large R&D investments and aspiration to have large revenue in the future. Valuations of LS firms are more often than not based on future expectations and not on actual earnings (Brännback et al. 2009)

In LS research it is common to study firms that are publicly traded and have established business records. According to Wolff (2001), four tiers of firms from market value over US$5billion to under US$800million can be identified. Carsrud et al. (2008) proposed a fifth

tier for firms that are mostly privately held and have market value under US$25 million, such as the firms in this study. These firms often lack finance, a clear market, revenues and skilled management and are of urgent need of support mechanisms (Brännback et al. 2009).

Five EEs have been selected that are known to be centers of Life Sciences to a greater and lesser extent in the US and Sweden. Four EEs concern regions with the highest concentrations of LS firms in Sweden: Lund, Gothenburg, Stockholm and Uppsala. One EE is located in NE Ohio in the US. See Alvedalen and Carlsson (2020) for more details about general features and the history of the 5 EEs, and their main differences.

The study is based om interview data with founders and management of LS firms, industry experts and representatives of support organizations in the EEs including regional LS investigators, regional LS investment managers, CEOs and top management of Science Parks and Universities, and regional government management. All firms were identified as growing or having high growth potential by local experts and were therefore interviewed.

The question that guided the research was what dimensions and mechanisms are at play in the scaling-up phase of a start-up firm in Life Sciences in regions in Sweden and in NE Ohio. Almost all of the interviewed firms were either successful in guaranteeing continued access to funding to a greater or lesser extent (product firms), or they were successful in sales and employment growth (service firms). This means that the interviewed firms provide a rich source of information with respect to their scaling up process.

During years 2015 to 2019, 40 interviews were conducted in total – seven interviews in Lund, six in Gothenburg, nine in Stockholm, six in Uppsala, and seven interviews in Northeast Ohio. 23 products firms and 5 service firms were interviewed, 9 MedTech firms, 5 Mixed/Pharmaceutical firms, and 14 Biotech firms. See the complete list of the interviewees in Table 1. Archival data such as annual reports, websites, industry reports and policy-related documents have been used as sources of secondary data. They were used to triangulate and to look into details of certain findings from the interviews.

Table 1 List of interviewees.

CSO – Corporate Spin-Off, USO – University Spin-Off, Na – not applicable.

Code	Source	Industry Sector/Expert role	Year registered
L1	Astra Zeneca	Pharma/Biotech	2011
L2	Astra Zeneca	Pharma	2011
L3	Astra Zeneca	Medtech	2013
L4	Astra Zeneca	Biotech	2013
L5	Lund Uni	Biotech	2000
L6	Regional government (Region Skåne)	Regional expert in Life Science	Na
L7	CEO Medicon Village Science Park	Top Management	Na
L8 (2 interviews)	Lund University	Top Management	Na
L9	Medicon Village Science Park	Middle Management	Na
L10	Lund University/Entrepreneur	University Management/Entrepreneur	Na
L11	Regional Council (Region Skåne)	Top management	Na
S1	Astra Zeneca/former Vinnova	National expert in Life Science	Na
S2	Biovation Science Park	Top Management	Na
S3	Management buy out	Biotech	2009
S4	KI and KTH	Biotech	2004
S5	KI	Biotech	2008
S6	Astra Zeneca	Biotech	2012
S7	KI Science Park	Top Management	Na
S8	Pharmacia	Biotech	2003
S9	KI and KTH	Medtech	2006
G1	Na	Regional expert in Life Science	Na
G2	Astra Zeneca	Pharma	2007
G3	Chalmers	Medtech	2005
G4	Uni of Gothenburg	Biotech	2010
G5	Uppsala and Uni of Gothenburg	Biotech	2005
G6	Small firm	Biotech	2004
U1	Lund Uni/Manchester	Medtech/Botech	1999
U2	Uppsala Uni	Biotech	2013
U3	Pharmacia(Biovitrum)	Biotech/Pharma	2009
U4	Uppsala Uni Innovation	Top Manager	Na
U5	Uppsala Uni (Financed by Pharmacia)	Medtech	2006
U6	Pharmacia	Medtech	2006
NEO 1	CWRU	Medtech	2006
NEO 2	CWRU	Biotech	2013
NEO 3	UH/CWRU	Biotech	2010
NEO 4	MS School of Medicine/CWRU	Pharma/Biotech	2013
NEO 5	Cleveland Clinic	Biotech	2007
NEO 6	CWRU & UH	Medtech	2002
NEO 7	Cleveland Clinic	Medtech	2014

