Entrepreneurial Ecosystems in Life Science Industry

A study of start-ups, scale ups and resilience of Entrepreneurial Ecosystems

Alvedalen, Janna

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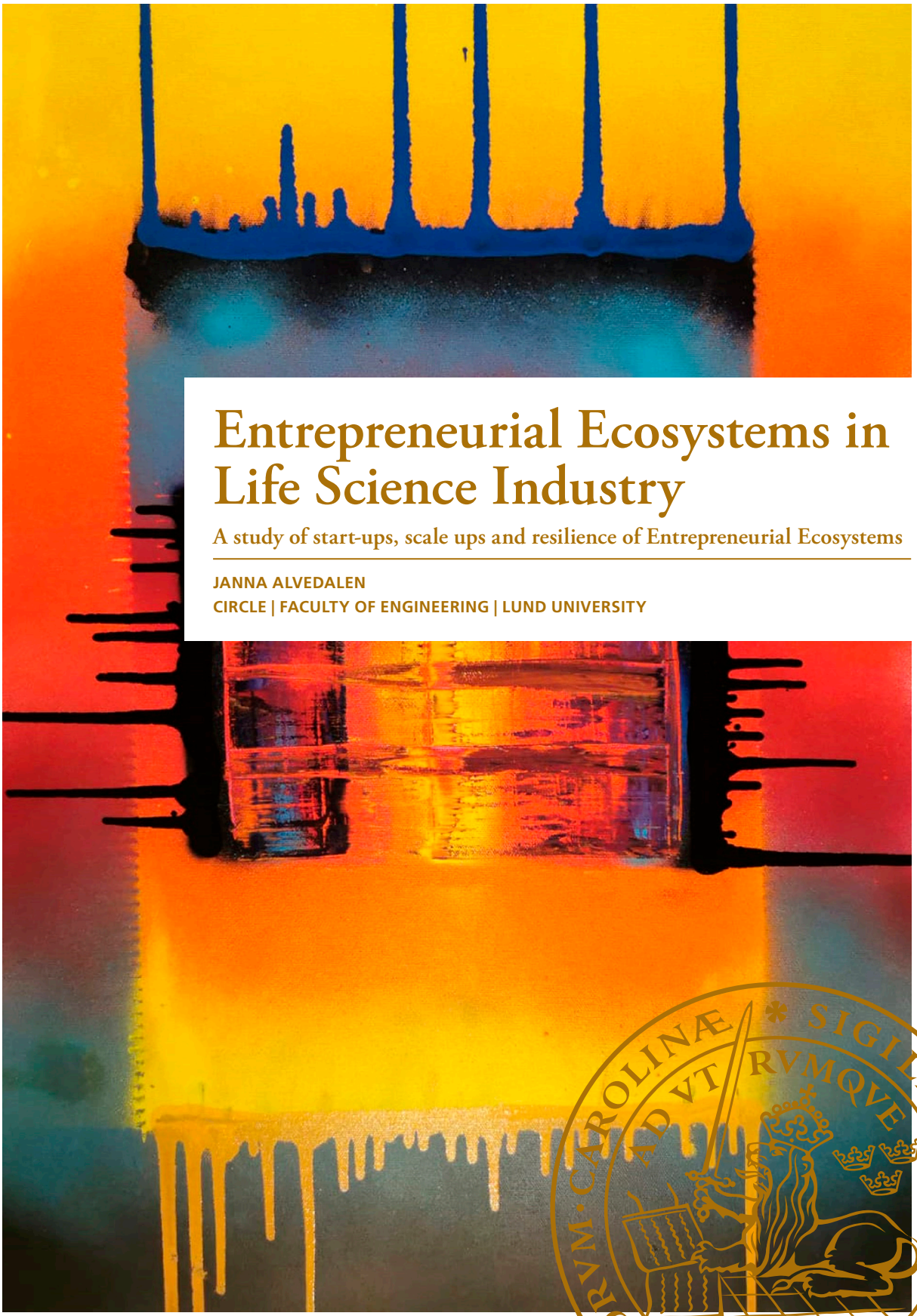

Entrepreneurial Ecosystems in Life Science Industry

A study of start-ups, scale ups and resilience of Entrepreneurial Ecosystems

JANNA ALVEDALEN
CIRCLE | FACULTY OF ENGINEERING | LUND UNIVERSITY

How can we improve the success of new innovative firms in a region?

BACKGROUND

M.Sc. in Entrepreneurship – New Venture Creation; Bachelor in Business Administration – Major in Marketing Management; Bachelor in Graphic Design.

After graduation I started my own business serving national and international clients in marketing and design projects. I also worked in an international IT consultancy firm and a national media firm within marketing and sales.

During my PhD I have been involved in teaching and grading courses in marketing, both at the bachelor (with 300-400 students per course) and master levels.

ABOUT THIS THESIS

This book is about Entrepreneurial Ecosystems. An Entrepreneurial Ecosystem (EE) is a concept that aims to understand the actors and factors important to new innovative firms in a region. Researchers found the EE concept under-researched and analytically weak, which also leads practitioners that use the concept to make uninformed decisions when supporting entrepreneurship.

Based on interviews with entrepreneurs and other actors in Life Science industry in five regions in Sweden and the US, this thesis shows how and why EEs look very different across regions. Also, how various key actors like venture capitalists, universities, hospitals and support organizations and their networks can be of help to new innovative firms.

This doctoral thesis makes Janna Alvedalen a PhD in Innovation Engineering

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A study of start-ups, scale ups and resilience of Entrepreneurial Ecosystems

Janna Alvedalen

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Abstract
The Entrepreneurial Ecosystem (EE) literature has presented itself as promising in recent years, as it adopts a systemic network approach on entrepreneurship. Despite its popularity, scholars have also raised some serious concerns, showing it is yet a rather underdeveloped concept. This dissertation addresses some of critiques on the EE literature by proposing four research papers that consist of conceptual and empirical studies. The thesis contributes first and foremost to the development of the EE literature by combining insights from other literatures including the ones on entrepreneurship, regional studies, resilience and social capital.

Conceptually, the dissertation takes stock of EE research based on a thorough literature review. The paper outlines the historical roots and antecedents of the EE concept, and it discusses the various definitions of EE, its constituent parts, and evolving trends in the EE literature. Most importantly, it critically assesses current findings and highlights a number of weaknesses of the EE literature. It comes to the conclusion that there is a lack of clarity with respect to a number of features of the EE concept. Based on this critical review, a future research agenda is presented that aims to tackle those weaknesses.

Empirically, the dissertation addresses some of these critiques in three empirical papers. For instance, the thesis conducts a comparative regional study and applies a multi-scalar approach to outline the specific nature and structure of EEs in Life Sciences in five regions in two countries – the US and Sweden. The role of linkages and institutions both inside and outside EEs are examined not only in general but also specifically for the scale-up process of Life Science firms in EEs. Hence, the thesis shows how EEs in different regions differ in how they support or hinder the growth of firms, highlighting the factors important specifically to productive entrepreneurship. The relative importance of factors (firm-specific and external factors) and how they influence each other are also examined. Moreover, the thesis also accounts for dynamics in EEs and their resilience. It studies a closure of a big multinational firm in an EE to see what implications it had for the functioning and transformation of the EE.

Finally, the dissertation offers a discussion on specific policies on EE that could improve the entrepreneurial performance of a region by (i) supporting an environment favorable to start-ups and growth of firms, providing basic conditions and stimuli (ii) supporting reinforcing mechanisms in EEs, and (iii) eliminating institutional and non-institutional obstacles.

Key words Entrepreneurial ecosystem, Life Sciences, Sweden, US, scale up, high-growth firms, resilience, place leadership, social capital, entrepreneurship, closure of large firm, productive entrepreneurship

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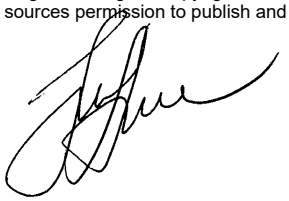
Signature 

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LUND
UNIVERSITY

About the cover:

Art is a state of being. A way to express our feelings and thoughts at a certain time in our life. Even if we don't remember those exact thoughts anymore, the result of them is here today, ready to be reinterpreted. Reminding us about something we forgot or to inspire us to something new – Mette Rasmussen (Malmö, 2021)

Painting: "Substance and flow". Acrylic on canvas
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MADE IN SWEDEN

To Elena, Ludmila, Yuri and Mette

Populärvetenskaplig sammanfattning

Hur kan vi stödja framgången hos nya innovativa företag i en region?

I min forskning fokuserar jag på Entreprenöriella Ekosystem. Ett Entreprenöriellt Ekosystem är ett relativt nytt koncept som syftar till att förstå de aktörer och faktorer som är viktiga för entreprenörskap och ger, eller inte ger, stöd till nya innovativa företag i en region.

Problemet är att flera beslutsfattare tyckte att Entreprenöriella Ekosystem konceptet var attraktivt men också otydligt vilket gjorde det svårt att implementera i praktisk politik. Forskare tyckte att konceptet var svagt utforskat och svagt analytiskt. Hittills har forskningen inte uppmärksammat alltför mycket det regionala och nätverksmässiga sammanhang i vilka nya innovativa företag växer fram. Konceptet förklarar att vissa regioner tillhandahåller mer gynnsam miljö för företagare än andra och hur företagare använder sina nätverk.

Det betyder att inte alla regioner är framgångsrika. Detta är olyckligt eftersom den ekonomiska utvecklingen i regioner beror på hur framgångsrika företagen är. Dessutom får den begränsade kunskapen om hur Entreprenöriella Ekosystem påverkas av lokala förhållanden och nätverk konsekvens för beslutsfattare som tvingas att ta beslut, som är svagt förankrade i forskningen, när de försöker stödja entreprenörskap.

Baserat på intervjuer med entreprenörer och andra aktörer inom Life Science-industrin i fyra regioner i Sverige och en i USA, drar jag slutsatsen att Entreprenöriella Ekosystem ser väldigt olika ut i olika regioner. Avhandlingen visar hur faktorer som lokal tillväxtkultur eller tillgången på finansiering stödjer eller hindrar tillväxten av nya innovativa företag. Dessa faktorer varierar mycket i deras roller i olika Entreprenöriella Ekosystem, och vidare hur dessa faktorer är starkt sammankopplade. Avhandlingen visar också att en nedläggning av en större aktör, som ett stort företag, när den hanteras på rätt sätt, kan leda till positiv utveckling i ett Entreprenöriellt Ekosystem på längre sikt.

Denna kunskap kan hjälpa intressenter som beslutsfattare, entreprenörer och andra aktörer att förstå hur ett Entreprenöriellt Ekosystem fungerar i olika regioner. Detta hjälper intressenterna att fokusera på de nyckelfaktorer som kan påverka företagens utveckling och hur olika nyckelorganisationer som till exempel investmentbolag,

universitet, sjukhus, finansiärer, supportorganisationer och deras nätverk kan stödja nya innovativa företag. Dessutom, blir det mer tydligt vilka åtgärder och vilket ledarskap som krävs när regionen ställs inför olika situationer som till exempel en kris.

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Acknowledgements

"Is it really possible to tell someone else what one feels?"

- Leo Tolstoy (Anna Karenina)

A PhD journey is a cognitive and an emotional exercise. Not seldom with extremes in both. I felt prepared for this exercise as I first worked in a few international companies and started my own business before pursuing this doctoral degree around entrepreneurship. And what an exciting journey I got! I have learned, achieved and experienced so much. There were many insightful and deep conversations, some tears, sleepless nights, amazing dinner parties and engagements with wonderful colleagues, friends and family. It was a holistic and world changing experience. I would like to thank each and everyone who has been part of my PhD journey.

My foremost gratitude goes to my supervisors. I would like to thank my main supervisor Professor Lars Bengtsson for believing in me, giving excellent support and pushing me to yet another level and completion of this thesis. It's hard to express how grateful I am for you being present, patient and always give quick and to the point feedback. I then want to express my sincere gratitude to my supervisor Professor Åsa Lindholm-Dahlstrand for taking me under your strong wing at the start, introducing me to key colleagues in my life and opportunities at home and abroad. I am also thankful to my supervisor Associate Professor Magnus Nilsson for you always being positive, open to conversations and supportive in times of despair. Truly, thank you all for investing time and effort in my learning through rewarding discussions and great advice.

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Friends, you have wondered where I went off for a few years, surfacing from time to time to request attention, love and support. I am forever thankful for hours long talks (e.g. Kevin Ohashi), visits, advice and happy distractions. I am also happy to have met new good friends during this time. You all are my source of energy.

And now I wish to say how deeply thankful I am to my family and my loved ones. My dear Mother, Elena, for always being there for me, for love, strength and support whenever I need it. My Father, Yuri, and Stepfather, Rolf, for your care and love. To my Grandmother, Ludmila, who is my core inspiration to pursue an academic career. My Uncle, Alexey, for making me laugh when…always. Words of encouragement from my relatives, extended family and family friends in different parts of the world warmed and inspired. Families Eickhoff, Berglind, Plusnini and Mikhalenok, thank you.

Большое спасибо за теплые слова, семьям Сухой, Плюснины и Михалёнок. Замечательно иметь вашу поддержку.

Once again, thank you all, I am looking forward to the next exciting chapter in my life, see you there.

Janna Alvedalen
January 8, 2021
Malmö, Sweden

List of appended papers

Article one:
Alvedalen, J., & Boschma, R. (2017). *A critical review of entrepreneurial ecosystems research: Towards a future research agenda*. Published in European Planning Studies, 25(6), 887-903

Article two:
Alvedalen, J. (2021) *Resilience after a large firm's closure: the role of place leadership, local resources, and social capital in the transformation of an Entrepreneurial Ecosystem.* Submitted to an international peer-reviewed journal.

Article three:
Alvedalen, J., & Carlsson, B. (2021). *Comparative analysis of five Entrepreneurial Ecosystems in Life Sciences.* Accepted for publication in edited volume by Prof. Robert Huggins titled 'Entrepreneurial Ecosystems in Cities and Regions: Emergence, Evolution, and Future', Oxford University Press.

Article four:
Alvedalen, J., & Carlsson, B. (2021) *Scaling up in Entrepreneurial Ecosystems: A comparative study of Entrepreneurial Ecosystems in Life Sciences.* Submitted to an international peer-reviewed journal.

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Chapter 1:
Introduction to the thesis

The introduction describes the studied phenomenon, the key literature, and the background to the problem. The aim, the research question of the thesis as a whole and the overview of the four appended papers are followed by the structure of the remainder of this thesis.

The Entrepreneurial Ecosystem (EE) literature has surged in popularity rather recently, as it adopts a systemic network approach on entrepreneurship and accounts for the regional context (Schäfer and Mayer 2019; Maroufkhani et al. 2018). The EE concept continues to attract much attention from scholars (Stam 2015; Spigel 2017), practitioners (Isenberg 2010, 2016; Feld 2012, 2020) and policy makers (Foster et al. 2013 ; Stangler and Bell-Masterson 2015). Despite its popularity, scholars have also raised some serious concerns, showing it is yet a rather underdeveloped concept (Stam & Spigel, 2016; Spigel, 2017). This thesis will contribute to tackling a number of weaknesses in the EE literature both theoretically and empirically.

What is the EE concept about? The concept stems from the view that new ventures are started by entrepreneurs that are connected to their environment. From an EE perspective, entrepreneurs and their context are viewed as a system of interconnected nodes delimited by geographical boundaries. EE sheds light on factors, actors and institutions that are interlinked and that support, or not, new innovative firms. Cohen (2006) was one of the first to use the concept of EE and defined it as follows: "… an interconnected group of actors in a local geographic community committed to sustainable development through the support and facilitation of new sustainable ventures" (p. 3). Stam and Spigel (2016) proposed a definition of EE that focuses on productive entrepreneurship and, more specifically, on firms that grow: "a set of interdependent actors and factors coordinated in such a way that they enable productive entrepreneurship within a particular territory" (Stam and Spigel 2016, p. 1).

