N°d'ordre NNT : LYSE3---

THÈSE de DOCTORAT DE L'UNIVERSITÉ DE LYON

opérée au sein de

L'Université Jean Moulin Lyon 3

Ecole Doctorale N° accréditation

EA3713

Discipline de doctorat : Sciences économiques et de gestion

Soutenue publiquement le 21/05/2019, par :

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"Science-Based firm performance and growth"

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UNIVERSITA' DEGLI STUDI DI PAVIA
DIPARTIMENTO DI SCIENZE ECONOMICHE E AZIENDALI

DOCTORAL PROGRAM IN ECONOMICS AND MANAGEMENT OF TECHNOLOGY

"Science-Based firm performance and growth"

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Doctoral thesis of

Andrea Setti

XXXI Cycle

ABSTRACT

This thesis proposes a theoretical and empirical framework on growth and development and offers elements and tools necessary to improve the understanding of the growth dynamics of SBFs. Throughout this thesis, emphasis has been placed on the study of SBFs dynamics related to their performances and growth. Prior further investigation, through the analysis of the main taxonomical contributions, a comprehensive definition of Science-Based Firms (SBFs) is formulated which incorporates the consideration that these ventures seek the application of scientific knowledge and technological skills to commercialize products at the core of their activities.

Applying the above mentioned definition, a first study was performed with the double objective to provide an updated, state-of-the-art picture of the SBFs and to critically examine the adoption of SBFs' performance determinants in order to be able to better comprehend the way in which SBFs' performances have been approached and suggest future directions in terms of focus of studies and methodological approaches. Results show that studies concentrate on firm-specific dimensions succeeding in some situations to explain SBFs' performances and in many other cases contradicting results emerged. In general, in the investigation, was outlined how the study of SBFs' performances, is still widely underdeveloped and indicators related to innovation capabilities and knowledge management such as innovation developments, technology development or knowledge transfer, seem more appropriate to infer the peculiarity of these firms. Moreover, from the findings emerged the necessity to adopt a holistic approach considering broader dimensions proposed for example by ecosystem theories.

Following a holistic methodology, an explorative study was conducted in the area of Lyon, France, adopting the Entrepreneurial Ecosystem (EE) approach. Thanks to the retrospectivity adopted, in this study was possible to underline the relationships underpinning between the elements of the ecosystem and New Science-Based Firms (NSBFs). Findings show that institutions coordinated and focused on the main capabilities and excellence of the area make an extraordinary contribution to the establishing of new companies. In general results show that the EE can be a consistent theoretical construct, especially during the first stage of NSBF's development. However, looking at the whole process of SBF creation, three elements stand out: government, university and investors, incorporating the lineages of the so-called triple-helix approach applied in most modern knowledge-based societies. The area of Lyon represents a successful application of this model, opening the debate on the analysis that at first, to understand SBFs' dynamics, a macro look at the institutional configuration is needed.

For the previous reasons, the focus of the investigation shift from micro and meso level to macro level in the third investigation. The last step of the dissertation research focused its attention on the Italian triple-helix model for the science-based industry. Collecting interviews among the most representative Italian institutions supporting SBFs and collecting precious insights among Italian SBFs, both established and nascent, a comprehensive understanding on "what went wrong" situation is shown providing insights into the relationship dynamics that did not occur to make the innovation system work efficiently. Moreover, possible streams for future researches and suggestion for policy makers are provided.

In general, this dissertation provided advancements for the understanding of SBFs' growth dynamics providing fresh insights for academics and policy makers in designing future studies and policies.

Keywords: Science-Based Firms, Performances, Growth, R&D, Entrepreneurial Ecosystem, Triple-Helix, Policy.

RÉSUMÉ

Cette thèse propose un cadre théorique et empirique portant sur la croissance et le développement et offre des éléments et outils nécessaires à l'amélioration de notre compréhension des dynamiques de croissance des EOS. Pendant tout ce travail de thèse, on a insisté sur les dynamiques des EOS en lien avec leurs performances et leur croissance. Avant toute enquête plus poussée, avec l'analyse des principales contributions taxonomiques, une définition générale des Entreprises à Orientation Scientifique (EOS) est formulée eu égard du fait que ces entreprises cherchent à appliquer des connaissances scientifiques et compétences technologiques afin de commercialiser les produits qui sont au cœur de leurs activités.

En appliquant la définition mentionnée ci-dessus, une première étude a été effectuée avec l'objectif double de présenter un portrait actualisé de l'état de l'art et d'examiner de manière critique l'adoption de facteurs de performance des EOS afin de mieux comprendre la manière dont on a étudié les performances des EOS et de suggérer un sens définissant l'axe des études et approches méthodologiques futures. Les résultats démontrent que les études se concentrent sur des dimensions spécifiques aux entreprises, ce qui permet, dans certains cas, d'expliquer les performances des EOS. Dans de nombreux autres, on a abouti à des résultats contradictoires. De manière générale, dans cette enquête, on a expliqué pourquoi l'étude des performances des SBF est encore largement sous-développée et les indicateurs en lien aux capabilités d'innovation et à la gestion des connaissances, tels que les évolutions de l'innovation, le développement des technologies ou les transferts de connaissances, semblent plus appropriés pour démontrer la spécificité de ces entreprises. De plus, à partir des résultats, on a abouti à la nécessité d'adopter une approche holistique prenant en compte des aspects plus variés, avancés par exemple par les théories des écosystèmes.

Suivant une méthodologie holistique, une étude exploratoire a été menée dans la région de Lyon, en France en adoptant l'approche des Ecosystèmes Entrepreneuriaux (EE). Dans cette étude, grâce à une démarche rétrospective, il a été possible de souligner les relations opérant de manière sous-jacente entre les éléments de l'écosystème et des Nouvelles Entreprises à Orientation Scientifique (NEOS). Les résultats montrent que les institutions coordonnées et concentrées sur les axes des capabilités principales et de l'excellence du domaine contribuent de manière exceptionnelle à la fondation de nouvelles entreprises. De manière générale, les résultats montrent que l'EE peut être une construction théorique cohérente, et particulièrement pendant le premier temps du développement des NEOS.

Cependant, en considération du processus complet de création des EOS, trois éléments se démarquent : le gouvernement, les universités et les investisseurs, s'inscrivant dans la filiation de ce que l'on appelle l'approche de la triple hélice, appliquée dans la plupart des sociétés du savoir modernes. La région de Lyon présente une application réussie de ce modèle, ce qui nous permet de débattre de l'analyse suivant laquelle une macro-observation préliminaire des configurations institutionnelles est nécessaire pour comprendre les dynamiques des EOS.

Pour les raisons précédemment évoquées, la perspective de l'enquête passera du niveau micro au niveau méso dans la troisième enquête. La dernière étape de cette thèse portera son attention sur le modèle à trois hélices italien dans l'industrie à orientation scientifique. En effectuant des entretiens dans les institutions italiennes les plus représentatives qui soutiennent des EOS et en recueillant des témoignages précieux dans des EOS, qui pourront être établies ou embryonnaires, une compréhension globale de situations où « quelque chose n'a pas bien été » pourra nous fournir des indices sur les dynamiques relationnelles qui ne se sont pas mises en place pour faire fonctionner de façon efficace le système d'innovation. Par ailleurs, des pistes pour des recherches futures et des suggestions aux décideurs politiques sont proposées.

De manière générale, cette thèse propose une évolution de la compréhension des dynamiques de croissance des EOS, donnant ainsi de nouvelles pistes aux universitaires et décideurs politiques pour la conception d'études et de politiques publiques à l'avenir.

Mots-clés : Science-Based Firms, Performances, Croissance, R&D, Ecosystème Entrepreneurial, Triple Hélice, Politiques Publiques.

ACKNOWLEDGEMENTS

Firstly, I would like to express my sincere gratitude to my supervisors Prof. Antonella Zucchella (University of Pavia) and Prof. Ulrike Mayrhofer (Université Nice Sophia Antipolis, IAE Lyon until 31st of August 2018) and my advisor Prof. Tommaso Minola (Uversità Degli Studi di Bergamo), for their continuous support of my Ph.D study and related research, for their patience, motivation, and immense knowledge. Their guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisors and mentors for my Ph.D study.

I big thanks goes to all the entrepreneurs and persons who gave me the opportunity to interview them during my researchers in Pavia and in Lyon. Their words and thoughts were very inspiring and provided me with fruitful insights that contributed to enrich my business knowledge and provided me with the opportunity to contribute to the scientific community. Moreover, the time spent with this people enriched me personally, making me think a lot about their personal experiences and how they overcome life challenges that brought them to the actual success.

I thank my fellow lab mates in for the stimulating discussions, for the sleepless nights we were working together before deadlines, and for all the fun we have had in the last three years. I thank very much this jury of excellence whose remarks, advice and comments have helped refine this work and mark the finishing touches. To be evaluated by a jury of this quality becomes an inspiration of the example to follow for entry into the academic world. A challenge that I hope to rise. I am grateful to all of those with whom I have had the pleasure to work during this and other related projects. Each of the members of my Dissertation Committee has provided me extensive personal and professional guidance and taught me a great deal about both scientific research and life in general.

Last but not the least, I would like to thank my family: my parents, my brother and my partner for supporting me spiritually throughout writing this thesis and my life in general.

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1. INTRODUCTION

Modern economies are characterized by an intensive application of knowledge, academic research and basic science discoveries which are translated in technological change and economic growth (Cohen et al., 2002; Feldman et al., 2002). Before these scientific discoveries in the form of scientific knowledge reach the market in a form of new products and services, they need to be converted to marketable products. This process involves complex technology transfer activities involving many individuals in society which nowadays represent one of the main challenges in knowledge-based economies (Fleming and Sorenson, 2004; Meyer-Krahmer and Schmoch, 1998). Among those activities, fostering innovation start-up creation represents one of the most effective instruments for technology creation (Lumpkin and Ireland, 1988; Timmons and Spinelli, 2003; Hayton, 2005). Supporting the creation and development of such firms has become one of the main priority policies for several countries, especially for the European Union (European Commission, 2005).

One of the keys to success for these policies is the creation of successful Science-Based Firms (SBFs). SBFs have at the core of their objectives to create innovation from science, reflecting the ability of hosting economies to obtain a competitive advantage from scientific discoveries (Casper, 2007) and their ability to transfer knowledge from basic research to market (Autio and Yli-Renko, 1998; Fontes, 2005; Rasmussen et al., 2006; DiGregorio and Shane, 2003). Moreover, SBFs are the crucial link between industry and science (Debacker and Veugelers, 2005; Perez and Sanchez, 2003) and have the ability to create new jobs in high value sectors (e.g. Clarysse et al., 2005; Di Gregorio and Shane, 2003; O'Shea et al., 2008; Shane, 2004).

But what is a Science-Based Firm? In their literature SBFs are usually compared to high-tech firms, not only for their high innovativeness but also because both firms typically relate on Research and Development (R&D) from the university research and in-house sources to develop new processes and products, as well as developing a high degree of acquisition based on secrecy, patents and tacit knowledge (Niosi, 2000). According to Autio (1997), SBFs are primarily engaged in the advancement of science whereas high-tech firms focus on the use of scientific knowledge in the development of innovation. On the other hand, Pisano (2006, 2010) argues that SBFs have the R&D projects as the main assets in the developing technologies. Niosi (2000) indicates that SBFs are prone to adopt technology-based innovation, which is characterized by the in-house R&D. The conception and development of an SBF both focus on a unique R&D process and on diversity in approach to commercialization of scientific knowledge. This is one aspect that makes the conceptual model of entrepreneurial SBFs different from high-tech firms in terms of the focus of scientific knowledge development and execution (Miozzo and DiVito, 2016).

Several studies have investigated the concepts and theories upon which the definition of SBFs is based. Both policymakers and academics have developed various definitions, based on what suits them or the context in which the definition is derived. It is worth noting that the previous studies have built their definition on the premise of the venture capitalist and a novel organizational form (Pisano, 2010), an institutional enacted process (Moray, 2004), university spin-offs (Lubik & Garnsey, 2016; Hagedoorn et al., 2018), regional economic development (Bathelt et al., 2010), and industrialization (Garvin, 1983). Pavitt (1984) studied sectoral patterns and based his taxonomy of SBFs asserting that, compared to other firms, they have copious R&D investments concentrated on basic research activities. In 1990 Stankiewicz made a step forward referring to SBFs as operating in the "scientification of technology". According to Pisano (2010), Science-Based businesses were viewed as the novel organizational form depicting the forms of biotechnology as a science business. Thus, Pisano defines SBFs as the "entities that both participate in the creation and advancement of science and attempt to capture financial returns from this participation."

However, a common definition that has been adopted by most academics is similar to the two-dimensional definition adopted by Moray (2004). According to Moray, the definition of Science-Based Firm as a spin-off depicts: (1) a new company formed by a faculty member, doctoral student or a staff member who left a university and founded a company; and (2) a core technology which is transferred from the parent organization. The later dimensional definition supports the earlier definitions and views held by Smilor et al. (1990) as a university spin-off based on technology from the universities. Also, within the context of another four-dimensional definition by the Organization for Economic Co-operation and Development (OECD), Science-Based spin-offs are companies that must meet the following criteria: (1) "one of the founders is an employee of the Public Research Organization (PRO)"; (2) "the company licenses a technology from the PRO"; (3) "a PRO has equity in the company"; or the said company is formed when (4) "the PRO directly established the company" (Callan, 2001).

Based on the above definitions of SBFs and other definitions therein, it is quite difficult to choose the correct and universal definition of an SBF that can be applied in all contexts and fields of study. The review of these definitions indicates that a science-based firm/business is defined in terms of the founder, the objectives for which it was formed, and the associated organization. It is therefore important that the present study focuses on providing a clear and direct definition that can be applied in all areas of research other than the business researches. As observable from previous definitions, it is possible to understand that a science-based venture relies on basic research to reach scientific advancements and create marketable innovations. The peculiarity of these firms which distinguish them from the others is that an SBF does not only seek advancement in science but also foresees the exploitation of the related technologies, the feature that distinguishes them from research public institutions, universities and research centers. For this reason, for the investigation of this thesis and as the suggestion for future research, we will adopt the definition of an SBF as "*a firm or entity that tries to advance science by performing basic research activities and tries to obtain a financial return from the related scientific discoveries*". Thus, this definition of an SBF incorporates the consideration of the use of ventures that apply the technical principles and require the application of scientific knowledge and technological skills to commercialize products.

Studies on SBFs show that these ventures have peculiar characteristics mostly associated with their strong commitment to R&D activities (e.g. Mangematin et al., 2003, Mustar et al., 2006). SBFs are usually characterized by a higher level of market and technology uncertainty (Pisano, 2006) which is moderated by the presence of scientists or founder-scientists holding a key role in the firm (e.g. Kenney, 1986; Liebeskind et al., 1996; Murray, 2004), for example, facilitating the knowledge transfer necessary to overcome the initial stage, making nearby universities the optimal location (Kenney, 1986; Liebeskind et al., 1996; Murray, 2004; Owen-Smith and Powell, 1998; Zucker et al., 1998). Uncertainties (market, technological and scientific) are the major obstacles for the sustainability and success of SBFs (Miozzo & DiVito, 2016). Therefore, R&D is performed in the SBFs as a strategy of successive reduction of uncertainty, which is achieved during the acquisition of information, having a highly iterative process (Pisano, 2006).

SBFs differ also from traditional high-tech firms on the modality of growth. Some of them experience an early growth due to the participation of external mature corporations, in this case incumbent firms (Colombo et al., 2010; Miozzo et al., 2016). Compared to a typical high-tech firm which completes the prototyping phase during the initial phase of growth, in SBFs this phase takes much longer (Kazanjian, 1988). SBFs have a unique set of resources which are mainly dedicated to scientific research – R&D investments – compared to other organizations (Pavitt, 1984).

Another peculiar characteristic of SBFs defined by Pisano (2006) is represented by the mechanisms of financing. Venture capital for SBFs assumes a double role: initially they represent the main source of financing and later become a source of governance structure. Some limitations could arise from the dichotomy between technology development (typically 5-10 years) and the exit horizon of venture capitalists (3-5 years). Also, the amount of capital required for longer R&D terms is different. In fact, SBFs require a huge financial involvement before reaching scientific advancements. High capital is also needed to compensate for the lack of facilities they need such as clinical testing, regulatory processes, manufacturing and distribution, or marketing.

SBFs frequently emerge as research spin-offs from university researches or R&D departments of industrial firms (Mustar et al., 2006; Knockaert et al., 2011; Rasmussen et al., 2011). Examples of SBFs are present in various high-tech scientific sectors such as biotechnology (e.g. Pisano, 2006, Zucker et al., 1998), pharmaceuticals (e.g. Gambardella, 1995) and semiconductors (e.g. Holbrook et al., 2003). The peculiar characteristics and the high heterogeneity of SBFs (e.g. Mangematin et al., 2003, Mustar et al., 2006) make the study of these ventures even harder than other firms that had led to a high fragmentation of studies, contradictory findings and lack of clear understanding on an SBF's dynamics (formation, growth, success, etc.).

Literature reviews on this topic, which are relatively old, show an increasing number of studies facing issues of SBFs, but results are very fragmented (Djokovic and Souitaris, 2008; O'Shea et al., 2008; Rothaermel and Thursby, 2007). SBFs' topics in the literature are very broad. Studies on SBFs may look into impacts generated by SBFs at national level (e.g. Vincett, 2010; Wallmark, 1997) or at regional level (Smith and Ho, 2006; Chrisman et al., 2005; Garnsey and Heffernan, 2005; Berggren and Dahlstrand, 2009); links between start-up conditions and performance (e.g. Clarysse et al., 2007, 2011; Colombo et al., 2010; Hayter, 2011; Rasmussen et al., 2011; Salvador, 2011). Studies may also comprise different individual levels of analysis, considering the dynamics of mainly scientists and academics (e.g. Bercovitz and Feldman, 2008; Fini et al., 2009; Toole and Czarnitzki, 2007; Grandi and

Grimaldi, 2005; Gurdon and Samsom, 2010). Or studies may also look at institutions at University level (e.g. Moray and Clarysse, 2005; Heirman and Clarysse, 2007; Colombo et al., 2010; Grandi and Grimaldi, 2005).

Continuing with the research streams, it is possible to find in the literature studies that seek insights from external context dynamics (Nerkar and Shane; 2003; Heirman and Clarysse, 2007; Lindelof and Lofsten, 2005); studies that compare academic versus non-academic Science-Based ventures (e.g. Ensley and Hmieleski, 2005; Munari and Toschi, 2011; Zhang, 2009) and finally studies that try to analyze the process of venture creation and what makes SBFs successful (Rasmussen et al. 2011; Zahra et al., 2007; Valentin et al., 2007).

Studies on success of SBFs provide contradicting results. Some authors point out that new Science-Based ventures, thanks to their smaller and leaner structures, have fewer difficulties in commercializing radical innovations than incumbent firms (Chesbrough and Rosenbloom, 2002; Danneels, 2004) and they play a more active role in pursuing the development and diffusion of technology (Thursby et al., 2001), taking their advantage from technologies which established firms fail to deliver to the market (Thursby et al., 2001) or do not consider as attractive (Markham et al., 2002). Recent studies on SBFs have shown that these ventures represent one of the most effective ways for the commercialization of research from public institutions such as universities and research labs (Rasmussen et al., 2008; Wright et al., 2007), answering to the call for entrepreneurial universities which is at the center of the recent public debate (e.g. Clark, 1998; Etzkowitz, 2003). Despite the positive findings/outcomes that the creation of SBFs bring to the society, some studies however on the other side point out that in general these firms have slow or rather disappointing growth rates (e.g. Harrison and Leitch, 2009; Pisano, 2006, 2010; Orsenigo, 2001, 2016).

Successful SBFs are at the center of knowledge-based societies due to the benefits they bring to the society (e.g. economic growth, employment), but the literature right now fails to deliver clear and comprehensive results on how an SBF grows and what makes an SBF successful. This is probably due to the peculiar characteristics of these firms that make the study of SBFs very hard to undertake; even the approval of a common definition can be problematic and complex. For those reasons the present discussion will focus on answering the questions "How do SBFs grow? And what makes an SBF successful?". To provide an answer to that two-part research question, three main steps are taken and represented in Chapters 2, 3 and 4. A summary of research questions and objectives is presented in Table 1.1.

Table 1.1. Summary of dissertation's research questions and objectives

SECTION	RESEARCH THEME	RESEARCH QUESTION	GOALS
All chapters	Science-Based Firm's (SBF) development and growth	*"How do SBFs grow and what makes an SBF successful?"*	- Understand the growth phenomenon of SBFs; - Understand the appropriate way to study SBFs' growth dynamics; - Contribution to the definition of SBFs. - Narrowing SBFs' research stream.
Chapter 2	SBF's performance determinants	*"What are the key performance parameters to evaluate an SBF?"*	- Review the extant literature of SBF's performance; - Understand what are the most appropriate parameters to evaluate SBFs according to their characteristics.
Chapter 3	Entrepreneurial Ecosystem approach in SBFs	*"How do SBFs grow within the EE?"*	- Understand how the EE works for SBFs; - Apply a holistic approach to the study of SBFs; - Understand if the EE is a suitable framework for the study of SBFs.
Chapter 4	Triple-Helix framework drawbacks in SBFs	*"Is the Triple-Helix framework the definitive approach?"*	- Picture a "what went wrong?" situation; - Provide different settings or alternatives to the Triple-Helix framework for SBFs.

During the first research, due to the fragmentation of studies and confusion about SBFs' performance determinants, a first review of the extant literature was performed with the double objective of at first providing an updated, state-of-the-art picture of the SBFs and secondly and most importantly (for the purpose of this elaboration), to critically examine the adoption of SBFs' performance determinants in order to be able to better comprehend the way in which SBFs' performances have been approached and suggest future directions in terms of focus of studies and methodological approaches. For this purpose, a systematic literature review taking an integrative approach has been adopted as the first step of the comprehensive research. In contrast with traditional narrative reviews, systematic reviews adopt a replicable, scientific and transparent process which minimizes the reviewer's bias through the analysis of an exhaustive plethora of literature and provides detailed information about the decisions, procedures and conclusion of the author(s) (Cook et al., 1997). Due to the fragmentation and lack of studies, an integrative approach to review the literature is adopted allowing the integration of qualitative findings with quantitative inferences (Rodgers and Knafl 2000, Whittemore and Knafl 2005). From the review, there emerged findings such as inconsistences in studying performance determinants (or inadequacy of performance parameters) of SBFs. For these SBFs to succeed, they need – due to their characteristics and R&D orientation – a combination of factors such as political sphere, legal environment and cultural factors that, combined together, provide a boost effect in the development of a New Science-Based Firms (NSBFs), which drives the foci of analysis for a better comprehension of their dynamics, from a micro-level to a meso-level incorporating a wider spectrum of angles of analysis.

Given the previously mentioned findings, the second step of investigation foresees the integration of a holistic methodology that not only comprises all the elements surrounding an NSBF, but also considers contextual elements specific to a territorial area. Following this methodology, an explorative study was conducted in the area of Lyon, France, adopting the Entrepreneurial Ecosystem (EE) approach (Isenberg, 2010; World Economic Forum, 2013; Stam and Spiegel, 2017). Adopting a retrospective analysis was possible to perform a long-term of analysis of the findings through interviews. Retrospectivity in this study was possible due to the sensitive nature of the events that characterized the core subjects of the interviews. The study adopting EE approach shows that institutions coordinated and focused on the main capabilities and excellence of the area, make an extraordinary contribution to the establishing of NSBFs, especially during the initial part of their life-cycle where networks, investors and human resources are at the center of firm's agendas. After this initial period, the influence of the EE loses its strength, opening the boundaries to a much broader scope which includes foundations, incumbent firms, clients and institutions at international level. The private sector, even if not directly involved, plays a fundamental role in this process indirectly through controlled firms or international presence. Although every area is unique and the study focuses on science-based firm growth created in the area of Lyon, the results show that the EE can be a consistent theoretical construct, especially during the first stage. However, looking at the whole process of SBF creation, three elements stand out: government, university and investors, incorporating the lineages of the so-called triple-helix approach applied in most modern knowledge-based societies. The area of Lyon, inserted in the Region Auvergne-Rhône-Alpes, represents a successful application of this model, opening the debate on the analysis that even a meso-level of analysis in not sufficient to fully explain the growth dynamics of SBFs; a macro look at the institutional configuration is needed.

Given the above findings and the necessity to adopt a macro a theoretical construct allowing a macro look to SBFs, the triple-helix model was identified as the most adopted by modern economies; model which many countries and areas around the world still struggle to develop, especially for SBFs (with a strong emphasis on biotechnology) (Pisano 2006, 2010). Moreover, it is possible to observe only few attempts to provide an alternative model for innovation in the science-based industry (Orsenigo, 2001, 2016). For this reason, the last step of the dissertation research focused its attention on a considered failure example rather than successful triple-helix model: the science-based industry in Italy. Collecting interviews among the most representative Italian institutions supporting SBFs and collecting precious insights among Italian SBFs, both established and nascent, a comprehensive understanding on “what went wrong” situation is shown providing insights into the relationship dynamics that did *not* occur to make the innovation system work efficiently. Moreover, possible venues for future researches and suggestion for policy makers are provided.

2. SBFs and performance factors, what should we do? An integrative systematic review of the literature.

In modern economies characterized by an intensive application of knowledge, academic research and science discoveries have a well-recognized value for technological change and economic growth (Cohen et al., 2002; Feldman et al., 2002) but converting such discoveries into new products or services is a complex task (Fleming and Sorenson, 2004; Meyer-Krahmer and Schmoch, 1998). In this scenario, Science-Based Firms (SBF) play a fundamental role by putting together industry and scientific research (Debackere and Veugelers, 2005; Perez and Sanchez, 2003), carrying on the bipolar objectives of advancing science, and capturing its financial value (Pisano, 2006).

SBFs reflect the ability of national economies to gain competitive advantage from scientific discoveries and innovations (Autio and Yli-Renko, 1998; Casper, 2007, Fontes, 2005; Rasmussen et al., 2006; DiGregorio and Shane, 2003) and actively contribute to country's employment creation adding new job positions in science-based sectors (e.g. Clarysse et al., 2005; Di Gregorio and Shane, 2003; O'Shea et al., 2008; Shane, 2004).

Emerging SBFs have a higher probability to successfully commercialize radical innovations than incumbent firms, due to their smaller and leaner structure (Chesbrough and Rosenbloom, 2002; Danneels, 2004) and showing more commitment in the development and diffusion of technology (Thursby et al., 2001). In addition, NSBFs are able to commercialize technologies that other firms fail to deliver to the market (Thursby et al., 2001), taking advantage from radical innovations, which are not attractive for incumbent firms (Markham et al., 2002).

Over the years, studies on SBFs outlined that they possess distinctive characteristics which differentiate them from any other company (e.g. Mangematin et al., 2003, Mustar et al., 2006). First of all, they usually characterized by a higher level of market and technology uncertainty. This is related to the nature of research and development phases, which are often longer and more expensive. As an example, SBFs spend longer time to complete the prototyping phase (Pisano, 2006; Kazanjian, 1990) when compared to traditional firms; they foresee the intervention of large corporations that facilitate early growth (Colombo et al., 2010; Miozzo et al., 2016); and they require a unique set of resources which are mainly dedicated to scientific research (Pavitt, 1984) whose outcome is, by nature, uncertain. The peculiar characteristics of these firms operating in different knowledge intensive industries, make their investigation even harder when compared to their counterparts, i.e. high-tech firms.

The business model that characterize the actual science-based businesses derives from the first great pioneer in biotech industry born during the 70s: Genentech. Its goal was to exploit a new technology which uses bacteria to produce drugs. Genentech established a new era for the development of new molecules from both the scientific and business approach, adopting an innovative business model for the commercialization of such scientific discoveries. This model foresees three main footsteps: the involvement of universities in technology transfer activities towards the private sector; funding from venture capital or public equity markets to support the initial development; and dedicated markets in which these firms license their know-how to large corporations. This approach is still the most adopted in science-based sectors, such as biotechnology, pharmaceutical, nanotechnology and advanced materials (Pisano, 2006).

Since Genentech and the diffusion of SBFs adopting this approach for commercialization of science, the academic literature started to pinpoint different manifestations of these firms, i.e. research spin-offs and R&D department spin-offs (Mustar et al., 2006; Knockaert et al., 2011; Rasmussen et al., 2011) or under the lens of high-tech scientific sectors, such as biotechnology (e.g. Pisano, 2006, Zucker et al., 1998), pharmaceuticals (e.g. Gambardella, 1995) and semiconductors (e.g. Holbrook et al., 2003). These studies, to our knowledge, failed to adopt common sampling criteria, leaving selection open to interpretation and common sense of scholars.

We argue these streams of research suffer from the lack of taxonomical efforts, leading to a gap in the identification of a common definition. In this light, the seminal work of Pavitt (1984) on sectoral patterns based his taxonomy of SBFs that they have copious R&D investments concentrated on basic research activities in comparison to other firms. Lately, Autio (1997) studying the taxonomy of New Technology Based Firms (NTBFs) made the distinction between science-based NTBFs and engineering-based NTBFs, classifying the latter in firms which undertake applied research to innovate and identifying as science-based the firms that undertake basic research for the development of new technologies. A more recent work of Pisano on biotechnology firms introduced in 2006, defined Science Based

Businesses as those businesses that attempt to advance science and seek a financial return from their application.

Despite their diffusion and recognized importance, it is still not clear how to develop and make successful a science-based venture. The last review on this topic is ascribable to the work of Mustar et al. (2006) which reviewing studies on research-based firms find limited examinations on firm performances and a lack of efforts in defining a taxonomy which could explain differences in their performances. Ten years after Mustar et al. (2006)'s review, the comprehension of SBFs' performances is still beyond comprehension. As outlined by Pisano (2006, 2010) these firms are more capable to commercialize scientific innovation growing strongly in sales and attracting funding from the public and private market, but their cumulated profitability over years is still below zero. Other studies on SBFs provide empirical evidence that the majority of research spin-offs remain small (e.g. Mustar et al., 2006) and non-academic spin-offs have better performances than academic spin-offs (e.g. Ensley and Hmieleski, 2005).

The fragmentation of the studies on performances and the lack of a common definition makes the argumentation underpinning performance factors of SBFs very much unclear. Efforts to understand why these firms have failed to succeed and what are the real factors enhancing the success of these ventures is needed in order to progress our understanding of these particular ventures. Without a clear comprehension of those factors enabling the growth and development, studies still rely on chance and luck in investigating them leaving the issues about SBF's success still open to debate.

To address the above mentioned issues, we apply a definition that incorporates prior taxonomies and follows the guideline provided by Pisano (2006): *"a SBF is a firm or entity that tries to advance science performing basic research activities and tries to obtain a financial return from the related scientific discoveries"*. Thus, this definition of SBFs incorporates the consideration of the use of ventures that apply the technical principles and requiring the application of scientific knowledge and technological skills to commercialize products. Adopting a comprehensive definition will be possible to make clarity in the field and extrapolate the core elements for these firms. Second we select and systematically review the key contributions in the top journals of management, entrepreneurship, innovation and strategy in order to provide updated relevant evidences of SBFs' performances.

Applying an integrative method for systematic literature review we argue that the confusion regarding these ventures is given by the standardization of performance indicators without considering the idiosyncratic characteristics, that makes SBFs unique. We suggest a broader approach considering performance factors that takes into account the unique growth patterns, characteristics, and dynamics that could place under the same umbrella the different forms of SBFs that may assume in the literature and may provide a more comprehensive view.

In the following section we illustrate the methodology, in section 3 the sample selection will be described followed by the analysis of the findings in section 4; the discussion in section 5 and the conclusions in section 6.

2.1. METHODOLOGY

The easiest way to synthetize data from the extant literature is through a narrative approach, summarizing a group of studies but without a real attempt to generalize them (Greenhalgh, 1997). As suggested by Tranfield et al. (2003), a systematic review of the literature (SLR) in management science provides the quality of the evidence synthesis which is nowadays demanded. The SLR takes its origin form the field of medical sciences, where poor judgement of the existent literature has caused many issues for both further advancements and in terms of misleading recommendations (Cook et al., 1997). The SLR is a method that allows researchers to produce synthesis of the findings in a systematic manner outlining the most relevant results and reorganizing them in a more comprehensible way (Peckham, 1991).

In contrast with traditional narrative reviews, systematic reviews adopt a replicable, scientific and transparent process which minimize the reviewer's bias through the analysis of an exhaustive plethora of literature and provides detailed information about the decisions, procedures and conclusion of the author(s) (Cook et al., 1997). Such characteristics make the SLR a comprehensive and unbiased research which represents not only a preferred method in respect to traditional narrative literature review, but also results to be the most valuable method to evaluate extensive literature. When systematic review analyzes quantitative data, the result is meta-analysis, when SLR reviews qualitative studies, the result is the so-called qualitative systematic review. Undertaking systematic reviews is nowadays considered as a fundamental scientific activity (Mulrow, 1994). Given the pre-conditions of fragmentation and limited number of studies on SBFs which do not allow a meta-analysis, a qualitative systematic review results to have a better suit.

The purpose of this study it is not to summarize empirical data, but rather provide a consistent picture of what the literature has been done and provide evidences that allow us to comprehend how SBFs perform and what we can do to advance the understanding of this topic. In order to collect as much information as possible, we implement an integrative approach which provides the advantage to include both methodologies, qualitative and quantitative, to reduce single-study weaknesses and to improve internal and external validity (Rodgers and Knafl 2000, Whittemore and Knafl 2005).

The integrative approach is commonly used in medicine studies to provide evidences regarding the accuracy and results of medical procedures, adding to the information coming from statistical inferences the data provided by patient's observations. This allows reviewers to consider data but also contextual inferences (Campbell, 1984). This approach, given to its nature, answers to the call for a broader observation of the findings providing sources from different angles. Due to the consolidated procedure on how to review the literature in medicine (Davies and Crombie, 1998) for the present work follows both the guidelines provided by Cochrane Collaboration's Cochrane Reviewers' Handbook (Clarke and Oxamn, 2001) and the National Health Service Dissemination (2001).

2.1.1 Sample selection method

SBFs may assume different facets in academic researches, e.g. academic spin-offs, technology based firms, high-tech ventures, etc. making the identification of dedicated studies even harder than other topics. To overcome this issue, a preliminary study is necessary to identify the more appropriate key words to be included in the research string. To identify such terms, it was at first applied the string "science based firm" in Scopus database which provided a list of 34 papers representing a first repository of SBFs studies. Further was done an analysis of these studies in order to identify other key terms that these authors used in referring to this kind of firms in the form of origin of the firm (such as knowledge and technology) and new terms as nature of the firms (such as company and enterprise).

Applying the new key words to the string we continued to refine the research results until obtaining a comprehensive list of the most relevant parameters regarding the origin and the nature of SBFs for the composition of the part of the string identifying SBFs. A list of 22 items regarding the origin of the SBFs and a list of 18 terms to identify their nature was finally obtained as shown in Table 2.1. In compliance with the need to target only studies that attempt to advance the understanding of science-based firms we did not include terms referring to sector specific domains such as biotech, pharmaceuticals, chemical etc, but included keywords used to identify research streams such as academic entrepreneurship, knowledge management, innovation management and so on.

Given the objective of this study to isolate performance evidences using both qualitative and quantitative approaches that directly and indirectly address performances, general parameters are used in order to include a wider range of studies. Thanks to the integrative approach is possible to include evidences from studies that target directly or indirectly performance parameters. The parameters we used are only four and as we said very general grow*, performance*, outcome*, success*.

The string was composed by combining origin factors indicating the main domain of the firm, such as academic, knowledge based, high tech etc. with nature of the firm key words representing the forms that firms can be identified, for example company, enterprise, venture, spin off. The combination of origin and nature terms produced a list of 396 research terms (N. Origin x N. Nature x Perf.) that were furtherly combined with the four performance parameters. This allowed us to obtain an extensive research query, including all combinations of terms regarding SBFs (see Table 2.1).

To identify the relevant contributions and accomplish with the requirements for the validity and reliability of methodology (Tranfield et al., 2003), we considered only contributions rated at least 3 stars, according to the 2015 rankings of the Chartered Association of the Business Schools (ABS rank). We included only journals in the field of innovation, management, entrepreneurship and strategy. From our preliminary study, we decided to apply an exception for the Journal of Technology Transfer, since this journal emerged as a repository of relevant contributions for SBFs studies. To facilitate the selection of the papers, we applied the query for the selected journals using Scopus database, including all contributions up to the 31st December 2016. We additionally filtered for "business" and "management" studies, excluding all other fields from our search.

Table 2.1. Terms composition

Origin of the firm	Nature of the firm	Performances
academic	*compan**	*grow**
high tech	*enterprise**	*performance**
high-tech	*entrepreneurial firm**	*outcome**
*innovat**	*firm**	*success**
knowledge based	*new venture**	
knowledge-based	*spin off**	
new technology based	*spin out**	
new technology-based	*spin-off**	
research	*spin-out**	
research based	*start up**	
research-based	*start-up**	
science	*venture**	
science based	*business*	
science-based	*spinoff**	
*scientist**	*spinout**	
scientist based*	*startup**	
scientist-based*	*SME**	
technology based	*small and medium entrepr**	
technology-based		
university		
university based		
university-based		

For the analysis of the findings we adopted the PRISMA (preferred reporting items for systematic reviews and meta analyses) statement to organize the review and systematically report findings. PRISMA is a complex of procedures and guidelines for systematic reviews to help to ensure a transparent and complete reporting of the findings in a systematic manner (Liberati et al. 2009).

2.1.2 Sample selection analysis

We applied the query in the database Scopus filtering for top journals identifying an initial list of 652 contributions in the field of management, innovation, entrepreneurship and strategy as shown in Table 2.2. We can observe that the journal of *Small Business Economics*, *Journal of Technology Transfer*, *Research Policy*, *Technovation* and *Journal of Product Innovation Management* are the journals with the most contributions with more than 50 articles each.

Analyzing titles, abstracts and introductions was possible to exclude papers regarding other thematic areas, and to exclude reviews, theoretical papers, and articles in press to comply with replicability parameters that a systematic literature review requires. We isolated only articles reporting an empirical investigation and being officially published. The screening process produced a list of 266 articles that were furtherly assessed for eligibility.