Methods inspired by grounded theory (Glaser and Strauss 2017; Charmaz 2006; Gioia et al. 2013) were used to code and analyze the data. We employed an abductive approach (Dubois

and Gadde 2002) in order to strengthen the understanding of the initial findings at the analytical steps where data produced themes that were compared to the EE literature. Inspired by Roundy (2019), seven steps were taken to analyze the data on the EEs: (1) Inductive focus - broad focus for the factors impacting EEs; (2) First-order coding - initial concepts were identified and labeled by section-by-section coding of the transcribed interview material; (3) Second-order coding – initial codes were reduced/grouped according to similarities; (4) Theoretical aggregation – abstraction of codes into themes, iterating between the data and the EE literature; (5) Recursivity – tentative theoretical explanations on factors of influence were developed during the analysis, (6) Pattern identification triangulation – emerging themes and their explanations were subject to 'constant comparison and contrasting' within and across data sources; (7) Data organization – Atlas.ti, a qualitative data management program was used in the different stages of the analysis. Examples and quotations from the data are shown in the findings below.

4. Results of the comparative analysis of scale-up factors in five EEs

This section briefly presents the main findings on the scale-up factors derived from the interviews and related documents in the five EEs in Life Sciences (LS). A distinction is made between growth factors specific to the firm (Section 4.1) and growth factors external to the firm (Section 4.2). We will report differences between the five EEs only when these stand out.

4.1 Firm-specific growth factors

Orientation towards market and growth

Orientation to growth refers to the ambition of a firm to develop the firm past its start-up phase. The goal of many LS firms is to take an innovation to the market or as close to the market as possible. Firms in NE Ohio show a strong ambition to grow from the start. It is common to go through different growth stages before a firm partners up with a large firm for large clinical trials, production and distribution. Product firms perform pre-clinical and clinical studies. Clinical development includes three phases. Phase I trials examine safety for use in humans, phase II trials study dosage and efficacy, and phase III trials focus on showing superiority over existing treatments. The costs increase dramatically from one phase to the next due to the increasing number of participants. Production, marketing and distribution are additional costs that come after the product has been approved by a regulatory agency. It is

common for small firms to partner up with/sell to large firms at certain stages of development. Firms can apply for large VC money and go through clinical trials, production and distribution on their own, but that is very expensive and rare. Firms in NE Ohio often plan to raise money themselves until phase two or even as far as to the third phase of clinical trials. These firms do not want to sell to large firms too soon, in order to keep control of product development for longer. Firms want to demonstrate stronger and more reliable results that would make it easier and give more negotiating power when they partner up with big pharma companies. For example, entrepreneurs described future strategies on how the firm would focus on claims that are closest to certain customers even if the technology has wider application and describe how the firm would take responsibility for growth.

'We'll have to work with early adopter institutions that are just driven to be on the cutting edge of these certain types of technologies…Going from there, we can collect data to support a broader launch to any hospital that performs endovascular surgery' – NEO 7 (product firm)

LS firms in Swedish regions tend to show lower growth ambition in general. Firms in Uppsala and Stockholm mention opportunities and plans for expansion in terms of employment and sales more clearly than LS firms in Gothenburg and Lund. In Lund, this can be due to firms being in their earlier stages of development, in comparison to other regions. Service firms that aspire to grow, grow mostly organically with their expanding customer base but, in a few instances, also by acquisition, for access to certain technologies and/or sharing costs. In Gothenburg EE, with a few exceptions, the researcher-entrepreneur is usually not a big risk taker or a skilled businessperson, and does not always have firm growth as ambition. Many firms are hoping to sell off a product/license without growing bigger. However, firms also realize the inhibiting factor of staying small. Lund firms mentioned that higher numbers of employees in a LS firm contribute to more knowledge sharing and learning. Low growth ambition for employment growth among Lund micro firms is also associated with labor laws making hiring employees hard and expensive. And lack of competences of the entrepreneur and the management about how to grow an LS firm in business terms has also a negative impact on growth orientation and inhibits the understanding of growth opportunities in an EE.

Technological/scientific expertise

The technologies on which firms' idea and firms' patents are based often come from senior researchers with long experience in their scientific fields and impressive CVs. Technological competences in service and product firms in LS need to be sustained and developed during the scale-up phase to be valuable. The initial technological and scientific expertise of a firm is important but not sufficient due to the fast speed of development in the field. There is a need to stay at the frontier of one's research and constantly be updated about new developments, publish with leading experts and keep innovating. This is achieved by connecting to experts in other research centers, giving key people shares of the firm or employing them on contract basis, making the structure of the firm virtual and flexible.

