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TUOMO HEINONEN

Innovations in Regenerative Medicine

Science fiction or a potential new industry?

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Science fiction or a potential new industry?

ACADEMIC DISSERTATION
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…

Kun ensimmäisen vuoden teekkarina pääsin töihin automaatiotekniikan laitokselle TTY:llä, en osannut aavistaa, miten paljon se lopulta vaikuttaisi myöhempiin vaiheisiin elämässäni. Olen kiitollinen Matti Rajalalle niistä kaikista mitä moninaisimpia asioita koskevista keskusteluista, joita kävimme töiden ja opiskeluni lomassa, ja jotka jatkuvasti haastoivat minua ajattelussani. Pitkälti hänen vaikutustaan on, että lopulta lähdin valloittamaan vuortani ja tekemään väitöskirjan.

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…

Tampereella, 12.10.2016

Tuomo Heinonen

ABSTRACT

Regenerative medicine (RM) is a new way to cure patients besides traditional medicine and surgery. RM includes products from all the pillars of healthcare, i.e. pharmaceuticals, biopharmaceuticals, medical devices and cell therapies, to deliver clinical outcomes. Globally, the cell therapy industry is just emerging, and while RM also draws upon non-cell-based treatments, stem cell-based products and services have some of the most fascinating opportunities and hopes in regards to previously incurable diseases. In this dissertation, the focus is on stem cell-based products and services. The main research question is how academic research-based innovations occur and can be transferred to new businesses and therapies in the RM sector. Theoretically, this dissertation builds on innovation systems, innovation-related medical technology literature, and competence bloc theory. Medical technology literature identifies aspects of medical technology innovation emergence and how its elements are conceptualized within health innovation systems. Competence bloc theory provides a good explanation for how business emerges and what competencies are required. This dissertation followed a constructive research approach and a single-case study methodology. The empirical data consists of 24 interviews and relevant secondary data (reports, publications, statistics, etc.). Using empirical data and background literature, a construction was developed in order to explain how innovation occurs at the system level and to identify the actors that are involved.

TIIVISTELMÄ

Regeneratiivinen lääketiede (RegenMed) on uusi tapa hoitaa potilaita lääkehoidon ja kirurgian ohella. RegenMed sisältää tuotteita ja palveluita kaikista terveydenhuollon osa-alueista, kuten lääkkeistä, biologisista lääkkeistä, lääkintälaitteista ja soluterapioista. Globaali soluterapiateollisuus on vasta kehittymässä ja vaikka RegenMed tukeutuu myös ei-solupohjaisiin hoitoihin, kantasolupohjaiset tuotteet ja palvelut tarjoavat joitain kiinnostavimpia mahdollisuuksia aikaisemmin hoitamattomien sairauksien hoitamiseen. Tässä väitöskirjassa tarkastelun kohteena ovat erityisesti kantasolupohjaiset tuotteet ja palvelut. Päätutkimuskysymys on miten akateemiseen tutkimukseen perustuvat innovaatiot syntyvät ja miten niistä voi syntyä uutta liiketoimintaa ja hoitomuotoja RegenMedin alalla. Teoreettisesti tutkimus pohjautuu innovaatiojärjestelmiin, innovaatiokirjallisuuteen lääketieteellisistä teknologioista ja competence bloc -teoriaan. Kirjallisuus lääketieteellisen teknologian innovaatioista tuo esille aspekteja, jotka liittyvä innovaatioiden syntyyn, ja näitä elementtejä on konseptualisoitu terveysinnovaatiosysteemi-viitekehyksessä. Competence bloc -teoria puolestaan antaa erityisesti hyvän selityksen miten liiketoimintaa syntyy ja mitä kompetensseja siihen vaaditaan. Tämä väitöskirjatutkimus noudatti konstruktiivista lähestymistapaa yksittäisen tapaustutkimuksen metodologiaan perustuen. Empiirinen aineisto koostuu 24 haastattelusta ja oleellisista toissijaisista lähteistä (raportit, julkaisut, tilastot, jne.). Väitöskirjassa kehitettiin empiiriseen aineistoon ja taustakirjallisuuteen perustuen konstruktio, joka selittää miten innovaatio syntyy järjestelmä-tasolla ja mitkä toimijat liittyvät siihen.

CONTENTS

LIST OF PUBLICATIONS

Article I Sotarauta, M. and Heinonen, T. (2016). The triple helix model and the competence set: human spare parts industry under scrutiny. *Triple Helix,* 3(8), 1-20.

Article II Heinonen, T. and Ortega-Colomer, J. (2015). Regenerative medicine as an emergent cluster in Tampere Region. *Journal of Entrepreneurship, Management and Innovation,* 11(4), 139-160.

Article III Heinonen, T. (2015). Management of innovation in academia: A case study in Tampere. *Journal of Technology Management and Innovation*, 10(2), 198-210.

Article IV Heinonen, T. (2016). Potential for 21st century's academic health centers to revolutionize healthcare: Lessons to be learned from Tampere, Finland. SENTE Working Papers 36/2016. Tampere.

Article V Heinonen, T. (2016) Regenerative medicine cell therapy financial market: How to finance potential innovations. In: Sotarauta, M., Heinonen, T., Sorvisto, P. and Kolehmainen, J. (Eds.) Innovation Ecosystems, Competencies and Leadership: Human Spare Parts and Venture Finance Ecosystems under Scrutiny. Tekes Review 329/2016. Helsinki.

LIST OF ACRONYMS

AHC	Academic health center
ARM	Alliance for Regenerative Medicine
ATMP	Advanced therapy medicinal products
BioMediTech	Institute of Biosciences and Medical Technology
GMP	Good manufacturing practice
ERIS	Entrepreneurial regional innovation system
FVCA	Finnish Venture Capital Association
HIS	Health innovation system
iPSC	Induced pluripotent stem cell
IPO	Initial public offering
IP	Intellectual property
IPR	Intellectual property rights
IRIS	Institutional regional innovation system
M&A	Merger and acquisition
NIH	National Institutes of Health
NIS	National innovation system
PE	Private equity
PoC	Proof of concept
PoCC	Proof of concept center
R&D	Research and development
Regea	Regea Institute for Regenerative Medicine
RIS	Regional innovation system
RM	Regenerative medicine
SIS	Sectoral innovation system
TEKES	The Finnish Funding Agency for Technology and Innovation
VC	Venture capital

PART I

1 Introduction

In the field of medical technology, science and technology are interdependent and essential elements of innovation (Gelijns and Rosenberg, 1995). Those sectors of medical technology that draw from an analytical knowledge base, e.g. biotechnology and pharmaceuticals, are especially dependent on the progress of scientific research conducted in both academia and industry. Universities are major actors in producing new knowledge and technology (Niosi et al., 1993; Autio, 1998; Malerba, 2002), even though there is no standard recipe for their role in innovation systems (Charles, 2006), and during the last few decades a growing number of universities have officially adopted a third mission in which they are more deeply involved in the translation of research to societal use[1].

This dissertation focuses on regenerative medicine (RM), which is a new way to treat patients besides drugs and surgery (Polak et al., 2010) by replacing or regenerating human cells, tissues or organs (Mason and Dunnill, 2008a). It is also a good example of a sector where universities push new technologies towards a societal use, and hence fulfil expectations regarding the third mission. RM draws from all the industries in healthcare: pharmaceuticals, biopharmaceuticals, medical devices and cell therapies, although the focus of this dissertation is mainly on cell-based therapies. The RM sector, and especially the cell therapy industry, is emerging in Western countries and is reliant on universities. There are great expectations that the science-based innovations being developed are used for the good of society. RM is a hot topic within the scientific world. In their recent article published in Nature Biotechnology, Kang et al. (2016) introduce a tissue-organ printer that can produce

[1] The role of universities in society is discussed from different perspectives in the literature, e.g. Mode 1 and Mode 2 (Gibbons et al., 1994) or triple helix (Etzkowitz and Leydersdorf, 2000). One of the main differences between Mode 1 and 2 is that in Mode 1 problems are set and solved in the context of a specific community (mainly academics), whereas Mode 2 is outward looking towards society and utilizes a broad range of perspectives (Gibbons, 2000). Etzkowitz and Leydersdorf (2000) argue that Mode 2 is a return to traditional views about a university whereby it is integrated deeply in societal life. A similar idea is presented in the triple helix, whereby academia, industry and state are strongly interconnected.

human-scale tissue constructs of any shape. Even though it sounds like science fiction, in the article they describe how they used the printer to produce an ear which was transplanted in a mouse. Their biomechanical analyses showed that maturation strengthened the ear tissue construct in the mouse. Although there is still a long journey to use in hospitals, Kang et al. argue that their method could produce constructs that may be sufficient for translation to patients.

In Tampere, which is the case region for this dissertation, the emergence and development of the global RM sector and accompanied demand is highly relevant to Tampere's opportunities to commercialize its potential RM innovations. Currently, the RM sector in Tampere is based on academic research and a few innovations have emerged from it. Regarding the RM sector, two universities in Tampere have a strong scientific foundation and results and a good relationship with the hospital where clinical operations are conducted, as well as potential products. In Tampere, one of the success stories of science happened in 2007 when the upper jaw of a patient was fixed with a tissue-engineered bone transplant. This transplant was cultivated from stem cells isolated from the fat tissue of the patient and combined with a biomaterial scaffold, which stayed in the patient's abdominal muscle for eight months. To this date, over 25 operations have been conducted for different patients under the advanced therapy medicinal products (ATMP) hospital exemption regulation. The ATMP hospital exemption makes it possible to conduct experimental treatments but systematic production is not permitted. Even though there are some innovations emerging at the university, there is no local industry in this sphere and the global industry is also just emerging. In Tampere and elsewhere, the big question is whether these science fiction-like innovations are actually successful and able to proceed from laboratories to hospitals on a large scale.

1.1 Motivation

The main motivation for this dissertation comes from the challenges of commercialization. It is important to understand how product opportunities based on university research could be commercialized and what it takes within the RM sector. Commercialization is assumed in this dissertation to be a necessary step in order to diffuse these new stem cell-based products with regular hospital services, and thus commercialization is the focal point of this study. The important role of industry is widely acknowledged in the process of medical technology innovation, for example Blume (1992) argued that for diffusion of new medical technology to

occur, incentives for both manufacturers and clinicians are needed. Furthermore, it is important to understand the systemic nature of innovation and commercialization. Consoli and Mina (2009) stressed the importance of this by arguing that systemic and dynamic aspects of innovation in healthcare are often assumed, i.e. innovation is studied in isolation from the broader socio-economical system. They state:

> "scholars of innovation, who would be best equipped to capture the overarching systemic and dynamic aspects of innovation in healthcare, seem to have underinvested in this important topic and left the debate to health economists, health policy and health management scholars." (Ibid.:298)

Systems of innovation are often studied from different perspectives with defined geographical, sectoral or technological boundaries. In this dissertation, the health innovation system (HIS) approach is used as a theoretical basis (Consoli and Mina, 2009; see more in section 2.2). This sums up the main actors in medical technology innovation, i.e. academia, industry and hospital, and describes how these actors interact (see also e.g. Blume, 1992; Gelijns and Rosenberg, 1995; Metcalfe et al., 2005). HIS borrows insights from innovation system approaches (national, regional, sectoral and technological), but is not by any means one-dimensional (Consoli and Mina, 2009).

The three main elements of HIS are: a scientific community, a technology market and a health delivery system. In the RM sector, these are intertwined as academia is also responsible for medical technology development to some extent (Heinonen, 2015). Many studies in medical technology literature more or less assume the existence of firms in the technology market and their (and the system's) ability to commercialize potential innovation is taken as granted. However, in the emerging RM sector, the technology market is at the beginning of development and there are no manufacturers readily available capable of developing new technologies. There have been several waves in the development process of the industry and the last one happened globally around the year 2005, as the change of the focus in the firms appeared from academically interesting areas of research to translation into products (Mason, 2007). At the same time, the funding sources for firms turned from private to public. To understand market emergence in the RM sector, it is important to understand the commercialization process in the HIS framework in the current stage of development. Thus, an important aspect to understand is how technology transfer from academia to the technology market and finally to hospitals actually occurs. An understanding of the technology market is important, because commercialization is not a simple task in biosciences, as Hopkins et al. (2007:567) states:

> "The translation of advances in bioscience into new technology is far more difficult, costly and time-consuming than many policy-makers believe"

For governments and their policy-makers, it is important to realistically understand the building blocks and processes in the RM sector that enable the commercialization of potential innovations. Without an understanding of these processes, investing tens or hundreds of millions in the research and development of RM products, and hoping that these investments pay themselves back, is just gambling.

1.2 Aim and contribution

The aim of this dissertation is to explore the system-level nature of innovation in the RM sector and to study the important elements of it more deeply. The main research question in this dissertation is:

> How academic research-based innovations occur and can be transferred to new businesses and therapies in the RM sector?

To support the answer of this main research question, the following research questions are made and answered in the independent articles:

> RQ-1: What are the essential competencies of the emerging RM sector (Article I)?
>
> RQ-2: What hinders the emergence of an RM cluster and how do innovations emerge locally in Tampere (Article II)?
>
> RQ-3: What are the specific concerns for technology transfer in the RM sector, and how can these challenges be overcome (Article III)?
>
> RQ-4: What is the potential role and structure of academic health centers in the development of the RM sector, and what managerial and policy implications do they bring (Article IV)?
>
> RQ-5: How does the financial market locally affect a university's potential to commercialize technologies in the RM sector (Article V)?

By answering the research questions, this dissertation contributes at a general level to the understanding of how science-based technologies and innovations occur and can be commercialized in the early phase of an emerging industry in the healthcare sector. At a more detailed level, how academic innovations translate to products in the RM sector and what are the important system-level elements in the process are examined. This dissertation utilizes competence bloc theory to explain

the market processes that guide the translation of academic research and innovations into an industry[2]. Competence bloc theory presents an ideal set of actors and competencies, yet describes well processes in the technology market. Competence bloc theory covers the exploration, development and feedback phases in Blume's (1992) theoretical framework where he compared four different careers of medical technology development and produced a categorization of development phases[3]. The competence bloc actors and their existence in Finland will be discussed later in this dissertation (Article V). In short, some of the actors do not exist readily in Finland and only partially on a global scale. It is uncertain if companies in other fields of medical technology are interested in early RM inventions and innovations. Hence, the important question is how entrepreneurial firms are able to carry ideas from academia to industry, grow large enough, and finally industrialize and sell products to hospitals.

The relationship between academia and industry is widely discussed in literature regarding innovations in medical technology. Even though the linear innovation process is criticized (see e.g. Blume, 1992, Gelijns and Rosenberg, 1994; Morlacchi and Nelson, 2011; Nelson et al., 2011), regulation forces the product development phase in biomedical industries to follow the linear innovation process. However, as within the history of medical technology, the actual innovation process in the development of a new therapy is often not linear. Even in the case of Tampere, in this context, it is not a surprise that bone growth therapy treatments are given to real patients even though no clinical trials have been conducted for it, and hence it has not been commercialized yet. Using the categorization of Blume (1992), this bone growth case is in the exploration phase or in the beginning of the development phase, and the question is how this (and all other innovations) can be commercialized and released to the market. Part of the challenge is that early phases of the required clinical trials (phase I and II) should be conducted in academia, and only then would venture capitalists invest in a company (Parson, 2008; Mason et al., 2011). Even though it means to some extent that academia should share the risk with firms, who

---

[2] Briefly, in competence bloc theory, the continuum of innovator, entrepreneur and industrialist describes how inventions turn into products, while venture capitalist funds entrepreneur and exit-market provides an incentive for both of them (Eliasson and Eliasson, 1996). See a more detailed description about competence bloc theory in section 2.3.

[3] According to Blume (1992), the career of medical technology has four phases: exploration, development, diffusion, and feedback. See a more detailed description in section 2.2.

would hopefully industrialize the solution later, in the current stage of RM sector development, a risk-sharing approach might be one of the only ways to actually proceed to commercial products and services. As briefly described in section 3.1, industry building in the RM sector was previously relying on R&D conducted in firms, before financiers moved away because of poor commercial results. The challenges relating to this assumption of how to proceed are at the focal point of this dissertation and thus it is important to understand the processes that guide the translation of science-based innovations to industry. For example, Toner and Tompkins (2008) have recognized the need for the scientific community to reduce the risk on inventions by initial validation and intellectual property protection in the development of medical technologies (regarding this 'proof of concept' development, see e.g. Auerswald and Branscomb, 2003; Maia and Claro, 2013; Heinonen, 2015). Finally, in the case of the emerging RM sector, the question is not only about an emergence of a niche industry around some specific new medical technology but also about the emergence of a wider sector with firms that could develop and commercialize new medical technologies and act as industrialists for a wider set of new medical technologies.

1.3 Structure

This dissertation consists of two parts: introductory essay and original articles. The introductory part is organized as follows. The first section explains the motivation, aim and contribution of this dissertation. The second section presents relevant theoretical background and key concepts, including innovation systems, innovation in medical technology, and competence bloc theory. The third section provides both an overview of the RM sector and the case description in more detail. The fourth section presents the methodology and the fifth section offers an overview of the articles and their findings. The sixth section introduces the developed framework, which explains how innovation occurs in the RM sector. The seventh section provides an example of a medical technology development pathway in the RM sector. The eighth section provides some discussion about theoretical contributions and policy implications. Finally, in the ninth section the conclusion, limitations and future research opportunities are presented.

The second part consists of five independent articles that have provided the basis for the introductory essay. A summary of these articles is presented in the fifth section of the first part. These articles were written between 2014 and 2015 reflecting

on the main research question of this dissertation from different angles and at different levels of analysis.

2 Theoretical background

2.1 Systems of innovation

Schumpeter (1934) has had a significant influence on innovation studies[4]. Based on his ideas, innovation can be defined as:

> "new and improved products and processes, new organizational forms, the application of existing technology to new fields, the discovery of new resources, and the opening of new markets." (Niosi, 1993:209)

Schumpeter talks about innovation within the context of firms and how, one way or another, it has a positive commercial impact. Since this basic definition of innovation provided by Schumpeter is at the level of the firm, scholars have subsequently transferred it to the macro level as they have begun to think of systems of innovation that aim to produce, modify and diffuse new technologies in the public and private sectors (Freeman, 1987). Fagerberg et al. (2012) showed in their study how innovation and technology keywords link two distinct literature clusters: organizing innovation (firm level) and innovation systems. To this date, literature regarding innovations and innovation systems is vast and has many branches. Lundvall, Freeman and Nelson are among the first authors to have been actively discussing innovation systems (Lundvall, 1985, 1992; Freeman, 1987; Nelson, 1993). Freeman (1987) introduced a national innovation system concept in his study about Japan. Later, Nelson used this concept in his comparison of science and technology systems between the US and other nations (Lundvall et al., 2002). During the 1990s, the systemic nature of innovation was emphasized with many concepts having their focus elsewhere than the national level (Lundvall et al., 2002). These concepts included, for example, regional innovation systems (see e.g. Cooke, 1992; Cooke et al., 1997; Cooke and Leydesdorff, 2006; Asheim and Isaksen, 2002; Asheim and Gertler, 2005) and sectoral innovation systems (Brechi and Malerba, 1997; Malerba

[4] Invention and innovation are the basic concepts of innovation studies. Fagerberg (2005:4) provides a simple distinction between them: "Invention is the first occurrence of an idea for a new product or process, while innovation is the first attempt to carry it out into practice"

and Orsenigo, 2000; Malerba, 2002, 2005). In the beginning of the 2000s, Lundvall et al. (2002) argued that nobody expected the innovation system approach to be so diffused as it was at that time. They suggested that the reason for such wide diffusion might be a failure in macroeconomics and politics to deliver an understanding and control of the factors that affect international competitiveness and economic development. The other potential reason they describe is that deep division of specialization among policy institutions and analyzers of policies became such a big problem that an analytical concept was received gladly by innovation and technology policymakers to bypass these problems. Indeed, innovation systems could provide an analytical tool to understand complex interactions between different actors:

> "A national system of innovation is the system of interacting private and public firms (either large or small), universities, and government agencies aiming at the production of science and technology within national borders. Interaction among these units may be technical, commercial, legal, social, and financial, inasmuch as the goal of the interaction is the development, protection, financing, or regulation of new science and technology." (Niosi et al., 1993:212).

According to Lundvall et al. (2002), focus on national innovation systems is controversial as we live in a time where globalization and international processes have become increasingly important. Nevertheless, studies show that a national innovation system is important for innovation activities and has its advantages as an analytical tool (Lundvall et al., 2002). National and regional innovation systems focus on how different sectors or clusters are co-operating with a territory's government and innovation supporting infrastructure at the national and global level (Cooke et al., 1997). Since a national innovation system is obviously geographically limited to one nation, the difference to a regional innovation system is not always clear. However, it is not possible to understand a national innovation system by simply combining all regional profiles (Cooke et al., 1997).

Cooke et al. (1997) argued that the innovation system concept does not have to be restricted to the national level and thus, in their article, they tried to identify key dimensions of regional innovation systems with an aim to provide an operational concept. Autio (1998) explained regional innovation systems as having two main building blocks with appropriate knowledge, resources and human capital flowing and interacting between them: a knowledge application and exploitation sub-system, and a knowledge generation and diffusion sub-system. According to Autio, the knowledge generation and diffusion sub-system includes universities, technology and workforce mediating institutions, public research institutions and educational institutions; whereas the knowledge exploitation sub-system includes industrial

firms, customers, competitors, collaborators and contractors with vertical and horizontal networking. The international character of a knowledge adoption and exploitation subsystem depends on the customers, contractors, collaborators, and competitors and their degree of internationalization. A regional innovation system has external influences from national and international innovation system institutions and policy instruments, but also from other regional innovation systems.

Regional and national innovation systems incorporate many sectors. Malerba (2002, 2004) brought a sectoral view to innovation systems by arguing that innovation and technological change are highly dependent on the sector, and national differences play only a small role within the same sector, except for some elements at the national level, such as regulation and patent systems. In his work, Malerba (2002) conceptualized a sectoral system of innovation and production. As he argued, an innovation system approach brings an assumption into the study of sectors that innovation is not emerging in a void but instead is a collective process. Hence, a sectoral innovation system concept provides a useful tool for analyzing a sector, as in different sectors the dynamics and knowledge bases are different (Malerba, 2005).

In addition to regional innovation systems, the concepts of institutional and entrepreneurial regional innovation systems (IRIS/ERIS) have been developed to distinguish between coordinated (IRIS) and liberal (ERIS) market economies (Cooke, 2004; Asheim and Coenen, 2006; Asheim, 2007). Based on the institutional and coordinated market economy dichotomy, institutional and entrepreneurial innovation systems present two fundamentally different approaches to the innovation system framework. The entrepreneurial regional innovation system is based on venture capital, entrepreneurs, scientists, market demand and incubators to support innovation. In the institutional regional innovation system, technology and innovation are path-dependent and institutions are incrementally growing to meet the needs of the sectors, whereas in the entrepreneurial regional innovation system, systemic elements are flexible and adjustable because the system is driven by venture capital (Cooke, 2004). In mature sectors, strong regional systemic elements of the innovation system are useful when accompanied with a sectoral innovation system that has existing technologies, demand and institutions. Liberal market economies have some advantages compared with coordinated market economies in industries characterized by radical innovative activities, a knowledge base drawn from science, project organizations and unknown futures (Cooke, 2004; Asheim and Coenen, 2006, Asheim, 2007). ERIS is called a venture capital driven system by Cooke (2004) mostly because it gets its dynamism from local venture capital,

entrepreneurs, scientists, incubators and market demand. ERIS, being both adjustable and flexible, does not easily end up in a lock-in situation (Asheim and Coenen, 2006).

Many studies about innovation systems focus on the institutional innovation system approach in European countries, especially in Nordic countries, where a strong emphasis on institutional innovation systems exists (Cooke, 2004; Asheim and Gertler, 2005; Asheim and Coenen, 2006). However, institutional innovation systems might have a gap of supporting institutions and elements for emerging industries. Hence, in coordinated market economies, innovation policies should understand and recognize the need for finance drivers to make new industry with radical innovations viable – whereas in liberal market economies this is a built-in feature. In later stages, when the industry is more mature, a coordinated market economy might have an advantage in being able to sustain the industry whilst contributing incremental innovations. However, traditionally the regional and sectoral innovation system literature does not concentrate on entrepreneurship and venture capital as an integral part of the system. Instead, innovation system policies are more concentrated on horizontal networking that might have an impact on profitability when vertical networking with customers is positively correlated with growth (Autio, 1998). For innovation policies to be effective in emerging sectors, a better understanding of market creation mechanisms is required. This calls for a focused approach where actors shaping the future of the sector are taken into account. One such focused approach could be a firm-centered viewpoint for innovation systems, as Metcalfe et al. (2005) describe when they discuss how firm-centered micro-innovation systems emerged in the case of intra-ocular lenses. They argue:

> "What we are dealing with are knowledge intensive medical services and the innovation systems that sustain them and transcend traditional sector boundaries.
>
> --
>
> The competitive activities of rival firms are central to the way the innovation system develops. The process of competition is reflected in the attempts of rival firms to build their own 'local' concentrations of innovation resources. That is to say, they develop proprietary micro-innovation systems as part of their strategies to support their ongoing search for competitive advantage." (Ibid: 1301)

In their case study, the relevant system consists of national healthcare systems as well as a medical sector cutting across national borders integrated by transnational

medical device firms and an international community of clinicians. For firms to sell their products and services to public and private healthcare providers, it is important to link these two levels (national healthcare systems and the international medical sector) with networks of clinicians and suppliers.

2.2 Innovation in medical technology

Health-related technologies cover a wide range of technologies starting from science-based technologies, such as biotechnology and pharmaceuticals, to engineering-based technologies such as medical devices (Meyer-Krahmer and Schmoch, 1998). According to Blume (1992), conventionally the term 'medical technology' includes collectively drugs, devices and procedures, and this definition is applied in this dissertation as well. Djellal and Gallouj (2005) categorized innovation in medical technology more profoundly as biomedical or bio-pharmacological innovation, tangible innovation (technological systems including capital goods, small items of equipment, diagnostic or therapeutic equipment), and intangible innovations (care protocols, diagnostic or therapeutic strategies, etc.). Social innovations are also important in health systems, and unlike new products, social innovations do not have centralized production and widespread adoption but instead adaption to local conditions as needed (Gardner et al., 2007). Regarding innovation in medical technology, different industries have different types of innovation processes (Blume, 1992; Gelijns and Rosenberg, 1995). In biomedical industries (also in RM cell therapies), in many cases innovation and at least product development follows a linear innovation process whereby research produces ideas that are tested with animals and later in clinical trials[5], and finally adopted to use (Gelijns and Rosenberg, 1994; Mason and Dunnil, 2008b). However, particularly with medical devices, Gelijns and Rosenberg (1994) claim that a linear innovation

[5] The regulation process consists of several stages. First, in pre-clinical trials animals are usually used to prove the concept. Then there are three phases where safety (phase I), efficacy (phase II) and final confirmation with a large group of people (phase III) are studied. Currently, the major share of regulated stem cell therapies also follow a similar process.

process[6] is only part of the truth and many innovations are based on subsequent modification of existing technologies for the needs of the medical sector.

The systemic nature of healthcare is described in the HIS framework (Figure 1), which builds on the literature of innovation systems and medical technology, and which consists of the components of the system and presents the dynamics of change in terms of technology development and its diffusion to medical practice (Consoli and Ramlogan, 2008; Consoli and Mina, 2009). As HIS outlines the essential components in medical technology innovation processes, there are several forces behind those enabling advancement in medical practice: advances in scientific understanding of a disease; advances in technological capabilities enabling the development of diagnosis, therapies and treatments; and learning in clinical practice enabling advances in medical diagnosis and treatment (Nelson et al., 2011).

[6] One way to view technological development is that science is a source of new technology. This belief is defined as a linear innovation process covering the following sequence of phases: basic research, applied research, development, and production and operations (Stokes, 1997). In biomedical research this means that biomedical scientists have an idea, which moves from laboratory to animal models, to the development phase, and finally to hospitals (Gelijns and Rosenberg, 1994).

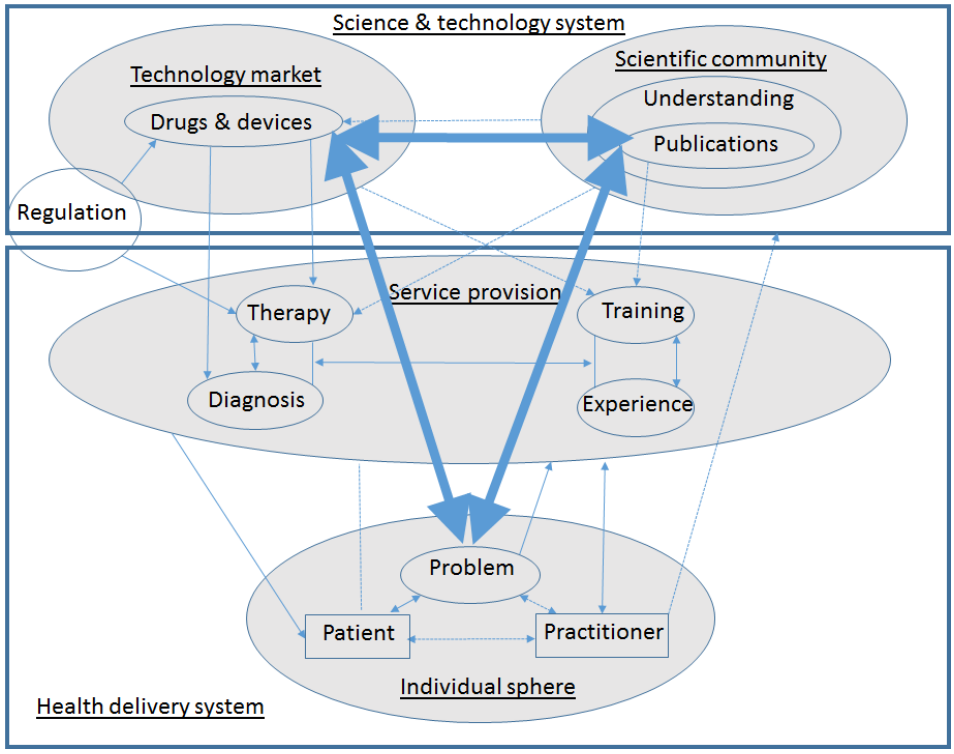

Figure 1. Health innovation system adapted from Consoli and Mina (2009) (Source: Heinonen, 2015)

In the HIS framework, the scientific community consists of clinical and medical staff and university departments, e.g. pharmacology, biology, genetics, informatics, engineering (Consoli and Mina, 2009). This close linkage between researchers and hospitals is also essential in the development of new products in the RM sector (McMahon and Thorsteinsdottir, 2013). Research hospitals are important in the diffusion of knowledge, intermediating between basic science and clinical trials, and providing practical and important feedback for medical technology manufacturers (Consoli and Mina, 2009). The health delivery system is an important subsystem in which the hospital plays a major role and in which there are two interdependent levels regarding medical technology innovation, i.e. the international medical sector level and the national level (Metcalfe et al., 2005).

In the medical device sector, innovation processes and discoveries are distributed between clinicians, academics and firms (Blume, 1992; Gelijns and Rosenberg, 1995; Metcalfe et al, 2005). Blume (1992) argued that incentives for both industry and clinics makes the diffusion of new medical technology possible. For example, in the

case of x-ray imaging, advances have been based on collaboration between radiologists and manufacturers, and a similar pattern between manufacturers and clinicians has been the case with many other medical technologies as well (see Blume, 1992). The relationship between industry and academia is one of the systemic aspects of medical technology innovation in general (Metcalfe et al., 2005). Additionally, the supply and demand sides both contribute to the innovation process (Gelijns and Rosenberg, 1994) and there is an interdependence between health care service deliverers and manufacturers (Metcalfe et al., 2005). There is a symbiotic relationship between medical practitioners and the medical device industry, since practitioners are dependent on new technologies and industry is dependent on practitioners who help by utilizing the innovations (Blume, 1992). These systemic interdependencies are outlined in the HIS framework. To provide a structure for the analysis of medical technology innovation, Blume (1992) categorized its phases as follows:

1) Exploration: In this phase first prototypes are made, and publications that report successful use of new medical technology. Medical and industrial communities become aware of achievements. There is plausible evidence that a new principle works.

2) Development: Begins with first human experiences by medical technology prototype and ends with commercial manufacture and market release.

3) Diffusion, evaluation and assessment: New medical technology is integrated to medical practice and is institutionalized in practice and diffused to routine use at some level. Hospitals make the decision if they purchase the new technology.

4) Feedback: Development of improved models and search for new applications if technology is successful. Manufacturers or users find ways how to improve commercially available models. This phase might begin just after successful commercialization.

Even though Blume has used the categorizing for the analysis of medical devices, a similar categorization seems to apply to medical technology innovation in general. However, there might be differences between different technologies, for example regarding division of labor during the exploration and development phases. In biomedical research, public investments are accompanied with industrial manufacturers of new technologies as they invest a significant share of their annual sales to research and development (Gelijns and Rosenberg, 1994). Division of labor might also change, as has happened in the RM sector. Lysaght et al. (2008) described how in the 1990's most R&D was conducted in firms, which is no longer the case.

Regulation is another important aspect of innovation in medical technology. Governmental regulation aims to form criteria to govern the innovation process (Blume, 1992) and in current economies, regulation becoming increasingly strict is an important factor that affects the development of medical technology. In the case of ultrasound development, barriers of entry were extremely low and even a one-man company has previously been able to modify a product and start to sell it (Blume, 1992). Compared to today's world, even the simplest device intended for medical use, has to go through a specific regulatory process and fulfill the quality requirements. As regulation governs the development process of new medical technology, those technologies aimed for scientific or medical research, as well as, e.g., innovations in surgery, are excluded in some cases. For example, in the US, regulatory approval for drugs was already quite strict in the 1960's and, in the case of beta-blockers for heart disease, regulatory approval took many years, whereas at the same time cardiac surgeons had a competitive advantage over cardiologists as they developed surgical technology without a need for regulatory approval (Gelijns and Rosenberg, 1994).

Regarding the role of clinicians and academics, academic health centers (AHC) are seen to be important in the medical technology innovation process. AHCs are responsible for conducting medical teaching, research and clinical practice. According to Anderson et al. (1994), contributions of AHCs in medical technology innovations are as follows:

- development of new technologies, techniques and applications
- adoption of new devices, therapies and procedures
- evaluation and assessment of emerging and established technologies and practices
- advice to public and private sectors

Since the availability and development of alternative and competing technological opportunities influences the development and diffusion of medical technology (Gelijns and Rosenberg, 1994), there are some aspects that make the diffusion of medical technology difficult: uncertainty after introduction of new medical technology; complex interactions between practice and understanding; and a complex selection environment (Gelijns et al., 2001). Even after a new product is ready and it is possible to start selling it, much of the uncertainty only reduces after extensive use (Gelijns and Rosenberg, 1994). Medical devices are faced with an even higher incremental change after adoption than pharmaceutical products (Gelijns and Rosenberg, 1994).