For the eligibility analysis, following the review protocol, a scrutiny of all the sample selection sections of each paper was performed in order to isolate only those studies which responded to the adopted definition previously provided: *"a SBF is a firm or entity that tries to advance science performing basic research activities and tries to obtain a financial return from the related scientific discoveries"*. According to the definition, are included only those studies which explicitly approached case studies on firms performing basic research activities to provide products or services.

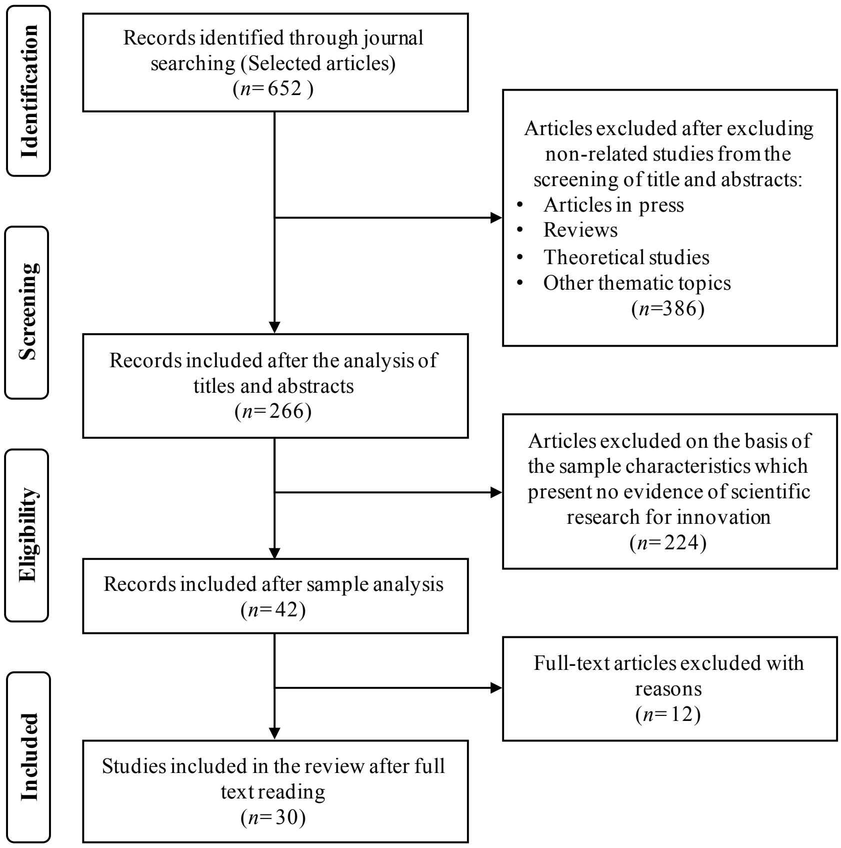
Table 2.2. List of journals

Journal	**ABS Rank 2015**	**Initial count IDENTIFICATION**	**Final count INCLUDED**
Academy of Management Journal	4*	2	
Academy of Management Perspectives	3	2	
Academy of Management Review	4*		
Administrative Science Quarterly	4*		
British Journal of Management	4	5	1
Business and Society	3		
Business Ethics Quarterly	4		
California Management Review	3	4	
Entrepreneurship and Regional Development	3	21	1
Entrepreneurship: Theory and Practice	4	9	1
European Management Review	3	1	
Family Business Review	3		
Global Strategy Journal	3		
Harvard Business Review	3	13	
International Journal of Management Reviews	3	2	
International Small Business Journal	3	17	1
Journal of Business Ethics	3	49	
Journal of Business Research	3	37	2
Journal of Business Venturing	4	42	1
Journal of Management	4*	2	
Journal of Management Inquiry	3		
Journal of Management Studies	4	7	
Journal of Product Innovation Management	4	51	
Journal of Small Business Management	3	14	
Journal of Technology Transfer	2	85	2
Long Range Planning	3	10	2
MIT Sloan Management Review	3		
R and D Management	3	30	2
Research Policy	4	80	7
Small Business Economics	3	89	4
Strategic Entrepreneurship Journal	4	3	1
Strategic Management Journal	4*	12	1
Strategic Organization	3		
Technovation	3	65	4
Total		**652**	**30**

As example for exclusion were not included studies with samples of firms performing R&D activities but not related to scientific advancements or there was no evidence related to scientific progress (basic research connection). Were also excluded studies relying on samples selected mainly on the basis of generic sector parameters (ICT, innovative, high-tech), samples of academic founded new ventures where was not possible to find scientific research (e.g. generic academic spin-offs); or service-based firms which are not science-related (excluding firms performing specific services for life-science industry), and manufacturing firms which do not perform science-based R&D activities.

The sample selection process led to an exclusion of 224 articles which did not matched the selection criteria leading to an eligible sample of 42 papers. In Appendix 1 a comprehensive table including the selected studies is provided. In the column "Inclusion justification" is provided the rationale behind the choice of inclusion and in the column "Quotations from the paper" is reported the extraction of the text from which the justification is based. The last step for eligibility was text screening that led to a further exclusion of 12 contributions. In Figure 2.1 the PRISMA diagram show the process that brought at the list of 30 papers included in the study and then listed in the following section in Table 2.3.

Figure 2.1. PRISMA flow diagram



2.1.3 Description of the studies

Studies on SBFs are increasing over last years, a demonstration is represented by the search in Scopus shown in Figure 2.2. As the figure shows, since the 70s studies referring to SBFs where very rare. During the 80s scholars started to approach these term but it is during the 90s that this research stream really emerged, probably due to the boom of the biotech industry. In 2003 and 2004 the studies adopting the term Science-Based Firm, decreased, but in the 2006 and 2007 a positive trend started again, trend that continues during the last years.

Figure 2.2. Academic articles and proceedings on Science-Based firms in Scopus Database (accessed 5 September 2018)

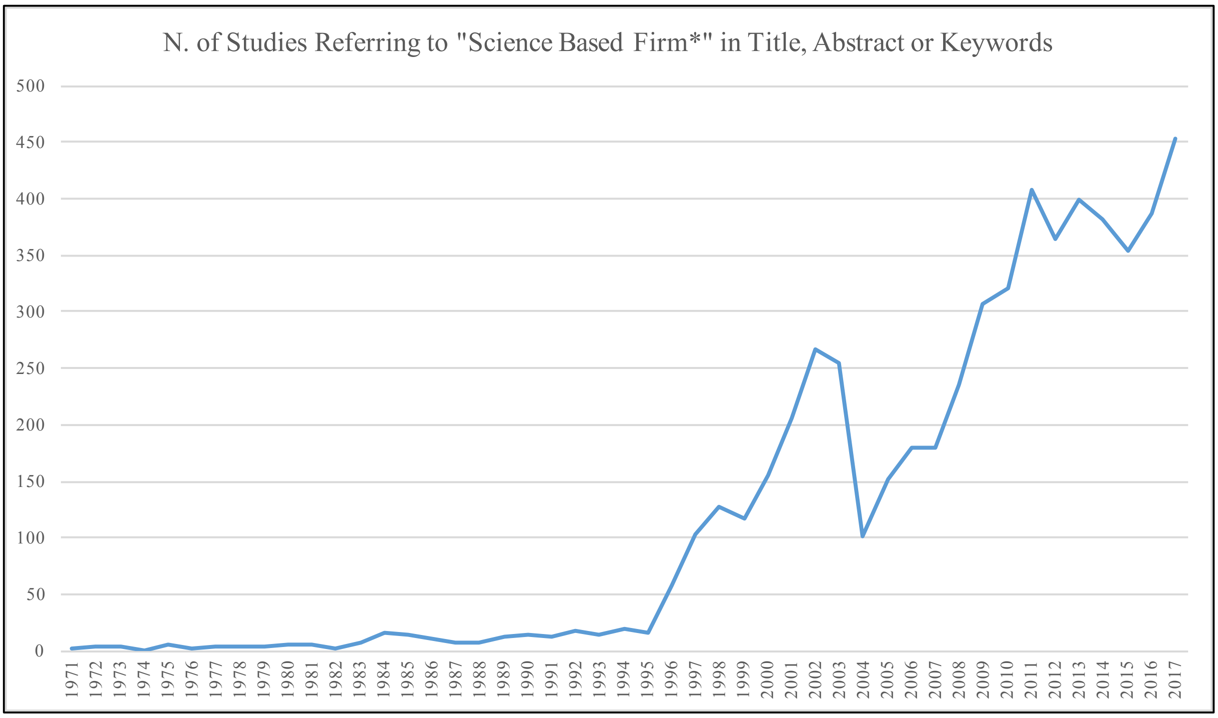
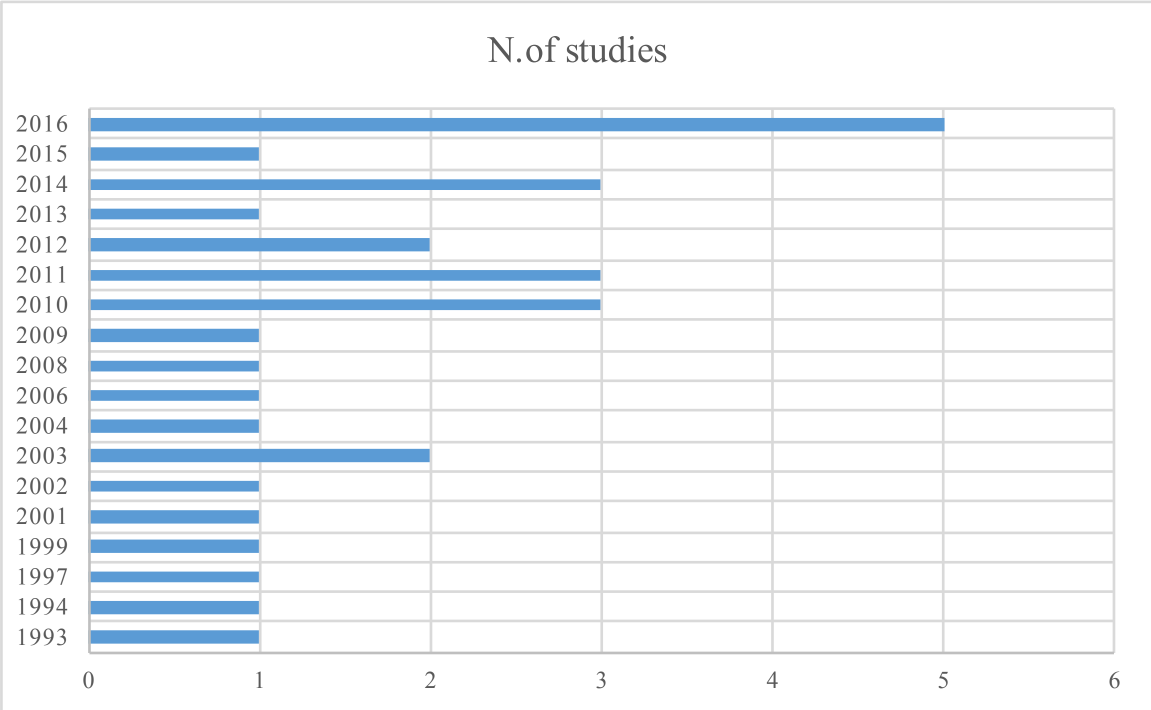


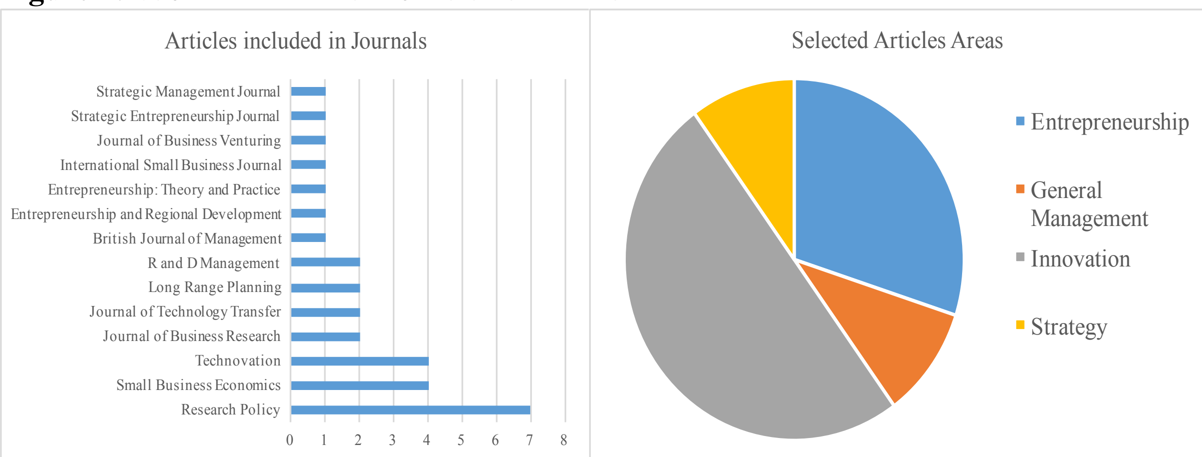
Figure 2.3 shows the selected studies outlining the increasing attention of SBFs topic during the last years and from the Figure 2.4, is possible to observe that papers focusing on SBFs and their performances are concentrated mainly in 14 journals. Most contributions are to be found in three main journals, *Research Policy* (7), *Small Business Economics* (4), and *Technovation* (4) where half of the empirical works are concentrated. The others are the *Journal of Business Research*, *Journal of Technology Transfer*, *Long Range Planning* and *R & D Management* with two contributions for each journal. The *British Journal of Management*, *Entrepreneurship and Regional Development*, *Entrepreneurship: Theory and Practice*, *International Small Business Journal*, *Journal of Business Venturing*, *Strategic Entrepreneurship Journal* and *Strategic Management Journal* standing comprehend one contribution.

Figure 2.3. Number of studies per years



Having a first look at the time in which data are collected in the selected articles, emerge that the booming of studies looking at the SBFs' performances phenomenon started in the 90s in conjunction with the booming of the Biotech industry as observed previously in Figure 2.2. It is not surprising that the biotech firms were frequently targeted as main source of sampling in understanding the performances of SBFs. Other typically targeted sectors were the life-science industry including pharmaceuticals and human health. Nanotechnology, defense and semi-conductors were also important sources for the understanding of the factors influencing SBFs' performances.

Figure 2.4. Journals and areas of selected articles



The geographical distribution of the selected articles was mainly concentrates in the European area, 25 studies out of 30 with a particular focus on the UK (4), France (4) Italy (3) and Belgium (3). Only five studies posit their attention on a sample concentrated in North America (4 in US and 1 Canada) and only 2 in Asia, 1 in Japan and 1 in Singapore[1].

A comprehensive list of the selected studies is provided in table 2.3 in a chronological order. The ID will be used as reference in the following tables and figures. In the table, information regarding sample and the methodology adopted by the different authors are provided. After the selection we can observe that in the samples are included mainly two types of ventures. The first is the represented by firms which are either new or dedicated ventures resulting from the spin-off or spin-out activity of a scientist's research, a research lab, a corporation, or an R&D project. The other is represented by incumbent corporations that try to develop scientific discoveries dedicating copious R&D investments on scientific research in order create new products or services (e.g. Pharmaceutical corporations, biotech, green-tech etc.).

Observing the two columns Business entity and Industry, is possible to identify five main categories: "Academia"; "Technology-Based", "Sector Specific", "Research-Based"; and "Science-Based". "Academia" refers to the stream of research that mostly targeted academic spin-offs and university spin-offs. In this category are included those studies that focused mainly on academic entrepreneurship and the new venture creation. The samples are represented by firms which foundation is based on scientific research conducted at an academic institution and founded or co-founded by researchers that had worked on the scientific findings at the academic institution in question, or by the university itself. Frequently scientists maintain their connections with the university to access to the academic network in order to overcome the lack of competences and to obtain resources.

The "Sector Specific" subject comprehends studies focused on the in-depth analysis of a single industry studies and especially verified for the Biotechnology industry. In "Technology based" stream, the division of New Technology-Based Firms dominate the scene. The samples are represented by a subpopulation of high-tech firms which most frequently are new ventures. Effectiveness of supporting programs for new high-tech ventures is in many cases the main issue of analysis. In the "Research-Based" domain the focus is on the development of founder(s)' research. The main goal of these firms is the creation of new technologies

[1] The sum is higher than 30 because two studies had more than one country of analysis.

Table 2.3. Studies data

ID	Reference	Business entity	Industry	Size of the sample	Country of analysis	Affiliation	Theoretical foundations	Qualitative	Quantitative	Longitudinal	Cross sectional	Period of analysis	N. of observations	Research Strategy	Data collection method	Type of analysis
1	Segers (1993)	New Techonology Based Fimrs (NTBFs)	Biotechnology, pharmaceutical, semi-conductor	3	Belgium	n.d.	n.d.	1	0	1	0	inception up to 1993 (most recent 1983)	3	Case studies	n.d.	Analysis of qualitative data
2	Quéré (1994)	Basic research unit	Defense electronics	1	France	no	n.d.	1	0	1	0	1972-1987	1	Case studies	n.d.	Analysis of qualitative data
3	Reitan (1997)	New Techonology Based Fimrs (NTBFs)	n.d.	64	Norway	Yes	n.d.	1	1	0	1	1993	64	Survey	Questionnaires, interviews, archival data, reports	Quantitative: ratios analysis
4	Pfirrmann (1999)	New Biotechnology Enterprises (NBEs)	Biotechnology	35	Germany	Yes, university associated firms	n.d.	0	1	0	1	1997	n.d.	Case studies	Questionnairs and interviews	Analysis of qualitative data
5	Nilsson (2001)	Biotecnology firms	Biotechnology	3	Sweden	Yes	n.d.	1	0	0	1	1998	3	Case studies	n.d.	analysis of qualitative data
6	George et al (2002)	Science Based Basic Research Firms	Biotechnology	147	US	No	n.d.	0	1	0	1	1998	2457	Case studies	Databases	MANCOVA analysis
7	Mangematin et al. (2003)	Research-intensive Small and Medium Enterprises (SMEs)	Biotechnology	60	France	n.d.	n.d.	1	0	0	1	2000	n.d.	Survey	Interviews	Analysis of qualitative data
8	Meyer (2003)	Research Based Ventures	Nano technologies	4	USA and EUROPE	Yes	n.d.	1	0	0	1	2003	4	Case studies	Interviews	Analysis of qualitative data
9	Suzuki & Kodama (2004)	Technology based firms	Pharmaceutical and Electronics	2	Japan	n.d.	n.d.	1	0	1	0	1925-1999	n.d.	Case studies	Databases	Patent cross class analysis
10	Lawton & Ho (2006)	Technology based spin-off companies	Miscellaneous	64	UK	Yes	n.d.	0	1	0	1	2004-2005	64	Case studies	Databases	Ratios analysis, turnover analysis, basic statistics
11	Durand et al. (2008)	Biotecnology firms	Biotechnology	313	France	n.d.	n.d.	0	1	1	0	1994-2002	1624	Case studies	Databases	Random-effects negative binomial regressions; generalized least squares (GLS)
12	Bruni &Verona G. (2009)	Science Based Firms (SBFs)	Pharmaceutical	6	Europe	No	Dynamic Capabilities	1	0	0	1	2003-2005	31	Case studies	Interviews	Qualitative data analysis

Table 2.3. Studies data (continued)

ID	Reference	Business entity	Industry	Size of the sample	Country of analysis	Affiliation	Theoretical foundations	Qualitative	Quantitative	Longitudinal	Cross sectional	Period of analysis	N. of observations	Research Strategy	Data collection method	Type of analysis
13	Vincett P.S. (2010)	Research-Based Academic Spin-Offs Companies (RASCs)	Miscellaneous	n.d.	Canada	n.d.	n.d.	0	1	0	1	1998	n.d.	Case studies	Databases	Comparisons and estimators
14	Belussi et al. (2010)	Life science Firms	Life science industry: biomedical, biotechnology, pharmaceutics and computer science industry applied to the medical fields.	78	Italy	n.d.	Regional Innovation System (Evolutionary theories of economic and technical change)	1	1	0	1	2005	78	Case studies	Semi-structured interviews	Qualitative data analysis; negative binomial regression.
15	Bonardo et al. (2010)	Science Based Entrepreneurial Firms (SBEFs)	Miscellaneous	131	Europe	Yes, university affiliations	n.d.	0	1	0	1	1995-2003	131	Case studies	Databases	Poisson regression; Cox proportional hazard regressions;
16	Clarysse et al. (2011)	Young Technology based firms	Miscellaneous	6	Belgium	n.d.	Resource Based View	1	0	1	0	2002-2008	409	Case studies	Interviews, press releases and press articles	Qualitative data analysis
17	Knockaert et al. (2011)	Science Based Entrepreneurial Firms (SBEFs)	Miscellanous	9	Belgium	n.d.	Knowledge-based Theory; Upper Echelons Theory	1	0	1	0	2010 (year of publication -1)	n.d.	Case studies	Interviews	Qualitative data analysis
18	Alegre et al. (2011)	HIgh-Tech SMEs	Biotechnology	132	France	n.d.	Dynamic Capabilities	0	1	0	1	2002	132	Survey	Questionnaires	Structural Wquations Modelling (SEM)
19	Yagüe-Perales & March-Chordà (2012)	Research Spin-offs	Biotechnology	32	Spain	n.d.	Resource Based theory and Dynamic Capabilities	0	1	1	0	1998-2004	102	Case studies	Databases	Standard dichotomous regression analysis
20	Wang & Shapira (2012)	New Nanotechnology-based firm (NNBFs)	Nanotechnology	230	US	Yes	n.d.	0	1	1	0	1996-2005	1539	Case studies	Databases	Tobit model

Table 2.3. Studies data (continued)

ID	Reference	Business entity	Industry	Size of the sample	Country of analysis	Affiliation	Theoretical foundations	Qualitative	Quantitative	Longitudinal	Cross sectional	Period of analysis	N. of observations	Research Strategy	Data collection method	Type of analysis
21	Yagüe-Perales & March-Chorda (2013)	New Techonology Based Fimrs (NTBFs)	Human Health	173	Valencia-Spain	n.d.	n.d.	0	1	0	1	2009	173	Case studies	Databases	Factor analysis and ANOVA analysis.
22	Benghozi & Salvador (2014)	Research Spin-offs	Miscellanous	155	Italy	n.d.	n.d.	0	1	0	1	2007	155	Survey	Questionnaires	Regression
23	Stephan A. (2014)	Research Spin-offs	Miscellanous	121	Germany	Yes	n.d.	0	1	0	1	2004	121	Case studies	Databases	Propensity score matching (PSM)
24	Visintin & Pittino (2014)	University spin-off	Miscellanous	103	Italy	Yes	Upper Echelons	0	1	0	1	2000 - 2006	103	Case studies	Databases	Hierarchical regression method
25	Scholten et al. (2015)	Academic Spin-offs	Miscellanous	70	The Netherlands	Yes, university	Social Network Structure	0	1	0	1	2013	70	Survey	Questionnaires	Hierarchical multiple OLS regression
26	Ziaee Bigdeli et al. (2016)	University spin-outs	Life science industry	3	UK	Yes	n.d.	1	0	0	1	2011 - 2013	n.d.	Case studies	Interviews	Qualitative data analysis
27	Miozzo & DiVito (2016)	Science Based Firms (SBFs)	Biotechnology	35	UK and Netherlans	n.d.	Resource Based View	1	0	1	0	2006 - 2014	74	Case studies	Interviews	Deductive and inductive
28	Lubik & Garnsey (2016)	University Spin-Outs	Advanced materials	3	UK	Yes	Resource based View and Ecosystem Analysis	1	0	1	0	n.d.	n.d.	Case studies	Semi-structured interviews	Inductive analysis
29	Quintana-García & Benavides-Velasco (2016)	Dedicated Biotecnology Firms (DBFs)	Biotechnology	229	USA	n.d.	Dynamic Capabilities	0	1	1	0	1983 – 2009	229	Case studies	Database	Hierarchical regression analysis.We
30	Subramanian et al. (2016)	Research Scientists and Engineers (RSEs)	Biotechnology	366	Singapore	n.d.	Human Capital and Functional diversity	0	1	1	0	2004 - 2008	720	Case studies	Database	Negative binomial model in hierarchical piecewise panel regression analyses

undertaking basic scientific research. In the last category, "Science-based", authors targeted directly the science-based industry including heterogeneous industry sectors stressing on the creation of new innovations with the application of scientific research.

Only 12 of the 30 studies explicitly adopted a dominant theoretical framework. The theoretical view mostly applied was the Penrosean resource-based view followed by the Teece, Pisano and Shuen's dynamic capabilities. Among the authors that adopted the resources-based view we can find Yagüe-Perales and March-Chordà (2012), Clarysse, Bruneel and Wright (2011), Miozzo and DiVito (2016), and Lubik and Garnsey (2016) which looked mainly on how resources can represent a source of superior performance. Studies on dynamic capabilities (Bruni and Verona, 2009; Alegre et al., 2011; Quintana-García and Benavides-Velasco, 2016) were concentrated on different firm's innovation.

Subramanian et al. (2016) adopted human capital and functional diversity theory, Knockaert et al. (2011) and Visintin and Pittino (2014) used principles from upper echelons theory and principles from knowledge-based theory, and upper echelons theory were used again by Knockaert et al. (2011). These theories were mainly adopted to explain how human resources and the top management team are related with performances.

Looking at the methodologies and the research questions reported in table 2.4[2], a first distinction should be done between studies directly targeting the performances of SBFs in their research questions and studies that were included because reported performance findings during their research despite not directly addressing them. Their inclusion was given thanks to the query string that captured the word "success" and "performance" in the abstract, title and keywords. This was the case of two studies, the first is of Mangematin et al. (2003) in studying the dynamics of business models and the second is Nilsson (2001) which investigated the characteristics of Swedish biotechnology firms.

The research questions show a lack of maturity in facing SBFs' performances, most of the themes were approached only once or twice with mixed methods and approaches. In fact, for example, the thematic regarding knowledge management was approached by Knockaert et al. (2011) performing a qualitative and longitudinal analysis on knowledge transfer of academic spin-offs and by Alegre et al. (2011), Yagüe-Perales and March-Chorda (2013) and Stephan

[2] Research questions were textually reported whether explicitly indicated in the text or rephrased according to the analysis of the text.

(2014) that used quantitative and cross sectional approach to explain the impact of the knowledge management on performances and on the knowledge management industry. From the methodology point of view, in the articles, there is an equal separation between qualitative and quantitative approaches, and between longitudinal and cross sectional analysis.

Table 2.4. Research questions of the selected articles

ID	Research questions (rephrased)
1	**WHAT** is the impact of strategic partnering on New Technology Based Firm-survival and growth in Belgium?
2	**WHAT** are the economic peculiarities characterizing the functioning of a research lab unit?
3	**ARE** public measures are able to foster technical entrepreneurship?
4	**WHAT** pattern can be considered to describe the development process of NBEs? Are service and product/process development activities of NBEs geographically bounded within the regional environment?
5	**HOW** firms are established, positioned, financed? How they build and keep the competence within the Swedish biotechnology context?
6	**ARE** links with universities beneficial to the company's operations?
7	**HOW** business models are characterized in Biotech firms? **WHAT** are the dynamics?
8	**WHAT** are the impacts of support mechanisms on the development of start-up companies in a science-based environment?
9	**WHY** persistence does matter? **WHAT** are the mechanisms with which technological diversification contribute to the business expansion?
10	**WHAT** are the performances of Spin-offs generated in the Oxfordshire area?
11	**WHAT** are the effect of the technological application diversity, alliances, rent potential...? On the biotech firm's performances?
12	**HOW** dynamic capabilities influence the SBFs' value creation?
13	**WHAT** are Economic impact of Research-Based Academic Spin-off Companies? Are they convenient for the government?
14	**HOW** life-science firms perform in an Open Regional Innovation System?
15	**WHAT** is the propensity of acquire or being acquired of a Science-Based entrepreneurial firm?
16	**HOW** and **WHY** environmental dimensions and bundles of resources interact to create different growth paths?
17	**HOW** can knowledge be transferred and employed in SBEFs in order to enhance SBEF performance?
18	**WHAT** is the effect of Knowledge Management practices on firm's innovation performances?
19	**WHAT** are the differences in performances between biotechnology research spin-offs and non-biotechnology spin-off firms?
20	**HOW** do new small technology-based firms that collaborate with universities benefit from spillovers associated with resources of university scientists?
21	**WHAT** are the differences in performances between New Technology-Based Firms (NTBFs) and others in a knowledge intensive industry?
22	**WHAT** is the effect of Industrial partnerships on research spin-off's performances?
23	**ARE** public research spin-offs more innovative than comparable knowledge-intensive firms?
24	**HOW** entrepreneurial team demographic variables may create an appropriate balance between the scientific and business orientations, generating a positive impact on USO performance?
25	To **WHAT** extent does human capital (i.e., prior experience and knowledge) leverage the effect of bridging ties on the early growth of academic spin-offs?
26	**HOW** USOs' BMs evolve? HOW the interactions within and between their core BM components can ultimately result in sustainability and scalability?
27	**HOW** does fast growth of science-based firms occur? How is speed of early growth shaped by the institutional setting?
28	**HOW** firms use resources to realize market opportunities? How value creation is influenced by the wider value chain?
29	**HOW** gender diversity in top management teams (TMTs) and indicators of innovation capabilities can attract investment at the initial public offering (IPO) of research-based firms?
30	To **WHAT** extent diversity of educational levels among research scientists and engineers (RSEs) in the context of a firm's level of technological diversity influences innovation performance?

The most frequent research questions were posited for the analyses of the antecedents of SBFs' performances using mainly questions such as "what", e.g. what is the impact? what are? to what extent? reflecting the willingness to find a causal relationship between determinants and their effect. At the context level two were the studies that emphasized the role of the entrepreneurial context in which firms were established. Segers (1993) used technological partnership of small firms located in the Belgium area with incumbent firms as antecedent to explain the impact on performances. Lawton-Smith and Ho (2006) instead measured the performances of the spin-offs generated in the Oxfordshire area taken in consideration the entrepreneurial environment in which there were formed.

At the firm level is possible to find more authors that tried to explain the factors which effect the performances posing the accent on the firm idiosyncratic nature. This is the case of George et al. (2002), Wang and Shapira (2012) and Scholten et al. (2015) that analyzed the themes of network effecting performances, followed by Alegre et al. (2011), Bengozi et al. (2014) and Subramanian et al. (2016), Suzuki and Kodama (2004), Bonardo et al., (2010) which respectively analyzed the themes of knowledge management, industrial partnerships, diversity, innovation capabilities and mergers and acquisitions as determinants success factors of the SBFs.

Durand et al. (2008), despite not being the only one that performed a single industry sample analysis (see e.g. Nilsson, 2001; George et al., 2002; and many others) were the only study posing a particular emphasis on the economic impact of choosing a particular strategy for a single industry, biotechnology, recognizing distinctive characteristics in respect to other industries. Yagüe-Perales and March-Chorda (2013) and Stephan (2014) used tested quantitatively the sector or subsector effect. Reitan (1997), Meyer (2003) and Vincett (2010), investigated the knowledge formation in the situation in which support mechanisms play a central role in the venture formation and performance.

The "how" and "why" questions were the most frequent questions that looked mostly into the way in which performances are formed at context and firm levels. Belussi et al. (2010) looked into the context of Regional Innovation Systems through the lens of open innovation, while Clarysse et al. (2011) used the interactions between environmental dimensions and resources to explain the different conduct in the different growth paths.

The other authors on the behavioral dimension, concentrated on the firm level looking into the functioning of the firm. Bruni and Verona (2009) focused on how dynamic capabilities influenced the valued creation, Knockaert et al. (2011) made an empirical analysis on how the knowledge is transferred to enhance SBFs performances; Visintin and Pittino (2014) looked into the variables of the entrepreneurial team to determine the right balance between scientific and business orientations; the management of resources was the focus of Lubik and Garnsey (2016) to generate a competitive advantage. Quintana-García and Benavides-Velasco (2016) verified how gender diversity in the top management team composition influence the success of an initial public offering of a SBF. It is notable to observe that no empirical works are focused on behavioral aspects formed at industry and support mechanisms levels. At the industry intersection, Yagüe-Perales and March-Chordà, 2012, made a contribution arguing on dynamic capabilities between biotechnology research spin-offs and non-biotechnology spin-off firms.

Four main authors looked into the how SBFs evolve. Miozzo and DiVito (2016) from the growth point of view arguing about the speed of growth within the framework of the institutional setting. Pfirrmann (1999) within the context dimension, looked into how the environment effects the SBFs performances. Quéré, (1994) made an in-depth analysis on the scientists working in a business unit of an incumbent firm questioning on the evolution of the unit over the years and on its impact on the innovation capabilities of the organization. Evolution of business models and the interactions of their components were adopted by Ziaee Bigdeli et al. (2016) to explain the sustainability and scalability of the SBFs. Industry level analysis and support mechanisms were neglected in studying the evolution of SBFs.

2.2. ANALYSIS OF THE FINDINGS

For the analysis of the findings, thanks to the integrative approach, both qualitative and quantitative sources of knowledge will be combined. In order to harmonize the analysis of the data and making comparisons possible, both factors influencing performances and factors being affected were reported with their reciprocal effect, with a plus sign indicating a positive impact, minus for negative and zero for no significant relationship. For the contributions adopting a quantitative approach with a testing of causal relationships were taken in consideration the dependent and independent variables tested, for the qualitative analysis the variables and relationships were deduced from the argumentation of the findings.

A total number of 108 observed variables influencing SBFs performances were collected from the analysis of the articles and then re-grouped in similar categories as showed in Table 2.5. On the vertical dimension, performance determinants are grouped in four main categories: "Firm-specific" taking in consideration specific characteristics of the firm such as capital, management of knowledge, size or strategy. The second dimension "Relationships", considers relationship variables such as affiliations, partnerships with other firms or the influence of the

Table 2.5. Variables groups.

Dimension	Determinants	Growth			Financial			Economic			Innovation			Market			Internationalization			TOTAL			ID
		-	0	+	-	0	+	-	0	+	-	0	+	-	0	+	-	0	+	-	0	+	
Firm-specific	Financial Resources			2																-	-	2	5, 27
	Experience		1							1						1				-	1	2	12, 22, 25
	Human capital	1	2	1		1	2		1	1			2			1		1		1	5	7	2, 8, 13, 15, 19, 24, 27, 29, 30
	Innovation capabilities			2			2	1	1	1		2	5							1	3	10	4, 9, 11, 12, 17, 23, 27, 29, 30
	Knowledge Management												3							-	-	3	2, 18
	Profitability			1																-	-	1	15
	Sector		1						2											-	3	-	21, 22
	Size			1						2										-	-	3	15, 22
	Strategy	1		2						1										1	-	3	7, 21, 28
	Type of firm	1		1			1		2				1					1		1	3	3	22, 23, 19
Relationships	Affiliations	2		2		1	1						1			2				2	1	6	23; 16; 10; 15; 28; 20, 15
	Collaboration with scientists						1													-	-	1	20
	Industrial partnerships			3				1	1				3							1	1	6	5; 11; 28; 1; 14; 22;
	Networks			4	1	1	1						1			1				1	1	7	25; 5; 20; 28; 6
External actors	Incubation						1													-	-	1	8
	Supporting programs	1		1			1	1		1										2	-	3	3, 8;13
	TTO support			1			1													-	-	2	26
	Incumbents firms	1																		1	-	-	16
	Venture capital			1									1							-	-	2	16
Environment	Ecosystems			3																-	-	3	4, 22, 28
	Location								1				1							-	1	1	23
	TOTAL																			**11**	**19**	**66**	

firm's network. The "External actors" group of variables considers those external entities that directly or indirectly interact with the firm; and "Environment" considers contextual variables related to the external conditions.

On the horizontal dimension of Table 2.5, the group of determinants intersect with six performance measures: "Growth" which includes of growth in sales, employees, or growth by mergers and acquisitions. "Financial" performances consider mainly the ability of the firm to obtain additional funds for example a successful IPO or venture capitalists financing. "Economic" performances incorporate those indicators such as return on sales (ROS), productivity or rent generation. Are considered "Innovation" performances those indicators such as industrial applications of the new technology, the ability to progress the R&D, number of patents or the type of innovations they produce; in other words, all indicators that reflects the ability of the firm to innovate. "Market" performances reflect the impact of the firm in the market represented by both the performance of the firm's product or services in the targeted markets and even the ability to the company to be acquired. The last performance group "Internationalization" considers the ability of the firm to be international.

2.2.1 Firm-specific

The first determinant listed in Table 2.5 is the financial resources which reflects the ability of the firm to obtain founds. Miozzo and DiVito (2016) and Nilsson (2001) outlined that respectively the early fundraising and the access to capital have a positive impact of firm's growth. Funds allow ventures to get access to a unique set of resources which are fundamental for the growth of the firm and in particular for the science-based firms which to advance science require costly and rare equipment or highly skilled personnel. To be noted Miozzo and DiVito (2016) concentrated only on the initial development of the firm, so the effect of the financial needs could be lower in the next stages of the firm's life.

Firm's experience could intuitively be related to performances, but in the selected studies only few of them took in consideration these aspects. Results demonstrate that experience may not be related to the firm's success, in fact, prior entrepreneurial experiences of the firm was found not significant with the growth in terms of employment. Scientists play a key role in the firm's activity, as we will observe later, but looking into their experience in research, the impact on early growth remain not significant (Scholten et al., 2015). Different is the case of market experience. Bruni and Verona (2009) observed a positive effect on the success of

SBFs' products. In their study on the pharmaceutical sector, they noticed that having a better comprehension of the market's characteristics and dynamics leads innovation decisions toward more attractive scientific discoveries for the market, resulting as a consequence, more successful.

Human capital was one of the most frequent theme approached by authors of this topic, 9 out of 30 found evidence about the impact of human capital on performances. The results are not always consistent. First of all, we need to make a distinction between findings on the presence of scientists in the firm, and studies analyzing the composition of the top management team (TMT).

Scientists have proved to be crucial for the performance of the firm, Vincett (2010) in his study found positive strong relationship between physicists working in research-based spin-offs and their impact on the Canadian's economy. The presence of scientists seems to be crucial not only at firm level but also at country level. Yagüe-Perales and March-Chordà (2012), observed the presence of scientists as founders outlining that their presence provides a superior growth in terms of size and turnover but having them in the position of the founders has no effect on the international performance, through international patents, and no effect on the profitability of the firm.