Firms require not only strong expertise in their technologies but also ability to translate their research into a product. The translation mechanism is important to understand what type of customer will be relevant for the product. In NE Ohio, the managerial and expertise on how to go from academic research findings to a product, expertise that can be obtained through support organizations like BioEnterprise and TTOs are regarded as crucial by firms. Firms are close to their research groups and have tight contact with core people nationally involved in the technology that requires adaptations as the product takes form. Service firms are using researchers and highly expensive equipment on contract basis from the local research center.

To develop the technology, LS firms in Lund strive to employ skilled researchers, are in tight connection to their core research group at the University, and are connecting to the best experts in their field in other EEs both in Sweden and abroad (like US, Spain and UK). Those types of collaborations are guided by strict agreements and done in order to publish and add new knowledge but do not involve the firms' products/candidates, to avoid IP issues. Service firms in Lund are based on the expertise of entrepreneurs acquired at Astra Zeneca. They have mixed types of collaborations – either just delivering services or working on a patent candidate together. In Gothenburg and Stockholm, several firms are based on research by world-known professors. Some firms are making their products available to different customers and researchers globally to understand different application areas and to register new patents together with them. Stockholm firms are collaborating with universities and registering patents with "kick back model" to pay the researchers when the patent would make money. Gothenburg firms were wishing to have more collaborations like that, so smaller firms could register more patents and grow using their production and business abilities. In Uppsala, the main expertise of several product and service firms comes from the

large firm Pharmacia. They chose to be strict with not patenting with customers and rather growing their services offers. Their core technological expertise is residing in their human capital, often from the local university in the EE. Specifically, entrepreneurs in Lund and in Uppsala reference their high local networking quality as one of the success factors for their firms' growth.

Management knowledge for transition from start-up to scale up phase

Competent and experienced entrepreneurial management in LS firms should assist the transformation of the firm from the start-up phase with pre-seed funding and registration of patents into a scaling-up firm. More specifically but at specific times, it should assist development of the technology into a product, handle regulatory issues, develop local and international links with relevant support and funding organizations and customers, keep a focused strategy to reach the customers/market, have skills required to go through an IPO when relevant, attract and manage human resources and the culture of the firm and manage the growing complexity of the infrastructure of the firm. Firms across all EEs confirm that specific scale-up related business knowledge is needed in the management team in terms of CEO and the board of directors. However, the specific type of business knowledge a firm requires will change with different stages of development and the type of the business model (e.g. service or product). This type of knowledge seldom resides in the researcher-entrepreneur and can be acquired outside of the firm. Personal networks and recruitment agencies are often used to find the right people for the right stage of development of the firm. Firms in NE Ohio emphasize the need of having management with business expertise to develop fully the company after the start-up phase and to do successful exits earlier.

'As an academic you don't have the skill set to go pitch a business opportunity to the business community and the investment community. That's what the executive was for. He had done this before with another, more technology-driven, company' – NEO 3 (product firm).

It is crucial to have competent management that enables the transition of the product from academic to industrial phase, and to move the molecular candidate from pre-clinical to clinical testing. Strong skills are required how to get the right amount of money for the growth phase and to manage clinical trial and regulatory work for obtaining FDA approval. Technology transfer offices at the Cleveland Clinic and Case Western Reserve University or support organizations like BioEnterprise have been involved from the start and have helped to

make connections to key people. However, these people are not always present in the EE and often need to be recruited from other parts of the US.

LS firms in Sweden recruit highly competent management with entrepreneurial experience at a later stage, where LS firms in Ohio acquire that type of knowledge earlier. Due to the Swedish firms' need of reaching the international market, the management also needs to have experience in international sales and knowledge about regulatory issues in other countries. Ohio firms and their management are operating under the same institutional conditions as those in other U.S. regions and can benefit from a large national market and talent pool.

Gothenburg and Lund have many firms that are still in pre-clinical stages and need skills that attract funding and establish connections with large firms for the future licensing of their products. Uppsala and Stockholm firms are older in general and are already manufacturing and selling their products or services. Hence, they require knowledge in legal issues for partnering with customers and managing growth-pains of the firms at the organizational level. Another important point is that managers should have a good understanding of managing a growing entrepreneurial firm rather than managing a large firm.

Adopting business model and internal infrastructure for growth

A business model (BM) represents the plan for successful development of a firm. As a LS firm acquires more funding, develops its products and grows organically or by acquisition, the business model needs to evolve too. Firms in NE Ohio mentioned that different phases of development require different ways of operations and different types of management to drive these changes. In NE Ohio, scaling up a certain part of firms' service offer would require significant investment in infrastructure with highly expensive equipment which they now are renting from the research center within the university (The Center for Proteomics and Bioinformatics). Investing in such equipment would not be profitable for small firms and hence infrastructure can be a hindering factor for growth. Product firms in NE Ohio are receiving larger amounts of growth capital, are furthest into clinical trials, are working on FDA approvals and prototypes at research or commercial level, but also waiting for their products to have options for application. Hence, they are in need of different partners and BMs are forming in the process.