How did the EE concept emerge and develop? A key source of inspiration has been the neo-Schumpeterian economic school of thought that claims that entrepreneurs develop new innovations and thus play a key role in the development of society at large (Hanusch and Pyka 2007). The entrepreneurship literature has generated

important insights how new firm formation can be facilitated, and what are its effects on economic development (Acs 2006). However, the link between entrepreneurship and economic development has also been debated for a while, as not many firms survive and grow (Storey 1994; Parker 2004). In order to explain entrepreneurship, scholars have looked into individual qualities of entrepreneurs such as their attitude to risk, and they have discussed if entrepreneurs are born with certain unique traits (McClelland 1961; Kerr et al. 2017). Scholars (Oakey 1995; Gorman et al. 1997; Henry et al. 2005; Gabrielsson and Politis 2012; Drucker 2014) have also looked at different types of competences that are needed in new firms such as technical and managerial knowledge. However, not much attention has been given to the context in which entrepreneurial activity is embedded (Welter and Gartner 2016). Consequently, scholars have discussed a need for a holistic framework that integrates both individual and contextual factors to understand entrepreneurship (Shane 2003; Acs et al. 2014).

One way of looking at the role of the context for entrepreneurship is to follow a systemic view on entrepreneurship. This idea builds on older literature (Dubini 1989; Van de Ven 1993) that argues that entrepreneurship is embedded in networks of relationships (Johannisson 2000; Nijkamp 2003; Stuart and Sorenson 2005; Lefebvre et al. 2015). Interconnected actors relevant to entrepreneurship can influence each other in highly complex ways. This requires a holistic, systemic approach, rather than a reductionist approach that focuses merely on separate parts (Roundy et al. 2018). This comes close to what Ackoff (2008) calls 'systems thinking': "systems thinking looks at relationships (rather than unrelated objects), connectedness, process (rather than structure), the whole (rather than just its parts), the patterns (rather than the contents) of a system, and the context" (p.86). However, while scholars have embraced the need for such a systemic view on entrepreneurship to understand entrepreneurial dynamics, systematic empirical evidence is still rare.

Another crucial context variable is the location of entrepreneurship. According to Delgado et al. (2010), a stronger economic effect from entrepreneurship is expected when new firms cluster in places, rather than when they develop in geographical isolation from each other (Rocha 2013; Audretsch 2013). A large number of European countries focus their efforts on supporting entrepreneurship and firm clustering, with the aim of promoting economic growth and competitiveness (OECD 2009). However, research has shown that not all regions are blessed with high entrepreneurial activity. The level but also the nature of entrepreneurship differs across regions to a large extent. The Global Entrepreneurship Monitor has reported different types of entrepreneurial activity in different regions and countries (Reynolds et al. 2005; Stam et al. 2011). This may be due to institutions (Sine and David 2010; Gertler 2010), support structures (Johannisson 2000) and networks (Boschma and Ter Wal 2007; Giuliani 2007). Ignoring the regional context explains why studies often find the link between entrepreneurship and economic development not that straightforward (Backman and Lööf 2015) Some regional

contexts might be more favorable to stimulate entrepreneurship. But more importantly, these regional contexts might also explain why entrepreneurship in some regions does not translate into economic development (Fritsch and Storey 2014). For instance, regional factors might block the scaling-up process, preventing entrepreneurial firms to become high-growth firms in certain regional contexts. This requires understanding of which regional factors matter (Feldman 2001; Sleuwaegen and Ramboer 2020).

So, a key objective of the EE literature is to apply a systemic approach to entrepreneurship. However, the EE concept is still underdeveloped. Stam (2015) has mentioned issues like EE being an undertheorized and loosely defined concept, using insufficient types of measurements, and drawing generalizations from mostly successful case studies, like Silicon Valley. Stam (2015) also discussed problems such as listing relevant elements without providing clues for how these elements influence each other. Moreover, there is no consensus on what is understood by a network, and the consequences of missing elements for the functioning of an EE are still underexplored. The way geography is treated in the EE literature is still poor. For instance, there is a lack of studies that have looked into the importance of both local and non-local linkages for entrepreneurship, and little to no regional comparative studies have been conducted. Finally, most EE studies have adopted a static approach, ignoring the dynamic development of EEs over time (Mack and Mayer 2016).

Aim and Research Questions

The main objective of this PhD project is to tackle a number of the above-mentioned shortcomings in the EE literature. This PhD project will use and combine insights from different literatures such as the entrepreneurship literature, the innovation studies literature, and the literature on regional studies. This makes it an interdisciplinary research project, which is a prerequisite to describe and explain a complex phenomenon such as entrepreneurship (Sauvé et al. 2016). The empirical research in the PhD project will be carried out at different levels of analysis: at the level of individuals (as embodied e.g. in entrepreneurs, employees and political leaders), organizations (e.g. firms, universities, capital suppliers), industries (life science industry), institutions (as embodied in regulations, business cultures and policies, among others), and places at various scales (regions, countries).

Based on the preceding arguments, the **aim** of the thesis is:

To identify and address limitations of the Entrepreneurial Ecosystems literature by studying how actors, factors and their interactions impact entrepreneurial firms in life sciences in different Entrepreneurial Ecosystems.

Particular focus of this thesis is on the Life Science (LS) industry. The LS industry represents companies whose activities contribute to human health including the development of pharmaceuticals, medical devices and treatments. LS is a highly innovative industry, an important contributor to economic growth, and crucial for the well-being of societies. LS is crucial for promoting healthy life through for instance the development of medical innovations, which is part of the Global Goal for Sustainable Development, Agenda 2030 (Government Offices of Sweden 2020). The current pandemic situation has triggered interest from politicians across the globe in issues like the roll out of medical innovations in an effective manner. Increasing our understanding of EE in Life Sciences is therefore essential also from a societal point of view.

The LS industry includes three sectors: Pharmaceuticals (Pharma), Medical Technology (MedTech) and Biotechnology (BioTech). The LS industry is an ideal case to study entrepreneurship from an EE perspective. First, the LS industry is known to be concentrated in a few places in various countries. Therefore, studying LS opens the opportunity to look at entrepreneurship in a comparative regional setting. It is expected that the level and rate of entrepreneurship in LS will differ between locations because EEs differ across geographical locations. Second, the LS industry relies heavily on connections between many actors such as university, funding bodies and large firms both locally and globally (Owen and Hopkins 2016; Carlsson 2012).

LS is known to be an industry with high risk/high reward ratio. It is highly dynamic, has a strong need for capital and knowledge resources, and it has long average product development time. This makes it a good case to adopt a systemic view on entrepreneurship and study the strength and nature of different links in EEs. Third, policy makers show a strong interest in supporting the LS industry. New innovative firms in LS are vulnerable organizations because they suffer from little resources and a lack of strong reputation. This makes that policy makers need to understand their needs well, in order to support them (Brännback et al. 2009).

Advancing the understanding of entrepreneurship through the lens of EEs is valuable for four reasons. First, it offers insights into how the interlinked actors and factors at different regional levels impact entrepreneurship. Taking such a systemic take on entrepreneurship will increase our understanding of how firms are supported or hindered by the actors, links and structures of EEs in different contexts. In the case of LS, this can be seen, for instance, in the lack of strong connections between entrepreneurs and universities and how that restricts the flow of e.g. human capital and the making of connections to customers and funding bodies. Second, it showcases the mechanisms, and relationships between them, that drive different phases of development of firms in different EEs. Distinction is made between start-up and scale-up phases. The start-up phase refers to the initial steps of the firm both prior and after its registration. The scale-up phase refers to the phase after the registration of the firm when the initial patents have been acquired and the

product/service is shaped for the market. In the case of LS, the start-up phase requires highly risky investments and strong local research connections, and it works as the phase for establishing future important connections with e.g. Venture Capital (VC) investors for the scale-up phase. Third, it provides insights into the multi-scalarity of actors and factors that play a critical role in entrepreneurship. It shows how a combination of global factors (such as the need for reaching global markets and global players), national factors (such as national policies and laws) and regional factors (such as a local collaborative culture) may lead to specific entrepreneurial outcomes in EEs in the LS industry. Fourth, it explains the reasons why entrepreneurship in LS differs between different territorial contexts. This study focuses on two countries (the US and Sweden) and four regions in Sweden, to enable comparisons between countries, and between regions within the same country.

In order to contribute to the development of the EE literature, the research question of this dissertation is: *How do actors, factors and their interactions impact the start-up, scale-up and resilience of entrepreneurial firms in different EEs?*

To capture the aim and the main research question, four sub-questions guide the conceptual and empirical studies of this thesis.

- *What are the strengths and weaknesses of the Entrepreneurial Ecosystem concept?*
- *Which actors, factors and interactions are at play in EEs in different regions, and how do they impact the dynamics of entrepreneurial firms?*
- *Which actors, factors and interactions are at play in the scaling-up phase of entrepreneurial firms in different EEs in different regions?*
- *Which actors, factors and interactions can be held responsible for the transformation and resilience of an EE when confronted with a shock (i.e. the closure of a major local company)?*

Overview of the articles

To address the aim and the research questions, this dissertation contains four articles that are published or under review in peer-reviewed academic journals and academic books. See summary in table 1.2. They were written in the period 2015-2020. Summary of all four articles and their connection to the overall aim of the PhD thesis are presented here.

Article one: *A critical review of entrepreneurial ecosystems research: towards a future research agenda.*

This article critically examines the state of the EEs literature and identifies key limitations. It presents definitions and elements of the EEs and highlights some shortcomings of EE research, such as a lack of a clear analytical framework and the lack of a multi-scalar perspective. Furthermore, it provides suggestions for future research on EE, some of which are taken up by the subsequent articles.

Article two: *Resilience after a large firm's closure: the role of place leadership, local resources, and social capital in the transformation of an Entrepreneurial Ecosystem.*

This article addresses one of the research gaps identified in the EE literature, which is the lack of a dynamic perspective. The paper studies the surprisingly positive transformation of the EE of Lund in LS, after the closure of a large pharmaceutical multinational firm. It sheds light on factors such as place leadership that may enhance the resilience of an EE.

Article three: *Comparative analysis of five Entrepreneurial Ecosystems in Life Sciences.*

This article explores and compares five EEs in LS in the US and Sweden. The paper addresses several limitations of the EE literature: it presents a comparative and multi-scalar (different geographical scales) approach to EEs and it explores the systemic structure of EEs. The article outlines commonalities and differences between EEs in different geographical contexts, and it explores how that impacts the rate and nature of small innovative firms. It highlights how different actors, factors and interactions operate in distinct geographical and institutional contexts, underlining the importance of a territorial perspective on EEs.

Article four: *Scaling up in Entrepreneurial Ecosystems: A comparative study of Entrepreneurial Ecosystems in Life Sciences*

This article investigates what actors and factors impact the scaling-up phase of innovative start-up firms in different EEs. Key enablers and barriers to scaling-up in EE for LS are identified as factors specific to firms and factors external to firms. The article explains how these factors are interconnected and differentiated across distinct geographical and institutional contexts in four regions in Sweden and one region in North East Ohio, US.

Papers 1, 3 and 4 were co-authored with other researchers, while paper 2 is single-authored. Table 1.1 presents more information on the papers, like the main unit of analysis, the contribution statement in each paper, and the current publication status of the papers.

Table 1.1: The contribution statement, unit of analysis and publication status of the appended papers

Papers	Author(s)	Contribution statement	Unit of analysis	Publication Status
I.	Alvedalen, J. Boschma, R.	I am the main author. I took full responsibility for reviewing and synthesizing the EE literature and I have shared responsibility for writing up the paper.	The EE literature	- Published in European Planning Studies (Taylor & Francis) - Presented at Eu Spri conference 2016
II.	Alvedalen, J.	Single-authored	The resilience mechanism in EE	- Submitted to an international scientific journal - Accepted to conference European Academy of Management (EURAM) 2020 - Published in Circle working papers
III.	Alvedalen, J. Carlsson, B.	I am the main author. I shared responsibility for data collection and data analysis. I was responsible for the framing, and writing most parts of the manuscript. First draft was developed in collaboration over a long time covering joint conference paper presentations, changes and comments.	The EEs in 5 Regions	- Accepted for publication in forthcoming edited volume by Prof. Robert Huggins titled 'Entrepreneurial Ecosystems in Cities and Regions: Emergence, Evolution, and Future' (Oxford University Press) - Presented at e.g. 2017 RENT XXXI - RESEARCH IN ENTREPRENEURSHIP AND SMALL BUSINESS - Accepted to conference CSEEE 2021: International Conference on Systemic Entrepreneurship and Entrepreneurial Ecosystems - Published in Circle working papers
IV.	Alvedalen, J. Carlsson, B.	I am the main author. I was responsible for data analysis. I shared responsibility for the data collection. I was responsible for the framing, and writing most parts of the manuscript. First draft was developed through changes and comments.	The scale up process in EEs	- Submitted to an international scientific journal - Published in Circle working papers

Table 1.2: Aim and research question of the thesis and summary of appended papers with research questions and purpose.

Aim of the thesis: To identify and address a number of limitations of the Entrepreneurial Ecosystems literature by studying how actors, factors and their interactions impact entrepreneurial firms in life sciences in different Entrepreneurial Ecosystems

Research question of the thesis: How do actors, factors and their interactions impact the start-up, scale-up and resilience of entrepreneurial firms in different EEs?

Research papers	Specific Research questions	Purpose
Paper 1. A critical review of entrepreneurial ecosystems research: towards a future research agenda	What are the strengths and weaknesses of the Entrepreneurial Ecosystem concept?	To critically review the EE literature, identify research gaps and suggest future research agenda that is addressed in the empirical papers.
Paper 2. Resilience after a large firm's closure: the role of place leadership, local resources, and social capital in the transformation of an Entrepreneurial Ecosystem	Which actors, factors and interactions can be held responsible for the transformation and resilience of an EE when confronted with a shock (i.e. the closure of a major local company)?	Develop an understanding of the dynamics of EE by studying why and how the structure of actors, factors and interactions responded to an internal shock and what the EE transformed into.
Paper 3. Comparative analysis of five Entrepreneurial Ecosystems in Life Sciences	Which actors, factors and interactions are at play in EEs in different regions, and how do they impact the dynamics of entrepreneurial firms?	Explore and compare across different regions how EEs are structured systemically by identifying key actors, factors and their connections, describe their roles, geographical level of operation and impact on the dynamics of entrepreneurial firms.
Paper 4. Scaling up in Entrepreneurial Ecosystems: A comparative study of Entrepreneurial Ecosystems in Life Sciences	Which actors, factors and interactions are at play in the scaling-up phase of entrepreneurial firms in different EEs in different regions?	Explore and compare across different regions how certain parts of structures of EEs impact the scale up process of the entrepreneurial firms.

Structure of the dissertation

This compilation PhD thesis consists of a Kappa (general introductory chapters or a 'coat' in Swedish) and four appended articles. The aim of the Kappa is to provide an overview of the research problem, a background for the empirical studies, and it explains the applied methodologies. The overall contribution of the thesis is then summarized and discussed in relation to the overall aim and the main research question. It concludes with policy implications.

The Kappa consists of the following chapters:

Chapter one (this chapter) is an introduction that provides the underlying practical and theoretical motivation and the background for the research project. The current literature is problematized and choices of the research context are explained. The chapter presents the aim and the guiding research questions of the thesis. An overview of the papers and their relation to the overall aim is presented.

Chapter two introduces the theoretical framework to the research topic. It provides a literature review on the Entrepreneurial Ecosystem research in terms of definitions, antecedents and critiques. It concludes with a motivation for the thesis.

Chapter three concerns the research design. It outlines the ontological and epistemological perspectives that are applied in the thesis, the main methodological considerations and the methods used for addressing the research questions. Furthermore, the data sources, the data collection and the data analyses are described and motivated.