The ownership of the firm at the top management team level are source of superior market performance. Bonardo et al. (2010) demonstrated that founders can exercise their power to grow through mergers and acquisitions. It derives that founder-scientists due to their equity interests are more prone to grow differently from typical scientists and academics which are more innovation and research oriented (Wright et al. 2007) looking for an improvement in their academic career and develop their academic interests rather than setting up a fast growing venture (Meyer 2003). The presence of business professionals in the board of directors enhance the attractiveness of venture capitalists and the IPO success making SBFs more successful in financial performances (Meyer, 2003).

Looking at the characteristics of human capital, no impact has attributable to the gender diversity in the TMT (Quintana-García and Benavides-Velasco, 2016) suggesting that gender diversity in SBFs are not a source of superior performance. On the contrary the diversity of the TMTs in terms of education (Subramanian et al., 2016), functions (Miozzo and DiVito, 2016) and profiles, academic and non-academics (Visintin and Pittino, 2014), are positively related to innovation performance, early growth and growth in sales and employees. This is in line with the previously mentioned lack of capabilities showing that a heterogeneous group of mindsets perform better in different aspects in respect to a homogeneous group.

Together with human capital determinants, innovation capabilities are frequently studied in the literature (9 out of 30). As we could have expected to higher innovation capabilities are associated higher performances, as is observable also in the table 2.5, is possible to find many positive relationships. Advanced stage in technological development is related to a superior growth (Miozzo and DiVito, 2016; Pfirrmann, 1999), in fact, the speed to product or service from the R&D is positively associated to be more attractive in terms of stock disinvestments (Knockaert et al., 2011). Findings supported by Quintana-García and Benavides-Velasco (2016) which recognize how the value of the patents (number of citations), products on the market and number of products under development is directly related an IPO success.

SBFs core capabilities are related to scientific discoveries, in fact, persistent accumulation of knowledge was found positive related to innovation performances (Suzuki and Kodama, 2004). Applying these core capabilities in different fields SBFs are able to obtain economies of scope. Innovation capabilities are source of superior economic performances: Vincett (2010) in studying basic research activities, recognize that basic research in research-based firms is a strong benefit on the final outcome outlining that governmental investments on research-based spin-offs should target basic research providing superior returns and economic growth. Innovation output in SBFs, as we would have expected, is a direct result of the R&D intensity, the higher is the amount of efforts in the creating new innovations the higher is the innovativeness as a whole (Stephan, 2014, Bruni and Verona, 2009).

Among the innovation determinants it's a different story if we consider different technological applications of innovations. Durand et al. (2008) in their study on rent generation and rent appropriation of research oriented or service oriented biotechnology firms, argued that in the case of different technological applications (technological diversity measured in number of applications) there is negative impact on return on sales of research oriented firms, arguing that not necessarily science and money go together. Instead, in line with the previous innovation determinant findings, technology diversity resulted positively related to innovation performances (Subramanian et al., 2016, Suzuki and Kodama, 2004).

This indicate that if the firm is diversifying its R&D efforts in different fields results to be more innovative but less profitable.

Innovation performances result to be improved by knowledge management practices (Alegre et al., 2011), knowledge transfer within the firm and a conjunctive appraisal at research and strategic level of the firm. The transfer of knowledge within the all units of firm seems to have a strong positive effect on the final innovation performances and help the firm itself to overcome the different stages of product to market. In fact, the lack of market information at research unit level due to the miscommunications between the strategic and R&D departments is translated in a minor innovation performance in terms of different industrial applications (Quéré, 1994).

No impact of sector has been found in the previous researches. Sector has no impact on growth considered in sales and size (Yagüe-Perales and March-Chorda, 2013) and no impact on productivity and profitability performances (Yagüe-Perales and March-Chordà, 2013; Benghozi and Salvador, 2014).

Two authors mentioned findings on the size of the firm effecting performances. On one size we have Bonardo et al. (2010) that found that growth by merger and acquisition and the ability to make profit is positively related to firm's size, which makes sense. Benghozi and Salvador (2014) also argued that size is positively related to the added value but with low impact.

On the strategy of the SBFs on performances, we found three main studies providing evidences. The first of Yagüe-Perales and March-Chorda (2013) which looks at the difference in strategies adoption considering being product oriented or service oriented a positive relationship on cost per employee is possible to be found. Same effect on growth in employees and revenues. Another study related to the strategy is the one of Mangematin et al. (2003) which found that market oriented business models enhance firm growth and performance besides innovation oriented business models limit the growth of the firm. This is a representation of the actual debate on the science business and its major challenge: overcome the dichotomy between science progress and commercialization of the innovations which SBFs usually face. In the study of strategy and performances, particular relevant are the investigation of Lubik and Garnsey (2016). They looked at how business models adaptation can be a source of value creation, recognizing the importance of the adaptation of the strategic posture within the embedded ecosystem.

Yagüe-Perales and March-Chordà (2012) found evidence that SBFs based on previous research has a better chance to obtain financial support from venture capitalists, being more attractive than their counterparts. Profitability in SBFs is not significantly related to spin-offs founded on previously research activities and it is not related to sector effect (Yagüe-Perales and March-Chordà, 2012, 2013), which is not directly effecting also the productivity (Yagüe-Perales and March-Chordà, 2013).

A contradicting result is represented by the negative influence for spin-offs based on previous research (Yagüe-Perales and March-Chordà, 2012). This could be explained by the lack of entrepreneurial capabilities of the scientist-founders or the lack of management skills (see e.g. Mustar et al., 2008, Pisano, 2010). No significant results are related to the type of the firm, for example being an LTD or LLC or INC (Benghozi and Salvador (2014).

2.2.2 Relationships

Several are the authors that made a contribution on the relationships variables of SBFs. These variables are represented by the relationships that ventures have with external entities such as university linkages, academic networks, technological partnerships or contracts with incumbent firms.

The affiliation determinant sees different authors involved. The first affiliation analyzed is the affiliation with universities and research institutes. These affiliations proved to be very effective during funds' collection making those SBFs with university affiliations more attractive to venture capitalists (Clarysse et al., 2011) and importantly university links are considered crucial in the SBF's growth (Lubik and Garnsey, 2016; Lawton Smith and Ho, 2006; George et al., 2002). A negative relationship is observed for the growth by acquisition which seems to be negatively related to the presence of the university as affiliate and the presence of venture capital (Bonardo et al., 2010). This is probably due to the conservative posture of the university which is more rigid toward expansion and slower in taking such growth venues. Findings also supports the evidence that the affiliation with the institute of origin in research-based spin-offs is beneficial in making radical innovations (Stephan, 2014).

Also collaborations with scientists affect positively the probabilities of obtaining funds due to their associated extended network (Wang and Shapira, 2012), supporting the previous findings that SBFs which have direct connections with the scientific and academic world perform better in terms of growth, financial resources and innovation.

Partnerships and in particular technological partnerships are the topics which received a considerable attention. Durant et al. (2008) in their study on French biotech firms, recognized that alliances with incumbent firms produce a beneficial effect on innovation performances generating more patents and articles but at the opposite but they have a negative impact on rent appropriation (ROS). These findings foster the argumentation on the real effect of big corporations and their collaboration with small ventures. Several evidences are found also on the growth of SBFs having industrial partnerships, finding a positive relationship between the two (Lubik and Garnsey, 2016, Nilsson, 2001, Segers, 1993). Intuitively, technological partnerships are positively linked with innovation (Segers, 1993) supporting the previous findings.

These findings foster the argumentation on the real effect of big corporations and their collaboration with small ventures. In a later study of Benghozi and Salvador (2014); in studying spin-offs with and with-out traditional industrial partnerships they found no significant effect in the relationships with other firms which are typically incumbents. They also suggest that, according to the studies of Steiner (2002, 2004) industrial partnerships should be contextualized and cannot be studied following the traditional approaches.

Networks have a positive impact of firm's performances. Meyer (2003) provides evidences that the firm's network helps in obtaining a successful IPO; Nilsson (2001) suggests that networks in academia in terms of links with researchers support the SBF's growth, which is line with the previous findings on the university and academic affiliations. Findings supported by Lubik and Garnsey (2016) considering networks in general and findings provided by Scholten et al. (2015) recognize that bridging ties is beneficial for the early growth new ventures obtaining more source of knowledge from different angles.

Relationships, as observed from our findings, represent a source of greater performances for SBFs which give them access to resources and capabilities that alone cannot reach. Firm growth has extensively recognized being related to the close collaborations with incumbent firms, universities and founder's networks.

2.2.3 External actors

Surprisingly on the incubation effect we only found the evidences provided by Meyer (2003) that looking into incubated firms, found that those businesses as part of incubators providing complementary services such as business consultancy or access to business network proved to be more effective during the launch of the initial public offering, enabling them to obtain founds easily.

Targeted R&D programs are representing both economic and financial success for a SBF (Vincett, 2010, Meyer, 2003). But looking at direct financial aids, Reitan (1997) argued that are important for the survival and foundation rate of SBFs, but influence negatively the level of the turnover and the employment rate. Despite R&D programs have proved to be very effective, the direct financial transfers as support policy resulted to be detrimental as suggested by Reitan (1997) which in line with Teece (1986) suggest that aids targeting complementary resources and capabilities are much more effective than direct financial transfers, because are more effective in establishing the underlying infrastructure.

Clarysse et al. (2011) looked into the growth of firms and the incumbent competitors of SBFs. For these firms the presence in their specific value chains of incumbent firms was observed as having a negative impact due to the massive complementary assets that these large firms possess. This support the actual debate on SBFs and NTBFs on the importance for small firms to rely on partnerships with incumbent firms which as previously observed are not necessarily translated in superior profits (or economic performance in general).

The presence of venture capitalists that provide capital for the firm are detrimental for the employment creation and innovation performance providing the resources needed to speed up the R&D process (Clarysse et al., 2011).

Ziaee Bigdeli et al. (2016) outlined from their case studies that the technology transfer office (TTO) providing a medium level support to these ventures provides a boost in terms of growth enabling them to learn about their technological capabilities and allowing them to adapt their business models. It was also found detrimental for the ensuring of seed funding. On the contrary an high level of support should not be implemented in order to avoid structural dependence from supporting institutions.

2.2.4 Environment

Evidences from the context are related to the ecosystem and the location of the firms. Regarding the former, Lubik and Garnsey (2016), in their argumentation of business models of advance material sector, underline the importance of the ecosystem in terms of access to resources, networks, collaborations which is translated in superior growth. Ecosystems are an effective vehicle of success which cannot be neglected in the conceptualization of SBFs' growth as supported by Pfirrmann (1999) which recognized that firm's environment is essential to fully comprehend the growth development patterns.

Concerning the location, Benghozi and Salvador (2014) in their study on Italian spin-offs recognized that for a spin-off being located in the north, south, center or islands does not affect the venture's value creation calling for a broader prospective for the analysis of the firm in their embedded ecosystems. Stephan (2014) identifies that variations in the location attributes explain the differences in innovation productivity between research spin-offs and others. The differences in location characteristics outlined by Stephan (2014) supports the evidences of the importance of context which SBFs are related.

2.2.5 Summary of the findings

As SBFs being recognized having idiosyncratic characteristics and behaviors, they are also unique in the way they perform. As we observed in the previous paragraph, rarely factors associated to superior economic performances are to be found, indicators such as size and the research intensity explain economic performances but in a limited way. Interestingly, despite innovation capabilities have proved to be a source of superior outcomes, the research applied on different technological fields was found negatively related to performances. This could rely on the fact that more technological fields require also superior resources and given the nature of the R&D activities which SBFs perform, also require huge resources for their development. No significant relationships on economic performance have been found regarding the geographical location nor on the presence of scientists as a member of the founding team.

SBFs having a service-oriented strategy has been observed of being more profitable. SBFs providing services are more capable to produce initial profits rather than the counterparts that take years before to generate any source of income. Providing initial services could be a way to finance or partially finance the R&D which is the core activity of these firms. Supporting programs are recognized as being a reliable source of economic and financial performance but only if targeted, in fact, merely financial transfers are argued as being not beneficial in the long run helping only at the inception with the constitution costs but not with the further advancements for the technology development. At policy level, programs directly targeting specific actions are needed in order to support these ventures.

Looking at profitability we partially agree with Durand et al. (2008) arguing that science and money do not always go together. Science it is not recognized convenient in terms of profitability, but probably due to their nature, profitability could not be the most appropriate parameter to judge the performance of science especially looking at SBFs at the initial development phase. This can be connected to many reasons, for example to the different objectives of the science stakeholders: on one side there is the scientist which the main objective is to advance science, advance in the academic career and probably more interested in an exit option rather than the continuity of the venture in the future; and on the other side the venture capitalists that wants to increase the market value and gain on the differential of the shares' disinvestments, rather than make profits. Another reason could be connected to the intrinsic R&D orientation of these ventures posing less attention on market objectives.

The previous argumentation is supported looking at the financial performances, when do science and money go together but in a different way. Research-based firms and firms established on a previous research are more able to attract financial performances than other firms, making SBFs more attractive. The affiliation with research institutes is seen as a stronger probability of R&D success making the firms collaborating with them more attractive. Also incubated firms receiving consultancy services are proved to be more trustworthy to venture capitalists, same thing associated with the presence of business professionals in the board of directors which increase also the probability of an IPO success. SBFs, in comparison with other firms are more capable to obtain financial resources especially if they demonstrate the managerial and research capability with affiliations and the presence of professionals. No evidence is provided on the strategy and financial performances; more studies are needed to investigate this relationship.

Looking at factors influencing growth, the stage of technological development, size, profitability and the ecosystems are the major determinant of SBF's growth. In line with what previously outlined, incumbent firms are considered a source of major growth for SBFs confirming that incumbents plays a central role in the development of new or small science ventures. Financial resources are particularly important at the initial stage of the venture's growth and the business model strongly influence the further growth. A particular focus is placed on the embedded ecosystems, which has been recognized as a strong source of growth but no studies have looked in depth on investigating this element. Also, innovation capabilities have a positive connection with growth performances.

R&D diversification, accumulation of knowledge, knowledge transfer, R&D intensity are all determinants directly affecting innovation outcomes. The research and development activities are related to innovation outcomes which is not surprising. Interesting is that different applications of the R&D outcomes not related to innovation capabilities outlining that diversification in technology applications and innovations are not always related. The ecosystems are an important determinant also on innovation performances, in fact, from different locations of the ventures is translated in different innovative capabilities. Affiliations together with technological partnerships, as previously observed for financial performances are also strong determinants of innovation success; this is probably the explanation of the superior ability to obtain financial resources from venture capitalists.

Only one study looked at the internationalization of the SBFs analyzing the international patents having no significant results, and only one study looked on market performances adopting the knowledge of the market determinant identifying that the ownership on the top management team and the market knowledge impact on the firm's performances in the market.

2.3. DISCUSSION

In this section the main findings from the analysis of the performance factors will be discussed outlining the main results, issues and possibilities for further improvements for the advancement of this thematic area.

Starting with fundraising issues, studies in the sample chose to concentrate on the initial stage of the development which is the focal stage for the majority of firms to acquire resources necessary to develop the initial product or services. As we know the R&D development of SBFs is a very long process that takes several stages going from preclinical to clinical trials before reaching the final product and the related market. The entire process can take several years 10 to 15 (DiMasi et al., 2003) with financial injections around $2.7 billion in case of drug development during its course. (DiMasi et al., 2016; O'Hagan and Farkas, 2009). This makes it necessary to model accurately how expenses of drug development are spread over time and how the outcomes can be modified through performance evaluation and management. Therefore, Longitudinal studies could be appropriate to take in consideration the all steps of development considering the needs of capital at different time periods.

The role of the founder within the organization is still not fully comprehended. It was observed that the presence of scientists which are also funders provide a superior performance but still their full potential and limitations remain undisclosed.

The ownership in the top management team influences significantly firm's performances. We found that a possible dichotomy between the founders and stakeholder objectives could be a source of explanation on the taxonomy of SBFs performances, questions such as "what are the objectives of the founders?", "What is the final goal of the scientists?", "How objectives impact on performances?" Should be answered. Studies on innovation says that user entrepreneurs (e.g. end-user entrepreneurs, professional user entrepreneurs, and hybrid end user/professional entrepreneurs) were the first to bring in many key innovative products or services into the real market in industries as diverse as sporting goods, medical devices, and juvenile products (Baldwin, Hienerth, & von Hippel, 2006; Shah & Tripsas, 2007). However, there is little information available regarding the demographic characteristics of user entrepreneurs and their prevalence. How startups founded by them compared to other innovative startups? The real objectives of these ventures could be different from a typical firm making the firm profitable could not be the real final aim, i.e., the scientist-founder could pursue a one-deal exit strategy with no intent to end up in the market.

Moreover, the initial intention of developing a firm affects significantly regarding further development and performance outcomes of a firm. If the firm was just intended to help in achieving short-term goals and academic or professional development of a researcher, it is challenging a venture to sustain in the future. Most of the time, these results in technology transfer to a big and well-established firm. This relation could be explained further using the agency theory where contracts and decision making principles are framed to elucidate anticipations of agents and compensation structures designed to align principal-agent selfinterests. For example, licensing of a patented drug molecule by an academic research scientist to a pharmaceutical drug development company.

The success of the development could depend on the composition of the top management teams. TMTs we need to know more about the role played by the founders. Studies on TMTs show that typically in other firms' founder is a full-time executive of a company. However, this is not the same in SBFs, where the scientific founder does not work full-time in the firm. There are several questions to estimate the performance and growth of the firm. How is that influential? What is the impact on the development of these firms? How is it technically feasible without the full-time supervision of a scientific founder? What could be the future goals of the venture? Who are the other stakeholders in the TMTs? What are the plans and continuous efforts to increase the market value of the firm and fund-raising approaches? Whether the innovation is strategically aimed to put into the market in planned time duration?

We know about the proven importance of scientists and how crucial they are for SBFs. We know that scientists working or being present are crucial but we don't know the real effect impact. Evidence that a mixed top management team provides superior innovation performances but its impact and dynamic should be better studied. Sometimes, the gap between professional understanding and subjective knowledge in the TMT could cause a detrimental effect on the overall development plan and the success rate of a firm. Noteworthy, there are no studies regarding the direct relationship between the market and product development plans and financial performances of SBFs. It is essential to study this relationships and factors affecting them (e.g., market need, market size, market barriers, competitive products, product price, and effectiveness) for SBFs including the specific areas such as pharmaceuticals, chemical industries, biotech, and medical devices firms.

Presence of business professionals: these firms mostly lack managerial expertise, studies on SBFs showed that presence of business professionals proved to be effective regarding superior performances. At what stages professionals are needed? Having long R&D processes business skills are required? Which business expertise is mostly needed? Various studies have proven that the market knowledge significantly affects the success and growth of the firm. For example, the introduction of Recombinant DNA and it's the revolutionary potential for human health, made researchers protect their innovations through patent and subsequently license it to the industry as they lack business and managerial experience. In future, this turns out to be a vast source of significant revenue returns for that scientist and institute. Paradoxically, there is no evidence regarding innovation capabilities and performance are found, highlighting the deficiency of market expertise regarding successful product development, advertisement, marketing strategies, and product management (Griffin et al., 2013).

Innovation together with human capital was one of the aspects more investigated by the selected sample. Innovation capabilities are among the most important determinants of the SBF's success. Innovations expertise are at the basis for existence itself of these ventures being based on extensive research in scientific areas, in other words, SBFs must be innovative to be defined SBFs. Investments in innovation capabilities and nurturing this capability is a basic feature of excellent companies. This help in developing products, services and superior business performance results (Lawson and Samson, 2001). Firms that have developed their innovation capability consistently introduce high-value products to the market quicker and more efficiently.

The implication for managers is that they have to be constantly busy in developing and fostering innovation ability within their firms to grow and succeed in the markets. Incremental innovations build on the current knowledge to rectify and improve the performance of existing services and products, whereas radical innovations draw upon transformed existing knowledge to make fundamental changes that sometimes cause current services and products obsolete (Chandy and Tellis, 2000; Subramaniam and Youndt, 2005). It is widely acknowledged that to compete; firms require to build up capabilities to generate both radical and incremental innovations (He and Wong, 2004; Katila and Ahuja, 2002; Rothaermel and Deeds, 2004). We know that SBFs are compatible enough to receive financial resources if they potentially demonstrate their innovation capabilities including the presence of technical expertise and collaboration with prominent institutes and subject leaders but a more in-depth investigation of these capabilities should also be undertaken in relation with other internal and external aspects such as managerial capabilities, capability to attract funds, speed to market, speed to exit and so on.

As mentioned above, we know that innovation capabilities are crucial for the performance, i.e., funds capital, IPO, M&A. This could be strictly related to their intrinsic nature. What is still unclear is what is making them more innovative within SBFs. We have results on knowledge management practices: transfer of knowledge in MNCs. This is probably one of the main reasons why MNCs dismantled their internal R&D to move into a different strategy to innovate. What this strategy is, how it works and what are its dynamics are still unknown.

There are a few instances where the intensity and size of research affect the performance and growth of the firm. On the other hand, there are increase collaborations between academia and industry show that the mentality of SBFs is drawing a line between innovation centers and business unit. The saved cost of R&D infrastructure can be potentially used for further collaborations and developing influential market plans. These collaborations help these firms to focus more on profit taking with less investment at the start-up level. Also, this can be useful when technological fields are involved in the invention where multiple collaborations with related firms could help in potentially managing superior resources for the R&D. For example, authors that performed structural dynamic monopoly model study to identify the expected benefits from R&D collaboration, found that partnerships with research organizations help in reducing the sunk costs of innovation and that a firm's probability of investing in innovation or R&D increases with the level of performance (Amoroso, 2014).

Business models have typically been studied on service oriented or product oriented. We argue that this approach could not be the right measurement parameter to approach SBFs in general. Drug development oriented SBFs typically face long and immensely costly R&D expenditures in respect of SBFs which operate for example, in the medical device area. SBFs that produce services should also be distinguished between pure service firms that support other SBFs and SBFs that provide services as a complementary business to finance the R&D activity or cover operative costs and thus considered as business model tactic. The concept of consultancy firms for R&D has been growing since long and proven to be successful in the group of SBFs. Organizational consulting can help SBFs for R&D activity in a variety of ways, i.e. conducting an organizational review to analyze the fit of team roles, structure, communication and culture with the goals and mission, helping in the development plans and individual assessment, assisting in team building, creating collaborations, and fund-raising, performing data management and analysis. For examples, Contract Research Organizations (CROs). Still, these SBFs should be counted as scientific service-oriented companies rather than pure SBFs. These firms are proving more profitable over the period and having high-performance outcomes. SBFs providing services start making money in very short-time compared to SBFs which are involved in R&D takes one and a half decade to gain profit.

Service SBFs help in initial set-up, financing and management exposure. However, the success rate of such a start-up is a burning question, and it is mainly dependent on various factors including the market knowledge and expertise of the start-up group. Mostly, these start-ups have an excellent scientific background but lack business experience. Future studies on the performance determinants of start-up SBFs would enlighten further the growth share and impacts by start-up SBFs.

Moving toward external dimensions, affiliations with incubators, universities and research institutes has proved to be a source of additional resources and additional attractiveness for venture capitalists resulting in a superior growth and innovation performance. The context and the complex of the relationships of the venture follow through the entire technological development but little still clarity should be done about the interactions of the firm within the context, what is the design of the context, what are the contextual factors that impact on performances and many other aspects are still to be better understood. National policies for science parks and innovation clusters have been recognized as one of the major thrusts for the innovation-driven economy, which comes through SBFs. The development of science parks and innovation clusters is an initiative by the government to support business and technology transfer that encourages the startup, incubation, and development of innovation-driven knowledge-based businesses. They provide an environment where international businesses may develop close interactions with a particular center of innovation for their mutual benefit (Parry and Russell, 2000; Ferguson and Olofsson, 2004).

Embedded ecosystems are identified as an influential source of success and growth, but there is a lack of studies on the detailed investigation of this aspect. These ecosystems are a crucial role player in the performance outcome of SBFs, especially, different innovation capabilities. The questions are what are the differences and similarities between platform, user/open innovation, and ecosystem strategies? How these ecosystems comply with international collaborations and investments? How feasible for business units regarding incumbent transitions and hybrid businesses management? How do these challenges new and less intensive from the traditional closed (non-platform and non-ecosystem) firms?

Within universities, there are factors that determine the extent and the effectiveness of contribution to the SBF's. Such factors include; the central administration of the university, departments and their heads, existence and nature of research groups, scientists, and contributions from students. According to Siegel and Wright (2015), the correct collaboration between the stated factors, favorable policies and infrastructure greatly influence SBF's. Government institutions, business industries, and other stakeholders have been having high expectations from universities on the success and growth of the business, which according to the data available not met yet. However, some universities such as Massachusetts Institute of Technology (MIT) and Stanford University have embraced the expectations by acting as seedbeds of many high-grown/growing business firms. Mustar et al. (2008) found that the major reasons behind frustration about what is expected of universities are unfavorable policies and lack of sufficient infrastructure required for efficient and effective operation of students, departments, scientists, and central administration to promote academic entrepreneurship. Better policies and improved infrastructure are required. Therefore it is necessary for responsible authorities to emulate what available and what is happening in MIT and Stanford for a better future of SBF's.

There is no clear conceptual framework showing the relationship and the required actions for the SBFs to operate successfully in diverse macro external factors. Sometimes macro factors such as political and legal environment can deny a science-based firm a chance to operate, and mostly since the most of the operation principle of such firms are new, firms lack stands to claim their operation rights and a chance to grow, (Katz and Gartner, 2010). Therefore, there is need of studies and researches to be conducted to come up with solid definitions of macro factors about the operation of SBFs. Also, political leaders and governments are supposed to consider the formation and existence of SBFs during legislation. Based on these findings we suggest that an approach considering broader dimensions such as ecosystem should be adopted to better clarify the SBFs performances. For example, the entrepreneurial ecosystem approach, seeing the entrepreneurship outcome. As a result, the interdependence between actors and factors in a particular region (Acs et al., 2017, Stam and Spigel, 2017) could be suitable for a better understanding.

2.4. CONCLUSIONS

In this chapter, are reviewed multiple studies using an integrative approach and isolated performance evidence that address directly and indirectly growth, outcome, and success of SBFs. Several studies concentrate on firm-specific dimensions succeeding in some situations to explain SBFs' performances and in some other cases finding contradicting results. In our investigation we outlined how the study of SBFs' performances is still widely understudied and lack of clear results and common directions for the understanding of these ventures. As a result, is possible to identify several gaps that could inspire advancements in the field.

First of all, within the performance measures, profitability measures such as net incomes could not be the right parameter for the evaluation of SBFs performances. Other indicators related to innovation capabilities and knowledge management such as innovation developments, technology development or knowledge transfer seem more appropriate to infer the peculiarity of these firms and for this reason further investigations on the proper measures for performance evaluation of these ventures were suggested.

The present work also provides some managerial implications, first of all looking at the development of technologies, we suggest that a new science-based venture should be focused on the development of one core technology rather than try to develop many. We suggest also to have a heterogeneous top management team with complementary knowledge and importantly the presence of business experts together with scientists. Looking at the business models, we can suggest implementing services in support of the R&D financing. This could bring profitability performances in the short run and make the science-based business even more attractive for investors. We suggest given the heterogeneity and the lack of studies, to take these managerial suggestions with precaution. Some preconceived factors such as geographical locations, size, depth and extensiveness of research, the presence of scientists as a lead role player in SBFs are an important determinant of a performance measure for a SBF. This study reveals that either these factors have no significant relevance with economic performance or they have a very limited role in determining success and growth of the firm.

This study provides also evidence that policy makers should concentrate on designing ad hoc supporting programs which directly target only the special needs of these firms rather than direct financial transfers. Anyway, direct financial support is seen as positive but only at the initial stage of the venture formation. Afterward other needs such business consulting, access to specific resources such as human and technological are needed to continue the development of the venture. This paper also contributes to the advancements in the characterization of SBFs adopting a holistic definition which could be adopted by further studies. Providing also a comprehensive set of subpopulations relying on academia, technology-based, sector, research, and science-based, should help authors in undertaking future studies on SBFs.

Moreover, policy makers have a significant role to play in the establishment, growth, and success of SBFs. As mentioned earlier, unlike the other forms of business organizations, SBFs requires a constructive interdependency between sensitive institutions including universities, scientists, and research bodies (Rasmussen and Sørheim, 2012). Practically, it is costly for a single firm to foster such a network of dependency until a SBF is established and maintaining the link for the flow of necessary information for the operation. On the same note, legislation and budget allocation at all level of governance starting from national governments, to university administrations to include the interests of SBFs, (Rasmussen et al., 2011).

Some limitations have to be outlined, first of all, the analysis with an integrative approach of reviewing the literature is strongly characterized by judgment and interpretation that cannot be completely eliminated by the in advance established procedures, making the integrative analysis more sense-making rather than mechanical (Pawson, 2002). The results of the integrative analysis emphasize the central role of the reviewer(s) in the interpretation of the findings could bring to "a possible explanation" rather than providing one definite (e.g., Noblit and Hare, 1988). Another issue concerns the extreme contextualization of this approach (Fielding and Fielding, 2000) or the methods used in the qualitative analysis which are not entirely accepted by the academic community (e.g., Wolcott, 1990; Lincoln and Guba, 2005; Dellinger and Leech, 2007). Another limitation is related to the selection of the articles; the analysis has been conducted only on top management journals introducing the possibility to lose critical findings from empirical works in other journals.

3. Entrepreneurial ecosystems in Science-based firms: building a theoretical approach.

Despite the recognized importance of the context in the human actions, the entrepreneurship literature that typically relied on studies on individuals, teams and firms did not pay much attention on the contextual forces that regulates the behavior, choices, and performance of these entities (Phan, 2004; Davidsson, 2006; Autio and Acs, 2010). For these reasons, as suggested by several authors (see e.g., Acs et al. 2017), studies on entrepreneurial behaviors should consider contextual elements on their analysis in order to progress the comprehension of the entrepreneurial innovation dynamics which so far have not received enough attention (Autio and Acs, 2010; Autio et al., 2013; Bowen and De Clercq, 2008; Levie and Autio, 2011). Context dimensions should not be considered as proxy or control variables but should be seen as characterizing determinants of the entrepreneurial action (Johannisson, 2011).

In particular many authors recognized the importance to study entrepreneurship in broader settings such as geographical, human and temporal spheres (Autio et al. 2014; Spilling 1996; Van de Ven 1993; Zahra and Wright 2011; Zahra et al. 2014; Colombelli et al. 2017) calling for a more holistic approach that incorporates such dimensions (Alvedalen and Boschma 2017). To this extent, recent authors such as Isenberg (2010), Cohen (2006), Feld (2012), and World Economic Forum (2013) looked at the outcome of an entrepreneurial action as a result of multi-level processes and stakeholders, multiple actors and multiple contexts that together generate a different set of conditions attributable to different Entrepreneurial Ecosystems (EEs). Stam (2015) defines the EE as "a set of interdependent actors and factors coordinated in such a way that they enable productive entrepreneurship within a particular territory" (p.1765). Despite several definitions in the literature the one provided by Stam (2015) is the most comprehensive and adopted definition (Acs et al., 2017).

The EE approach argues that a set of common elements are the backbone of an ecosystem, where these elements are recognizable as accessible to local and international markets, available human capital, access to financial resources, support from mentors and regulated systems, a regulatory framework well-orchestrated and a strong presence of universities (Acs et al., 2017).

Despite the increasing attention on the study of EEs, this research stream is still in its infancy (Stam and Spiegel, 2017; Cavallo et al., 2018). Several are the contributions describing the ecosystem that at the regional level support entrepreneurship, examples are Sigel's (2017) work on Canadian ecosystems, and Mack and Mayer (2016) describing the area of Phoenix in Arizona. Acs et al. (2014) employed massive quantitative data to characterize the EEs but still, the literature remains very much fragmented, without reaching either consistent theoretical advancements or empirical evidence.

SBFs' growth and performance is a topic which is receiving, just like the EE, increasing attention in the literature. Results are still fragmented, for example, Durand et al., (2008) outlines the positive effect of alliances with incumbent firms, Scholten et al. (2015) discovered that academic spin-offs grow faster during the initial years, and the influence of the technology transfer office (TTO) has positive effect on sustainability and scalability (ZiaeeBigdeli et al., 2016), or for example that those businesses as part of incubators providing complementary services proved to be more effective during the launch of the initial public offering (Meyer, 2003). All these findings together provide the evidence that the study of entrepreneurship for SBFs call for a more holistic approach such as the EE.

For the obvious reasons, to answer to the research's gaps, we performed an explorative study in the area of Lyon, France, which is historically a vivid area for the formation of New Science-Based Firms (NSBFs) especially in the field of biotechnologies and pharmaceuticals. Our sample relied on both NSBFs, and on the most representative organizations in the area that support the development of these firms. With the double objective to advance the literature of both EE and SBFs, we at first identified the key elements of the EE of the area of Lyon within the region Auvergne-Rhône-Alpes, and secondly, determined the main configurations of this entrepreneurial ecosystem. Further steps were taken to understand how NSBFs develop and grow in the ecosystem and how they differ from other firms which are not part of that ecosystem. Data are shown and treated with longitudinally through a retrospective technique in a way to capture the causal effect relationships between firms and the other elements of the ecosystem and being able to build consistent constructs for theoretical formulation.

In the following section, research propositions are formulated through the analysis of the most recent and relevant findings in the literature. Section 3.2 is dedicated to the methodology, a thorough explanation of the methods and procedures used to find and treat data are shown. In

Section 3.3 a brief history of the ecosystem of Lyon and presented case studies adopted for the investigation. Section 3.4 proceeds with the analysis of the case studies followed by the discussion of the findings in section 3.5, and conclusions are presented in section 3.6.

3.1. LITERATURE REVIEW

The EE concept was first introduced in 1980s and 90s when entrepreneurship authors started to recognize the importance of the factors surrounding the individuals that influence the entrepreneurial process (Dodd & Anderson, 2007). Representatives of this shift from an individualistic approach to a more holistic approach are Pennings (1982), Dubini (1989), Van de Ven (1993) and Bahrami and Evans (1995), who with their seminal works coined the recent concept of EE. The latter is used to interpret the influence that regional economic and social factors have on the entrepreneurial process incorporating temporal, spatial, social, organizational, and market dimensions of context (Zahra, 2007; Zahra et al., 2014).

The study of contextual inferences in management and economics is not new. Previous findings can be found in mainly two research streams; the first resides within management literature studying business ecosystems, with this approach the emphasis is posted on the value generated by organizations in global markets (Acs et al., 2017). Business ecosystems principles see the collaboration between different actors that produce complementary products or services determine the final firm's success, or added value (Iansiti and Levien, 2004; Adner and Kapoor, 2010; Williamson and De Meyer, 2012). The second research stream adopting contextual elements is represented by the regional development literature that include concepts such as industrial districts, regional industrial clusters and regional innovation systems (Stam and Spiegel, 2017; Terjesen et al., 2017), focuses on regional performances emphasizing industrial labor division (Marshall, 1920), and cooperation between people and firms (Becattini, 1990) to succeed in international markets (Acs et al., 2017).

Despite the previous attempts that have provided evidence for the development of regional areas and the internationalization of firms, the characteristics of the entrepreneurial innovation in different contexts remain one of the main concerns (Autio et al., 2014). The entrepreneurship literature only recently moved its focus on context under the approach of the entrepreneurial ecosystem. This approach defined by Stam and Spiegel (2017) as a "*set of interdependent actors and factors coordinated in such a way that they enable productive entrepreneurship within a particular territory*", represents a tool to explain the entrepreneurial outcome of a determined geographical area. Like business ecosystem and regional development literature, the EE considers vital the interactions between different actors in the ecosystem but differs in considering the final output represented by the entrepreneurial action instead of looking at the success in international markets (Acs et al., 2017).

From a recent special issue in the *Journal of Small Business Economics*, Acs et al. (2017) outline the importance to advance the literature of entrepreneurship innovation using the approach of the EE especially considering the embedded heterogeneity of the entrepreneurial ecosystems that should not be neglected in designing policy-making (Brown and Mason, 2017), recognizing that every ecosystem is different and target policies should be designed incorporating these specificities. Also, for the EE to be successful it should enhance the performances of the actors involved in the ecosystem but still little is known about how the EE enhances such performances (Terjesen et al. 2017).

A first attempt to look at ecosystems as elements of SBF's performances is found in Pfirrmann's study (1999), which recognizes that ecosystems are an effective vehicle of success which cannot be neglected in the conceptualization of SBFs' growth. In a later work by Benghozi and Salvador (2014) on Italian spin-offs, they found that the location (north, south, centre or islands) does not affect the value creation calling for a broader perspective for the analysis of the firm in their embedded ecosystems. Stephan (2014) identifies that variations in the location attributes explain the differences in innovation productivity between research spin-offs and others. A recent work by Lubik and Garnsey (2016), in their argumentation of business models of the advance-material sector, underlines the importance of the ecosystem in terms of access to resources, networks, collaborations which is then translated in superior growth. There is evidence of a positive causal relationship between performances and contextual inferences, but how SBFs are influenced by these elements is still far behind of full comprehension.

Despite scant studies in SBFs and EE, findings of EE's elements affecting SBFs' performances can be found from those researches that had focused on separate elements of the EE with fragmented and sometimes contradicting results. We can observe studies that look at relationship factors such as affiliations with universities and research institutes. These affiliations make SBFs more attractive to venture capitalists (Clarysse et al., 2011) and university links are crucial for SBF's growth (Lubik and Garnsey, 2016; Lawton Smith and

Ho, 2006; George et al., 2002). A negative relationship is observed for the growth by acquisition which seems to be negatively related to the presence of the university as the affiliate and the presence of venture capital (Bonardo et al., 2010). Affiliations with institutions of origin in research-based spin-offs are beneficial in making radical innovations (Stephan, 2014). Furthermore, collaborations with scientists affect positively the probabilities of obtaining funds due to their associated extended network (Wang and Shapira, 2012).

Durant et al. (2008) in their study on French biotech firms recognized that alliances with incumbent firms produce a beneficial effect on innovation performances but at the opposite, they impact negatively on rent appropriation. Several pieces of evidence are found also on the growth of SBFs, having industrial partnerships, finding a positive relationship between the two (Lubik and Garnsey, 2016, Nilsson, 2001, Segers, 1993). Benghozi and Salvador (2014), in studying the spin-off's industrial partnerships with incumbent firms, found no significant effect on performances. Studies also concentrated on networks, found to have a positive impact of firm's performances (e.g. Meyer, 2003; Nilsson, 2001; Lubik and Garnsey, 2016; Scholten et al., 2015), especially academic networks with universities.