Some LS firms in Lund are changing their BMs when moving from service firms to becoming product firms. Small service firms built a consortium - Medicon Valley Inhalation Consortium - to take on larger customers and create new offers to adjust to the new growth opportunities. New service offers are developed as a response to connection with new customers and firms merge together to share costs and broaden the business offers. These changes require new competences, types of investments and links to regulatory, research and support organizations.

'*We started [with] service and then we changed quite a lot since the last year… Three years ago we decided that we focus only on immunology and we will do that based upon our technologies… we needed new competences for how to work with a product'*
– L5 (product firm)

Similarly, Gothenburg firms are in contact with many users in order to determine what type of application they will focus on for their product, which would inherently change the business model. Uppsala and Stockholm firms have products with a clearer focus in their BMs and are thinking more about production and adjustments of the products to the existing customers' needs rather than making changes in the way firms are operating. Service firms in Uppsala are planning to manage the growing complexity of the organization by spinning off entities to maintain flexibility, instead of adding another level of management (at e.g. 70 employees).

4.2 External growth factors

Funding

Funding at the scale-up stage is risky and requires large investments, as clinical trials become larger. The stage of transition from start-up to scale-up can be termed as "the valley of death", which comes after the seed funding has been used up, and next step trials still mean very high risks that require large amounts of funds.

In NE Ohio, seed money is often local and coming from CWRU, the Cleveland Clinic or/and public support and funding organizations. About $5-6 million is needed to cover the patenting and prototyping phases. Further into the initial steps of the scale-up phase, LS firms need "growth capital" and prefer to look for funding from VCs and different types of loans and matching funds offered by the state government. These also come from the Cleveland Clinic

and used to cover clinical trials phase I and often even phase II before partnering up with a large firm. The amounts firms have received for their initial trials were e.g. $45M. VC firms would preferably be dedicated Life Science VC firms. They would ideally have a lot of experience and show a risk-taking attitude, understanding that $30M investment could be just one step in the development. This requires a long-term commitment and even larger amounts when the product goes through clinical trials and acquires FDA approval. The growing investment needs would typically be acquired through the network of the initially investing VC firms. This type of VCs can be found in NE Ohio to some extent but is more common in other EEs in LS, like in Boston.

LS firms in NE Ohio feel there is enough of different types of seed-funding, supported by the strong reputation and networks of the Cleveland Clinic. However, they also feel there is a lack of "growth capital" regionally. VC's in NE Ohio seem to have shorter time frames and aim for exit already after five years. Investments of VC firms located outside of NE Ohio are limited, because VCs are generally skeptical to co-invest with partners in other regions that they don't know and have trust bonds with. Hence, VCs prefer to invest in their own EEs where their local networks are strong. LS firms in NE Ohio feel a lack of dedicated VC firms in the local EE that understand the specific needs and risks of the industry. Final clinical trials, distribution and sales of the drug further require up to $1billion and would be done by partnering up with a large pharma firm.

In Sweden, there tends to be an agreement about the lack of capital in general. Service firms in all Swedish EEs grow organically with their customers and have a hard time receiving state VC money. Gothenburg has least capital open to risk. Firms are acquiring funding in other EEs and other countries, setting up subsidiaries there. One firm needed ca 1M EUR for clinical trials to cross the "valley of death". However, local VC firms rather invest at a later stage. Even state VC funds like Almi are described as too risk averse which makes it hard for LS firms to receive loans. More international funding is available in the two EEs of Stockholm and Uppsala. An entrepreneur in Stockholm suggested that one should go to the stock market if firms want to grow. There are a few wealthy and knowledgeable Business Angels founded by former successful LS entrepreneurs that provide large capital for clinical trials up to a certain level. LS firms in Lund have been successful in acquiring seed and growth capital from a network of Business Angels (11 from Sweden and 1 from Norway).

Considering the lack of VC money available for several phases of clinical trials, partnering with a large firm early is important for the firms.

Large global firms

Large firms are crucial for the scaling-up of product firms in LS. It is extremely hard for small product firms to fully scale up on their own, due to the very large investments development and clinical trials require, which start at ca 50M EUR. Therefore, firms need a partner that can provide large investments and market access.