Chapter four describes the empirical context of the thesis in terms of industry and geography. The chapter presents the LS industry, followed by an outline of the regions the research is focusing on.

Chapter five accounts for the four appended papers. It states the research questions, and it presents the main findings and contributions of each article separately. It provides the basis for the synthesis of the individual arguments leading to the overall findings and contributions of the thesis in the subsequent chapter.

Chapter six provides a discussion and a conclusion based on the synthesis of the conceptual and empirical results. It explains how separate articles contribute to the main findings and the overall contribution of the thesis as a whole, by going back to the overall research question stated in the introduction. It concludes with presenting and discussing a number of limitations of the thesis, a few key areas for future studies on EE, and a number of policy implications.

Chapter 2:
Theoretical framework

The chapter describes the theoretical background for the thesis. It addresses the rise of the Entrepreneurial Ecosystem concept and its antecedents, definitions and elements. It, then, presents and discusses the critique of the Entrepreneurial Ecosystem literature. Motivation for the thesis concludes.

The rise of the Entrepreneurial Ecosystem concept

Being absent from economic theory for long, the entrepreneur was introduced by Joseph Schumpeter as a key driver of economic progress in his works in the 1900s. His core idea of entrepreneurship lies in the concept of "creative destruction" that refers to new combinations of resources – innovations – that are brought to the market by entrepreneurs, simultaneously creating new organizations and destroying old ones (Schumpeter 1942).

Entrepreneurship is considered crucial for economic development in several ways. According to Acs et al. (2014), the most important economic benefits derived from entrepreneurship are the creation of jobs (Blanchflower 2000; Shane 2003; Parker 2009), innovation (Acs and Audretsch 1988), productivity (van Praag and Versloot 2007), and the transfer of knowledge and technology from research to industry (Acs et al. 2009a; Grimaldi et al. 2011; Plummer and Acs 2014; Terjesen and Wang 2013). According to (Baumol 1996), it is productive entrepreneurship that contributes to the output of the economy. Entrepreneurial success is a rare phenomenon as many new ventures fail. Therefore, the above-mentioned indicators are measures of rare but much desired events (Shane 2003).

In the entrepreneurship literature, this has led to a search for factors than can explain successful entrepreneurship. Entrepreneurship scholars can be separated into two groups when it comes to explaining the entrepreneurial prevalence and success. One group assumes that entrepreneurs possess specific behaviors and traits such as tolerance for ambiguity (Schere 1982), willingness to bear uncertainty (Khilstrom and Laffont 1979), need for achievement (McClelland 1961), risk-taking propensity, locus of control, conscientiousness, openness to experience, emotional

stability, extraversion and agreeableness (Delmar and Davidsson 2000), being good leaders (Jensen and Luthans 2006), et cetera.

The other group focuses on regional and social environment in which entrepreneurship is situated (Van de Ven 1993; Spilling 1996; Aaboen 2009; Zahra and Wright 2011; Autio et al. 2014; Zahra et al. 2014). Studies show that places differ with respect to start-up activity, and that this uneven geography of entrepreneurship is persistent over time (Andersson and Koster 2011; Fritsch and Wyrwich 2014). Many new high-tech firms are created in clusters which are perceived to bring all kinds of benefits that compensate for the size disadvantage of small firms (Audretsch 2003). The opportunity structures and creative cultures in some regions have also been pointed out as important (Hackler and Mayer 2008). Scholars have investigated how regional factors like unemployment rate, population density, population growth, levels of labor skills and human capital impact start-up rates in regions. Key findings for that impact have been for population density (positive impact), population growth (positive impact), human capital and skill levels of the labor force (positive impact), and the mean of establishment size (negative impact) but findings are more inconclusive regarding the effect of unemployment (Audretsch 2003).

Another context that has been considered crucial for entrepreneurship is networks. The network approach to entrepreneurship stems from sociology (Aldrich and Zimmer 1986) and states that "entrepreneurship is a relational task, and is inherently a networking activity" (Dubini and Aldrich 1991, p.306). Focus of research has been on the personal network of the entrepreneur with the basic idea that entrepreneurship requires building of relationships that is embedded in social, political, and cultural contexts (Audretsch 2003). Institutions like laws and regulations, such as high taxes and administrative burden, may have a negative impact on start-up rates (Audretsch 2003; Bengtsson 2017; Holgersson and Aaboen 2019), but institutions also have an impact on the formation of entrepreneurial networks (Johannisson et al. 2002; Sine and David 2010). Culture and social capital have an impact on entrepreneurship through trust, for instance (Westlund and Bolton 2003; Nilsson 2019), but it is not always clear exactly in what ways (Westlund and Adam 2010; de Vaan et al. 2019).

In the last decade, scholars have developed a new literature on Entrepreneurial Ecosystems (EE). It did not really grow out of a huge dissatisfaction with the entrepreneurship literature, although the EE literature took up a number of critical points that had been debated in the entrepreneurship literature for some time. For instance, there was an increasing recognition that entrepreneurship studies should take a more systemic approach because it was considered crucial to study the interconnectedness of actors and factors that impact entrepreneurship (Audretsch 2003; Acs et al., 2014; Gustafsson and Autio 2011; Szerb et al. 2012; Qian et al. 2013). The EE concept has gained a lot of attention from researchers, practitioners and policy makers (Acs et al. 2014, 2017; Auerswald 2015; Stam 2015; Audretsch and Belitski 2017; Motoyama and Knowlton 2017; Spigel 2017; Stam and Spigel

2016; Autio et al. 2018; Schäfer and Mayer 2019). The term EE emerged first in the 2000s (Malecki 2018) and popped up as a buzzword across start-up related communities soon after (Isenberg 2010, 2011; Feld 2012, 2020), followed by reports of the World Economic Forum (Foster al. 2013) and the OECD (Mason and Brown 2014). What was crucial is that policy makers embraced EEs like the new pandoras box because they felt it could promote economic development in their regions through entrepreneurship and new venture creation (Stam and Van de Ven 2018).

Antecedents of Entrepreneurial Ecosystem concept

The roots to the EE concept can be found across different literatures (Acs et al. 2017a, b; Audretsch and Belitski 2017; Cavallo et al. 2019; Erina et al. 2017; Yun et al. 2017). Several concepts from other literatures have been compared to EEs (Spigel and Harrison 2018; Cao and Shi 2020) like industrial districts (Marshall 1920), clusters (Porter 1998, 2000; Delgado et al. 2010), (regional) innovation systems (Freeman 1995; Lundvall 1992; Cooke 2001), strategic management (Acs et al. 2017b), business ecosystems (Moore 1993; Adner 2017), and triple helix (Leydesdorff and Etzkowitz 1996). Many of these concepts deal with business strategies, knowledge creation and innovation, both within firms and how these are embedded in contextual settings such as places, networks and systems.

The geography of innovation literature has been particularly influential. This literature has demonstrated that only few places excel in knowledge creation and innovation (Audretsch and Feldman 1996). A key reason is that geographical proximity facilitates the sharing of (tacit) knowledge, which leads to inter-firm learning and innovation (Jaffe et al. 1993; Boschma 2005). Many industries, especially knowledge-intensive ones, tend to concentrate in a few regions where they enjoy local advantages, like a strong research infrastructure, and access to human and venture capital (Cortright and Mayer 2001, 2002). These local externalities have been described in concepts like industrial districts (Becattini 1990), learning regions (Asheim 1996), innovative milieu (Camagni 1991) and clusters (Porter 1998), to stress the importance of regions for entrepreneurship and innovation. What these concepts did not do fully is to incorporate and measure networks through which knowledge is channeled and learning takes place (Giuliani and Bell 2005; Boschma and Ter Wal 2007; Ter Wal and Boschma 2009).

The systemic view on entrepreneurship (Neck et al. 2004; Sternberg 2007; Ylinenpää 2009; Acs et al. 2014) found inspiration in the innovation system literature (Freeman 1987). This literature focused on interlinked actors and institutions and how they impact the generation, diffusion and use of innovations (Qian et al. 2013). However, some have argued that they have largely ignored the role of the entrepreneur and high-growth firms in the creation of new value (Acs et al. 2014; Acs et al. 2017b; Spigel and Harrison, 2018). Another literature that acted

as a source of inspiration in this respect was the ecosystem literature (Auerswald 2015; Auerswald and Dani 2018). EEs have been described as a metaphor for a human system and have been compared to a natural ecosystem and its functions (McMullen 2018). The key difference is that a natural ecosystem is self-regulating but not self-conscious, and the EEs have self-conscious elements. Hence, EEs are self-regulating too, but due to the self-reflection of actors, not due to natural processes (Kuckertz 2019).

What is an Entrepreneurial Ecosystem?

There are many definitions of entrepreneurial ecosystems. What they tend to share is that the entrepreneur is the key actor that utilises and develops the EE. EEs are considered communities of interconnected actors that depend on each other (Audretsch and Belitski 2017). EEs include interlinked entrepreneurs and the context in which they operate that together impact entrepreneurship in a region (Acs et al. 2014; Stam 2015). The quality of EEs is described in terms of the interrelation of the elements in EEs and related to the prevalence of high-growth firms (Stam and van de Ven 2019), but less so for serial entrepreneurs (Vedula and Kim 2019). EEs have also been described as interaction systems of stakeholders (Autio 2016) and complex adaptive systems (Roundy et al. 2018).

Qian et al. (2013) define an Entrepreneurial System as 'those economic, social, institutional and all other important factors that interactively influence the creation, discovery and exploitation of entrepreneurial opportunities' (p. 561). Mason and Brown (2014) describe EE as 'a set of interconnected entrepreneurial actors (both potential and existing), entrepreneurial organizations (e.g. firms, venture capitalists, business angels, banks), institutions (universities, public sector agencies, financial bodies) and entrepreneurial processes (e.g. the business birth rate, numbers of high growth firms, levels of 'blockbuster entrepreneurship', number of serial entrepreneurs, degree of sellout mentality within firms and levels of entrepreneurial ambition) which formally and informally coalesce to connect, mediate and govern the performance within the local entrepreneurial environment (p. 5). And Audretsch and Belitski (2017) describe EE as 'institutional and organisational as well as other systemic factors that interact and influence identification and commercialisation of entrepreneurial opportunities' (p. 1031). This latter definition relates to the knowledge and the ability of the entrepreneur to spot and seize new business opportunities (Gabrielsson et al. 2014).

The most commonly used definition of EE is by Stam and Spigel (2016). They define EE as 'a set of interdependent actors and factors coordinated in such a way that they enable productive entrepreneurship within a particular territory' (p. 1). This definition is also used in this thesis because it has good coverage of key features mentioned in other definitions, but it also includes explicit focus on productive

entrepreneurship and the role of geography. EEs are described to focus on generic business processes around firm creation rather than around a specific technology (Stam and Spigel 2016; Spigel 2017). Sussan and Acs (2017) and Song (2019) proposed and developed a framework for digital entrepreneurial ecosystem relying on technology in a broad sense as part of basic infrastructure, such as for e-commerce firms (Svingstedt et al. 2014; Vakulenko et al. 2019). Another developing stream of EE research considers sustainable entrepreneurship ecosystems (O'Shea et al. 2019) that target firms with business models focusing on sustainability (Wadin et al. 2017).

The EE literature aims to explain productive or ambitious entrepreneurship in particular, by 'individuals exploring opportunities to discover and evaluate new goods and services and exploit them in order to add as much value as possible' (Stam and Spigel 2016, p. 1). This description stems from Baumol's definition of productive entrepreneurship which is 'any entrepreneurial activity that contributes directly or indirectly to net output of the economy or to the capacity to produce additional output' (Baumol 1993, p. 30). The specific focus on productive entrepreneurship moves EE away from traditional studies on entrepreneurship that are concerned with self-employment and all new firms no matter their aspiration. Its focus is on scale-ups or high growth firms as these are expected to have the strongest impact on the economy, like new job creation (Gabrielsson et al. 2014; Mason and Brown 2017).

Most definitions of EE agree on a geographically defined border that includes factors necessary for entrepreneurship. Even if the geographically defined boundary can, in theory, be on any level (Qian et al. 2013), many EE studies focus on (high-tech) clusters such as Boulder County and Phoenix in the U.S., and Waterloo, Calgary and Victoria in Canada (Neck et al. 2004; Cohen 2006; Feld 2012; Mack and Mayer 2016; Spigel 2017). This makes research on clusters (Rocha and Sternberg, 2005; Delgado et al. 2010) relevant for the study of EEs (Mason and Brown 2014). Cukier et al. (2016) proposed to limit the geographical distance of an EE to 48.20 Km (or about 30 miles) or 1 hour's travelling time. However, this boundary is considered too rigid: boundaries are blurry and often changing, and therefore hard to draw, and interactions between actors often cross strict geographical boundaries.

Elements of Entrepreneurial Ecosystems

EEs are defined in terms of elements and the interaction patterns between these elements. For example, Spigel (2017) proposed ten cultural, social, and material interlinked attributes that reproduce an EE. Isenberg (2010) suggests that the interaction of the elements leads to specific configurations and results in unique EEs in different places. According to Isenberg (2010), EEs consist of six domains: (1) policy (leadership and government); (2) financial capital; (3) culture (success stories and societal norms); (4) supports (infrastructure, support professions); (5) human capital (educational institutions and labor); and (6) markets (early customers and networks). Other EE scholars have presented a list of factors like universities and human capital (Green et al. 2010; Rice et al. 2014; Allahar and Sookram 2019), support organizations (Aaboen et al. 2011), (private and public) customers, leadership, regulatory frameworks (Stam 2015), and institutions like openness to experimentation, tolerance for risk and failure, trust, and a positive image of entrepreneurs in society (Isenberg 2011; Spigel 2017; Muldoon et al. 2018). These elements are connected and interact in complex ways, and they develop and reinforce each other (Spigel 2017). The complexity lies in the many stakeholders with possibly different goals that are involved, the many causal chains of events with direct and indirect effects, the fact that no stakeholder can have a full overview of how an EE works, and the imperfect information sharing (Autio and Levie 2017). The complexity of interactions in an EE has led some researchers to suggest that EEs should be studied from a complex system approach and system theory (Roundy et al. 2018).

EEs are also seen as resource allocation systems where the entrepreneur brings together labor, capital, and knowledge (Acs et al. 2014; Autio and Levie 2017; Acs et al. 2018; Spigel and Harrison 2018). Entrepreneurial recycling is seen as one key element of resource provision (Spigel and Harrison 2018). However, in order for resources to be useful, they need to be accessed and activated by entrepreneurs through networks (Cao and Shi 2020). Liabilities of newness and smallness can hinder entrepreneurs to obtain trust and access resources that are locked in social circles (Mesquita 2007). These liabilities can, however, be mediated by the resources and networks that are provided by support organizations (Amezcua et al. 2013; Drori and Wright 2018; Goswami et al. 2018; Breivik-Meyer et al. 2019; Breznitz and Zhang 2019; Pustovrh et al. 2020). Interestingly, how support from the EEs is perceived and impact start-up activity can also depend on the gender of the entrepreneur (Alsos et al. 2006; Alsos and Ljunggren 2017; Hechavarría and Ingram 2019; Sperber and Linder 2019).

Effective governance of EE is a key element relevant for policy development (Isenberg 2011; Auerswald 2015; Stam 2015). It should account for multiple stakeholders that are involved at different levels which requires coordination of their commitments and alignment of their long-term visions (Rice et al. 2014; Motoyama

and Knowlton 2017; Goswami et al. 2018; Cunningham et al. 2019; Roundy and Fayard 2019). It has been argued that 'market failure' and 'systems failure' approaches to policy involvement can assume more static, hierarchical and siloed tactics than is helpful for holistic EEs (Lundström and Stevenson 2005). Hence, the collective governance should assess the impact on the system as a whole, and should follow a broad-based, concerted and enabling strategy, rather than focusing on economic or structural incentives separately (Auerswald 2015; Spigel 2017; Cao and Shi 2020). Brown and Mawson (2019) propose eliminating network failures, avoiding policy isomorphism, and using tailored interventions to the specifics of EEs as key policy lessons.