With relationship factors also external factors have been taken into consideration. Among the external factors, we can find the incubation effect which is positively related to obtaining funds (Meyer; 2003). Also, targeted R&D programs are positively related to performances (e.g. Meyer, 2003, Teece; 1982; Vincett, 2010) but at the opposite direct financial aids, they are not always found to be positively related to employment and sales (Reitan, 1997). Incumbent firms represent another element of debate; they provide unique resources, such as knowledge or specific assets, which smaller firms do not have access, and for that they should enhance growth, but evidence shows that their presence could be negative restraining the growth of the smaller competitors (see e.g. Clarysse et al.; 2011, Moray and Clarysse, 2005). The clear role of the incumbents for SBFs is still not clear.

Another external element that recurs in the study of SBFs is the presence of venture capitalists that provide capital for the firm are detrimental for the employment creation and innovation performance providing the resources needed to speed up the R&D process (Clarysse et al., 2011). ZiaeeBigdeli et al. (2016) outlined from their case studies that the technology transfer office (TTO) providing a medium level support to these ventures provides a boost in terms of growth enabling them to learn about their technological capabilities and allowing them to adapt their business models. It was also found detrimental for ensuring of seed funding. On the contrary, a high level of support should not be implemented in order to avoid structural dependence from supporting institutions.

As is possible to observe, previous studies provide different and sometimes contradicting results about the elements enhancing SBF's performances. Critical elements for SBF's growth are universities, partnerships, venture capitalists, networks, incumbent firms, but clarity on which are critical for SBFs and most importantly how these elements intervene in value creation is still far from being reached. Due to this fragmentation and misleading results, it is difficult to make a comprehension of the effects of the single elements of the EE, calling for a holistic approach that takes into consideration all these elements combined in a related context. For the previous reasons, this explorative study tries to answer the main questions: How Science-Based Firms are influenced by the elements of the Entrepreneurial Ecosystem? What are the most important elements of an EE and which are crucial for SBFs' development? And How the EE approach can be considered as a theoretical construct to explain the entrepreneurial outcome of Science-based firms?

3.2. METHODOLOGY

To understand how the EE enhances the entrepreneurial actions and disclose its dynamics, a longitudinal case study approach was employed to collect data and allow an inductive interpretation of the findings. A longitudinal case study approach is recommended for the investigation of phenomena with a causal effect over time (Plano Clark et al., 2015) and to examine a changing response in a given individual over the period (Cook and Ware, 1983). However, to suit the context and the proxies measured, the retrospective technique was adopted to allow the collection of qualitative data from the quantitative variables gathered and measured from selected points (e.g Plano Clark et al., 2015). Data were analyzed with the longitudinal case study, employing the retrospective technique to examine the causal effect relationships between firms and the other elements of the ecosystem over time.

The adoption of the longitudinal case study with the retrospective technique in the analysis of data provides various advantages to the research and the researcher. Together with its wide spectrum of applications in different fields, the method is effective in determining variable patterns over the period (McPhee, 1990; Stuart et al., 2002). This implies that the use of the longitudinal case study allows the researcher to appreciate a given cause as well as the effects of relationships between variables over time, and thereby make connections in a better way. Stuart et al. (2002) recommend that the use of longitudinal case studies ensure clear focus and even validity in a study; while Pettigrew (1990) found that the method is effective in allowing a research to be conducted on the development trends in an accurate manner. This functions follow the purpose of this research to outline the relationship in the formation of the SBFs and the role of the EE ecosystem.

In this study was asked to the interviewees to recall the main events that occurred in the development of the firms like for example receiving from a local institution. Ideally, for the founder or the entrepreneur that at that time had this interaction was considered a critical event very easy to recall. The event describing firm's development are then related to outcomes. As an outcome are considered important steps or milestones that the firm was able to achieve thanks to the "main event" such as in example a step further in the development of the firm, the establishment of the firm as a legal entity or developing firm's logo, development of a patent, hiring of skilled personnel for the R&D department and so on.

The collection of data was obtained between June and October 2017 in person or via Skype when impossibility to reach the interviewees occurred. For the investigation, two kinds of interviews took place. One interview was conducted with the actors of the ecosystem, where, there were those institutions considered crucial in the EE such as the business accelerators and clusters. The second interview was conducted with firms within the region of Lyon. A control case was obtained from a firm established in the Paris area. A comprehensive list of SBFs was obtained from the Lyonbiopole cluster website where firms in the region, both associated and not associated to the cluster, are listed. All firms on the list were firstly contacted through e-mail and upon their positive responses, an appointment at their offices was requested and agreed upon, followed by the interview. All interviews were recorded with the consensus of the interviewees and disclosure of a firm's identity allowed in most of the cases.

3.3. COLLECTED CASES

The EE of Lyon represents a great example of why, as suggested by Isenberg (2010) in his essay in the Harvard Business Review, we shouldn't struggle to replicate successful environments, such as the Silicon Valley, and we should shape ecosystems around local conditions. For this reason, the Lyon ecosystem fits particularly with the purpose of this study providing a consistent pool of case studies that were established in this area and received the influence of the ecosystem itself.

Two preliminary interviews were conducted at two of the major institutions in the area that support new firm growth respectively the Lyonbiopole specialized in networking activities and providing several services to biotech firms in the region, and Pulsalys which is a business accelerator for innovative firms. These two interviews were instrumental to get a picture on the entrepreneurial ecosystem of Lyon and getting familiar with the main supporting institutions and notice to mention to get first contacts for the case studies.

BRIEF HYSTORY OF THE MÉRIEUX FAMILY

The Lyon ecosystem finds its roots back in the nineteenth century anchored with the story of the Mérieux family known globally, for their contributions in vaccinology in human and veterinary applications. The history of this ecosystem starts in 1870 when Marcel Mérieux was born in Lyon from a merchants' family. He graduated at the École de Chimie de Lyon writing a thesis on a methodology that applies colorants to recognize microbes. In 1894 joined the Institute Pasteur in Paris doing mainly laboratory work. During this experience had the opportunity to work side by side with two key scientists, the fist is Louis Pasteur known as one of the three fathers of microbiology and famous for his discoveries of the principles of vaccination, microbial fermentation and pasteurization; and the second is Émile Rouxco-founder of the Pasteur Institute and responsible for the Institute's production of the first effective therapy for diphtheria. At the institute, Marcel Mérieuxmastered the manipulation of microorganisms, like the plague bacillus discovered by Alexander Yersin, and constantly dedicated his strengths in the fight against the lack of asepsis in medical environments (InstituteMerieux, 2017).

Convinced of the potentiality of his discoveries and moved by entrepreneurial purposes, tried to establish a laboratory for medical analysis in Paris, but after failing of this intent, decided to move back and to start his business in Lyon. In his city of origin started to produce antistreptococcic serum used to fight puerperal fever in the district of Vaise but still with no success in terms of commercial exploitation. Later, in 1897, founded the Marcel-Mérieux Biological Institute in the same city, established in a private villa built by his brother. The institute, called nowadays Sanofi Pasteur and part of the Sanofi-Aventis group, was destined to have a profound impact on vaccinology, and later in vitro diagnostics at the global level (InstituteMerieux,

A total of 15 interviews were collected and consequent case studies were collected. All firms in the sample are new science-based firms or recently established SBFs. Given the longer research and development phases which SBFs are typically subjected to, in comparison to high-tech or other traditional firms, for new SBFs are considered those firms which are not scale-up companies and most of the time are recently in the market or still in clinical trial. For this reason, a new SBF can be established ten years ago but still in the R&D phase.

Among the 15 firm cases, 13 are considered successful SBFs because they already received consistent amounts of funding or for already being in the market, in the clinical trial, or in approval phase. The remaining 2 firms are considered as control samples because they provide a different point of view: Cerma SA is considered a failure case after the bankruptcy occurred in 2017, and LPS Biosciences is established outside the Lyon entrepreneurial ecosystem. Qualitative data from interviews are implemented with secondary data used also for cross-checking. Data are shown according to a visual mapping method in a way to capture the causal effect relationships between firms and the other elements of the ecosystem and being able to build consistent constructs for theoretical formulation. In Table 3.1 the interview list is presented and Table 3.2 details about the cases are shown.

Table 3.1. Interview table

ID	Firm	Interviewee	Interviewee's function	Date of interview	Duration of interview
1	**ABL Lyon**	Marc Essodaigui	General manager	22/09/2017	0:45:49
2	**Alaxia**	Philippe Bordeau	Co-founder and VP Innovation and Business Development	20/09/2017	0:29:34
3	**Bioxis pharmaceuticals**	Frederic Bertaina	Co-founder and CEO	25/09/2017	0:41:10
4	**Case4**	Interviewee4	COO	21/09/2017	1:03:39
5	**Stragen Services**	Annie-Claude Benichou	Co-founder and General Manager	25/09/2017	0:27:34
6	**Calixar**	Emmanuel Dejean	Co-founder and CEO	07/09/2017	1:34:00
7	**Bio Elpida***	Gilles Devillers	Co-founder and CEO	06/09/2017	0:33:48
8	**Neolys Diagnostics***	Gilles Devillers	Co-founder and CEO	06/09/2017	0:40:59
9	**CFL biotech***	Gilles Devillers	Co-founder and CEO	06/09/2017	0:21:44
10	**Carpaccio**	Rudy Marty et Brian B. Rudkin	Founder and CEO	30/08/2017	1:20:53
11	**SameSame**	Alexandre Boulmé	Founder	06/09/2017	0:52:12
12	**Anaquant**	Tanguy Fortin	Co-founder and CEO	06/09/2017	0:44:23
13	**Cerma S.A.**	Dr Emile Hiltbrand	Co-founder	19/09/2017	1:02:43
14	**LPS-BioSciences**	Frédéric Caroff	Co-founder and CEO	05/10/2017	0:48:43
15	**Mathym**	Julien Alberici	Co-founder and CEO	27/09/2017	0:38:32

In the next parts of this section, each case study is presented. Figures will show the firm's storyline in which the main events that changed the course of action and their direct consequences are shown in the central part of the figure and on the external part of the storyline the elements of the entrepreneurial ecosystem that allowed or supported such events or outputs are represented in a grey box.

Table 3.2. Cases table

ID	Firm	Application market	Activities	Technologies	Main activity description	Year of foundation	Year of market entry	Last available turnover M€	Employees	N. of scientists	Financing received	N. of patents
1	**ABL Lyon**	Immune, AutoIm & Inflam. diseases - Neurological diseases - Oncology	Diagnostics - CRO	Analytical & Diagnostic services - Cell Therapy - cell biology - Biobanking - Antibodies - Protein - Peptide	Analysis of biomarker samples (serarch for immuno-response) mainly during clinical and pre-clinical trials	2011	2011	1.2	n.a.	n.a.	n.a.	n.a.
2	**Alaxia**	Infectiology - Parasitology - Pneumology	Therapeutics, Pharma or Biotech	n.a.	Therapeutic solutions for respiratory diseases (cystic fibrosis)	2008	/	/	10	9	15 m	5
3	**Bioxis pharmaceuticals**	Dermatology & Cosmetology - Wound healing	Medical device - Technology provider (Derma fillers)	Biomatarials - Disposable & Implants - Regenerative medicine	Production of biomaterial scaffolds for tissue regeneration	2010	2017	n.a.	11	6	3 m	4
4	**Case4**	Oncology	Therapeutics, Pharma or Biotech	Antibodies , Protein, Peptide	Development of therapeutic molecules for cancer treatment	2008	/	/	10	6	30 m	5
5	**Stragen Services**	Therapeutics, Pharma or Biotech - CRO	Pharmaco-vùigilance and regulatory	n.a.	Supports biotech and pharmaceutical companies for every aspect of pharmaco-vigilance and regulatory aspects	2009	2009	n.a.	10	6	n.a.	/
6	**Calixar**	Immune, AutoIm & Inflam. diseases - Infectiology - Parasitology - Neurological diseases	Therapeutics, Pharma or Biotech - Technology provider	Genomics & Proteomics, Biochips - Vaccine - Antibodies - Protein - Peptide	New innovative and patented technology for extraction of membrane proteins and antigens without denaturation	2011	2011	0.8	2	7	2 m	5

Table 3.2. Cases table *(continued)*

ID	Firm	Application market	Activities	Technologies	Main activity description	Year of foundation	Year of market entry	Last available turnover M€	Employees	N. of scientists	Financing received	N. of patents
7	**Bio Elpida***	Immune, AutoIm & Inflam. diseases - Oncology - Others	CMO (contract manufacturing organization)	Cell Therapy - cell biology – Bio-banking - Regenerative medicine - Others	Development of innovative cell therapy products (Advanced Therapy Medicinal Product as define by the EMEA) based on cell culture and immunology approaches	2009	2009	2	23	15	n.a.	n.a.
8	**Neolys Diagnostics***	Oncology	Diagnostics	Analytical & Diagnostic services	Diagnostic on patient's cancer treatment in radiotherapy	2014	/	/	4	4	4 m	4
9	**CFL biotech***	Oncology, immunotherapy	Diagnostics	Analytical & Diagnostic services	Bio-marking of resistant cancer cells	2013	/	/	0	0	n.a.	n.a.
10	**Carpaccio**	Various	Analysis of muscular fibers	Analytical services	Rapid analysis of muscle fibers in support to R&D processes	/	/	/	1	1	/	n.a.
11	**SameSame**	Speech disorder	Therapeutics	Software	Support to patients affected to speech disorders with the usage of an innovative interface	/	/	/	2	1	/	n.a.
12	**Anaquant**	Infectious diseases-Parasitology - Oncology	CRO (contract research organization) - Technology provider	Analytical & Diagnostic services - Screening services - Antibodies - Protein - Peptide	Production and analysis of proteins and biomarkers using mass-spectrometry	2014	2016	0,25	7	7	/	1
13	**Cerma S.A.**	Oncology	Therapeutics	Medical device, cateter vapor injections	Device to inject vapor for cancer treatment	2001	n.a.	n.a.	5	5	20 m	>1

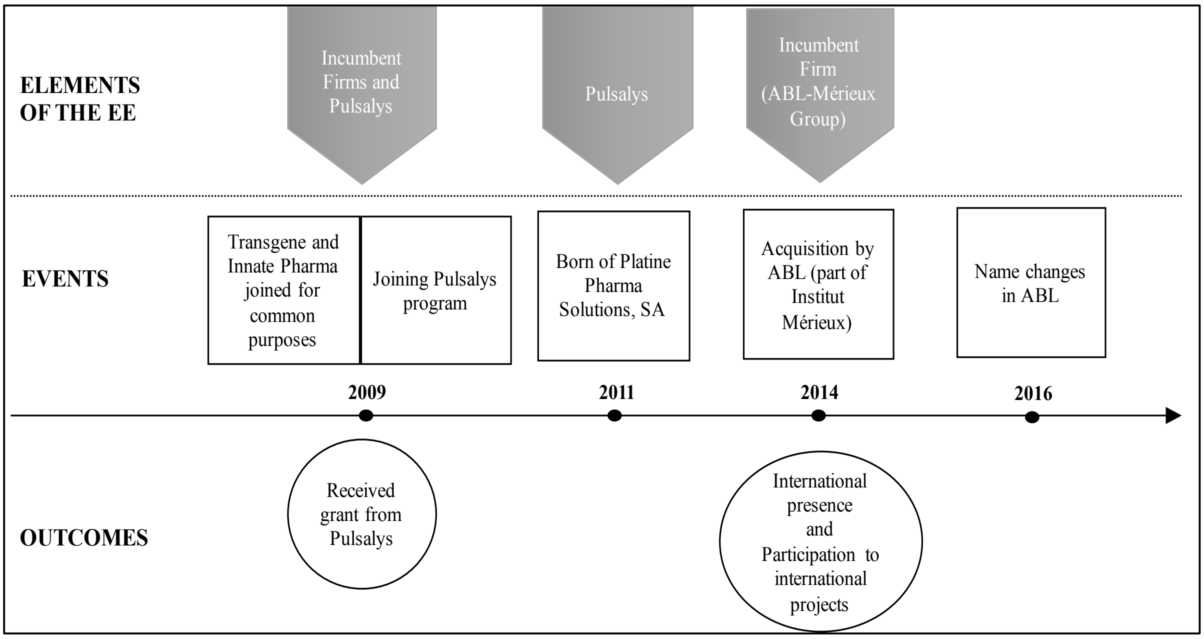
Table 3.2. Cases table *(continued)*

ID	Firm	Application market	Activities	Technologies	Main activity description	Year of foundation	Year of market entry	Last available turnover M€	Employees	N. of scientists	Financing received	N. of patents
14	**LPS-BioSciences**	Immune, AutoIm & Inflam. diseases - Infectious diseases-Parasitology - Oncology	Therapeutics, Pharma or Biotech - CRO	Analytical & Diagnostic services - Vaccine - Others	Production of purified LPS (lipopolysaccharide) from specific bacteria	2011	2012	0.3	8	>6	200 k	n.a.
15	**Mathym**	Dentistry & Odontology - Orthopedics & Traumatology	Medical device - Technology provider	Chemical synthesis services & medicinal chemistry - Disposable & Implants - Nanotechnology	Production of nanomaterials for dental industry	2014	2017	0.125	10	>3	3 m	1

3.3.1. ABL Lyon

Dr Marc Essodaigui is a scientist with a PhD in molecular biophysics with long experience in the field of biotech technologies for over 20 years. He joined ABL Lyon in 2016, a company which was called Platine, until its acquisition from ABL Inc. in 2014. The company was originally founded by two other biotech companies; Transgene, a company specialized in the development of immunotherapies and Innate Pharma, company based in Marseille also specialized in immunotherapies and mostly in immuno-oncology. These two firms joined the efforts to create a service company specialized in immuno-monitoring and immune response. Since these two companies are developing immunotherapies, they needed to have specialized help to put some lights in the immune-response once they inject their treatments into their patients. Both companies have a clinical stage and clinical trials, so in 2011, under the support of Lyonbiopole through a project grant, started the Platine's project which took two years for the complete creation of Platine Pharma Solutions, SA.

Figure 3.1. ABL Lyon's development



In 2014, 3 years later the company was acquired by Advanced BioScience Laboratories Inc. (ABL), a multination which is based in the US. They specialized in bio manufacturing and bioanalytical services very are very much complementary with Platin was doing in Lyon. The incorporation in the ABL group allowed the small spin-off to provide customers with an international support expanding access to the US-based branch. Interestingly the ABL group is part of the InstitutMérieux which as introduced before brings our roots back to Lyon's history.

ABL Lyon, and even before Platine, is a leader in Europe being the sole company able to provide their services for immuno-response and biomarkers detection offering the largest panel of solutions exploiting its unique technology for molecule detection. ABL major business is developed for clients which are in clinical and pre-clinical trials in which standards are very strict. They have worked in several drugs development fields such as cancer, infection diseases like HIV, neurodegenerative diseases like Alzheimer, multiple sclerosis, inflammatory diseases like crone diseases.

Before the acquisition, the business was mainly focused on client's clinical trials in phase 1 where the number of candidates and the number of the analysis are limited comparing to other clinical stages, in fact in phase 1 the number of samples can be around 300 or 400. After the acquisition by ABL Inc. the firm strengthen its capabilities in order to be able to work on the larger trials including clients operating in phase 2 and phase 3 which comprehend larger scale studies reaching about 20, 30 thousand candidates. The core technology was developed before the entrance of ABL Inc. and what they did was to push its technology and increase the performances the quality of the controls and to expand services.

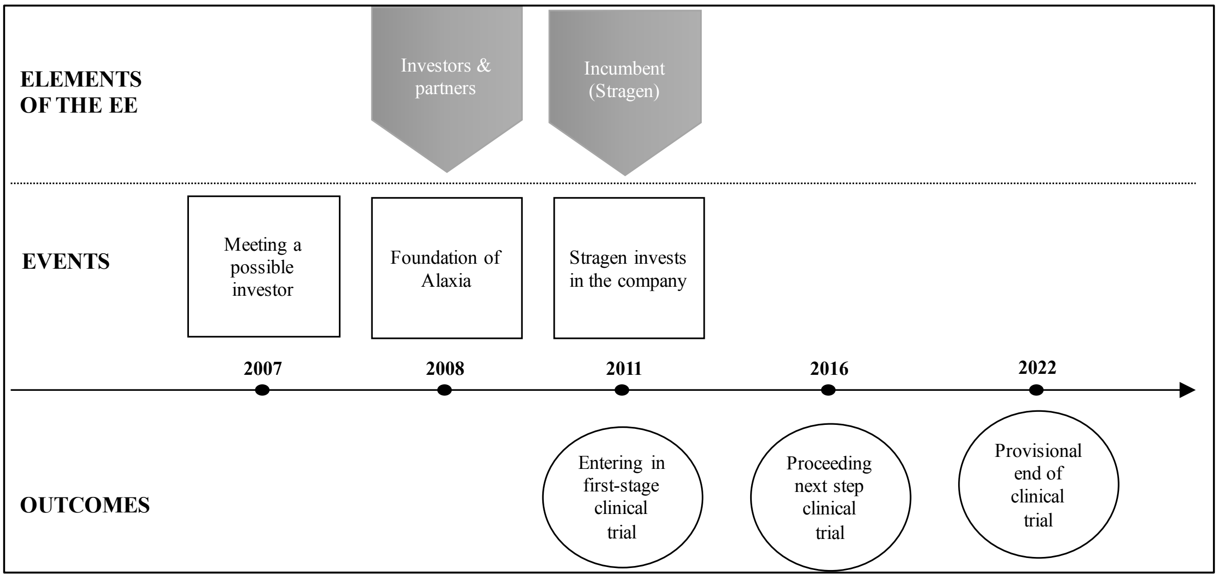
With the inclusion in ABL Inc., the firm also benefit from the holding controlling ABL inc. which is the InstitutMérieux. Being part of the group allowed ABL Lyon to get access to a bigger network of players in biotech and pharma industries enabling the firm to participate in diverse innovation projects which they did not have access before.

3.3.2. Alaxia

Dr Philippe Bordeau is an engineer in food science and is the co-founder and VP Innovation and Business Development of Alaxia SAS. The entire idea of Alaxia born when Dr Bordeau was working with antimicrobials for food safety and realized during his research is that he was using a microbiota for food and this was missing in healthcare.

The idea needed a financial support and is when in 2007 Dr Bordeau met his co-founders interested in patenting and developing the drug. The co-founder is a non-profit organization held by private donors. The development of this drug is aimed at the treatment of cystic fibrosis and one member of the family's donors is affected by this disease.

Figure 3.2: Alaxia's development



Alaxia was founded in 2008 and started its first research on the drug in order to do the first round of toxicological studies, the very first step of drug development. Thanks to the first studies in 2011 found another investor based in Switzerland named Stragenwhich invested in Alaxia in order to transcend their research and to support with pharmaceutical expertise and skills and to put the products on the right track to the market. Since 2011 Alaxia did a lot of in vitro studies in vivo ex vivo and right now thanks to the expertise and resources received from Stragen, Alaxia is now in clinical trial in which the product crossed part of the first stage.

Now the firm is doing safety study in cystic fibrosis population and the next big step was to show the efficacy which would be the turning point for its completion or its failure. The clinical trial should be completed by 2022 because being in rare diseases; studies have smaller proportions using a lesser number of patients. Alaxia does not have any products in the market performing only R&D and generating about 2, 3 million losses every year. The funds received so far from investors are around 40 million euros.

3.3.3. Bioxis Pharmaceuticals

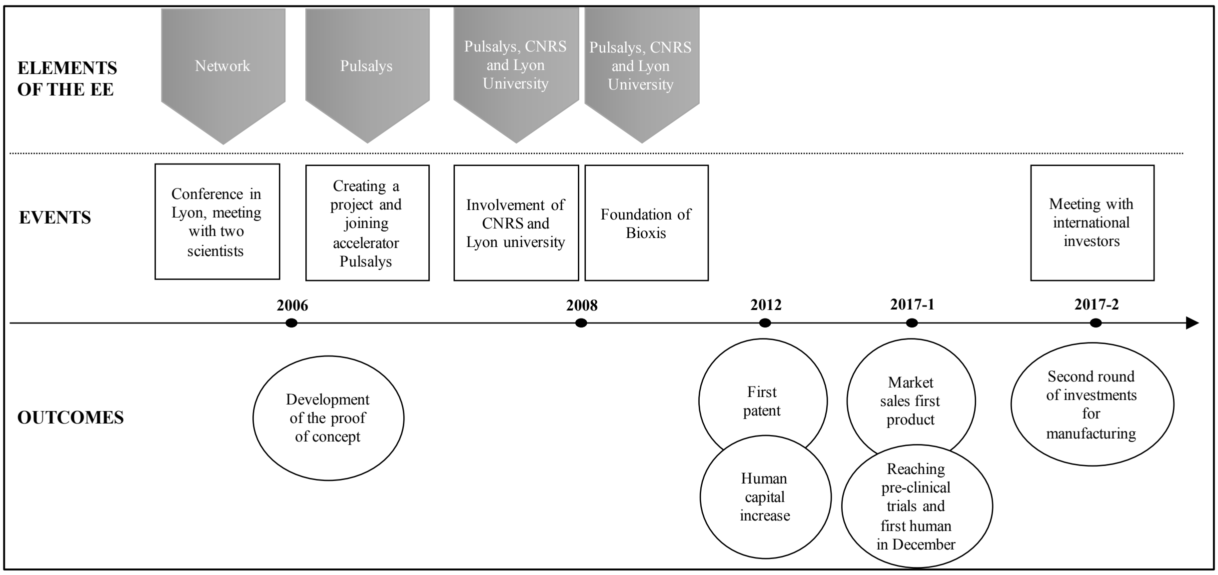
Dr Frederic Bertaina is the co-founder and CEO of Bioxis Pharmaceuticals. He has experience in several pharma industries in Paris but also spent several years in New York and

Moscow. The first main event occurred in 2006 during a conference in Lyon where the scientists behind the discovery of the application of chitosan, a type of fibre derived from chitin, a substance that develops in the hard outer shells of crustaceans such as crab, crayfish, shrimp and squid, presented their idea as regenerative component for the healthcare industry. Having a background in the cosmetic industry Dr Bertaina saw the potential application of this biotechnology for dermal fillers.

After a short time of projecting, Bioxis, which was still was not formally constituted yet, was accepted at the accelerator Pulsalys as the development project. During this period Bioxis was able to develop the proof of concept and received support from the CNRS (Centre National de la Recherche Scientifique) and the University of Lyon thanks to the involvement of the scientists that were developing the idea.

In 2010 Bioxis Pharmaceuticals was formally established and in 2012 the process of research and development produced the first patent based on chitosan. After the first patent, the firm started to build a team of researchers before there was only one researcher from the university, and to have a small office and small lab that allowed Bioxis to strengthen its research being able to produce 4 more patents on chitosan and one in the Hyaluronic acid application.

Figure 3.3. Bioxis's development



Being in the medical device segment the R&D process is faster comparing to drug development as a consequence after 5 years of research the firm was able to complete the preclinical trials in mid-2017 and test to the first human by December of the same year and hopefully being in the market by 2019.

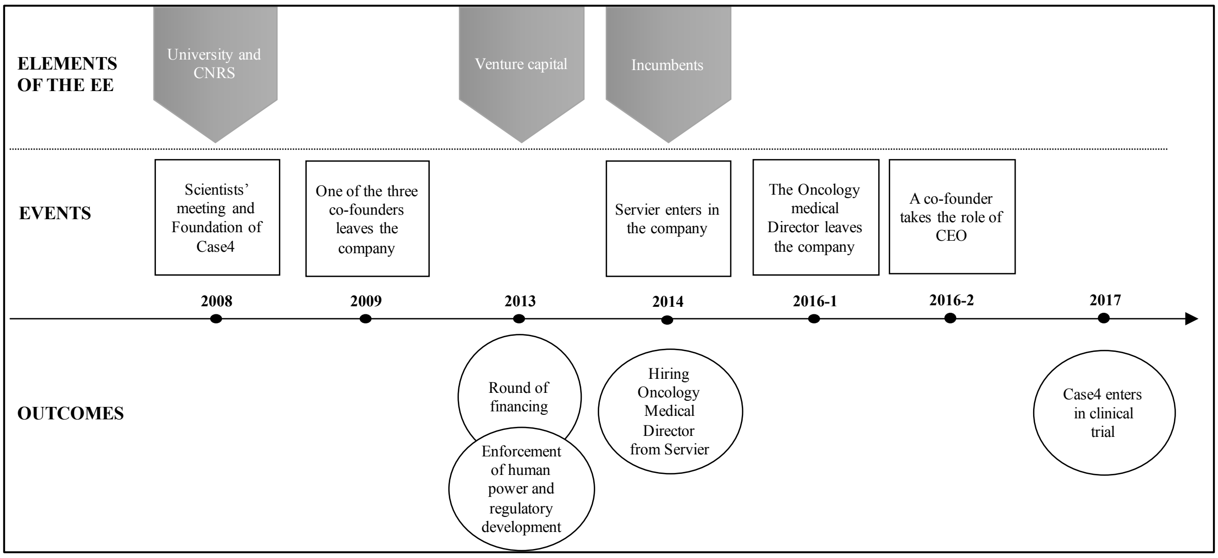
The other big step obtained by Bioxis was also the introduction in the market of the first filler which was not based on the patented technology that was being developed in parallel having a sold out even before producing the fillers. This filler is made from an existing technology based on hyaluronic acid. Sales are generated globally within 20 different countries, mostly in Europe but also more exotic countries such as Emirates, Iran, Thailand and Chile.

Together the entrance in the market and reaching pre-clinical trials allowed Bioxis to obtain a substantial second round of investments attracting local investors but also foreign investors from Russia and China. These rounds of investment were meant to Bioxis to make a huge progress in the development of its products by establishing a manufacturing site in Lyon.

3.3.4. Case4

Case4 is a biotech company located in the Léon Bérard cancer centre and focuses its activity mainly on the identification of biological targets. The two co-founders are scientists that work at the hospital and research centre and developed a new technique for developing molecular antibodies that can target specific Dependence Receptors: "*In this targets with our molecular antibodies we stop the interaction between the molecules and the other one and by destructing this interaction we have an anti-cancer activity, basically cancer will stop to interact with other cells and dies. It's a little bit more complicated, more or less, that's the dynamic in very simple terms*" (Case4 Pharma).

Figure 3.4. Case4 development



So far the company developed its first biological target called Netrin1 which started the clinical trial at the beginning of 2017. The company is a research-based company that has collaborations and collected money from different investors. As is possible to observe from figure 4 Case4 was founded in 2008 by the scientists behind the discovery of Netrin1 after years of research and work and the university and CNRS labs.

In 2009 an important event occurred when on the founders left the company due to personal reasons and the company struggled to find a new balance between the parties. After 2009 the development of the Case4 1 goes smoothly until in 2013 a venture capital fund invests in the firm. The injection of financial resources allowed the firm to enlarge the stuff and start regulatory development.

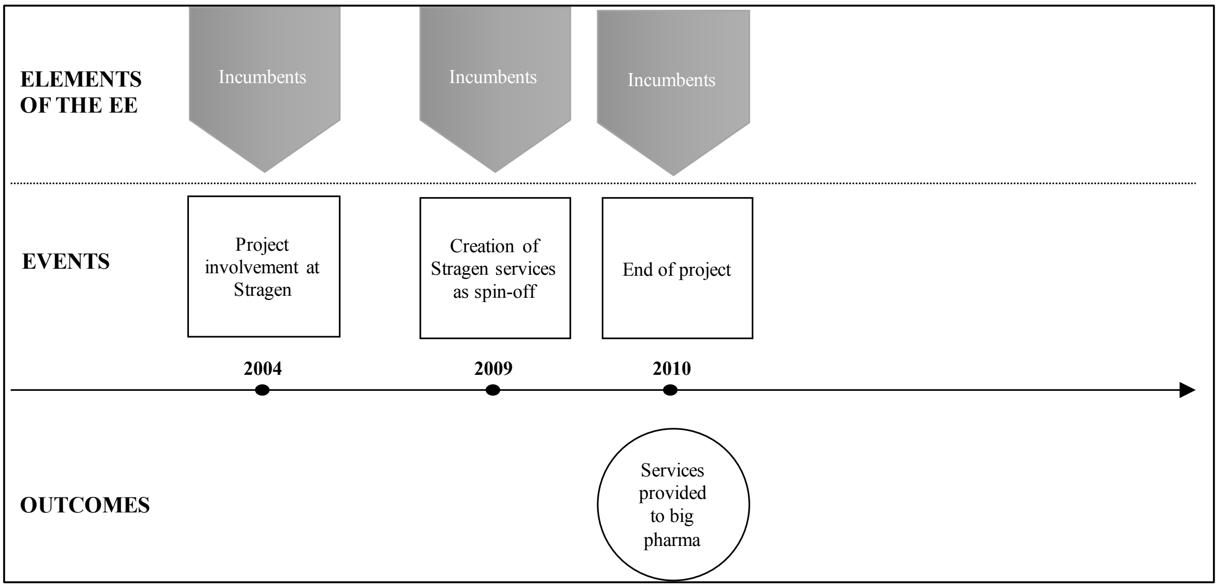
The year after a new entry by Servier, a French company which revenues are around 4 billion euros, which provides to Case4 the necessary resources to proceed in the development of the firm also with the involvement of an Oncology Medical Director from Servier which should bring to the new science-based venture the knowledge and experience that the company need. After two years, in 2016, the medical director leaves the company which leads one of the two co-founders to take the role of CEO and directly control the firm development. In 2017, Case4 completes the pre-clinical and enters in the clinical trial.

3.3.5. Stragen services

Stragen is a service provider which offers support and ad-hoc solutions for pharmacovigilance and clinical development strategies. It includes a wide range of activities for pharmacovigilance that goes from the basic compliance of pharmacovigilance such as Registration/updates in EudraVigilance, to QPPV (Qualified Person Responsible For Pharmacovigilance) responsibility and Risk management activities including case processing, safety reports, literature review, signal detection activities and many more.

Stragen service is a spin-off of aSwiss pharmaceutical group Stragen Pharma SA, which business is mainly oriented in generic products. In 2004, Dr Annie-Claude Benichou, joined this group for working on innovative products because despite being mainly a generic company, Stragenalways have some non-generic projects, so she joined them for their first project outside the generics which was a product in onco-ematology and she developed all the aspects concerning the clinical affairs. The drug is now commercialized in the US market.

Figure 3.5. Stragen Services's development



At the end of the project and given the experience obtained at Stragen, Dr.Benichou desired to start her own business in the service industry. Due to the success story, Stragen decided to invest in a new venture and co-founded Stragen Services and in 2009 the company was formally created. The business is established in Lyon and not in Geneva, the Stragenheadquarter's, because of the Europen Community regulations that oblige pharmacovigilance providers to be established in the European Union. The synergy between Dr.Benichou and Stragenwas a success case, Stragen Services now has 10 employees, among them six are scientists, and runs services for 30% inside the Stragen group and 70% for other pharmaceutical companies.

3.3.6. Calixar

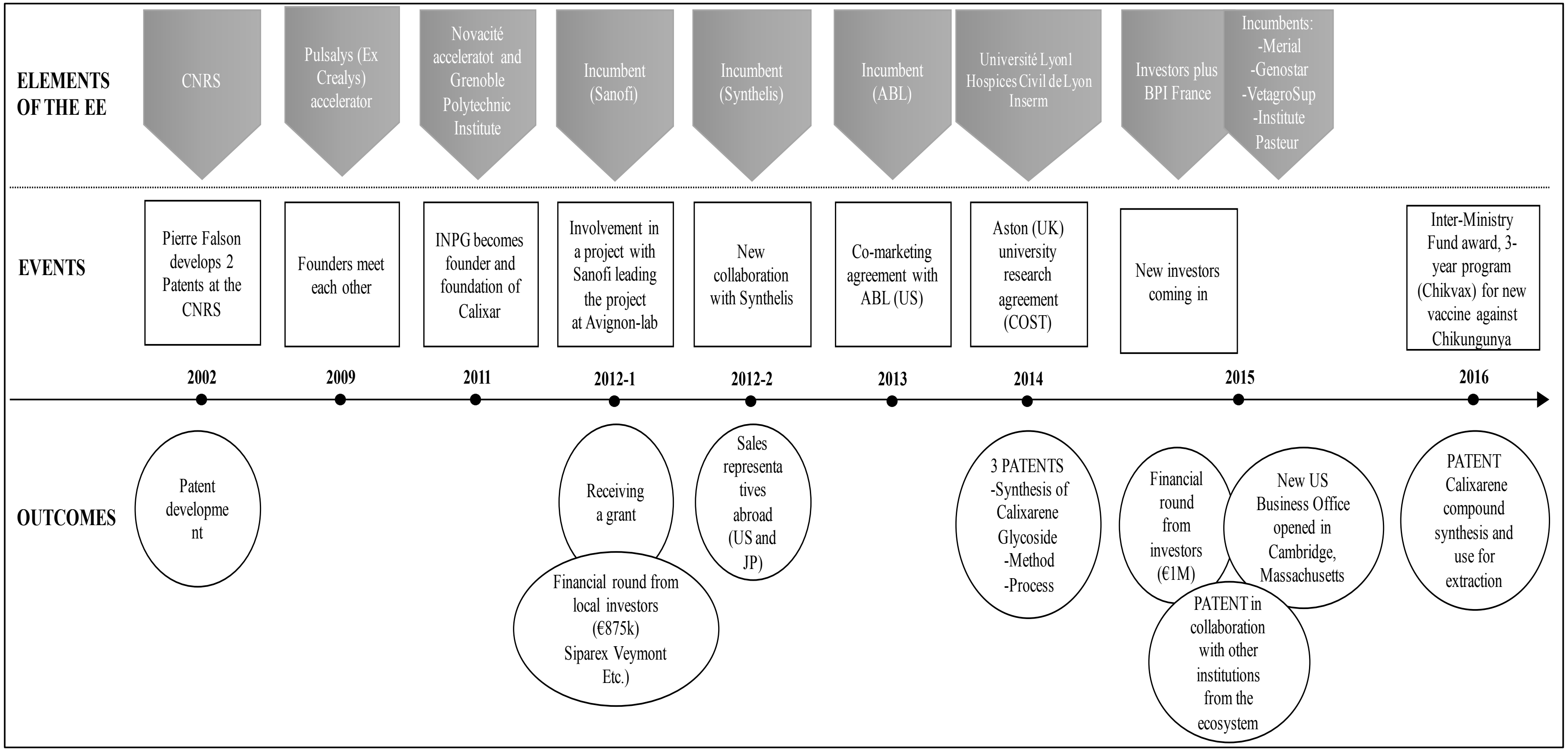
Calixar is a biotechnology firm located in the city of Lyon specialized in the isolation and crystallization of native and functional membrane proteins with a special calixarene compound. This venture is the result of the research done by Dr Pierre Falson a former research director at the CNRS (Centre national de la Recherches Scientifique) which developed new patents regarding this new technology. Later Dr Falsonmet Dr Emmanuel Dejean expert in innovation management and R&D destined to be the future CEO and Chairman of Calixar. The encounter occurred at the incubator Pulsalys (at the time called Crealys) during a meeting organized by this institution to promote the establishment of new projects. After less than 2 years the firm was formally established with the involvement of the INPG (Institut National Polytechnique de Grenoble) that served as the third founder. In Figure 6 a representation of the development timeline is shown.