In NE Ohio, the ambition is to get acquired by a large firm after successfully completing phase II or phase III clinical trials exactly because it is almost impossible for a small firm to be able to handle production, marketing and distribution themselves. In some cases, a firm can choose to IPO to access capital for growth. Big pharma firms are seen as challenging to work with in pre-clinical stages due to internal bureaucracy and lack of specific knowledge. Therefore, firms prefer to do at least phase one themselves which costs ca $1M. In order to attract the attention of large firms, initial clinical data is key and opens doors. However, there are no large firms present in NE Ohio which is mitigated by the strong connections of the Cleveland Clinic and CWRU with large firms in other EEs to establish partnerships.

In the EE of Gothenburg, selling to a large firm as soon as possible is often the ambition. However, there have not been many acquisition deals because there are not enough large firm buyers in the local EE, and small LS firms do not yet have strong results to show from clinical trials. Firms that proceed with clinical trials and are interested in strategic collaboration for later stages, work on establishing relationships with large firms early on. In recent years, AZ in Gothenburg has been more active in investing in firms in later stages and in supporting growth of firms by operating an incubator inside their facilities that gives access to employees with large firms' expertise. Small firms also establish subsidiaries in countries like the US or Japan in order to perform clinical trials and get FDA approval faster for their target market and be closer to the acquisition units of large firms there. LS firms are primarily looking for collaborations in specific projects and out-licensing of one candidate, rather than selling the whole firm. Some firms in Lund and Uppsala sold licenses to international large firms which still required years of collaboration with the customer to make the product ready for the market. This shows that making a sale/partner up in LS in Sweden is most often international, long-term, and tailored to a large firm buyer.

The departing of the large firm Pharmacia in Uppsala and Stockholm had consequences for scaling-up of local LS firms. In the past, Pharmacia contributed to the growth of firms through access to "big pharma know-how", and through collaborations, spin-offs and investments. This all disappeared. On the other hand, highly skilled labor became locally available. The closure of AZ sites in Lund and Stockholm gave small LS firms access to skilled labor, although this gave them only a temporary boost.

Human capital

Availability of high-skilled labor is crucial for scaling-up. In NE Ohio, local supply of human capital and a rich academic environment are key for scaling-up LS firms. Affordable costs of living help to attract labor from outside of the EE. Service firms source most experts as consultants from the Cleveland Clinic or CWRU. Many firms hire employees from different places on consultancy basis, to keep flexibility due to high uncertainty of projects. Employees move more freely across the U.S. compared to the Swedish EEs. Swedish EEs rely on local labor markets to a greater extent than LS firms in NE Ohio.

In Gothenburg, AZ has been investing large amounts of money to attract skilled international employees to the region. In the Uppsala EE, employees are rotating between large and small firms. Firms in Stockholm and Lund EEs experienced a surge of skilled employees when AZ closed down its research in these locations: it gave them access to excellent consultants but also to plenty of good employees that boosted their scale-up process. Lund EE is a special case because of its close location to the labor market of Copenhagen. Local universities are important suppliers of employees to the firms in all EEs. Uppsala university seems to have very strong connection with firms that hire just on recommendation. Key researchers are brought into the firms as consultants. National links are more important specifically for the high-end type of expertise.

Support organizations

Support organizations play a crucial role in scaling-up process in EEs in LS. In NE Ohio, there is a large variety of financially strong support organizations that are aligned in their goals and efforts towards growth. Several local organizations, both private and private/public partnerships, try to recruit firms to the regions and support local LS firms linking them to networks and expertise that enable the transition from academic to industrial phases. Some of

these organizations are set up primarily to help new start-ups grow from incubation and acceleration to commercialization. They work with state and federal agencies to provide not only advice but also funding. Some of this funding, especially seed capital, is in the form of grants or equity out of their own resources. Other funding leverages state and federal funding (especially Small Business Innovation Research grants) and/or private venture capital. Most importantly, these local and state agencies invest their own funds by taking equity stakes in the scaling up of start-up companies.

In contrast, support organizations in Sweden were not described by our interviewees as financially strong, well-connected or having the right business knowledge. They are mentioned as useful in the start-up phase rather than the growth phase. Support organizations tend to have less focus on growth in their efforts and more focus on the registration of new firms.