Overall, the new features of the EE concept, in comparison to the antecedents, lie in (i) a strong focus on the entrepreneur, entrepreneurial opportunity and the small firm (Autio et al. 2018); (ii) the interlinked factors in the system (Isenberg 2010, 2011; Cao and Shi 2020); (iii) the dynamic interplay between agency (entrepreneur) and structure (environment) (Acs et al. 2014); (iv) a focus on productive entrepreneurship (Stam and Spigel 2016); (v) the fact that the entrepreneur is both the outcome, the leader and the input to the system (Feldman 2014; Lindholm-Dahlstrand et al. 2019); and (vi) a focus on (local) networks and institutions.

Critique of the Entrepreneurial Ecosystem literature

However, it also became clear early on that the EE concept was weakly founded in academic research (Stam 2015; Stam and Spigel 2016). The EE is a relatively new concept, and the EE literature has been subject to fundamental critique on a regular basis. It is yet theoretically weak despite very recent contributions. The aim of the thesis is making an attempt to address a number of these shortcomings. The critique can be briefly summarized as follows.

First, the EE concept has been accused of providing a too weak analytical framework (Autio et al. 2018; O'Connor et al. 2018; Scaringella and Radziwon 2018). There is a lack of a clear analytical framework that shows what elements cause what effects (Stam 2015; Stam and Spigel 2016). Lists of elements and factors that are known to enhance entrepreneurship have been proposed without any hierarchy in impact (Motoyama and Watkins 2014). The complex interactions of the elements have also not been fully disentangled.

Second, the complex interactions in the EE are described as a system of networks but this systemic take on EE has not yet been fully developed. There is no universal agreement of what is understood by networks in the EE literature. Neck et al. (2004) defines a network as 'a set of nodes (for example, persons, organizations) linked by a set of social relationships (for example, friendship, transfer of funds, overlapping membership) of a specific type' (p. 201). Spigel (2017) presents networks as the

'presence of social networks that connect entrepreneurs, advisors, investors, and workers, and that allow the free flow of knowledge and skills' (p. 8). What is also confusing is that the EE literature considers networks as the connections between the different elements in the system and at the same time suggests that networks are one of the elements involved. Moreover, the network literature and social network tools have not been used fully in studies on EEs with few exceptions (e.g. Ratih et al. 2018), in contrast to studies in entrepreneurship literature where egocentric networks and social networks (e.g. Stuart and Sorenson, 2005; Shih and Aaboen 2019) and the role of weak ties and structural holes (e.g. Ter Wal et al. 2016) have been investigated.

Third, the EE literature tends to struggle with the way geography is treated. There is a lack of regional comparative approaches. EE studies have often focused on particular regions and showed differences between those (e.g. Acs and Armington 2006; Motoyama and Watkins 2014), but they have been reluctant to explain the reasons behind the differences. Moreover, studies of an EE tend to concentrate on a particular area but do not apply a multi-scalar approach in which they investigate systematically the role of both local and non-local links and institutions that operate at different spatial scales. The role of non-local/global knowledge for firms in EEs, coming through non-local/global links have been highlighted by Bengtsson (2004), Malecki (2011) and Grillitsch and Nilsson (2015), for instance. Mason and Brown (2014) underlined the impact of multinational firms on EEs by attracting skilled labor and generating spin-offs, or opening up global markets for local firms (Neck et al. 2004).

Fourth, the framework applied by the EE literature is still mostly static, with some exceptions (e.g. Mack and Mayer 2016; Colombelli et al. 2017; Cantner et al. 2020). It has not explored fully how the different elements and connections in an EE change over time. Moreover, few studies on EEs have yet investigated how these dynamics may affect the operation and well-being of its entrepreneurial firms and the evolution of the EE as a whole. Hence, a full picture of the dynamics of structures, interactions, and governance in EEs is still lacking (Mason and Brown 2014; Lefebvre et al. 2015; Mack and Mayer 2016; Cao and Shi 2020). This is despite that fact that in more recent contributions, the EE concept has shifted from a static to a more process based approach (Spigel and Harrison 2018). This has highlighted the discussion about the role of different actors and institutions in different phases of the evolution of an EE (Walsh and Winsor 2019), also in the context of the Covid-19 pandemic crisis (Ratten 2020) and Brexit (Sohns and Wójcik 2020).

Motivation for the thesis

This thesis will address some of these critiques on the EE literature by proposing four research papers that consist of one conceptual and three empirical studies. The thesis contributes first and foremost to the development of the EE literature by combining insights from other literatures including the ones on entrepreneurship, resilience and social capital. The thesis does not aspire to contribute to the literatures it borrows from.

The first article is a conceptual paper. It takes stock of EE research based on a thorough literature review. The paper outlines the historical roots and antecedents of the EE concept, and it discusses the various definitions of EE, its constituent parts and the evolving trends in the EE literature. Most importantly, it critically assesses the current findings and highlights a number of weaknesses of the EE literature. It comes to the conclusion that there is a lack of clarity with respect to a number of features of the EE concept. Based on this critical review, a future research agenda is presented that aims to tackle those weaknesses.

Some of these critiques are addressed by the three empirical papers. For instance, the thesis conducts a geographical comparative study and applies a multi-scalar approach to outline the specific nature and structure of EEs in different places and different countries. The role of linkages and institutions external to the EEs are examined not only in general but also specifically for the scale-up process of firms in EEs. Hence, the thesis shows how EEs of different regions differ in how they support or hinder the growth of firms, highlighting the factors important specifically to productive entrepreneurship. The relative importance of factors (both firm specific and external factors) and how they influence each other are also examined. Moreover, the thesis also accounts for dynamics in EEs, linking it to the resilience literature. The thesis studies a closure of a big multinational firm in an EE to see what implications it has for the functioning and transformation of the EE.

The remaining critiques are addressed in the future research agenda that is presented in the concluding chapter 6.

Chapter 3:
Research Design

This thesis follows the scientific method. Research on social phenomena deals with more ambiguous issues than research in natural sciences. This is due to the high complexity and variations in social objects, and the fact that social objects are not only socially understood or interpreted but also socially produced or constructed. This requires researchers to deal with higher uncertainty which reflect the imprecise nature of theoretical concepts and measurement tools. Considerations that guide the work of researcher stem from ontology, epistemology and methodology chosen for the research project at hand. Ontology refers to the nature of the world - the way the researcher views the world and the nature of things. Epistemology refers to our knowledge about the world - the way the researcher can study the world, how she can recognize the world and the things under study. Methodology and methods are concerned with the strategies and tools that are used to collect, sort and analyze data which help to address the research question of the study. The underlying ontology, epistemology and methods applied in this thesis are described and explained below.

Ontological and Epistemological Perspectives

Critical Realism's search for causation and explanation of social events is an attractive trait of philosophy that can be used for policy recommendations that address societal problems (Fletcher 2017). Critical realism (CR) emerged in the 1970s based on a fundamental critique on both the positivist view and the constructionist view, claiming that reality cannot be reduced to human knowledge about the reality (Denzin and Lincoln 2011). Critical realism can be seen as being placed between on the one hand the positivist/neo-positivists view which focuses on what can be observed and measured, and on the other hand the subjectivist/constructionist view which focuses on things that are fully constructed by our minds (Bhaskar 1998). Positivist/neo-positivists consider going beyond what can be observed to be metaphysics and subjectivist/constructionists leave the question of ontology unresolved, choosing to ignore the discussion what should be considered as "reality".

As a philosophy of science, CR takes an explicit interest in ontology and states that there is an external reality which is independent of what people can experience with their senses or what they think. This implies that ontology (the nature of reality) cannot be reduced to epistemology (our knowledge/experience of reality) (Fletcher 2017). The vaster reality is unobservable to the extent that we cannot know it to any degree of certainty. Therefore, human knowledge can only take up a small part of it (Fletcher 2017). The CR ontology is stratified, meaning that it separates between the transitive domain (where knowledge about the world is constantly changing) and the intransitive domain (the relatively stable reality). The transitive domain acknowledges that our knowledge is always fallible and incomplete (Sayer 1999).

According to Bhaskar (1978), reality is approached by the critical realist through layered and emergent properties which interact and produce social events. The lower-level entities (the empirical) interact via certain mechanisms (the actual) and produce effects which constitute higher-level entities (the real). Hence, reality is multi-layered and constructed in three ontological domains – the empirical, the actual, and the real (Bhaskar et al. 1998). One of the layers, the real, is objective and independent of our understanding. The other one, the empirical, is subjective and directly tied to our understanding (O'Mahoney and Vincent 2014). The domain of the *real* contains the unobservable, it exists regardless of our observations and theories about it. In the thesis, for instance, these can be regarded as the structures that causally impact the way EEs work, no matter what the actors believe or know about them.

The domain of the *actual* includes events that actually happen no matter if they are experienced or interpreted. Those events are often different from what is being observed at the empirical level (Danermark et al. 2002). The domain of the *empirical* contains the observables that can be sensed and interpreted by humans (Bhaskar 1978; Danermark et al. 1997). These are represented by data that are collected and analyzed. In this thesis, for instance, this applies to firms that expressed they are pleased with the amount and quality of interactions they had with universities. Thus, the unobservable structures cause the events that we can observe and the task of the researcher is to understand those through abstraction of the context and the description of specific observables in order to understand the social world (Sayer 1999). The interpretations between the different layers in CR require intensive research design such as case studies that provide rich material (Danermark 2002; Easton 2010).

Epistemologically, the observations and our abstractions of them are biased, theory-laden and fallible (the transitive domain of knowledge). Hence, the theories we derive from them will be subject to change with time, as new and better observations become available (Moutinho and Hutcheson 2011). In the thesis, the mix of constructs and perspectives coming from many stakeholders in the EE are ways to provide an understanding of the 'reality' of the EE.

And every new theoretical development of EE based on that large amount of possible inputs should be subject to scrutiny. Critical realism focuses on providing causal mechanisms that explain the *trends/tendencies* - what might happen - rather than trying to predict what will happen and generate laws, because social world is too complex for defining a deterministic regularity (Brown et al. 2002; Danermark et al. 2002). The complexity adheres to the EE being a social object that is both socially produced and socially defined. This implies that findings in the thesis can add to, support, modify or reject existing tendencies and ideas of EEs.

Another important tenet of CR is that it claims that structure and agency have powers of their own (Carter and New 2005). In particular, CR is interested in how human agency transforms and reproduces social structures over time (Archer 2010; Bhaskar 2014). This is relevant to the concept of EE, as it aims to study the dynamic interplays between agents and structure in an EE. The EE concept places the entrepreneur at the core of the ecosystem, and investigates how she impacts and is being impacted by the context of the EE.

The methodological implications of Critical Realism

Grounded theory approaches (Strauss and Corbin 1994) have been popular among critical realists for data collection, coding and analysis (e.g. Yeung 1997; Maxwell 2012; Oliver 2012). However, it has also been stated that CR is not purely inductive, it uses abduction and retroduction, and it is a more of a theory- and researcher driven approach (Fletcher 2017). Hence, the Charmaz's (2006) approach to grounded theory with abstractions to analytical categories have been better appreciated by critical realists (Oliver 2012).

Practically, CR methodology involves several key steps how to get closer to the domain of the *real* which include identification of demi-regularities, abduction, retroduction and corroboration. Demi-regularities are discovered in the process of abstraction of key events that are carefully identified. Abstractions of the domain of the *empirical*, the observed events, highlight how actors act and strive to visualize parts of the domain of the *actual*, describing what actually happened (Wynn and Williams 2012).

In the interview data of this thesis, factors like funding and institutions with their related key processes have been examined as such. It is through qualitative data coding, possibly with the support of analysis software that demi-structures can be effectively identified (Fletcher 2017).

After identifying demi-regularities through coding, abduction will take the thick description to a more theoretical level (Fletcher 2017). Abduction iterates the findings with existing theories and concerns 'inference or thought operation,

implying that a particular phenomenon or event is interpreted from a set of general ideas or concepts' (Danermark et al. 2002, p. 205).

This thesis has followed a similar inductive approach in the empirical papers, especially at the start of the research project with searching for demi-regularities through coding of the interviews. It then continued by the use of abduction with closer connection and iteration of findings with the existing EE and other literature during the data analysis. Research on EE from the CR perspective is valid, because the EE concept provides a unique research opportunity to see interesting demi-regularities, due to the many different actors and linkages in an EE from the empirical point of view, and due to the interdisciplinarity of theoretical approaches for the process of abduction from the conceptual point of view.

Retroduction is another step that takes the analysis to deeper levels and closer to the reality by focusing on the causal mechanisms and settings that have led to the observed trends (Bhaskar 2014). The researcher tries to explain what has caused the demi-regularities she discovers by moving back and forth between the different levels of reality – the *empirical* and the *actual* -also by engaging with existing research. To take one example from the thesis, after having identified a lack of international funding, it was examined what was the cause of that. Low evaluations of firms, which in their turn were dependent on the availability of local funding and entrepreneurial management, were identified as plausible causes.

Corroboration is used as the final stage in order to confirm and support the discovered mechanisms by triangulation across different sources and by looking at competing and alternative explanations of the phenomenon (Denzin 1970; Danermark 2002; Wynn and Williams 2012). The goal of corroboration is to get closer to the 'objective' view and the best representation of the *real* at hand (Sayer 1999). In the case of EEs, the somewhat common understanding of the phenomenon across different interests and different data sources produces explanations that are specific to each EE and that can help actors involved to make well-supported decisions that can impact many other actors at once.

Methodology of this thesis is qualitative and inductive, inferring theoretical concepts from observed data. This is done because of a lack of existing research on EEs in life sciences, but also because this thesis aims to generate new knowledge, instead of testing existing theory (Eisenhardt et al. 2016). Inductive reasoning is open-ended and exploratory and provides an opportunity to understand the complexity of actions by various actors and impacting factors and their connections in EEs. The abductive approach (Dubois and Gadde 2002) was used in order to iterate the observed tendencies with existing literature and strengthen the process of abstraction.

In sum, the research design of this thesis follows the principles of CR. The following section describes the methods, such as case selection, data collection, and analysis of the data.

Methods, data and analysis

Case studies, case selection and interviewee selection

Due to the explorative nature of the research question of this thesis, case studies were selected as the research method. Case studies are a necessary method for capturing complex social phenomena and answer questions like 'how' and 'why' that lead to deeper explanations than statistical tests of a narrowly defined hypothesis (Flyvbjerg 2006; Yin 2017). According to Flyvbjerg (2006), any study of human actions requires context-dependent knowledge as predictive theories are not truly possible in that realm. The 'force of an example' should not be underestimated, and it is indeed possible to generalize on the basis of even a single case, as done in article two of the thesis. Moreover, articles three and four in the thesis follow a case-based research design but based on a comparative approach, comparing multiple regional cases (that is, five EEs). A comparative approach can add to the robustness of outcomes (Stake 2005), but more importantly, it demonstrates how similar factors in the EE lead to different results (illustrated by different entrepreneurial dynamics) in different geographical contexts (Griffin and Ragin 1994).