Calixar is a biotech firm founded in 2011 but the initial development started in 2009 and the first milestone was reached even years before in 2002. The first event that is represented by the creation of two patents by its investor Dr Pierre Falson working at the CNRS. After the creation of these new protein extraction techniques lasted 7 years before the other important event occurred in 2009 when Dr Falson met Dr Dejean and decided to jointly commercialize the research. The encounter happened at the business accelerator Pulsalys (at that time called Crealys) where Dr Dejean was collaborating and looking for a business venture to develop. The ecosystem in Lyon, in this case, was very strong allowing the two founders to meet and giving to the firm the first boost. In fact, the name Calixar, the logo and the initial marketing campaign was developed by the accelerator allowing also the access to a ministerial grant.

Pulaslys, as many accelerators in France, helps entrepreneurs to develop the initial plan for commercialization called “proof of concept” in which a committee judges the idea and its potential, after the proof of concept if finalized and approved the acceleration program begins. The fact of being part of this selection process, allowed Calixar, to gain the reputation among the players in the field bringing the firm to the next crucial event that is the foundation of the firm in 2011.

Given the reputation obtained by Pulsalys (ex Crealys) and under the support of another accelerator in the area Novacité, specialized in supporting innovative start-ups, gained the attention of the Polytechnic Institute of Grenoble which became like a third founder for the two. Obtained the support of the Polytechnic in 2001, Calixar was officially funded in 2011. After its foundation, Calixaratively participated in the ecosystem life of Lyon area being able to participate the year after its foundation in the joint project with one of the biggest players in the ecosystem and worldwide, which is the Sanofi group and a big biotech company in Lyon, Shyntelis. Establishing a laboratory in Avignon Calixar participated actively in the R&D process of the project which attracted the attention of local investors and led the firm to its first round of investments obtaining nearly one million euros from Health Angels Rhone-Alpes, Veymont Finance, Grenoble Angels, Savoie Angels and Siparex, all local players.

Figure 3.6. Calixar's development



In the same year, Calixar obtained also a partnership with Shyntelis, one of the project partner, for the production of the compounds necessary for the protein extraction. In this way, Calixar after one year of its foundation was able to boost its production capacity with a local partner. With the renewed capacity Calixar wanted to start selling abroad and acquired new sales representatives in Japan and the United States. The year after in 2013, Calixar entered into a co-marketing agreement with a US-based company called ABL. This firm even if is based in the states has a direct connection with the Lyon area being part of the Meriaux family. In this case, the ecosystem of Lyon pushes the company abroad and

not directly on the territory of origin extending its boundaries. In 2014 Calixar poses another important step for its research, joining COST project for the on the immune response for the development of a new patent on the innovative manufacturing process for high-performance influenza vaccines in collaboration with Aston University.

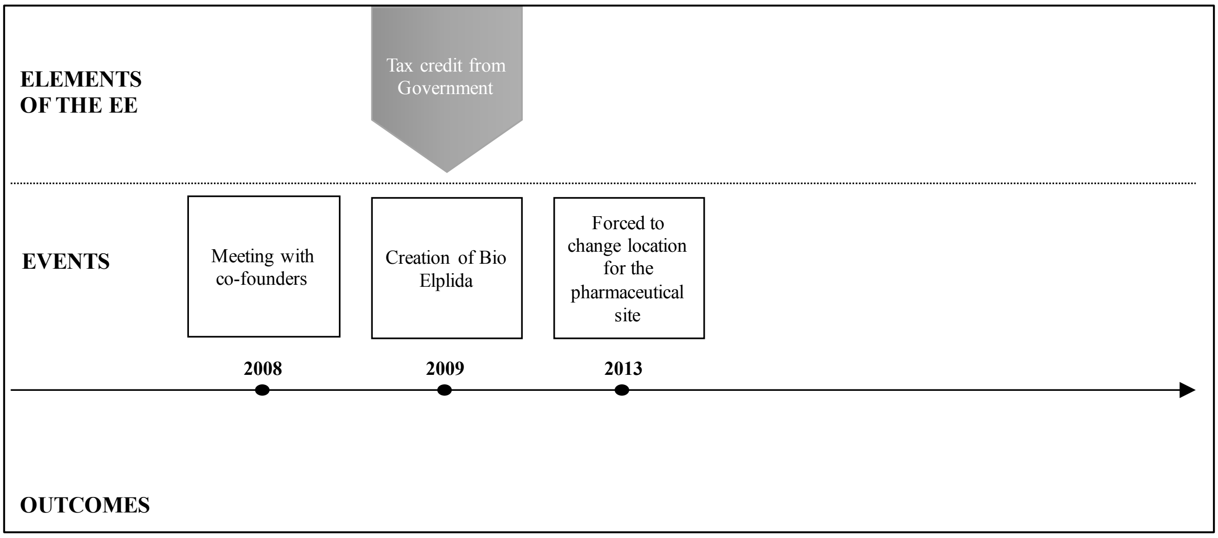
After the initial steps is easy to connect the interaction with the outcomes, but after few years the firm starts to reach first results in terms of research and development which is very difficult to allocate to a single event and it could be more related to the experience gained during their collaborations and the presence of the inventor-founder Pierre Falson which oversee the scientific achievements. These achievements find their most expression in 2014 and 2015 when Calixar develops three new patents with the participation of Université Lyon1, Hospices Civils de Lyon and Inserm.

In 2015, publishes another patent with Mérial, Genostar, VetagroSup and Institute Pasteur and strong if its results receive another round of investments for another million of euro which allow the firm to open a new business office in the Cambridge area in the state of Massachusetts strengthening its presence abroad.

3.3.7. Bio Elpida

Behind Bio Elpida, there is the entrepreneurial drive of Dr.Gilles Devillers which is trained in pharmacy and he holds a master science degree in engineering and an MBA in finance, marketing and innovation. Dr.Devillers after 20 years of work experience in big pharmaceutical multinationals at first and start-ups in England. Is during his last experience as a business development manager that grew the awareness that starting up his venture was the right move to do. In 2008Dr.Devillers leaves his job and moves to Lyon where together with his business partner Dr BenoîtPinteur, found Bioelpida.

Figure 3.7. Bio Elpidas's development



Bioelpida is CMO (Contract Manufacturing Organization) specialized in cell therapy, prokaryotes, molecular antibodies, filler finish and other services. Bioelpida works with pharmaceutical companies that do not have the resources or simply find it more convenient to sub-contract the production of their drugs during the clinical trials. In fact, Bioelpida so far produces pharmaceutical compounds only destined for trials on humans. For most pharmaceutical companies it is convenient because the regulations for the manufacturing of pharmaceutical products are very costly and requires specialized equipment.

Since it's creation Bioelpida saw a steady growth with stable financial resources coming from a UK based biotech company and steadily increasing revenues. The main event is ascribable to 2013 when they were forced to move the location of the company, as a result, there were delays and Bioelpida decided to but the new physical location rather than sign a rental contract. Now the company's clients are moving forward with the clinical trials so Bioelpida is now planning to expand its production sites.

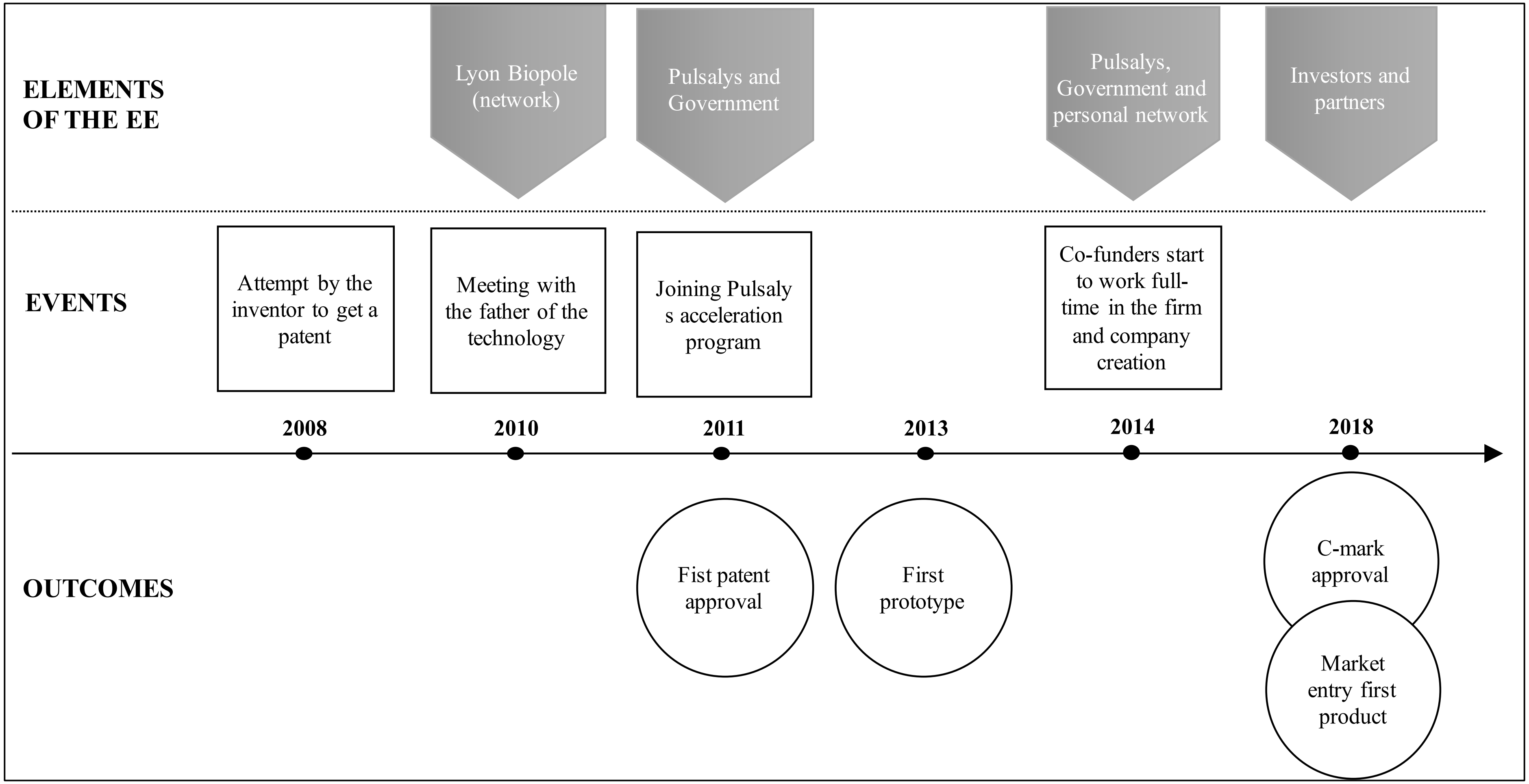
3.3.8. Neolys Diagnostics

Neolys Diagnostics develops innovative and efficient solutions for the reduction of side effects in radiotherapy treatments. The business is concentrated on mainly four pillars, the first is the development of capsules that applied to machines for radiotherapy are able to establish in advance if a patient will show side effects after the treatment. This technique is totally revolutionary because right now there is no in-advance evaluation of possible complications causing to at least the 20% of the individuals threated to develop serious side-effects. The second pillar is the analysis is the mapping of the patient's side effects going to radiotherapy and to determine the right dosage and intensity of the treatment for a specific patient. This evaluation happens through a biopsy of a small portion of patient's tissue. This analysis is very rare and there are few laboratories running this tests, for this reason, Neolys is planning to also have a laboratory for the European market analysis. The third pillar is represented by the software that helps therapists in combining all the information and being able to target in an easier way the cancer cells during radiotherapy treatments.

Neolys Diagnostics as Bioelpida has been funded by Dr Gilles Devillers together with Dr Nicolas Foray, and Dr Julien Gillet-Daubin all three having part of the same Devillers' network. Dr Foray is the scientist behind the technology and the meeting with Dr Devillers took place in 2010 at the organization that after became the Lyonbiopole. The struggle started in 2008 when the inventor Dr Foray tried to get the patent of his discovery but the initial attempt with the government (in France the invention can be patented by the university, but must be approved by the central authorities) failed. After the meeting between the two started to come the grants and support from Pulsalys and the Government with the incentives, as a result in 2011 Neolys gets the first patent approval.

After two other years of work, in 2013 was produced the first prototype and in 2014 the commitment of the co-founders became greater when they received more support from private investors and public institutions. This round of financing allowed the co-founders to work full time in the firm bringing the company to its first C-mark approval and entrance in the market in 2018.

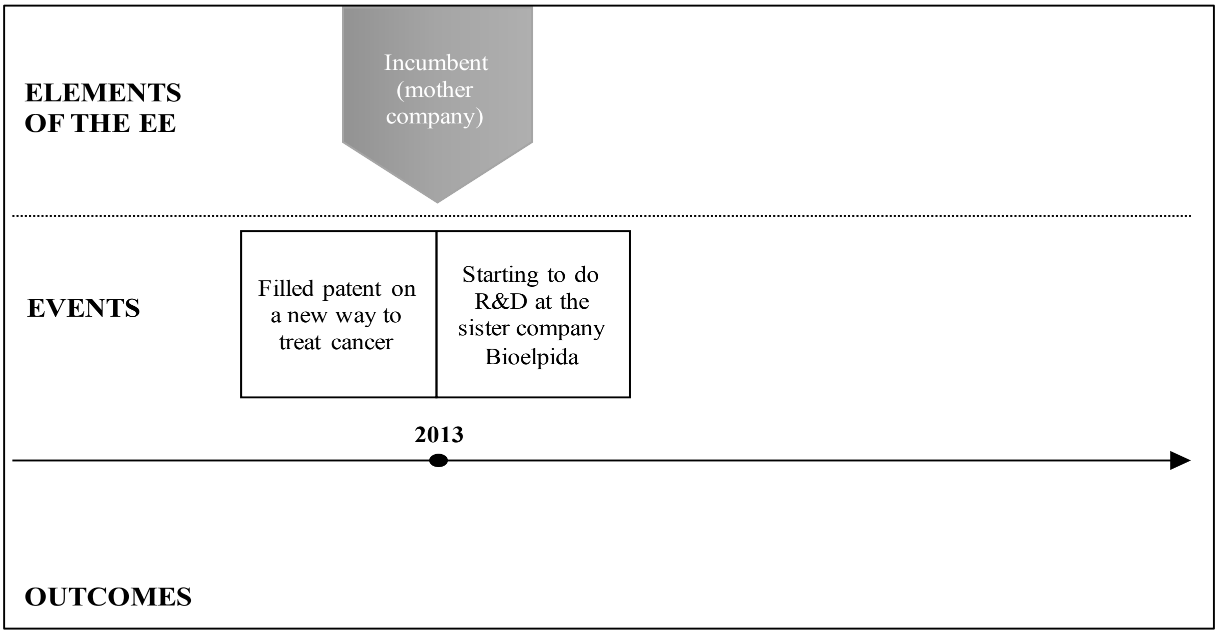
Figure 3.8. Neolys's development



3.3.9. CFL Biotech

CFL biotech is the last of the three firms founded by Dr Gilles Devillers and his partners. Devillers with his partner Dr BenoîtPinteur developed this idea through their holding company in 2013 when they decided to fill a patent. From now on this firm is developing its R&D processes within the bigger company of the three founded which is Bio Elpida which resources are partially used for CFL. The firm operates in the field of immunotherapy to treat the most resistant types of cancerous cells. CFL base its science on an existing technology invented in 1923 which targets resistant cells and activate the immune system in order to expel them.

Figure 3.9. CFL's development

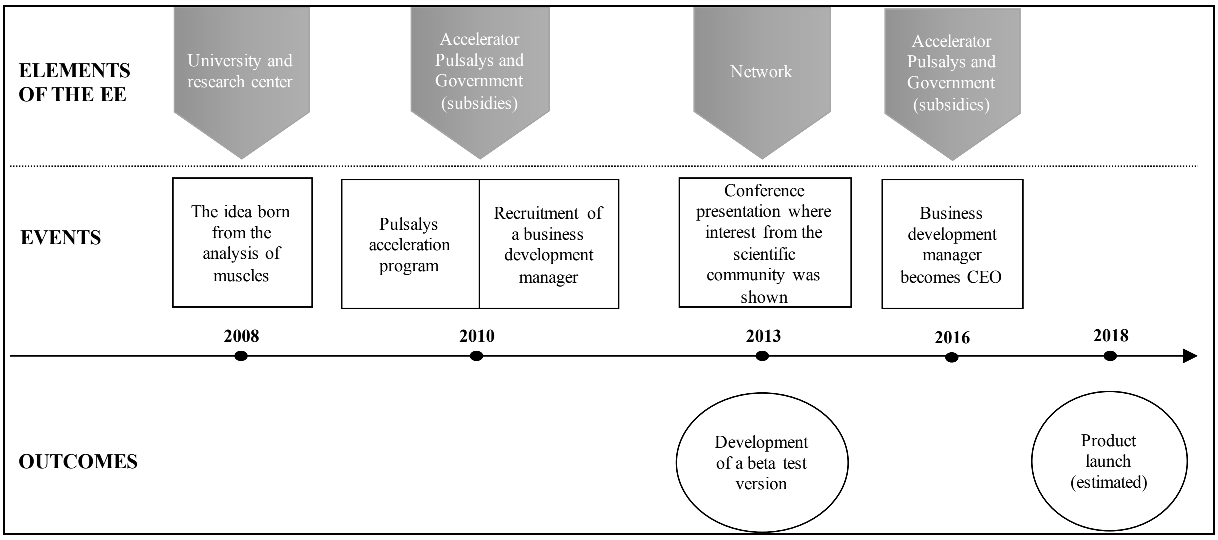


3.3.10. Carpaccio

Carpaccio is an online service for automatic analysis of microscope images of muscle cross-sections. This operation usually made manually saves a lot of time to researchers and laboratory analyst in analyzing muscle fibers that nowadays are used to do all the counting manually investing a lot of time in counting and cataloguing thousands of fibers.

Dr Brian B. Rudkin is the man behind the idea, is an expert in molecular and cellular neural biology in related cancers. In 2008, during a research on a new molecule expressed as a protein, which could impact upon muscles and other cell types conferring positive physiological response, DrRudkin had to study muscles in order to understand the response of this molecule on muscles. Not being an expert in muscle analysis learned pretty soon that the entire operation takes days to complete with current technologies.

Figure 3.10. Carpaccio's development



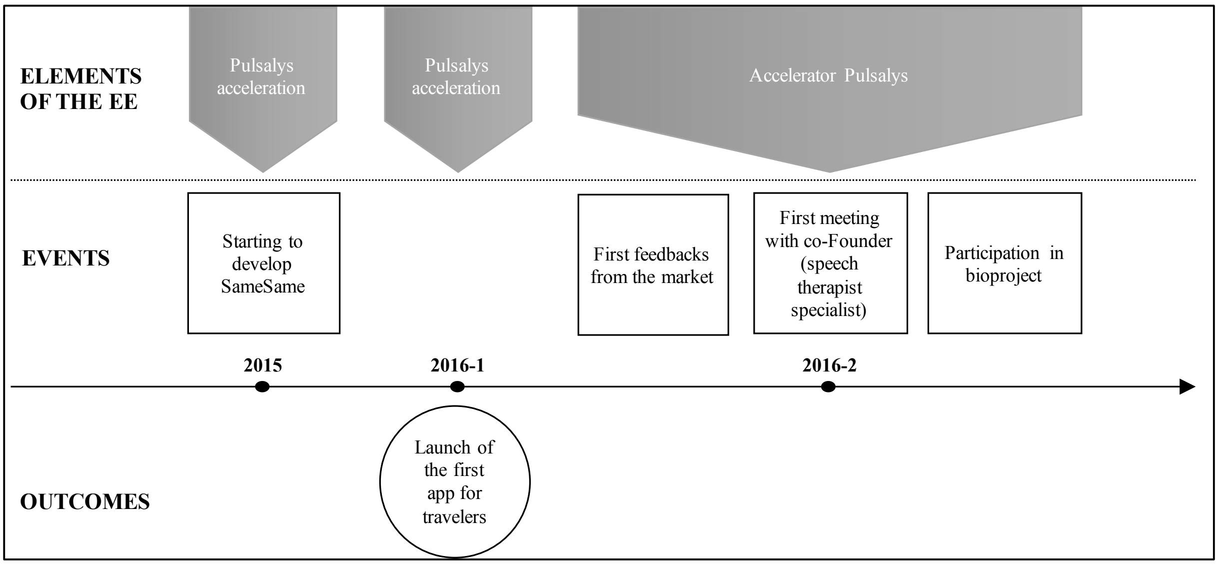
From that experience, Dr Rudkin started to formulate his business venture until in 2010 had the chance to join the firm accelerator Pulsalys that supporting his idea was able to recruit his development manager Dr Rudy Marty which is a physicist with several years of research experience. Within the Pulsalys framework and the support from the Government's incentives the venture started to progress but without the formal foundation to maintain the status of the young start-up which allows getting access to governmental support.

Over the year the only employee, Dr Marty worked full time on the Carpaccio software meanwhile Dr Rudkin continued his promotion of the idea to conferences and meetings catching the attention of the scientific community. The support from institutions and network allowed them in 2013 to obtain the first beta test version. In 2016, Dr Marty became CEO of the company and in 2018 the first launch of the Carpaccio's platform is planned.

3.3.11. SameSame

SameSame is a start-up project which was created initially as a travelling application in which pictures could be shown on the screen and repeated in the specific native language that a traveller needs. The project was started in 2015 by its founder Mr Alexandre Boulmé who had communication troubles in China during his studies and therefore developed this idea.

Figure 3.11. SameSame's development



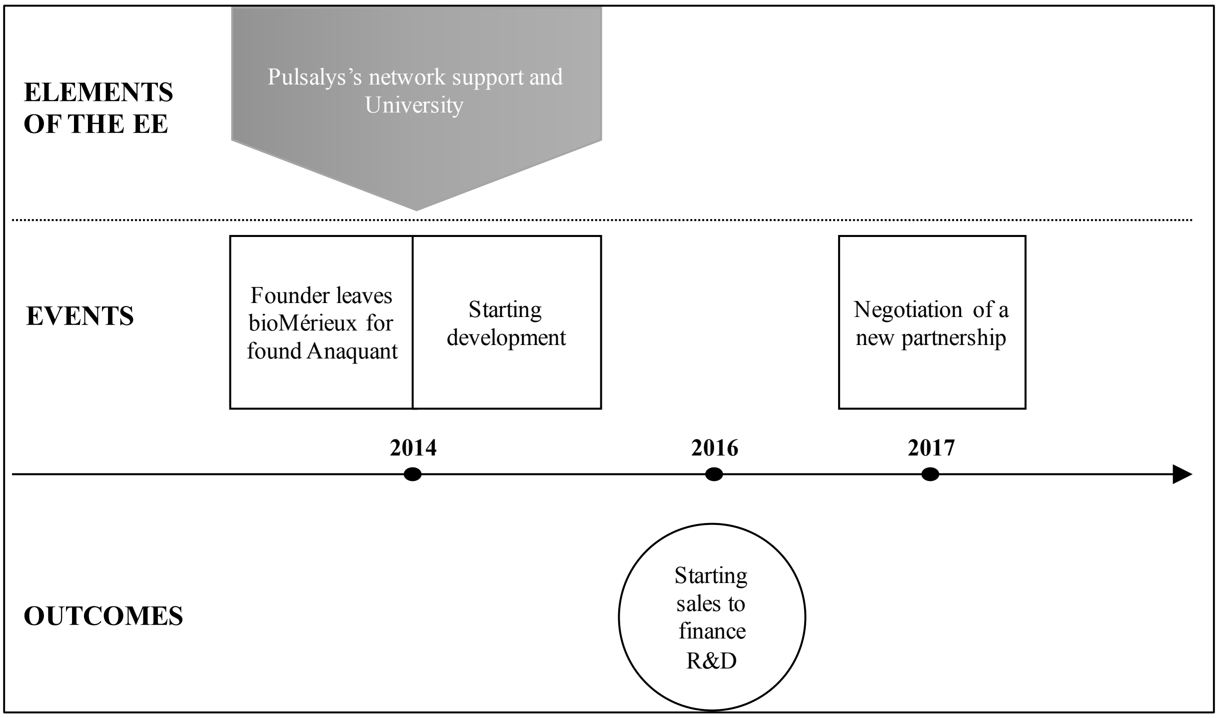
Coming back to Europe, Mr.Boulmé decided to establish his activities in Lyon after being accepted by the Pulsalys accelerator. That helped him to find the resources to launch the first version of the app SameSame. After a few weeks on the market, Boulmé discovered that the app did not have much success among travellers but had quite results among speech therapists that used his app to communicate with their patients. In 2016, the shift of the business had definitely its turn when Boulmé met his co-founder, a French speech therapist located in another city.

Since then the two co-founders are developing SameSame as an application for aphasia treatment. Aphasia is a person's condition which does not allow people affected by brain damages to fully comprehend and formulate language. Since then SameSame is receiving support from Pulsalys and it's still developing its business model and looking for financial support.

3.3.12. Anaquant

Anaquant's co-founder is Dr Tangui Fortin an expert in biomarker validation using mass-spectrometer which after working at the bioMérieux and at the University of Lyon for few years decided to leave his jobs and in 2014 Anaquant was formally born. The decision to establish this company was taken together with his Professor and co-founder Dr Jerome Loren that during his P.hDin analytical sciences introduced him to the mass-spectrometry analysis and already had experience is service providing.

Figure 3.12. Anaquant's development

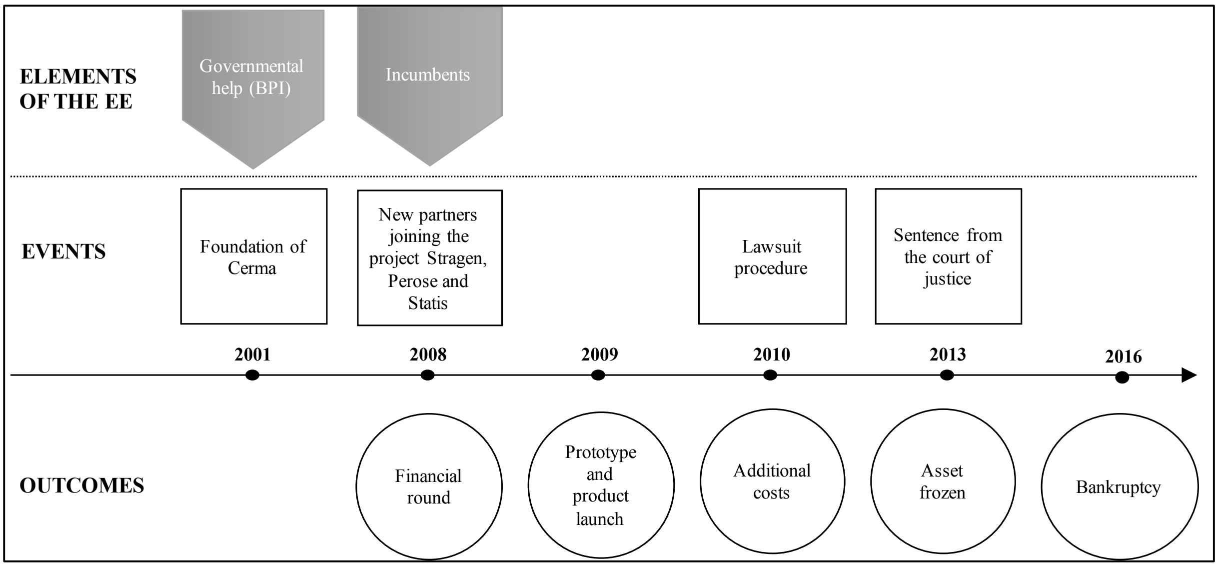


Since then Dr Fortin started the development of the firm based on a two-steps business model: the first is the service providing through mass-spectrometry analysis and the second is the production of standard proteins for the analysis. Under the support of the University at the Institute of analytical sciences and Pulsalys, Anaquant was able to start the business and begin to generate revenues in 2016. In 2017, Anaquant has seven employees and due to the R&D efforts was able to place new products in the market selling personalized beads.

3.3.13. Cerma

Cerma and Cerma Vein, which is part of the same group Cerma, is a company working in the medical devices field. The idea behind joining of these companies was of Dr Emile Hiltbrand a doctor now retired, working in the nuclear medicine field. The company was founded by him one of his colleagues at the hospital of Geneva, Switzerland, and a surgeon established in Chamonix in France. The Cerma's technology was based on the production of catheters able to infiltrate, at first vapour, and later drugs for cancer treatment. The project started in 2001 when Cerma was born and initially received a substantial investment from the BPI, the bank for innovation investments in France, which allowed them to develop their idea and patent the product.

Figure 3.13. Carma's development



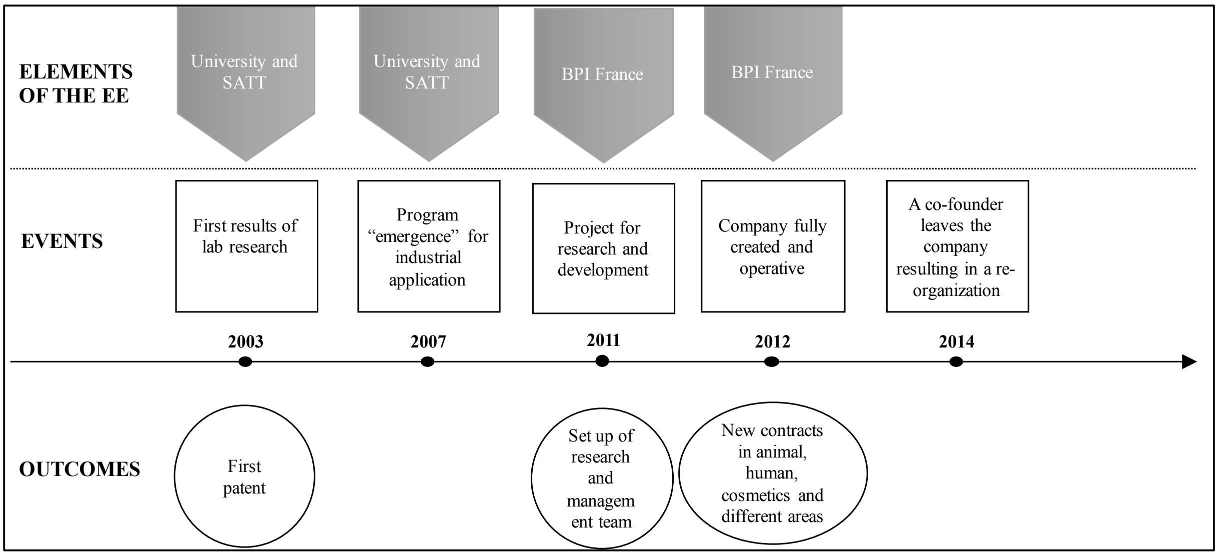
In 2008 after 7 years of R&D developments, Cerma got the attention of big players such as Stragem, Perose and Statis which decided to invest in this venture. After one year Cerma was ready with prototyping and in the same year started to sell creating a European network with several distributors across the country. In 2010, a lawsuit procedure advanced by the development manager that claimed to be fired unfairly causing a collapse of the already fragile financial structure. In 2013, a sentence from the Court of Justice caused the freezing of their assets and in 2016 bankruptcy occurred. During this time of struggle, Cerma tried to get help from their investors but they didn't receive any more support, for this reason, they had to shut down the business.

3.3.14. LPS-Bioscience

LPS is a Biotech Contract Research Organization specialized in bacterial endotoxins. Mainly operates in the vaccine industry, in vitro diagnostic, cosmetic, and medical devices making endotoxins more accessible to pharmaceutical companies. It is located in the southern part of Paris and works closely with the Lyon area due to the multitudes of clients that are active in Lyon.

LPS started its journey as many biotech companies do at the laboratory. In 2003 the first patent was developed with the collaboration of the SATT (Sociétésd' Accélérationdu Transfert de Technologies) framework. In 2007 the company through the support of the BPI (the French bank for innovation) started a new path for company creation. The project called “emergence” aimed at the identification of possible application of scientific discoveries and in the specific they looked at the possible commercial application for LPS patent.

Figure 3.14. LPS’s development

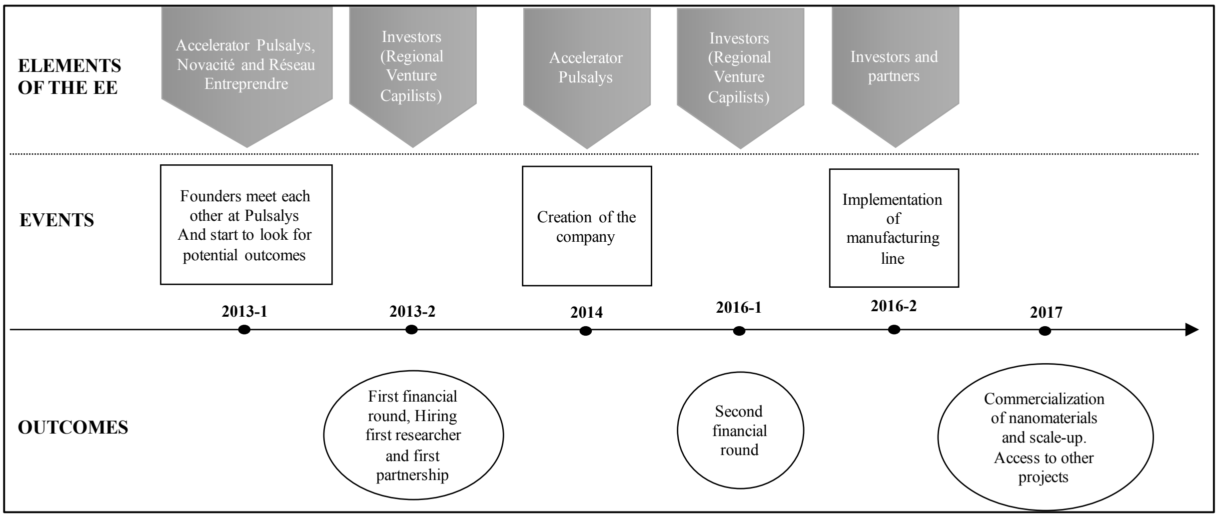


In 2011, LPS was able to gain access to another program with BPI for the creation and development of the firm. One of the co-founders Dr Martine Caroff which were head of the research lab created a team and started to develop the company. In 2012 Dr Martine Caroff together with Dr Jean-Marc Cavaillon and Dr Frederic Caroffand a post-doc researcher joined and the company was formally created and operative. In the same year of foundation, LPS was able to obtain important contracts covering different areas such as animal and human care, and cosmetics. In 2014, the firm had to re-organize after one of the co-founders left the company.

3.3.15. Mathym

Mathym is a nanotechnology company which is specialized in inorganic nanoparticles dispersed in liquids. Mathym is dedicated to the development, manufacturing and commercialization of its nanomaterials within the biomedical field. The two co-founders Dr Julien Alberici and Dr Frederic Chaput firstly met in 2013 at Pulsalys, where Dr Alberici a business expert was looking for entrepreneurial opportunities and Dr Chaput a researcher at the CNRS (Centre national de la Recherches Scientifique) was looking for someone able to bring his technology to the market.

Figure 3.15. Mathym's development



The two immediately started to work together and were able, in the same year, to get the first round of investments from a regional venture capitalist that allowed them to hire the first researcher, to have a biomedical division and sign the first industrial partnership. In 2014thanks to Pulsalys program they were able to formally establish Mathym and one year and a half later in 2016, they reached two important steps: raising a second financial round and because of that the implementation of a manufacturing line. In 2017, Mathym was able to scale-up its nanomaterials' production and is planning to commercialize three more types of nanomaterials by 2020 combined with several R&D projects.

3.4. ANALYSIS OF THE ENTREPRENEURIAL ECOSYSTEM

A list of the main events that took place in firms' development were codified and are showed in appendix 1. Eight main categories are identified: Acceleration program, External contingency, Formal foundation, Founders, Human capital, Investors and Partners, Network and R&D/development. The categories and the descriptions were analyzed in more details in the next sections. Also, elements of the EE interacting with firms were distinguished in Accelerators, Government, Incumbent Firm, Investors & Partners, Network and University and Research Centers. These were the main factors identified in the Lyon's ecosystem that, through interactions, had a major impact on firm's development bringing leading to a set of performances such as Clinical trial phase, Contingency, Funds/Grants, Growth in human resources, Growth in sales, Internationalization, Market entry, Patent, Prototype.