'[employees in support organizations] *those people have often worked as administrators, project leaders in big pharma etc., they are not the people that have developed a business themselves…even less knowing the international arena….and you can sit there for 25 years, no rotation back into business'* – G6 (product firm)

Support organizations in Lund show a defensive attitude. This is illustrated by statements that a firm should be careful with employing people because that is expensive. Funding is often given to one project at a time which makes it harder to employ more people for several projects. Uppsala has been one of the few EEs in Sweden where incubators are mentioned as good sources for growth networks specifically. When firms are promoted on the "hot list" by the regional government, like in Stockholm EE, this has a motivational impact. SwedenBio in Stockholm EE, which is a national private organization linking up LS firms in Sweden, has been particularly effective in arranging conferences and meetings between large international firms and small firms to find future partners. In Lund EE, Medicon Village Science park has in recent years supported the innovation side of local firms, stimulating resources relevant for the scale-up of LS firms.

Local open and growth culture

There is a remarkable difference between EEs located in the US and Sweden in the extent to which a local growth culture is present that promotes, or not, scaling-up processes. In NE

Ohio, the culture of collaboration with aligned focus on growth among different actors in the EE provides a strong facilitating effect for firm growth in the EE. The attitude of VC firms is more growth visionary and VCs are better aligned with the large investment needs and time frames of the LS industry. Uncertainty among investors is mitigated by the strong reputation of the CWRU and the Cleveland Clinic. However, even in NE Ohio firms say that the culture can become even stronger and more intense like in other LS hubs such as Boston in the U.S. and Cambridge, UK where investors and entrepreneurs are even more soaked into the intricacies and are more tolerant of the risks associated with the industry. IP in NE Ohio plays a protective signaling quality role. There is also certain regulation in place like Biologics Protection Act in order to prolonger patents for drugs ca 12 years that take very long to develop. Other new drugs both in Sweden and in US, generics – copies of existing drugs with expired patents, only require smaller clinical trials to show similarity to the existing drug, which considerably shortens product to market time and investments.

In Swedish EEs, the goals among different actors are often not aligned or lack specific growth focus, making the EEs split rather than coordinated in their attempts to support the scale-up of LS firms. Entrepreneurs in Stockholm EE mention it is hard to grow firms in Sweden for various reasons including a desire to keep full control over the firm and not taking in investors. Although Lund EE had the largest increase of firms in Biotech and Medtech in Sweden in recent years, the number of employees did not increase much, indicating that most of the new firms are micro firms (Carlsson et al. 2016). Direct investments of governmental funding into LS firms in Gothenburg seem to have a dampening impact on their growth ambition because the entrepreneurs do not “put own skin in the game” and lose the urgency to grow. In Gothenburg EE, patents and approvals from organizations like European Food Safety Authority are required for credibility and important for small firms to register in order to market themselves and attract large firms as collaborators. Firms in Gothenburg get faster FDA approvals in U.S. than in Europe which is important for giving them quick access to the market. Still, Swedish EEs are in the process of supporting individuals with structural support like TTOs and accelerators that have been in place in NE Ohio already for decades. However, these new structures promoting growth in Swedish EEs are still at a much weaker stage in comparison and there are clear differences in success between the regions.

'What is lacking in Gothenburg which is different from Stockholm and Lund, is that the open innovation idea is very active in Lund….there are differences how we do it in Gothenburg compared to Lund' – G2 (product firm).

This firm moved later from Gothenburg to Lund for the benefits they perceived in that EE.

Universities

While there are more than 60 colleges and universities in Northeast Ohio, Case Western Reserve University (CWRU) is clearly dominant in life science research. It is not the largest in terms of number of students, but it is the only university in the region classified as a research university (based on its large research funding and the fact that two-thirds of its students are graduate and professional school students and only one-third undergraduates).[1] CWRU is one of the central actors that plays an important role in scaling-up of local LS firms. It does so in providing skilled human capital, strong reputation, networks with VC firms, links with large firms inside and outside of the region, and access to research infrastructure like equipment.

In Sweden, universities are important in providing a strong research environment and skilled human capital in the EEs. Universities in Stockholm and Uppsala support LS firms by attracting investors and providing links to customers. Uppsala University is the most active university in all Swedish EEs in LS that supply small firms with "everything" from customers to research projects and human capital.

'University is important for us in all sense – supply us with staff, infrastructure, customers, projects…Supply us with everything. People from university have called me to collaborate' – U3 (service firm).

However, despite the strong reputation of Swedish universities, they are not mentioned as strong actors that impact the scale-up phase of local LS firms. Universities in Sweden do not have as much value for VC attraction as in NE Ohio. Scale-up firms in Lund and Gothenburg mentioned how they collaborate with researchers in their field in other countries. Few

[1] All the interviews in NEO were with companies that came out of either CWRU or the Cleveland Clinic.

collaborations are with Swedish universities. However, such collaborations are often focused on increasing knowledge for publishing rather than directly working with the core compound of the firm. TTO's of Swedish universities have been criticized for not providing the competence that can support the scale-up phase of the firms.