The logic of case selection in this thesis is seen as an important aspect of establishing methodological rigor. Validity is often called for, which means the extent to which an EE truthfully represents the studied social phenomena (Lincoln and Guba 1986; Hammersley 1990; Altheide and Johnsson 1994). Validity and reliability or "typicality" are achieved by purposeful case-study selection with cases that represent the EE phenomenon accurately. This thesis examines five cases of EEs that are strategically selected based on their location and degree of spatial concentration of the LS industry, covering different types of regions and different countries. Strategic selection of cases increases the generalizability/transferability of case studies (Flyvbjerg 2006). Furthermore, cases were chosen to show variations in the phenomenon e.g. maximum variety cases (Silverman 2011). The EE in North East Ohio (US) represents an extreme case, compared to the Swedish EEs, due to big institutional differences between the US and Sweden. Moreover, during the study there was a discussion whether to research Stockholm and Uppsala as one case - as often done in reports - or to separate them into two separate cases. The latter choice was selected because Stockholm and Uppsala have shown variation in how EEs function, even though the EEs are geographically very close and interconnected. There is a point in both maximizing similarities among cases and maximizing heterogeneity among cases (Przeworski and Tuene 1970). When maximizing similarities among cases like between the four cases of EEs in Sweden, theoretically significant variations are found and are used for explanations of the phenomenon. When cases are also extremely heterogenous, like when Swedish EEs are compared to the extreme case of the US case, we can see similarities in spite of

the case differences. For example, the identified factors, actors and their connections in the EEs were compared both between similar systems and with a highly different one, which shows their robustness even for a small number of comparative case studies (Goggin 1986). Furthermore, the EE in North East Ohio is not the most extreme case that could have been chosen in the US. Other studies have investigated the more known EE of Silicon Valley. The EE in North East Ohio is to a certain point less extreme in how it operates, and thus provides a somewhat lesser gap with the Swedish EEs. This can help the findings to be more transferable across the cases. Hence, the cases of the five EEs were carefully chosen so that they are able to address the research question and to support the validity, reliability and transferability of the research findings (Lincoln and Guba 1986).

Who should be interviewed in each EE also required a certain logic of selection which was applied in all empirical papers. Forty interviews have been held with key actors that represent small firms and experts in the EEs. The general sampling strategy of interviews has been purposeful sampling that provided interviewees knowledgeable about the functioning of EEs in different places. All empirical papers are based on the same or overlapping group of interviews that are selected by information-oriented sampling strategies, which means that the interviews were chosen to maximize the information that could be obtained. Two papers are comparative case studies. One paper is a single case study on the transformation of the EE of Lund and uses a subset of the interviews. During the interviews, different views were surfacing that seemed to be very different, depending on the type of firm interviewed. Hence, there was a clear need to talk to different types of firms. To cover different variations among the respondents that offered extreme deviations or interesting insights (Stake 2005), interviews were performed with firms that covered product firms, service firms, or a mix of both. Also the interviewed firms represented the three sectors in LS (MedTech, BioTech and Pharma), and the interviewed experts represented both private and public organizations.

Analytic induction was used during interviewing as a means to strengthen the validity of the research. This means that the data was collected until the initial hypothesis survived the test of new information. This was adjusted when new information falsified it, until further study was not revealing new aspects (Silverman 2011). For example, the idea about the differences in the way service vs product firms were acting in the EEs was tested on similar firms in the same EE, and then compared to other EEs in order to refine the understanding. And the idea that firms like Astra Zeneca and Pharmacia had strong but also very different impacts on their EEs was tested with new interviews and confirmed when interviewees would repeatedly support the ideas that were tested.

New interviewees were identified by referrals in the interviews - snowballing strategy, which was especially helpful for the hard to obtain extreme and intrinsic interviews. Sometimes firms and experts were suggested with a name during the interviews, and sometimes a list of interesting people to interview was provided

after the interviews. Initially, experts were identified on the websites of local organizations or government in each EE.

Thus, the interview selection was not based on statistical sampling but rather on purposeful and theoretical sampling, by identifying and covering the topics of interest (Yin 2017) and the interviews that could be highly informative (Flyvbjerg 2006). So, the selection of the interviews as well as the selection of the cases of the EEs were performed in a way to increase validity, reliability and transferability (Miles et al. 2013).

Reliability is about showing the stability of the findings and how the study can be reproduced (Altheide and Johnsson 1994). It was achieved by being transparent and consistent in the research process (Lincoln and Guba 1986), for example, by using software (e.g. Atlas.ti) to store and analyze the data. Another means of achieving reliability was to use the same interview guide with discussion topics on EE as the basis for the interviews, for making triangulation among interviews, and for comparing initial findings between the involved researchers (Silverman 2011).

Transferability is related to generalizability and refers to the ability to transfer obtained knowledge to other contexts and stakeholders, rather than finding one valid theory (Miles et al. 2013). It is achieved through detailed descriptions of the different actors, factors and their connections in each paper and the research context of each EE, so that future studies have the possibility to compare these with their own EE contexts (Lincoln and Guba 1986). Purposeful sampling of both cases that are very similar and very different, and using the comparative case study design allow for replication and analysis in different types of future cases of EEs

Data sources

To understand the actors, factors and their interactions in the EEs, 40 open-ended semi-structured interviews have been conducted. Interviews as a method are advantageous due to access to hidden voices and opinions around the EEs that normally are not asked, and they give a good understanding of change processes and institutional contexts (Schoenberger 1991). A disadvantage of interviews is that they do not give the researcher direct access to the 'facts' or events but rather give 'representations' of experiences (Silverman 2011).

The interviews were done with founders and the top management of entrepreneurial firms in the Life Science (LS) industry in the five regions in Sweden and the US. Regional experts in LS such as national LS investigators, investment managers for a region, CEOs of science parks, and university and regional government management were also interviewed. These actors were discovered to be of importance through consultation of EE research and a snowball procedure during the study. The data collection was preceded by several meetings with the co-author of the empirical papers who was already very familiar with the LS industry from

earlier research. The first interviews in EEs were done with interviewees that were assumed to be highly networked and to possess broad knowledge of the various actors and important historical events, such as a manager at the Medicon Village Science Park in Lund. Initial contacts were found through websites of the relevant organizations if not via referrals.

The suitable interview candidates were obtained by 'snowballing' sampling through a list of start-up companies that were received from local experts on the LS industry and through referrals in the interviews. Selection criteria, based on the discussion about the logic for case/interview selection outlined earlier, concerned the location of firms, year of registration, activity in all three sectors of LS (Pharmaceuticals, Medical Technology and Bio Technology), and firms selling services and/or products. The goal was to obtain rich information representing different perspectives and interests. Therefore the researcher strived to include interviewees with variations. For example, after reading documents and doing some interviews, it became clear that large firms like Astra Zeneca and Pharmacia had major impacts on EEs. Hence, it became interesting to talk to interviewees that would be able to inform about that in detail.

Semi-structured interviews were found to be most suitable for addressing the research questions. They enable guidance via certain pre-defined broad themes while they also provide flexibility to explore unexpected ideas that present themselves during the interviews (Silverman 2011). To keep a structure around the interviews, an interview guide was developed through back and forth discussions with the co-author of the empirical papers. The interview guide included general topics of interest concerning EEs and was designed in a way that allowed openness for unexpected discoveries during the interviews.

The interviews started with an invitation to describe the firm or their job in relation to a LS start-up, probed around interesting points that were taken up, followed by asking about other topics of interest in the interview guide that were not mentioned by the interviewees themselves. With time, as interesting topics arose in interviews, these were also discussed in the interviews that followed. The interviewees were informed via email conversations prior to the interviews about the researchers involved and the background of the study. Each interview started with a light chat, introduction and reply to any questions, to establish a positive connection with the interviewee.

The interviews were mostly conducted in person, but also by phone in the period 2015-2019. In order to collect the large amount of interviews, the interviews were done in 6 batches. 2 batches were interviewed during the year 2015 – one in Lund and one in Gothenburg, 3 batches were spread over year 2016 – two in Stockholm and one in Uppsala, and the last batch was interviewed in Lund in the year 2019. The last batch was focusing more specifically on the transformation of an EE which is covered in paper two. During the early data collection, it was discovered that what

happened in Lund was remarkable and different compared to other places that experienced similar changes. It presented itself as an interesting case to zoom in on later, in order to understand better the dynamics of the EEs. Making interviews in batches provided the opportunity to take breaks between the interviews, to get acquainted with, and to reflect on the collected information. The last interview batch in Lund also gave the opportunity to 'close' the circle and test the findings drawn from the first interviews in this EE. Each interview lasted typically between 50 minutes and two hours.

Table 3.1 shows a summary of the interviews in the five EEs: four Swedish regions (Gothenburg, Lund, Stockholm and Uppsala) that dominate LS in Sweden, and one LS region in the US (North East Ohio). Twelve interviews have been conducted in Lund, six in Gothenburg, nine in Stockholm, six in Uppsala, and seven in North East Ohio (NE Ohio). The 7 interviews in NE Ohio were conducted by one of the co-authors, while the other 33 have been conducted by the author of the thesis alone, or jointly with one of the co-authors. Almost all of the interviews have been audio-recorded, a couple had to be recorded by note-taking instead.

Table 3.1: Data sources and methods for empirical papers

Region of EE	Industry	Primary data source(s)	Secondary data source(s)	Used in Methods	Article(s)
Lund, Sweden	Life Science	12 interviews	Publicly available policy-related documents, firm's registry online, annual reports, websites, industry reports, news articles	Single case study and comparative case study; semi-structured interviews; document analysis	Article 2 Article 3,4
Gothenburg, Sweden	Life Science	6 interview	Publicly available policy-related documents, firm's registry online, annual reports, websites, industry reports	Comparative case study; semi-structured interviews; document analysis	Article 3,4
Stockholm, Sweden	Life Science	9 interviews	Publicly available policy-related documents, firm's registry online, annual reports, websites, industry reports, news articles	Comparative case study; semi-structured interviews; document analysis	Article 3,4
Uppsala, Sweden	Life Science	6 interviews	Publicly available policy-related documents, firm's registry online, annual reports, websites, industry reports	Comparative case study; semi-structured interviews; document analysis	Article 3,4
NE Ohio, US	Life Science	7 interviews	Publicly available policy-related documents, websites, industry reports and overviews	Comparative case study; semi-structured interviews; document analysis	Article 3,4

Source: author's summary.

Furthermore, information about perspectives of different stakeholders, display of activities, networks and components of the EEs, have also been collected through several types of archival data. Secondary data such as firm's registry online, annual reports, websites, industry reports and policy-related documents were used to prepare the interviews and learn more about the EEs under study. This type of data was used not only to give detail to the study but also to triangulate and corroborate the findings. However, due to the fallible nature of the research as according to the critical realism ontology, future research might find new angles of the existing findings, even in a replication study.

Data Analysis

Making interviews in batches over the years and having time between the interviews provided the opportunity to engage with the data by looking at the notes and documents while taking courses and reading research papers. The data analysis more explicitly followed a systematic process (Yin 2011) that is in line with critical realist ontology and epistemology described above. The first step concerned the transcription of the interview material. Most of the interviews were transcribed by the author of the thesis and some (seven) by a transcribing service. The ones that were not possible to audio-record (four), notes were taken and rewritten in the word document as soon as possible. The transcripts were read through and shared between the co-authors. Over time, coding strategies and summaries of the interviews in form of conference and working papers were also shared between co-authors and discussed in order to establish a shared view. Also feedback on the findings from the interviewees was obtained and have been helpful to double check and sharpen the findings when needed.

The methodological steps for analysis of the data were inspired by grounded theory (Strauss and Corbin 1994; Charmaz 2006; Gioia et al. 2013). Which means to discover demi-regularities by producing data driven codes, abstract the codes into themes and thinking in steps of going from the raw data and first order codes to second order themes and aggregated dimensions. The following steps of the analysis were applied to the data for all empirical papers.

The interviews contained a lot of rich information and it took a good while to get familiar and navigate the information. The author of the thesis was new to the industry and the research topic which brought a fresh look on possible explanations for how EEs and their functions could be understood. But it also took a long time to identify the key components and make logical connections across the data.

After the transcription, reading through the interviews to grasp the backgrounds of the interviewees and described activities (Ryan and Bernard 2003) and making notes of interesting points in the interviews by hand, the transcripts were uploaded to software for qualitative analysis. To discover the demi-regularities, the data was

coded section by section in the transcripts with assigned initial codes. First this was done in NVivo, which was a good way to learn how an analysis software works and this way of coding gave the possibility to search for certain phrases and words much faster than if it would be done with pen and paper. After a while, that software was found cumbersome and the coding was redone from the start in Atlas.ti instead. This time the coding was more structured and labeling was more precise with labels and sub-labels also because the author was more familiar with the interviews the second time around. Initial coding concerned to give labels to the chunks of texts. For example, in paper two, one of the first order codes was named "*Global – firm – Globally I have personal contacts"* and it was based on the raw data quote *"…Globally I have personal contacts at senior management level and we are invited to come and present what we have"*, and another first order code was named "*Network - firm - Networks drive business"* was based on the raw data quote: *"… even in the places we have not been to ourselves, there is of course quite high likelihood that somebody, who we have worked with in the past, works there now. That is really how we have seen all of our businesses come".* The point was to see what topics interviewees were talking about. Sometimes their own words were used to create labels, and see what regions had their specific views on certain topics. Several topics naturally were mentioned more than others and were given more value than others by the interviewees. Some information around the same topic could be contradicting which made the researchers evaluate the tensions between the information. These topics led further to defining higher order categories and themes (Charmaz 2006) and represented demi-regularities in the data. For example the codes "*Global – firm – Globally I have personal contacts" and "Network - firm - Networks drive business"* were combined into a theme called "*Former networks for customer acquisition"*. In order to identify higher order categories easier, the manual technique of cutting and sorting was used (Ryan and Bernard 2003). The codes and the related raw data quotes were printed from the coding software, cut in pieces of text and grouped into themes by walking around and moving them across large floor space, which gave a better overview compared to a computer screen. According to Becker (1998), theme development must happen in the continuous dialogue with the raw data, since themes summarize large parts of a phenomenon, that is why both codes and raw data quotes were printed out.

Furthermore, it was important to understand why these demi-regularities/themes were emerging and what was the reason for the importance they were given by the interviewees. This was the next step of the analysis - the process of retroduction and the discovery of causal explanations. This was done as analytical notes about the different themes were written, sketches of diagrams by hand, listening to the recordings of the interviews when things were unclear, and re-reading transcripts. This was helpful to understand, make connections and triangulate within and across the large number of interviews. In order to strengthen the recognition of the demi-regularities and their explanations, an abductive approach (Dubois and Gadde 2002) was used. This means that the researcher was moving between initial patterns seen

in the data and the EE literature. For example, in paper four, the specific role of human capital in the scale-up process was initially overlooked in the data before the EE literature was reviewed again and inspired to check the specific importance of that factor. During the whole process, the corroboration of the findings was done through triangulation across interviews, cases and secondary sources like websites, LS industry and organization's reports. This was done to generate a consistent story and to strengthen further the reliability of the findings.

Writing up the papers

As mentioned in Table 1.1., the conceptual paper that outlined the shortcomings of the EE concept and presented a future research agenda was published first. Paper three that compared all five cases is empirical and developed over a long time with several rounds of data analysis and presentations of different versions at international conferences. It is now accepted for publication as a book chapter. The comparison between the different EEs highlighted the unique development of events that happened in Lund EE. Hence, in parallel to paper three, paper two started to develop. It is single authored and zooms in on one case - Lund EE - and its dynamics. The different viewpoints on EE that the papers two and three provided have given the opportunity to understand the strong impact of certain agents in the EE. Following several findings from papers two and three, such as the finding that different aspects of EEs are activated depending on the development phase of firms, and discovering a lack of comparative research on the topic of high-growth firms in an EE setting, paper four focused on the scale-up process in entrepreneurial firms in EEs. Papers two and four have been submitted to international journals for review.

Ethics

Research ethics must always be considered in research of any kind, as they govern interactions between researchers and their research objects. Several ethical issues have been considered for this study. It was necessary to obtain consent from the participants and make clear what participation included. Asking for consent was supported by giving information about (i) the research project, (ii) the backgrounds and motivations of the researchers, (iii) the duration of the research, and (iv) what information was expected from the participants. The information was provided both in writing, by email, and also verbally at the event of the interview. Consent was obtained by email when participants accepted to be interviewed. All participants assured confidentiality in the reporting of the results before the data was collected, except in the cases where the participants agreed to be disclosed by name in the text and by direct quotations. In such cases, quotations were shown to the participants

for acceptance. Almost all results have been reported in an aggregated manner and for the obfuscation of the names of individuals and the firms, pseudonyms were used to ensure privacy. The documents that were used were publicly available or willingly shared with the researcher by the participants.