Since the focus of this research was to understand how the actors of the EE bring their contribution to NSBFs' development, in the following paragraphs each element is described separately, outlining events that occurred and hypothetical impact on NSBFs' performances. Prior to the in-depth analysis, the following statements indicate the effectiveness of the EE, outlining how the area of Lyon with its supporting ecosystem and showing how actors seem to be the right place to establish an NSBF. The reasons why this ecosystem is a mainstream example of "good" ecosystem are several; first of all, it's a flourishing and growing area:

> *Bio Elpida. "When I arrived in Lyon when we created Bio Elpida were around 60 biotech companies in Lyon, we are more than 200 now big or small, this among the 60 start-ups we were more established like Sanofi and now a lot smaller start-ups"*

Another important characteristic is the entrepreneurial spirit:

> *Anaquant. "Lyon it's a very good city to create to found a company because you have a lot of help like Pulsalys the chamber of commerce you also have the innovative, in the science area here in Lyon you have the Lyonbiopole cluster and the so it's very dynamic, the city is very dynamic and for me is a good place to found a company in science"*

The specificity and the limited dimension of the area, Lyon is very much concentrated on biotech and immunology, for this reason companies are attracted by this area for the center of excellence that represents and the network of different actors operating in the area is a collaborative and established network, the proximity of Switzerland as homeland of many multinational corporations increases the strangeness of the ecosystem:

> *Bio Elpida. ...I moved to Lyon specifically for what they are doing, it is just the place to be and it's easy, everybody helped here… … specific in biotech and oncology.*

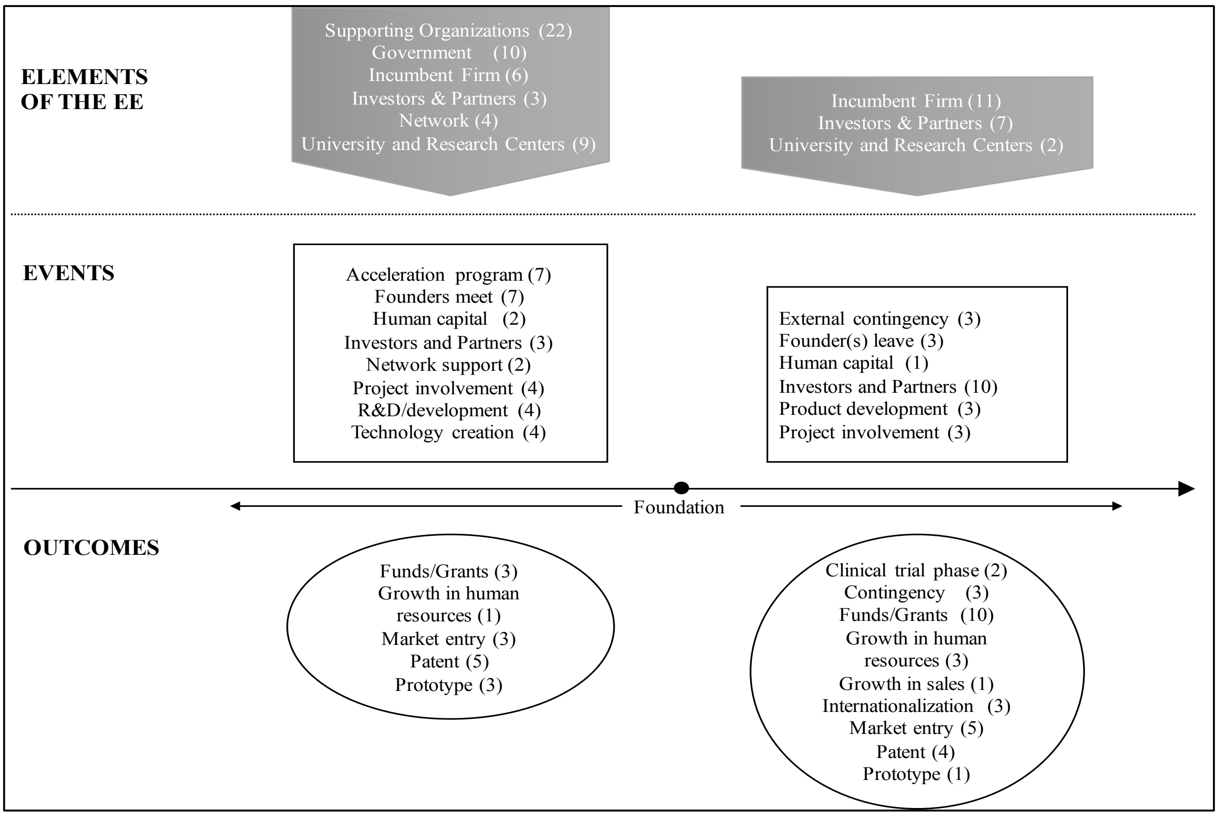
> *Bioxis. "Specially for example we have some problems with the equipment so sometime you have to call someone to repair and we need to quickly do it, it happens that you call and they say okay maybe we can come tomorrow or even this morning because we are in Sanofi we can come in the afternoon. There is a very big biotech cluster that even in Paris you don't have it, the problem with Paris of course you have even bigger companies in biotech but it is very spread everywhere in Paris and Paris is very large, here in Lyon is very small you it's very convenient to meet people and to*

have this kind of relationships everybody knows somebody let's say and at least even you don't know people you could ask and it's in a very short to meet them to organize things and then we have also Genevewhich is not that too far and also Switzerland in general is also a huge biotech cluster"

Summarily, from the evidence collected, Lyon ecosystem is a representative example of "good" ecosystem for different reasons: growing number of new firms, high entrepreneurial orientation, specificity, limited dimension, well-established network and geographical position. As a conclusion, the Lyon EE is a representative example of the subjected analysis.

From the analysis emerged a clear distinction between two periods in firm development, the first if a period before formal foundation in which the firm has not yet completed its genesis. Typical is the situation in which a scientist who has scientific discoveries but no clear idea on how to commercialize it. In this phase, the venture is a mere project in an embryonic stage. The second phase is related to after formal foundation, in this situation the firm is active and there is a clear plan to commercialize the scientific discovery or technology. For the previous reasons a representation of the main elements of the analysis is shown in figure 3.16.

Figure 3.16. Elements of the analysis



Source: author's elaboration

3.4.1. Accelerators

The incubators and cluster associations in the entrepreneurial area of Lyon are crucial to start new science businesses. Critical events that occurred related to accelerators are mainly related to the first phase of firms' development. At this stage NSBFs are not formally founded yet and typically are participating in an incubation process and they assume the form of project or business idea. As it is observable from the figure, accelerators elements and related events concerning NSBFs' development disappear in the right quadrant of the figure 1 where the second stage of firm's development is showed.

> *ABL. "For the creation foundation of the company clearly GrandLyon, Lyonbiopole have been extremely important to help in building these projects, now that we are part of the larger group their role for us is probably lower"*

As expected, many key events are then related to the phase of acceleration programs that these organizations provide. Together with acceleration programs important events for firm's development are related to founders. These organizations were in many occasions detrimental for the founders to meet each other in the occasion of events organized during the incubation process. NSBFs, as observed from the case studies, is most of the time composed by at least two persons, one is the father of the scientific discovery or technology and the other is a business person, often with a scientific background, who takes charge of the coordination of the venture.

> *Calixar. "The advantage of Lyonbiopole was clear because at the beginning as we started in the incubator of Lyon… … you can propose your project to the incubators and incubators assessing your project can help you to grow the idea to grow the project before you create the project and thanks to the when I joined Calixar. I contacted the incubator to know if they had some projects that looked for business developer or for future CEO so they propose me to meet some teams which looked for this kind of people and I met this two researchers and we fit together and I decided to take the project as project leader at the beginning to be the future CEO and because the project involved academic research from the CNRS, at the beginning we can grow the project inside the incubator... ...Because we were members of this incubators we*

were member of the Lyonbiopole cluster so before creating the company we were also part of the cluster's network, so this was the big advantage."

Neolys. "I met the founder of the technology in a network between Lyonbiopole and Pulsalys, the idea of these meetings was to have scientists presenting their projects and industrial people hearing and collaborating, I saw a presentation that was wow! So I decided I would do something with that"

Accelerators had the pivotal role to turn these ideas or projects into nascent organizations; in fact, many events related to accelerators are the formal foundation. There is a reflection of the performances that these firms experienced during this period such as receiving grants mainly from these institutions, or making advancements in terms of research achievements in filing patents and progress the R&D. It is possible to state that interactions with business accelerators, in some cases specialized in biotech or cancer treatment helped the nascent science venture to reach the first milestones in firm accomplishments in terms of R&D and project development.

Business incubators and networks in the entrepreneurial ecosystem are important actors as described above, but some limitations regarding their functions were outlined by the interviewees. First, these institutions lack of specialization, this is mainly ascribable to the main goal of these entities which are broad and not very specific for a business. On the other side these accelerators helped different kind of businesses supporting a bigger crowd of entrepreneurs operating in different fields such as technology, manufacturing, services etc. Interviewees feel like specialized supporting systems for science-based sectors should be implemented.

The second limitation is related to the high set of standards and requirements that they have to meet: a private partner is required to join some services such as grants for patent development and most of the times these new ventures they are asked to pay back the help received, for example in a form of exclusive license fee for the patents they have helped to develop.

Bioxis. "They did not finance us they did not give us one penny so for me is mainly limitations are like two ways, the first they are nor scientific neither in the business so that's difficult to be always in the middle. Another similar thing for me the limitation is the fact that we have a new rule saying that when we call SATT we have to be at *least financed 50% by private sector I think and might be beneficiary in five or ten years and currently this what could not work for me because even if companies pay fees to universities (referring to patents) of course it could work sometimes with some patents that are huge but not every time. Asking this organization, a grant is stupid because it gives them a lot of pressure. I had a discussion with my IP layers and they told me yeah now it's better to negotiate with this big groups that with these people because they are tough in negotiation, they need money because they need to show like it's in the law they need like 50% revenue from the industry and that's quite out for them"*

As outlined before and from the following quote, business incubators and networks at the inception of the firm seems to have a are strong impact. However, after a specific period, when the first steps for the initiation of the venture are taken, their intervention loses relevance.

3.4.2. Government

As for the accelerators, government intervention seems very strong at the beginning before formal foundation. Most of the interviewees outlined how France and the French government helped them with its polices to create a new innovative company.

LPS. "The credit tax for research is really important for us because we are doing a lot of research and 30% of the time that we stand on this research is reimbursed by the state so it's really important""

Alaxia. "Basically to start a biotech company it's very easy. We have a good environment to do so. After that the problem is to find investors. Because we have a huge support from the tax credit and BPI and I think that are very very good"

Calixar. "In France when you create a company science-based company with certain quantity of R&D and if you are totally independent, not totally but we have this specific status you know this status of in French is -jeune entreprise innovante- innovative young company, this status is for all the industrial fields, biotech, all fields… …This status to use advantages in terms of taxes helps a lot…

Government plays a fundamental role for the pushing of innovation also from the employees point of view because allows innovative firms to hire highly skilled employees, for example holding a PhD, with tax incentives.

Carpaccio. "So this is a particularity of France where people such as Rudy which was allowed to have unemployed was also allowed to have this particular status to work on projects which is a founder of a company"

Mathym. "there is a big advantage to be located in France, that's called the fiscal paradise for the creation of innovative company, for the first eight years of the after the creation of the company you have advantages in terms of tax, instead of paying something like 25% on wages we are paying 22% on wages as tax, we've got some research tax credit which means for example if we are employing in France new PhD people we got some tax credit equal to their wage, so that means for three years their more or less is true, we got many many ways of subsidies so that's really easy to create an innovative company"

Under the umbrella of SATT (Les Sociétés d'Accélération du Transfert de Technologies) and BPI France, the bank for innovation and the tax credit incentives that an innovative firm can benefit provides to the country a good environment to start a new and innovative venture. Many respondents benefited from these kinds of incentives and funds, which are considered them as crucial to begin with the process of company creation not only the role of seed money provider but also as a guarantee that the business as potential in relation to private investors which are anyway needed at the certain point of development.

LPS. "France It is the bank of innovation and the maturation program was called let me remind me, "emergence" so they did it in 2007 and during a few years they started a program where they had some contacts, information with companies to see whether there was a business, possible business with this technology"

Mathym."…The role of BPI the French public bank, is major actor in financing and supporting innovation and creation of innovative companies, this is very important to all innovative companies and everybody will talk about BPI, it's really a help we received many loans, many subsidies many, they are very central very useful, very supportive for work in such as Mathym"

Together incentives and funds from the government are connected to performances, as for accelerators, of new patents and receiving funds. In addition, government support arises in superior growth of human resources.

3.4.3. Incumbent Firm

Differently for the previous, incumbents' interactions have a stronger impact during the second phase rather than the first. But some interactions are registered in the initial phase as well. Prior to foundation, point of interactions with incumbent firms are mainly related to the involvement of these organization in projects that led to spin-offs or spun-outs of new firms. An example is provided from the following quotation.

> *Stragen. "So Stragen services is a very small service provider in medical affairs and for pharmacovigilance mainly work for pharmaceutical companies, the history of Stragen service is from a small pharmaceutical group which is the main business is oriented in generic products… … we created this Stragen Services which is a small affiliate of Stragen group dedicated to services in this area, so we are implemented here the group is located management is located in Switzerland in Geneva and we kept Stragen Services here in France because the European Union, the fact that one working in pharmacovigilance responsible person for pharmacovigilance due to regulation must be established in the European Community"*

Despite during the initial phase incumbents' presence is mainly related to creation of new science venture due to spin off activities, after foundation their interactions are related to joined participation in projects providing network opportunities to NSBFs and acquisitions or participations in these nascent firms. The participation or acquisition brings to the venture an increased amount of resources and an extended network to benefit from.

> *Alaxia. "Alaxia is a biotech R&D recording lab. Biotech is done here but regarding C&C (chemistry manufacturing and control of the drug) is done from Geneva. Regarding regulatory is done from Geneva, as we are working with Stragen we use a headquarter skills in Geneva where a pool of pharmacists is there. Regulatory stuff there"*

Cerma. "We got 9 millions from BPI, we presented also project to private companies and we come with companies, Transgene, Statis and Perose and us we had to find 11 millions and the other company big company"

Case4. "[Do you have collaborations with big corporations right now?] That's what we are looking for, so we are in contact with companies, with big pharmas but at the moment no, the idea would be to have one of these companies as next steps as I was mentioning before, we are discussing with them"

Calixar. "R&D it's a long process which multistep of assessments so we have the chance to get some grants like that through this process in 2012 in developing a new vaccine against leptospirosis that's why filed a patent with other partners for this consortium of this grant, and we were leader in the proposal which was big company Sanofi group at the origin and so the French government say okay we the project is okay so after they decided how to finance each partner so we were financed by the community of the city of Lyon in fact… …It's very useful because it's very difficult to advance, don't have any you have some grants but it's rare you need to set up a collaborative project and it is difficult to hire directly grants if you are not supported by big companies in these collaborative projects you need to put some guarantees on the table to have grants and most of the time it's more loans you need to reimburse grants, grants is more for academic teams but it's becoming rare that's why French companies try to have grants from European Union, it's very difficult below 10% the chance, it's a lot of work we tried to get these subsidies but it's hard reach in getting subsidies within European schemes, we succeeded in gaining subsidies grants from French government but because we were in specific collaborative projects with big companies you know"

In this particular context, the presence of the family Mérieux under the umbrella of the Institut Mérieux in the area of Lyon shapes the entire entrepreneurial ecosystem, through history this group has created a network of excellence through partnerships, participation and acquisitions of firms becoming a World leader. This presence is very much stronger in Lyon and as it is observable, many firms in our sample have some connections in some way with the Mérieux group.

ABL. "ABL belongs to a larger group which is based in Lyon and it's a prestigious group and we are proud of it which is Institut Mérieux. I don't want to give you wrong numbers, we are a range of 13.000 or 15.000 stuff members which encompasses several companies including the world leader in molecular diagnostics of infection diseases called bioMérieux so it has offices and subsidiaries in like 140 countries worldwide, it includes also a company called Mérieux Nutriscience which is a World leader again in food safety… …so it includes also Transgene our former founder focuses on immunotherapies, cancer and infection diseases. It includes also an investing firm called Mérieux Développement. The roots of Institut Mérieuxis very deep they were the original founders, Sanofi Pasteur a world leader in Human vaccines, they also founded some years ago Merial which is also part of BoehringerIngelheimwhich is a world leader in animal vaccines and many many other companies"

Bioxis. "In Lyon mostly they are linked to Sanofi or to bioMérieuxthen most of investors are based in Paris and like marketing people, journalists, everything mostly based in Paris, so marketing better to be in Paris but for R&D Lyon is perfect"

From the analysis of the main events and performances, is possible to identify incumbent firms as one of the main players in the entrepreneurial ecosystem from which nascent SBFs benefit. In fact, interactions with incumbents bring the formation of new firms or support their development by participation, acquisition or joint projects. Performances associated to incumbents are initiation of clinical trial phase, receiving of funds, growth in human resources and internationalization. Interactions with incumbent not only help NSBFs to acquire resources but also allow the extension of the firm from European base to an international one.

3.4.4. Investors & Partners

Among investors and partners are considered those entities which are not incumbent firms or public institutions such as venture capitalists, investments funds, business angels, etc. that invest in the development of scientific discoveries. These actors are mostly present after the formal foundation of the firm, in the initial phase the key events for firm's development are mostly related to the participation of the foundation of the firm. Later these actors are related to funds and access to resources.

Case4. "In terms of investors Lyon is not that big place, there are big venture capitalists called Eclosionthat invested in the firm… …other constrains in the development of the drug is financing, it's very the key thing, because it's not easy to find financing and because we are a lot of companies actually and so the competition it's quite hard… …there are so many, because we are working in oncology, oncology is very a hot topic so there is money for oncology investors that want to invest in it but on the other hand it's really crowded field also"

3.4.5. Network

As network in this analysis is referred mainly to personal network or network of scientists, it is notable to consider that the accelerators analyzed before have a strong network effect due to the numerous initiatives that they promote. In the analysis, these two types of network have been kept separate on purpose in order to clearly separate these entities from other forms of networks that can origin also from outside the perimeter of the EE. Main events related to network are mainly verified during the initial stage and mostly related to the identification of an investor and meeting a co-founder. After this initial stage, the network was not found involved anymore as firm's development element.

3.4.6. University and Research Centers

Universities and research centers are key factors that make their presence valuable throughout the all life of the NSBF. The new ventures having a strong orientation toward science, they are very much related to universities and research centers wherein most of the situations the scientific discovery or technology, that is the core of the new venture's business, has been developed there. In fact, in most of the cases, the scientist father of the idea is a researcher or associate to one of these institutions. These institutions are the key to develop the science underpinning the venture participating actively in the R&D process and filling out numerous patents. Among these institutions is possible to observe the University of Lyon and the National Center for Scientific Research.

Key events related to university and research centers regards mainly the formal foundation, participating actively in the venture, the development of the technology, where the scientist-founder is involved in the research at the center, and sometimes related to funds where they contribute economically to the new venture. As a consequence, performance indicators are mainly patents, playing the role of partner or silent partner in the scientific discoveries.

LPS. "At the beginning it was a university laboratory, with technology that was attempted in 2003 and the patent was done because there was the industrial saying one technique of the lab was interested and could be patented, after few years the patent was done and the SATT"

Calixar. "With investors in R&D internal, we used to patent at the origin from the national research center, so we have exclusive license for these two patents and after we developed other two patents"

Neolys. "(talking about the co-founder) he is not paid by the company is still doing research, and what we do we have a collaboration agreement, everything that is going out of the research center is leading the IP is coming into this and all the data we generate comes back to the research center for Nicolas to build big database and understand more things and so it's a virtuous circle, he knows exactly what we are doing and he prepares the next domain of activities"

Mathym. "My co-founder is researcher from CNRS which means he is fully employed by CNRS, it is still the case today, there is a possibility for French researchers to allocate money for full time company creation, if you are inventor of a patent which is exploited by a company which you are participating into the creation you have the right to spend 20% of your time dedicating to the company, so he remains CNRS researcher and employee, he is not fully employed by Mathym but he can spend some time working here"

Bioxis. "I founded Bioxis Pharmaceuticals in 2010 currently it was thorough meeting with two professors at Lyon. They were working on healing technology based on chitosan biopolymers and my idea was to use what they used to do for wound healing to derma filler, so during the first two years I finalized just the proof of concept with some low money with founds and my money too and I was still working so in the beginning was very strong partnership with Lyon University, Center of National of Scientific Research CNRS, and also Pulsalys which was in charge of managing this *collaboration. Then at the end of these two years we got the first patent and proof of concept that we shared with this university"*

Also the resources that these two key actors provide are of huge impact, in fact many new SBFs have scares resources but the two are optimal in providing laboratories, facilities and the knowledge from the patents they develop.

Case4. "The origin of the academic lab is based in Léon Bérard and it's still based in Saint Léon Bérard so since the beginning we are close to the Saint Léon Bérard not just in terms of location but in terms of interactions, so the Saint Léon Bérard helped us a lot in the past because we have for example we had the premises we are in today so we pay a rent for it but it's quite advantageous, great and the we can use infrastructures of the center for example you know there are for research very expensive materials and it can cost 100 thousands euros for you know very sophisticated complicated machines so we can use these machines we don't have to buy them so we had a lot of benefits from this close interaction in the center here. Also the clinical trial is based in the center here so it's really easy to interact with people from the center to follow up what's happening in the trial. So it's rather I would say a benefit from the interaction with the center more than Lyon area, of course there is Lyonbiopole and other potential companies we can work with so yes it's nice to be in this environment"

Anaquant. "The first main step for us is the possibility to be here at the institute of analytical sciences because it's very important and we have access to instruments and to mass spectrometer we have access; it costs around 300.000 euros so we have access to those instruments, is important for us of being here"

3.5. DISCUSSION

Previous studies on EE of Isenberg (2010, 2011), Feld (2012), World Economic Forum (2013), and Spigel (2017), provide a comprehensive list of characteristics that an EE should have in order to be successful. However, there is still few knowledges about the dynamics of the interactions between these elements and firms. The present study opens the debate on several aspects that policymakers and practitioners should consider, including possible areas for future studies while embracing the EE approach.

As it is showed in the findings section, the boundaries of the ecosystem vary according to time and the stage of the firm's development. SBFs, especially, NSBFs, need to accomplish the R&D process prior to their launch and operations in the market. In respect to other businesses, the R&D takes several years before completion (Morris et al., 2011; Parcharidis & Varsakelis, 2007); the R&D process usually starts years before foundation at research centers and laboratories where a first patent has been developed (Steffensen et al., 2000). During this stage, the EE successfully supports new SBFs in accomplishing important footsteps from the design of the commercialization of science to reaching scientific results.

First, this study proved that EE is anchored in the history of an area, which in this case is the history of Lyon, France. As mentioned above, there is a repetitive pattern that is seen at the center of the family Mérieux. The history of this family shaped distinctively the ecosystem, which is clearly the place to be for a new firm operating in biotechnologies and especially in the field of immunology. Big companies, universities and supporting institutions are in some way connected and even shape themselves around the center of excellence of the Mérieux family. Through the Institut Mérieux, SBFs invest in many new businesses and behold participations in several corporations in different medical fields. These findings, follow the vision that local dimension is a predominant aspect of the entrepreneurial activity and sustained by many authors (e.g. Acs et al., 2017; Anselin et al., 1997; Florida et al., 2017). For this reason, it is possible to assert that the characteristics and the major strengths of the EE depend directly on the historical achievements that shaped the actual local condition.

Despite its importance the local dimension loses its strengths in the long run. At the initial stage this dimension seems very strong but in a later stage becomes less relevant opening up to dimensions that consider broader prospective supporting authors such as Autio et al. (2018) which identify the entrepreneurial opportunities outside the local boundaries. Even though internationalization of NSBFs is verified for example in terms of participations with foreign corporations, commercialization in overseas markets, international projects, pushing for an internationalization of the firm's network; the analysis indicated that internationalization were baked by the Intitutute Mérial so that they can be seen as an extension of the Lyon's entrepreneurial ecosystem. All these cases point towards the importance of Intitutute Mérial in nurturing SBFs through the EE platform, to represent the much expected internationalization indicators. These findings again support the uniqueness of each territory and ecosystems should be shaped around local conditions (e.g. Isenberg, 2010; Feld, 2012) where excellences are particularly strong and evident.

Supporting organizations are successfully related to the possibility of firms to reach important steps of their life cycle such as filling new patents, moving forward with the R&D process, joining projects that foresee collaborations with incumbent firms or research centers and receiving funds in form of grants or seed money. These interactions are considered fundamental for the firms to move the initial steps; in particular, these organizations have the important role as facilitators speeding up consistently the formation of potential ventures. This supports authors that foresee supporting institutions such as business incubators as powerful policy instrument (e.g. Grandi and Grimaldi, 2005; McAdam and Marlow, 2008; Dee et al., 2011; UKBI, 2012).

After the initial phase, as shown previously in Figure 1, NSBFs have fewer interactions with local institutions and business changes consistently. The venture after the first stage reaches the status of formally founded and support from institutions becomes weaker. Typically, at this stage, important steps in R&D are completed making progress with patents and development of what is typically called “proof of concept”. At this stage, new ventures seek for investors in order to finance the further steps of product development. The EE plays again an important role from the institutional point of view through its actors such as the Lyonbiopole cluster, organizing activities with local and international investors but it’s influence is weaker in comparison to the incumbents’ position.

Government was cited many times as fundamental element for firm’s development especially at the initial stage. Government intervenes directly backing supporting institutions and indirectly though polices such as tax incentives that was cited several times by the interviewees. This interventions were cited during the initial stage but even though not directly mentioned, the Governmental intervention is present throughout the entire development process. What makes Government’s intervention very powerful is the interconnection of the actions with the ecosystem and its elements such as private sector (incumbents) and academia.

Due to their strong need for specific assets, at a later stage NSBFs show lack of complementary assets that only big corporations can compensate showing a high degree of complexity (Teece, 1986) that leads to inclusion of incumbent firms as necessary partners for new science-based ventures. Even after receiving financial support, firms struggle in progressing of the R&D. Similarly, SBFs takes longer time complete the process. In fact, events enhancing firm's development are mostly associated with investors seeking funds or actively engaging other investors, which in case of research centers contribute to not only monetary but also scientific discoveries. Typically, science firms employed in developing drugs are largely in need of money, thus concentrating for years only on R&D and accomplishing clinical trials. For these firms, interactions with incumbent firms are essential. The above mentioned need for complementary asset is especially driven by the need to accomplish clinical trial phases by drug based SBFs. This was mainly true because entering in a clinical trial represents a huge step for an NSBF. Moreover, in the first stage of the clinical trial, the interest of incumbent firms could be very high and acquisitions may occur, giving such scientists an investment opportunity. Therefore, from this investigation, it was established that SBFs need support on those studies, in order to prove a positive influence on NSBFs. In fact, those large firms provide the necessary resources translated into access to international collaborations, laboratories, skills and competencies that given the nature of scientific firms, it would not be possible to access without them. These evidences are in contrast with authors that supports theories that incumbent firms constrain firm's resources and NSBFs should build on niche markets to avoid predatory incumbents (Davidow, 1986; Hagedoorn and Schakenraad, 1994; Christensen, 1997; Moore, 2002). On the opposite incumbents for NSBFs are considered fundamental partners through the entire process of venture creation.

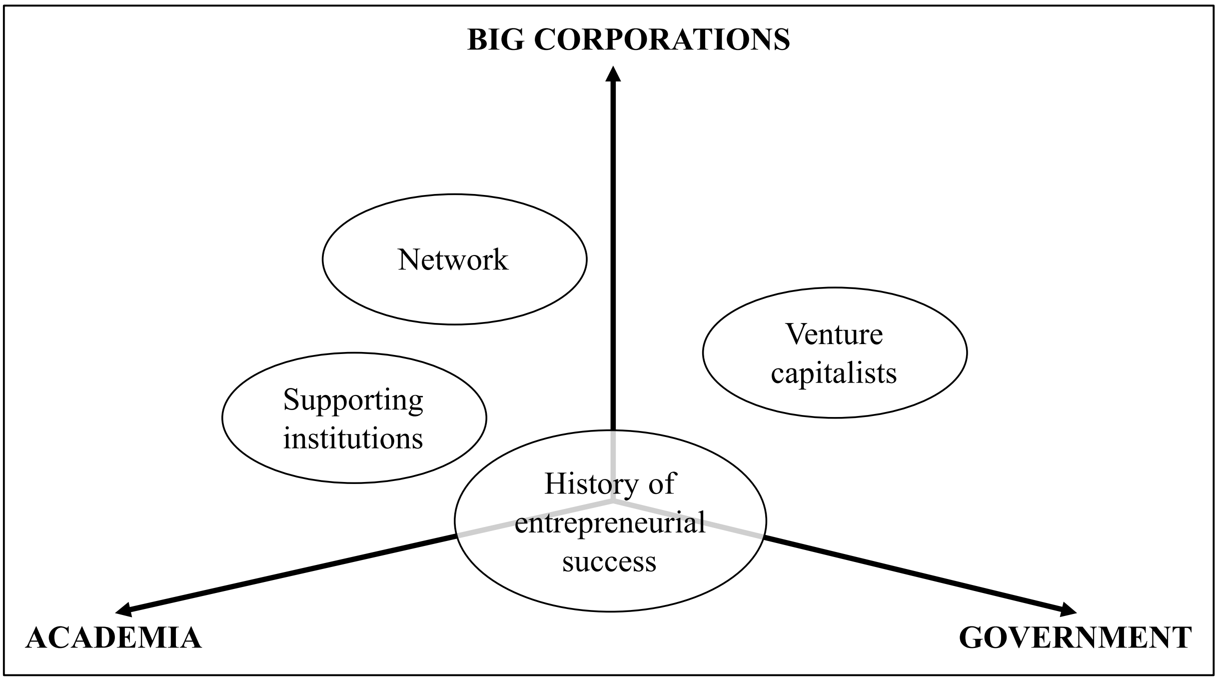
Investors and partners have an intuitively strong presence throughout the full development process because of the copious amount of funds that these firms need and are necessary reach the main milestones of the R&D development. However, even though they provide financial injections their role is somehow marginal in respect to big corporations and incumbent firms that not only provide funds but also complementary assets as observed previously. For this reason, venture capitalists play along incumbent firms which are considered essential in the process of firm's development.

Networks in form of entrepreneur's networks assume a marginal role and is considered relevant only at the initial stage for project seeking or seed money. Networks are mainly developed within the supporting institutions such as the Pulsalys and Lyonbiopole within the EE.

Universities and research centers represent the main repository of actors that start the technology transfer process providing the main scientist-founders seek advancement in science exploiting the venture to advance the study of their discoveries (Gurdon & Samsom, 2010); but in most of the situations, they do not leave their positions in academia to join and fully exploit the commercialization of science. For this reason, they seek co-founders with business backgrounds willing to take control of the. This could be the possible solution to overcome the dichotomy between science advancement and profit seeking that is usually verified in SBFs (e.g. Mustar et al., 2006, Pisano, 2010).

Despite the issues previously described, academia, in terms of University and research centers, together with Incumbents and Government represents the third pillar for NSBFs' development as showed in Figure 3.17. These three elements represent the most important elements in the entrepreneurial ecosystem at both initial and later stage. The relationship of these three elements with at the center the history of the area and the other elements (supporting institutions, network and venture capitalists) as satellites.

Figure 3.17. Composition of Science-based Entrepreneurial Ecosystem



Source: author's elaboration

From the investigation emerged that these three elements are fundamental for the functioning of the EE calling for a broader prospective which looks at macro conditions rather than micro, for the development of NSBFs. In fact, looking that the model, the three pillars recall the three helixes from the triple-helix framework elaborated by Etzkowitz and Viale (2010) which foresee interaction between the three elements of the triple-helix as main element for innovation settings in knowledge-based societies (Etzkowitz, 2003). These interactions *"generates a reflexive sub-dynamic of intentions, strategies, and projects that adds surplus value by reorganizing and harmonizing continuously the underlying infrastructure"* (Etzkowitz and Leydesdorff, 2000: 112–113). The interaction dynamics leads to a system which is able to create new knowledge and innovation (Etzkowitz and Leydesdorff, 2000; Leydesdorff and Etzkowitz, 1998).

3.6. CONCLUSIONS

The study provides to the EE approach, showing that institutions coordinated and focused on the main capabilities and excellence of the area make an extraordinary contribution to firm birth especially during the initial part of science-based firm's development where networks, investors and human resources are at the center of firm's agenda. After this initial period, the influence of the entrepreneurial ecosystem loses its strength, opening the boundaries to a plethora of SBFs which comprehends foundations, incumbent firms, clients and institutions at the international level. Thus, this is a proof that EE enhance the entrepreneurial actions. Importantly, the results show that the EE can be a consistent theoretical construct and further studies should take place to advance this promising approach.

SBFs due to their peculiar characteristics need to receive specific support. In this investigation was outlined that the EE approach is a potential methodology for a better comprehension of SBFs' performances. Despite its importance, limited effects are ascribable to later stage of firm's development when due to the peculiarities of science-based businesses enlighten the need for entities such as government, incumbent firms and universities calling for methodologies that takes in consideration a broader spectrum of analysis of SBFs rather than micro analysis of firm's development like the Triple-Helix analisys.

Moreover, this study contributes to the study of SBFs' performances, including parameters that scholars could use to evaluate both SBFs and EEs supporting science firms. The performance indicators outlined are the clinical trial phase, contingency, funds and grants, growth in human resources, growth in sales, internationalization, market entry, patent, and prototype. As is possible to observe, there are indicators which are consistently used in the study of performance such as growth in sales, human resources, number of patents and funds; but at the opposite, there are parameters that are rarely considered in the study of their performances. Instead, those parameters are considered as key results for both entrepreneurs leading SBFs and investors that are looking for potential businesses.

4. Supporting Ecosystems in Science-Based industry: missing links and future agenda. The Italian case

Innovation and technology have been recognized as boosters of growth in modern knowledge-based economies (Lundvall et al., 2002; Rooney et al., 2005). This is the reason why several countries around the globe have focused their supporting activities on fostering innovation through intensive polices with the scope of facilitating the exchange of knowledge. The goal of many societies over the years is, in practice, to fill the gap with the United States and Japan which for several years have dominated the podium of the World's most innovative economies (Lalkaka, 2001; Carayannis and von Zedtwritz, 2005; European Commission, 2005; Etzbowitz et al., 2005; Chandra and Fealey, 2009). Among the reasons for US predominance in the innovation sector, US legislation played a central role with the proposal of the Bayh-Dole Act of 1980 (Decter et al., 2007; Powell, Owen-Smith and Colyvas, 2007), which promoted commercial pursuit of innovative ideas in the previously untapped sector of academia. The act revolutionized the framework of intellectual property rights, by formalizing the right of universities to claim ownership on the outcome of federally funded research (Jelinek and Markham, 2007), thus allowing the formation of new ventures around Science-Based discoveries, which were previously not considered marketable due to their radical nature.

The Bayh-Dole Act is probably the most representative act of the US government's support toward universities and industry in order to enhance entrepreneurship, technological and scientific innovations. These schemes reflect the dynamics of triple helix model introduced by Etzkowitz and Leydesdorff (1995) which in the last two decades produced fresh insights in creating innovations in modern knowledge based societies (Meyer, 2012). This "model for analyzing innovation in a knowledge-based economy" (Leydesdorff and Etzkowitz, 1998: 198) poses the focus on the modalities that university, industry and government interconnections are fundamental to generate innovations (Etzkowitz and Leydesdorff, 2000: 112–113). It has been demonstrated that these interactions lead to a system which is more capable, in respect to those systems in which these interactions are not present, to create new knowledge and innovation (Etzkowitz and Leydesdorff, 2000; Leydesdorff and Etzkowitz, 1998).

Within the triple helix framework, one the best vehicle to technology creation is start-up creation (Lumpkin and Ireland, 1988; Timmons and Spinelli, 2003; Hayton, 2005) and supporting the creation and development of such firms has become one of the main priority policies for several countries and, especially for the European Union (European Commission, 2005). Among these policies of support for start-ups, academia represents the ideal environment, since its ecosystem may contain various entrepreneurial entities necessary to foster entrepreneurship such as: incubators, accelerators, science parks and technology centers (Smilor et al., 2007). Universities nowadays have the enlarged task to support technology transfer and entrepreneurship in different ways: providing entrepreneurship-based classes; establishing academic entrepreneurship centers; supporting the formation of new o-campus entrepreneurs through the creation of alumni idea contests and commercialization funds (Siegel and Wright, 2015).

In this scenario Science-Based firms (SBFs) are an important element of a country's economic growth for mainly two reasons: they represent a thermometer for the intensity with which modern economies are able to benefit from the work of science and innovation (Casper, 2007) and secondly they represent a key element for a country's technology transfer process (DiGregorio and Shane, 2003). SBFs are crucial for the development of new technologies been able to fill the gap between science innovation and product commercialization. This bond with technology development and commercialization is increasingly considered as an indispensable for early commercialization of new technologies (Shane, 2004; Gill et al., 2007).

The creation of New Science-Based Firms for the commercialization of scientific discoveries, has an increasing trend World Wide and in particular in the United States, Japan, Korea, Europe and China which nowadays is investing increasing resources in R&D and commercialization. In Europe countries such as Denmark, Sweden, Germany and France take the lead of the knowledge revolution but not all countries are performing in the same way. In Italy the public and private investments in R&D are decreasing since the 2008's financial crisis and more and more academics and researchers are leaving the country seeking better conditions (Pianta et al., 2017).

Despite many studies tried to delineate a Triple-Helix framework since its conceptualization (e.g. Ryan et al., 2018; Ranga et al., 2008; Benner and Sandström, 2000; Casas et al., 2000) and also recent attention has been paid to this topic, for example the top journal Technovation dedicated a special issue on it (Linton, 2018); it is very difficult to find studies that face the inability to put in place these scheme and tries to identify possible reasons and possible solutions to a model that seems deeply eradicated in modern societies.

In this chapter, through the analysis of cases among the most representative institutions and firms in Italy in the Science-Based industry, will be performed an explorative study on the Italian Industry-Academia-Government's relationships and the main issues that impeded Italy to establish a successful triple-helix scheme for innovation. After analyzing and summarizing the main issues, we provide possible solutions on how to progress the impasse that characterizes the Italian framework of innovation and commercialization of science.

The following section goes through the Triple-Helix describing the fundamental principles of the framework, in section 4.2 the methodology is presented followed by section 4.3 with the analysis of the main findings. Section 4.4 is dedicated to the discussion in which the main argumentations arisen from findings are discussed and the finally in section 4.5 conclusions and suggestions for future research.

4.1. LITERATURE REVIEW

Over the years, governments and states always fought the battle for innovation especially during and after events that re-shaped the world's perception. For example, during the World War II when nations were deeply involved in developing more sophisticated weapons; or for example after the Russian Sputnik in 1957 where other modern economies tried to fill the technological gap. The Japanese boom in the 70s pushed governments in developing new ways to create more innovations (Etzkowitz, 2018).

Innovation systems differ from each other. At one of the extremes there is Japan's innovation system and the so-called National Innovation System (NIS) in which limited governmental resources are concentrated on specific industrial areas limiting the growth of the others (Freeman, 1987). In the United States, on the other side, innovation is characterized by initiatives from the bottom in which government is considered as a limitation (Mazzuccatto, 2013). Both approaches foresee micro and macro actions with the intervention of the government that operating at meso-level enhances innovation through cooperative initiatives.