2.3 Competence bloc theory

For the emergence of new industry, it is important to have the required mass of resources, skills and activities to enable a cumulative process with momentum (Avnimelech and teubal, 2008). However, according to Cooke (2004), most regions and many nations have poor linkages between knowledge generation and knowledge exploitation. The linkage between knowledge generation and knowledge exploitation can be found from competence bloc theory, which describes the process from invention to commercialized product. The competence bloc approach is based on a venture capital-driven system and suggests that it is necessary to have a critical mass of competencies if sustainability of economic success is desired.

In competence bloc theory, Eliasson and Eliasson (1996) identified the necessary elements for the emergence of biotechnology industry in the early 1990's. In this dissertation, competence bloc theory is used as a framework to describe market creation mechanisms and new business creation in the RM sector, because in this respect biotechnology and the RM sector are sufficiently similar. They define a competence bloc as:

> "Only a competence mass sufficiently large to generate large-scale industrial success we call a competence bloc" (Eliasson and Eliasson, 1996: 15).

On top of a high-quality research base, it includes those actors and competencies that are needed for economic success. However, there should be a sufficiently large number of actors of the competence bloc in order to ensure that allocation of resources is done efficiently by terminating losers and recognizing winners as fast as possible. Eliasson and Eliasson describe two types of errors that can happen in innovative R&D ventures because uncertainty cannot be estimated by rational calculations:

> 1) losers are kept on for too long,
>
> 2) winners are rejected. (Eliasson and Eliasson, 1996: 9)

Competence bloc theory makes an assumption that the economy is organized most efficiently when companies aim to do experiments. In fact, they argue that in biotechnology, product development is experimental by nature. Competence bloc fits into the categorization of Blume (1992), introducing an innovator that is active in the exploration phase; an entrepreneur, industrialist and venture capitalist in the development phase; and customers in the feedback phase. In this way it describes the infrastructure that is needed to create, select, recognize, diffuse and exploit new commercially viable ideas (Eliasson and Eliasson, 1996). Table 1 presents the actors

and their tasks. Marketing knowledge and manufacturing skills should be integrated with these competencies.

Table 1. Actors of competence bloc (Eliasson and Eliasson, 1996).

Actors	**Tasks**	**Function in infrastructure**
Customer	Active, competent and resourceful.	Demand
Innovator	Connects technical specializations.	Creation
Entrepreneur	Selects commercially potential innovations.	Selection
Venture capitalist	Recognize and finance commercially viable opportunities.	Recognition
Industrialists, business leaders and financial experts	Bring new product to full-scale production.	Exploitation
Exit-market	Expectation for reasonable or better profit for those who are successful.	Incentive

The role of customers is important already in the development of the product as they are the main source for demand, and so can help companies create better products (Eliasson and Eliasson, 1996). The role of customers is also important during the feedback phase (as described in Blume's (1992) categorization), since customers provide feedback after commercialization and thus help develop improved products.

Johansson (2010) introduced inventor and skilled labor as complements to competence bloc theory. Indeed, they are important actors, even though the

distinction between roles of innovator and inventor might be somewhat 'fuzzy'[7]. In reality, the role of innovator might embody several potential actors, e.g. Reynolds et al. (2013) argue that in some cases venture capitalists are active in combining intellectual property from universities and forming a team, because they see a potential new technological opportunity. By doing so, venture capitalists actually cross-over the roles of innovator, entrepreneur and venture capitalist. Regarding skilled labor, it is difficult to form a successful enterprise without competencies in manufacturing and other important functions.

Entrepreneurs are key actors as they are responsible for selecting commercially exploitable innovations. In accordance with competence bloc theory, Hopkins et al. (2007) argued that in some cases small firms are more efficient in transforming new ideas into potential business cases than the in-house R&D departments of large companies. There is also significant uncertainty in medical technology innovation. It is difficult to know if either the technology opportunity is viable in the first place or if the business analyses regarding costs and market size are correct, hence firms (industrialist type) try to reduce uncertainty by taking government subsidies and/or taking over a firm (entrepreneur type) with established links to a market (Blume, 1992). The businesses of entrepreneurs should be scalable so that it is worthwhile for venture capitalists to invest in them. Venture capitalists are necessary actors because they recognize and fund those entrepreneurs who are able to make a commercially viable product. Venture capitalists have a pool of venture capital (VC) that is defined as:

> "Independently managed dedicated pools of capital that focus on equity or equity –linked investments in privately held, high growth companies" (Gompers and Lerner, 1999:349; cited in Avnimelech and Teubal, 2006).

It is possible to make a distinction between venture capitalists and private equity (PE) companies, since venture capitalists invest in privately held and high growth companies[8], whereas PE companies focus on both high growth and mature companies – either private or publicly traded (Avnimelech and Teubal, 2006).

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[7] Inventors by definition have a new idea (invention), whereas innovators combine different inventions and technologies together. In this dissertation, the role of innovator embodies both inventor and innovator for the sake of simplicity.

[8] There is a narrow definition where the company is between one and five years old, and a broad definition where the company is between one and ten years old, according to Avnimelech and Teubal (2006).

Venture capitalists should allow entrepreneurs to aim at winning. Because venture capitalists are able to invest in high-risk ventures, type 2 errors can be reduced, since an entrepreneur is given an opportunity in uncertainty. If the entrepreneur cannot win, the project will be terminated and the entrepreneur is able to start a new one. To convince venture capitalists about a company in the RM sector, it is beneficial to have a strong medical need, savvy management and intellectual property (Parson, 2008). Additionally, simpler but superior products and scalability of manufacturing can help ensure a company's success (Parson, 2008).

An environment that enables expectations for great profit is an essential incentive for entrepreneurs and venture capitalists in competence bloc theory[9]. A viable stock market is also important as it enables additional finance drawing later after an IPO. In both the IPO and M&A, the industrialist is the one who continues development of the product to full-scale production. This makes the role of industrialists very important also, as they have the resources and competencies to scale-up production and actually deliver the product to market. In the market, it is important to have a high-quality product, third party endorsements for the product, and an effective sales and marketing strategy (Prescott, 2011).

[9] This environment is known as an exit-market where transfer of a company's shares (stocks) is made. Exit is an important event for venture capitalists as they are able to monetize their shares of the company. This event happens through an initial public offering (IPO) on the stock market or in the merger or acquisition (M&A) of the company.

3 Context of the study

3.1 Overview of the RM sector

Definition of terms evolve over time, and this too has happened with the term 'regenerative medicine'. Scholars have used RM fluently as a synonym for tissue engineering and cell therapies. Mason et al. (2011) argued that no one should anymore pretend that RM and cell therapies are the same. Even though these overlap, Mason and Manzotti (2009) and Mason et al. (2011) argued that the cell therapy industry should be called an industry in its own right, alongside pharmaceuticals, biopharmaceuticals and medical devices. The cell therapy industry's core technologies are cells and tissue engineering (in which both cells and non-cell based scaffolds are used in combinations). Mason et al. (2011) argued that RM draws upon all the healthcare sectors (pharma, biopharma, medical devices and cell therapies) and thus is not a platform technology but a treatment approach. Polak et al. (2010) presented a similar viewpoint by saying that RM is likely to transform the way medicine is practiced by providing another option besides pharmacological and surgical procedures. How should RM then be defined? Mason and Dunnill (2008a:4) gave a simple and broad answer to this:

> "Regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function".

There are also other viewpoints. The National Institutes of Health (US) defined RM more narrowly (NIH, 2015:23):

> "A field of medicine devoted to treatments in which stem cells are induced to differentiate into the specific cell type required to repair damaged or destroyed cell populations or tissues."

In a broader manner, Messenger and Tomlins (2011: H10) provided a structured listing of some of the aspects that RM covers:

1. Cell-based therapies, i.e. utilization of stem cells
2. Tissue engineering, i.e. combination of cells and materials
3. Biomedical engineering, i.e. medical devices mimicking the functions of organs

4. Gene therapy, i.e. genetic material is delivered to cell to manipulate its behavior

Hence, broadly speaking, RM includes all kinds of approaches to restore or establish normal functions. In this dissertation, the terms 'regenerative medicine' (RM) and 'RM sector' are used to cover approaches that try to regenerate human cells, tissues or organs with the help of stem cells, and thus is more or less synonymous with the cell therapy industry and is in line with the definition provided by the National Institutes of Health (NIH).

The NIH (2015) provides basic information about stem cells. Simply, stem cells can be categorized as embryonic or non-embryonic (adult) stem cells, both having the ability to differentiate to other cell types. Already in 1981, scientists found a way to derive embryonic stem cells from mice. Subsequently, in 1998 embryonic stem cells were isolated for the first time from humans (human embryonic stem cells). The next big breakthrough happened in 2006 when researchers were able to reprogram adult cells into a stem cell-like state. These new stem cells are called induced pluripotent stem cells (iPSC). Regarding embryonic stem cells, the ethical and political environment[10] is the biggest obstacle for the use of stem cells obtained from human embryos (Harvey, 2010). This issue was partly resolved in 2006 when iPSCs were discovered. However, it is not certain if iPSCs and embryonic stem cells are identical (Amabile and Meissner, 2009). There are also other interesting avenues for the use of iPSCs. For example, in drug development more than 90% of drugs fail in clinical trials due to lack of sufficient efficacy or unanticipated toxicity (Rubin, 2008). Rubin (2008) suggests that the use of iPSCs could resolve some of the problems, as patient-specific models could be used for screening purposes to guide more predictive drug discovery and toxicity studies.

The two main categories of stem cell therapies are allogeneic (use of external cells) and autologous (use of a patient's own cells). Which one is more viable for business purposes has been discussed, though there is a lack of consensus (Martin et al., 2006; Parson, 2008). Product development in the RM sector is very similar to the

[10] According to McMahon and Thorsteinsdottir (2013), the Catholic Church in Brazil was successfully against the use of human embryonic stem cells for research purposes, but in China or India, no such issues existed in their use. Even in the US (2001-2009) George W. Bush banned federal funding for research on human embryonic stem cell lines (Murugan, 2009). Among EU countries, different regulations exist regarding the use of human embryonic stem cells and some are more permissive (e.g. UK, Sweden and Belgium), while others are more restricting (European Science Foundation, 2013).

biotechnology sector. The following aspects characterize the biotechnology sector according to Eliasson and Eliasson (1996):

1) Biotechnology originated in academia, and an academic research laboratory is essentially important.

2) Production in the biotechnology and pharmaceutical industry is mostly development work in the laboratory and marketing. After a clinically tested and officially accepted product, the actual manufacturing cost is relatively insignificant.

3) New discoveries are based on several disciplines and scientific knowledge. Thus, a diverse environment is beneficial for innovations and industrial applications.

4) New product development is experimental.

The difference with biotechnology can potentially be found from point 2, mainly due to a lack of consensus for the business model (allogeneic vs autologous therapies). Especially if an autologous therapy (patient's own cells) is used, the cost of the therapy might be even higher as more clinical operations are needed.

Martin et al. (2006) claimed that two waves of attempts to commercialize stem cells and to develop an industry have shaped the RM sector. In the first wave (1980's to 1990's), the US was dominating, and during the second wave (mid-1990's to early 2000's), Europe had a stronger presence. In the second wave of RM sector development, Lysaght et al. (2008) claimed that most of the research was conducted in the private sector (mostly in venture-backed start-up companies), and even though breakthrough ideas emerged in academia, only ten percent of activity in the field was accounted for by government-supported research in academia (Lysaght et al., 2008). They described the second wave (early 1990s through 2001) as "the best of the times", but afterwards (between 2001 and 2003) came a crash making the period "the worst of the times" (Ibid., p. 306). Martin et al. (2006) argued that there is huge uncertainty regarding the future of the RM sector. According to them, some firms were able to grow by selling tools and services, whilst simultaneously working towards the long-term objectives of novel cell-based therapies. However, many of these were poorly funded, small companies. Mason (2007) looked optimistically to the future and spoke for a new era in the RM sector "RM 2.0" to begin in 2005. Here, the firms' focus is on commercially successful products and a technology push is coupled with a market pull. Today, approximately 10 years later in 2016, RM sector products have not yet widely found their place in the regular hospital treatment curriculum, but there are still signs that the industry is growing.

Even though commercialization is an important question and the RM sector is rapidly progressing, according to McMahon and Thorsteinsdottir (2013), major

developing countries (Brazil, China, India) do not emphasize patenting. Conversely, in the US, intellectual property was seen to be important in the study by Johnson et al. (2011), and established companies in particular had trouble expanding the intellectual property base they owned. In the EU, different countries have different regulations regarding what can be patented in the case of human cells derived from embryos (Mason and Dunnill, 2008b).

Salter et al. (2014) presented a current schema for different stem cell therapy innovation models (Figure 2). According to them, the majority of global activity is in the domain of models II, III and IV, and only a few marketed stem cell therapies have been generated by model I in the global stem cell market. While models I and II are the *de facto* models used in Western countries, in some other countries (non-Western) it is possible to find stem cell therapies where models III and IV apply. As they argue, the challenge with model I is that it is extremely expensive and slow, and thus there is a gap between the promise of stem cell science and the reality of the limited amount of therapies being provided through model I. The reason for slowness and expensiveness is that, in reality, the scientific innovation model process is cyclical, and linear progress is often interrupted. However, model I is the one currently used by the US and EU. In the EU, these products are called ATMPs. Model II is used in the EU and is based on hospital exemptions within the ATMP regulation. By the end of 2012, there were approximately 40 products under the ATMP hospital exemption and 18 products in the UK under the 'Specials' scheme, which is the UK's national implementation of the ATMP hospital exemption. (Salter et al., 2014).

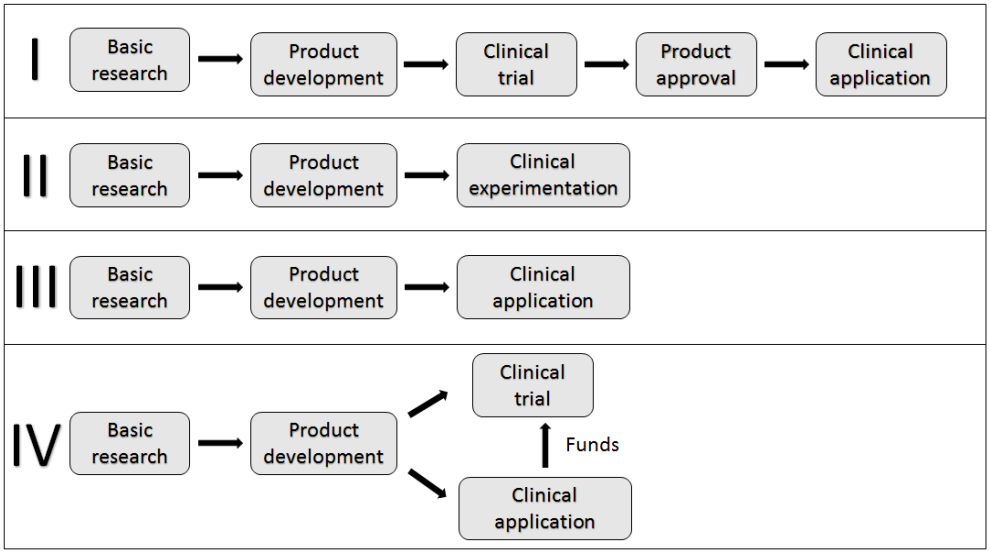

Figure 2. Different stem cell innovation models of the global stem cell market according to Salter et al. (2014).

An interesting case is model IV where revenues from stem cell therapies are used to fund official stem cell therapy clinical trials. By using this kind of business model (either model III or IV) it is possible to make revenue from medical practice before any official registered products are available for the Western market. How ethical it is, is another question and discussion, including issues such as how patients should be informed, lack of any peer-reviewed control of therapies, and lack of regulatory bodies (see e.g. Gunter et al., 2010; Lindvall and Hyun, 2009). In addition, there is a fifth model in Japan, where legislation was changed in 2013 and a new regulatory pathway created, in which it is possible to verify the efficiency of a new stem cell product in the market and only its safety must be confirmed prior to clinical trials (Japan Times, 2013). This change radically reduces the time spent on clinical trials before sales.

3.2 Description of the case

According to Stokes (1997), scientific research can be divided between pure basic research (Bohr's quadrant), pure applied research (Edison's quadrant) and use-inspired basic research (Pasteurs's quadrant). The case studied in this dissertation locates in Pasteur's quadrant, as the need for RM therapies comes from real patients

and medical problems that cannot be solved easily any other way. At the same time basic research is needed, as there is no deep understanding of how stem cells actually work and why things happen.

The case studied for this dissertation is located in Tampere, Finland. In Tampere, there are two main universities, the University of Tampere and Tampere University of Technology. In 2005, the University of Tampere, Tampere University of Technology, Pirkanmaa Hospital District, Pirkanmaa University of Applied Sciences[11], and Coxa, the Hospital for Joint Replacement, jointly established the Regea Institute for Regenerative Medicine (Regea). Regea was established in order to exploit the strengths found in Tampere, i.e. biomaterials and stem cell research[12]. Tissue engineering was identified as a potential application field for the expertise found in the biotechnology cluster of Tampere. The first application was developed very quickly, and in 2007 the first experimental clinical treatments were given to patients. Since then altogether over 25 patients have been treated with this therapy, and some patients have even come from overseas. In 2011, the two universities established a joint institute, the Institute of Biosciences and Medical Technology (BioMediTech), which is a home base for approximately 250 scientists. The combined technological and biological expertise from the two universities allows BioMediTech to develop medical technologies based on interdisciplinary research.

It is remarkable that in both Regea and later BioMediTech, clinicians are also involved in the development of technologies. Regarding bone growth therapy, patients have been operated on in several university hospitals within Finland, lately in Tampere. The university hospital of Tampere is located on the same campus as BioMediTech, making collaboration easier. Research in RM is conducted at BioMediTech and not in the university hospital and school of medicine, which focuses on other research areas. In 2012, the common research strategy of BioMediTech, the University Hospital of Tampere, Institute of Medicine, and the Institute of Health Science, stated that a joint research organization, the Tampere Health Research Center Kauppi, should be established in order to support scientific breakthroughs, innovation, and new businesses. In the later strategy of the University Hospital of Tampere (2014-2016), one of the goals was that resources should be

[11] Pirkanmaa University of Applied Sciences and Tampere University of Applied Sciences subsequently merged – constituting Tampere University of Applied Sciences.

[12] See Sotarauta and Mustikkamäki (2015) to better understand the history regarding RM sector development in Tampere from the early seeds of change until the establishment of BioMediTech.

improved and combined for the Tampere Health Research Center Kauppi to make it really happen. Hence, this agglomeration of BioMediTech and the university hospital is a strategic one, and provides research groups with the possibility of having a practical clinical need as a goal. It also gives support and feedback during the innovation process. Even more important is that innovations can be utilized in the clinical practice environment.

At the regional level, some important regional development projects have helped in the development of the RM sector in the Tampere region, namely: BioneXt (2003-2010), the Biosensing Competence Center (2007-2010) and HealthBIO (2007-2013). At BioneXt Tampere, the mission was to acquire resources, expertise, and investments in Tampere. They especially supported the fields of tissue engineering, biomaterials, immunology and bio-ICT in activities such as leading-edge research, product development, clinical applications and commercialization of biotechnology. At the Biosensing Competence Center, the mission was to bridge the gap between basic research and product creation in the fields of tissue engineering and clinical diagnostics. Proof of concept (PoC) development was seen to be important in this bridging and they invested in commercialization projects, core infrastructure, and IPR protection services. HealthBIO was a national program focusing on nationally significant areas of biotechnology, which in Tampere meant human spare parts in the RM sector. In this program, the Finnish Funding Agency for Technology and Innovation (TEKES) introduced its new proof of concept financial instrument, which was intended to help in the translational phase of research. In BioMediTech, this financial instrument is important in order to perform PoC development within the university.

During the establishment phase of BioMediTech, TEKES granted funding for BioMediTech to establish a strategic research program called Human Spare Parts[13]. In this program, the unmet needs of medicine are targeted with stem cell research and supporting technological research. BioMediTech selected eight groups for this program: four groups from technological disciplines and four groups focused on stem cell research. The aim of this research program is to produce commercial innovations besides basic and applied research. The Human Spare Parts research program is under scrutiny in this dissertation, as it is the main 'vehicle' for RM sector development in Tampere. At BioMediTech, there are other groups focusing on

[13] The term 'strategic research' reflects the Australian school of thinking, whereby strategic research is located between tactical (immediately applicable) and pure research (highly abstract) (Stokes, 1997).

different areas of health and medicine, but these groups are not part of the Human Spare Parts research program.

RM research has received attention in the Tampere region and a local newspaper has mentioned stem cells quite frequently in their news, as presented in Figure 3. Local and national public agencies have invested a significant amount of money in RM research, hence there are great expectations that it produces a new field of expertise and business in Tampere. For example, The Council of the Tampere Region promotes BioMediTech as one of their spearheads. Together, groups from BioMediTech have a track record of over 100 patents and 10 spinoffs, and hence there is commercial experience in the research groups. However, none of these spinoffs is directly from the Human Spare Parts research program. Therefore, it is a fascinating question, asked by this dissertation: how those ideas emerging from RM research could be commercialized and diffused for wider use.

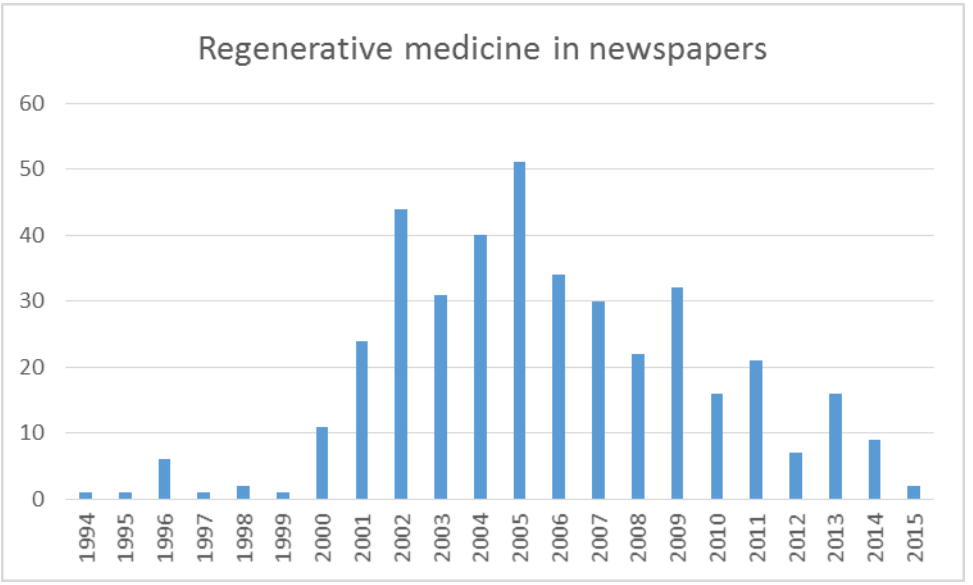

Figure 3. RM related articles in the local newspaper Aamulehti (391 articles) and Finnish business newspaper Kauppalehti (11 articles). Terms "stem cell" and "human spare parts" were used to collect the articles (October 29, 2015).

4 Methodology

4.1 Research design and method

Critical realism is the philosophical basis for this dissertation. According to Maxwell (2012), critical realists claim there is a world that exists independently of one's perceptions, theories or constructions (ontological perspective), but at the same time accept constructivistic and relativistic understanding to epistemology meaning that people have their own perspectives and standpoints. Critical realists try to minimize the difference between the reality and people's perspectives and standpoints, by using triangulation by which different perspectives are collected in order to represent the reality as correctly as possible. Even then, as Häkli (1999) mentions, the research process cannot produce the reality itself but only a representation of the reality, because the source of knowledge (reality) itself is not dependent of its representation. It is important to recognize that there most probably is a bias between reality and its representation. This is the difference with constructivism, in which reality is how people understand it to be. Critical realism paves the way for this dissertation, as the aim is to see realistically how new products in the RM sector emerge. It means that the role of the researcher in this dissertation becomes crucial to the interpretation of different sources of information in order to see beyond the informants' own perspectives, ideas and ideals.

Due to the practical aim of this dissertation, a constructive approach was chosen as a guiding research design. Neilimo and Näsi (1980) divide research approaches between conceptual, decision-oriented, action-oriented, and nomothetical approaches. In addition to these approaches, Kasanen et al. (1991, 1993) introduced a constructive approach. The relationship between these different approaches is described in Figure 4. It should be stressed here that the constructive approach belongs to business and management studies and differs significantly from constructivism, which is used in social sciences and which interprets reality based on human experiences. The aim in constructive research is to provide a useful tool or construction in the context of a firm. Kasanen et al. (1993) discuss the placement of the constructive approach among other research approaches, resulting with it ending up at the apex of normative and empirical elements. The normative element simply

means that the results are meant to guide management in the operating of the firm. The empirical element refers to the direct and pragmatic empirical connection, although the constructive approach also has a strong connection to theoretical analysis in order to innovate a new entity. Although the constructive approach is intended for management and business studies, it has also been used successfully in dissertations on innovation studies (see e.g. Harmaakorpi, 2004; Uotila, 2008). However, the leap from the firm environment to a broader system including several organizations is not a straightforward one. In the context of a firm, managers make the decisions, but who is the decision maker at the system level? Hence, the application of the construction could be broader. The construction developed in this dissertation should be useful not only for policy makers and BioMediTech, but also for other actors who are dealing with the commercialization of stem cell therapies. It should provide a comprehensive understanding about important elements in the commercial development of RM cell therapies.

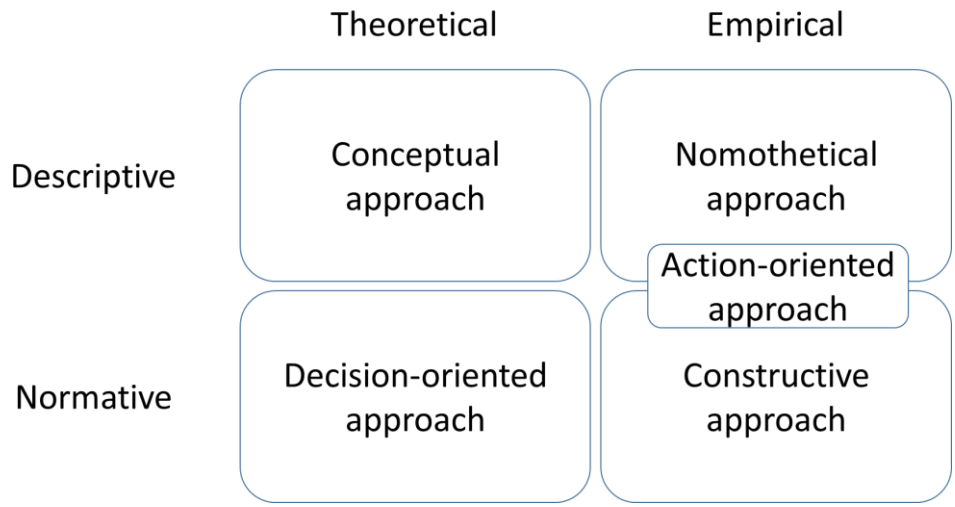

Figure 4. Positions of different research approaches (Kasanen et al., 1991, 1993).

This dissertation follows a qualitative case study methodology in data collection, since this allows the investigation of a phenomenon within its real-life context, thus providing the holistic approach needed in a constructive approach (Yin, 1994). Qualitative research searches for a certain quality that is typical for the studied phenomenon or that makes the phenomenon different in comparison to others (Stenbacka, 2001). Case studies usually rely on multiple methods for gathering data, and hence their design is complex (Marshall and Rossman, 1999). Implementation

of a case study is required when the relevance and practical functionality of the construction is one of the goals (Kasanen et al., 1993). In case studies, it is important to make a distinction between the specific case and the topic of the research (Laine et al., 2007). In this dissertation, the Human Spare Parts research program at BioMediTech is the target case because it can provide understanding about different aspects of RM cell therapy commercialization. The practical problem of this research also comes from BioMediTech.

Constructive research comprises the basic elements described in Figure 5. The aim of constructive research is to produce a construction, which is useful in both practice and theory. Hence, the theoretical contribution and real-life practical functionality are important aspects of the developed solution of the problem. Several steps guide the process in constructive research, although the order of these steps might vary (Kasanen et al., 1993):

1. Find a practically relevant problem, which also has research potential
2. Obtain a general and comprehensive understanding of the topic
3. Innovate, i.e. construct a solution idea
4. Demonstrate that the solution works
5. Show the connection to theory and the research contribution
6. Examine the scope of applicability of the solution

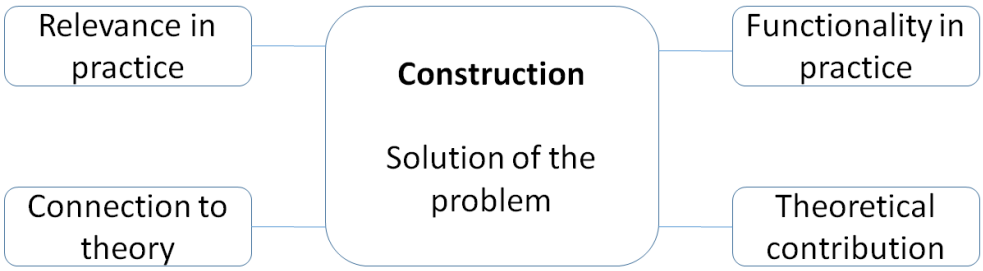

Figure 5. Elements of constructive research approach (Kasanen et al., 1991, 1993).

These steps were followed in this dissertation as well and are explained in the following paragraphs:

Step 1: As was previously described, the motivation for this dissertation comes from the challenges BioMediTech faces in the commercialization of stem cell

therapies. Commercialization in the RM sector is a practical and relevant problem, which BioMediTech and many other universities face.

Step 2: The research topic was studied via a literature review focusing on commercialization in the RM sector and what the challenges are. In addition, relevant blogs, webpages, news items and articles, etc., were read in order to acquire a comprehensive understanding. It became evident that hospitals have a significant role in commercialization, and medical technology innovation literature was studied in order to understand these aspects. HIS especially provided a holistic understanding of the innovation systems surrounding medical technology and medical practice. Competence bloc theory provided a great understanding regarding the actors and competencies needed in the commercialization of new products. This was essential since HIS does not explain how highly-regulated and costly products based on university R&D are commercialized. Instead, it gives an assumption that the technology market provides drugs and devices for the purposes of hospital therapies, which is not the case in the RM sector. Thus, there was a challenge to make a connection with a theory that satisfactorily explains how the commercialization process proceeds. Nevertheless, competence bloc theory was identified, and after careful consideration seems to explain the process in the RM sector as well as it does in the biotechnology sector.

Step 3: For the building phase of the construction, HIS and competence bloc theory were utilised as inspiration from the outset. The construction developed over time as more experience was gained from interviews and literature. Altogether, the development included four main iterations. In the first iteration, the idea of PoC was embedded in the HIS and in the second iteration (mainly due to comments received from the research group's internal seminar) this was simplified but still retained in the form of the HIS (presented in the form of a conference paper at the end of 2014). The third main iteration was developed in early 2015 and later published in Article III. Finally, the fourth iteration, which provides a more holistic picture, is presented in section 6.1 in this dissertation. The construction was discussed with academics and practitioners in the field throughout the process, and in this way its appropriateness and relevance has been enhanced.

Step 4: According to Kasanen et al. (1993), there are three distinctive market tests: a weak market test, a semi-strong market test, and a strong market test. The weak market test is passed if any manager is willing to apply the construction in their actual decision-making. The semi-strong market test requires wide adoption by companies in order to be passed. The strong market test is even stricter. It requires that the semi-strong market test is passed and that those business units using the

construction obtain better financial results compared to those business units not using it.

In the case of this dissertation, the construction is not developed in the context of a firm but instead emerges from the intersection of two universities and a globally emerging industry, and provides a holistic, system-level understanding of how innovation emerges and is commercialized in the RM sector. Regions are not identical, but it is reasonable to expect that the main elements in successful commercialization are the same. However, no decision makers in business, academia or politics have implemented the construction in their decision-making yet. The future will show if the construction passes the weak market test.

Step 5: A system-level perspective of innovation was chosen from the beginning in order to holistically understand innovation and commercialization in the RM sector. Thus, there is a theoretical connection to competence bloc theory and HIS in the construction. In this way, the construction intermediates between medical technology literature and innovation system literature.

The construction has several scientifically interesting elements that are studied in individual articles (I-V) in this dissertation and each article has an independent contribution. The research contribution of the construction lies in understanding the link between the technology market, hospitals and academia in the development of innovation in the RM sector.

Step 6: Kasanen et al. (1993) argued that generalization already happens if a useful construct has been designed, as it is likely that the solution works in other firms of the same type as well. Thus, the question of generalization is what principle does it reveal (Kasanen et al., 1993). In this way, the market test of the construction and its generalization or scope of applicability is strictly connected. In this dissertation, it is difficult to conclude about the generalization of the construct, as the market test has not yet been passed.

4.2 Data collection

The primary method of collecting data was by interviewing. Secondary data, in the form of academic publications, newspapers, websites and blogs, was used to understand commercialization processes and industry emergence in the RM sector, as well as to develop relevant questions for interviews. The majority of interviews focused on commercial matters within the Human Spare Parts research program, in which the aim is to conduct interdisciplinary research and develop innovations based

on different technologies and disciplines, and ultimately develop new ways to cure patients, as was described earlier in section 3.2. The interviewees from BioMediTech were team leaders, IPR and regulation-related staff and other key personnel. Interviewees were selected based on their formal position within the organizations. In a few cases, secondary sources and suggestions for interviewees helped to select the relevant person for interviewing. The author of this dissertation conducted altogether 24 interviews as described in Table 2.

Table 2. Details of the interviews.

Organization	**Number of interviews**	**Level**
BioMediTech	15	Local
University Hospital of Tampere	3	Local
Firm	1	Local
Regional development agencies	2	Regional
Ministry of Employment and the Economy	2	National
The Finnish Funding Agency for Technology and Innovation	1	National

Interview themes were based on a competence set model[14], which was developed at the beginning of the research project (in which the author of this dissertation was a contributor): "Innovation Ecosystems, Competencies and Leadership - Human Spare Parts and Venture Finance Ecosystems under Scrutiny (2014-2015)" (Sotarauta et al., 2016; Article I in this dissertation). The author of this dissertation developed the specific interview questions. The themes and main topics in interviews were:

[14] One exception is an interview with the regional development agency that was conducted as a second interview and focused more on the history of the RM sector in Tampere, and the regional and financial aspects of RM sector development in Tampere.

1. Research environment
    - Role of applications and their commercialization process
    - Collaboration (hospitals, overseas)
    - IPR
    - Level of scientific research compared to overseas
2. Finance
    - Research funding
    - Establishment of firms
3. Firms and their activities
    - Role of scientists
    - Impact
    - Establishment requirements (general, phase of research)
    - Customers
4. The technology market
    - Finland's opportunities
    - Differences with other countries
5. Legitimization – including both ethical and legislative questions
    - Impact of ethical questions in market emergence or in research
    - Supportive and negative aspects of legislation in RM
6. RM as a systematic production
    - Role of hospitals and firms
    - Process for introducing new stem cell products in hospitals / hurdles
    - Training
7. Added value

For each theme, several questions were asked with an aim to understand the current situation in the RM sector and how interviewees understood the situation themselves. Interviews were semi-structured because not all themes, or specific

questions related to a theme, were relevant to ask from all the interviewees and for many themes, clarifying questions were required.