Chapter 4:
Research context

The research context of this thesis consists of a geographical and industrial dimension. Geographically speaking, the empirical studies cover two very different countries - Sweden and the US - and EEs in five regions with high concentrations of high-tech firms in Life Sciences. The focus across all EEs is on the LS industry, which is therefore one constant parameter around which comparisons across the different EEs are made.

Life Sciences

The Swedish government has defined the LS sector as follows: 'The life sciences sector includes companies, higher education institutions, and public stakeholders at municipal, regional and state level whose activities contribute to promoting human health. The sector comprises research, higher education and innovation, the development of pharmaceuticals, medical devices and treatments, as well as prevention, implementation and monitoring' Swedish Government (2020). High-technology industries and LS industries in particular are considered a crucial driver of economic development but they also positively impact society in much broader terms like health, well-being, et cetera (Bhide 2003; Scholten et al. 2004). New technology-based ventures bring innovations to society and contribute to job creation and industrial renewal (Acs and Audretsch 2005; Schoonhoven and Eisenhardt 2012). New ventures carry out entrepreneurial activities and are considered more vulnerable and unstable compared to incumbent firms (Petersen and Ahmad 2007). They suffer from liabilities of being small and being new, they have fewer resources, they struggle with gaining legitimacy, and they have to manage new markets and immature technologies (Stinchcombe 1965; Shepherd et al. 2000; Aaboen et al. 2006; Nagy and Lohrke 2010). The environment they are in is often highly dynamic and driven by fast technological change which puts high pressure to bring innovations first (Flatten et al. 2015). High-tech firms in LS are in need of support which requires understanding of what enhances or impedes their development (Sandström 2014). Having very few successful high-tech firms is

considered a serious problem by policy makers in Europe (European Commission 2010) and Sweden (SwedenBio 2018).

The LS sector has a variety of characteristics that are crucial for addressing the research questions of the thesis. First, the LS industry depends on many interlinked actors and institutions which makes it an ideal case to study it from a systemic framework like EE (Pucci et al. 2020). Second, the LS industry is highly dynamic with many entries and exits of firms. In this respect, it provides an unique case to study entrepreneurship and how start-ups survive in such a dynamic setting . Moreover, the LS industry in Sweden in particular has been characterized by some extreme events like the closure of big pharmaceutical firms that enables to study the transformation and dynamics of EEs where these extreme events occurred. Third, the LS industry is heavily concentrated in clusters (Cortright and Mayer 2001; Casper 2007; Moodysson et al. 2008), which makes it a suitable case to study entrepreneurial dynamics from an EE perspective. Fourth, the scaling-up process in LS firms requires many involved actors both at the local and global scale, which makes LS a perfect case to apply a multi-scalar approach.

LS firms with established business records that are often publicly traded and have high market values are researched more often than smaller firms that are privately held. It is the smaller firms that often lack finance, skilled management, and a clear market (Brännback et al. 2009). Entrepreneurial firms in the LS industry face high risks and have to overcome many obstacles, because the average product development takes about 12 years. 80% of R&D investments are not recaptured which makes it a high-risk industry, it requires large financial resources, and it involves many actors at the global scale (Batiz-Lazo and Holland 2004; Brännback et al. 2009). The development stage of LS firms is where the scale-up process occurs which follows after the discovery stage and after patents have been approved. The scale-up process in LS looks rather different between pharmaceutical, medical technology and biotechnology firms but often include works with formulation, toxicology and clinical trials (phases I-III). These are required to meet standards of regulatory agencies in the country of application that allow them to sell products to customers (Batiz-Lazo and Holland 2004). The product requires to be produced, distributed and sold to a large market which is often global. Especially orphan drugs, drugs that target a certain rare disease for which patients are few and distributed all over the world, the global market outreach and government support is crucial. Service firms in LS can have revenue early on, but product firms in LS need large investments and need to show promising future revenues on which the financial evaluations of the firms is often based (Brännback et al. 2009).

Geographical context

LS firms are often found clustered in regions in different countries and those clusters are known to vary in performance (Carlsson and Braunerhjelm 2002). This thesis studies LS firms in two different countries, Sweden and the USA. While the American ecosystem has worked outstandingly well for creating commercially successful LS firms (Owen and Hopkins 2016), Europe has been trying to copy this for a long time, but with limited success (Casper 2007). The thesis has studied five Entrepreneurial Ecosystems in LS in total, of which four are located in Sweden (Lund, Gothenburg, Stockholm, Uppsala), and one in North East Ohio in the US. Reasons for making comparisons between industries in Sweden and Ohio in terms of similarities (population size, overall level of development and industrial structure) and differences (economic policy/different institutional context and industrial development) have been discussed before (Braunerhjelm and Carlsson 1999; Carlsson and Braunerhjelm 2002). Furthermore, the closeness of the research team to the geographical context supported control of the quality and consistency of the collected data.

Table 4.1 provides an overview in terms of population, number of employees, and number of establishments in each of the five EEs.

Table 4.1: LS industry in five EEs. Data from Sweden shows year 2010 (Carlsson et al. 2016) and data from Northeast Ohio shows year 2017 (BioOhio, 2019)

Region	Population	Number of employees in LS	Number of LS establishments
Lund(Malmö)	90.000 (300.000)	10.200	360
Gothenburg	580.000	7.800	350
Uppsala	170.000	3.500	140
Stockholm	1.100.000	16.800	670
Northeast Ohio	4.500.000	22.500	1.300

Source: author's compilation

Uppsala is a university city of ca 170,000 inhabitants that is located close to Stockholm and which hosts over 100 LS firms with 3,500 employees. In 2006, 70% of the employees were employed by the top five largest firms. The largest sector in terms of number of firms is Medical Technology, followed by Pharmaceuticals and Biotechnology (Uppsala BIO 2021). Uppsala University is one of the key actors in the EE, as it generates innovations in LS, offers technology transfer services, and it acts as a central node through which small and large firms connect. Pharmacia is a large multinational firm that has been another key actor in the EE. Although Pharmacia was dissolved in 2012 by several mergers and acquisitions, it had established a highly collaborative culture in the EE. Universities and firms have been collaborating for several decades, which boosted the rate of successful spin-offs. Despite Uppsala's small size, there are over 20 entrepreneurial supporting organizations, science parks, innovation centers, and (university) holding companies.

The Stockholm EE which contains the city of Stockholm and the adjacent area of Södertälje[1] has a population of around 1,000,000 and hosts ca 50% (ca 700 establishments) of all Swedish LS firms. It is the epicenter of the LS industry in Sweden. LS employment amounts to ca 17.000 people. Large firms such as Astra Zeneca and Pharmacia have left a strong mark on the EE. There is a strong LS tradition that exists for decades. Most entrepreneurial firms are small. There are also many sales offices of global giants that monitor closely new developments. Important academic organizations including the Royal Institute of Technology, Karolinska Institute, the Karolinska University Hospital, the University of Stockholm, and the Science for Life Laboratory are all found in Stockholm EE. A large number of Science Parks and entrepreneurial support organizations is also found in the EE, such as the Karolinska Innovation Science Park, the Biovation Science Park, and SwedenBio. Access to funding is largest in Stockholm EE compared to the rest of Sweden, with many business angels, venture capitalists and international funding organizations.

Gothenburg hosts a population of around 580,000 people. There are ca 7,800 people employed in ca 350 LS establishments in the local EE. Astra Zeneca has had a strong and historical impact on the EE, together with hospitals (Sahlgrenska University Hospital) and universities (Chalmers and Gothenburg Universities and Sahlgrenska Academy). Rapid growth in medical technologies is supported by a strong local ICT sector. Pharmaceuticals and biotechnology are also strong sectors in the EE (Business Region Gothenburg 2021). There are several network organizations supporting small LS firms such as science parks and incubators, but collaborative activities across actors in EE are relatively new. This may be due to the closed and secretive culture of Astra Zeneca that has been a major firm in the EE for decades. However, Astra Zeneca's recent change in strategy towards open innovation and collaboration has started to generate new positive impacts on the EE.

Lund has about 92,000 residents and is a university-dominated city (similar to Uppsala) in southern Sweden (Skåne county). Sweden's third largest city, Malmö is located next door. There are ca 350 LS establishments with ca 10,000 employees in Lund/Malmö. Lund EE is a member of Medicon Valley - a large LS cluster that also covers Denmark and the Copenhagen area with 40,000 LS employees (Medicon Valley Alliance 2021). Lund is one of the most newly dynamic EEs in Sweden. Many new firms started after the closure of Astra Zeneca's research center in 2011. After closure, LS employees have increased in Skåne county from 16% to 27% of Sweden's total LS employment (Sandström, 2014; SwedenBio, 2020). Biotechnology and pharmaceuticals are the main sectors among the small firms. The Medicon Village (MV) Science Park was established in 2012 in the former Astra

[1] Södertälje, is situated ca 40 km southwest of Stockholm. Astra's main research center was located there before the merger with Zeneca happened in 1999. The world's largest pill-making facility, Astra Zeneca's main manufacturing plant, is located there now.

Zeneca facilities which has boosted new firm formation and strong collaborations between Lund University, local firms, support organizations, and governmental agencies.

North East Ohio is located in the state of Ohio, US and has ca 4,5M residents. In 2017, the EE was home to 1,313 LS establishments, employing 22,509 people that were mostly working in the Medical device and equipment sector (BioOhio 2019). The Cleveland Health-Tech Corridor is a cluster that hosts over 170 Life Science firms and some world leading health organizations, academic centers, and business incubators. The central players in the EE are Western Reserve University (CWRU), University Hospitals (UH) and the Cleveland Clinic Foundation (CCF). These LS organizations represent some of the largest in the US and they act as important collaborators and clients to the firms. The Cleveland Clinic is the 4th largest research hospital in the US, employing 45,000 people in NE Ohio and 67,000 people globally. It has three research centers and $300M+ in research funding. There are effective entrepreneurial support organizations for technology transfer as well as funding both at CCF and UH: two-thirds of all LS start-ups in the EE originate there.

Chapter 5:
Summary of Appended Papers

Each paper in the thesis explores how EEs impact entrepreneurial firms in LS in different regional contexts. Together the papers contribute to a better understanding of how actors, factors, and their interactions in EEs impact entrepreneurial activity in regions.

Paper I

Title

A critical review of Entrepreneurial Ecosystem research: towards a future research agenda

Purpose and the Research question

The objective of the paper is to provide a comprehensive overview of the development of publications on EEs, to present a critical review of EE research, and to develop a future research agenda. The research question for the study is: 'What are the strengths and weaknesses of the EE literature, and what are the main issues to be addressed in future research?' Paper one lays the foundation for the research avenues that are addressed in the subsequent empirical papers.

Theory and Methods

The conceptual study provides a literature review of publications on EEs based on article search in well-established electronic databases that revealed 477 unique relevant publications. The paper discusses the popularity of the EE concept, compares it to the similar concept of Entrepreneurial System, discusses the rationale behind the EE framework from an entrepreneurship studies perspective, and looks into the antecedents of EE research.

Findings

The study reveals that, despite growing popularity, the EE concept suffers from several shortcomings: (1) it lacks a clear analytical framework that makes explicit a distinction between causes and effects, (2) EE research has failed to utilize network theory and network tools; (3) the role of institutions at different spatial scales are underexplored; (4) EE studies lack a comparative and multi-scalar approach; and (5) the EE literature is not considering the dynamics and evolution of EEs over time. The research agenda for tackling these shortcomings contains the following: to combine the network and EE literatures to enrich the EE concept in theoretical and analytical terms, to give more attention to and integrate institutions more deeply into EE research focusing, among other things, on institutional change and the role of institutional entrepreneurs, and finally to bring in an evolutionary perspective that compares different EEs at different evolutionary stages over time.

Paper II

Title

Resilience after a large firm's closure: the role of place leadership, local resources, and social capital in the transformation of an Entrepreneurial Ecosystem

Purpose and the Research question

The objective of this study is to identify factors that might hinder or enhance the resilience of an EE when confronted with a shock – the closure of a large multinational firm in the EE. The pharmaceutical giant Astra Zeneca closed down its research facility in Lund, Sweden, which was first seen as devastating to the EE. The underlying research question is: 'What factors can be held responsible for the transformation and resilience of an EE when the EE is confronted with a shock?' This paper addresses one of the research gaps identified in paper one, that is, the one concerning the dynamics of the EEs. It also uses insights from paper three about the structures of different EEs and the role of certain agents.

Theory and Methods

The EE literature provided few clues on the effects of shocks on EEs. Therefore, theoretical concepts from neighboring literatures were borrowed. The EE literature was connected to theories on regional resilience, place leadership (PL), and social capital, in order to develop a comprehensive framework for understanding the resilience of EE in times of crisis, and to explain the subsequent positive transformation of the EE. The paper is based on a qualitative case study. Analytical steps for qualitative research on EEs by Roundy (2019) were followed. The study

also applied an abductive method of analysis (Dubois and Gadde 2002) of interviews and documents, which means that initial patterns that are recognized are iterated with the existing literature to support the process of theorizing.

Findings

A sudden closure of a large firm can have a major negative effect on an EE. This study finds instead positive effects in the aftermath of a major firm exit in an EE. It shows how agency and resources transformed the EE into a dynamic center for LS. The study demonstrates that three factors were important: (i) a new type of governance in an EE, called Entrepreneurial Place Leadership (EPL), (ii) related local resources, and (iii) social capital, in terms of ties between place leaders and ties between former employees of the large firm. All three factors are closely intertwined and depend on each other. It shows how a negative shock to an EE, when handled properly, can be turned into a positive development in the EE in the longer run.

Paper III

Title

Comparative Analysis of Five Entrepreneurial Ecosystems in Life Sciences

Purpose and research question

The purpose of this study is to explore and compare the nature of five EEs in Life Sciences in Sweden (Lund, Gothenburg, Stockholm, Uppsala) and in Northeast Ohio (NEO) in the US. The aim is to outline which factors impact the rate and nature of entrepreneurship in LS in the different EEs, and at what spatial scales. The research question of the study is: 'Which actors, factors and interactions are at play in EEs in different regions, how do they impact the dynamics of entrepreneurial firms, and to what extent do EEs differ in that respect?' This paper addresses a number of the gaps identified in paper one, namely the need for a systemic approach, the need for a comparative regional and multi-scalar approach, and the need for a perspective on EE that accounts for the role of institutions. It lays the foundation for understanding the dynamics of EEs in paper two and the importance to tie the impact of different actors and factors to certain processes in entrepreneurial firms, such as the scale-up process, which is addressed in paper four.

Theory and methods

Few studies on EE to date have adopted a comparative qualitative approach. Prior research on how to measure and compare EEs had taken a more quantitative approach, or followed a multi-country comparison approach. This paper combines the strengths of both multi-region comparative and qualitative approaches. It compares two countries (Sweden and the US) with very different institutional contexts and five EEs with different features through own data collection based on interviews and documents. The analytical steps for qualitative research on EEs by Roundy (2019) were followed. The study also applied an abductive method of analysis (Dubois and Gadde 2002) which means that initial patterns that are recognized are iterated with the existing literature to support the process of theorizing.

Findings

EEs look different in distinct geographical and institutional contexts. The study demonstrates how important it is to take a territorial perspective on EE. The paper revealed nine dimensions in which EEs can differ: University-Industry links, the role of Large Firms, Entrepreneurial Support infrastructure, Funding, Global links, Institutions and IP, Local/National links, Entrepreneurial Management, and the role of Hospitals. The most striking difference was found between the EE of North East Ohio on the one hand, and the Swedish EEs on the other hand. This strong influence of the national dimension was reflected in the stronger involvement of regulatory agencies and the government, and the more entrepreneurial and growth-oriented attitude of relevant actors in the US, as compared to the Swedish EEs. The differences among the Swedish EEs were also significant in several dimensions, e.g. in the role of universities and the legacy of large firms.