Government involvement may assume different manifestations: in most European countries, for example, the government intervention is more explicit than happens in the United States where government tends to adopt indirect actions rather than direct (Etzkowitz, 2018). It is important to notice how the different innovation approach to innovation in the US allowed them to witness the growth of innovative ecosystems such as Route 128 and Silicon Valley in which the university is empowered to participate actively in the innovation process in comparison to countries in which government leads the action. In both systems government intervention either direct or indirect, is considered to be fundamental in order to start and arbitrate systematic innovation in the economy (Edquist, 2003).

From the early twentieth century industrialized and industrializing countries have registered triple-helix dynamics in the attempts to fill the gap between countries or within regions involving the typical three actors: University, Industry and Government (Etzkowitz & Zhou, 2017). The interdependent interaction between the three elements of the triple-helix concept represents the main element in the attempt to improve the innovation settings in knowledge-based societies (Etzkowitz, 2003). These interactions "generates a reflexive sub-dynamic of intentions, strategies, and projects that adds surplus value by reorganizing and harmonizing continuously the underlying infrastructure" (Etzkowitz and Leydesdorff, 2000: 112–113). The interaction dynamics leads to a system which is able to create new knowledge and innovation (Etzkowitz and Leydesdorff, 2000; Leydesdorff and Etzkowitz, 1998).

The triple-helix scheme of innovation foresees academic entrepreneurship extending the traditional research oriented spirit of universities (Etzkowitz and Viale, 2010) converging businesses and academia in a virtuous cycle for innovation (Bjerregaard, 2010), given their objectives' dichotomy: "scholars wish to publish; industries wish to gain financially from collaboration; and policy-makers represent the public interest, but also want to win elections" (Park and Leydesdorff, 2010: 647). In a recent Triple-Helix prospective, the political intervention incorporating civil society is the key to harmonize the different points of view of the three actors and promote innovation amongst business, politics and academia (Bi et al., 2017; Cavalli, 2007; Kayser, 2017; Perren and Sapsed, 2013).

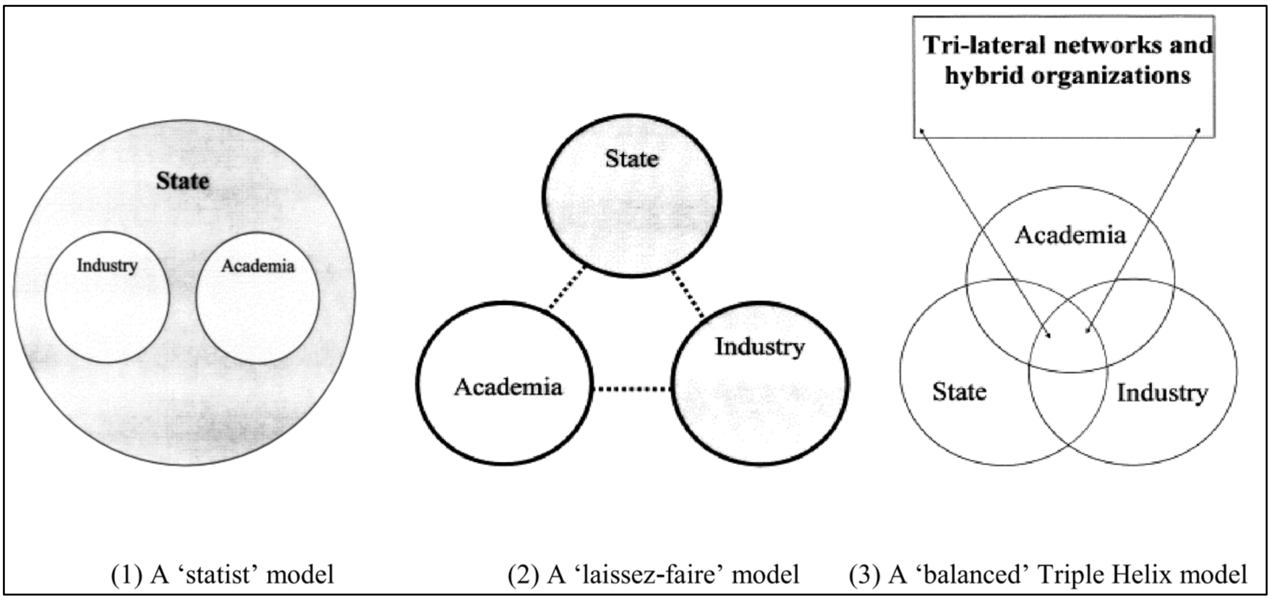
4.1.1. Triple Helix framework

The origin of the Triple-Helix concept, University-Industry-Government interactions, takes its inspiration from works conceptualizing industrial innovation from the first half of the twentieth century like Marshall (1920) and Schumpeter (1942) and subsequently considered by Lowe (1982), Sabato (1975) and Mackenzi (1982) opening up the debate on how we examine, specify and define reality in a transition from industrial economies to knowledge-based economies (Etzkowitz & Zhou, 2017). The concept of triple-helix as we know it today, is ascribable to the more recent work of Etzkowitz (1993) and Etzkowitz and Leydesdorff (1995) and thanks to further developments (e.g. Etzkowitz and Leydesdorff, 1997, 2000; Leydesdorff, 2006) becomes one of the most adopted framework by policy-makers in designing regional, national and international polices in knowledge-based economies (Etzkowitz, 2018).The cooperation between the three actors of the Triple-Helix, University-Industry-Government, is a key aspect of innovation polices for many countries such as Europe that within Europe2020 strategy included the Innovation Union among the 7 flagships initiatives that promotes as a response to the innovation gap that Europe is facing during the last years (European Commission, 2011; Geoghegan-Quinn, 2012).

This framework foresees a reinforced role of universities from many prospectives. Due to the dismantling of industrial R&D departments and the shifting of the R&D costs over academic infrastructures and due to the diffusion of governmental polices that promote the collaboration between industry and academia (Slaughter and Leslie, 1997); universities introduced in addition to their prior missions, teaching and research, the so called "third mission" which includes among the main goals of the university the involvement in the innovations' economic development (Etzkowitz, 2003). With the increasing of such relationships, the role of universities in generating scientific discoveries grew over time becoming fundamental for the economic growth of knowledge-based societies (Godin and Gingras, 2000). Moreover, universities started to teach courses on entrepreneurship, leading students not only toward new professional careers, but also promoting academic entrepreneurship and promoting their ideas through the creation of organizations such as incubators and science parks which offer intensive courses and mentoring programs for the commercialization of technology and the formation of new enterprises (Etzkowitz, 2008; Almeida, Mello and Etzkowitz, 2012).

Researches on Triple-Helix since its conceptualization developed two main research streams. The first is neo-institutional that adopting case studies and comparative studies, takes in consideration the different manifestations of the Triple-Helix and the different mechanism with which this framework enhances regional and national systems (e.g. Etzkowitz, 2003, 2008; Etzkowitz and Leydesdorff, 1996, 1999, 2000; Benner and Sandström, 2000; Inzelt, 2004; Etzkowitz et al., 2005; Boardman and Gray, 2010; Lawton Smith and Bagchi-Sen, 2010; Saad and Zawdie, 2011). The main configurations that emerged so far are the "statist" model in which the State takes the main lead over the other two actors controlling and limiting innovations, this is the typical situation that can be found for example in Russia and China. The second configuration is the "laissez-faire" which sees the industry taking the main role in innovation with the other two actors, Government and University, provide skilled human resources , in the case of university, and infrastructures in the case Government, this is the typical example of US innovation framework (Etzkowitz, 2008). A new configuration is emerging in modern economies which sees the three actors in "an endless transition" in which a continuous re-balancing of relationship produces systemic dynamics of innovation (Etzkowitz and Leydesdorff, 1998). In Figure 4.1 the three models are showed.

Figure 4.1. Triple Helix configurations



Source: Etzkowitz and Leydesdorff (2000)

The second stream considers the three elements of the model as cohesive parts of society that interfering with each other through market choices, innovation and system controls, convey through particular links and institutionally adjust by transactions and interpretations (Leydesdorff 1994; 1997, 2000; 2008; Etzkowitz and Leydesdorff, 1995; Leydesdorff and Etzkowitz,1998). Studies on this stream base their assumptions on two main theories: theory of social systems of communication (Luhmann, 1975, 1984) and mathematical theory of communication (Shannon, 1948). Authors in this research stream look for repetitive dynamics in networks and organizations that shape the relationships between the actors (e.g.

Leydesdorff, 1996, 1997, 2000, 2006, 2008; Etzkowitz and Leydesdorff, 1995; Leydesdorff and Meyer, 2006; Dolfsma and Leydesdorff, 2009). Neo-evolutionary authors measure the intersections of the Triple-Helix with probabilistic measures mainly in two dimensions: one functional between science and market, and one institutional between private and public which looks at the degree of reciprocal influence and adjustment in multi-level dimensions, university, industry and government (Leydesdorff and Etzkowitz, 1996, 1998).

4.1.2. Triple-Helix, relationships between the three helixes

A successful triple-helix model is a model in which virtuous relationships between the three actors are established (Etzkowitz, 2008). Interactions between helixes have different manifestations which reflect the collaborative nature of the framework, in fact, in this triadic model the tensions between the actors are turned into synergies toward a common goal generating favorable situations for the helixes and the knowledge-based society (Heerwagen, Kelly and Kampschroer, 2010). As a consequence of the converging of the objectives and the importance of the three protagonists of the model, a shared authority in guiding the innovation process is needed in a sense that each helix should choose to collaborate rather than dictate the terms in order to reach the common purposes (Rubin, 2009).

Together with shared authority, the system needs a substitution effect in the situation in which of the actors does not fully fulfill the desired purposes (Etzkowitz, 2008). Examples are ascribable to the government when promoting venture creation through public investments and provisions extends its traditional role of control and regulation and provide for activities which are typically industry related (Gebhardt, 2012). Another example is represented by universities that being traditionally involved in teaching and research, promote entrepreneurial support and promote start-up creation, or vice-versa, when industry finance research (Etzkowitz, 2018). Also government actions can be substituted in the case, for example, of missing innovation lead. In this situation firms and universities may take over setting the future orientation of innovation in a region or a country (Ranga et al. 2008).

Additionally, among the relationship dynamics that may occur within the triple helix model, networking is one of the major activity that may surge between the industry, government and academia. Networks may have different outlines, they can be formal or informal or structured as regional, national or international (Etzkowitz, 2018). Networks between these actors have been studied in the literature under different configurations such as "techno-economic networks" (Callon, 1992), "networks of innovators" (Cusumano and Elenkov, 1994; DeBresson and Amesse, 1991; Freeman, 1991), "neither market nor hierarchy" (e.g. Powell, 1990). Academia's networks outstands among the different kind of networks, which in order to extend research in a knowledge society requires openness, becoming non-linear and interactive (Kaufmann and Tödtling, 2001), have proved to have a great impact on in the social, economic and political sphere (David et al., 1999, Steinmueller, 1994).

4.2. METHODOLOGY

For this study a qualitative approach suits the final ends which is to understand the issues related to the dynamics of the relationships between the three actors of the Triple-Helix: University-Industry-State. The qualitative approach allows to focus on micro-foundations enabling the analysis of the interactions that occur during knowledge creation activities that together have an impact on the Triple-Helix framework at the macro level (Ankrah et al., 2013; Tippmann et al., 2013). The involvement of face-to-face interviews is likely to produce richer insights on the exchange of knowledge and the process of knowledge creation (Michailova and Mustaffa, 2012).

The qualitative approach will be adequate to explain the contemporary phenomenon knowledge creation process generated by the interactions between the elements of the Triple-Helix (Yin, 2009) and to capture and understand the dynamics of the recent context in which these relationships take place (Eisenhardt, 1989). As research method case studies are used resulting to be an optimal instrument to investigate contemporary phenomenon within real life context (Robson, 2002:178). With case studies is possible to obtain a better understand of the context and its process (Morris & Wood, 1991). The case study strategy allows to answer to the questions "why", "what" and "how" these relationships occur and to establish a more reliable framework multiple case studies are employed to collect enough data to grant generalization (Yin, 2003).

Given the intangible nature of the knowledge formation among University-Industry-Government, a case study approach it is the methodology that better capture this phenomenon (Akwei and Peppard, 2006; Carpenter et al., 2003; Lawson and Samson, 2001) and avow the author(s) to analyze variables which are which are very much embedded in the surrounding context (Rouse and Daellenbach, 1999; Yin, 1989).

Table 4.1. Case studies summary

Name of firm/institution	Category	Activity description
Case1	Academic start-up	Academic spin-off specialized in development and commercialization of monoclonal antibodies for targets in cancer therapy.
Assobiotec	Public institution	Italian Association for the Development of Biotechnology, represents approximately 130 businesses and science and technology parks operating in Italy across the various fields that use biotechnology: healthcare, agriculture, the environment, and industrial processes.
Case3	Academic start-up	Innovative start up working on System Integration and IT consulting.
Case4	Academic start-up	Leading company in the testing field, able to evaluate and improve the performance of derma-cosmetic and pharmaceutical products, medical devices, dietary supplements, biocides, medical and surgical devices, dangerous preparations, e-cigs, e-liquids and other Nicotine Delivery Systems
Bioindustry park Silvano Fumero	Science park	Services for the support of science ventures including physical space, science services, business services, project's assistance, and accelerations programs.
Cluster Alisei	National Cluster	Italian's Life-Science cluster, its mission is to provide the link between business requirements, institutional priorities and existing needs in terms of innovative healthcare solutions.
Lombardy Life-science Cluster	Regional Cluster	Its mission is to favor the aggregation of resources, bringing together industry, academia and clinical community to support the advance of life sciences in Lombardy.
Molmed	Listed company	MolMed S.p.A. is a medical clinical stage biotechnology company focused on research, development, manufacturing and clinical validation of cell & gene therapies for the treatment of cancer and rare diseases.
Case9	Academic start-up	It deals with the separation and characterization of nanomaterials and the development of silicon materials.
Case10	Academic start-up	Offers consulting services in the design of natural and synthetic complex polymers for tissue engineering, of therapeutic and diagnostic recombinant proteins, as well as the setup and validation of analytical techniques and the design of innovative therapeutic.
Zambon Zcube	Private accelerator	ZCube is a research venture of the Zambon Group which organizes an acceleration program for the creation of new Science-based start-ups.

The qualitative approach revolves around micro-foundations that help the analysis of the interactions take place during innovations and knowledge creation activities. These interactions have an effect on the Triple-Helix network at the macro level. The case study strategy permits to answer to the questions about factors, reasons, and mechanisms of these relationships between three pillars. To establish a more bona fide framework, multiple case studies are employed to pull together enough data to grant generalization and make the conclusions stronger.

The case study selection was done through at first personal network connections and furtherly through snowball sampling. Case studies were selected for their representative nature in the study. For this reasons were included persons representing institutions in the public sector and in the private sector that have an extensive knowledge and experience on the selected topic. In Table 4.1. a summary of the case studies is showed and in table 4.2. information about the interviews are presented.

Table 4.2. Interview table

ID	Name of firm/institution	Interviewee's function	Date of interview	Duration of interview
1	Case1	Co-founder	19/01/2017	0:22:53
2	Assobiotec	President	17/04/2018	0:30:20
3	Case3	Co-founder and CEO	17/01/2017	1:03:37
4	Case4	Operation Manager	31/01/2017	0:34:43
5	Bioindustry Park Silvano Fumero	General Manager and COO	22/03/2018	1:53:10
6	Cluster Alisei	Cluster manager	27/03/2018	0:40:05
7	Lombardy Life-science Cluster	Cluster manager	27/03/2018	0:37:02
8	Molmed	CEO	17/04/2018	0:28:01
9	Case9	Co-founder	19/01/2017	0:34:29
10	Case10	Co-founder	17/01/2017	0:35:59
11	Zambon Zcube	Chief of Innovation	19/06/2018	0:45:36

4.3. ANALYSIS

The aim of this paper is to outline the main issues that the Italian system incurred in the application of the Triple-Helix scheme. Especially the intent is to highlight the main issues that did not allowed these three actors to successfully establish relationship dynamics that are at the core of the success of this innovation model widely used in knowledge-based economies. Through the analysis of the interviews the main findings are outlined with the support of the main quotes that seems to better exemplify the main functional issues that these entities faced during their careers within the Triple-Helix framework. The Paragraph is divided according to the single elements following in order Government, Industry and University.

4.3.1. Government

Governmental issues are probably the most cited and contentious element of triple-helix composition. The first element of controversy outlined by the interviewees is the public supporting system which seems not to be adequate to the needs of Science-Based ventures and the initiation of the technology transfer and consequent commercialization of science. The main reason related to the perception of inadequacy toward public support is directly related to the limited financial resources that are allocated to the support of technology transfer activities.

Institutions that should have a pivotal role in the encounter between industry and government and should support Science-Based ventures at different stages of their growth, for example providing orientation services for new firms looking for investors, provision of seed money for the proof of concept phase, help on intellectual property, etc.; are not able to provide any of those services because they basically do not have budget and limit their activities to networking activities. The lack of resources is translated in limited services making public institution less attractive to firms that do not fully see the potential of these entities and are reluctant to join or to collaborate with such institutions.

> *"Companies have to understand why they should be there, what kind of services you offer, not having any public funding we do not even have the possibility to create proper services because it is not possible to finance them" (Life-science cluster)*

> *"The strongest cluster for Science-Based firms in Italy, Lombardy life-science cluster, I think that has one part-time employee, all the activity of the cluster is managed by 4 people, what does it mean? It means that we do not believe in it, a person that it is supposed to have all the necessary competences to work with all the working groups made by entrepreneurs, it is not possible, we do not believe in it" (Bioindustry park)*

> *"It would be nice to have other kind of services, for example a legal service more focused on biotechnologies, or simply somebody that shares with company's new announcements that the municipality does with the Lombardy Region given the importance of funds and the leverage effect that they have. From the legal point of view the protection for what is the intellectual property especially related to patents" (Case1)*

Another focal point of the Triple-Helix difficulties in the creation and growth of Science-Based ventures is represented by the Italian legal system and the composition of its regions. The Italian public machine seems heavily overwhelmed by the fragmentation of the Italian territory which comprises 20 regions equally divided that are additionally divided by a second layer of administrative divisions in provinces. In comparison to other countries such as France which as a bigger territory with 18 regions in total and 13 of them are metropolitan regions and 5 are overseas regions; or the federal republic of Germany which has 13 state areas with 3 city states, Italy results to be highly fragmented making public administrative work even harder. Regions divide Italy not only in territory but also for economic results showing better performances in the north of the country and poorly preforming in the Regions located in the south. These divisions also make them competing; competition that is exacerbated by the scant resources available. The result is that different territorial entities are rarely open to collaborations.

> *"I always wondered why Piedmont and Lombardy which are important regions for Science-Based sector, they never thought to make a unique cluster for example… …in the past we tried to do the MiTo for life-science, the problem is political with capital letter p, parochialism logic exist and continue to be present, why should I work with others that take my resources away. In France they unified some regions because there are advantages in terms of economies of scale and in Italy we are thinking about doing it… …for Science-Based firms means to open the possibility to find competences and resources" (Bioindustry park)*

Another problem that makes the creation of new Science-Based firms even harder is political. The continuous changes in the political asset and the perpetual re-organization of the public machine provokes instability in political actions as well. Many interviewees pointed out the difficulties that the different ministries have to face in putting in place new polices and most of all guarantee their continuity. The results are high fragmentation of institutions and lack of coordination.

> *"In the region, the office of economic development has been split in two between companies and research and development, the problem is that the resources are very limited and when the department of economic development put in place some actions it is not obliged to involve other departments, for example the welfare department start a project, involves the office of economic development to include firms, but forgets about us that we are under university and research that we have the firms that are more incline to participate in projects and make innovation, we need an institutional stimulus" (Life-science Cluster)*

Also at the central level the issues outlined at the regional level are the same, as outlined from the interviews the Ministry of Health is usually more active and only recently is moving the first steps to better understand the needs of Science-Based firms; for example in facilitating the access to the clinical trial tests but, as pointed out by our interviewees, this Ministry is totally independent from the Ministry of the Economic Development which is the ministry that have more resources and established relationships with firms. In this scenario clusters that are coordinating activities at regional and national level, Lombardy Life-Science cluster and Alisei, are under the coordination of a third Ministry, the Ministry of University and Research, that lacks of communication with the other Ministries. With lack of resources and no collaboration between institutions, had-hoc polices for Science-Based are rarely implemented. Several interviewees outlined as example the French government that allocating resources for instruments such as the "tax credit" together with other incentives for research make the Science-Based start-up very attractive. Given limited resources, rare direct actions for the support of Science-Based firms and lack of communication between public institutions, the actions of the government is perceived not as much effective as expected.

> *"There is an incapacity of the regional entity to be competent and be flexible enough because if you are willing to make it work, you design it properly" (Life-Science cluster)*

The dialogue between private and public institutions fatigue to excel, one of the main reasons seems to be the Italian legal system which does not provide effective measures to empower public institutions willing to establish collaborations. Universities or public research centers before to make an arrangement have to pass through time and resource consuming process which requires many steps and may layers of approval.

> *"we collaborate a lot with public institutions… …the feeling is that unfortunately should be some resources there, some tools that allow these people to make rapid decisions based on specific processes, now they do not have them" (OpenZone)*

Bureaucracy, within the legal system represents one of plagues for Science-Based firms, another example is represented by the cluster management, the board of the life-science cluster is composed by 14 members and its composition changes frequently. These changes require a lot of work in terms of bureaucracy and having limited resources already makes the entire functioning of the cluster at risk. Collaborations are even more complicated by the different compositions of the supporting institutions that assume different legal forms.

> *"In addition the cluster as it is created, should not obstacle other subjects that offer services, here the difference from other types of entities created in the country" (Life-science cluster)*

To summarize the issues outlined for the Italian institutional framework for Science-Based firms is represented by a missing coordination between institutions that are in continuous competition; lack of continuity in political guidance, political instability that creates a continuous misalignment of public polices; a legal system that slows down the creation of new ventures and sometimes impedes new small firm to grow; polices that do not fully reach the desired outcomes; and lack of ad-hoc polices for the Science-Based sector.

4.3.2. Industry

The Italian entrepreneurial landscape is characterized by high fragmentation of firms which is typical of this country. The high fragmentation is usually associated with limited resources. As observed in the previous paragraph, giving the limited investments of the Italian government in supporting technology transfer and Science-Based venture creation, firms and other supporting institutions rely mostly on the European Union framework to get access to additional financial support for research or product development projects. Also the participation to initiatives such as Horizon2020 becomes difficult due to the financial involvement that such programs require, most of the time the cap of maximum 50% that can be financed by the European Union and the remaining should be financed by the firm. The Science-Based investment requires a consistent amount of financial resources, and due to the micro dimension of Italian firms, is difficult to make step forward without the support of big private or public investors.

Difficulties in participating to such programs is not related only to the financial incapacity of small firms but also to the different targets that these projects promote. For example, one mission of the European Union is filling the gap between regions establishing relationship between regions which experience a elevated performances and regions which are less virtuous. The issue in this case is the concentration of Science-Based firms that are mostly in the north which is the most advanced area of the Italian territory. For these reason, also firms that are capable of doing investments struggle in finding other partners.

In addition to the fragmentation of firms, interviewees outlined the lack of big players or incumbents organizations that with their resources, intellectual and financial, drive a regional or national sector. In Italy these organizations are missing:

"In Italy firms that operates in innovative therapy field are Molmed, with cell & gene therapies, something in Chiesi for regenerative therapy, there is the private-public reality of Telethon that is no-profit with the hospital-university San Raffaele which is private and not much more" (Palmisano)

During the last decades the Italian pharmaceutical panorama witnessed a radical change due to both the acquisition by foreign entities of important players, and the decline of big Italian players such as Farmitalia, Carlo Erba, Lepetit, Montecatini. Is notable to outline that the players mentioned above, were firms that made important discoveries in the chemical and pharmaceutical world, performing outstanding R&D projects and obtaining results that still have an important echo nowadays. The loss of scientific knowledge and influence from these players weakened the national Science-Based sector leaving small and new firms without an anchor firm that drives the Science-Based system. This phenomenon causes the fragmentation of the next generation Science-Based firms and the lack of resources led them to choose secondary markets instead of competing in the bigger ones. As a consequence, the Italian SBFs were able to succeed and grow in niche markets but leaving the "big slice of the cake" to foreign multinational corporations.

The substitution that occurred over the years and the seek for markets in which to survive pushed the Science-Based market from in-lab knowledge production to manufacturing oriented firms pushing for the proliferation of genericists, in the case of pharmaceutical firms. The shift caused a positive effect in the short run in terms of jobs creation and gross domestic product, but the lost in investment in R&D projects left the Italian Science-Based sector without firms capable of leading the national science-based system.

"They were replaced by firms that made a total legit work, they generated GDP, generated taxation, created employment but they were mostly involved in developing the commercial activity during the 90s, years of great growth for the Italian economy mostly deriving from the license and commercialization of others' products rather than creating new one in their laboratories" (Assobiotec)

The Italian entrepreneurial landscape for Science-Based firms is not only characterized by lack of big players and high fragmentation of firms, but also by a weak venture capital system.

"One of our firms it has been acquired by an American company, in Italy nobody gave them a penny, exept for two business angels at the beginning, the first round was done with French and Norwegian investors and immediately got 20 million euros, from one million previously received jumped to 20 millions in one shot, this could never be possible in Italy, in practice nobody is able to invest 20 million euros… …here only one investment fund invested, big Venture Capitalists came from France, Switzerland, Norway, United States. Here there are fewer resources so we have to help firms that received money from others" (Bioindustry Park)

Most of the interviewees outlined the limited capacity of Italian venture capital investors, which do not want or are not able to make investments in Science-Based sector. There are several reasons, one of them outlined during the interview is the risk taking attitude which in comparison to other countries result to be lower. Italian venture capitalists are more incline to invest in something less risky, a pharmaceutical new venture could take more than five years before producing any revenues, time which is doubled or tripled for biotech firms. This could be intrinsic with the Italian culture, more cautious rather than risk taking.

To summarize the Italian entrepreneurial landscape for Science-Based firms is possible to assert that is characterized by small dimension of firms with the consequence of fewer resources and lesser chances to grow in comparison to other Science-Based firms located in our countries; high fragmentation of firms though a the country with a concentration in the north; absence of big players with a long history of R&D success because were acquired by foreign companies or dismantled, that caused the concentration on the manufacturing side dismantling R&D laboratories; Science venture capitalists that are not able to make substantial investments and business angels with low propensity toward risk.

4.3.3. Academia

University research is a crucial part of a national innovation system but the participation of university's units differs across countries. In the United States with the Bay Dohl Act the American government empowered universities to own their own inventions and benefit from their commercialization, in other countries such as Sweden and Italy, is in place the so-called "professor privilege" that foresee the ownership of the invention to faculty members. In this way universities that provided the labs and payed the researchers to perform the discovery, are not able to benefit from scientific advancements leaving the privilege to inventors to patent it. This system as outlined by the interviewees, represents nowadays one the major limits for technology transfer activities, which is incorporated in the universities' third mission offices. Academics are rarely interested in going through the costly procedure of patent the discovery or even to go through the creation of a new venture, but are more prone to publish their researches in academic journals to enrich their academic status. This dichotomy between the third mission need for technology transfer and academic's thirst for academic prestige make the commercialization of science even harder.

> *"Professors are judged by publications and impact factors, if we combine to these parameters also the number of patents, number of contracts, number of joint ventures, number of start-ups or even the amount of royalties that he/she generates he/she will be forced to find agreements, it is not possible in Italy for the professor privilege… …organizations have no motivation to develop and increase the value of research because it has no benefit" (Assobiotec)*

> *"We have research that is not able to be communicated in an effective and efficient way, our territory needs to close this gap teaching to who does research how to prepare it to be attractive and become a product which has a real value for the market and not simply because made of publications and help our small firms to become attractive to the big players" (Cluster Alisei)*

The perpetual cycle that has been created in the academic field for which scientific discovered are preferred to be public rather than commercialized, shaped also the entire culture of the academic world that does not see opportunity in venture creation looking at it as a continuum of the academic activity not realizing the full potential of science commercialization. It happens that there is a general propensity by researchers and scientists to prefer basic research and public scientific discoveries rather than invest part of their time in doing technology transfer activities that could take precious time from their research work.

> *"In Italy nobody really believes in Science-Based firms, these firms are seen like, I'm generalizing obviously, as an element, a gemmation of the academic world in which the gem remain directly linked to the academic world, that means that we do not have many start-ups but if we look at how many start-ups have grown, academic, we start to worry" (Bioindustry park)*

> *"It is considered a less privileged work because it does not allow further publications but only wasting time, they are more interested to research" (Cluster Alisei, Life-science cluster)*

It is important to notice that with the issues outlined before for the firm and government framework, university has its excellence but struggle in the main activity of technology transfer which is a central focus for many modern knowledge economies: technology transfer.

> *"We find many difficulties in translating basic research and sometimes we have the feeling that the opportunity that Zambon is offering is not taken by these institutions" (OpenZone)*

> *"To create an academic spin-off it is a very complex task. We need visibility from the university point of view. We need support from the administrative point of view, elements that an accountant is not fully capable to suggest. In general, have the support of someone that has a clear picture of the specific environment, an expert that not only within the science park, but also within the university that is able to clarify some contradictory aspects and simply the procedures to launch a new firm" (Case10)*

> *"In our national system we have a huge gap in soft and transfer skills, our scientists are great scientists but there are great at that, how can we pretend that a scientist becomes an entrepreneur if in 8 years of studies he/she did not attended even one course in project management, he/she is a great scientists but is not able to manage an entrepreneurial project. We saw this lack of competences especially when the team is composed by all researchers" (Fumero Bioindustry Park)*

Another issue is the fragmentation of the main actors involved in scientific research. Miscommunication outlined before plus fragmentation of institutions make the job of identification and divulgation of science even harder.

> *"For example, during our last meeting we had to explain for 40 minutes, that we do not want to squeeze start-ups, we do not want to take the technology from universities and exploit it, we want to participate in projects, take-off that start, so the culture must change, the university's culture of start-up development and on how to be an academic entrepreneur, this should change from the government" (OpenZone)*

A summary of the main issues concerning the three helixes outlined in this paragraph are listed in Table 4.3.

4.4. DISCUSSION

This study is focused on the identification of issues related to the development of the supporting ecosystems in Italy in the Science-Based industry. This research analyzes Triple-helix system in Italy through case studies among the most representative institutions and SBFs in Italy. The purpose of the analysis is to help in identifying possible resolutions to establish a successful triple-helix scheme for innovation and commercialization of science. We have described the basic principles of Triple-Helix framework and then taken a qualitative approach to infer the issues related to the relationship dynamics between University-Industry-Government as three pillars of Triple helix framework. These relationship dynamics are the heart of the progress and sustainable growth of this innovation model widely used in knowledge-based economies. We have outlined the experiences from different entities showing interconnections between Government, Industry, and University.

Table 4.3. Triple-Helix issues in the Italian Science-Based venture creation

TRIPLE-HELIX	TOPIC	ISSUES
State	**Supporting system**	*Limited financial resources*
		Limited attractiveness toward private parties
		Limited and ineffective actions
	Legal system	*Fragmentation of the territory*
		Bureaucracy
	Political	*Inability to implement effective polices*
		Separation of powers
		Lack of collaboration
		Lack of ad-hoc polices for Science-Based firms
Industry	**Limited dimension of firms**	*Lack of resources*
	Lack of incumbent firms	*Lack of knowledge and capabilities*
		Lack of industrial guidance
	Entrepreneurial history	*Shift from R&D to manufacturing*
		Weak participation in the venture creation process
		Low risk taking attitude
	Venture capital	*Few dedicated investors*
		Limited investment capabilities
Academia	**Professor privilege**	*Lack of involvement in venture creations*
		Lack of incentives to participate in technology transfer activities

A qualitative approach was used to understand the lacunas that hold back the dynamics of the relationships between Government-Industry-University and to provide possible resolutions for the identified hurdles. Based on the case studies, is discussed below the current lacunas of the relationships between Industry-Government, Government-University and University-Industry and possible resolutions to enrich the relationship stronger to have well-established Triple-Helix network as observed in developed countries.

4.4.1. Industry-Government relationships

As per the case study, we observed that the Governmental issues are probably the main role player and a litigious element for not having a well-established triple-helix system in Italy. The government policies and regional restrictions as a most powered entity among the three pillars make the decisions of Industry and University more critical and dependent. Even though having less role in real innovation, development, and enrichment of knowledge, the ruling capacity of the government makes it most effective player in maintaining the balance between relationship dynamics. Our case studies suggest that the public supporting system appears not to be capable of meeting the needs of Science-Based ventures, the foundation of the technology transfer and concomitant commercialization of science. There is a lack of Government supported Institutions that can play a pivotal role in the connection between industry and related government departments. This kind of institutions provides consultancy services and support to the Science-Based ventures at different stages of their growth including start-ups in the Science-based firms. The consultancy services can be regarding investors hunting, provision of incubating facility for the proof of concept phase, help on intellectual property rights, making collaborations, taking government approvals, identifying potential resources, short-term and long-term plan development, etc. The current support systems are not able to provide such crucial services because of budget restrictions and lack of standard policies, orientations and long-term planning. Due to the deficiency of resources in government based firms which ultimately translated to circumscribed services provided by the public institution, make it less attractive to collaborate with from the eyeshot of big science-based firms.

Importantly, The Italian public machine appears to be massively overwhelmed by the atomization of the Italian territory in around 20 regions that are equally divided and further subdivided by a second layer of administrative divisions in provinces. This highly fragmented public regulatory system of Italy makes it more arduous to develop the collaborative systems easily. These divisions are not just geographically but also for economic outcomes which resulted in better growth and performances in the North regions compared to the South. These economic differences further lead to the development of competition within the country which becomes worst by the lack of resources in undeveloped regions. Even though the competition is many times positive factor for high-quality performances and growth, such competitions break the skeleton of the country by the lack of collaborative growth among regions.

Moreover, the continuous instability of the government, reorganization of the public machine and political asset eventually lead to changing policies also. Our case studies demonstrated the difficulties in making new policies and exercising amendments in the existing policies that different ministries have to confront even after being in the same system. These results in further fragmentation of departments due to lack of coordination and outcome-oriented discussions. In this scenario, various clusters in Italy that are providing consultation between the regional and national level are operated through a third Ministry is known as the Ministry of University and Research. Due to lack of coordination within government policy makers and collaborations between different government institutions make it challenging to implement the new policies for the sustainable growth of science-based firms and many times small-scale industries of startups suffer a lot due to the unorganized system. Several countries implemented the policies such as tax credits, financial assistance for incubation, research incentives for startups and budding small scale science-based industries. This kind of policies may support further development of small industries with potential innovations and ideas for commercialization of science.

4.4.2. Government-University relationships

Our study reported that the Italian legal system does not provide effective measures to support public institutions willing to establish collaborations and commercialize science. The process of getting approval for collaboration and commercialization of ideas requires several steps and layers which are time-consuming, laborious and demotivating. Further improvements in the approval process to make it easier and fast could help in developing more incoming requests for collaborations. Also, Bureaucracy within the legal system is a considerable hurdle for Science-Based firms specifically the management board group composition is volatile, and changes in the board members require further downgrading of a system where we already have issues of limited resources. This even makes collaborations worst and less likely to happen by the different compositions of the supporting institutions that assume different legal forms. The Italian entrepreneurial landscape is characterized by high atomization of firms typical of this country and intuitively limited resources. Also, the confined investments of the Italian government in supporting academic research, science-based venture creation, collaborations, and technology transfer through university.

The innovations and development become more challenging when an institution tries to fill the gap left by the government. Institutions that tries to act as accelerators of Science-Based firms find the obstacle by the government. The insufficient cooperation by the government resulted in firms and other supporting institutions depend heavily on the European Union framework for the additional financial support for research, collaborations, development of infrastructures or product development projects. However, this is also limited by a maximum cap of 50% that can be financed by the European Union, and the remaining capital must come through private firms which makes the situation worst

Notably, the retention of brain power within the countries is also a challenging task for the government. The insufficient amount of funding available to universities for research projects, research scholars and scientists, make them relocate in other countries. This results in less intellectual science brains available for innovations in the country and in long-sight it affects countries self-dependency and reliability. The fragmentation of the main actors involved in scientific research, miscommunication and less cooperation by the government outlined before making the job of identification and divulgation of science even harder.

4.4.3. University-Industry relationships

American government authorized the institutions to patent their inventions and further commercialization whereas in Italy this rights goes to the inventors as the "professor privilege." Ultimately, universities are not able to receive the remunerations from scientific discoveries which discourage the institution for supporting innovations. The scientific discovery becomes personal in this case which may not be a good indication for the sustainable growth of the society and country. We have demonstrated this system in our case studies which delineated the major limitations for technology transfer.

The lack of big SBFs or organizations in Italy, which can direct a regional or national sector for the innovation and growth, is also a major limiting factor for the development of an ecosystem. This was further aggravated by the acquisition of important players, those made important discoveries in the chemical and pharmaceutical world, by foreign entities. The loss of scientific knowledge, experience, and influence from these companies weakened the national science-based sector leaving small companies behind with no experience-based drive for the development of the Science-Based ecosystem. Ultimately, this phenomenon further leads to less impact of country's SBFs in international markets even though they were able to grow in the niche markets. Also, the lost in R & D investment lead Italian science-based sector more into the generic product rather than innovations and downgraded the support for the national science-based ecosystem due to limited innovation resources.

The Italian entrepreneurial landscape is also characterized by a weak venture capital system due to several reasons such as risk-taking the attitude which in comparison to other countries result to be lower. The pharma or Biotech sectors take at least 12-15 years to return the investment which is not attractive for Italian venture capitalists. Importantly, the eternal inclination of academic inventors for publishing the scientific discoveries rather than commercializing it does not fit for the venture creation. It usually occurs that scientists are more interested in doing basic research and publishing the findings instead of giving attention to translational research and technology transfer which is the ultimate growth factor for the development of the strong science-based ecosystems within a country. Countries which already struggle competing with limited resources have great difficulty to support academic entrepreneurial actions with the objective of commercialization of science. On the other side university organizations struggle to identify and communicate scientific and entrepreneurial actions.

4.5. CONCLUSION

In conclusion, this chapter outlines the missing coordination between government institutions, lack of continuity in political guidance, political instability that creates a continuous misalignment of public polices, a legal system that slows the creation of new ventures and sometimes impedes new small firm to grow, polices that do not fully reach the desired outcomes; and lack of ad-hoc polices for the Science-Based sector. This study has also demonstrated certain factors that limit the growth of science-based ecosystems through lacunas rooted from the other two pillars of Triple-helix network: universities and companies.