'[TTOs] can free of charge help to make an IP analysis, they have processes around that, but what they can contribute with is extremely marginal. It is standard forms that one is filling out about the potential of the idea…But it is the execution [of that idea] that is everything' - G3 (product firm).

What is also mentioned is that Swedish universities should be more open to small firms for sharing equipment and expertise.

Hospitals

In NE Ohio, similar to CWRU, the Cleveland Clinic plays a central role for firm growth in the local EE. While there are several major hospital systems (including University Hospitals associated with the CWRU Medical School and the Cleveland Clinic Health System) and numerous hospitals in Northeast Ohio, the Cleveland Clinic is the largest with 45,000 employees locally and 67,000 worldwide. It is the 4th largest research hospital organization in the U.S. and has over $300 million in research funding annually. It has research collaboration with life science researchers around the globe. It is also a major partner with local organizations promoting life science in Northeast Ohio. As a result, the Cleveland Clinic supplies access to growth networks with local and non-local actors and gives legitimacy to the firms it spins off. It also provides funding to entrepreneurs in various ways, and legal and managerial support tailored to LS firms.

In Sweden, hospitals are not mentioned as an important actor for firms' growth. This is partly due to the still pre-clinical stages of development of the firms. However, LS firms in Gothenburg are doing their clinical trials in the US instead and collaborate with hospitals there, in order to be closer to their preferred market and to acquire FDA approval. In Gothenburg, the role of the hospital was heavily criticized for reasons of inefficiency and non-collaboration with small firms. LS firms in Stockholm also are wishing for better collaborations with the hospitals to develop their product. In Lund, some connections with

local hospitals have been established, but these are based on personal connections rather than being encouraged by an open access system.

5. Conclusions and discussion

This study has shed light on the scaling-up process in EEs which has so far remained an underexplored topic in the EE literature. The study revealed 11 factors that impact the scale-up process in the LS industry. The analysis shows that firm-external factors but also firm-specific factors drive or limit scaling-up of firms. These factors matter to a greater or lesser extent across the five Entrepreneurial Ecosystems in Sweden and the US.

A key firm-specific factor turned out to be the growth ambition of the entrepreneur. In the Swedish EEs, this growth orientation appears to be lower than in the US case. This factor therefore acts as a stimulus for high-growth firms in North East Ohio but can be considered a barrier to high-growth in LS in Sweden. Management competence is also found important, especially the ability of the management to combine scientific and market knowledge and to implement a strategy to accommodate growth within the organization. Growth of firms is also connected to the build-up of reputation and trust during the start-up phase. Trust that builds up among actors in the EE by observing how start-ups start and grow will unleash the resources needed down the line. Therefore, the start-up and the scale-up phases require their specific mechanisms but also depend on each other to a considerable degree.

Firm-external factors are also important for scaling-up in EEs. The amount of funding in Sweden in terms of VCs and Business Angels is not sufficient and is too risk-averse for the growth needs of LS firms. There is a lack of foreign direct investments and large firms in the country that help product firms in taking the next step to clinical trials. This is in contrast to NE Ohio where supply of (risk) capital is more available, although there is a shortage of 'growth capital' in the local EE. Large firms are needed to scale-up projects and the relationships with possible partners that should be established early on to build trust and legitimacy before it is time to license out. Large partners are found globally rather than locally which requires small firms to establish global links through different means early on and already during the start-up phase. The global dimension is vital early on for firm growth in EEs in LS. Universities and hospitals in Sweden, except in Stockholm and Uppsala, are not taking an active role in the development of EEs for LS, in contrast to NE Ohio. Even if

organizations within universities in Sweden have the responsibility to enhance economic development like TTOs, those organizations do not play a strong role in scaling-up process in Life Sciences. In NE Ohio, CWRU and the Cleveland Clinic have strong collaborations with different actors and take active part in promoting economic development of the region. Support organizations in Sweden are not focusing on growth of LS firms as much as those in NE Ohio, which also weakens the availability of growth-oriented networks and resources. So, EEs need to align growth-oriented institutions (culture and policies), resources and networks that feed into the specific and external factors of firm growth.

Another crucial outcome of the study is that the two types of factors (i.e. firm-specific and external) are closely intertwined. For instance, the lower growth orientation of LS firms in Sweden is strongly connected with the external environment in which the EEs are situated, like a more risk-averse business culture, or more restrictive employment policies in Sweden. This low growth ambition can also be due to the culture in academic organizations in Sweden that is typically driven more by non-profit oriented incentives like publishing. The management competence inside LS firms is also directly related to their capacity to absorb the available growth resources from the external environment, and their need to reach international markets or not. The low availability of growth funding hampers the initial scale-up stages which in turn can impact the strength of global evaluations of firms and subsequently hamper the attraction of foreign capital to Sweden.