Paper IV

Title

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

Purpose and research question

Entrepreneurial firms in Life Sciences face many difficulties in the scaling up process. The purpose of this study is to identify factors that are supportive to or hindering the scaling up process of Life Science firms in EEs. The study investigates how the factors are connected and whether the factors differ between five EEs in LS in Sweden (Lund, Gothenburg, Stockholm, Uppsala) and the US (North East Ohio).

The main research question of the study is: 'Which actors, factors and interactions are at play in the scaling-up phase of entrepreneurial firms in different EEs, and to what extent do EEs differ in this respect?' This paper builds on findings about the important actors, factors and their connections in paper three but focuses on those that are important specifically in the scale-up phase of LS firms. The paper addresses several gaps defined in paper one, such as the use of a comparative multi-scalar approach, and the role of institutional environments.

Theory and methods

Theories on factors that propel growth of small firms have focused on firm-specific factors such as experienced leadership and market orientation, and firm-external factors, such as pools of skilled workers, regulations and links to universities. The EE literature has yet devoted little attention to the scaling-up phase in a systemic way. A comparative approach that analyzes those processes across different EEs has also been lacking. The study applies a qualitative method and follows an open and explorative approach that enables a better understanding of this under-researched phenomenon. Data analysis has been inductive (Dubois and Gadde 2002), iterating among detected patterns and the existing literature, to support the process of theorizing. Furthermore, a comparative case study approach has been applied in order to reveal similarities and contrasts among EEs.

Findings

The results of this study identify firm-specific and firm-external factors that are important to high-growth firms in EEs in Life Science. The study shows how these factors enable or hinder the scaling-up process in EEs, how these factors vary greatly in their roles across distinct EEs, and how these factors are strongly interconnected. The identified factors include growth ambition, technological expertise, management competence, business model alteration, funding, global firms, human capital, support organizations, local growth culture, hospitals and universities. Other findings are that the start-up and the scale-up phases depend on each other, and that scale-up factors have multi-scalar qualities that stretch outside of the EEs.

Chapter 6:
Conclusions and Discussions

This chapter returns to the main research question of the thesis, provides concluding discussion of the results and the overall contribution. Then synthesis of findings shows how the research gaps from the theory chapter have been addressed in the different appended papers. Limitations, future research agenda and policy implications conclude.

Through tackling the main research question, the thesis aspires to address limitations of the EE literature by studying how actors, factors and their interactions impact entrepreneurial firms in life sciences in different EEs.

Conclusion – the overall contribution

Let us return to the key research question of the thesis: *"How do actors, factors and their interactions impact the start-up, scale-up and resilience of entrepreneurial firms in different EEs?* This thesis provides insights in how EEs in LS differ in the way actors, factors and their interactions support, or not, the start-up, scale-up and resilience of entrepreneurial firms**.** Conceptually, it contributes to the further development and refinement of the EE concept by addressing a number of limitations of the EE literature. Empirically, it contributes to the literature on EE by investigating structures (the extent and the way actors and factors interact in specific contexts and how this contributes to entrepreneurship), processes (the level and nature of the scaling-up process), and dynamics (what makes an EE resilient to a shock). This is done by adopting (i) a systemic approach, (ii) a comparative perspective, (iii) a dynamic view, and (iv) an institutional approach in the different appended papers.

The conceptual contribution of the thesis is that it has uncovered a number of shortcomings in the EEs literature, showing that the EE concept is still underdeveloped. Based on this critical assessment, a thorough research agenda has been presented that can be used for the further development of the EE concept. The topics of this research agenda include: (i) the enhancement of the analytical framework, with an explicit distinction between causes and effects, (ii) the

utilization of network theory and network tools, (iii) addressing more explicitly the role of institutions; (iv) the application of a comparative regional approach; (v) the exploration of multi-scalarity in EE; and (vi) addressing the dynamics of EEs over time. When taking up these research topics, it will provide the EE literature with a stronger theoretical and conceptual foundation. Another contribution of the thesis is that this further refinement of the EE concept can only be realized when following an interdisciplinary approach, combining insights from several disciplines, like entrepreneurship studies, regional studies, innovation studies, network theory, sociology, and institutional theory.

Empirically, this thesis has analyzed EEs in space and time, where their structures relate to space and their dynamics relate to time. Structures of EEs are described in terms of the presence of actors and factors that are important to entrepreneurial firms and how they are connected. The systemic view underlines that the role of each actor and factor in an EE that cannot be understood in isolation. They are linked in different ways, showing weak or strong linkages, as summarized in Figure 6.1. Dynamics of EEs are described in terms of resilience, drivers of change, and phases of development. A key empirical contribution of the thesis is that the structures and the dynamics of EEs show remarkable differences across regions, even when the industry is the same. The thesis has also shown empirically the relevance of a multi-scalar perspective. Actors in an EE can be connected across different geographical scales. Those links are also subject to change, depending on the development phase of a firm.

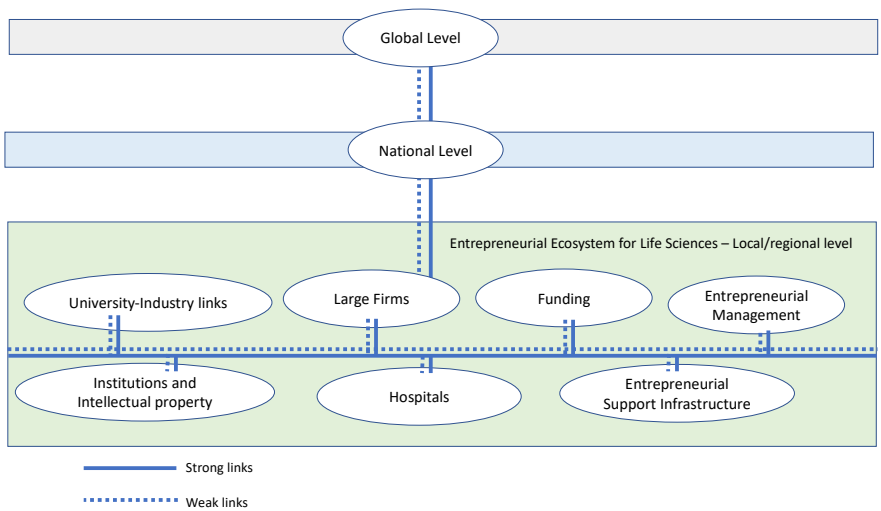

Figure 6.1 Structure of Entrepreneurial Ecosystems in Life Sciences: actors, factors, and their connections

The empirical analysis revealed that the structure of the EE in NE Ohio seems to be most developed among all EEs in the thesis. NE Ohio has actors with rich resources that are highly connected at different geographical scales. Universities, local support organizations and LS firms are supported by large governmental investments and a strong market-oriented growth culture. In comparison to NE Ohio in the US, all Swedish EEs have a hard time to transform their firms into global firms because risk capital and the right competences are largely missing. Nevertheless, Swedish EEs are doing well when it comes to the support of the initial stages of small firms in LS. Large firms had a positive impact in some Swedish EEs in various ways, contributing, for instance, to a local collaborative culture. In NE Ohio, there is no strong presence of large firms, but similar positive effects are produced by other local players like the Cleveland Clinic and local universities. But above all, the comparative analysis showed that the different factors are strongly interlinked in an EE, which implies that an improvement in one factor cannot be realized without taking care of other factors. This clearly shows the value-added of applying a systemic approach to entrepreneurship studies.

The thesis showed that the scaling-up of firms is supported or hindered by factors in an EE that are both specific to firms and external to firms, and that these external factors can be found at different geographical scales. This is summarized in Figure 6.2. The main motivation was that the EE literature devoted little attention to the scaling-up phase. The thesis followed studies on high-growth firms that showed that the scaling-up process is influenced by firm-specific factors (e.g. Aaboen et al. 2006; Mason and Brown 2013) and factors external to the firm (e.g. Cavallo et al. 2019; Spigel and Vinodrai 2020). The empirical outcomes in paper 4 confirm that both firm-internal and firm-external factors (both internal to the EE and external to it) are important for the scaling-up process in EEs. The thesis also found many differences between EEs when comparing the scaling-up process across the five EEs, because the factors that stimulate or hold back scaling-up are often region-specific. The scale-up process seemed to be more successful in NE Ohio, and to a lesser extent in Stockholm. Generally, smart capital is largely missing in the Swedish EEs to help firms scale-up to the global level. In the NE Ohio, the attitude is more market and growth oriented among key actors, and there is a stronger focus on building large LS firms. But more importantly, the paper also show that these factors are closely interconnected, revealing strong interdependencies and complementarities that impact the scale-up process in EEs. Moreover, the combination of factors and their interplay that affect scaling-up have their own specific configuration in each EE. Factors external to the EE that support or not scaling-up also showed impacts on the EEs.

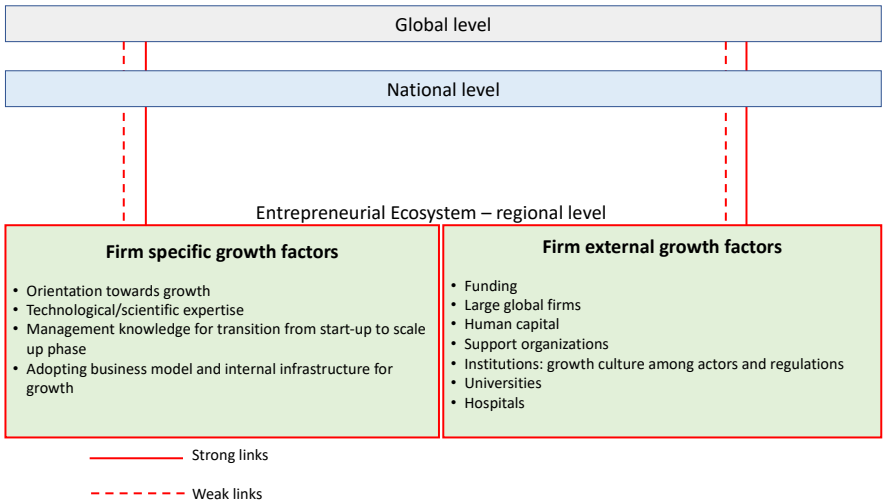

Figure 6.2 The scale-up process in Entrepreneurial Ecosystems in Life Sciences

EEs are also changing over time. The thesis has shown empirically that when an EE encounters a shock, regional leaders (including institutional and business entrepreneurs), social capital and local resources are important factors that can make an EE resilient. These factors help an EE to work through the crisis in the short-term and make transformations in the longer term. This is what happened in the EE of Lund where a new dynamic LS center Medicon Village was created, after the closure of a large research facility of Astra Zeneca. This is summarized in Figure 6.3. Both public and private regional leadership was key to initiate and design the transformation process. The thesis shows that, when handled properly, shocks can be a source of new positive developments, destroying old institutions and providing space for new dynamics. In particular, the recycling of entrepreneurs has been found key in terms of the knowledge and the capital they bring back into the system.

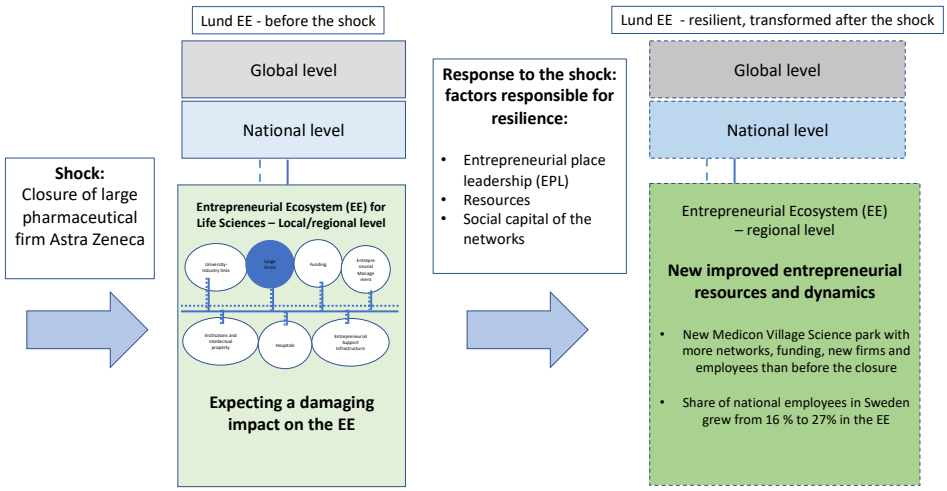

Figure 6.3 Resilience of the Entrepreneurial Ecosystem in Life Sciences in Lund

Synthesis and discussion of findings

The EE concept started to be applied fast, due to the high interest in policy circles in particular, where policy makers felt it could promote economic development in their regions (World Economic Forum 2013; Mason and Brown 2014). At the same time, the EE concept was also strongly criticized for its poor analytical framework and weak foundations in academic research (Stam 2015; Autio et al. 2018; O'Connor et al. 2018; Scaringella and Radziwon 2018; Stam and Spigel 2016). In that context, paper 1 aimed to contribute to the state of the art of the EE literature. After systematically examining research on EEs, paper 1 developed a critique on the EE literature and presented a future research agenda. Some of the contributions of this conceptual paper are briefly described below, and it will be explained which of these contributions have been addressed in the empirical papers of the thesis. More specifically, four contributions are briefly discussed one by one: (i) the systemic approach, (ii) the regional perspective, (iii) the dynamic perspective, and (iv) the institutional approach.

Systemic approach. Paper 1 found that the EE literature promotes a systemic approach to entrepreneurship studies but concluded that little reference was made to network theory, and network tools were hardly applied. Instead, the EE literature used to present lists of elements and factors (Green et al. 2010; Isenberg 2010; Rice et al. 2010; Acs et al. 2014; Spigel 2017), without explaining how those elements are interconnected and what elements cause what effects (Stam 2015; Stam and Spigel 2016). Even though this thesis has not applied network methods, systemic

effects have been investigated in the empirical papers. Papers 3 and 4 applied a systemic approach, and showed that factors that impact entrepreneurial processes are closely interconnected in EEs. More specifically, the papers show how start-up and scale-up factors in the EE impact each other in mutual and often reinforcing ways. Similarly, papers 2 and 3 found systemic effects both at the level of EEs but also beyond that and showed how links between agents and the structure of an EE affect outcomes in EEs.

Regional perspective. Paper 1 stated that the EE literature followed a regional approach from the start, but few studies in EE took a comparative regional perspective, and there was no discussion what is the relative importance of factors and linkages with actors outside the EE. Studies often tended to concentrate on one particular area (Isenberg 2010; Motoyama and Watkins 2014; Spigel 2017), and when they compared particular regions (Acs and Armington 2006; Motoyama and Watkins 2014), they hardly explained the reasons behind differences. The literature either compared regions quantitatively via indices (Acs et al. 2014), or it described differences qualitatively between a couple of EEs (Spigel 2017). A qualitative regional comparative approach has been applied in papers 3 and 4, comparing five EEs. They present strong evidence there is a need to differentiate between EEs in different regions. The thesis shows how EEs are structured and behave differently on many aspects. Especially there was a striking difference between the two countries – US and Sweden. But also within a quite homogeneous country like Sweden, there were remarkable differences between EEs, despite the fact that these EEs are part of the same national institutional context and follow the same industry-specific regulations. If we look at commonalities across EEs, Paper 3 supported the finding of Motoyama and Knowlton (2017) that the interactions between different support programs create a favorable cohesive environment for growth and showed that it holds across different institutional contexts. Moreover, very few studies on EEs have applied a multi-scalar approach that examine systematically the role of local and non-local links and relevant institutions that operate at different spatial scales (Malecki 2011). The empirical results of the thesis show that the regional approach should not limit itself to the geographical boundaries of an EE that are blurry anyhow. Instead, studies on EEs should embrace a multi-scalar perspective that goes beyond a regional approach that focuses only at the level of an EE. The thesis shows that actors and factors outside the EEs also matter for the development of firms in EEs. One interesting finding was that global links are important early on in the life of a LS firm, while the EE literature suggested that global links might matter only at a later stage in the development of firms (e.g. Spigel and Vinodrai 2020).