In addition to qualitative data gained from interviews, quantitative secondary data was used in order to study the financial situation regarding commercialization in the RM sector. The financial situation of the global RM sector was obtained from the Alliance for Regenerative Medicine (ARM). The ARM has gathered data from the RM sector since 2011. However, only the years 2013 and 2014 are fully comparable because no harmonized data was previously available due to the emergence of the industry. Data for the years 2011 and 2012 was estimated from the reports of the ARM. In Finland, it was not possible to gather RM sector data due to the lack of such data. Instead, the Finnish Venture Capital Association (FVCA) provided national Finnish data regarding the pharmaceutical and drug delivery, and drug development technology sectors between 2007 and 2013. The biotechnology sector was excluded, because it was not possible to separate out biopharmaceutical firms. The data included investments from three private venture capitalists, three public venture capital organizations, and non-disclosed foreign venture capitalists. In the case of the Finnish investors, the data included both domestic and foreign investments. Venture capitalists in these sectors provide an indication of how much finance is available in Finland for new firms and products requiring clinical trials.

4.3 Reliability and validity

Reliability and validity are considered important for assessing the quality of research results (Fidel, 1984), even though there is no single set of validity and reliability tests available in case study research (Riege, 2003). Reliability refers to the degree to which the repetition of the same research design, under conditions that are constant, produces the same results (Fidel, 1984). In a case study-like setting, reliability is somewhat problematic because conditions are not usually constant (Fidel, 1984). Assessment of overall reliability is even more difficult in constructive research, as one of the steps in the research process is to innovate the solution idea based on theory and empirical material. Thus, to ensure reliability, it is important to describe the research process (Stenbacka, 2001), which can be found in section 4.1 in this dissertation.

Validity refers to the extent to which the researcher studies what they promised to study (Fidel, 1984). Stenbacka (2001) proposes that validity in qualitative research can be achieved by strategically choosing volunteer interviewees who are part of the

problem area. In this dissertation, interviewees were selected based on their position relative to the RM sector, and thus it can be expected that they have an understanding of the problem area. Furthermore, in constructive research, market tests eventually show the validity of the construction (see more detailed description in section 4.1). As discussed previously, the construction in this dissertation has not yet passed any market test. However, discussions with practitioners in the field of RM cell therapy commercialization support the validity of the construction. Also, as was described earlier, the construction was developed and tested during different phases of development with both practitioners in the field and academics, which eventually improved the applicability of the construction and thus its validity.

5 Overview of articles

5.1 Introduction to articles

This dissertation consists of five articles aiming holistically to study the main elements of RM sector innovation. Figure 6 describes the positions of the articles within a theoretical framework. Papers appear on different levels: macro-level (Articles I, II and V), meso-level (Articles I, II and V), and micro-level (Articles III and IV). Here, macro-level covers the national and international level, while micro-level is the organizational level. In addition to different levels, these articles try to illuminate different aspects of the RM sector.

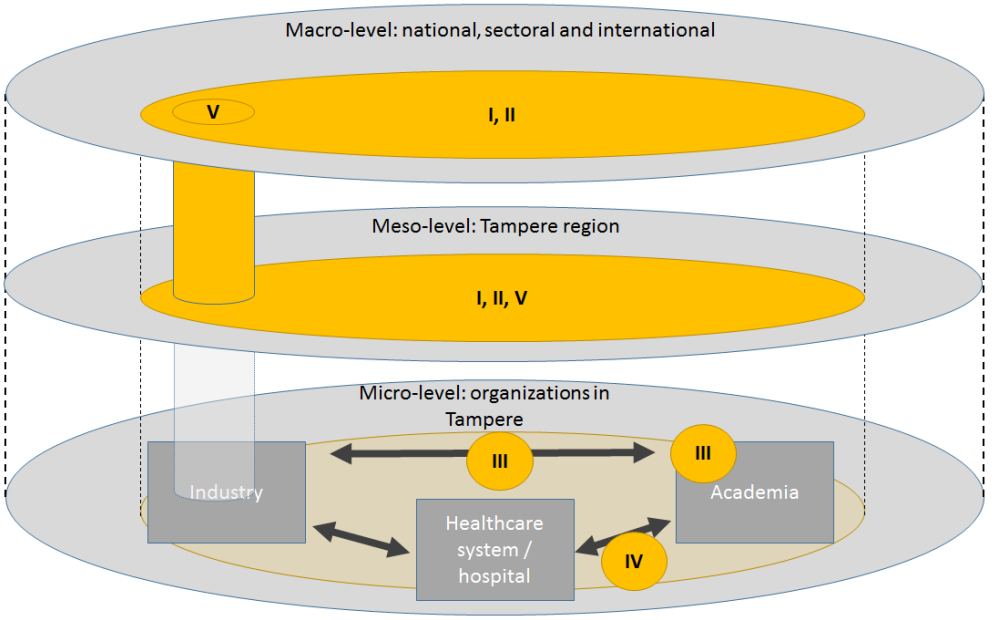

Figure 6. Positions of articles.

The aims of the articles, their theoretical backgrounds, and their focuses, are summarized in Table 3. The main results of the articles are presented in sections 5.2 - 5.6.

Table 3. Summary of articles.

	Aim	Theoretical background	Data	Focus
I	To study what kind of generic competencies are called for in the emergence of a new science-based industry and how generic competencies interact in the context of academia, business and government.	Innovation system literature, competence bloc	Secondary data, interviews	Competence set needed for an emerging industry.
II	To study cluster emergence in the RM sector by discussing what the obstacles are and how innovations emerge.	Innovation system framework, competence bloc	Secondary data, interviews	Elements of local emergent cluster in Tampere.
III	To scrutinize an approach to technology transfer and commercialization.	Medical technology literature, HIS, technology transfer literature	Secondary data, interviews	Technology transfer from academia to wider use and PoC development.
IV	To show the potential role and new structure of AHC in development of the RM sector.	Medical technology literature	Secondary data, interviews	Role of AHC and how it should be organized in order to be successful in the RM sector.
V	To study how financial markets affect the university's possibilities to commercialize new technologies.	Competence bloc	Secondary financial data, interviews	Financial market and its effects in the local competence bloc.

5.2 Article I: The triple helix model and the competence set: human spare parts industry under scrutiny

In the first article, a competence set model is introduced to better understand what are the essential generic competencies in the emerging RM sector industry. The competence set model draws from innovation system literature and the competence bloc theory and provides seven themes. Each theme includes a variety of capabilities that construct a generic competence at the system level. The themes are: knowledge creation and diffusion, entrepreneurship, finances, legitimization, market formation, systemic production, and end-value. These are discussed in the context of the Tampere region. In Tampere, knowledge creation is the strongest component of the competence set. BioMediTech has good connections in the RM sector and it has introduced innovations in which stem cells are utilized, even though these have not been commercialized yet. Although the question simply seems to be about technology transfer, the challenge is that some of the other generic competencies are missing, despite being highly relevant and needed.

Systematic production refers to those processes that are used to translate science-based discoveries to the healthcare system. There are two main ways to transfer scientific discoveries to clinical use: via firms or via hospitals. Even though systematic production has been on the agenda in Tampere since the beginning of RM-related research, the core actors have not been able to go forward in this avenue. The first experimental treatments have been delivered in the hospital, yet the university hospital has not actively attempted to get RM incorporated in its standard repertoire.

In Tampere, it is understood that the RM sector market is global and hence, international connections have begun to be established. However, the generic competencies required in order to exploit market opportunities are not sufficiently developed. There have been altogether about 10 spin-offs from groups at BioMediTech but the firms have not grown significantly. Currently, BioMediTech has not actively identified any entrepreneurs who could take the technologies developed and exploit them in the global market. However, there have been PoC projects initiated at BioMediTech and the atmosphere towards commercial solutions is favorable. Regarding financiers, the situation in Finland is challenging as RM sector products are not yet the focus of venture financiers in Finland. Hence, venture capital has to be sought from abroad, but thus far no strong connections have been established.

Legitimization includes both the ethical and legislative issues that have significant consequences in the emergence of the sector. Ultimately, it is about acquiring social acceptance for innovation. In Finland, ethical and regulative issues have not been a major problem. From a legislative viewpoint, experimental treatments are conducted under the ATMP hospital exemption, and from an ethical viewpoint, the use of adult stem cells has not initiated a great debate or discussion. There has also been a limited public debate and discussion about end-values in Tampere, the lack of which might be one of the reasons why this emerging industry is not developing as fast as it could.

Finally, it is concluded that a balanced competence set is highly desirable. The Tampere case shows how difficult it is to move forward from high-level research if some of the generic competencies are missing at the system level.

5.3 Article II: Regenerative medicine as an emergent cluster in Tampere region

The second article focuses on the emergence of a science-based RM cluster and what hinders its growth. Motivation for this article was to gain understanding of how a cluster could emerge and what the mechanisms for emergence are in the science-based sector. Thus, instead of utilizing cluster theory, competence bloc theory was used to explain how an emergent cluster could transit from the formation phase to the development phase. A theoretical framework of innovation systems by Kuhlmann and Arnold (2001) was used to structure the empirical part of this study.

The RM sector has a huge gap in financing for innovations. One of the most critical issues in this field is that academics should conduct phase II clinical trials before it is reasonable to establish a company. For companies, the question of life and death is about surviving from start-up funds to later-stage funds, assuming that they are able to attract a talented management team and are able to take care of other requirements. Start-up companies also have some limits for handling the large quantity of cells that are required for therapies. Regulations also outline the pathway to commercialization. It is not merely about creating a cost-efficient manufacturing process, but also about proving that the product is safe and efficient. There are four distinctive innovation models and ways to approach regulation in cell therapies: scientific innovation, Western medical innovation, non-Western medical innovation, and medical and scientific innovation. The scientific innovation model is the one the EU and US use. The Western medical innovation model, i.e. the ATMP hospital exemption, is used in the EU. The non-Western medical innovation model is non-

regulated, making it difficult to identify if products are safe or not, and nor is their efficiency known, as no scientific evidence is required. The medical and scientific innovation model is a combinatory one, as non-regulated therapies are used to fund clinical trials. Scholars have argued that both scientific and non-scientific models are needed because not all therapies are eligible for clinical trials. However, the safety of patients must be ensured in all cases.

Several elements of an emerging science-based cluster in Tampere are addressed in this study: history, the industrial sphere, demand, education and research, the legal and political sphere, and funding. The industrial sphere in the RM sector is not developed in Tampere, as it lacks firms. However, there is a demand for solutions in clinical care and for tools and devices at the university. Education and research are the strongest sectors in Tampere, but the legal and political spheres are also favorable towards innovations. Funding has been mostly based on public sources.

There are several policy implications regarding development of the RM sector in Tampere. First, it is necessary that there is provision of specified funding schemes in order to develop science-based innovations and to continue development in early clinical trials at the university. The second implication is the importance of local and global connections between agents to exploit potential in the region. The third implication concerns the need for an increased number of firms in the region. This can be supported by encouraging a practice-oriented environment in which it is possible to put innovations to use at a very early phase.

5.4 Article III: Management of innovation in academia: A case study in Tampere

In the third article, technology development and transfer activities at BioMediTech are studied. In general, technology transfer usually happens too early and hence, lately some proof of concept centers (PoCC) have been established in order to minimize associated problems. Personnel strongly connected to local business networks should manage the PoCC. In the PoCC, inventions are nurtured longer and the PoC is developed in order to ease the translation phase. In the PoC development phase, the commercial concept is initiated, including IPR and production processes. One challenge in the PoC phase is a lack of funding, and a PoCC is suggested as an answer for this.

At BioMediTech, support for innovation development is at the core of activities. IPR specialists are employed within its core facilities and research services to identify,

as early as possible, potential inventions and to assist with contracts. BioMediTech has a GMP level laboratory, making it possible to provide cells for clinical purposes. Especially important is the Human Spare Parts research program, which allows groups from several different disciplines to work together. In particular, the combination of stem cell groups and technology-oriented groups is advantageous because technology groups are able to develop tools for stem cell-focused groups.

Since the Human Spare Parts research program was established in order to perform strategic research with aspects of both translational and basic research, PoC development is one of the focus areas in BioMediTech. PoC projects are established independently in order to initiate commercialization and prove the commercial feasibility of a concept. In PoC projects, BioMediTech has knowledge about technologies and firms have market understanding. TEKES funds these projects with a specific financial instrument. Important aspects in commercialization are the actual technology and its required regulation. Therapies require clinical trials, whereas some technologies, especially those for research purposes, are not regulated at all.

Collaboration between clinicians and research groups allows a focus on relevant questions that arise from medical needs. A good example is bone growth therapy. This therapy has been applied to over 25 patients thus far and results look promising. However, in this case commercialization is difficult because clinical trials should be started. In order to do this, a lot of funding is needed and BioMediTech might not be able to do it alone. Information from literature and from the interviews conducted, confirms the understanding that it is not reasonable to transfer this development to a firm before phase II clinical trials are completed and, until then, development should be continued in academia.

BioMediTech has developed better technologies for research purposes than those currently available on the market because of collaboration between the groups. In some cases, the developed bone growth therapy allows clinicians to treat patients better than the state of the art therapies. However, how to commercialize and diffuse these innovations to wider use is a difficult question. In this article, it was studied how a PoC needs to be developed within academia before being transferred to the technology market, where an industrial firm could commercialize it. Before technology transfer, information flow from the technology market to academia is required in order to understand the market needs and to develop a commercially viable concept. The therapy product can then be sold to hospitals, and later maybe diffused as part of medical practice. Government regulation is important during this process, but so also is government funding.

5.5 Article IV: Potential for 21st century's academic health centers to revolutionize healthcare: Lessons to be learned from Tampere, Finland

In the fourth article, the purpose was to show how a broader view of AHCs would be advantageous for the development of the RM sector. By definition, AHCs conduct clinical and biomedical research, provide patient care, and are responsible for medical students' teaching. AHCs are also important actors in advancing healthcare as they can, for example, develop medical technology innovation and foster an entrepreneurial culture. In general, AHCs have four tasks regarding new medical technology: development of new technologies, techniques and applications; adoption of new devices, therapies and procedures; evaluation and assessment of emerging and established technologies and practices; and the provision of advice to public and private sectors.

In this article, five themes important for AHCs in the context of the RM sector were identified from interviews: a combination of basic research and technology development; a focus on products and applications; relevance to clinicians and hospitals; commercial savviness; and mission orientation. A combination of basic research and technology development is advantageous, since the development of new therapies also requires complementary technologies. In the Human Spare Parts research program, groups from scientific disciplines and more technology-oriented disciplines work together. Collaboration between them enables an iterative process of new technology development for the purposes of RM sector innovation. A focus on products and applications allows the AHC to provide patient care in experimental stem cell therapies even though they have only been proven in the laboratory and official clinical trials are not ongoing. In the case of bone growth therapy, without a strong aim to develop a solution for a perceived clinical problem, this kind of product might not have ever been developed. Relevance to clinicians and hospitals is essential. Hospitals are places for clinical experiments and trials, and here clinicians are the key actors. Even though development of therapies occurs in academia, clinicians conduct operations in hospitals. Hence, an AHC is the ideal place to conduct research and clinical experiments. Commercial savviness is necessary in order to get firms interested in research and potential outcomes. Thus, it is important to organize research activities in a way that, for example, the IP will be protected. At BioMediTech, researchers are taught to be aware about business opportunities and, even though they are not in business themselves, they are still able to speak about opportunities and assist in initial commercial activities. Finally, the mission of finding

new ways to cure patients provides motivation for organizing research and to reach towards a common goal. To succeed in this mission, research program funding is an important tool as it enables different groups to work together.

Regarding innovative environments, old structures should be broken and interdisciplinary research promoted because within the RM sector, disciplines from outside of health sciences are also able to produce innovations. A place where clinical experience, stem cell research and technology development meet is crucial for the development of innovations in the RM sector. However, AHCs have not adapted stem cell research yet. For example, in Tampere BioMediTech is responsible for research and product development, and the role of the AHC is to provide a place for clinical operations. Thus, it is argued in this article that it would be beneficial for RM sector emergence if AHCs would adopt RM in one way or another. It is suggested that this process could be through a loose organizational structure based on collaboration, as has partially happened in Tampere. Later, a more formal RM department could emerge in the AHC if RM is to be institutionalized into day-to-day healthcare in the future.

5.6 Article V: Regenerative medicine cell therapy financial market: How to finance potential innovations

In this fifth article, the financial system of the RM sector was studied. The article consists of three levels of analyses: the global financial market, the national financial market and a local competence bloc. At the global level, the aim was to scrutinize how financing in the RM cell therapy market is progressing. As the available financial data is global, it is not possible to scrutinize it locally or regionally. Hence, in the case of Finland, pharmaceutical sector data was gathered in order to identify what the potential in Finland is for RM cell therapy products. The local competence bloc in Tampere was then studied in order to see the affect of the global and national financial situation.

In the global financial market, the role of VC is relatively small ($2,13B), if compared to milestone payments that grew fourfold from 2013 to 2014 ($8,9B). It also means that established companies (e.g. pharmaceutical / biopharmaceutical companies) are interested in the R&D that development stage companies are doing, and hence, the future seems to be positive regarding the role of industrialists in the RM sector. However, how these are applicable to EU countries is not certain, as the majority of firms are in North America. According to one recently published article

(Ford and Nelsen, 2014), a change has occurred in the global investor landscape, as large pharmaceutical and biotechnology companies are now investing in the early stages of product development. It reflects well the situation regarding milestone payments.

In Finland, the situation is very different. Between 2007 and 2013, the annual average size of one investment for pharmaceutical and drug delivery companies, and for drug development technologies sector-companies, was between 0.1M€ and 0.7M€ – including both private and public investments. The average investment size of foreign private investments is larger (average 1.23M€ between 2007 and 2013), but still the amount is very modest. There are only a few pharmaceutical companies on the Finnish stock market and this might reflect the low financial potential of this sector. With this in mind, it is not surprising that in Tampere the situation regarding bone growth therapy is not favorable in terms of finances, and finance has to be sought from overseas for clinical trials. In general, even though BioMediTech is commercially aware, there are no local firms linked to it and potential entrepreneurs have not been identified. However, public funding is readily available, even though it seems to be insufficient for the further development of stem cell therapy innovations.

In general, according to Hale and Apotheker (2006), the difference between the US and Europe is that venture capitalists in the US are able to fund potential firms for longer with sufficient levels of finance. In Europe, investments are relatively small and drip-fed over many investment rounds. This has been seen especially with pharmaceutical and drug development company investments in Finland. Regarding the finances required for a company in the fields of biotechnology or RM cell therapy, a careful estimation is around $160M for product development. In Tampere, potential and relevant strategic partners and finance providers are not available locally for companies in the RM sector, even though the human resources and early adaptors might be available. All of these aspects make the development of the RM sector a challenging case in Tampere.

6 Constructed framework for RM sector innovation

6.1 Constructed framework

In this dissertation, the interest is in understanding how new medical technology can be commercialized in the RM sector. The complex system around commercialization is sketched and simplified into the developed construction presented in Figure 7. The construction is theoretically based on the HIS framework and competence bloc theory. As already discussed briefly in section 4.1, the HIS framework alone is not sufficient to explain the RM sector, as it assumes that there is a viable technology market. The difference can be found in the role of the university as a developer of new medical technology. In general, firms are contributing to new drugs and medical devices, but in the RM sector universities have an important role in early technology development, and in these cases, regulation is also affecting academia. Hence, the construction tries to clarify and to conceptualize these findings. In this construction, HIS is simplified and combined with competence bloc theory and the empirical findings of this dissertation. Several aspects of the health delivery system (presented in HIS) are simplified into medical practice. The role of clinicians and patients is emphasized here, as according to empirical research made in this dissertation, they are one of the main contributors for new therapies within a hospital. The curiosity of individual clinicians enables experimental therapies for patients who are in need of solution for their disorder. A similar simplification is made regarding the scientific community in order to emphasize the innovation process.

In this construction, the role of the public sector was made visible, as public funding is a major way to advance the RM sector, and regulation is the way to ensure safety and effectiveness of new therapies. In addition, the public sector has a great role in legitimizing the RM sector by these and other actions. However, the public sector is simplified in the construction. In reality, the public sector accounts for the entire infrastructure that is needed for health delivery and academic operations, as well as for the technology market. In addition, in Tampere many regional and national agencies and programs and institutions have been important drivers in creating the potential for excellent research and innovation. The strategic Human Spare Parts research program is one of these important government funded projects

regarding RM sector development in Tampere. As governments have to finance the emergence of the RM sector, the Human Spare Parts research program is a great tool in this mission as it covers both basic research and translational research. In this way it is possible to conduct not only high-level basic research, but also translational activities towards PoCs – especially since TEKES will fund some of the PoC projects essential for successful technology transfer from academia to industry. In an optimal situation, PoCs are transferred to the technology market, where firms continue the development. However, in the current financial situation of the RM sector, it is assumed that universities will have to continue development after a successful PoC to preclinical studies and early clinical trials, in order to scientifically show safety and effectiveness[15].

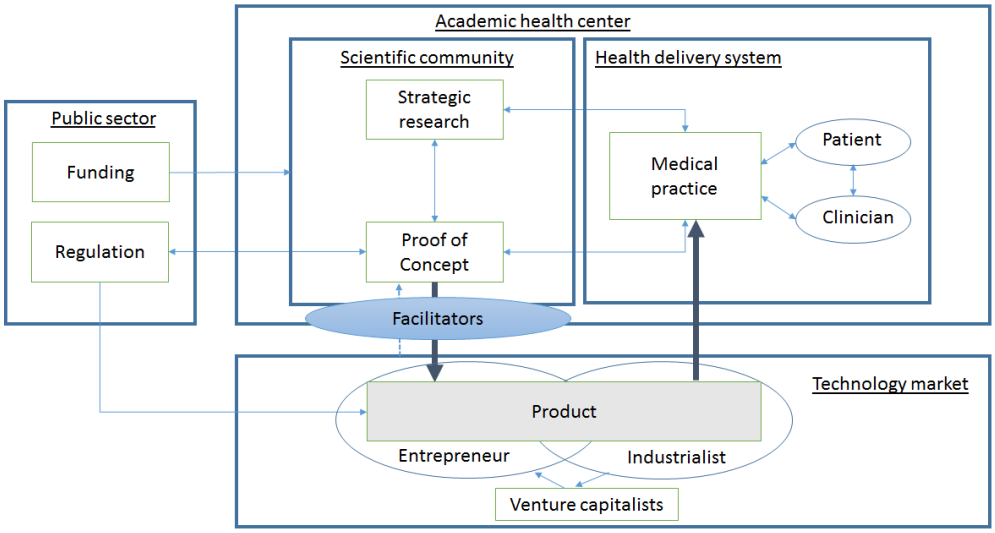

Figure 7. Construction to understand innovation in the RM the sector.

Information flow from the technology market to PoC development is crucial as it enables the development of a PoC towards a commercially viable product concept. A technology market has the resources and competencies that are needed in order to commercialize the innovation. In this construction, competence bloc theory is adapted to show relevant actors. After an invention and a sufficient PoC has been accomplished in academia, an entrepreneur is required to take care of further

[15] One of the purposes of animal studies is to assess PoC (Gee, 2014:541). However, in order to get investors interested, it is essential to get proof that the concept works in humans as well.

development. In an optimal situation, competent entrepreneurs would be interested in PoCs already during the time the PoC is being developed in academia. In this kind of situation, entrepreneurs could identify commercial opportunities and bring the market viewpoint to the PoC development. Since entrepreneurs are not always readily available, in BioMediTech for example, market understanding and advice is sought from technology market experts for PoC projects. Facilitators between the technology market and the scientific community could contribute greatly to successful technology transfer. Some examples of useful facilitators are PoCCs, RM translational centers, or other organizations trying to ease technology transfer and assist at the start of clinical trials. It is important for facilitators to have good networks with relevant technology sector actors.

Finally, during phase III clinical trials, the competences and resources of industrialists should be available in order to continue to full-scale production. However, vast financial resources are needed to reach this point and to continue further, and thus venture capitalists are important actors. Competent venture capitalists would invest in potential entrepreneurs and that way enable product development in the technology market. In many cases, entrepreneurs are able to access governmental grants and funds from other sources in the beginning, but venture capital remains one of the main ways to fund later phase development of a company. Incentives for entrepreneur and venture capitalists, as described in competence bloc theory, come from the existence of an exit market. Venture capitalists and entrepreneurs make their profits as entrepreneurs transform to industrialists, either through acquisition or through IPO. In the case of acquisition, an established company acts as an industrialist, whereas in the case of an IPO, the entrepreneur more-or-less undergoes a transformation into the role of an industrialist. Entrepreneurial competences can also be found in established companies, and if this is the case, the company itself could already have the necessary resources to act as an industrialist.

A great challenge in the RM sector is in the financing of RM cell therapy innovations. Figure 8 shows the current situation in the RM sector based on information from published articles and presentations (see e.g. Mason, 2007; Mason and Dunnil, 2008b; Parson 2008; Johnson et al., 2011; Mason et al., 2011; Bonfiglio, 2014). The reaction to the financial gap is that universities have been expected to nurture innovations further and even start early clinical trials. Some countries have established funding centers (e.g. RM translational centers) for cell therapy clinical trials (Mason et al., 2011).

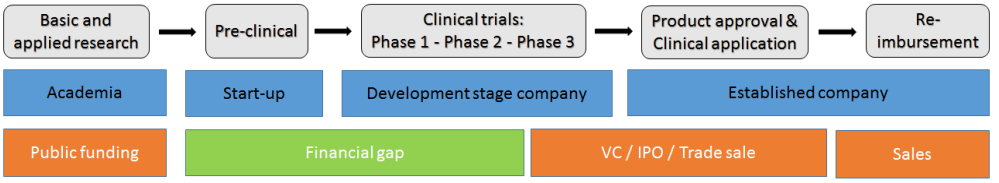

Figure 8. In the first row, the process of creating new RM therapy products is shown, in the second row the active organization form, and in the third row funding sources.

Figure 9 shows how different investment rounds are distributed in the case of firms and the how the situation currently seems to be in the RM sector. The reality is that the amount of financing required is huge. Even though there are some life science sector investors active in the RM sector (e.g. family/friends, angels, foundations, pharmaceuticals/biotech companies), there is still a gap for financing early clinical trials. Bonfiglio (2014) suggests that RM companies should find funding for early pre-clinical and PoC development from public sources, philanthropists, advocacy groups, and for pre-clinical development from angel investors. Still, the most profound advice is to stay within the university until phase III clinical trials.

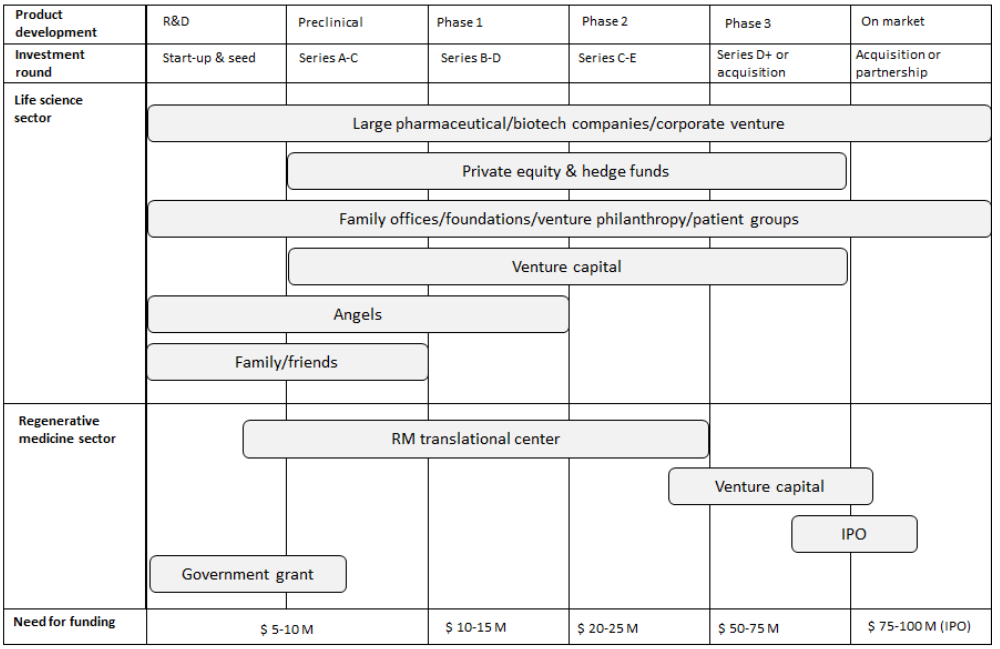

Figure 9. Sketch of funding schemes for stem cell therapy (Bonfiglio, 2014; Ford and Nelsen, 2014; Author's own reasoning).

Conceptualization of AHCs is a significant part of the construction. Without a strong connection between academia and clinics, early experiments do not happen so smoothly. Here, academia involves also other disciplines outside health sciences that are relevant in RM sector development. In the case of Tampere, the original idea for bone construction therapy came from medical practice, but academia (non-AHC) was responsible for further development, and innovation was based on collaboration between clinicians and academics. Thus, it is difficult to say where innovators are located in the construction because they can be anywhere. However, it is certain that both RM researchers and clinicians are needed in the development of innovations. Since AHCs might be the first adapters of new therapies, they are also crucial in their development. Hence, the role of hospitals spans from the beginning to the end of the life cycle of RM cell therapies.

Finally, in the current era of healthcare, regulation has its presence everywhere. While RM cell therapies are developing, regulators are not sure how to respond to all the new issues that use of these cells brings to discussions, and thus, interaction between regulators and academia is important during the research phase and in developing a PoC. To gain official approval for new therapies, clinical trials are required to show safety and efficiency. After successful clinical trials, the regulatory agency grants permission for marketing the product. However, even after regulatory approval, it is not yet certain that a new therapy will be diffused to hospital practice. New therapies need reimbursements from the national healthcare sector and insurance providers so that patients can afford to use them. Only the future can show how widely reimbursements for RM cell therapy products will be provided.

6.2 Potential for Tampere in RM stem cell therapies

The majority of firms in the RM sector are in the US, even though emerging countries like India, China and Brazil are investing vastly too (McMahon and Thorsteinsdottir, 2013). These developing countries seem to understand that in order to compete in the RM sector, they need to be active from the very beginning. As Salter and Martin (2001:528) note:

> "basic research is crucial for the strategic position of industrialized nations in the world economy, and for remaining at the leading edge of technology"

Similarly, Porter (1990) suggests that only through creation and assimilation of knowledge may a competitive advantage be created, yet he also reminds us that a nation cannot be competitive in most industries. Therefore, whether or not to be

involved in the basic research and development of therapies in the RM sector is a crucial question for a small country like Finland. Finland, and Tampere within it, has invested in basic research in order to compete in the RM sector, and in this way have already decided to be involved in the RM sector. Concentration on basic science and experimental treatments in the RM sector have additional advantages other than purely commercial aspects of RM cell therapies[16]. In this section, however, commercial aspects are discussed. To be a small player in the global RM sector market is not necessarily the most assured way to achieve a competitive advantage, because of the vast amount of finance needed for the development of therapies. Moreover, the competition is tough.

Even though scientific competence and knowledge in Tampere is high in the RM research field, funding opportunities are limited nevertheless. Without significant funding, it is not possible to start the expensive clinical trials that are required in the Western world for new therapies. Although regulations and a scientific approach to RM stem cell therapies are good for safety, it also makes the development process slow and costly. However, even though there are challenges with funding and regulation, there are also advantages in Tampere. One of the definite advantages is the ATMP hospital exemption. As was previously mentioned, in Tampere several patients have received treatment with a therapy that has not yet been proven in clinical trials. This is only possible due to the good relationship between hospitals and academia, and a risk tolerating regulation scheme in the EU. However, there is only a limited number of actual treatments permitted before it is considered to be a regular therapy that has to comply with clinical trial requirements. The future for this therapy and subsequent ones is uncertain, as clinical trials should be started, and these require funding.

Porter (1990) explains national advantage with a diamond of four attributes: factor conditions, demand conditions, related and supporting industries, and firm strategy, structure and rivalry. In Tampere, factor conditions are relatively good as there is a skilled labor force and infrastructure, and due to demand, development of stem cell therapies has already begun. Still, the home market demand for stem cell products is limited and international markets and the development of these are the

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[16] Sotarauta et al. (2016) argue in their report that concentration on basic science at this stage of the RM sector development could be advantageous in the future, if RM therapies are readily available in the hospitals, even though no commercial breakthroughs happen. The hospital and university are better prepared to exploit new RM innovations, as they have become familiar with them.

only hope for success. Other attributes are more or less lacking. There are no internationally competitive supporting industries in the RM sector. Tampere and Finland lack firms in the RM sector, and it is unlikely that domestic funding alone is enough for the creation of any new firm. In Tampere, there are high technological capabilities and a willingness to produce commercial innovations in academia, but there seems to be a lack of the commercial competencies that are needed in this mission[17]. Hence, it might be that only a few companies will arise from Finland in the RM sector. There might be other possibilities for success if the development of therapies that are regulated under the ATMP hospital exemption are continued. If these therapies are successfully developed and used for the good of patients, then case-by-case it would be possible to consider whether it is possible to conduct pre-clinical studies and early clinical trials in academia. Subsequently, therapies could be transferred to some established company or a new firm could be started. Regarding commercial competencies at BioMediTech, researchers are aware of commercial opportunities in the RM sector and are able to speak the same language, but in the end, they are academics. It appears crucial for the future of successful commercialized therapies and technologies, that business personnel from technology market firms are involved in the development of PoCs in order to make the business cases viable.

[17] This is analyzed from the competence bloc viewpoint in Article V in this dissertation as well.

7 Development of new medical technology in the RM sector

According to literature and the interviews conducted, early technology development in the RM sector is mostly conducted under the responsibility of academia in collaboration with hospitals. As academia should nurture new therapies in early clinical trials in order to show that they really are safe, efficient and effective, they also have to ensure that they are commercially viable. Hence, innovation and commercialization are two intertwined aspects of new medical technology development. Morlacchi and Nelson (2011) suggest that the evolution of new therapies occurs in the middle of three co-evolving pathways: learning in practice, advances in biomedical scientific research, and improvement of the ability to develop and use medical technologies (see also Nelson et al., 2011). These three pathways occurred in the case of bone growth therapy. A crucial part in the development of the therapy has been the clinical environment and learning from the experiments. Biomedical research has provided the scientific basis for stem cell-based therapy, but improvements and the use of new technologies have also been crucial to accompany the biomedical research progress.

In Tampere, without close cooperation between academic hospitals and Regea (later BioMediTech), therapy innovation in the creation of missing cranial bones probably would not have emerged. This is similar to the development of X-ray imaging that is discussed by Blume (1992), whereby collaboration between radiologists and manufacturers produced solutions that were more advanced. As already stated, the significant difference is that in the case of Tampere, the university plays the role of an industry partner as well. Funding from the Human Spare Parts research program provides an opportunity for groups to focus on research and to reach shared goals instead of several disparate goals of individual research groups. It also facilitates close collaboration between groups from different disciplines, which creates a favorable environment for innovations. Some of the technologies developed are specific solutions to problems faced in stem cell research. In these cases especially, the combination of technology groups and stem cell groups in the research program is beneficial. The significant role the university has to play in the R&D phase makes RM sector product development different from the wider

spectrum of other medical technologies. In the future, as the RM sector further develops and grows, the situation will most probably change and manufacturing companies take a bigger role in the R&D phase.