The comparative analysis also revealed that enabling and limiting factors differ between EEs in LS to a considerable degree. The most outstanding difference is between NE Ohio on the one hand, and the Swedish EEs on the other hand. These two countries belong to very different institutional systems, as reflected in their labor regulations and business cultures, which resulted in differences in growth ambitions, supply of risk capital, and the responsiveness of local organizations such as universities, hospitals and support organizations. But also within Sweden, the study found remarkable differences between the 4 EEs in Life Science. For instance, LS firms in Uppsala and Stockholm showed more growth ambition than their counterparts in Gothenburg and Lund. More international funding is available in Stockholm and Uppsala, and their local universities support LS firms with attracting investors and providing links to customers. This shows how important it is to adopt a territorial approach to EEs for our understanding of what factors are important in scaling-up processes, and why some EEs have developed more successful cases of high-firm growth.

Such a territorial approach to the study of EEs is important for another reason. While external factors stimulate scaling-up in LS, this does not necessarily mean that these factors are available at the local EE and can be accessed at that level. The study showed that some firm-external factors important for scaling-up operate at the national or even international scale, not at the level of EEs. For instance, national regulations like labor laws are important for high-growth, and the importance of large firms for scaling-up in LS is a factor that is often located outside the relevant EE, as large partners are often found globally rather than locally.

This study also raises new questions which need to be taken up in future research. First, this study has focused on the factors that promote high-growth firms in EEs. However, little is known of the effects of high-growth firms on the evolution of EEs. Second, this study has investigated the scaling-up phase in LS, and which factors form enablers or barriers to high-growth. It would be interesting to make a comparison between different phases of the growth cycle of a LS firm (start-up, transition phase, scale up phase), and determine which factors are important in each of these stages, and what an EE means to that. Third, when following a territorial approach, EE studies should adopt a multi-scalar approach (Alvedalen and Boschma 2017) and explore which spatial scale matters most in which phase of the firms' growth, and how. Fourth, the EE concept is a systemic concept that looks at the relationships between actors. A step forward in the EE literature is to adopt a network approach (look at flows of knowledge, capital and labor), and assess the effects that small firms' positions in networks have on their probability to scale-up successfully. Fifth, each factor has been described in general terms considering the space limit. Future research should take a closer look at mechanisms in each factor and their interface with other factors. Sixth, we made comparisons between US and Swedish EEs where differences among national institutions are strong. How institutional contexts differ among EEs in Sweden in detail, e.g. in terms of trust, would be an important avenue for further investigation.

The study showed that the impact of public policy is widespread in EEs in Life Sciences. It works through the direct funding of universities and (collaborative) research, the education of people, the development and enforcement of regulations, the establishment of support organizations, the provision of risk capital to LS firms (direct investments, subsidies, loan guarantees, matching funds etc.), et cetera. From the many potential roles of policy, we

choose to focus on only a few. The study revealed factors that acted as barriers to scaling-up processes in Life Sciences that might be tackled by specific policy intervention.
Considering firm-specific factors, first, there is a need for support to innovative firms to have access to growth-oriented management that is competent in life science, business and has international experience. This can be done through promoting national and international networks of firms via support organizations and TTOs. Second, connecting small firms to relevant actors in the EE early on could increase their reputation and trust they need to unleash resources they require. Considering firm-external factors, first, there is a need for access to more growth capital in terms of public and private funds. Public authorities should consider being more active and offer larger funds, matching funds, cheap loans etc. for the scale-up stages of the firms so that firms can reach further in their clinical trials, get higher international evaluations, and attract international capital. Second, in order to increase the vital global links of the small firms (with large firms and research institutes), actors in the EE like support organizations, universities and hospitals should work together and share their networks while supporting the reputation of small firms. Third, connections between universities, firms, and research hospitals can be strengthened through labor mobility across these organizations and through shared projects. Fourth, the expensive infrastructure and the expertise of the hospitals and the universities should be more accessible to small firms. Fifth, TTOs within universities in Sweden need to extend their growth networks with large firms and investors and employ the type of management skills that can support the scaling-up process of LS firms. Their employees should be encouraged to rotate between firms and organizations on a regular basis. And finally, local, regional and national support organizations and government should align their objectives towards supporting the scaling-up stages of LS firms in Sweden and foster culture of growth and higher risk tolerance in the EE.

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