Dynamic perspective. Paper 1 argued that the EE literature has been weak in applying a dynamic perspective, although notable exceptions are Mason and Brown (2014) and Mack and Mayer (2016). In particular, studies had barely investigated how shocks may affect entrepreneurial firms and the evolution of the EE as a whole

(Mason and Brown 2014; Lefebvre et al. 2015; Mack and Mayer 2016). Such a dynamic approach has been taken up in paper 2 by looking at how resilient an EE can be after a shock, due to the closure of a large global firm in an EE. Based on a case study of Lund EE, the study showed that the shock triggered new entrepreneurial dynamics in the region, how EE moved to a new phase of development due to the impact of policy, and how some factors had to be in place before other factors could be activated. The paper also shows how agency in general and the governance of an EE (in terms of place leadership with certain entrepreneurial characteristics) in particular can impact the evolution of a dynamic center in Life Science. The study gives support to the hypothesis of Roundy (2017) that resilience and interaction between micro- and macro-processes in an EE are tightly connected. Interestingly, while Roundy (2017) hypothesized that coherence is a macro-process mostly found at the level of the EE, Paper 2 shows that coherence at the micro-level, as for instance embodied in trust among groups of entrepreneurs, contributed to the resilience of the EE of Lund. Moreover, the paper contributes to the EE literature by linking it to the growing literature on regional resilience (Garud et al., 2010; Simmie and Martin, 2010; Boschma 2015a; Xiao et al. 2018) that investigates the impact of different types of shocks on regional development.

Institutional approach. Paper 1 pointed out that any study on EE should follow more explicitly an institutional approach both at the micro-level (institutional entrepreneurs) and at the macro-level (e.g. culture, social capital and regulations). Institutions are regarded as crucial because they have an effect on the intensity and nature of linkages in an EE (Qian et al. 2013). Consequently, institutions are expected to be more supportive in some regions than in other regions which impact the rate of entrepreneurship. Roundy (2016) states that both regional beliefs about entrepreneurship and regulations play an important role in a region. Spigel and Vinodrai (2020) discusses the role of entrepreneurial recycling and the institutions at play. This thesis found empirical support for these statements, showing that institutions act as promoter (or not) of entrepreneurship in EEs, and that social capital plays an important role in connection to entrepreneurial recycling in EEs. In particular, paper 2 found evidence that social capital was supportive in dealing with a crisis in an EE, and papers 3 and 4 provided empirical evidence for the role of institutions in EEs at different spatial levels, comparing EEs in different national (Sweden and the US) and regional institutions (within Sweden).

Limitations and future research agenda

In order to push the development of the EE literature forward, this thesis proposes a research agenda for future studies. The thesis takes its basis in research gaps that it has identified and has been trying to address. The more profound limitations of this thesis are, therefore, those parts of the gaps in the literature that the thesis was

not able to address. Hence, the limitations and the future research agenda are discussed in an overlapping manner.

The Life Science industry has been studied in this thesis. This focus on one industry may imply that the factors the thesis found important are very specific to that sector. In other words, the structures of EEs identified are not only region-specific but may also be sector-specific. The thesis also highlighted that Life Sciences is a heterogenous sector itself, consisting of different sub-sectors like Medtech, Pharmaceuticals and Biotech that tend to use certain factors in EEs differently. This calls for further studies that explore how the specificity of sectors might influence the nature and evolution of EEs. Such a research agenda in EE would contribute to a better understanding of EEs, which according to Spigel and Harrison (2018) "… has remained largely industry agnostic" (p. 156).

Another limitation of the thesis is the lack of using network tools (as pointed out in paper 1). The thesis has followed a systemic approach, looking at all kinds of links that connect actors and organizations in an EE. This thesis has exposed many of these links (and the lack of those), and which links were more or less important in different EEs. However, what the thesis did do only to a limited extent is to exploit network tools. This is what is needed in future research on EE to gain more understanding of the systemic nature of EEs. It would bring in the development of new ideas drawing on network theory that could be tested in a network framework. For instance, it would allow to study what impact positions of small firms in networks can have on their ability to scale-up. Moreover, it would enable us to describe and characterize EEs in terms of networks features and, therefore, compare their structures more precisely. Network analysis at the micro-level can take up research questions like: what types of entrepreneurs link with which organizations, and which organizations are boundary spanners in EEs (Boschma and Ter Wal 2007; Ter Wal and Boschma 2009). Interesting questions at the macro-level of the EE can be addressed, like what network structures in EE perform better (Balland et al. 2013; Auerswald 2015; Ter Wal et al. 2016), what linkages in EE matter in particular (Partanen et al. 2014), which network structures in EEs are more resilient (Crespo et al. 2014), and whether EEs with a high proportion of non-regional linkages would exhibit more entrepreneurial dynamics.

Another limitation of the thesis is that the comparative approach in papers 3 and 4 provides a rather static picture of the five EEs. Future research on EEs should take a more dynamic approach. One way of doing that is to make a comparison between the different stages of development (start-up, transition and scale up) of a Life Science firm and determine which factors in an EE are important in each of these stages. This would provide a more systematic understanding of what are the important factors as EEs evolve over time. Paper 2 in the thesis takes a more dynamic approach but looks only at the impact of a shock on the evolution of an EE. Mason and Brown (2014), Mack and Mayer (2016) and Cantner et al. (2020) provide excellent examples of such a dynamic approach, looking at the evolution of

EEs over time that is embedded in an analytical framework. An interesting research direction can be to add a network perspective to the evolutionary approach on EEs. This can help examine the evolution of links in networks similar to the literature on cluster dynamics (Ter Wal and Boschma 2011).

This thesis has adopted a regional perspective, comparing EEs in different geographical contexts. This study has also demonstrated that the geographical boundaries of an EE are blurry and hard to define. Important linkages between actors often cross these geographical boundaries and demonstrate that key connections can lead far outside of the EE. Furthermore, factors that have impact on the entrepreneurial firms can be positioned outside these strict boundaries, such as national regulations or large companies in other countries. Research should identify actors and factors that matter, explain which spatial scale (regional, national, international) matters most, how they matter, and in which phase of the development of a firm. This would also generate novel insights that are relevant for an dynamic approach to EEs. First, it could reveal how the roles of geographical scales are likely to change during evolution of an EE. Second, it could determine to what extent non-local links beyond the strict boundaries of an EE can substitute or complement the local links in an EE.

This thesis has also looked at the role of institutions at different spatial scales e.g. national institutions in Sweden and the US, and regional institutions such as trust at the level of EEs. The institutions were studied as static. However, institutions change with time. How institutions change over time in connection to the evolution of EE can be interesting to study in future research. These institutional changes can be researched both at the macro-level (changes at the level of the EE) and at the micro-level (how individuals and groups impact institutions). For institutional change at the micro-level, the literature on institutional entrepreneurship (Battilana et al. 2009) and place-based leadership (Beer et al. 2019) could be used for reference. It can be important to investigate what actors are responsible, how they change institutions, and if they are supported or hindered by factors in the EEs

It was not the objective of the thesis to evaluate which of the EEs in Life Sciences was most successful, even if some of the EEs seemed to be more successful than others. The thesis focused on the role of factors and the links between actors in EEs, and how that affected the start-up and scaling-up process and the resilience of firms in EEs. The comparative approach was not used to define which of the EEs could be seen as more successful either. Furthermore, the goal of the study was not to assess the economic effects of EEs. However, these questions are still very relevant and should be taken up in future research. This requires understanding of how to define the indicators by which entrepreneurial success of EEs can be measured, and how to assess the economic effects of EEs (e.g. on employment or productivity).

Policy implications for Entrepreneurial Ecosystem

What policy implications can be derived from the thesis that can support the development of the innovative firms? The study has shown that the role of public policy is widespread in EEs in Life Sciences at multiple scales (national, regional, local). But public policy also works differently in different contexts because the attitude of society towards public policy and the configuration of EEs (like their main elements and how they interact) differ to a considerable degree (here the differences between the US and Sweden are especially relevant). This means that governments have to take into account context-specific structures, functions and problems of the EEs when designing a policy. For instance, policy in the EE 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 funding to Life Science firms (through direct investments, subsidies, loan guarantees, matching funds etc.). From the many potential roles policy can take in EE, the thesis chooses to focus on only a few of them when discussing possible implications. Moreover, policy implications are mainly discussed from the Swedish perspective rather than the US perspective.

The thesis would argue that the justification for specific policies on EE is to improve the entrepreneurial performance of a region by (i) supporting an environment favorable to start-ups and growth of firms, providing basic conditions and stimuli (ii) supporting the reinforcing mechanisms in EEs, and (iii) eliminating institutional and non-institutional obstacles. Due to the systematic nature of the EEs, policy should ensure not only the enhancement of the quality of actors and factors that make up the EE (Stam 2018), but also address system failures in EEs that block entrepreneurial dynamics in EEs. This implies that policy in EE should address not only market failures (a common rationale of government interventions) but also address system failures (Teece 1992; Carlsson 2016). And when tackling system failures, policies in the EE should also consider how they impact the whole system and not only certain actors.

While EEs cannot be fully governed by public policy, it is possible to set directions, taking into account the context-specific structures in an EE. The thesis has shown that EEs in LS function in different ways. This implies that policy should account for the context-specificity and align its policy actions (Stam 2018; Liguori and Bendickson 2020). The insight that every EE in LS has its own specific structures and links sets also limits to what can be learned from other places and how national measures can be made effective in specific regional contexts.

The type and strength of policy should change with time as an EE develops and "reinforces" itself (Feld 2012, 2020; Liguori and Bendickson 2020). The role of policy makers could at one time follow a 'back seat' approach (enabling things), or take a hands-on approach (active involvement), depending on the certain needs in the EE connected to the start-up and scale-up processes that entrepreneurial firms

experience. Overall, evolutionary and systemic approach to EE policy should be considered (Carlsson 2016).

A critical lesson learnt that is certainly not unique to this study is that access to capital in EEs in Life Sciences is fundamental to ensure successful entrepreneurship. What an EE in LS in particular requires is smart capital that can be provided by investors that have entrepreneurial and industry-specific knowledge and that have long-term commitment and access to large amounts of funding. However, from the EE perspective, it is relevant to consider which different investors and their linkages have most impact at what stages of firms' development. Interviews revealed that funding in the early stages (the pre-seed/seed phase) can be larger in Sweden and should be provided by more actors in order to avoid selection by only a few funding actors. Existing venture capital firms can be selective and capital can flow only to certain types of technologies in different EEs, as shown by Cortright and Mayer (2001). Hence, it can be relevant to understand and support or adjust those flows.

Governmental investments provided at various regional scales should be better aligned in terms of goals/incentives and develop a stronger orientation towards long-term growth of firms. The way government funding is distributed in Sweden seems to be unpredictable to firms and puts power for selection into the hands of government officials. This can be avoided by setting clear criteria for all firms and their projects which makes firms eligible to funding when they reach it.

Private investor communities (business angels) are important sources of funding but can be inaccessible to those that are outside the main networks. Hence, supporting the openness of networks and helping those communities to connect to different entrepreneurs can spread resources more efficiently in the EE. Entrepreneurs that become private investors after a successful exit (recycling of entrepreneurs) should be encouraged to take part in governmental funding programs for matching investments, to network with other private investors (also abroad), and to spread their entrepreneurial knowledge in the system.

There is also a need for access to more growth capital in terms of public and private funds. As a firm moves up the growth ladder, public authorities need to consider becoming more active. They could offer larger funds, matching funds, cheap loans etc. for the scale-up stages of firms, so that firms can reach further in their clinical trials, get higher international evaluations, and through that attract international capital. Attraction of foreign investments can be through funding applications or partnering up with a large global firm, making firms better globally connected and more visible to boost international evaluations further. In the case of acquisitions of small firms, which is often the goal of Life Science firms especially in Swedish EEs, the value can be collected by the EE through policies that make the buyer commit to reinvest into the local EE.

In Swedish EEs, entrepreneurial support organizations play an important role but they should focus more on the growth phase of the entrepreneurial firms by

embracing a stronger growth and market oriented culture, providing access to specific type of entrepreneurial/management knowledge, and assisting in making connections to global players. This is because appropriate managerial knowledge seems to be lacking in many entrepreneurial firms at the start, when researchers often shoulder business responsibilities as well as scientific responsibilities which is too much for the researchers to handle, with rare exceptions. Entrepreneurial support organizations need to be stronger, involving more people with growth-oriented managerial knowledge, international sales experience, and close connections to the Life Science industry. Specifically, people should be rotating between innovative firms and support organizations to make sure to keep the internal knowledge of the support organizations up to date. To stimulate entrepreneurial recycling in which entrepreneurs altruistically pay back to the EE in terms of their knowledge can be an effective mechanism.

Entrepreneurial support organizations could act as hubs and promote national and more importantly international network connections to key actors, such as large firms, hospitals in other countries, and knowledgeable people. Entrepreneurial support organizations at different geographical levels should be well connected and complement each other, as advocated by Hoover (2020) and Liguori and Bendickson (2020). Local, regional and national support organizations should align their objectives towards supporting the scaling-up stages of LS firms in Sweden and foster a culture of growth and risk tolerance similar to NE Ohio. In order for firms to better navigate the different types of support they need, they should hire relevant expertise that can represent boundary spanners which connect different actors in the EEs.

Policy implications for Swedish EEs at the national level can concern stimulation of shared projects and labor mobility across the actors (support organizations, universities, firms, and research hospitals) in the EE. What the studies in the thesis tend to show is that academic and private organizations work against each other if they do not value each other's experience and knowledge. This requires that actors start to acknowledge and exploit the value of their experiences and knowledge to a larger extent, that is, business experience in universities, and academic knowledge in firms. Labor mobility and hybrid employments seem to be important vehicles to better infuse knowledge from academia/health care into businesses and back.

Another policy implication is that there is a larger need for collaborations between large organizations and small firms in EEs on the basis of mutual respect. These networks can support the reputation of small firms on the global market which is a crucial aspect for reducing uncertainty for investors. The expensive infrastructure and the expertise of the hospitals and the universities should be made more accessible to small firms.

Policy makers should also be more aware of what they can do to support resilience in an EE in the face of crisis (Kraus et al. 2020; Velt 2020). The study on Lund

reminds us how important the type of governance is to overcome a crisis in an EE. This has been referred to as Entrepreneurial Place Leadership in the thesis. The positive transformation of the EE would not have started without the entrepreneurial action of local leaders from both private and public organizations. This case shows that the successful governance of an EE should incorporate a more risk-tolerant entrepreneurial mindset that can be found in leaders in both public and private domains that include current and/or prior entrepreneurs. More in general, policy should think how to deal with inevitable failures that occur in EEs. Ways of doing that is to create a forgiving culture for failure, to facilitate the reallocation of left-over resources, and to target and exploit experienced entrepreneurs more specifically.

Although breakthrough innovations have not been studied in this thesis, supporting breakthrough innovations is likely to be important for securing a strong economic development in EEs in the longer run. EEs should be careful not to become locked in certain economic structures and institutions. Therefore, EEs should strive to be open systems and adopt open innovation strategies in the way the EE in LS in Uppsala has done. This can be achieved by supporting diversity of ideas and knowledge in an EE, and by establishing open networks that connect groups but also cross the boundaries of an EE. Furthermore, diversity in an EE will be more beneficial when it includes related assets such as complementary resources and knowledge (Boschma 2017), because these can yield effective collaborations and encourage interactive learning in an EE (Balland and Boschma 2021).

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