However, apart from purely scientific progress and new clinical solutions, tension between product development and academic research occurs, because there are contradictory forces in the form of a desire for commercial outcomes, such as new products, services, and patents, but also for high-level science and scientific publications. Commercialization is a challenge for academics, as traditionally they are not commercially aware, nor interested in commercial aspects. At BioMediTech, research leaders are educated in commercial awareness, which makes it easier for them to speak about commercial aspects of potential applications. It does not solve the problem of commercialization, but at least mitigates it somewhat.

Commercialization, however, is a central objective at BioMediTech. Since the Human Spare Parts research program provides basic funding for involved groups, it is easier to develop potential commercial applications for which it is possible to obtain dedicated funding from TEKES in order to do initial commercialization activities. PoC development is important in academia in order to make successful technology transfers to industry. However, after the publicly funded research and development phase, gaining private financing for medical technology innovations is essential but complicated in Finland, especially in the case of RM cell therapy technologies. Even though it could be possible for BioMediTech to conduct all the clinical trials themselves, and continue the provision of the therapy, the required clinical trials are so costly that private investments might be needed anyway. To obtain private funding, the market potential has to be big enough in order to provide a good incentive for investors and entrepreneurs, and the product must be scalable for industrial large-scale manufacturing. It might be a challenge for universities to address such commercial aspects in PoC development projects. BioMediTech has not found local industrial partners, and entrepreneurs do not exist within academia. Thus, market insights for PoC development projects are sought from industry experts. Regarding commercial results, only the future will show if the PoCs will be commercially viable and successful.

A great lesson to learn from Tampere is that a close collaboration between technology groups and stem cell groups should be encouraged one way or another. Even though they already had a collaboration before the Human Spare Parts research program, the program itself was an important facilitator. Even more important might be clinical experience within the research groups. From the RM sector viewpoint, stem cell research experience, technology-oriented experience and clinical experience

should be intertwining in AHCs, and the development of medical technologies should be encouraged and developed as far as possible in order to transfer to industry. In Tampere, the establishment of Regea and later BioMediTech were the first steps in this direction, but even closer collaboration between BioMediTech and the University Hospital of Tampere would be beneficial for the emergence of a local RM sector industry.

Later, in the more mature phase of the RM sector, local regions might transform to support the RM sector through some of the industrial transformation processes described by Lester and Sotarauta (2007). In this way the RM sector would be institutionalized into regional and national innovation systems as well. However, as is discussed in Article I, a viable industry needs a specific set of competencies that are essential in order to sustain the emergence of the RM sector, which currently lacks several of these competencies. Nevertheless, the future in global level is promising as pharmaceutical firms are apparently entering to finance the RM sector. However, regulation is tough in the RM sector, and as many discoveries are made in academia, there is a hurdle to transfer these discoveries to clinical trials. Within the EU, the ATMP hospital exemption is potentially an excellent regulatory driver for new RM sector products, as it allows patient treatments in the early phase of new medical technology development. However, an interesting question is what will be the role of ATMP hospital exemptions in the EU market in the future, and do they foster or hinder the development of commercial products – as firms could feel that public sector actors easily bypass their efforts in clinical trials.

8 Discussion

8.1 Theoretical and practical contributions

At a general level, it is clear that there are systemic elements in the RM sector, but it is maybe too early to speak about a mature sectoral innovation system. The RM sector is clearly embedded into the Finnish national innovation system and the regional dimension of it. However, it is not possible to describe much of the practices of the emergence of a new sector, nor explain its underlying processes. The role of innovation systems has been essential nevertheless; institutional actors have facilitated the development of the RM sector in Tampere. Among other aspects, actors in national and regional level have supplied important funding. Supportive regulation and IPR are also important nation-wide elements affecting the innovation process. In addition to funding, regional actors have provided BioMediTech and its antecedents with essential support and expertise to develop their operations.

The development of the RM sector in Tampere visibly highlights the difference between coordinated (e.g. Nordic countries) and liberal market economies (e.g. the US) described briefly in section 2.1. Based on this dichotomy, the concepts of IRIS and ERIS (respectively) were developed and discussed by some innovation scholars (see e.g. Cooke, 2004; Asheim and Coenen, 2006; Asheim, 2007). In Tampere, strong institutions have provided the possibility to develop a strong scientific base for the RM sector. The challenge is how to go forward to create commercial solutions. Eliasson and Eliasson (1996) argued in competence bloc theory of a need for venture capitalists in providing opportunities for high-risk projects in the market. This venture capital-led development is a central idea in entrepreneurial regional innovation systems, since venture capital provides a dynamic environment for some businesses to grow, and for others to die then start again with new ideas. Since liberal market economies have benefits for science-based industries with radical innovations and unknown futures (Cooke, 2004; Asheim and Coenen, 2006, Asheim, 2007), it is not a surprise that many RM sector firms have emerged in the US.

Thus, following Kolehmainen's (2016:414-415) reasoning regarding the sum or local concentration of local dimensions of innovation environments of firms and other organizations establishing a local innovation environment, it is tempting to

argue that the RM sector in Tampere is a local nexus of different forms of innovation systems at different levels (national, regional, sectoral) still having its own systemic nature, which cannot be explained by merely focusing on regional, national or sectoral innovation systems. Because of this, in this dissertation, the construction was developed to explore this systemic nature and to explain innovation in the RM sector. At a more detailed level, the construction has both practical and theoretical contributions as it connects competence bloc theory and HIS in order to describe how new RM cell therapies could be developed, commercialized and brought to use in the hospital. Based on insights from the biotechnology sector, Eliasson and Eliasson (1996) explained with competence bloc theory the actors and competencies that are needed for the sustainable success of new businesses. Consoli and Mina (2009) conceptualized in HIS how the technology market, academia and health care sector are linked together. In HIS, an assumption is made that there is a vibrant technology market from where new drugs and devices come. However, this is not the case in this development phase in the RM sector. Instead, it is very difficult to start a new company and get VC funding in the RM sector without evidence from phase II clinical trials (Parson, 2008). The consequence is that early clinical trials should be conducted at the university (Mason et al., 2011). The empirical case of bone growth therapy in this dissertation shows that in the RM sector, the university has been solely responsible for the exploration and development phases, as described by Blume (1992), although the development phase naturally is not finished yet as no commercial manufacturing is happening and clinical trials have not begun. If therapies developed at BioMediTech at some point move forward to clinical trials and to firms, competence bloc theory offers insights into how the process works in the technology market.

It is crucial to understand commercial processes within the RM sector technology market, as in general there are no established companies innovating and developing new products, which is the case in more mature healthcare sectors. The empirical findings of this dissertation support the findings of other scholars (see e.g. Auerswald and Branscomb, 2003; Gulbranson and Audretsch, 2008; Maia and Claro, 2013) regarding the importance of PoC development in academia, since the PoC has the key role in making innovations ready for technology transfer. Beside technological aspects, there are also commercial and regulatory issues in PoC development that have to be taken into account. Mason and Dunnil (2008b) pointed out the importance of widely accepted technical standards because the lack of an early agreement on standards might be damaging to new industries. The empirical findings of this dissertation support both this and the findings of both Metcalfe et al. (2005),

who argue that regulation co-evolves with the innovation process and the market, and Messenger and Tomlins (2011), who argue that clear and efficient regulation actually supports medical technology innovation.

The other significant element is the relationship between academics and clinicians. Bornstein and Licinio (2011) argued that splits between research and daily clinical practice reduce the efficiency of the translational activities of potential research. This same issue is discussed in Article IV in this dissertation. Bornstein and Licinio discussed translational medicine in general, but this is an even bigger challenge in the RM sector, where AHCs have not adopted stem cell products in their standard repertoire – albeit in Tampere this is not totally true on a small scale regarding bone growth therapy treatments. On a wider scale, the challenge remains. In the construction, RM research was explicitly included in the AHC, and not the other way around. In this way it was possible to stress the importance of an innovative environment and the connection between academic research and clinical practice.

Finally, there are several challenges or barriers to the establishment of firms. Since most of the R&D is conducted in academia, the question for technology transfer is whether scientists and principal investigators are willing to work or consult with industry, or is a scientific career more important. Murray (2002) argues that co-mingling between academic and technical communities happens through key scientists, and thus for firms, academic scientists are important actors in the commercialization process. Regarding a workforce, there should be only a few problems, as a flow of university graduates is in many places continuous and only a portion of them find a place in the university. For a firm to survive in the longer run, a portfolio of products might be needed, and to overcome "the valley of death", scarce funding has to be used wisely. However, regardless of all the challenges, there is still hope. As Messenger (2011) stated, there clearly exists a route to market because some RM products have already entered the market.

8.2 Policy implications

A few policy and managerial implications have been developed, mostly for the purposes of BioMediTech and the Tampere region. As some of these implications are relevant elsewhere as well, it is important to understand the context-specific elements of each place. Thus, the same implications cannot be applied identically everywhere. As Porter (1990: 74) stated:

> "We need to know, very simply, what works and why. Then we need to apply it"

For the Tampere region, it is important to have local firms involved in the development of the emergent RM sector. Currently, there are no strong connections between BioMediTech and local biotechnology firms. In order to develop a flourishing local RM sector in Tampere, local firms are needed, either new or established. In the long term, this might foster the emergence of PoCs, as firms – the potential manufactures – will already be involved during the development phase of potential products. It also makes development less dependent on public funding since partial funding could be obtained from firms. At the same time, firms would be able to expand their product repertoire. Regarding new start-ups, lack of potential entrepreneurs seems to be a problem in commercialization activities. Since commercialization of potential products requires both business and engineering skills, an appropriate combination of these skills could be gained by education. Currently, both engineers and business personnel are educated at the universities in Tampere, but people with appropriate combinations are rare.

Lack of sufficient finance is a problem for the development of stem cell therapies, as these require costly clinical trials. As a minimum requirement, international collaborations are needed in order to secure sufficient finance for early clinical trials, which can be aided by sufficient policies. However, the Finnish financial market should grow remarkably in order to provide Finnish companies with enough funding for early and late clinical trials. Emergence of specific funds for RM sector innovations should be encouraged and aided by public policies. Since most of the activities are currently conducted with public funding, private funds are especially needed.

The role of facilitators between academia and the technology market is important and should be developed and integrated with actions in Tampere. A translational center for RM sector products could help translational activities, as it would provide funding and business expertise. A similar concept would be a PoCC, where PoCs could be developed further in order to secure a successful technology transfer. Finally, the loose collaboration between the university hospital and BioMediTech could be developed further. Strategies where the establishment of the 'Tampere Health Research Center Kauppi' have been discussed seem to be a step in the right direction in this matter.

9 Conclusion, limitations and future research opportunities

The aim of this dissertation was to study the systemic nature of innovation in the RM sector and how new product opportunities could be commercialized. In the independent articles (I-V) several aspects were tackled regarding the RM sector: competencies needed for industry emergence (Article I), a mechanism for how firms emerge and supporting aspects in Tampere (Article II), PoC development in academia (Article III), the potential role for AHCs in the development of innovations (Article IV), and what the financial situation looks like in the RM sector (Article V). Based on the research in this dissertation, it can be said that the RM sector has the potential to be more than science fiction hype. However, as discussed throughout this dissertation, there are some preconditions and requirements that need to be established and developed further in order to see a new body parts producing industry emerge. Some of the most significant elements are PoC development at the university, competence bloc expansions, and a sufficient financial market. Of course, in addition the actual science has to move forward without world scale catastrophes or malpractices.

In this dissertation, some parts of the systemic elements in the RM sector were studied empirically in Tampere, where most of the activities are still located within academia and the hospital. As was shown, the role of the hospital is significant in the early experiments of innovation and in the adoption of innovation, and thus it was suggested that AHCs should reach toward stem cell research and innovation. In this way, scientists would be able to collaborate with clinicians from the very beginning and research would be focused more straightforwardly on the real world problems clinicians encounter with patients. The ATMP hospital exemption provides a way to perform treatments without expensive clinical trials, and in this case, a close collaboration with an academic hospital is highly beneficial. However, the question remains as to how these product opportunities could diffuse to wider use. Even though there is no exact formula, the technology market has an important role in this process since clinical trials are required for new products. As these need vast amounts of finance and time, firms and venture financiers (especially venture

capitalists in later phases) are the actors that potentially have the necessary resources and competencies.

There are some challenges identified in this dissertation regarding the commercial emergence of the RM sector. First, sufficient funding is a major problem globally but especially in Finland. Second, commercial competencies must be developed and acquired within academia in order to assure translation of innovations to the technology market and later to hospitals. Third, regulation is a major issue in the early developments of the RM sector, even though in the EU there are some potentially beneficial aspects in non-commercial activities. However, RM cell therapies require clinical trials. These need time and vast funding and, to obtain money from venture capitalists, a sufficient market potential is crucial. Since some of the commercial decisions in the current situation have to be made already in academia, academics need some commercial competencies in order to perform PoC in a proper way to ensure prospective private funding.

Although there are promising product opportunities at BioMediTech, the current financial market is not sufficient for RM cell therapies in Finland. Hence, for the future of these products, finance must be found from overseas, and the domestic market should be developed in the direction where it would be able to provide at least sufficient early financing for potential products. At the same time, it is important to support PoC development at the university to ensure successful technology transfers. The current reality seems to be that early clinical trials should be conducted in academia before it is reasonable to start a company. This has significant consequences for universities, as they should be able to develop commercially viable concepts and find the funding for these.

This dissertation is a step forward in order to understand the system-level nature of innovation in the RM sector. Limitations of this study come from its single case study design, which is difficult to generalize. As was discussed already in the methodology sections, a working construction in one place implies that it might be generalizable in similar situations. However, it might take time to achieve a real implementation and results (Kasanen et al., 1993). Thus, even though this dissertation followed a constructive approach, it is difficult to make even a weak market test as such, as it requires the use of the construct in decision-making, which is difficult to prove or to notice in the case of system-level constructions. Lack of empirical data from firms is another major limitation in this dissertation. An attempt is made to bypass this with competence bloc theory, but ultimately, the commercialization process and content of the technology market is based on

secondary sources, and only limited insights from the empirical study of this dissertation were obtained in this respect.

Future research opportunities would include multi-case studies. It would be beneficial to study a successful case and the important elements in transferring product concepts to a firm and later to hospitals, and unsuccessful cases where this has failed. There are also several interesting questions regarding the technology market in the RM sector, since in this study the global venture finance situation was only briefly touched upon. The interesting questions would be regarding how research is transferred to firms in the RM sector, how successful companies have developed products for the technology market, what kind of finance providers there really are in the RM sector, and how products are diffused to hospital practice. Regarding firms, financing is another interesting question: how are they able to obtain the needed financing and what is the actual amount of finance required? Another interesting research avenue would be an action research that focuses on how product concepts from BioMediTech (or from other product-focused research institutes) could be transformed into businesses and competitive products. Here, researchers would have a good opportunity to facilitate the development of the commercialization process. The theoretical interest in this kind of research would come from technology transfer dynamics and hence contribute to potentially increasing PoCC discussion. Finally, one interesting research avenue would be the role of hospitals in the institutionalization of RM cell therapy innovations. As current regulation forces firms to conduct clinical trials, could ATMP hospital exemptions or other similar arrangements allow AHCs to provide new advanced therapies for citizens without a commercial purpose.

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Triple Helix

RESEARCH Open Access

The Triple Helix model and the competence set: human spare parts industry under scrutiny

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Abstract

The main aims of this paper are (a) to construct a generic conceptual model for the Triple Helix model based on competence sets and hence (b) to identify the system-level generic competencies needed in the emergence of a new industry. This paper suggests that to gain additional analytical leverage on the Triple Helix model, we need to study it also by focusing on generic competencies called for in the interaction between the main institutional spheres. Hence, there is a need to focus on interacting and conflicting system-level generic competencies that either enhance or hamper innovation processes. It is believed here that a competence set is the core of any Triple Helix constellation, but it is also believed that different competencies are manifested in a variety of ways depending on the nature of the specific system and related industries. The competence set model is elaborated upon by using the emergence of human spare parts industry in Tampere, Finland, as an illustrative case to highlight the otherwise conceptual discussion.

Keywords: Innovation system, Competence, University, Regenerative medicine, Human spare parts, Finland

JEL classification: O31, O32, O33

Résumé

Les objectifs principaux de cet article sont : (a) de construire un modèle conceptuel générique de Triple Hélice basé sur le jeu des compétences et ainsi (b) d'identifier les compétences génériques au niveau système nécessaires à l'émergence d'une nouvelle entreprise. Cet article suggère que pour obtenir un effet de levier analytique supplémentaire sur le modèle de la Triple Hélice, il importe de l'étudier également en mettant l'accent sur les compétences génériques nécessaires à l'interaction entre les principales sphères institutionnelles. Par conséquent, il est nécessaire de s'appesantir sur les compétences génériques d'interaction et d'antagonisme au niveau système qui favorisent ou handicapent les processus d'innovation. Cet article admet que le jeu de compétences est le cœur de toute constellation de Triple Hélice; il admet également que les différentes compétences se manifestent d'une variété de façons, selon la nature du système considéré et les entreprises associées. Le modèle de jeu de compétences est conçu en utilisant comme illustration l'émergence de l'industrie des pièces de rechange humaines à Tampere, en Finlande, pour mettre en évidence une discussion autre que conceptuelle.

Resumen

Los principales objetivos de este trabajo son: (a) la construcción de un modelo conceptual genérico para el modelo de la Triple Hélice en base a "conjuntos de competencias," y por tanto (b) identificar las competencias genéricas a nivel de sistema necesarias para el surgimiento de nuevas industrias. Este documento sugiere una mejora al modelo de la Triple Hélice que consiste en elevar la importancia de competencias genéricas dentro del análisis institucional. Por tanto, enfatizamos la necesidad de centrarse en la interacción y el conflicto de competencias transversales a nivel de sistema que pueden exacerbar o dificultar los procesos de innovación. Creemos que un conjunto de competencias es el núcleo de cualquier constelación de la Triple Hélice, pero también creemos que las diferentes competencias se manifiestan en una variedad de formas, dependiendo de la naturaleza de cada sistema de innovación y cada industria. Ilustramos el modelo propuesto de conjuntos de competencias con un análisis del surgimiento de la industria de prótesis humanas en Tampere, Finlandia.

摘 要

本文的主要目的是:(一)基于竞争力集构建三螺旋的一般概念模型;(二)确定在一个新产业出现过程中所需要的系统级的一般竞争力。本文认为,为了获得分析三螺旋模型的其他分析工具,我们也需要专注于要求主要机构范畴之间相互作用的一般竞争力研究。因此,有必要聚焦于相互作用和相互冲突的系统级一般竞争力,不论它是加强还是防碍创新过程。在此我们相信:一个竞争力集是所有三螺旋星座的核心;我们也相信:不同的竞争力通过各种不同方式表现出来,取决于具体的系统和相关产业的性质。通过人类备件产业在芬兰坦佩雷的出现,本文详细说明了竞争力集模型,以此作为典型案例突出这个相反的一般概念的讨论。

Аннотация

Основными целями данной статьи являются: (а) создание общей концептуальной модели Тройной спирали, основанной на компетенциях, и, опосредованно, (б) определение соответствующих компетенций, учитывающих специфику условий формирования современной промышленности. В настоящей работе выдвинуто предположение, что для достижения дополнительных преимуществ в рамках модели Тройной спирали, мы должны проанализировать общие компетенции, необходимые для взаимодействия основных институтов друг с другом. Так, существует потребность в общих умениях в области деловых переговоров и решения конфликтов, которые опосредованно могут как улучшить, так и затормозить инновационный процесс. Существует мнение, что набор компетенций составляет основу Тройной спирали, а также что различные компетенции проявляются по-разному в зависимости от условий, в которых складывается такая система, и отраслей, относящихся к ней. Модель набора компетенций разработана с использованием индустрии подготовки кадров в Тампере, Финляндия в качестве примера, способного проиллюстрировать ведущиеся обсуждения.

Resumo

O objetivo desse artigo é: (1) de construir um modelo conceitual genérico para o modelo de hélice tríplice baseado em conjunto de competências e, portanto, (b) de identificar as competências genéricas no nível do sistema necessárias na emergência de uma nova indústria. Esse artigo sugere que para ganhar vantagem analítica adicional no modelo de Hélice Tríplice, é necessário estuda-lo também se concentrando nas competências genéricas requeridas para a interação entre as principais esferas institucionais. Consequentemente, existe uma necessidade de focar na interação e nos conflitos no nível das competências genéricas que tanto fortalecem quanto prejudicam o processo de inovação. Acredita-se que um conjunto de competências definido é o coração de qualquer uma constelação da Hélice Tríplice, mas também se acredita que competências diferentes são manifestadas de diversas maneiras dependendo da natureza do sistema específico ou das indústrias relacionadas. O Modelo de definição do conjunto de competências é elaborado com base na emergência da indústria de reposição de peças humanas em Tampere, Finlândia como um caso ilustrativo que põe em evidência a discussão de outra forma conceitual.

Multilingual abstract

Please see Additional file 1 for translation of the abstract into Arabic.

Introduction

Universities have increasingly been seen as the core instruments of local, regional and national economic development. This may be a result of the observation that, as many traditional industries have been hollowing out, and as many local economies have been losing their leading firms, the university often emerges as one of the few solid and locally rooted resources to draw upon. It is one of the cores in the dynamic interaction between 'the three institutional spheres', universities, industries and government, fostering entrepreneurship, innovation and economic growth (Etzkowitz and Leydesdorff 1997; Etzkowitz 2008). The core idea of the Triple Helix model revolves around three

basic premises: (1) universities are playing a central role in innovation side by side with industries and governments; (2) while earlier innovation policy was to a large extent designed and implemented by governments, today, it is fairly commonly an outcome of complex interplay between governments, industries and universities; and contradictorily, the Triple Helix also argues that (3) in addition to taking care of their traditional functions, the three institutional spheres adopt new roles and also perform the roles of the other spheres. In this model, actors taking non-traditional roles are seen especially important and potential sources of innovation (Etzkowitz and Leydesdorff 1997; Etzkowitz 2008).

Drawing upon their literature review, Cai and Cui (2015) maintain that the Triple Helix model has not been free of problems. It is criticised for remaining at an abstract level, lacking solid theoretical basis at a microlevel, not adequately addressing the issues emerging when actors adopt each other's roles and lacking the contextual sensitivity across countries and social settings (Cai and Cui 2015). Additionally, in spite of the fact that the concept of competence is, at least implicitly, strongly linked to the Triple Helix literature, it has only recently gained more attention (Ranga and Etzkowitz 2013). Lester (2007, 1) crystallises the increased need to better understand competences related to innovation systems by arguing that there are clear differences in the overall capabilities of nations and regions to adapt to the global economy with equal success. Some simply seem to be better in taking up new technological and market knowledge and to apply it effectively. In Triple Helix constellations, competences (in direct and/or indirect interaction) generate, stimulate and/or frame the overall functioning of a system and its transformation (Eliasson 2000). Consequently, as suggested by Ranga and Etzkowitz, competences also shed light on the ways main actors come together in 'consensus spaces', and move to construct 'innovation spaces' for realisation of the goals articulated in a consensus space (see Ranga and Etzkowitz 2013). Our earlier studies in Finland reveal that while the main actors may trust each other's integrity and trustworthiness, they may have difficulties in trusting mental models and specific profession-based capabilities of 'the others' (Sotarauta et al 2003).

This paper suggests that to gain additional analytical leverage on the Triple Helix model, and the three spaces in the core of it, we need to study it also by focusing on generic competences called for in the interaction between the main institutional spheres. The concept of generic competence refers to those higher order abilities that are called for to learn, innovate, anticipate and create and/or to generate conditions for learning and innovation (cf. Brown 1994; Wadhwa and Rao 2000).

As suggested by the ever expanding Triple Helix literature, there is a need to find a way to link the concept of competence in the debate by reaching beyond the narrow organisational view. For these reasons, this paper constructs a *competence set* model aim being to contribute to the Triple Helix debate. This paper is built on an assumption that, when enhancing the interaction between the three institutional spheres, there is a need to understand how a set of competences can be shaped for a more productive collaboration. It is exactly to this end, the competence set model is introduced to discuss the interconnected nature of generic competences required in innovation, business growth and economic renewal. The second assumption thus is that by the competence set model, it is possible to understand how competences are spread across the three institutional spheres and several organisations. The competence set is a configuration

of competences that in direct and indirect interaction generates new knowledge as well as its diffusion and valorization (see Eliasson 2000).

The two interrelated research questions we set out to address are what kind of generic competences are called for in the emergence of a new science-based industry and how do generic competences interact in a Triple Helix constellation. For this end, the focus in this paper is on system-level generic competences instead of the competences of an individual organisation. The concepts of competence and the competence set are elaborated upon by using the emergence of human spare parts industry in Tampere, Finland, as an illustrative case to highlight the otherwise conceptual discussion.

Towards a competence set model in the context of Triple Helix

The concept of core competence

In organisation and management studies, the concept of core competence has become one of the key concepts in the efforts to understand why some firms succeed while others do not, and, as it is believed in this paper, it has a potential to add analytical leverage also in studies focusing on Triple Helix constellations. The key rationale in bringing these fairly disconnected bodies of literature together is that there is much to be learnt across these broad fields of knowledge. In competence thinking, the basic idea is that an organisation should comprehend its own core competences and capabilities in order to utilise the resources available (Pralahad and Hamel 1990). It is also assumed that competences change more slowly than products and markets, and hence, the identity of an organisation should not depend on products and markets but on something more lasting, something that lies at the very core of the organisation's activities and success (Tuomi 1999, 82–83). Durand (1998, 306) connects competences directly to an organisation's resources and property and to individual and organisational capabilities, knowledge, processes, routines and culture. Javidan (1998, 62) uses the concept of competence to refer to the combining and coordinating of capabilities cutting across functions. Core competence, drawing upon the theory of Pralahad and Hamel (1990), may be defined predominantly as a collective learning process across the innovation system. For its part, generic competence is taken here to be specifically capability and expertise that is potentially common to several organisations in a Triple Helix constellation but may also be embedded in a single organisation that has a central position in a system. Generic competences are thus distributed over many operations either within an organisation or across them, and therefore, from the Triple Helix point of view, it is essential to approach them from systemic instead of organisational perspectives. For that purpose, a conceptual link between competence thinking and Triple Helix is constructed by a competence set model.

From competence bloc theory to competence set model

The competence set model is inspired by the competence bloc theory (Eliasson 2000), but as the competence bloc theory was mainly constructed to better understand and explain business growth in biotechnology, it needs to be extended with additional competences to provide an analytical tool for broader scrutiny of Triple Helix constellations. The competence of actors and their interaction determines the quality of a competence set and, as assumed here, also interaction in the context of a Triple Helix.

Additionally, a set of competences attracts competent investors who contribute positively to the attractiveness of a Triple Helix constellation (Eliasson 2000). A minimum critical competence mass and variety are needed before a Triple Helix becomes truly functional, and, according to Eliasson and Eliasson (1996), the following actors usually play central roles (modified slightly): (a) competent and active customers and users, (b) innovators who combine new knowledge and technologies in novel ways, (c) entrepreneurs who identify profitable innovations and prepare them for initiation in the market, (d) competent venture financiers who recognise and finance the entrepreneurs, (e) exit markets that facilitate ownership change and (f) industrialists and other established actors who take successful innovations to industrial-scale production. (Eliasson and Eliasson 1996).

Eliasson (2000) strongly associates competences with the selection of winning technologies and corporate winners, and conversely losing technologies and corporations, and thus, it adds analytical leverage to the Triple Helix relationships that are, according to Cai (2014), 'about competition and cooperation for resources, redistribution of power, and network building'. However, importantly, the Triple Helix model reminds that the question is not only about selection of 'winners' and 'losers', or individual companies or narrow industrial sectors, but also more profoundly and broadly about extensive collaboration across institutional spheres for economic growth and renewal. Thus, the question is about how new knowledge emerges, how it generates variation and how selection is made, and thus, moving beyond the narrow organisational and sector-based approaches is fundamental to better support construction of knowledge, consensus and innovation spaces that play a central role in Triple Helix constellations (Ranga and Etzkowitz 2013).

As Ranga and Etzkowitz (2013) maintain, the main ingredient in a knowledge-based economic development is the creation of a knowledge space that, according to them, 'encompasses the competences of knowledge generation, diffusion and use of the Triple Helix components'. They define consensus space to refer to a venue that brings together actors from different organisational backgrounds and perspectives for generating new strategies and ideas, the ultimate goal being novel discoveries and related innovations. For its part, innovation space refers to new organisational mechanisms that are geared towards 'the development of local innovative firms, in parallel with the attraction of talent and innovative firms from elsewhere, the creation and development of intellectual and entrepreneurial potential, and competitive advantage for the region and the country' (Ranga and Etzkowitz 2013, 247).

Applying Eliasson's (2000) conceptualisation, the competence set is defined as a configuration of generic competences that in direct and indirect interaction generates new knowledge as well as its diffusion and valorisation. In other words, competence set is a group of competences, which belong together or are usually found together. Basically, the competence set refers to the ability to achieve new forms of competitive advantage by highlighting the need to continuously renew competences so as to achieve congruence with the changing environment. Moreover, the competence set model may prove useful in the many efforts to boost innovation spaces, i.e. finding new ways to combine capital, technology knowledge and business expertise. It therefore follows that a competence set is a collection of generic competences widely distributed across the three institutional spheres and hence highlights that competences can be consciously

reconfigured, redirected, transformed and appropriately shaped, and integrated into existing competences as well as external resources (cf. Teece et al. 1997). Conversely, missing and/or poor competences may freeze interactive innovation processes and lock them in the past.

A sole focus on actors and the relationships between them, typical of innovation system studies, may even blur the view on how systems actually function and what drives them; hence, it is important to make a distinction between organisations and competences. By approaching actors indirectly through competences, it might be possible to clarify and specify the roles that they play in translating new knowledge into viable products and services. For these reasons, the main rationale in constructing a competence set model is (a) to specify what kind of competences are called for in a Triple Helix constellation and (b) to identify the competences that keep a Triple Helix constellation continuously adapting to changing economic landscapes. The competence set may thus also be used (c) to serve as a tool in a search for systemic failures as well as shared interests, problems, opportunities and capabilities, as suggested in the management literature (Pralahad and Hamel 1990). Consequently, a competence set model is an analytical tool geared towards identifying how different competences of many actors could be integrated with one another both horizontally and vertically in such a way that a constructed set would serve both the entire system and actors embedded into it. The assumption here is that generic competences need to be identified and analysed empirically case by case but a thematic framework is needed to guide the search.

The thematic framework was constructed by identifying studies focusing on innovation system functions, as generic competences are by necessity linked to the most important functions of any innovation system (see Lundvall et al. 2002; Lundvall and Lorenz 2006). In the literature on innovation system functions, *knowledge development and diffusion* is, quite self-evidently, acknowledged as a key function (Edquist 2005; Hekkert et al 2007; Hekkert and Negro 2009; Bergek et al 2008; Liu and White 2001). For his part, Eliasson (2000) does not discuss knowledge development as such, as his theory is dealing more with selection of winning technologies instead of sources of innovation. Most of the key authors include *market formation*, *framing* and *creation of strategic awareness of new technologies* and *mobilisation* in their discussion of the key innovation system functions (Edquist 2005; Hekkert et al 2007; Hekkert and Negro 2009; Bergek et al 2008; Jacobsson and Bergek 2004; Rickne 2000). Eliasson (2000), Hekkert and Negro (2009) and Bergek et al (2008) also incorporate in the set of system functions *entrepreneurial activity*. Edquist (2005), Hekkert and Negro (2009), Bergek et al (2008) and Rickne (2000) remind about the importance of *legitimization*, and Eliasson and Eliasson (1996) pay extensive attention to *venture finances*. In line with Liu and White (2001), Eliasson and Eliasson (1996) add *detection of end-values* in the debate while Edquist (2005), Hekkert and Negro (2009), Bergek et al 2008, Liu and White (2001) and Rickne (2000) emphasise the importance of *interaction* by highlighting networking, exchange of knowledge and bringing together complementary knowledge.

Following the close reading of the literature on innovation system functions, the competence set model was constructed to cover seven themes for the empirical work on the generic competences. Framing, mobilisation and networking were left out from the framework, as, instead of being system functions, they were identified as generic

capabilities cutting through all the functions, and as such, they are embedded in the core competence thinking as well as the Triple Helix model (see e.g. Russel et al. 2015). Instead, drawing upon Eliasson (2000) and Liu and White (2001), industrial production or *systematic production* was included in the analysis, as it appears as important in the institutionalisation of innovations. The seven themes are the following: (1) knowledge creation and diffusion, (2) entrepreneurship, (3) finances, (4) legitimisation, (5) market formation, (6) systematic production and (7) identifying potential end-values. It is important to keep in mind that the seven functions, labelled here as themes, are not generic competences as such but they are used in the identification of them. Quite naturally, each of the themes includes a variety of specific capabilities that construct a generic competence. In a system-level analysis, the interaction of identified competences provides further empirical analysis with a point of departure in identifying the specific capabilities in a context of a specific transformation process of a specific Triple Helix constellation.

Methodology and case

This paper follows a single case study design to illustrate and highlight how the constructed competence set may play out with a case. The study covers the theoretical middle range in that it aims to understand the emergence of a new industry in its unique context and construct a conceptual model for adding analytical leverage to the Triple Helix model.

The emerging regenerative medicine concentration in Tampere and the prospective Finnish human spare parts industry serves as an example of emerging industry (see Sotarauta and Mustikkamäki 2015). It does not yet have a direct antecedent in the economy and thus entails the need to construct new competences and/or transform existing ones to support the birth and enlargement of an embryonic industry. The empirical study began in 2014 with the analysis of secondary data, including relevant journals, related newspaper articles, annual reports and respective policy documents. This phase identified the state of the art of the human spare parts industry both locally and globally. Next, 24 people, involved in different capacities in the development of regenerative medicine in Tampere, Finland, were interviewed in 2014 and early 2015. Fifteen of the interviewees were employees of BioMediTech (a joint institute of the University of Tampere and the Tampere University of Technology), and the rest of the interviewees were from local and regional development agencies, Tampere University Hospital, Ministry of Employment and the Economy, the Finnish Funding Agency for Innovation (TEKES) and a local firm. The interview themes were drawn from the competence set model and, in practice, comprised the seven generic competences (see Fig. 1). The main aim was to construct an understanding of what system-level generic competences are needed to enhance the emergence of science-based human spare parts industry and describe the current situation in Tampere. Competences and capacities related to actual scientific work, knowledge production, are not elaborated, but their importance is, of course, acknowledged, as they form the core in the emergence of any science-based industry.