We evidenced that small dimension of companies, high fragmentation, lack of resources and lesser chances to grow, the absence of field leaders, academic restrictions and hurdles for technology transfer, low risk seeking orientation of investors are the primary reasons for the limited development and growth of the science-based ecosystems. In future, changes in the government policies for in favor of foreign investments and regional support for the development of science-based firms, the motivation of academicians to indulge more into translational research and technology transfer would enhance the further growth of current small-scale industries to big players in a decade or two.

5. GENERAL CONCLUSIONS

This thesis proposes a theoretical and empirical framework on growth and development and offers elements and tools necessary to improve the understanding of the growth dynamics of SBFs. Throughout this thesis, emphasis has been placed on the study of SBFs dynamics related to their performances and growth. Successful SBFs are at the center of knowledge-based societies due to the benefits they bring to the society (Debackere and Veugelers, 2005; Perez and Sanchez, 2003) but the literature right now fails to deliver clear and comprehensive results on how an SBF grows and what makes an SBF successful. This is due to the peculiar characteristics of these firms that differentiate them from other firms (e.g. Mangematin et al., 2003, Mustar et al., 2006), make the study of SBFs very hard to undertake.

These characteristics can be summarized in intensive R&D (Niosi, 2000) and more engaged in in the advancement of science Autio (1997); longer prototyping phases (Pisano, 2006; Kazanjian, 1990); they foresee the intervention of large corporations (Colombo et al., 2010; Miozzo et al., 2016); they require a unique set of resources for scientific research (Pavitt, 1984). In general, the conceptual model of entrepreneurial SBFs consistently differ from other firms such as high-tech, in terms of the focus of scientific knowledge development and execution (Miozzo & DiVito, 2016).

These difficulties are furtherly weighted by the lack of a clear definition. For this reason, the first contribution regarding the definition of SBFs is undertaken before to reach a better comprehension of SBF's performances. After analyzing some of the main definitions adopted by previous studies (e.g. Pisano, 2006, 2010; Smilor et al., 1990; Moray, 2004; Pavitt, 1984; Stankiewicz, 1990); theoretical formulation is represented by the adoption of the comprehensive definition in order to isolate and exacerbate the idiosyncratic peculiarities of these firms. After the analysis of these definitions emerged that the peculiarity of these firms which distinguish them from the others is that an SBF does not only seek advancement in science but also foresees the exploitation of the related technologies, leading to the formulation of the SBF's definition as: "a *firm or entity that tries to advance science by performing basic research activities and tries to obtain a financial return from the related scientific discoveries*".

Given the above mentioned premises, the present research focused on answering to the main two questions "*How do SBFs grow? And what makes an SBF successful?*". To provide some answers to this global question, it has been broken down into three main research questions, each of which was treated in the previous chapters (a summary of the main contributions is presented in Table 5.1.):

Chapter 2: *"What are the key performance parameters to evaluate a SBF?"*

Chapter 3: *"How SBFs grow within the EE?"*

Chapter 4: *"Is the triple-helix framework the definitive approach?"*

Table 5.1. Summary of main contributions

SECTION	RESEARCH THEME	RESEARCH QUESTION	OBTAINED RESULTS
Thesis *Science-Based firm performance and growth*	Science-Based Firm's (SBF) development and growth	*"How SBFs grow and what makes a SBF successful?".*	- Performance indicators cannot be limited to economic performances, but should consider the R&D peculiarities; - The growth and development of SBFs should consider macro factors such as country's polices, academia and industry. - Alternative models for knowledge-based societies are needed to foster the creation and development of SBFs.
Chapter 2 *SBFs and performance factors, what should we do? An integrative systematic review of the literature*	SBF's performance determinants	*"What are the key performance parameters to evaluate a SBF?"*	**Micro level** - Characterization of SBFs adopting a comprehensive definition; - Identification of performance determinants to be adopted in further studies given the idiosyncratic characteristics of SBFs; - Outlined the need for a holistic approach to study SBFs.
Chapter 3 *Entrepreneurial ecosystems in science-based firms: building a theoretical approach*	Entrepreneurial Ecosystem approach in SBFs	*"How SBFs grow within the EE?"*	**Micro/Meso level** - Entrepreneurial Ecosystem as appropriate measure for SBFs evaluation but it is not enough for a full comprehension of SBFs' growth; - Limited effect in the long run; - Need for a framework considering macro dimensions.
Chapter 4 *Supporting ecosystems in Science-Based industry: missing links and future agenda. The Italian case*	Triple-Helix framework drawbacks in SBFs	*"Is the triple-helix framework the definitive approach?"*	**Macro level** - Misalignments, limited intervention of the Government and lack of communication are the main causes for the failure of the Triple-Helix framework; - Alternative models are needed for knowledge-based economies; - Industry should be a substitute for the Government's intervention.

In Chapter 2 multiple studies using an integrative approach are reviewed isolating performance evidences that address directly and indirectly growth, outcome, and success of

SBFs. First of all, this chapter contributes to the advancements in the characterization of SBFs adopting a holistic definition which could be adopted by further studies, providing also a comprehensive set of subpopulations relying on academia, technology-based, sector, research, and science-based, should help authors in undertaking future studies on SBFs.

A second contribution is related to performance measures. This study outlined that previous studies concentrate on firm-specific dimensions succeeding in some situations to explain SBFs' performances and in many other cases contradicting results emerged. In general, in the investigation, was outlined how the study of SBFs' performances is still widely underdeveloped and lack of clear results and common directions for the understanding of these ventures. In the specific, within performance measures, profitability measures such as net incomes resulted to be inadequate for the evaluation of SBFs performances. Indicators related to innovation capabilities and knowledge management such as innovation developments, technology development or knowledge transfer, seem more appropriate to infer the peculiarity of these firms.

From this first study was observed that so far no clear conceptual framework was previously adopted to show the relationship and the required actions for the SBFs to operate successfully in diverse external factors. Sometimes factors such as political and legal environment can deny a science-based firm a chance to operate, and mostly since the most of the operation principle of such firms are new, firms lack stands to claim their operation rights and a chance to grow, (Katz and Gartner, 2010). Based on the findings and given the peculiar characteristics of these firms, a more holistic approach to study SBFs was than proposed and furtherly adopted in Chapter 3. Considering such broader dimensions proposed by ecosystem theories could be a better approach in explaining SBFs' growth dynamics. For example, the entrepreneurial ecosystem (EE) approach, seeing the entrepreneurship outcome as a result of the interdependence between actors and factors in a particular region (Acs et al., 2017, Stam and Spigel, 2017).

Adopting the EE approach following the work of authors such as Isenberg (2010, 2011), Feld (2012), World Economic Forum (2013), and Spigel (2017), the third chapter shows that institutions coordinated and focused on the main capabilities and excellence of the area make an extraordinary contribution to firm birth especially during the initial part of SBF development where networks, investors and human resources are at the center of firm's agenda. After this initial period, the influence of the entrepreneurial ecosystem loses its strength, opening the boundaries to a plethora of SBFs which comprehends foundations, incumbent firms, clients and institutions at the international level. Thus, this is a proof that EE enhance the entrepreneurial actions. Importantly, the results show that the EE can be a consistent theoretical construct and further studies should take place to advance this promising approach. Despite its importance, limited effects are ascribable to later stage of firm's development when due to the peculiarities of science-based businesses institutional entities such as government, incumbent firms and universities are needed. These findings outline that methodologies which consider a macro spectrum of analysis of SBFs, rather than micro and meso level analysis of firm's development, are fundamental for a complete understanding of SBF's development. The Triple-Helix framework which considers Academia, Industry and Government results to be the optimum framework to evaluate science-based ventures (adopted in Chapter 4).

A second contribution of Chapter 3 is related to SBFs' outcomes. In the investigation entrepreneurs outlined performance parameters that scholars could use to evaluate SBFs in EEs studies but also could be adopted by other studies on performance evaluation. The performance indicators outlined are the clinical trial phase, contingency, funds and grants, growth in human resources, growth in sales, internationalization, market entry, patent, and prototype. As is possible to observe, there are indicators which are consistently used in the study of performance such as growth in sales, human resources, number of patents and funds; but at the opposite, there are parameters that are rarely considered in the study of their performances as outlined in Chapter 2.

Chapter 4, adopting the Triple-Helix frameowork outlines the missing coordination between government institutions, lack of continuity in political guidance, political instability that creates a continuous misalignment of public polices, a legal system that slows the creation of new ventures and sometimes impedes new small firm to grow, polices that do not fully reach the desired outcomes; and lack of ad-hoc polices for the Science-Based sector. This study has also demonstrated certain factors that limit the growth of science-based ecosystems through lacunas rooted from the other two pillars of Triple-helix network: universities and companies. We evidenced that small dimension of companies, high fragmentation, lack of resources and lesser chances to grow, the absence of field leaders, academic restrictions and hurdles for technology transfer, low risk seeking orientation of investors are the primary reasons for the limited development and growth of the science-based ecosystems. In future, changes in the government policies for in favor of foreign investments and regional support for the development of science-based firms, the motivation of academicians to indulge more into translational research and technology transfer would enhance the further growth of current small-scale industries to big players.

This thesis also provides some managerial implications, first of all looking at the development of technologies, new science-based venture should be focused on the development of one core technology rather than try to develop many. Is preferred to have a heterogeneous top management team with complementary knowledge and importantly the presence of business experts together with scientists. Looking at the business models, it is suggested to implement services in support of the R&D financing. This could bring profitability performances in the short run and make the science-based business even more attractive for investors. Some preconceived factors such as geographical locations, size, depth and extensiveness of research, the presence of scientists as a lead role player in SBFs are an important determinant of a performance measure for a SBF. This study reveals that either these factors have no significant relevance with economic performance or they have a very limited role in determining success and growth of the firm.

Policy makers should concentrate on designing ad hoc supporting programs which directly target only the special needs of these firms rather than direct financial transfers. Anyway, direct financial support is seen as positive but only at the initial stage of the venture formation. Afterward other needs such business consulting, access to specific resources such as human and technological are needed to continue the development of the venture. Moreover, policy makers have a significant role to play in the establishment, growth, and success of SBFs. As mentioned throughout the thesis, unlike the other forms of business organizations, SBFs requires a constructive interdependency between sensitive institutions including universities, scientists, and research bodies (Rasmussen and Sørheim, 2012). Practically, it is costly for a single firm to foster such a network of dependency until a SBF is established and maintaining the link for the flow of necessary information for the operation. On the same note, legislation and budget allocation at all level of governance starting from national governments, science, and research related departments, to university administrations to include the interests of SBFs, (Rasmussen et al., 2011).

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LIST OF TABLES

LIST OF FIGURES

APPENDIX 1.

ID	Authors	Title	Source	Inclusion justification	***Quotations from the paper***
1	Segers J.-P. (1993)	Strategic partnering between new technology based firms and large established firms in the biotechnology and micro-electronics industries in Belgium	*Small Business Economics*	From the description of the three business cases and the extent text is possible to observe the scientific research that they put in place to create new products.	*The case of Plant Genetic… ...PGS originates initially from academic incubators, i.e. the genetic engineering laboratories of the universities of Ghent and Leuven.... ...Corvas International, Inc…. ...The company intends to commercialize synthetic drugs for the improved treatment and prevention of major cardiovascular diseases… … Micro-electronics… ...the regional government of Flanders (Belgium) therefore created Imec as part of a science and technology programme to promote research and applications of micro-electronics, in the fields of very large scale integration systems design methodologies, advanced semi-conductor processing and micro-electronics education and training.*
2	Quéré M. (1994)	Basic research inside the firm: Lessons from an in-depth case study	*Research Policy*	It is a study based on a business unit of a corporation, there is an evidence of basic research and the presence of scientists working on it.	*This case study concerns the Thomson-CSF basic research unit.... ....The reason for that change is the failure of the initial objective. Indeed, the number of new products or processes moving from basic research to industrial applications was, in fact, very limited.*
3	Reitan B. (1997)	Fostering technical entrepreneurship in research communities: Granting scholarships to would-be entrepreneurs	*Technovation*	The program targeted scientists and academics to promote the commercialization of research as a result from universities and research institutions. Evidence of science-based R&D.	*The scholarship programme was first announced in Spring 1982 by the Research Council of Norway. The programme has a two fold goal(Waag¢etal.), 1993a):* *1. to provide scientists and academics wishing to start an NTBF the necessary time, competence and money to assess whether the key conditions for launching the enterprise are present or not;* *2. to contribute to faster commercialization of R&D results from universities and research institutions through venture spin-offs.*
4	Pfirrmann O. (1999)	Neither soft nor hard - pattern of development of new technology based firms in biotechnology	*Technovation*	The sample includes new biotech firms as resulting spin offs from research laboratories, universities and industrial corporations. Evidence of science-based businesses.	*The aim of our analysis is to provide some insights into the development of biotechnology start-ups focusing on specific aspects of research and development (R&D), production and collaboration behavior… ...The majority of biotech company founders stems from research institutions, either from universities (23%) or from labs outside the university (54%) (see Table 2 and Fig. 3). Other sectors outside research, such as industry or the medical sector play a marginal role.*
x	Lee J. (2000)	Challenges of Korean technology-based ventures and governmental policies in the emergent-technology sector	*Technovation*	From the description of the firms the three cases are based on scientist applying research to produce innovation.	*3.1. Medison Co., Ltd* *Medison is one of the most successful VCs in Korea. It was spun off from the Korea Advanced Institute of Science and Technology (KAIST), the research-oriented graduate school of applied science. The founder, Min- Hwa Lee, with a Ph.D. in electronics engineering, and his six cofounders, were graduate students and tech-nicians who were involved with a research project on ultrasonic scanner technology funded jointly by the government and a local medical equipment manufac- turer.* *3.2. Dooin Electronics Co., Ltd* *Dooin was established in August, 1990 by young engineers who were spun off from LG Electronics Co. Ltd, one of the biggest consumer electronics in Korea. Most founders of that company hold a master degree in electronics or computer science. The company name 'Dooin' has its own peculiacharacters; it means that this...* *3.3. Turbo-Tek Co., Ltd…*

APPENDIX 1. *(continues)*

ID	Authors	Title	Source	Inclusion justification	***Quotations from the paper***
5	Nilsson A. (2001)	Biotechnology Firms in Sweden	*Small Business Economics*	Biotechnology case studies, research-intensive or based on research discoveries. Strong evidence of science-based businesses.	*The core of this study is based on case studies of five biotechnology firms within these areas… ...The two most research-intensive firms in the case studies performed for this study were founded by researchers in academia… ...Two other firms in the case studies were built on discoveries bought from researchers in academia… ...The fifth firm in the case studies is a spin-off from the last firm mentioned. The founders wanted to focus and go deeper into a specific area and thus created a firm in order to realize their plans.*
6	George G., Zahra S.A., Wood Jr. D.R. (2002)	The effects of business-university alliances on innovative output and financial performance: A study of publicly traded biotechnology companies	*Journal of Business Venturing*	Biotechnology research based, from the description of the sample and the authors approach is ascribable to the case of SBFs with strong research-intensive R&D.	*This process yielded 147 publicly traded firms with a primary business focus in human gene therapy, diagnostics, and therapeutics.... ...To test the above hypotheses, data were collected from the biotechnology industry. This rapidly growing industry has a strong science-based basic research thrust that requires inputs from different streams of specialized knowledge (Hamilton, 1996).*
7	Mangematin V., Lemarié S., Boissin J.-P., Catherine D., Corolleur F., Coronini R., Trommetter M. (2003)	Development of SMEs and heterogeneity of trajectories: The case of biotechnology in France	*Research Policy*	The authors target biotechnology SMEs with a description with a strong presence of scientists involved in the R&D process.	*For analysing the factors stimulating firms' growth and determining business models based on their activities, a sample of 60 firms was selected amongst the 200 biotech firms in France (Lemarie and Mangematin, 2000).... ....Biotech SMEs are science-based. On average, R&D expenditures account for over 40% of the turnover. These SMEs obviously belong to a high-tech sector, where 76% of the founders have a scientific background and 14% are well-known scientists.*
8	Meyer M. (2003)	Academic entrepreneurs or entrepreneurial academics? Research-based ventures and public support mechanisms	*R and D Management*	They target cases focalized in the exploitation of science based innovations.	*Our focus in this article is on support mechanisms and the impact they have on the development of start-up companies in a science-based environment. We will look here at four case histories drawn from a more comprehensive effort to explore corporate activities aiming to exploit novel science-based technologies (Meyer, 2000). The four cases looked at here were start-ups that originated in a university or public sector research environment.*
x	Heirman A., Clarysse B. (2004)	How and why do research-based start-ups differ at founding? A resource-based configurational perspective	*Journal of Technology Transfer*	Despite they started from a wide range database in high-tech sector, the authors refined the sample to select the research based start-ups making phone interviews.	*We found, however, that about half of the 27 RBSUs could also be identified by three other listings of high-tech companies: (1) The academic spin outs generated in Flanders between 1991 and 1997; (2) the portfolio of venture capitalists (VCs) investing in early stage technology firms; and (3) a database of SMEs requesting government support. These sources seems to be a more efficient way of identifying the population of interest. It is important to note that these sources are not mutually excluding cases. Obviously, some firms received venture capital, government subsidies and turn out to be a spin out. What makes our database unique is that we performed a phone survey to each company in these listings to discern if they are in effect an RBSU. Table I gives an overview of our sampling method.*
9	Suzuki J., Kodama F. (2004)	Technological diversity of persistent innovators in Japan: Two case studies of large Japanese firms	*Research Policy*	Two large firms which apply science for product development.	*Canon and Takeda chemical industries.*

APPENDIX 1. *(continues)*

ID	Authors	Title	Source	Inclusion justification	*Quotations from the paper*
x	Powers J.B., McDougall P. (2005)	Policy orientation effects on performance with licensing to start-ups and small companies	*Research Policy*	They target research extensive and intensive universities and they evaluate the performance through the success of the spin offs which use licensed technologies from the university of origin. Science derivation.	*Our sample included 134 US research extensive and research intensive universities as defined by the Carnegie Classifications of US collegiate institutions and that were geographically spread across the contiguous United States. The universities included 92 public and 42 private institutions. The sample was identified based on data reported in the annual licensing surveys of the Association of University Technology Managers (AUTM, 2003) that were used primarily to derive the support and selectivity measures for this study.*
10	Lawton Smith H., Ho K. (2006)	Measuring the performance of Oxford University, Oxford Brookes University and the government laboratories' spin-off companies	*Research Policy*	It is shown that they have laboratories and they come from research centers of universities. There is a possible comparison between SBFs and other academic spin-offs.	*Further investigation up to the end of March 2005 reduced this number to 114, divided into spin-offs with university/laboratory IP (64 firms) and with founder affiliation (50)—academics, students and technicians.*
x	Kodama M. (2007)	Innovation and knowledge creation through leadership-based strategic community: Case study on high-tech company in Japan	*Technovation*	Big corporation which create new products with research and development with scientific research.	*NTT DoCoMo, Japan*'s largest mobile communication ope*rator.*
11	Durand R., Bruyaka O., Mangematin V. (2008)	Do science and money go together? The case of the 156evelo biotech industry	*Strategic Management Journal*	They include all Biotech firms in France which are engaged in in biotech research which is extremely science-based.	*However, to study the dynamics of an entire national biotech industry, we build a dataset that includes all French firms involved in biotech… …This effort represents the most extensive research ever conducted on the French biotechnological industry, and includes all firms that claim to be engaged in biotech research and that are thus classified in the census of biotech enterprises conducted regularly by the French research and technology ministry.*
12	Bruni D.S., Verona G. (2009)	Dynamic marketing capabilities in science-based firms: An exploratory investigation of the pharmaceutical industry	*British Journal of Management*	The sample relies on firms which are very development-based R&D intensive.	*The final sample is composed of two global R&D-oriented American players (USPharma-Alfa and USPharma-Beta), two global European firms, one more R&D oriented (EUPharma-Alfa and EUPharma-Beta), and two local European players (LocPharma-Alfa and LocPharma-Beta), less R&D oriented but still competing to introduce innovations they developed in-house (Table 1).*
13	Vincett P.S. (2010)	The economic impacts of academic spin-off companies, and their implications for public policy	*Research Policy*	They target research-based spin-offs.	*While all research builds on earlier international work, the immediate precursor of research-based academic spin-off companies ("RASOCs") is almost always research in their home country. Thus, the benefits accruing to that country would not have occurred absent that country's funding of AR. We specifically focus on Canadian AR in the "NSExm": the NSE ex-cluding the medical and health sciences, but including life-sciences and engineering.*
14	Belussi F., Sammarra A., Sedita S.R. (2010)	Learning at the boundaries in an "Open regional innovation system": A focus on firms' innovation strategies in the Emilia Romagna life science industry	*Research Policy*	Life science firms very representative sample furthermore in the selection procedure they excluded those not involved in pure services making the sample eligible as science-based.	*The empirical context of this study is the life science industry in Emilia Romagna. Our definition of the sector includes the following specialisations: biomedical, biotechnology, pharmaceutics and computer science industry applied to the medical fields. Therefore, our study does not focus only on dedicated biotech enterprises, including all firms active in the knowledge areas of the modern life science industry…. ….During the sampling procedure we excluded firms involved only in…*

APPENDIX 1. *(continues)*

ID	Authors	Title	Source	Inclusion justification	*Quotations from the paper*
15	Bonardo D., Paleari S., Vismara S. (2010)	The M&A dynamics of European science-based entrepreneurial firms	*Journal of Technology Transfer*	They target firms which are the result of the founder's research activities or firms resulted from the research activity of the universities affiliated. Firms with strong research-based foci.	*We identified as SBEFs those companies that had been developed by faculty members, based on their research, or companies created to development on research carried out in universities. Our definition of SBEFs was in keeping with the literature. However, in Sect. 5, we disaggregate the sample of SBEF firms with and without formal involvement of academics in the TMT…*
16	Clarysse B., Bruneel J., Wright M. (2011)	Explaining growth paths of young technology-based firms: Structuring resource portfolios in different competitive environments	*Strategic Entrepreneurship Journal*	R&D intensity firms, they are not all Science based, but within the sample it could be possible to isolate findings regarding science-based firms.	*We define 'young technology-based firms' as companies founded from 1991 to 2002, which develop and commercialize new product/services based on proprietary technology or skills… …development of sorting technologies; development of prepress software solutions; development of a genomics technology platform; development of a nanobody technology platform; development of biometric verification technology platform, Development of a generic payments processing platform.*
17	Knockaert M., Ucbasaran D., Wright M., Clarysse B. (2011)	The relationship between knowledge transfer, top management team composition, and performance: The case of science-based entrepreneurial firms	*Entrepreneurship: Theory and Practice*	Firms are selected among the science based firms, in the table that describe the sample is possible to observe that they all had a research based creation of a new technology	*Today, IMEC is Europe's leading independent research center in the field of microelectronics, nanotechnology, enabling design methods, and technologies for ICT systems…* *…and/or the leading professor of the research group at the PRI from which the venture's technology originated…*
18	Alegre J., Sengupta K., Lapiedra R. (2011)	Knowledge management and innovation performance in a high-tech SMEs industry	*International Small Business Journal*	They used all biotech firms very homogeneous. The paper analysis the knowledge development of these firms which are science based by nature given their formation and development of knowledge itself	*We test our hypotheses by conducting a survey in the context of a single industry: biotechnology companies in France… …The target population of this study was narrowly defined to include a homogeneous set of firms.*
x	Abramo G., D'Angelo C.A., Ferretti M., Parmentola A. (2012)	An individual-level assessment of the relationship between spin-off activities and research performance in universities	*R and D Management*	Spin-offs taking in consideration scientific research of their founders with affiliations.	*The survey identified 326 university spin-offs founded in Italy in the period under observation, from which were then excluded (1) those founded by scientists not holding a formal university faculty ; and (2) those where the founding members position all belonged to SDSs that are not included in science and engineering. The final dataset is composed of 284 spin-offs.*
19	Yagüe-Perales R.M., March-Chordà I. (2012)	Performance analysis of research spin-offs in the Spanish biotechnology industry	*Journal of Business Research*	In their sample selection they target only those firms which are science-based.	*The study focuses on dedicated biotechnology firms (DBFs), excluding purely pharmaceutical firms and those that operate in the biotechnology sector for exclusively commercial purposes.* *The dependent variable in this analysis is BIORESEARCHSPINOFF, a dummy that divides the sample into research spin-offs and other bio- technology firms….* *….academic research carried out in universities or other academic research institutions of the same kind, and (b) the scientist who was the originator of the particular pre-foundation academic research is also the founder or one of the founders of the company.*

APPENDIX 1. Inclusion of the sample *(continues)*

ID	Authors	Title	Source	Inclusion justification	***Quotations from the paper***
20	Wang J., Shapira P. (2012)	Partnering with universities: A good choice for nanotechnology start-up firms?	*Small Business Economics*	They target an extremely R&D and knowledge intensive segment such as nanotechnology. In the paper they also target scientists working in these firms in which they perform research.	*The nanotechnology sector is used as a case study in this paper due to its knowledge-intensive nature and close connections with university science research. Nanotechnology involves the manipulation of molecular-sized materials to create new products and processes with novel features due to nanoscale properties and is widely anticipated as a major driver of new technology-based business and economic growth over the next two decades (PCAST 2005; Lux Research 2006… ...We do not include firms that were previously established (based on other technologies) which have subsequently added or moved into nanotechnology research and production.*
x	Okamuro H., Nishimura J. (2013)	Impact of university intellectual property policy on the performance of university-industry research collaboration	*Journal of Technology Transfer*	They select firms according to sector from a research institute in Japan. This supposignly presume that are all firms based on previous research.	*Our empirical analyses are based on original survey data.7 After a pre-test with a smaller sample, we conducted a postal survey with a structured questionnaire in the summer of 2008 covering 9,882 Japanese firms with 20 or more employees in the fields of biotechnology, microelectronics, and software; we obtained 1,732 responses (a 17.5 % response rate). We selected these three technology fields to represent the major science- based industries in which UIC is especially important (Meyer-Krahmer and Schmoch 1998). Our sample firms were extracted from the company database of Tokyo Shoko Research (TSR), a major credit research institute in Japan, according to their own three- to four-digit level industry classification, and the directory of the Japan Bioindustry Association (JBA).*
21	Yagüe-Perales R.M., March-Chorda I. (2013)	Performance analysis of NTBFs in knowledge-intensive industries: Evidence from the human health sector	*Journal of Business Research*	The sample relies on knowledge-intensive firms in three segments very science-based oriented. Thet stress also the R&D intensity which is very high (due to the science developments)	*An empirical analysis over a broad sample of firms located within the Valencia region and pertaining to three knowledge-intensive Human Health sectors: Biomedicine, Medical equipment and Bio-Agro Food, (all R&D-oriented Human Health sectors (R&D-HH)) follows from the desire to figure out distinctive features of the performance in NTBFs. These subsectors are the most intensive ones in terms of R&D activities.*
22	Benghozi P.-J., Salvador E. (2014)	Are traditional industrial partnerships so strategic for research spin-off development? Some evidence from the Italian case	*Entrepreneurship and Regional Development*	They target research spin offs founded by scientists, they built a database in a very through way in order to include only those ventures that were created for the development of new technologies from research activities.	*Considering that the usual definition of SO includes, in general, companies built out of R&D and is not only restricted to those participated by a university, we completed our first list with the Italian science park and incubator tenants list. Since science parks and incubators do not make any difference between SO and start-ups, we set up direct contacts (telephone and e-mail) with university staff as well as science park and incubator personnel. It gave us the possibility to filter the first list excluding firms not linked to the academic world. SO founders are scientists and not managers; therefore, differences might be expected in the way they run their company and in their performance, according to they call or not for complementary competencies and assets through TIP.*

APPENDIX 1. Inclusion of the sample *(continues)*

ID	Authors	Title	Source	Inclusion justification	*Quotations from the paper*
x	Gauthier C., Genet C. (2014)	Nanotechnologies and Green Knowledge Creation: Paradox or Enhancer of Sustainable Solutions?	*Journal of Business Ethics*	Nanotechnology is a sector representative of science based firms. They also check for knowledge formation (through patents). In this case is representative of science based firms.	*To identify those firms involved in nanotechnology, we built a database of firms that have patented or published in nanotechnology, using a validated search strategy based on keywords (Mougotov and Kahane 2007) to extract patents from the EPO PatStat at the European Patent Office1 (which collects data from 73 offices worldwide) and publications from the ISI/web of Science. We elicited 617,000 nanotechnology patent applications (from a total of over 65,000,000) between 1990 and 2009 (see Appendix 1 for details). We thus identified 14,845 firms involved in nanotechnology worldwide, of which 9,447 were patenting firms (2,716 both publishing and patenting; 6,731 only patenting) (Fig. 2), responsible between them for 323,918 nanotechnology patent applications over that period.* *To uncover economic and financial information about the nanofirms that create green knowledge, we then matched this database against ORBIS,2 a comprehensive global database that combines information on some 60 million companies, from.....*
x	Lejpras A. (2014)	How innovative are spin-offs at later stages of development? Comparing innovativeness of established research spin-offs and otherwise created firms	*Small Business Economics*	The sample targets research spin-off with R&D activities.	*Moreover, companies provided information on how they were created, as: (1) a spin-off from a university, (2) a spin-off from a research institute, (3) a spin-off from another company, or (4) other type of firm foundation. In this study, we distinguish between the research spin-offs*—that is, companies that spun off from a university or a research institute (hereinafter, spin- offs)—and firms created in other ways.
23	Stephan A. (2014)	Are public research spin-offs more innovative?	*Small Business Economics*	The sample directly targets the research spin-offs, which are science based being concentrated on the advancement of science.	*Based on answers to one question regarding the origin of the company, I can differentiate between company and research spin-offs, and for the latter I can further distinguish between spin-offs that evolved out of a university setting and those that were created by a research institute (Pirnay et al. 2003).*
24	Visintin F., Pittino D. (2014)	Founding team composition and early performance of university-based spin-off companies	*Technovation*	Using the definition of Fini et al., 2011 and their definition fits with our definition: firm founded by previous scientific research....	*For the purpose of this research we adopted the definition of USO provided by Fini et al. (2011): a university spin-off is a company that has either the university among the founding shareholders or at least one academic (full, associate, assistant professor, PhD student, research fellow) among the founders. Two features distinguish therefore a USO in our perspective:* *the presence of at least one founder who was employed at the university at the time of start-up and the commercialization of a technology originally developed by academic research activity.*
25	Scholten V., Omta O., Kemp R., Elfring T. (2015)	Bridging ties and the role of research and start-up experience on the early growth of Dutch academic spin-offs	*Technovation*	The sample criteria was to include firms based on previous scientific researches and founded by their researchers	*To be included in the database, a potential spin-off had to be an autonomous company, based on scientific research conducted at an academic institution and founded or co-founded by researchers that had worked on the scientific findings at the academic institution in question.*

APPENDIX 1. Inclusion of the sample *(continues)*

ID	Authors	Title	Source	Inclusion justification	*Quotations from the paper*
26	Ziaee Bigdeli A., Li F., Shi X. (2016)	Sustainability and scalability of university spinouts: A business model perspective	*R and D Management*	Three firms which are academic spin-offs representing a subsample of SBFs.	*USO_A: Founded in 2010 in partnership with the University and the United Kingdom's NHS Trust. The firm specializes in the design and development of Assistive Living Technologies and Services (ALTS), such as computer-based applications for assisted living purposes* *USO_B: Established in 2008 through a partnership between the NHS Foundation Trust and the University to focus on focusing on developing, validating…* *USO_C: Established in 2001 through the collaboration with the University TTO to focus on systems biology drug discovery through patented platforms*
x	Hayter C.S. (2016)	Constraining entrepreneurial development: A knowledge-based view of social networks among academic entrepreneurs	*Research Policy*	Inclusion because it targets researchers that founded a start-up, and surpassingly with what said in the introduction should be startup based on their research activities, as a consequence science-based	*"Academic entrepreneurs, defined here as university faculty who establish a spinoff company based on their research (Shane, 2004), play a particularly important role in the founding and development of university spinoffs."*
x	Hayter C.S. (2016)	A trajectory of early-stage spinoff success: the role of knowledge intermediaries within an entrepreneurial university ecosystem	*Small Business Economics*	They specify that are all spin offs based on technology developed after a research activity.	*As noted, all spinoffs were established based on technologies derived from federally funded research*
27	Miozzo M., DiVito L. (2016)	Growing fast or slow?: Understanding the variety of paths and the speed of early growth of entrepreneurial science-based firms	*Research Policy*	The sample is mixed including also firms which produce services, and hybrid firms which produces services and make research. The majority are science based with applied research given the specialization of the sectors in which they operate. Is possible to derive findings regarding SBFs	*The focus on the biotechnology segment of the pharmaceutical industry is representative of entrepreneurial science-based firms because these firms require extensive financial resources for an extended period of time to develop new products in emergent scientific and technological areas with high levels of uncertainty.*
x	Miozzo M., DiVito L., Desyllas P. (2016)	When do Acquirers Invest in the R&D Assets of Acquired Science-based Firms in Cross-border Acquisitions? The Role of Technology and Capabilities Similarity and Complementarity	*Long Range Planning*	They target biotech firms which are representative of SBFs.	*We focus on the acquisitions of six biopharmaceutical firms in the Cambridge, Oxford, and Manchester areas in the UK. The biopharmaceutical industry is an ideal setting for our study for two reasons. First, our research question focuses on the effect of cross-border acquisitions on the continued investment and development of acquired technological assets of science-based firms. Biopharmaceutical firms operate upstream in the value chain or product-development trajectory, generate product- and firm- specific knowledge and represent the complexity of R&D in science-based businesses.*
28	Lubik S., Garnsey E. (2016)	Early Business Model Evolution in Science-based Ventures: The Case of Advanced Materials	*Long Range Planning*	The sample relies on three firms which apply R&D for scientific discoveries and their commercialization.	*Case 1: Metalysis; Case 2: Nanomagnetics; Case 3: Apaclara*

APPENDIX 1. Inclusion of the sample *(continues)*

ID	Authors	Title	Source	Inclusion justification	***Quotations from the paper***
29	Quintana-García C., Benavides-Velasco C.A. (2016)	Gender Diversity in Top Management Teams and Innovation Capabilities: The Initial Public Offerings of Biotechnology Firms	Long Range Planning	Dedicated biotechnology firms are firms with a scientific R&D.	*The research setting of this paper is provided by dedicated biotechnology firms (DBFs) that completed an initial public offering in the United States, during 1983–2009... ...Biotechnology firms tend to be involved at the riskiest stage of the drug development process.*
x	Soetanto D., Jack S. (2016)	The impact of university-based incubation support on the innovation strategy of academic spin-offs	Technovation	Inclusion because they have included the condition of technology created at the university impiyng a Science-Based R&D activity.	*We delineated the population of spinoffs from these universities based on the following criteria. First, the firms needed to satisfy the condition of commercialising knowledge and technology created at the university. Second, at least students, graduates or academic staff had to be actively involved in the firms. Further, the firms needed to satisfy the condition of receiving support from the in- cubators or university.*
30	Subramanian A.M., Choi Y.R., Lee S.-H., Hang C.-C. (2016)	Linking technological and educational level diversities to innovation performance	Journal of Technology Transfer	The article is focused on science based firms promoted by the government for the development of their technology.	*The Agency for Science, Technology, and Research (A*STAR) was established to be the nation's supplier of scientific, engineering, and technology talent to commercial enterprises by offering scholarships to individuals to enroll in science and engineering-based disciplines....*

APPENDIX 2

INCIDENT CODE	EVENTS DESCRIPTION
Acceleration program	Joining Pulsalys program
	Creating a project and joining accelerator Pulsalys
	Joining Pulsaly s acceleration program
	Pulsalys acceleration program
	Participation in bioproject
	Founder leaves bioMérieux to found Anaquant
	Program “emergence” for industrial application
External contingency	Forced to change location for the pharmaceutical site
	Lawsuit procedure
	Sentence from the court of justice
Formal foundation	Born of Platine Pharma Solutions, SA
	Foundation of Alaxia
	Foundation of Bioxis
	Foundation of Netris
	Creation of Stragen services as spin-off
	INPG becomes founder and foundation of Calixar
	Creation of Bioelpida
	Co-funders start to work full-time in the firm and company creation
	Foundation of CFL
	Provisional foundation of Carpaccio
	Provisional foundation of SameSame
	Founder leaves bioMérieux to found Anaquant
	Foundation of Cerma
	Company fully created and operative
	Creation of the company
Founders	Conference in Lyon, meeting with two scientists
	Scientists’ meeting
	One of the three co-founders leaves the company
	The Oncology medical Director leaves the company
	Founders meet each other
	Meeting with co-founders
	Meeting with the father of the technology
	First meeting with co-Founder (speech therapist specialist)
	A co-founder leaves the company resulting in a re-organization
	Founders meet each other at Pulsalys and start to look for potential outcomes
Human capital	A co-founder takes the role of CEO
	Recruitment of a business development manager
	Business development manager becomes CEO
Investors and Partners	Acquisition by ABL (part of Institut Mérieux)
	Name changes in ABL
	Meeting a possible investor
	Involvement of CNRS, and Lyon university
	Meeting with international investors
	Servier enters in the company
	INPG becomes founder and foundation of Calixar
	New collaboration with Synthelis
	Co-marketing agreement with ABL (US)
	Aston (UK) university research agreement (COST)
	New investors coming in
	Negotiation of a new partnership
	New partners joining the project Stragen, Perose and Statis

APPENDIX 2 *(continues)*

INCIDENT CODE	EVENTS DESCRIPTION
Network	Transgene and Innate Pharma joined for common purposes
	Creating a project and joining accelerator Pulsalys
	Project involvement at Stragen
	End of project
	Involvement in a project with Sanofi leading the project at Avignon-lab
	Inter-Ministry Fund award, 3-year program (Chikvax) for new vaccine against Chikungunya
	Conference presentation where interest from the scientific community was shown
	First feedbacks from the market
	Project for research and development
R&D/development	Preparation for clinical trial
	Pierre Falson develops 2 Patents at the CNRS
	Attempt by the inventor to get a patent
	C-mark approval
	Starting to do R&D at the sister company Bioelpida
	Filled patent on a new way to treat cancer
	The idea born from the analysis of muscles
	Starting to develop SameSame
	Starting development
	First results of lab research
	Implementation of manufacturing line