The term regenerative medicine was forged in 2000 and is now widely used to describe biomedical approaches to healing the body by the stimulation of endogenous cells to repair damaged tissues or the transplantation of cells or engineered tissues to

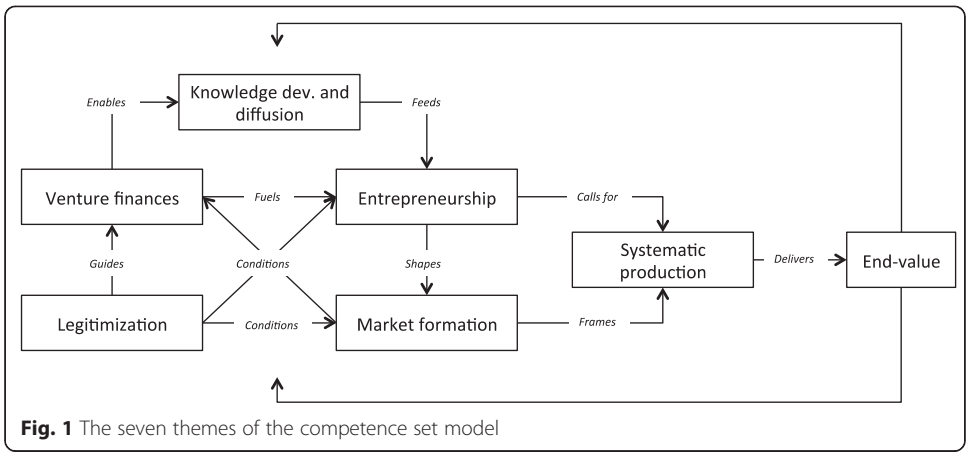

Fig. 1 The seven themes of the competence set model

replace diseased or injured tissues (Riazi et al. 2009). The basic unit in regenerative medicine is a stem cell. Stem cells are biological cells found in all multicellular organisms. The potential of stem cells in clinical treatments is based on their multipotent ability. Stem cells are able to regenerate tissues and organs and act as building blocks for all tissues in the body (National Institutes of Health 2009). Regenerative medicine (RM) forms the third discipline in human healthcare alongside medicine and surgery (Polak et al. 2010), and, from a business point of view, cell therapy is defined as a fourth pillar in the healthcare industry alongside pharmaceuticals, biopharmaceuticals and medical devices (Mason and Manzotti 2009). Regenerative medicine has grown rapidly, and scientific achievements have created hopes for new treatments for severe incurable diseases, such as diabetes, Parkinson's disease, cancer and heart diseases. The promise of regenerative medicine is very exciting, but simultaneously, the cost of product development, and most notably clinical trials, for high-end applications is very high (Mason and Dunnil 2008a, 351).

In Tampere, the scientific research on regenerative medicine is based on close collaboration between the University of Tampere and the Tampere University of Technology, and the first discoveries were based on collaboration between biomaterial engineers, clinicians, cell biologists, technical experts and animal model experts (Sotarauta and Mustikkamäki 2015). The two universities institutionalised their collaboration in 2013 by establishing a joint research institute, Institute of Biosciences and Medical Technology (BioMediTech), that is a home base for approximately 250 scientists from the two universities. The unique nature of science and technology created at BioMediTech can be illustrated by the fact that in 2008, for the first time in the world, a patient's upper jaw was replaced with a bone transplant cultivated from the stem cells isolated from the patient's own fatty tissue (Sotarauta and Mustikkamäki 2015). The patient had lost roughly half of his upper jaw because of cancer and traditional medicine was unable to offer remedial treatment. In the process, the scientists were able to produce new bone cells by combining stem cells and biomaterials and then grow them into a jawbone of the correct shape and size (with the aid of a titanium frame) inside the patient's stomach muscle (Bionext 2010; Sotarauta and Mustikkamäki 2015).

In 2014, the international evaluation panel that carried out an extensive evaluation of the research activities at the University of Tampere concluded that 'research conducted at BioMediTech has an excellent standing nationally and internationally and the

number of research projects and output from these projects is commensurate with the size of the Institute'. The evaluation panel also concluded that the projects are innovative and have clear translational potential in each thematic area of research (Hakala and Roihuvuo 2014). For its part, the international evaluation panel also asked how it would be possible 'to move discoveries from the laboratory or classroom to the clinic and ultimately turn these into products, policies or public information that impacts society' (Hakala and Roihuvuo 2014).

The human spare parts industry discussed through a competence set

Systematic production

Systematic production refers to all those processes and methods that are used to transform science-based discoveries into permanent elements of a healthcare system. In regenerative medicine, the pressure to detect commercially viable products and services is increasing steadily but the issue of how to move from research and development to systematic production has not been fully answered yet (Mason and Manzotti 2009). One of the ways to translate the potential embedded in the scientific research into the market is via firms. However, the progress in regenerative medicine, especially in stem cell-based products, has been fairly modest, as it is fairly commonly seen that there ought to be clear evidence from phase II clinical trials before even pursuing the commercialisation phase (Parson 2008). The other option is to diffuse potential regenerative medicine services into medical practice through hospitals.

The prospective human spare parts industry is deeply embedded in scientific research, and those firms that would be interested in operating in the field need to have access to cutting edge research (Prescott 2011). Conversely, universities are expected to nurture innovations further into clinical trials before aiming at commercialisation in contrast to what is usually the case in medical innovation or what is normally expected before establishing a start-up and obtaining venture finance for it. In the field of regenerative medicine, firms need to have access to cutting edge research, as the scientists introduce new ideas and have the personal level networks needed for generating funding and establishing a start-up (Murray 2004; Prescott 2011). Therefore, the role of scientists becomes more prominent than is the case in many other fields of medicine as the markets are underdeveloped and as the demand is only beginning to emerge. Consequently, in a new science-based field like regenerative medicine, the scientific community needs to be competent not only in science but also in shaping the technology market, as they may be the only actors who can understand the potential embedded in the science and technology in question. This again calls for novel competences, and for these purposes, governments, e.g. in the USA and UK, are establishing regenerative medicine translation centres and funding clinical trials in cell therapy (Mason et al. 2011).

Our interviews clearly revealed that the questions related to systematic production, either commercially or non-commercially, have been on the agenda in Tampere since the early days of regenerative medicine-related research (early 2000s) (Sotarauta and Mustikkamäki 2015). Interviewees revealed how the idea of establishing a 'Hospital for Advanced Therapies' for treating patients suffering from facial bone deficiencies, and thus exploiting revolutionary new technology, moved to preparatory phase but did never materialise. Additionally, a special planning group designed a business plan for a

university-based venture, but it was not executed either. As a member of the management team put it: 'The world [referring to the universities in question and global markets] was not ready for those ideas yet, nor were we'. Indeed, the core actors have not found solutions for moving forward beyond clinical experimentations, except licencing technology to an external party, and it is obvious that the generic competences, in the system broadly speaking, were not as developed as those in actual science.

The university hospital either has not made any major efforts to establish regenerative medicine in its standard repertoire, and it has not proactively constructed required competences. As a joint municipal authority of 22 municipalities, its mission is not to serve as an 'innovation platform for new technology' but to provide approximately one million Finns with a timely and equal access to specialised medical care. It, however, conducts clinical research and operates in close collaboration with the university. The university hospital is not likely to adopt a more strategic approach in the near future if there will not be significant pressure either from the society at large (in practice the public healthcare policy) or abundant number of individual medical doctors. In the future, the hospital's attitude towards regenerative medicine may be crucial; it is not only becoming legitimised part of the Finnish healthcare systems but also in moving towards large-scale systematic production.

In addition, the University of Tampere, the institutional home of regenerative medicine, is the most social science-oriented university in Finland, and hence, its experience in technology transfer and commercialisation is weak and related competences have been almost non-existent. For its part, BioMediTech has pushed the university to develop its competences on these fronts. To construct the commercialisation competences, BioMediTech has utilised the so-called Tutli funding that is a funding programme of TEKES. It is a specific government policy tool not only to support the commercialization of potential scientific discoveries but also to construct related competences within universities (Heinonen 2015).

Market formation

What makes the situation especially challenging is that regenerative medicine is a fairly new and quickly evolving form of science, and human spare parts industry is in an embryonic state. It is a well-known fact that radical innovations do not penetrate economies without emergence of a new market or significant changes in an existing one, and therefore, understanding the dynamics of market formation is seen here as one of the generic competences. Even though understanding of market formation is considered here as one of the generic competences in a competence set, its driving forces are more often than not considered as exogenously defined, and typically, it is seen to follow linear change patterns. Market formation is often described as proceeding from a nursing phase to a bridging phase to a mass market (Jacobsson and Bergek 2004), and each of these phases is associated with specific barriers and challenges (Dewald and Truffer 2011, 287). An elaborate understanding of market formation processes needs to take into account the co-evolution of the technological, institutional, political and user-related aspects of innovation and related markets (Dewald and Truffer 2011, 286). Even though it is

virtually impossible to influence the market formation from a single location, it is vitally important to construct competences to monitor and understand market formation dynamics for seizing the opportunities when they emerge. In locations like Silicon Valley, with abundant influential actors from different areas of the market, it is possible to witness markets evolving, but in more peripheral locations like Tampere, there is a need for active competence building for entering emerging markets. In Tampere, it is well understood that there is a need to reach international markets and funding sources, as the country is small and opportunities thus limited. It is also understood that there is a need to strengthen the collaboration with the Finnish hospitals to gain first-user references close to home and make sure that the benefits of the science in question are available in the country that has funded the research.

In BioMediTech Tampere, strategic awareness about emerging markets is fairly good at a general level but shared generic competences to exploit emerging opportunities are not well developed. Additionally, the core actors in Tampere are not familiar with the international markets, specific to those products and services BioMediTech is specialising in, and there is no systematic monitoring of them either. BioMediTech has received public funding from national and local sources to strengthen its capacity to operate in the global markets but the specific competences to monitor and assess the emergent human spare parts industry are not systematically developed, and the interviews indicate that their relevance as a part of the system are not fully understood. BioMediTech Tampere has been fairly inward looking and has not aimed at tapping into expertise of public and/or semi-public development agencies that has been established to be of support to these kinds of commercialisation efforts. Instead, there are signs of widening gap between BioMediTech, development agencies and also firms. This is due to many national factors (see below), the most important local issue being that the earlier fairly well-established sharing of joint and individual competences (see Sotarauta and Mustikkamäki 2015) has been fading away as the universities have been struggling with the many internal issues related to founding a joint institute between two individual universities. However, BioMediTech and local and regional development agencies are slowly awakening to realise the consequences of unbalanced local system, and new competences are being built but they are still in their early phases of development.

At all events, the human spare parts industry has only begun to emerge; the market formation has barely begun. It is an emerging industry without an established position yet. According to Alliance for Regenerative Medicine (ARM 2014), there are approximately 700 companies globally in the field of regenerative medicine (out of which 247 companies are dedicated to cell therapies). ARM divides the emerging market to four sub-groups: therapeutics and devices (56 %), tools (19 %), tissue banks (13 %) and services (12 %). According to Grand View Research (2013), in 2013, the estimated size of the regenerative medicine market size was $30.16 billion from which the stem cell technology market was $12.8 billion. Depending on what industries are included in regenerative medicine, market size estimations vary greatly but as the clinical trials proceed, also, the science push increases.

Entrepreneurship and venture finances

As entrepreneurs take advantage of new business opportunities generated by new knowledge, and as they turn the potential of new knowledge, networks and markets into new business opportunities (Hekkert et al. 2007), their generic competences related to market understanding are of importance in moving towards commercialisation and potentially also making regenerative medicine an elemental part of the healthcare system. Additionally, entrepreneurs possess generic competences that enhance generation of diversity and diffusion of new knowledge (Drucker 2014; see for university-run enterprises, Zhou 2014). Entrepreneurial activity is usually considered one of the core activities in selecting viable alternatives from emerging ideas and knowledge (Hekkert et al. 2007). Quite naturally, in contrast to a scientist, whose main motivation is to create new knowledge and thus also novel opportunities, the entrepreneur's motivation revolves around the practical actualisation of these (Drucker 2014).

In BioMediTech, as explained in the previous sections, the competences related to science and technologies have developed favourably but business formation has yet to emerge. There have been over 10 spin-off firms as well as around 100 patents from BioMediTech and its predecessors, but the firms have not grown substantially. In Tampere, there are several biomaterial firms but, at least so far, no such entrepreneurs have surfaced, which would exploit the science and technology created in BioMediTech. Furthermore, there are no discussions between existing firms in Finland and BioMediTech or strategic efforts to create a nourishing local ecosystem for start-ups to emerge and grow. The current commercialisation strategy of BioMediTech focuses more on detecting major international dedicated actors to collaborate with than aiming at creating a local start-up ecosystem. All in all, our interviews clearly indicated that the general atmosphere towards the idea of having start-ups linked to BioMediTech is favourable, and there are several projects aimed at developing proofs of concept and raising funds for the next stages, but, as the competences related to boosting start-up community are still poorly developed, the international incumbents are seen as a favourable route forward. At BioMediTech, several explicit support measures to strengthen the entrepreneurial competences have been launched. These include recruiting additional staff with complementing capabilities in issues related to commercialisation, patenting and licencing; training scientists for commercialisation and seeking help to construct local competences from the USA and Belgium. Indeed, our interviews indicated clearly that these have been necessary but not sufficient measures if other competences in the system do not develop favourably. The efforts are more based on strengthening competences in a single organisation, instead that of an entire system, and therefore, the measures do not meet the scope of challenges.

Public funding has been extensively received to support the emergence of regenerative medicine but private venture finance has not found its way to Tampere, and hence, there is a need to find a proper balance between finding dedicated incumbents to collaborate with and supporting establishment of venture finance-backed start-ups to showcase the local scientific potential and, of course, to grow by themselves if possible. A well-functioning Triple Helix constellation requires competent venture financiers who recognise and finance the entrepreneurs, and hence, for their part, play an important role in the selection process. As previously shown, the catalytic role of venture financiers is often crucial in the emergence of new industries (Florida and Kenney 1988;

von Burg and Kenney 2009). The challenge for new ventures is to 'carve out a new market, raise capital from sceptical sources, recruit untrained employees, and cope with other difficulties stemming from their nascent status' (Aldrich and Fiol 1994, 645). Moreover, as Pisano (2006) argues, biotechnology is a challenging sector for three reasons: (a) the uncertainty of the outcomes of the science and technology, (b) the heterogeneous and complex nature of the science, and (c) the need for long cumulative learning. All this calls for patient and future-oriented funding. These observations describe the situation BioMediTech is facing very well.

Additionally, the difficulty is that there are no Finnish venture capitalists that would invest in regenerative medicine, and as a whole, Finnish venture capital is a scarce resource (Sorvisto and Sotarauta 2016). The competences to fund the commercialization of regenerative medicine are poorly established in Finland. For these reasons, to raise venture capital BioMediTech needs to seek it from abroad but the abilities to sell the idea to a foreign venture capitalist have yet to emerge, and there are no real connections to potential venture capital sources, i.e. 'independently managed dedicated pools of capital that focus on equity or equity-linked investments in privately held, high growth companies' (Gompers and Lerner 1999, 349).

The emerging human spare parts industry in Tampere is not alone in its lack of entrepreneurial activity and difficulties in acquiring funding for commercialisation (see Hellman et al. 2011; Johnson et al 2011; Martin et al 2006), as it is the anatomy of the industry in itself (Pisano 2006). All this may be due to the fact that, in spite of huge promises, the market for the human spare parts industry has yet to emerge, and therefore, the competent companies and entrepreneurs have not seen the business opportunity yet in a broad sense. As suggested, a standard venture capital model is not working in cases where a large amount of money (e.g. $100 million) and time (e.g. at least 10 years) are needed to finalise a product (Reynolds et al. 2013). In regenerative medicine, technological risk and burn rates are high, and a combination of high risk and long time-span is not a lucrative opportunity for a financier. For these reasons, according to Mason (2007), since the early enthusiasm of the 1990s, the funding in regenerative medicine has switched from venture capital and pharmaceutical firms to public finance, philanthropists and military sources. Regenerative medicine is a fairly typical case of an emerging science-based field that draws heavily on public funding, and private venture financiers become interested in the potential of its innovations only in the later phases of clinical trials (Parson 2008).

Mason (2007) states that three factors make it possible for a new venture to succeed: expert business management, simple but superior products and scalability of manufacture (Parson 2008). Consequently, for a venture capitalist to be convinced about a market potential of a novel product or service: (a) medical needs must be clearly identified, (b) savvy management team needs to be in place and (c) intellectual property needs to be protected (Parson 2008). Prescott (2011) also highlights the importance of third party endorsement for the product and an effective sales and marketing strategy. In Tampere, there are not savvy management teams attached to the local system that would possess the competences needed in moving forward, and neither there are products nor services packaged for international markets. In consequence, the generic competences needed in exploiting the opportunities in the emergence of new industry are still to be constructed.

Legitimisation

Simultaneously, with the high hopes embedded in regenerative medicine, the emerging human spare parts industry faces both complex ethical and legislative issues and difficulties typical to new emerging industry, and hence, its emergence cannot be fully grasped without full appreciation of the issues related to legitimisation.

As innovation needs to become part of an incumbent regime, a new emerging industry needs to establish itself as a part of several systems (Hekkert and Negro 2009; Aldrich and Fiol 1994). To accomplish this, various actors need to innovate against the logic of those systems that are supposed to support them, and thus, generic competences related to legitimisation may be of utmost importance. It is worth reminding that the question is not about legitimating human spare parts industry in one specific system but several systems and hence broadly in the society. In the case under scrutiny, these are not only healthcare, science and innovation systems but also local/regional economic development systems.

Lack of legitimacy may be among the main obstacles for new ventures operating in emerging industries and/or markets, as new products, services and processes need to overthrow the existing regime. That, of course, frequently causes uncertainty and social anxiety. Consequently, reduction of social uncertainty and dealing with resistance to change are among the generic competences needed in an innovation system. These are here combined under the concept of legitimisation. Legitimisation refers to the socio-political process of legitimacy formation through actions by various organisations and individuals. Central features are the formation of expectations and visions as well as regulative alignment, including issues such as market regulations, tax policies and directions of science and innovation policy (Bergek et al. 2008). Legitimisation is about acquiring social acceptance of innovation, and it is a process that makes an innovation conform to the prevailing institutions (norms, values, habits and regulations) and/or to a process that targets the change of institutions for something new to emerge (Bergek et al 2008). Legitimisation is one of the most central selection mechanisms in any Triple Helix setting.

Earning legitimacy is a demanding process, as a society is unfamiliar with the industry and new innovations related to it. The human spare parts industry is not well defined yet, and there are only few or no standards and/or products and services against which society can judge the industry as appropriate. Of course, conversely, ambiguous or non-existing standards and services also present a great opportunity for a new venture in an emerging industry, as they may take a lead in defining the industry, determining the standards for it and establishing a dominant design for an entire field, and thus create legitimacy for the industry. In practice, it is rare that one single actor might be in a position to push for legitimacy alone, and more often than not it calls for actions from public, private and academic actors. There are multiple ways to legitimate a new industry. At the organisational level, ventures must build trust with customers, firms in related industries and industry members. They also need to develop a knowledge base by clearly defining issues (e.g. the level of abstraction, use of existing knowledge, internal consistency) (Aldrich and Fiol 1994),

Mason and Dunnil (2008b) point out the importance of widely accepted technical standards because the lack of early agreement on standards might be damaging to the human spare parts industry. Currently, in developed countries, it is, of course, almost

impossible to bring new therapies or medical devices into clinical use without any regulatory approval. Regulatory bodies, though, are not always up to date about biomedical scientific understanding and possibilities of technology, and thus, there are examples of evolutionary trajectories where regulation co-evolves with the innovation process and the market (Metcalfe et al. 2005). Statutes concerning clinical medical research in general cover much of the stem cell-based research, and only a few countries have adopted legislation devoted to stem cell research per se. In Finland, the ethical atmosphere and legislation have mostly been permissive (Stem cell research in the Nordic countries 2007).

In Tampere, realised experimental treatments have been regulated under Hospital Exemption for Advanced Therapy Medicinal Products (ATMP). Even after several successful experimental treatments, and established expertise to cultivate bone tissue from stem cells, regulators do not fully know what the regulatory details are for these kinds of new products and treatments in Finland. There actually is an on-going dialogue between the regulators and representatives of BioMediTech to find out what is actually required and how to carry it out, and thus, the Tampere case confirms the earlier observations that regulation co-evolves with the innovation process and the market in the emerging industries (Metcalfe et al. 2005). In Finland, regenerative medicine is well legitimised in the science system including science and innovation funding but it is not as well legitimised in the healthcare system, as the treatments are mainly case-by-case experiments rather than established parts of the standard repertoire of the hospitals and the entire system. According to our interviews, in the hospital, the individual medical doctors comprise the core in the efforts to exploit the discoveries of regenerative medicine, and thus to legitimise it in their own specialisation areas, and so far, there has only been few champions for these efforts. Therefore, the limitation of a physician's responsibility regarding harm done to a patient during a treatment may have a major impact on clinical practice as well as new product and service development. If physicians alone carry the responsibility, the will to take risks at individual level is small compared to a situation where the government, hospital or a system as a whole carries part of the liability. In Finland, physicians are fairly well positioned to experiment with new technologies as the responsibility is shared in the system.

End-values

Liu and White (2001) suggest that, in the spirit of demand-led innovation, end-use-generated innovation needs to be better acknowledged than earlier recommended in the innovation system literature. However, in the early stages of regenerative medicine-related products and services, it is fairly hard to see user- or demand-led innovation emerging. The entire field is pushed forward by new developments in science, and the 'customer imagination' is not developed enough to demand new kinds of services. However, as the field is characterised by high hopes and global hype, there are a variety of expectations. Public policymakers and funding bodies are looking forward to increased employment and globally leading positions in a new trending field; our interviews revealed that this is the case in Tampere too. Scientists, for their part, aim to push the scientific frontier forward but also seek citations and fame. And of course, ultimately, there are incurable or difficult to cure diseases and thus plenty of patients who might benefit from scientific breakthroughs in regenerative medicine providing

them with new hope. In all cases, potential and actual beneficiaries of innovations in regenerative medicine consist of heterogeneous sets of actors that all have their own hopes and fears. Expectations are not as clear as we might assume; any Triple Helix is a nexus of many expectations and desires, and hence, consensus spaces are of importance, but not easily constructed and maintained. Therefore, it is important to scrutinise what the potential end-results might be by focusing on not only the end-use of specific innovations, or demand-led innovation, but also the end-values various actors expect to get out of it. It is important to note that 'a firm', 'product' or 'service' is not an end-value, as is often seen, but the value generated for the society, economy and individuals at large.

In Tampere, there have been only limited discussions, not to mention public debates, on the end-values, and it may be that the lack of public debates are among the reasons why legitimisation processes are still uneven depending on the sub-system, and why market offerings have been slow to emerge, and why the Tampere University Hospital has not adopted a more strategic attitude towards it. In Tampere, there are no efforts to boost public discussion on the public and/or private end-values of the money invested in regenerative medicine either, and it seems clear that there is no widely shared awareness of the importance of public debates in the emergence of a new industry and thus no competences to set these in motion. Perhaps, the human spare parts industry has not begun to emerge in Finland, as it is globally underdeveloped, funding is scarce but also because there is no public debate concerning the end-values or potential risks involved in regenerative medicine and human spare parts industry.

The core actors have not understood the value of generating a public discussion on the future prospects of regenerative medicine and human spare parts industry more broadly. As the end-values are only vaguely debated outside the scientific and some policy circles, it also is difficult to begin a systematic construction of such competences that are needed in taking major steps forward. In addition, there are no 'innovation evangelists' who would work for increased awareness of the emerging industry and build a critical mass and competent management teams of support for it. An evangelist is a special role in the system with established competences in promoting the use of a particular technology through talks, bonding with gatekeepers, writing articles for professional as well as general media, blogging, boosting user demonstrations, presenting recorded demonstrations or the creation of sample projects (Beatty and Gordon 1991; Lucas-Conwell 2006). Innovation evangelists are playing an important role in the construction of collective beliefs that again are central in a design of new strategies (Sotarauta 2016) and construction of related competences.

Conclusions

This paper suggests that to truly understand the dynamics of the Triple Helix model and how new discoveries are commercialised and diffused into the society, there is a need to study also interacting generic competences that either enhance or hamper collaboration in Triple Helix constellations. Moreover, it is believed that construction of well-functioning innovation and knowledge spaces, and related consensus space, calls for novel ways to analyse and develop interrelated but differing competences from Triple Helix instead of organisational perspectives (see also Ranga and Etzkowitz 2013). For these purposes, a set of generic competences was introduced and discussed, and it

was also shown how they play together, or not, in a specific case. The dominant generic competences are related to the generation of new knowledge and the selection of winning knowledge, products and/or services and retention of them in the economy, but, as was shown, several other generic competences are called for in the system to make a lasting impact on the society, to institutionalise the new discoveries. As the case study reported in this paper shows, it may be difficult to move beyond scientific excellence in an emerging field, in which not all the generic competences have developed yet to support each other. Any Triple Helix constellation is by definition a complex ensemble of actors, and as the Tampere case also reveals, in the course of events, it may be fairly difficult to see how the lack of competences related to making sense of emerging markets, debating potential end-values and legitimisation may end up hampering the functionality of consensus and innovation spaces, and thus also seemingly straightforward commercialization efforts.

The main obstacles in a case under scrutiny are related to insufficient funding, difficulties in the technology transfer processes, poor understanding of emerging markets and acquisition of capabilities needed in the form of competent management teams. Many of these issues are beyond what can be expected from universities only, and quite naturally, the emergence of the human spare parts industry is dependent on many competences of all three institutional spheres of the Triple Helix model. It might be possible to argue, for example, that the local university hospital, owned by the local government, ought to integrate new treatments into its standard repertoire, but, in practice, the mix of potential end-values are poorly identified and not properly debated, and thus, it is difficult for the hospital to take necessary measures or even understand what is at stake. And here, the competences of social scientists and/or local politicians might prove invaluable. Moreover, it would be easy to suggest that the universities ought to strengthen their competences related to entrepreneurship, market formation, technology transfer and commercialization, but as important, it is to ask where complementary competences could be found from and how they could be tapped into and integrated into the local Triple Helix constellation. So far, they have been found in the USA and Belgium. In addition, there is a medical technology-specialised local development agency that played a central role in the early phases of regenerative medicine (see Sotarauta and Mustikkamäki 2015), but as the role of intermediaries has been questioned in the Finnish innovation system, it has been disintegrating from more recent developments. Interestingly, from a national innovation system point of view, this may be a well-argued position but, from a competence set point of view, well established, much needed and valuable local competences have been side-tracked more or less unintentionally.

The conclusion, and proposition for future on studies on triple helices, is that a balanced competence set influences positively the functionality of Triple Helix constellations, and more specifically knowledge, consensus and innovation spaces in the core of them, and provides all three institutional spheres with a tool to customise their interaction. It is important to note that the generic competences and a competence set based on them may be universally needed but their manifestations vary across countries and regions; different actors may introduce different generic competences depending on the past path, the system and the expertise of individual actors. Thus, the concept of competence set provides a tool to discuss the roles of various actors in a Triple Helix, and the competences they bring into play, and especially to detect poorly developed or non-existing competences.

Additional file

Additional file 1: Translation of the abstract into Arabic. (PDF 273 kb)

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Regenerative Medicine as an Emergent Cluster in Tampere Region

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Abstract

Clusters are important for regional economies and emergent clusters are in a key position, as a means of adding more diversification to the current economic activity by involving new technologies and industries. Science-based industries may be the most promising in this regard since they are encouraged to develop and enhance the economic imaginaries of territories under the umbrella of radical innovations or in the name of broadening the current economic model based on mostly traditional industries. Regenerative medicine (RM) could be an example of these so-called emergent clusters. Regenerative medicine is highly dependent on academic research, which means that local territories must fund the research in this field and, hence, they expect some returns as well. As territories do not typically have existing industries specifically in RM, these industries must emerge or expand from existing ones. Regenerative medicine involves a wide spectrum of different technologies and industries that are likely to form a cluster and benefit from it if successfully developed. The first aim of this paper is to show how some obstacles eventually impede the proper development of these emergent clusters. The second aim is to shed light on how innovations emerge in the cluster and what are the main implications for the territory. In this study, existing literature is used in order to describe the technology market and commercial aspects of the RM sector. Empirically this study is based on the emergent RM cluster in the region of Tampere in Finland. Analysis of 24 conducted interviews helps to contextualize the emergence of the RM cluster in Tampere, where academia is both the booster and the driver of the emergent RM cluster. Commercialization of research in the RM field is one of the goals at the university, even though there are no commercial outcomes yet available. This study contributes to the understanding of emergent cluster development in science-based industries in their embryonic and early stages. Major challenges are pointed out in an emergent cluster that calls for tailor-made socio-economic policies at the meso-level. Tailored policies matter in science-based clusters, and specific sectors in specific stages of development need specific policies in order to become matured clusters.

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Keywords: *regenerative medicine, emergent cluster, commercialization, innovation, competence bloc, technology market.*

Introduction

Clusters are important for regional economy as they include different industries working together (Saxenian, 1994). Many traditional clusters e.g. textile, IT, automotive, food, energy, etc., include matured industries (Iammarino & McCann, 2006). As scientific development in universities goes forward, there may be possibilities to create new industries and even new clusters, as many different technologies are often needed in order to fully exploit scientific research (Stoerring, 2007; Stoerring & Dalum, 2007). In this study, the regenerative medicine (RM) sector is used as an example of a new emergent science-based cluster (Pavitt, 1984). Globally in the RM sector, commercial development is only in its early stage, and innovation is dependent on academia, research centres and hospitals (McMahon & Thorsteinsdottir, 2013). The future of the RM sector is highly dependent on university-based research, overcoming the financial gap, and the emergence of firms, and in the process of RM sector development, hospitals play a significant role as an endpoint of therapies.

Conceptually this study contributes to the cluster life cycle theory by discussing the commercial engine that enables growth and introducing some empirical evidence from the very early phase of a cluster life cycle. As clusters tend to speed up innovation, firm creation and growth (Baptista & Swann, 1998), new sectors like RM would presumably benefit clustering. However, due to the small number of commercial entities globally in the RM sector, it is not possible to study matured clusters and their early phases. Instead, an emergent science-based RM cluster in the Tampere region provides an opportunity to scrutinize the very early phases of a potential cluster *ex ante*. As a result of university-based innovations, it might be possible to see the emergence of new firms and the growth of existing firms who expand their product or service portfolio to the RM sector.

The first aim of this study is to show how some obstacles eventually impede the proper development of these emergent clusters in the RM sector. As the development of commercial RM products costs significantly and takes a long time, firms need to overcome these challenges. The second aim is to shed light on how innovations emerge in the cluster and what are the main implications for the territory. To answer these questions, a case study was conducted in Tampere, Finland. In Tampere, RM-related innovations are developed in academia with great hope for future economic growth, in terms of new firms, expansion of existing firms, and employment.

Cluster view on RM

The study of clusters as research objects traces its roots back to the 1990s (Porter, 1990). The main motivation for cluster analysis is to understand how a country/region (or whatever the level is being talked about) gains the competitive advantage of related sectors embedded in a region compared with other global competitors or other lower-scale (local) territories. However, studies on these matters have confirmed the existence of more appropriate conceptual frameworks, mainly from the innovation studies community, where technological change is included as one of the cornerstones to explain the dynamics of the sector. Another dimension included in the innovation systems framework is the multi-level perspective (Geels, 2002), in order to understand the correlation of the forces between actors (distributed agency) at different territorial levels (international, national, regional and local). Among different models proposed by innovation scholars, in this article we used as a theoretical background (Figure 1) the model of innovation system proposed by Arnold and Kuhlmann (2001). These authors propose a model that not only shows but also emphasizes the important aspect of demand affecting both industry and university, and is divided into final demand and intermediate demand. Political sphere influences are also analysed under this framework by including both government and policies that affect brokers between universities and industry, supporting infrastructure, and universities. In summary, three elements are present within this framework: 1) a set of institutions, which promote and enable innovations to occur; 2) the interactions between those above-mentioned players; and 3) the environmental conditions within which the system works. This functional view on innovation systems is treated in the work of Hekkert et al. (2007).

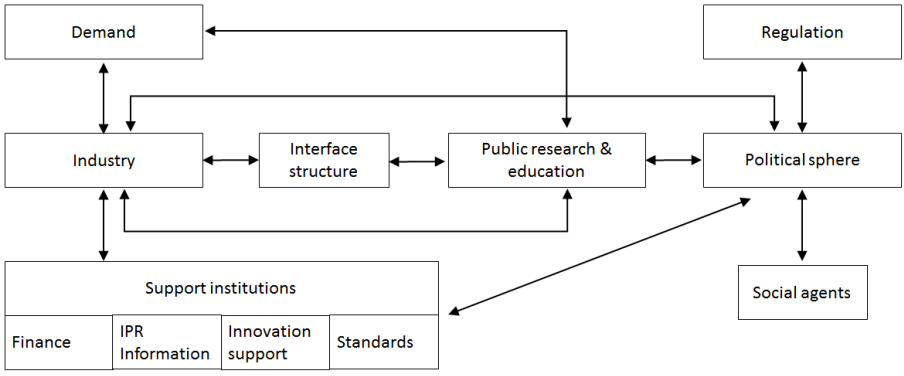

Figure 1. Theoretical framework modified from Kuhlmann and Arnold (2001)

Source: Original framework was presented in the order Arnold and Kuhlmann in the publication Kuhlmann and Arnold (2001).

Demand is an important aspect of the emergent cluster and in the RM sector it is quite complex. Is the customer a patient who gets treatment, the society who benefits from healthier people, or a hospital, which delivers the treatment? As in any sector, depending on the business strategy, firms produce different products at different points of the supply chain – for example, a firm producing compounds as a supplier, a hospital delivering generated bone to the patient, or a firm utilizing stem cells in a gene therapy. The other thing is that innovation requires different competencies in different phases. For this reason, Eliasson and Eliasson (1996) developed the competence bloc theory, which is a good starting point to evaluate the needed competencies for economic growth and successful innovations from both a business and innovation point of view, as the competence bloc is the infrastructure needed to create, select, recognize, diffuse and exploit new business ideas (Table 1). Eliasson and Eliasson (1996) argued that in the emerging biotechnology sector sustainable economic growth would be reached through entrepreneurs funded by venture capitalists, and winners later acquired by established companies acting as industrialists. It thus calls the human competencies that are needed to create new businesses and industrial success (Eliasson & Eliasson, 1996). This also describes the dynamics in the emergent science-based cluster. As universities are innovators, entrepreneurs are needed to carry emerging innovations forward. Competence bloc theory also implies that enough entrepreneurs are located in the territory so that venture capitalists are able to recognize those that are most viable ones. Those firms that are not viable will be terminated fast so that they have an opportunity to select another potential innovation to work on.

Table 1. Actors of competence bloc

Actors	Tasks	Function in infrastructure
Customer	Active, competent and resourceful. Products are never better than customers are capable of demanding.	Demand
Innovator	Connects technical specializations.	Creation
Entrepreneur	Selects commercially potential innovations.	Selection
Venture capitalist	Recognize and finance commercially viable opportunities.	Recognition
Industrialists, business leaders and financial experts	Bring new product to full-scale production.	Exploitation
Exit-market	Expectation for reasonable or better profit for those who are successful.	Incentive

Source: Eliasson and Eliasson, (1996).

The cluster life cycle follows four phases: formation, development, maturity and renewal/decline (Belussi & Sedita, 2009). First firms are established in the formation phase, followed by a significant growth in the firm population in the development phase. Maturity comes when firm population is stabilized. The competence bloc is especially important in the formation phase of the cluster and its subsequent development phase. In the biotechnology-related industries, start-ups tend to be those that develop innovations and established companies bring those new products to full-scale production. If needed competencies are not available, it is not likely that the development phase of the cluster will continue very far, if it begins at all. As the cluster grows (development phase), local firms are also able to innovate and that way expand their product offerings. At this point, the locus of activity in the emergent cluster shifts from academia to firms, even though academia and hospitals have important roles in creating new knowledge, innovations, being the places for clinical trials, and act as end-users.

Data and method

Empirical insights in this study are based on a single case study conducted in Tampere, Finland. Although it would have been more desirable to include more case studies in the research, the quest for a pluralist approach and a deep perspective allowed us to conduct only a single case study (Yin, 1989). This obviously does not support generalizability, but ensures a richer look at one emergent phenomenon on a global scale (Marshall & Rossman, 1999). The major share of interviews were conducted at the Institute of Biosciences and Medical Technology (BioMediTech), which is a joint institute of the University of Tampere and Tampere University of Technology. In BioMediTech, the Human Spare Parts research programme was the focus, as it is focusing on RM therapies and technologies. This article emphasizes the emergence of a cluster, which has its roots in the university level. The science-based cluster is in the formation phase, which means that no firms have emerged yet. Thus, inclusion of more firms in the interviews is not plausible and instead interviews focused to the university. Altogether 24 interviews were conducted (Table 2), and in all of the interviews the same semi-structured set of questions was used within the following main themes: research, entrepreneurship, venture finance, legitimization, market formation, hospital environment, and end-value. As a result these interviews gave a coherent view of how different actors at different levels understand the emergent RM cluster in Tampere. Other sources for information were relevant documents, articles and news that were used to describe the history of this emergent RM cluster as well as the industrial sphere.

Table 2. Conducted interviews, organizations and organization level

Organization	Number of interviews	Level
BioMediTech (University)	15	Local
University Hospital of Tampere	3	Local
Firm	1	Local
Regional development agencies	2	Regional
Ministry of Employment and the Economy	2	National
The Finnish Funding Agency for Technology and Innovation	1	National

Elements of the emerging RM sector with an impact on industrial development

In human healthcare, there have traditionally been two main disciplines: medicine and surgery (Polak et al., 2010) and RM could be a third one attempting to revolutionize healthcare. A short, simple definition of RM is provided by Mason and Dunnill (2008a: 4): 'Regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function'. Hence, RM uses medicine, surgery, and other disciplines as a multi-disciplinary field (Polak et al., 2010), and even though it is mostly based on cell therapy, i.e. the expected fourth pillar of the healthcare sector alongside pharmaceuticals, biopharmaceuticals and medical devices (Mason & Manzotti, 2009), it consists of a wide spectrum of different approaches and technologies. The set of potential industries is quite wide and is organised in different levels regarding the supply chain; for example, a firm that decides to concentrate on regenerative compounds is most probably a supplier to a firm concentrating on tissue engineering. Also hospitals are important for progress in RM because they provide the infrastructure for surgery and care of patients, but also ideas regarding current needs where RM therapies might help.

Major expectations for the RM sector are based on the use of stem cells. The biggest hurdle for the use of stem cells derived from human embryos is the ethical and political environment (Harvey, 2010) and in some EU countries it is not possible to have a patent relating to human cells derived from embryos (Mason & Dunnill, 2008b). In general, there are currently different laws among the nations in the EU and the US regarding the use of embryos (Mason & Dunnil, 2008b). With induced pluripotent stem cells (iPSC), found in 2006, it might be possible to overcome these hurdles and thus generation of iPSCs might have a major impact on RM (Amabile and Meissner, 2009). However, there are concerns if iPSCs are identical to embryonic stem cells and if not, what is the level of similarity for therapeutic and screening purposes?

Thus there are some challenges to be met before iPSCs can be used routinely in pharmacological screening and RM (Amabile & Meissner, 2009).

According to Martin et al. (2006), there were two waves of commercialisation and industry building in the RM sector – the first was between the 1980s and the 1990s, and a second wave from the mid-1990s onwards. In the first wave, the U.S. dominated, but in the second wave, Europe has established a stronger presence. According to Mason (2007), the problem is that funding in the RM sector (somewhere around 2005) has switched from venture capital and pharmaceutical firms to public finance, philanthropists and military products. Venture capitalists are not interested in investing in firms until later phases of the clinical trials (Parson, 2008). However, start-ups need funding for research, development, small-scale manufacturing, and early clinical trials (Mason & Dunnil, 2008b). Parson (2008) believes that for the majority of firms the future will depend on the possibility of moving forward from start-up-funds to later stage funds to sustain their products through clinical trials. For making this possible, one of the most relevant needs start-up companies in the RM sector is a competent management group (Johnson et al., 2011). However, Parson (2008) points out the limits of a start-up company in the RM sector, where a large amount of cells are needed for treatment in a large patient population and a small start-up company may not be large enough to conduct the required trials. Hence, another strategy for an entrepreneurial firm is to be acquired by a bigger company, which is a possibility for a venture capitalist to exit the company if involved, and the established company as an industrialist continues to bring the product to full-scale production.

Metcalfe et al. (2005) made an important point about the sustainability of the new technology and its requirements. According to them, commercial investments are sustainable only if there is a possibility of obtaining a necessary return from the market, and from this point of view, the development of demand and the role of regulation in establishing demand are both important. However, if the market is not fully established, technology development can be supported by non-commercial investment and instead of a technology 'pull', the only option that is left is to try technology 'push' with university based research.

For the companies in the RM sector it is important to have access to cutting edge research (Prescott, 2011). Academia and firms have several innovation co-operation activities, e.g. funding, licensing, consulting and advising between the scientific and technological networks in tissue engineering (Murray, 2002), and scientists with new ideas even have roles in RM firms bringing human and social capital with them (Murray, 2004). However, universities are expected to nurture innovation further in clinical

trials before establishing start-ups and obtaining venture capital for it; some countries are actually filling this gap by establishing government centres for funding cell therapy clinical trials (Mason et al., 2011). In Finland this is not the reality yet.

Hellman et al. (2011) argued about the need for collaborative interactions between scientists, physicians, investors, attorneys, regulators, political entities and patients in building a biomedical industry. The RM sector will need highly specialized hospitals and day-care centres where cells are implanted and therapies conducted, and thus, training for the clinical community must be conducted in order to be able to use products (Mason & Dunnil, 2008b). Regulatory bodies, though, are not always up to date about biomedical scientific understanding and possibilities of technology, and thus there are examples of evolutionary trajectories where regulation has co-evolved with innovation sequence and the market (Metcalfe et al., 2005).

Salter et al. (2014) make a distinction between different models in stem cell therapies (Table 3). Model I is the only solid scientific innovation model while the rest are so called medical innovation models. Medical innovation in cell therapy is defined the followed way: 'Medical innovation in cellular therapy may be viewed as ethical and legitimate use of non-approved cell therapy by qualified healthcare professionals in their practice of medicine' (Gunter et al., 2010, p. 966). The goal of medical innovation in cell therapy is always to be beneficial for the individual patient while the goal of scientific innovation is to obtain generalizable results (Lindvall & Hyun, 2009).

Table 3. Differences between stem cell innovation models

	Model I	**Model II**	**Model III**	**Model IV**
Scientific / medical innovation	Scientific innovation	Medical innovation (Western)	Medical innovation (non-Western)	Medical and scientific innovation
Regulation	Traditional with clinical trial, advanced therapy medicinal product (ATMP) in EU	ATMP Hospital exemption	Not regulated	Not regulated / traditional with clinical trial
Patient #	Unlimited	Single / small group	Large population	Large population
Product	Clinical application	Non-routine exercise	Clinical application	Clinical application
Ethics	Knowledge generation	Patient benefit	Patient benefit	Patient benefit
Acting professional	Scientist	Clinician	Clinician	Scientist / clinician

Source: Salter et al. (2014).

Gunter et al. (2010) claimed that those patients not eligible for controlled clinical trials should be able to choose unproven but scientifically validated cell therapy options. In addition, it is said that it is not optimal to develop stem cell therapies only via the medical innovation pathway alone (Lindvall & Hyun, 2009). Thus, there might be a place for scientific and medical innovation paradigms in the cell therapy sector, if researchers are competent and patients are truthfully and ethically informed (Gunter et al., 2010).

Currently in developed countries, it is almost impossible to bring new therapies to clinical use without any regulatory approval, as long as there is medical technology innovation involved. There are some exceptions, e.g. advanced therapy medicinal product (ATMP) Hospital Exemption in EU, which allows hospitals to do some clinical treatment without any clinical trials, but in these cases, treatment has to be non-routine treatment and regulatory authority has to approve it. Another problem is that there is no scientifically proven evidence that a product is efficient and safe. The other questions are whether these non-routine treatments can be understood as a new medical practice and what their role is in the development of the RM sector. With accumulated expertise, it is possible to serve patients, but it means that because of the ATMP Hospital Exemption regulation, treatments have to be conducted in the granted country and due to non-routine treatment not all who want to get it are eligible. Thus, regulation restricts medical innovation in very fundamental way, but also makes it safer.

Emergent RM cluster in Tampere

History

Biomaterial research has a long history in Tampere. Already in the 1980s there was advanced research in biomaterials, and researchers were able to develop a bio-absorbable screw to repair bone fractures (Sotarauta & Mustikkamäki, 2015). Two decades later researchers in Tampere were able to grow real bone tissue from patients' own stem cells. This progress and development did not happen in a vacuum, but included several organizations and programmes. One of the steps forward with regard to the RM sector in the Tampere region was the establishment of BioneXt Tampere (2003–2010). This organization was established in order to support tissue engineering, biomaterials, bio-ICT and immunology fields in acquiring needed expertise and investments.

Several organizations in Tampere established Regea in 2005 as a research institute with a focus not only on basic research but especially on clinical applications. One of the successes at that time was that the city of Tampere endowed a professorship for stem cell research to Regea. According to

interviewee: "the vision was from the beginning that this research generates commercial outputs". Indeed, only two years after the establishment of Regea they were able to conduct an operation with a real patient, in which a part of the patient's missing jawbone was reconstructed with stem cells taken from the patient's own fatty tissue. Over the ensuing years, this therapy has been used successfully in over 25 patients in cooperation with Finnish university hospitals, and lately in Tampere. Before the establishment of Regea, a good manufacturing practices (GMP) level laboratory in the University of Tampere was crucial in the development of the clinical tissue engineering application.

Some other initiatives also built a basis for the formation phase of the RM cluster in Tampere. The Biosensing Competence Centre (2007–2010) focused on regional strengths of tissue engineering and clinical diagnostics, and the national programme HealthBIO (2007–2013) focused and contributed to the biotechnology field in Tampere. HealthBIO was a biotechnology cluster focused on utilizing high competence in business and on developing supporting structures. In 2011, the University of Tampere and Tampere University of Technology established BioMediTech as a successor to Regea. BioMediTech continued the prospective stem cell research and the Finnish Funding Agency for Technology and Innovation (TEKES) granted BioMediTech the research programme, Human Spare Parts, which is still going on. Through this research programme, RM research in Tampere has continued to advance. As all initiatives have aimed to strengthen the biotechnology cluster in Finland and in Tampere, RM applications in particular were seen as a strength in which other competencies could be utilized.

Industrial sphere

The emergent RM cluster in Tampere includes many potential application areas in stem cell therapies, diagnostics and supporting technologies. Even though the financial need might be too high for stem cell therapies in relation to readily available funding resources, there are still possibilities for other supporting technologies and diagnostics, for example. In the Tampere region, only a few firms purely focus on stem cell-related services or products and the RM-focused industrial sphere is in a very embryonic formation phase. In life science fields, such as devices, ICT, biomaterials, pharma, and services, there are firms focusing on biomaterials and cell-related technologies, and, traditionally, health and biotechnology industries have been successful in Tampere. There have been few initial public offerings from Tampere in the biotechnology sector. One was in 1997 to the New York stock exchange and the other was in 2004 to the London stock exchange, even though experience from these did not really stimulate the growth of the local ecosystem on a large scale.

Regarding cluster development in the RM sector, there have been only a few small firms in Tampere dealing with stem cells. However, the Tampere region still has some potential firms in the biotechnology industry that could acquire potential RM-related applications and innovations from BioMediTech in later phases of cluster development. In this sphere, there have been over 10 spin-offs from the research groups in Tampere. The good thing for the local industrial sphere is that BioMediTech actively seeks opportunities to commercialize their research, and for this purpose they have established several internal projects. However, currently there are no active connections between small local firms and BioMediTech in order to exploit the potential applications BioMediTech has developed. Instead, BioMediTech seeks partners from established bigger companies abroad.

Therapy development is expensive in the RM sector and both BioMediTech and their stakeholders have acknowledged this. Around 2008, there was a plan to establish the Hospital of Advanced Therapies (HAT) to provide those therapies that Regea (predecessor of BioMediTech) was developing at that time, but eventually the implementation of HAT was suspended. BioMediTech has continued to deliver bone growth therapies through the hospital, though, and the university has planned to start a preclinical study to prepare official clinical trials in collaboration with other organizations. This therapy has in many ways been instrumental in this formation phase of the emergent RM cluster in Tampere, as it has shown the benefits that RM therapies can provide to patients, and has given proof to and hope for actors that there are possibilities in this sphere. It is very important for the potential development phase of this cluster that this therapy, as well as other potential therapies, will be transferred at some point to companies that have a link to the Tampere region. As suggested in the competence bloc theory, an entrepreneurial firm is most likely to carry potential innovation at the beginning and then later an established firm is likely to acquire it. Hence, it is important that BioMediTech also actively seeks connections to established companies and in that way make the Tampere region known to the potential industrialists. However, at the same time there is a need for local start-ups that can acquire innovations from BioMediTech, but also strengthen the competence bloc in the Tampere region in order to shape the way for the development phase of the cluster.

The Finnish market for all potential products is small, locally, and firms must look towards international markets to find customers. As one of the interviewees in the university said: “Whatever products we start to produce here, the market is global”. Thus, international conferences are important for practitioners, being places where it is possible to see in what direction the field is heading. It also means that patenting must be done wisely and rationally with regard to potential markets. This brings challenges for

BioMediTech (and all the universities) as they have to make choices as to what to patent and where. There is also a tension between scientific publications and patenting, which in some cases forces universities to patent too early so that researchers are able to publish their work. Potential market for products is the key thing for firms, and especially in the cases where university research is transferred to start-ups or existing firms. It is important for the emergent RM cluster in Tampere that potential firms are going to stay in the region and establish a manufacturing function. The development of a cluster might be the reason why firms choose to stay in Finland, even though the cost of manufacturing might be relatively high. It is important for local firms that they have the possibility to scale-up their production. However, currently the local competence bloc lacks industrialists but also related services like companies that can help to scale up the cell production. It is important for the process from the formation phase to the development phase of a cluster, such as the current science-based emergent RM cluster, that the emergence of local businesses and supporting services happens simultaneously. Locally there is also a need for a stronger interface structure between industry and academia in the RM fields.

Demand

Multi-level demand has been the most important aspect in this formation phase of the emergent RM cluster in Tampere. One of the other most important aspects is that real patients have been treated with bone growth therapy. This therapy is for patients' benefit, and in the end it is patients who create a demand for new RM therapies in general. In health care, however, hospitals and clinicians are the main actors who make decisions about the use of new therapies in patient care. Hence, clinicians contribute to this demand as well. This has also been the case in Tampere, as the clinical need has been the driving force for RM therapies and research and hospitals have been very active in creating the demand for this experimental therapy, which has not undergone any official clinical trials yet. As the development of RM therapies needs specialized tools, it also creates a demand. Solutions in the market are not always sufficient, and, hence, stem cell biology groups within academia have created a demand for better tools. As BioMediTech is a joint institute of two universities and there are research groups with technical disciplines in the Human Spare Parts programme, technology groups have been able to provide solutions to this internal demand from stem cell groups. In most industries, firms are the manufacturers of products and services. Here this is not yet the case. Instead, the universities and hospitals have been the main actors in the development of the new therapy and providing it to patients. In

order to proceed to the development phase of the RM cluster, the industrial sphere must take the lead.

The situation is currently positive in terms of new potential commercial offerings either for start-ups or established companies. Innovations created in BioMediTech (both tools and therapies) cannot be commercialized and brought to full-scale production without firms, and as scientific development advances, it will create more demand for different tools. Similarly, development of therapies requires full-scale production solutions. Hence, it seems that there are possibilities for the transition from the formation phase to the development phase of the cluster. However, for the future, an important question is whether the demand will grow big enough to attract investors and firms as well. Customers are in a key position in this as they create such a demand. Now academia is a customer for itself, but in the future, other customers will also be needed in order to develop the competence bloc.

Education and research

As in any university, education and research are two pillars in BioMediTech. There is also a third strong pillar, which is innovation promotion. Innovation is the key factor for possibilities for future economic activity in the RM sector in Tampere. As not all graduates are able to continue their studies as PhD students, the need for jobs is high and the supply of competent employees is secured. Regarding research, in recent years, one of the biggest research programmes in Tampere has been the Human Spare Parts research programme. In this programme, Tampere University of Technology and the University of Tampere combined their expertise in supporting technologies and stem cell biology. Together four groups from the field of technology and four groups from the field of stem cells joined the programme, in which the focus was on the advancement of health care with new therapies and solutions. In general, research groups in BioMediTech have a high rate of international collaboration.

The combination of stem cell research and technology expertise is important in advancing the RM sector. Because of this, it is possible to develop highly specialized solutions for stem cell research that are otherwise very difficult to find in the technology market. As these solutions have emerged from the research of BioMediTech, there are also other potential users for them, which creates opportunities for firms to grow and expand their product portfolio. The advantage is that researchers have already tested these new technological tools in practical work situations. These technologies are highly necessary in stem cell research and in subsequent applications. Hence, these form an important industry in the RM cluster, where other research groups in the RM sector are also potential customers internationally.

Hospitals are important in the RM sector, and research groups work in close collaboration with clinicians and hospitals, because this is the most efficient way to direct the research along the right path. The combination of university and hospital is also essential in order to provide bone growth therapy for patients. Currently, with regard to the utilized bone growth therapy, bone products are made in the university's clean room. From there the products are transferred to the hospital where hospital staff conduct clinical operations for patients. Without this close connection, it would be very difficult to see whether potential treatment really works. It is also beneficial for firms, as hospitals are experienced in working with stem cell-based products, which makes it easier for firms to approach them.

The interface structure between industry and academia is a part of the operations in BioMediTech as they approach industry directly. An important aspect in the emergence of the RM cluster in Tampere is the development of a proof of concepts (PoC) from the research of BioMediTech. With the PoC approach, BioMediTech is able to reduce the risk of failure in the technology transfer phase (Heinonen, 2015). According to an interviewee: "it is wise to stay in the university and conduct research, and progress until there is a clinical proof of concept". The development of PoCs is an efficient tool by which it is possible to combine technology and experience in the same package and transfer it to a firm. As the university is conducting the initial market studies and developing working prototypes, it is easier for firms to continue the development and be more prepared to exploit innovations commercially as well.

Legal and political sphere

BioMediTech and other organizations as well as firms, are part of the Finnish innovation system. This system consists of several organizations that are interlinked with each other. According to Kotiranta et al. (2009), even though there are several public organizations embedded in the national innovation system, only a few of them are relevant to the firms. Among those relevant organizations, the Technical Research Center of Finland (VTT) is relevant for large companies, and for all companies, universities and the Finnish Funding Agency for Technology and Innovation (TEKES) are relevant, according to the survey made by The Research Institute of the Finnish Economy (Kotiranta et al., 2009). Initiatives in Tampere are in line with the overall Finnish national innovation policy, which is rather technology-driven (Kotiranta et al., 2009). At ministry level, initiatives and actions are dependent on the political system, which also has implications at a governmental organization level. Hence, elections could radically change the chosen path. However, in Tampere the

exception was, as discussed in section 5.3 about demand, that clinical need triggered the scientific advances and the development of needed solutions. From the outset, regional actors have understood that to be in the front line, scientific and development efforts need to be focused, and one of the results of this was the establishment of BioMediTech and the Human Spare Parts research programme. Regional initiatives have had a strong influence and significance, and in a sense, the development of potential innovations was a bottom-up process that was first supported by regional development agencies and later by national-level innovation agencies.

In general, new therapies in the RM sector need to fulfil the regulatory requirements, including clinical trials, which has direct implications for both emerging firms and existing firms hoping to develop in the field of RM therapies. In the EU, it is possible to deliver RM therapies under a special ATMP hospital exemption, in which there is no need for clinical trials. National authorities are able to decide how many treatments it is possible to deliver with hospital exemption, and in Finland there is no strict limit in place. The ATMP hospital exemption is beneficial for the emergence of the RM sector in the EU, but for firms it is contradictory, as it makes it possible for governments to provide RM therapies with no clinical trials, and at the same time firms need to fulfil strict regulative requirements in order to exploit these commercially. In Tampere, ATMP hospital exemption is the way to provide treatments with bone growth innovation in RM. With regard to this therapy, there are plans to conduct official clinical trials in order to commercialize it. As regulatory approval is essential for new therapies, BioMediTech has a close connection with regulators in order to find a way to fulfil all requirements correctly. Even more, as one interviewee in BioMediTech said: “regulation has actually provided help to us”. Without regulation there would be always a little uncertainty how things should be done, and clear and efficient regulation might be a facilitator of medical innovation (Messenger & Tomlins, 2011). As the RM sector includes different technologies, not all of them are regulated as highly as stem cell therapies. Products that are solely for research purposes are not regulated at all. This enables technology transfer from BioMediTech to firms to take place more easily and faster.

Apart from developed technologies, use of the technologies also has consequences and challenges that are worth mentioning. For instance, it was essential for the first operations with regard to bone growth therapy, that the board of directors in the local hospital agreed and gave permission to conduct experimental treatment for patients (Mesimäki et al., 2009). However, the GMP level laboratory is crucial in the cases where cells for human treatment are prepared and, luckily, the GMP level laboratory and clean rooms were already in existence at the time of the first patients being

treated. In Finland, in those cases where clinicians did everything carefully, individual clinicians are not alone responsible if something goes wrong. This is an advantage for experimental therapies, as clinicians have more courage to perform operations. There are neither problems with public opinion nor high debate regarding their ethicality, which is very favorable for the use of stem cells in therapies.

Funding

Public funding is a key factor in the development of the RM sector in general, and specifically in the formation phase of the local cluster. In addition to the normal funding universities seek and receive for research, Regea and BioMediTech have received much public funding from TEKES, the Academy of Finland, the Council of Tampere Region, and the City of Tampere in order to develop the RM sphere in Tampere. For example, the Council of Tampere Region has provided funding for research facilities that have affected positively the progress in RM research. In 2011, BioMediTech received 10 million euros in funding from TEKES for the Human Spare Parts research programme for the years 2011–2014, which boosted the formation phase of the RM cluster in Tampere region significantly. Lately, TEKES granted another 4.5 million euros for the years 2015–2016. This basic funding for the Human Spare Parts research programme has made it possible to focus on long-term goals and strengthen collaborative structures between research groups.

The advantageous aspect for BioMediTech has been that TEKES funds PoC projects in order to facilitate technology transfer from university to industry. This allows BioMediTech to focus research commercialization on distinct projects that do not affect research projects too much. However, due to stable funding, it is possible in some cases to revert the PoC back to the research programme in order to develop it further. For future products that are based on university research, PoC development is essential. It is important to assess the market potential of these potential products, in order to transfer successfully innovation to industry. As PoC development is important, TEKES provides a financial instrument with which to achieve it. However, as stem cell products require long clinical trials, the financial aid that TEKES provides is not perfectly suitable, as TEKES requires faster outcomes, which are possible in the case of technological solutions. Even though RM cell therapy products are not suitable for PoC funding from TEKES, they are willing to support commercialization efforts in other ways. For example, with regard to bone growth therapy, there are plans to conduct studies toward clinical trials in collaboration with external partners and TEKES is willing to help financially in this process. However, for the development of RM therapies, it is particularly

important to have an endowment from which early clinical trials are funded in academia, as firms are unlikely to receive venture capital funding for early clinical trials, which are needed for a product to be approved. As one interviewee mentioned: “you can't establish a firm in too early stage. It is really expensive to operate a firm in this field, and it is the reason why venture capital is needed at some point". However, to conduct clinical trials in the university requires a lot of expertise and resources. Even though it is possible to develop products for scientific use at a much faster pace, for the future of the RM sector globally and related clusters, RM therapies are crucial.

Conclusions and implications

Prerequisite for the emergence of an RM cluster in Tampere is that academia is able to generate enough new knowledge and innovations for firms to use. A growing number of firms are able to exploit university-based innovations, which could lead to the emergence and growth of local firms. The RM sector requires multiple technology disciplines, which means that there might be several opportunities for firms to diversify. This eventually should lead the emergent cluster to a growth path due to the emergence of new firms and the growth (diversification) of existing firms, which subsequently leads to a situation where existing firms need new suppliers and service providers. The competence bloc in this process describes well how new firms emerge in the region and what it required. In the formation phase it seems to be especially important to get bigger companies involved as well, as those can act as industrialists for new companies later. The availability of industrialists is beneficial for both entrepreneurs and venture capitalists.

The main implications for policymakers concern requirements that are evidently important for the emergence of a science-based cluster and its further development from the formation phase to development phase. First, public funding is extremely important, as in the beginning there is no company structure investing in the future. A local cluster needs regionally specified funding schemes in order to conduct research in academia, but also to develop research-based innovations that can be transferred to companies. There should be appropriate funding to conduct early clinical trials in the universities as well, but it is also important to support the collaboration with industry from the very early phases of innovation. Second, collaboration among local agents (both public and private) is necessary in order to exploit fully the capacity in the region by, for instance, avoiding duplicity of efforts from related firms in undertaking a research/innovation project. International collaborations are also highly important in allowing learning, applying funding, and providing a wider demand, to mention just some examples.

Third, a growing number of firms is especially important for the local cluster. The science-based sector analysed here does not completely fit within the so-called linear model of innovation. On the contrary, it requires a complex interaction and prototyping between relevant actors. Therefore, the growth of firms might be supported by encouraging a practice-oriented environment and hence the use of emerging innovations would be more plausible.

In this study, some major challenges are pointed out regarding an emergent cluster, which call for tailor-made socio-economic policies at the meso-level. Science-based clusters obviously need tailored policies, as sectors are different, but related. Specific policies are also needed in different stages of the cluster life cycle, especially for an emergent cluster to proceed from the formation to the development phase and finally to become a matured cluster. With regard to the emergent RM cluster in Tampere, the development process is long and it might take still years to actually proceed from the formation phase to the development phase.

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Abstrakt (in Polish)

Klastry są istotnym elementem regionalnych gospodarek, a rozwijające się klastry mają szczególne znaczenie dla dywersyfikacji działalności gospodarczej poprzez nowe technologie i branże. Branże oparte na nauce są w tej dziedzinie szczególnie obiecujące dla tworzenia i wsparcia wizji rozwoju określonych terytoriów, dzięki innowacjom przełomowym lub wzbogaceniu obecnych modeli gospodarczych, działających w tradycyjnych sektorach. Branża medycyny regeneracyjnej (MR) stanowi przykład takich wyłaniających się klastrów. Branża ta jest silnie zależna od badań naukowych, co oznacza, że region musi inwestować w badania naukowe w tej dziedzinie, by spodziewać się określonego zwrotu z inwestycji. Regiony zazwyczaj nie posiadają rozwiniętych klastrów w dziedzinie MR, stąd branże te powinny wyłonić się z istniejących dziedzin działalności lub poszerzyć obecne sektory. Medycyna regeneracyjna angażuje szeroki zestaw technologii i sektorów, które mogą tworzyć klaster i korzystać z jego efektów, jeśli projekt odniesie sukces. W artykule zrealizowano dwa cele. Po pierwsze, przedstawiono bariery, które ograniczają rozwój młodych klastrów. Po drugie, określono w jaki sposób w klastrach tego rodzaju powstają innowacje i jakie jest ich znaczenie dla danego terytorium. Na podstawie przeglądu literatury przedstawiono rynek technologii i komercjalizacji w sektorze MR. Badanie empiryczne oparto na rozwijającym się klastrze MR w regionie Tampere, w Finlandii. Na podstawie 24 wywiadów przedstawiono kontekst tworzenia klastra w Tampere, gdzie sfera nauki inspiruje i stymuluje rozwój tej branży. Jednym z celów uniwersytetu jest komercjalizacja badań w dziedzinie MR, jakkolwiek na razie brak komercyjnych rezultatów. Badanie ma znaczenie dla zrozumienia rozwoju młodego klastra w branży opartej na nauce, w fazie zalążkowej i na wczesnych etapach rozwoju. Wskazano główne wyzwania dla powstającego klastra, które to wyzwania wymagają dostosowania polityki wsparcia na poziomie mezo-ekonomicznym. Dla klastrów opartych na wiedzy niezbędna jest ukierunkowana polityka, a określone sektory, na danym etapie rozwoju potrzebują specyficznych narzędzi polityki, aby osiągnąć fazę dojrzałości.

Słowa kluczowe: *medycyna regeneracyjna, wyłaniający się klaster, komercjalizacja, innowacja, blok kompetencji, rynek technologii.*

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Management of Innovation in Academia: A Case Study in Tampere

Tuomo Heinonen

Abstract

Universities have an active role in research commercialisation and hence, many universities have established a technology transfer office. However, technology transfer happens too early in most of the cases and commercial potential of innovation is not clear yet. Proof of Concept, which is developed in the university, is suggested to be a solution for this. In this single case study, Proof of Concept development and technology transfer in the regenerative medicine sector are studied in Tampere, Finland. It was shown how Proof of Concepts are nurtured alongside the research in the faculty. However, sufficient funding and market understanding is needed in order to develop a Proof of Concept that is possible to transfer to industry.

Keywords: technology transfer office; tto; technology transfer; proof of concept; proof of concept centre; poc; pocc; innovation; regenerative medicine; commercialisation;

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1 Introduction

Commercialisation of scientific breakthrough innovations in biotechnology depends on active involvement of scientists (Zucker and Darby, 1996). Hence, close and regular collaboration is needed between industry, hospitals and academics to make sure the commercial success of biomedical research (Juanola-Feliu et al., 2012). However, most university-based inventions are licensed at a somewhat embryonic stage and because of that, further development in cooperation with the inventor is needed for commercial success (Jensen and Thursby, 2001). The other issue with early stage disclosure and technology transfer is uncertain market potential for most of these inventions (Thursby et al., 2001).

As the role of the university has expanded from traditional research and education to actively seeking opportunities to develop applications and commercialise research (Juanola-Feliu et al., 2012), spin-offs and licensing are important ways to actualise this commercial role (Hoye and Pries, 2009; Juanola-Feliu et al., 2012). For the purpose of technology transfer, many universities have established technology transfer offices (TTO) to manage and protect intellectual property of universities and to facilitate commercialisation of university inventions through licensing (Siegel et al., 2004). Establishment of start-ups (SU) is another way to transfer university research into industry and TTOs have an important role in the SU formation process (Lerner, 2005). However, it is difficult to start a new venture based on university technology and most of those ventures do not generate wealth to universities (Lerner, 2005). Hence, according to Auerswald and Branscomb (2003), the most important and critical phase in the process of innovation is between invention and product development, which is defined here as the Proof of Concept (PoC) phase and which is the main concern of successful technology transfer. When entering the PoC phase, there should exists a technical concept, which is created, protected and has commercial value. In the PoC phase according to Auerswald and Branscomb (2003) and Maia and Claro (2013):

- technology is simplified to industrial form
- production process is defined enabling cost calculation
- intellectual property is developed
- commercial concept is created and verified
- appropriate market is identified and quantified

Challenge in technology commercialisation concerns the PoC phase and especially its lack of funding (Auerswald and Branscomb, 2003; Maia and Claro, 2013). Proof of Concept Centres (PoCC) are suggested to be answers to both lack of funding in early phases of new venture and problems associated with technology transfer. PoCC is complementary to TTO by speeding up disclosed technologies into the market (Maia and Claro, 2013) and in which funded researchers continue their research in their own laboratories (Gulbranson and Audretsch, 2008). According to Gulbranson and Audretsch (2008), PoCC needs a management team that is connected to local venture capital, technology and the industry network. A strong local business network is also needed for the reason that PoCC has to have courage to invest in unproven technologies (Gulbranson and Audretsch, 2008). Lately, Maia and Claro (2013) studied the impact of PoCC to technology commercialisation showing promising results, but in general, there is not long-term evidence about the role of PoCC in technology transfer.

2 Research questions

The aim of this study is to scrutinise the PoC approach to technology transfer and commercialisation in BioMediTech, which is a joint institute of two universities in Tampere, Finland; i.e., University of Tampere and Tampere University of Technology. One of the promising research fields in BioMediTech is regenerative medicine (RM), which is also referred to as the third discipline in healthcare beside medicine and surgery (Polak et al., 2010). In this field in BioMediTech, researchers develop both stem cell research supporting technological solutions and new stem cell therapies. However, the RM sector is emerging globally, and hence, development of PoC is especially important as there are not many companies that have enough resources to develop inventions forward. As innovation and commercialisation are central aims of BioMediTech, the following research questions for this study are relevant:

What are the specific concerns in technology transfer in the RM sector, especially in case of stem cell therapies?

How does BioMediTech overcome the challenges related to the PoC phase?

These are especially interesting questions, as in their study, Jensen and Thursby (2001) showed that a minority of licensed inventions involved some animal data and an even smaller proportion involved some clinical data, even though half of the inventions they studied were in medicine and nursing. Only 12 percent from the dataset they studied were commercially ready and for 8 percent manufacturing feasibility was clear. Therapies developed in the RM sector follow a commercialisation process similar to pharmaceuticals or biopharmaceuticals that is from animal studies to clinical trials and after three phases of clinical trials to product approval. The process is long, costs money and for university spin-offs, it is a difficult path on which to go. On the other hand, technologies and tools that support

therapies and research are much easier from a commercial point of view. In general, however, uncertainty and cost of development are just too high for these biomedical inventions, and it is for one of those reasons that TTOs are not making much money for universities.

3 Theoretical background

Innovation in health has a broad range from science-based innovations (e.g. biotechnology and pharmaceuticals) to engineering based innovations (e.g. medical technology) (Meyer-Krahmer and Schmoch, 1998). From an innovation and commercialisation viewpoint, these two categories have different requirements and processes (Blume, 1992; Gelijns and Rosenberg, 1995). Many medical technologies have emerged in collaboration between academics and manufacturing companies (Blume, 1992), and in the current era of TTOs, engineering based innovations might be more easily spun-off to start-ups or licensed to established firms. On the contrary, science based innovations are often highly regulated when concerning human health in terms of human cells or molecules, and thus the process is longer to final product and also costs more. The two critical characteristics of innovation in medicine are that new technologies have a high degree of uncertainty, and close interaction between developers and users is crucial to the development of medical technologies (Gelijns and Rosenberg, 1994; Gelijns et al., 2001). In all the cases, firms are still important, because even though merits of new product discovery are shared between firms and academic research, firms have distinctive and global capabilities in product development, management of the regulatory process for the approval of new drugs and devices, and the marketing and distribution of innovations (Consoli and Mina, 2009).

Thus, there are two major actors in the medical technology area: academic medical centres and industry, namely pharmaceutical, medical devices and biotechnology industries (Gelijns et al., 2001). The potential new industry is cell therapy, which includes the most fascinating opportunities in the RM sector and which is the focus in this study. Academic health centres are important, as they are places where medical research, clinical practice and teaching come together. Hospitals in general are the places of clinical practice and major channels through which new treatments are introduced revealing the potential or drawbacks (Metcalfe et al., 2005; Consoli and Mina, 2009). The role of hospitals should be understood more carefully also in the technology transfer activities, as hospitals and medical schools are important sources of new product ideas and advanced product-embodied technologies (Roberts and Hauptman, 1986). Similarly, Consoli and Mina (2009) claimed that research hospitals have a central role in the diffusion of knowledge, intermediating between basic science and clinical trials and giving important practical feedback for medical device manufacturers. Also in the RM sector hospitals play an important part in innovation, and the development of products requires a tight linkage between researchers and hospitals (McMahon and Thorsteinsdottir, 2013).

Medical innovation emerges from a complex and interactive process that is distributed over academics, firms and clinicians (Gelijns and Rosenberg, 1995; Metcalfe et al., 2005; Consoli and Mina, 2009). Hence, it is important from a technology transfer point of view to understand the innovation system and its elements in healthcare. Consoli and Mina (2009) conceptualised features of medical innovation in the health innovation system (HIS) that consists of three interconnected layers, i.e. the science and technology system, service provision in hospitals and the individual sphere (Figure 1). HIS builds on the earlier literature of medical innovation and work of Metcalfe et al. (2005), who focussed on the firm centred innovation system and on the linkage between the national healthcare sector and the international medical sector.

HIS is based on gateways and pathways of change, i.e. components of the system and interactions between components over time. Nelson et al. (2011) argued that there are three different pathways for medical progress: advances in scientific understanding of a disease; advances in technological capabilities making possible the development of new methods of diagnosis, therapies and treatments; and learning in clinical practice that is important for the advance of medical diagnosis and treatment. In general, the scientific community has a growing role in innovation and in the development of new devices, drugs and applications (Toner and Tompkins, 2008), and the connection between doctors and the scientific community is important (Consoli and Ramlogan, 2008). In HIS, the scientific community includes clinical and medical staff, and different university departments, e.g. pharmacology, biology, genetics, informatics and engineering (Consoli and Mina, 2009). It is possible for the scientific community to reduce the risk of inventions to fail caused by too early technology transfers if initial validation and an application for intellectual property protection follow invention (Toner and Tompkins, 2008) as well as other important tasks in the PoC phase (Auerswald and Branscomb, 2003). Hence, the main interest in this paper locates on the relationship between scientific and technology subsystems in the HIS and how medical technology innovations in the RM sector are transferred from academia to industry and in the end to hospitals.

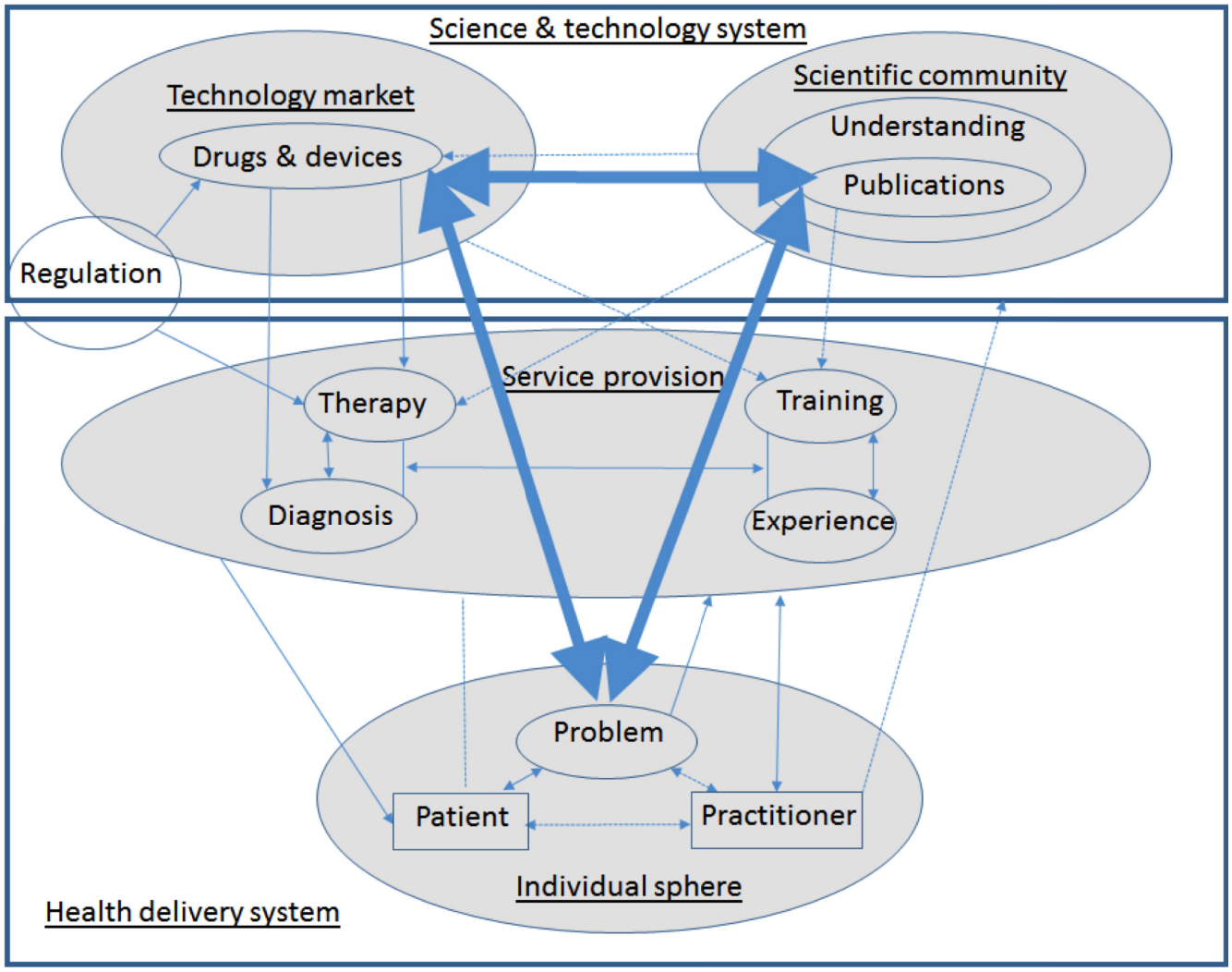

Figure 1: Health innovation system (Consoli and Mina, 2009).

4 Methodology

4.1 Background and context

Today in the regional level, BioMediTech is highly valued, e.g. the Council of Tampere Region has BioMediTech as one of their core promotions. Based on high-level scientific research, the formation of BioMediTech and especially the Human Spare Parts research programme in Tampere was an evolutionary process of several active and co-operating actors. From very early on, tissue engineering was seen to be a significant application area in the biotechnology sector of Tampere. Research groups in BioMediTech have a track record in creating patents (over 100) and spin-offs (over 10), and thus, it was natural that commercialisation was the focal point of the activities, and the aim was to get new firms in the attractive RM field.

An earlier history of BioMediTech is well documented in Sotarauta and Mustikkamäki (2014). University of Tampere, Tampere University of Technology, Pirkanmaa Hospital District, Pirkanmaa University of Applied Sciences and Coxa, the Hospital for Joint Replacement, established Regea, which is a predecessor of BioMediTech, in 2005. In 2011, BioMediTech started its operation and was granted a strategic governmental funding from the Finnish Funding Agency for Technology and Innovation (TEKES) for a strategic research programme called Human Spare Parts, with a focus to develop novel solutions in the RM sphere. At the regional level, BioneXt and Biosensing Competence Centre (BCC) shaped the way for BioMediTech earlier and in the national level the HealthBIO programme was important in other ways.

BioneXt Tampere (2003-2010) was an organisation with a mission to acquire resources, expertise and investments to Tampere. There was a focus on leading-edge research, product development, clinical application and commercialisation of biotechnology. Supported fields were tissue engineering, biomaterials, bio-ICT and immunology. Combination of tissue engineering, biomaterials and funding to professorship in stem cell research was an important basis for development of the RM field in Tampere. In 2007, two important initiatives started. HealthBIO (2007-2013) was a national programme that focused on nationally important areas of biotechnology, which was in Tampere human spare parts. In this programme, in Tampere was piloted also a new PoC financial instrument from TEKES that was aimed to help translation from research to products. The other initiative was Biosensing Competence Centre (2007-2010), which was established for the need of bridging the gap between basic research and product with a PoC in the biosensing field. BCC raised funding altogether 1.2MEUR for its operation, from which 0.12MEUR was used for commercialisation projects. BCC also invested in core infrastructure and IPR protection services. Instead of wide application fields of BCC, focus was given to regional strength areas of tissue engineering and clinical diagnostics. BCC had a major role in establishing the regional network for BioMediTech.

One of the advantages for BioMediTech is that it locates next to the University Hospital of Tampere. In 2012, a combined research strategy of BioMediTech, University Hospital of Tampere, Institute of Medicine and Institute of Health Science, stated that 'Tampere Health Research Centre Kauppi' should be established to bring scientific breakthroughs, innovations and new businesses. In the research strategy of the university hospital of Tampere for 2014-2016, one of the three goals was presented to be to improve and combine resources for 'Tampere Health Research Centre Kauppi'. Hence, a close relationship to hospitals enables BioMediTech to utilise its innovations but also to get awareness of needs, support and feedback.

4.2 Method

Findings of this study are based on a single case study conducted in Tampere, Finland. Focus in this study was in BioMediTech and its Human Spare Parts research programme. Combined research groups and expertise from these universities allow BioMediTech to conduct interdisciplinary research and develop innovations based on different technologies and disciplines. In this study, altogether 24 interviews were conducted: 15 of interviewees were from BioMediTech, 3 of interviewees were from University Hospital of Tampere and the rest were from local and regional development agencies, Ministry of Employment and the Economy, the Finnish Funding Agency for Technology and Innovation (TEKES) and a local firm with an RM focus. Commercial aspects of the Human Spare Parts research programme and the RM sector were central in interviews that included the following themes: Research environment, finance, entrepreneurship, market, legislation, hospital environment and end-value.

5 Findings

5.1 Innovation supporting environment

The aim of the Human Spare Parts research programme is to create applications and business from advanced research in stem cell and related technologies. Due to longer term funding, this research programme has had a significant impact on collaboration between different research groups allowing them to plan activities in a longer perspective and having professionals for several important aspects of innovation. The other advantage is the organisational structure of BioMediTech that supports management of innovation that emerges from their research:

1. Research programme Human Spare Parts research programme was established instead of several small and independent projects

2. Important elements of innovation were combined into this programme, i.e. strong interconnection between technology, clinical and science expertise

3. Facilities to support innovation, e.g. employed IPR experts

4. Appropriate research equipment infrastructure

Advantage of the Human Spare Parts research programme in BioMediTech is that it is able to combine technology and stem cell expertise together. Combination of biomaterials, stem cell research and supporting technology expertise is especially important and provides a competitive advantage for BioMediTech. As a result, they are able to develop new therapies, but also they are able to develop new technologies for stem cell groups for their needs. In the programme, four groups focus on stem cells and four groups focus on technology. In detail, stem cell groups focus on bones and tissues, neurology, ophthalmology and cardiology, while technology groups focus on imaging and signals, biomaterials, biomimetic environments and biosensors.

Organisation in BioMediTech supports and fosters innovation. There are personnel in core facilities and research services, which makes it possible to have help when needed. In addition, research facilities are shared between the research groups, which causes interaction between groups of different disciplines and produces new ideas. Generally, there is a lot of collaboration between the technology groups and the stem cell groups and it allows development of applications where technology is used for the advantage of stem cell research. Also clinical experience is present in the stem cell research groups and it makes the communication with hospitals easier. In those projects where real patients are involved, surgeries or other clinical operations are conducted in a hospital environment. For example, a therapy that is developed in BioMediTech is used in many clinical operations in several university hospitals in Finland, lately in Tampere.

IPR and regulations are in focal point of daily operations and for example, all publications are first checked from IPR's viewpoint if there is something that has to be protected. IPR personnel attend research meetings that allow them to follow projects and to address open questions without a need to explain background situations always. In addition, sometimes due to patent research, some ideas that were thought to be new were revealed to be already patented. In general, IPR and legal issue experts take care that patents cover important aspects of innovation and that contracts are suitable for technology transfer purposes.

Quality and regulatory affair professionals take care that everything is in order regarding regulation issues. BioMediTech and its predecessor organisations, especially Regea, have invested a lot to research equipment infrastructure, which is essential for research groups. Investments are funded by both internal and external sources. An important part of research equipment infrastructure in BioMediTech is a GMP laboratory that enables BioMediTech to provide cells to clinical use too. Actually, this GMP level laboratory is essential for these clinical procedures where cells are used.

5.2 The interdisciplinary collaboration in innovation

Clinical needs triggered the scientific and technological development in the predecessors of BioMediTech and now in BioMediTech. For example, in the case of the bone growth therapy for facial area bones, which is discussed later in more detail, the development started from concrete clinical need. This clinical need led to research with a purpose to have a treatment based on stem cells to solve a clinical problem and cure a patient. Development of this new therapy was possible because of strong expertise in biomaterials and stem cells in the Tampere area. It was also understood that there are many problems in scientific stem cell research that can be helped by technology and thus technology experts from Tampere University of Technology joined the Human Spare Parts research programme. There was collaboration before the Human Spare Parts research programme too, but in this programme, it was even more coordinated. Technology groups are able to develop different solutions to problems scientists faced with stem cells, and it has been an advantage for BioMediTech. Thus, interdisciplinarity is an important aspect in innovations that emerge in BioMediTech and it is not only the different competencies but also the collaboration between technology groups and stem cell groups. There is also a lot of interaction between clinicians and biomedical researchers in BioMediTech. Due to that, problems that arise from clinical practice give direction and motivation to research, and thus, it is possible to help real patients with applications emerging from research. Technologies that technology groups develop in BioMediTech are essential for stem cell researchers, as those technologies enable them to develop further their stem cell based innovations.

Figure 2 presents the development process of tools and technologies. In the first phase, the technology group discusses with the stem cell group in order to find out what are the needs of the group. In some cases, a technology or tool is missing totally and sometimes there is a product available but it is not good enough. If the technology groups

is able to develop needed technology for purposes of the cell group, the technology group first develops a prototype and test it. In some cases, different technological disciplines are needed in order to get a fit solution. After development, the technology group delivers it to the cell group for testing purposes and gets feedback to develop the technology further. The development process might take time from a few months to several years depending on the complexity of the needed technology or tool. Feedback is crucial in this process of development.

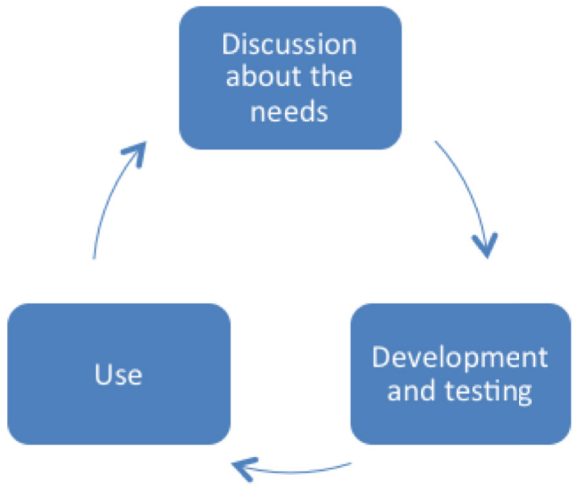

Figure 2: Iterative innovation process in tool segment where new technology is developed for purposes of stem cell groups.

Because all of the groups are in the Human Spare Parts research programme, there is a possibility to conduct several internal iterations easily. Finally, if the solution works and the cell team is happy with it, they might start to use the solution instead of the current commercial alternative. During the use of the product, user experience is gathered to improve the solution. However, only a small amount of batches is possible to deliver internally but larger scale production is not reasonable to expect from research groups. The outcome of these technology development projects is essential for stem cell research and therapy development. However, these developed technologies might sometimes have also commercial potential, and in the next chapter, the focus is on PoC development of these technologies but also therapies.

5.3 Proof of Concept development

The Human Spare Parts research programme was created as a strategic research programme that is between basic research and translational research. Thus, it is in the heart of the programme that product opportunities emerge and are developed further towards a PoC (Figure 3). In the early development phase, emerging inventions are patented and in the end, the goal is to license or sell the technology or spin-off a company. As development of PoC needs market understanding, commercialisation projects are established in order to obtain it from external sources. In some cases, there is a cooperation between BioMediTech and established companies to work towards PoC. In these cases, BioMediTech has a deep understanding about technology and firms have the market understanding.

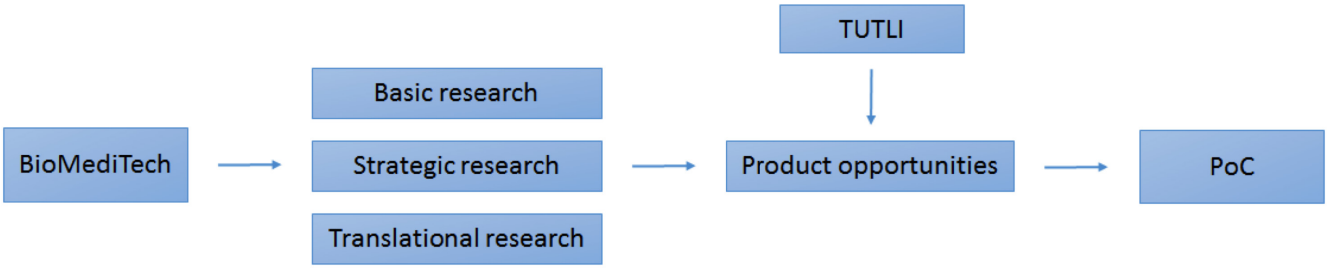

Figure 3: Steps towards a PoC in BioMediTech.

It is advantageous for BioMediTech that TEKES has a finance instrument called 'New Information and Business from Research Ideas' (TUTLI) to facilitate university based research commercialisation and to support it financially. The main purpose of those projects that get funding from TUTLI is to develop PoC that shows the commercial feasibility of technology. These projects are commercialisation focused and have several commercialisation related activities, e.g. initial market study, initial planning of business case, competitor analysis and study of exploitation option. The aim is to validate the concept and in some cases, the outcome is actually to change the concept, because the market is different from what was expected.

Commercialisation has been a focus area in BioMediTech, and researchers and group leaders are taught to think about commercial outcomes and applications in their research projects. However, it is acknowledged that researchers are not the right people to take commercialisation further, but they have an important expert role in the development of PoC. In BioMediTech, there are few TUTLI-financed projects established that aim to commercialise emerged innovations based on either technology or stem cells. These projects are seen as a good and important tool because they allow the development of a product concept outside the traditional research project. In these cases, it is beneficial to develop a product concept further in academia and that way make it easier for the firm to exploit it commercially. Several attributes affect commercialisation opportunities (Table 1).

	Technologies	Therapies
Exploitation	Short term	Long term
Need for funding	Moderate	High
Ease of getting funding	Moderate	Difficult

Table 1: Some characterisations of innovations.

There is a difference between technology commercialisation and therapy commercialisation. Some of the technologies are developed and proved inside the university for internal purposes and hence, there are already some proofs of technological viability. In these cases, a possibility for successful technology transfer is higher because application is in use. In case of therapies, clinical trials are required to prove the technical concept and early clinical trials should be conducted in academia because private funding for them is difficult to get due to the high level of uncertainty.

5.4 Therapy commercialisation: Bone reconstruction and transplantation

Tissue engineering is one branch of RM where human stem cells are used with scaffolds in order to make new tissue to grow some form. In the Human Spare Parts research programme one of the most promising technologies is a method to grow facial and cranial bone (Figure 4). First time in 2007, an upper jaw was fixed with a bone transplant, which was cultivated from the stem cells isolated from the fatty tissue of the patient (Sotarauta and Mustikkamäki, 2014) and over 25 patients have been treated to date. Treatments have been conducted in several Finnish university hospitals, lately in the University Hospital of Tampere. Even though several patients have been treated, there are no regular treatments in the market and clinical trials are not started yet. Instead, operations are conducted under advanced therapy medicinal products (ATMP) hospital exemption.

Regulatory and societal environments for stem cell therapies are rather advantageous in Finland. For example, regarding facial bone growth, the board of directors of the local hospital district gave their consent to the first clinical operation (Mesimäki et al., 2009). Regarding the therapy itself, ATMP hospital exemption allows clinical operations without official clinical trials, even though only limited amount of operations are allowed to be conducted every year. However, a possibility to do even a restricted amount of treatments might be a good evaluation point for investors to see if treatment and its concept is reasonably efficient for a business purpose. In this case, the first versions of therapy were not commercially viable enough and further development of PoC was required.

Even though treatments have been conducted and there is a know-how to cultivate bone tissue from stem cells, it is not totally understood why it all happens. This is why clinical trials are needed in order to verify the therapy scientifically. A regulatory pathway for this therapy is similar to the traditional regulatory path, for example in pharmaceuticals, but fewer patients are needed in later phases of the clinical trial. This regulatory pathway costs a lot of money and for universities it is difficult to fund it alone. Another issue is that even regulators do not totally know how to regulate these kinds of new products. There are discussions with regulators in BioMediTech about what they are actually required to do. The next phase in this development process of the new therapy is to start clinical trials. First, it is required to conduct pre-clinical studies, in which animal models are used, taking approximately 3 years. Currently this phase is started to prepare. Then clinical trials must be conducted including 3 phases and over 200 patients. Altogether clinical trials might take 5 years. After that, product approval from public and national authorities is needed. In the RM sector

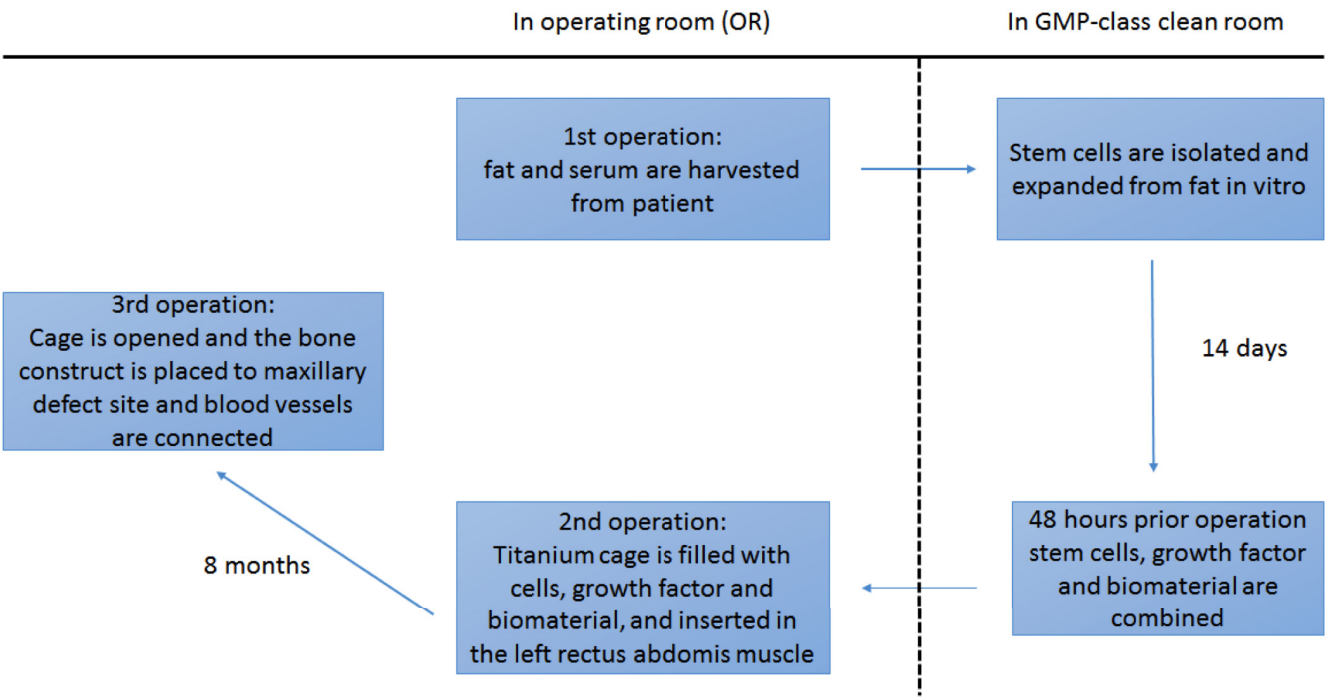

Figure 4: Schematic sketch of bone reconstruction process conducted in 2007 (Mesimäki et al., 2009).

regarding technology transfer, early clinical trials in the development of therapies should be conducted in academia. Venture capitalists would not invest in RM sector companies until later phases of clinical trials (Parson, 2008) that make the supply of funding a problem in the technology market. Actually, lack of funding in the PoC phase is not only restricted to the RM sector and therapies, but is a general problem (see e.g. Auerswald and Branscomb, 2003). Even though PoC and early clinical trials could be conducted in academia, it is not likely that the public sector alone could develop new therapies on the required scale (Mason and Dunnil, 2008). As Mason and Dunnil (2008) say, it is maybe possible with a small number of patients (Phase I/II and early Phase II), but after that also the private sector is highly needed. In the end, even after successful and approved products, there is a big uncertainty if nations with public hospitals and insurance companies want to give reimbursement for the new product.

6 Discussion

There are innovations developed and used in BioMediTech that are in some cases more suitable for use of research groups than alternatives in the technology market, even though these innovations are not commercialised solutions yet. Some of the solutions are used even in the patient care. The important question here is how to commercialise these innovations for the wider population use. It seems that traditional technology transfer from university to industry is just not appropriate enough, as academia has not developed those technological inventions far enough, and hence, the actual business potential is not known (Thursby et al., 2001). The other challenge is that inventors and scientists are needed in the process (Zucker and Darby, 1996; Jensen and Thursby, 2001).

Hence, the right time for technology transfer is a major question, and depends on several attributes like what is the technology and how is it regulated. In case of stem cell therapies, after successful early clinical trials, potential technologies could be transferred to the ownership of the company to get a private funding for it. Figure 5 presents a system level simplified sketch of innovation process based on findings of this study and health innovation system. It points out different aspects of a system level picture where the public sector, scientific community, technology market and health delivery system all are important elements.

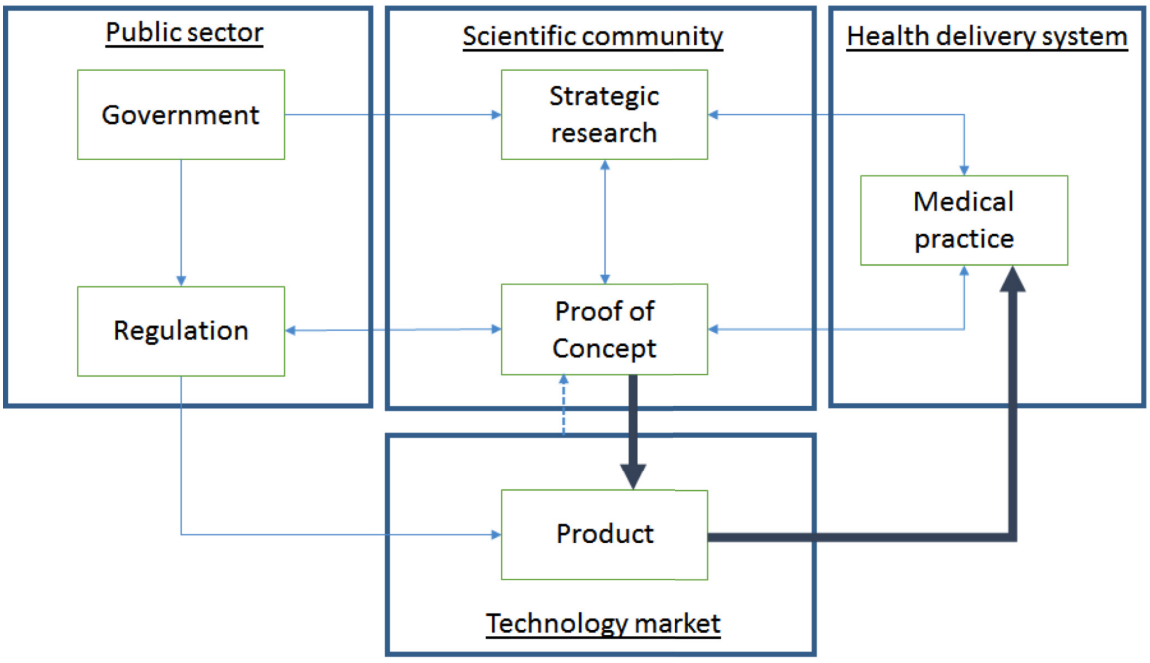

Figure 5: Simplified sketch of innovation process and technology transfer value chain between academia, industry and hospital (bolded arrows).

For the challenges of too early technology transfers, PoCC is suggested to be an answer. In the case of BioMediTech, the approach is different from the one that studies describe (Gulbranson and Audretsch, 2008; Maia and Claro, 2013), because technology transfer activities and development of PoCs are involved so deeply to daily operations. Also part of PoC funding is not from BioMediTech itself, but from public sources. The major challenge for BioMediTech is that in Tampere or in Finland, local venture capital, technology and industry networks do not exist for the RM sector, and thus it is not possible for the management team to connect to these locally, as Gulbranson and Audretsch (2008) emphasised. Hence, international connections are especially important and needed for a flow of information from technology market to PoC. However, the advantage for BioMediTech is the close connection to medical practice, and thus it is possible to get first-hand experience very early in the development of technologies.

An optimal situation in the therapy development would be that PoC is developed in co-operation between clinicians, academics and business experts to support successful technology transfer and commercialisation. In BioMediTech, there are no entrepreneurs readily available, and thus, the market understanding is acquired from business expert sources to guide the development of PoC. However, the challenge for them will be how to attract entrepreneurs in the later phases where spin-off is founded or PoC is transferred to an existing firm.

7 Conclusion

In this study, the aim was to study technology transfer activities and PoC development in BioMediTech. Two research questions concerned PoC development in BioMediTech and technology transfer in the RM sector generally. The important finding of this study was that there is a strong connection between strategic research and health delivery system as was described in the case of bone growth therapy. In this case, clinical experience is gained with real patients even though there is no commercial product existing. Clinical experience is important for the purposes of technology transfer, as it gives some proofs of viability of application. However, supply and value chain for new products are complicated crossing the scientific community, technology market and finally health delivery system in case of therapies or medical devices. The important question is how to transfer PoC from the scientific community to the technology market and facilitate institutionalisation of it to hospital service. Thus, in the PoC phase also customers have to be taken into account, as they are the main sources of feedback for innovation.

The other finding was that product opportunities are nurtured longer in the faculty for PoC development. Funding from governmental agencies is used in this development in order to understand the market and to prepare commercialisation of both technologies and therapies. In addition, there is a cooperation between BioMediTech and firms in PoC development. In the RM sector, development of therapies has a high level of uncertainty and it is difficult to get private funding for early clinical trials. Thus, universities are required to conduct early clinical trials themselves if they want to develop a new therapy in the RM sector. Development of therapies requires a wide range of expertise about stem cells and related technologies and hence, combination of different technology groups and stem cell groups and their common goal seems to be advantageous.

Development of PoC in academia seems to work well in BioMediTech. However, it is too early to say how well the model used in BioMediTech is working, as commercial output is not available yet and PoC developments are still going on. Another limitation of this study is that the Human Spare Parts research programme in BioMediTech is relatively small and focused, and is established in order to get new products. However, this study suggests that PoC development is important in order to do successful technology transfer, and in this process PoCC does not have to be an isolated entity but it could be more integrated to daily operations of the university.

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Potential for 21st Century's Academic Health Centers to Revolutionize Healthcare

Lessons to be Learned from Tampere, Finland

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Abstract

Academic health centers (AHC) play a significant role in innovation. New revolutionary fields in healthcare, like regenerative medicine (RM), however bring challenges to traditional AHCs in terms of organizing research and innovation. The author conducted an in-depth case study in Tampere, Finland where the author studied how AHC is organized in order to succeed in the RM sector, and found that combinations of technology and basic research, focus on products and applications, relevance to clinicians, commercial awareness and mission orientation are needed. It is argued that in order to be successful in RM research and applications, AHCs should focus on developing an innovative environment for new therapies, bringing commercial awareness to research, and be organized towards a common mission.

Keywords

Academic health center, AHC, regenerative medicine, innovation

1 Introduction

Academic health centers (AHC) in America are one of the success stories of the 20th century[1]. In the decades following WWII, a growth in federal funding for biomedical research and medical education strengthened the role and position of AHCs[2] that are still a central part of today's healthcare, also in Europe. For example in 2009, the UK announced that they granted official academic health science center (AHSC) status to 5 partnerships between universities and National Health Services, as they saw the potential to compete globally with established AHCs, for example in the U.S., Canada, Singapore, Sweden and the Netherlands[3]. However, a sufficient funding is a major challenge nowadays for AHCs[4,5].

AHCs have three things in common: involvement in clinical and biomedical research, commitment to specialized patient care, and commitment to teaching[6]. As medical innovation depends on interactions between universities, especially AHCs, and industrial firms[2], in healthcare there is a growing role with AHCs in innovation and the development of new devices, drugs, and applications[7]. One of the proposed new roles for AHCs are to act as an integrator in the discovery-care continuum in translational medicine[8]. AHCs play an important role in the innovation process because they are focused on treating patients and advancing healthcare[7].

Aim in this study was to show the potential role and structure of AHCs in development of the new regenerative medicine (RM) sector in healthcare, and what managerial and policy implications it brings along. RM can be defined as follows: 'Regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function'[9]. In this study, RM is associated with stem cell related applications and accessory technologies, even though in pharmaceutical, biotechnology and medical device industries there are RM applications too. This study is based on data gathered in Tampere, Finland. Finland has not granted any official AHC/AHSC statuses as such

for the combinations of universities and hospitals, but the five university hospitals in Finland are generally combinations of university institutes and hospitals comprising the main building blocks of the Finnish healthcare system and by definition are AHCs. In Tampere, a joint institute of two major universities (BioMediTech) are working together with a university hospital (AHC) in order to provide both needed accessory technologies for stem cell research and stem cell applications in the RM sector. It will be discussed in this study how these traditionally distinctive organizations (BioMediTech and university hospital) are essential in the development of RM sector and for the sake of RM should be understood as a one loosely connected AHC from the operational point of view.

2 Innovative responsibility of AHCs

In the literature, academic medical centers (AMC), AHSCs and AHCs are used more or less as synonyms and even though teaching, clinical patient care and research in medicine are building blocks of AHC there is no widely accepted precise definition for it[6]. Lately, a conceptual framework was proposed for AHCs adding following four dimensions to building blocks: health, innovation, community, and policy[10]. Indeed, innovation fostering environment is important aspect of AHCs[11] and AHC's roles as innovator and advancer of healthcare are widely acknowledged:

- Co-creation of medical innovation[2]
- Foster entrepreneurial culture[7]
- System integrator in translational medicine[8]
- Focus on treating patients and advancing healthcare[7]
- AHCs or commercial entities are usually responsible for running clinical trials with an aim to reach regulatory approvals[12]

Evolution of new therapy is dependent on progress in co-evolving pathways of clinical experience, medical devices and biomedical scientific understanding[13,14,15] and thus, AHCs are fruitful places for new therapies because expertise in clinical medicine, basic sciences and technology exist there in contrast to university-based innovation in medicine where only basic science and technology expertise are available[7]. AHCs are involved in innovation in medicine and there are four identified tasks for AHCs regarding medical innovation[6]:

- development of new technologies, techniques and applications
- adoption of new devices, therapies and procedures
- evaluation and assessment of emerging and established technologies and practices
- advice to public and private sectors

Straightforwardly, the responsibilities for AHCs include development to adoption and evaluation of emerging technologies to societal informing. Innovation in medicine is interdisciplinary and thus, old structures where different disciplines in academia are divided into separate departments might hinder innovation[16], and by breaking these borders, a new innovative environment could emerge where accidentally significant innovations could also occur as different knowledge is combined. While the juridical relationships with hospitals, medical schools and other components of AHCs might vary, e.g. medical schools and hospitals might be inside a university under shared ownership, or medical and other professional schools are part of universities and hospitals as a separate corporation[6], actual operations of AHCs are more important.

AHCs work with start-up companies, pharmaceutical companies and medical device companies in order to transfer academic inventions into commercial products and have a societal impact[7]. Processes by which new technologies are generated, and background conditions for innovation, are assumed to be very different in fields of healthcare[2]. Fields such as biotechnology and pharmaceuticals produce

science-based technologies[17], and in these fields, medical innovation is stimulated by potential demand for health improving technologies and advances in scientific and engineering knowledge, while it requires interdisciplinary research and involves the crossing of institutional boundaries[2]. Thus, the future paths of healthcare are highly dependent on the structure and competencies that are found from entrepreneurial and innovation fostering environments inside and outside AHCs.

3 Methodology

3.1 Context

In Tampere, which is the case examined here, the first official RM focused institution, Regea, was established 10 years ago in 2005 by University of Tampere together with Tampere University of Technology, Pirkanmaa Hospital District, Pirkanmaa University of Applied Sciences, and Coxa, the Hospital for Joint Replacement[18]. Thus, in Regea there was at the ownership level a connection between clinical medicine and academic research from the beginning. Later in 2011, Institute of Biosciences and Medical Technology (BioMediTech) was established as a joint research institute combining parts of University of Tampere and Tampere University of Technology, as a successor to Regea. Combined expertise from these universities make it possible to develop innovations where different technologies and disciplines are needed. University Hospital of Tampere is one of Finland's central hospitals working with the medical school of Tampere University. There is a lot of medical research in the University Hospital of Tampere, but stem cell based research is mostly in BioMediTech. Clinical operations with stem cell products, however, are conducted in the university hospital.

BioMediTech was established at the same time as the Finnish Funding Agency for Technology and Innovation (TEKES) granted strategic research funding for BioMediTech. With this funding, a

research program Human Spare Parts was established focusing on RM in order to address unmet needs of medicine with stem cells. Together eight groups were included in the program of which four were technology focused groups and four were stem cell biology focused groups. In addition to these groups, there are several other groups in BioMediTech that are not included in the Human Spare Parts program, and also in the schools of medicine and health sciences there are several different groups working with several health related topics. However, the focus here was in the Human Spare Parts program and the RM sector. From the establishment of Regea, tens of millions of euros have been invested in RM research and research facilities in Tampere area, and thus the expectations are high too.

3.2 Method

As an exploratory case study conducted in Tampere, Finland, data was gathered mostly from two organizations, BioMediTech and University Hospital of Tampere. In the Human Spare Parts program, RM is mostly based on stem cells and related technologies. In this qualitative study, 24 persons were interviewed in order to draw an in-depth systemic picture of the RM sector development and ecosystem in Tampere. Interviews were focused on the Human Spare Parts program, even though there are other programs and research groups in BioMediTech focusing on human health. Main themes in the interviews were research environment, finance, market environment, end-value and use of RM technologies. In BioMediTech, 15 interviews were conducted, in University Hospital of Tampere 3 interviews were conducted, and others were in local and regional development agencies, Ministry of Employment and the Economy, TEKES, and a local firm with a RM focus.

4 AHC striving for the future of medicine in Tampere, Finland

In the following themes, important elements of RM found in the Human Spare Parts program were studied with regard to AHC and its new potential multidisciplinary RM function: 1) combination of technological and stem cell research, 2) motivation towards products and applications, 3) clinical expertise in the stem cell groups, 4) commercially savvy groups, and 5) common goal and mission.

4.1 Combination of basic research and technology development

Basic research with stem cells is essentially important because it is in the core of the RM from which all the potential future applications occur. In the Human Spare Parts program, the focus is on different areas of human biology and clinical aspects, i.e. bones and tissues, neurology, ophthalmology and cardiology, where stem cells could be used in the future either directly or indirectly in order to improve health of patients. These groups are not located in the school of medicine nor university hospital, but in BioMediTech. However, there are also clinicians involved in the work of these stem cell research groups, and without this clinical link, it would be difficult to focus research effectively and wisely, or to conduct clinical experiments.

In addition to stem cell groups, four other groups in the Human Spare Parts program focus on biomaterials, biosensors, biomimetic environments, and imaging and signals. As technology and stem cell groups are in the same program with shared funding, it is natural for them to interact with each other. Interaction and collaboration is the key for development of new therapies and supporting tools. Stem cell groups are focusing on applications while technology groups focus on other tasks for the development of tools for stem cell groups.

This interactive work and feedback between technology and stem cell groups enables iterative development. It is essential because research in this field is in the frontline and commercial tools in

the market do not always fulfil the needs of research groups. Thus, it is a great advantage to be able to produce tailored tools within academia. However, in the end all advances are based on high competency in the field.

4.2 Focus on products and applications

Even though it is mostly basic research that is conducted in academia, in BioMediTech there is also a clear focus on products and applications. Existing examples can be found from adult stem cells group where clinical operations are conducted with real patients. The therapy is targeted to facial and cranial bone tissue regeneration from patient's own fatty tissue, and first operations were conducted already in 2007 and today over 25 operations have been conducted. This stem cell based therapy developed in Regea and continued in BioMediTech has been used in several university hospitals in Finland in order to treat patients. The latest operations have been conducted in Tampere University Hospital located on the same campus with BioMediTech.

Regarding this microvascular reconstruction of the maxilla[19], the hospital has a significant role. In the published process, first abdominal fat was harvested in the operating room (OR) for in vitro cell isolation and expansion in laboratory for two weeks. In the OR, after cells were placed in a custom-made titanium cage, the cage was inserted in the left rectus abdominis of the patient for 8 months. Then after several months, grown bone particle was inserted in the facial area. Together there were two surgeries first in the abdomen and then in the facial area.

There are no official clinical trials running regarding this therapy. Instead, these operations are conducted under hospital exemption within the Advanced Therapy Medicinal Product (ATMP) regulation in EU. ATMP hospital exemption is definitely the advantage that EU countries have in contrast to some other countries. This experimental therapy has no officially (in clinical trials) proven safety nor efficacy, and thus without ATMP hospital exemption it would not be possible to provide

this kind of patient care. The other remark is that without a connection between BioMediTech and Finland's university hospitals there are no possibilities for this kind of operation.

Therefore, within this kind of extended AHC it is possible to provide patient care with applications that are proven in the laboratory but not scientifically in clinical trials. However, without clinical trials, it is not possible to commercially exploit this as a product. To do so, clinical trials are needed to obtain product approval.

4.3 Relevance to clinicians and hospitals

RM research is mostly academia centered but there are several important aspects regarding hospitals too. RM constitutes a new stream in healthcare and it is inspired by current unreached needs of medicine. Thus, experience and expertise of clinical practitioners are a focal point of emergence in this field. Before any official clinical trials, hospitals are places for clinical experiments that are not otherwise possible to conduct. Hospitals are also the places for clinical trials. It is not a task for hospitals to commercialize new therapies, but they might have a significant role in acquiring first business references, obviously in clinical trials and also hospitals are able to find proper patients. It is also beneficial for hospitals as it allows them to be at the frontline regarding new treatments and drugs.

The role of the clinicians was significant in establishing Regea, which was the predecessor of BioMediTech. The first director was a clinician and there was a clinical need to grow bone, which was one of the reasons why development of this stem cell based therapy started. As development of this application occurs in academia, clinical operations are conducted in hospitals where the clinician is needed to do surgery. There are also other staff in the hospital, e.g. nurses that are needed in stem cell therapy operations. In Finland, the good thing is that even though the clinician has all the

responsibility to do the clinical operation correctly, hospitals take the responsibility for the outcome. This makes it easier for clinicians to join medical experiments.

4.4 Commercial savviness

In the cases of innovations that have a significant value for human beings but are not commercially viable, AHCs might play a role in funding, conducting clinical trials, and distribution of therapies. However, the main role for the current technology market is to spread those innovations that are commercially viable for global use. Regarding these commercially viable innovations, AHCs should collaborate with firms by enabling trials and regulatory approval. AHCs should also be proactive towards industries when they have developed an innovation and have some proof that it actually works. However, in doing all this, AHCs should be aware of commercial opportunities. They should also be able to deliver proven concepts. As researchers are not commercially aware naturally, maybe there would be place in the culture of AHCs where some training would be provided.

BioMediTech is active in finding commercial possibilities for research they are conducting and has employed IPR specialists to serve research groups to support this goal. In addition, researchers are trained to be aware of business opportunities regarding their research. Even though they are not business people themselves, they are able to talk and think about possible business opportunities and assist with IPR protection and initial market research, for example.

Regarding commercial applications there are identified short-term and long-term opportunities. Short-term opportunities include, for example, technologies that are developed for stem cell groups while long-term opportunities include stem cell therapies, where clinical trials are needed before commercial use. For example, therapy conducted under ATMP hospital exemption is a non-commercial product and product approval is not possible to obtain before successful clinical trials.

However, because of several clinical operations, there is some proof and understanding about the technological viability and limits of the concept being useful in the translational activities later.

4.5 Mission

All the groups involved in the Human Spare Parts program are dedicated to the mission of developing new therapies and drugs, because they obtain some funding and interesting applications in the field from it. This is also a fundamental reason why RM research in BioMediTech exists: a mission to find new ways to cure people. In the end, there are several levels where value is added with RM research and applications. For individuals, there is a clear value as they receive new kinds of treatments that are not possible otherwise to receive. For society, RM based therapies could enable longer working periods for their citizens and could reduce breaks in careers because of serious illness or trauma. There are good reasons why RM should be developed.

The environment where technology, stem cell research and clinical experience meet is crucial for innovation in the RM sector and thus organizations should have a common goal in order to develop a needed innovation environment and actual innovations. However, not all of these groups are focused on health related issues, and traditionally they would not be part of the work community of AHC. With the mission, it is possible to reorganize operations in meaningful ways and it allows teams to reach common goals. However, sufficient and wisely managed funding is an important aspect of succeeding in this mission. It allows those groups whose discipline is advantageous in the RM sphere to work alongside groups having their primary applications in the RM sphere. With the mission, it is also justified to focus on potential commercial applications too, because in many cases this is the only way to advance the sector.

5 Managerial and policy implications

It is fundamental for AHCs to be places where innovations occur and thus there is a need for breaking old department structures and promoting interdisciplinary research[16] in order to achieve innovative objectives. The revolution RM sector could bring to AHCs lies not only in the new techniques how patients can be treated but also in how these new opportunities are integrated into AHC. Especially cell therapy products possess a great opportunities beside pharmaceutical products, biopharmaceutical products and medical devices. If something is broken in the patient, it might be possible to regenerate new tissue or organ and repair the problem. Also some disorders that are not curable with medicines might in the future be possible to cure with, for example, stem cells.

As the RM sector is still in the early phases as a field of scientific, the development of new applications happens mostly in the academia. In the RM sector, disciplines outside health sciences are needed to develop and eventually provide new therapies. This is comparable to the medical device industry where innovation is really outward-looking by nature and is dependent on progress in several disciplines such as electronics, optics, computers and material sciences[2]. Regarding RM in Tampere, BioMediTech and University Hospital of Tampere together constitute a loose collaborative organizational structure where not only medical and biomedical research and clinical operations are conducted, but also complementary research and technology development. This is essentially important for the progress of the RM sector.

However, the loose organizational structure brings many challenges to the management of innovation as clinical operations and RM research are in the different organizations. Individual researchers collaborate easily across organizational borders and it is even possible that new experimental treatments emerge from these collaborations, as has happened in Tampere. Nevertheless, collaboration and ongoing dialogue are needed also in the management level of these organizations,

both in the strategic level and in the very practical level, e.g. in the calculation of the cost of a treatment as several human and material resources are needed in the operations, in the allocation of needed human resources, or in the training of involved personnel.

It would be beneficial to have a common strategy for organizations involved in the RM research and subsequent applications. In Tampere, for example, actors involved in the health sector research and medical operations have proposed that a research organization should be founded to unite existing medical and health research related departments and the university hospital through common services and research programs. Even though this is actually a general strategic initiative in the Tampere region and not intended specifically for the RM sector, this loose organization called Tampere Health Research Center Kauppi would have its own research strategy, in which RM is identified as one of the spearheads. Certainly, it would promote and facilitate communication between different departments and research programs.

6 Concluding remarks

Hospitals are needed for the provision of health services for human beings and in healthcare advancement of science and technology has been remarkable over the last century[20]. Through advancement of technology, there are more healthcare services available than ever. In the same time, the decision about what hospitals are able to offer is more and more difficult, as not all the possible treatments can be provided because of limited resources. Regarding RM products there is still a long journey to become regular hospital services.

As an emerging sector in healthcare RM demands a diversified knowledge base and thus would benefit if old department structures in the university could be passed and close collaboration between complementary technology development and stem cell biology could be connected in AHCs. In the

case studied here, most of the technology and stem cell expertise exist outside traditional medical research. In some sense, traditional AHC has no other role than taking responsibility of surgery and providing healthcare facilities for it, even though it should be the place, where innovations occur.

A lesson to learn from the Human Spare Parts program is that of combining different kinds of expertise. For example, technology groups bring expertise that can be utilized in RM research, too. They collaborate with stem cell groups and are essential in solving problems arising in stem cell research. In the organizational level, collaboration and communication are the most important aspects in an emerging field like RM. If RM will be institutionalized in hospitals more profoundly, there might appear collaborations that is more formal. When RM will be an institutionalized method to treat patients, most likely there will be a specific RM department in the AHC. However, what really constitutes AHCs in the future is a more difficult question, as different sectors aiming towards human health are dependent on different disciplines.

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3 Regenerative Medicine Cell Therapy Financial Market: How to Finance Potential Innovations

Tuomo Heinonen

3.1 Introduction

In human healthcare, there are four pillars: pharmaceutical, biotechnology, medical device and cell therapy industries (Mason & Manzotti, 2009; Mason et al., 2011). All of them are important, having distinctive core technologies and therapeutic products (Mason et al., 2011). While the others are more matured industries, cell therapy industry is an emerging one. Regenerative medicine (RM) that aims to restore or regenerate human cells, tissues or organs (Mason & Dunnill, 2008) draws from all the industries, but cell therapy industry is especially important. Hopes are great for RM, as it is a third discipline besides surgery and medicine, enabling not only treatment but also regeneration of body parts, hence, opening an avenue for many treatments that were not possible before (Polak et al., 2010). Cell therapy industry and RM depend on academic research and progress of science, and it is important for firms to have an access to high-quality research in academia (Prescott, 2011).

Product development in the RM sector is expensive and time consuming, because products have to go through clinical trials. Product development and firm creation became even more challenging as financing sources of firms changed somewhere in 2005, from venture capitalists, pharmaceutical companies, US stock market and NASA, to public finance, philanthropists and military (Mason, 2007). This change has led to problems with funding, as it is difficult to get venture capital (VC) financing until there is strong evidence from clinical trials (Parson, 2008). In the RM sector, the lack of funding is evidently a big challenge (Johnson et al., 2011). The change also means that universities have to develop potential products further. University-based start-ups and academic entrepreneurs have been studied a lot (Meyer, 2003; Hoye & Pries, 2009; Abramo et al., 2012), and in some studies, potential problems have been identified, e.g., good scientists may not be good managers of new venture (Bower, 2003; Lerner, 2005) and academia, in general, lacks market awareness (Bower, 2003; Johnson et al, 2011). Hence, a viable business environment is beneficial and essential for the successful commercialisation of these innovations.

Motivation for this study comes from challenges the RM sector faces in terms of funding for early clinical trials. It means that in many cases, academia has to manage the research and development (R&D) and subsequent early clinical trials by themselves. This study is based on a case study made in Tampere, Finland, aiming to scrutinise needed competencies and resources in this conquest. In particular, the aim of this study is to scrutinise the RM cell therapy financial market in the global and national level and its effects in the local level. The question is how the university is able to use its R&D efforts for advantage in the RM cell therapy field in order to commercialise developed technologies.

As most of the university-based technologies are transferred in the early phases of development, further development is needed (Jensen & Thursby, 2001). Especially for science-based

technologies, a significant amount of R&D is essential in order to find their way to market someday. R&D of these technologies can be conducted in start-ups (Druilhe & Garnsey, 2004) or it can be continued in the form of proof of concept in academia (Gulbranson & Audretsch, 2008; Maia & Claro, 2013; Heinonen, 2015). However, in both of the cases, successful commercialisation of these technologies requires an extensive amount of funding, especially in the case of science-based technologies, like RM cell therapy products. Hence, financial markets and end-users' acceptance is critical in determining the commercial success of new technologies (Bower, 2003). The RM cell therapy industry is similar to the biotechnology industry, where scientific research produces technological advances (Jensen et al., 2007) and thus, this study uses competence bloc theory (Eliasson & Eliasson, 1996) as a theoretical background, as it emerges from biotechnology viewpoint. Competence bloc provides a set of actors needed for commercial success. However, as this sector is a globally emerging one that lacks funding, product concept must be nurtured in academia longer. An interesting problem is how to finance and manage these potential university-based innovations. It makes no sense to conduct R&D aiming to develop a product in academia if there are no potential commercial venues and funding for the innovations.

3.2 Theoretical background

Eliasson and Eliasson (1996) developed competence bloc theory in the early 1990's for the purpose of explaining the development of biotechnology industry. Competence bloc theory consists of actors and their competencies that are needed for sustainable economic development. In the working competence bloc, allocation of resources is efficiently done by two rules: (1) losers must be terminated and (2) winners must be recognised as fast as possible. In this process, entrepreneurs are important actors in competence bloc, because:

- they are in a key position to select those innovations that can be exploited in a commercial way
- their businesses must be scalable so that money can be invested in them with the expectation of a good return of investment.

Other actors in the competence bloc are customers, innovators, venture capitalists and industrialists. In addition, Johansson (2010) introduced the inventor and skilled labourer to the theory. There must also be an environment where venture capitalists and entrepreneurs can expect better profit, i.e., an exit-market. Entrepreneurs, being able to attract venture capital, have to have a potential exit-market as an incentive for both themselves and venture capitalists. An exit for a venture capitalist in this context is through an initial public offering (IPO) or a trade sale. A viable stock market is important, as it allows companies to draw money from an IPO. In the case of a trade sale, the acquirer has the needed resources to continue development. In both cases, the role of industrialist is important, as it brings the product of the entrepreneur to full-scale production. The independent roles of the entrepreneur and the industrialist are important and, in some cases, small firms in the biotechnology sector are more efficient in carrying out discoveries than in-house R&D of large companies (Hopkins et al., 2007).

The role of venture capitalists is critical, as they recognise and fund those entrepreneurs who are capable and competent to make commercially viable products. Venture capitalists use

VC, which can be defined as: “independently managed dedicated pools of capital that focus on equity or equity-linked investments in privately held, high growth companies” (Gompers and Lerner, 1999: 349; cited in Avnimelech & Teubal, 2006). VC organisation (here, venture capitalists) is an organisation that invests in privately held, high-growth companies between one and five years old (narrow definition) or between one and ten years old (broad definition) (Avnimelech & Teubal, 2006). Then private equity (PE) companies focus on both high growth companies and mature companies, either privately or publicly traded (Avnimelech & Teubal, 2006). It is important for the purposes of a successful technology transfer to identify the appropriate market and create and verify a commercial concept, bridging the gap between invention and product development (Auerswald & Branscomb, 2003). Venture capitalists have an important role, not only in funding businesses, especially in the case of university-based technology. According to Reynolds et al. (2013), in some cases, a venture capitalist combined the IP from different universities and formed the initial team and firm because of seeing the potential for a new technology. However, Hall and Lerner (2010) point out that a VC model has its limits as a solution of funding gaps for regions where PE markets for venture-capitalist exits are not developed.

Regarding emergence of new industry, it is critical to create a needed mass of resources, skills and activities that make it possible to initiate a cumulative process with a strong momentum (Avnimelech & Teubal, 2008). Critical mass of competencies is needed in order to have a sustainable economic success. The customer needs to be active, competent and resourceful (Eliasson & Eliasson, 1996) and innovators find out how to put things together creating the technical aspects of innovation. Finally, a local ecosystem is important for start-ups, because it provides financing, labour and other resources needed. For start-ups, especially in the beginning of growth, quick access to diverse talent and possibility to hire fast is important (Reynolds et al., 2013). However, because of globalisation, it is possible for foreign firms to acquire local companies, and thus, it is a shorter period to leverage R&D in terms of production and associated national economic impact (Reynolds et al., 2013).

3.3 Methodology

Primary empirical data about local ecosystem in Tampere, Finland were gathered in 2014. The Finnish Funding Agency for Technology and Innovation (TEKES) has fostered development of this local ecosystem, as they have funded the Human Spare Parts research program in BioMediTech, which is a joint institute of the University of Tampere and Tampere University of Technology, and which combines biosciences and medical technology from both universities. In this study, a semi-structured theme interview was used as a method to conduct data. Altogether, there were 24 interviews: fifteen interviewees were from BioMediTech, three interviewees were from the University Hospital of Tampere, and the rest were from local and regional development agencies, the Ministry of Employment and the Economy, TEKES, and a local firm. The focus of the interviews was to obtain an overall understanding about the current RM ecosystem in Tampere and to address the following themes: research environment, finance, entrepreneurship, market, legislation, hospital environment and end-value.

Secondary financial data about investments were gathered from Alliance for Regenerative Medicine (ARM) and Finnish Venture Capital Association (FVCA). There are no regional data

available regarding RM, but ARM has moved forward with a global database, and most likely, they have found most of the major RM cell therapy and gene therapy companies in the field. At least it is possible to see the direction of the financial situation in RM cell therapies and gene therapies globally. Data about RM investments were gathered from ARM annual reports (years 2011-2014). As the industry is developing, reports were not yet standardised, and comparable numbers were possible to get only from years 2013 and 2014. However, for the purposes of this study, years 2011 and 2012 were estimated and calculated from known data to be as comparable as possible. Financial data of Finland were received from FVCA, including pharmaceuticals and drug delivery, and drug development technology sectors between 2007 and 2013. Biopharmaceutical sector was excluded here, because it is reported as part of biotechnology sector. Venture capitalists in these sectors are the closest ones who could invest in RM cell therapy firms in the future. Altogether, data included investments (in the case of Finnish investors, both domestic and foreign investments) from three private venture capitalists, three public VC organizations and some amount of non-disclosed foreign venture capitalists.

3.4 Findings

3.4.1 Global RM cell therapy financial market

Ford and Nelsen (2014) studied the change of the life science investor landscape. They link the start-up and seed phase funding to R&D, the next investment rounds to pre-clinical studies, and subsequent investment rounds to clinical studies. According to them, new investors have come to the investor landscape, and among these are family offices, foundations, patient groups and venture philanthropists who are active from the seed investments phase to the strategic partnership phase. Another significant change is that pharmaceutical and biotechnology companies have started to invest already in the R&D stage, and this change is also noticeable in the RM cell therapies, where milestone partnership payments have grown significantly. However, venture capitalists, even though they claim that they are active in early stages, are not often engaging in deals (Ford & Nelsen, 2014). If this is a situation regarding the life science sector, it is even more challenging in RM. However, as RM cell therapy industry develops further, it is advantageous for the companies that the existing investment landscape is more diverse than it used to be. Since venture capitalists are not willing to invest until in Phase II or Phase III, product development depends on other investors.

Nevertheless, the role of venture capitalists is important in the competence bloc. In the case of the emerging RM financial market, the amount of investments have started to grow recently (Figure 3-1), which is promising for the emerging RM cell therapy sector. What is remarkable is that from 2013 to 2014, partnership milestone payments grew from $2.4 billion to $8.9 billion (ARM, 2015). This means that pharmaceutical and biotechnology companies also support product development processes in the RM companies. This change is important for the future, because pharmaceutical and biotechnology companies have investment potential, but they are also possible acquirers, acting as industrialists.

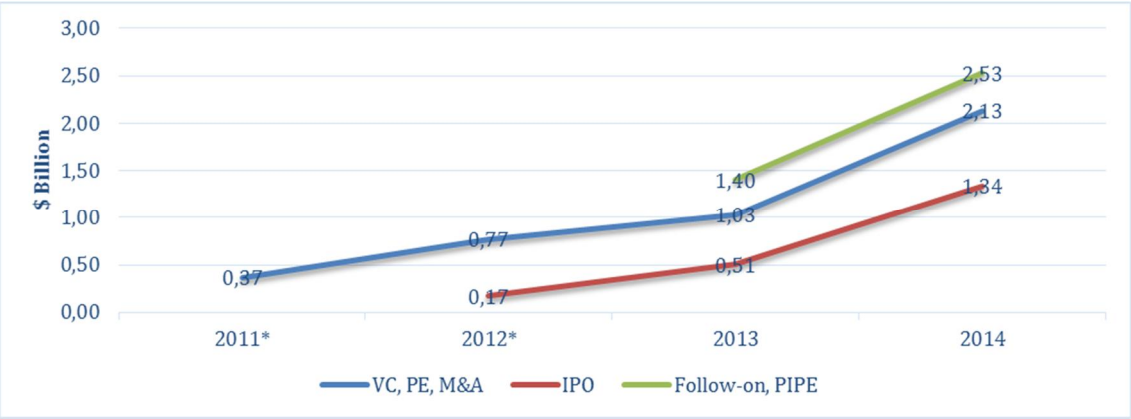

Figure 3-1. Investments in RM cell therapy and gene therapy. *) Numbers are estimations and VC, PE and M&A investments might include also PIPE (private investments in public equity) deals, while in 2012, the IPO number may also include follow-up investments.

Academia is important in the RM sector, not only due to the development of science but because current opinion in the RM cell therapy industry is that it is not reasonable to shift research to companies before there is clear evidence from Phase II clinical trials that the solution is working (Mason et al., 2011). This also means that a significant amount of R&D is conducted in the university environment instead of the firm. Around the year 2005, financial sources changed from VC to public financing, but now private investments seem to be growing again. Focus on commercially successful products (Mason, 2007) may have increased the number of potential products for investments, which is what may partially explain the growth in VC in recent years.

However, the lack of VC in the RM sector has led to a situation where universities should develop product concepts further, and in some cases, even conduct early clinical trials before the product opportunity is possible to transfer to firms and get venture finance for it. Even though the situation seems to be changing, this is still the common understanding among practitioners. Since there is a funding gap for early clinical trials in RM cell therapy, some countries have established RM translation centres to fill this gap and to fund cell therapy clinical trials (Mason et al., 2011). Some examples of translation centres are Catapult Cell Therapy in the UK, the Centre for Commercialisation of Regenerative Medicine (CCRM) in Canada, and the California Institute for Regenerative Medicine (CIRM) in the US. In Finland, the Finnish Funding Agency for Technology and Innovation has funded research translation projects with a dedicated pool of funding, but these projects are more general and do not focus only on RM.

According to Bonfiglio (2014), during the product development, the estimated need for grants is $5-10 million for academic research, and the need for venture investments is $10-15 million for Phase I, $20-25 million for Phase II and $50-75 million for Phase III. Then IPO or partnership deals should provide $75-100 million. IPO is important, because it helps companies to fund the long product development process (Reynolds et al., 2013) but also gives venture capitalists an opportunity to make an exit.

3.4.2 Potential Finnish RM cell therapy financial market

In Finland, there are only a few investors in the pharmaceutical and biopharmaceutical fields. Figure 3-2 presents the total amount of investments and the average investment size in the fields of pharmaceuticals, drug delivery and drug development technologies. These fields were chosen for this study, because they show the direction of the Finnish financial market regarding science-based firms that have a long product-development cycle and require a significant amount of money.

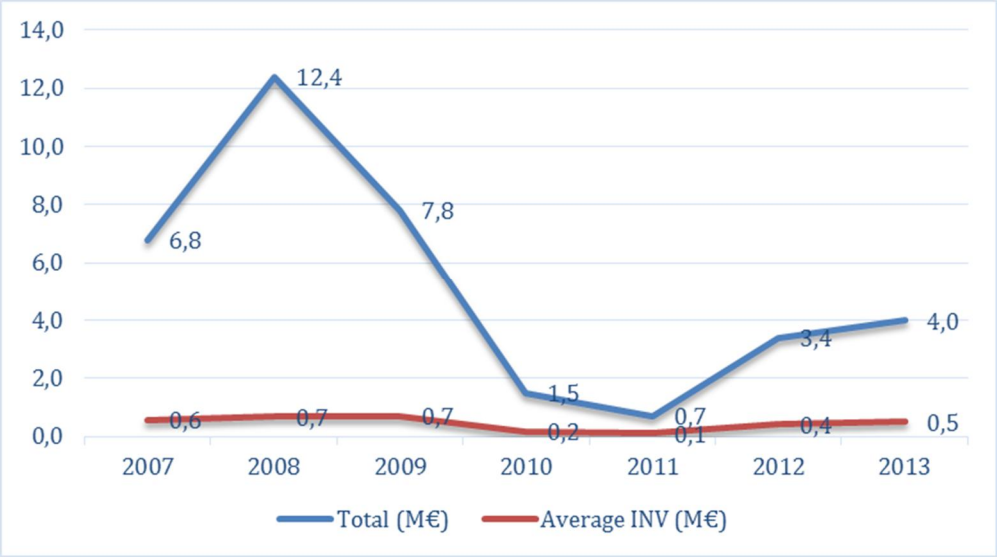

FIGURE 3-2. Total amount of investments and average investment size in Finland.

As is possible to see, between 2010 and 2013, investments were at a very low level. During this timeframe (from 2007 to 2013), there were three private investors. In addition, there may have been some venture capitalists and VC investments in these categories that are not documented in the statistics. From the documented ones, the only currently active private investor has in its portfolio, pharmaceutical companies, biotechnology companies and medical device companies but in recent years has had very modest follow-up investment rounds in the portfolio companies.

FIGURE 3-3. Distribution of number of investments and distribution of amount of investments between 2007 and 2013.

Figure 3-3 presents the distribution of these investments between public, private and foreign investors. Even though the amount of investments is similar between private, public and foreign investors, the public investors' average investment size is only 0.27 M€. In the private sector, the average investment size is 0.74 M€, and the foreign investors' average investment size is 1.23 M€. However, the average investment size does not automatically indicate how much firms actually receive from the investment round, because several investors might have invested in the firm. The overall picture of the Finnish financial market in this sphere is not spectacular and it is crucial for the future of Finland, somehow, to foster the growth in this financial market.

3.4.3 Local ecosystem in Tampere, Finland

The RM cell therapy ecosystem in Tampere is based mainly on the research and product development projects in BioMediTech. There are a few small biotechnology-related firms in the Tampere region, but most of them have no tight linkage with BioMediTech, even though there are some exceptions. In the biomaterial field, some of the companies in the region have been successful, but most of them have not been able to grow further. There are some exceptions, though. In 1997, a company from Tampere had an IPO in New York, and a few years later, another company acquired it. Later in 2004, another company in Tampere had an IPO in London, but later this company had to branch out from the stock market. Hence, there has been some experience with industrial success, but the experience has not stimulated the growth of the local ecosystem. One of the challenges is insufficient funding; hence, potential new business ideas just stay untouched, as there are no resources to push these forward.

In the RM cell therapy field, the strength of BioMediTech is that it is interdisciplinary and combines expertise and competencies from several disciplines. In 2011, BioMediTech got a significant research grant from the Finnish Funding Agency for Technology and Innovation (TEKES) for several years in order to develop novel solutions in different needs of healthcare, focusing on strategic research, which combines both basic research and translational research focus on innovations. BioMediTech chose four technology groups and four stem cell groups for this research program with an aim to develop new therapies, drugs and technologies. Even though new therapies were the goal, along the way, they have developed technologies and tools that have commercial potential as well. Many technological concepts co-evolve with stem cell research, and there is a strong feedback loop in the development of these tools and technologies. Regionally, there have been significant investments in research facilities in BioMediTech and its predecessors, e.g., in the form of the GMP-level laboratory.

The combination of stem cells and biomaterials was an advantage in the Tampere region and for the predecessors of BioMediTech. Based on these strengths, already in 2007, there was a experimental clinical therapy that was based on the early stem cell-based innovations to grow cranial bone and place it into defect sites. These cranial bones were cultivated inside a titanium cage in a rectus abdominis to get blood vessels to grow, too. R&D for this therapy was carried out in academia, and currently there are over 25 treatments conducted within the regulatory framework of an advanced therapy medicinal products (ATMP) hospital exemption without any commercial entities. An ATMP hospital exemption requires that treatment must be a non-routine treatment and conducted under the exclusive responsibility of a medical

practitioner. Thus, no clinical trials have been conducted for this therapy. However, because of several treatments conducted under ATMP hospital exemption, there is knowledge about clinical effectiveness. To get this therapy approved and commercialised, first pre-clinical studies have to be conducted with animal models, which take about three years to complete. Then clinical trials must be started, and altogether, over 200 patients need to be involved. After clinical trials, it is possible to get product approval from the public authority. Thus, even though the scientific level is high and real patients have been treated, the path for commercial products is still long.

Scientific research is dependent on public sector grants. In addition to scientific research, there have been many internal projects in BioMediTech that aim to initiate commercialisation of developed technology, tools or therapies and develop a proof of concept for them. The funding for these projects is through public grants received mainly from TEKES. The aim of the proof of concepts is to study market and commercialisation avenues for potential innovation from university R&D. In the case of therapy development, getting financing is not easy, and collaboration with foreign parties is initiated to conduct pre-clinical trials. Even though BioMediTech gets enough funding for pre-clinical trials, it is still uncertain if there will be enough funding for clinical trials. It is also always uncertain if pre-clinical trials or clinical trials will produce wanted results. The advantage for BioMediTech is that they have conducted several treatments in Finnish hospitals and the latest in Tampere, hence, they have been able to get feedback and gain experience.

BioMediTech is a research institute, even though it has a strong commercial aim and an entrepreneurial attitude. However, they currently have no entrepreneurs identified in BioMediTech who could take a product concept and bring it to the market. For those projects that aim for proof of concept development, business experts are employed from outside the BioMediTech. Local firms are loosely connected to BioMediTech, and most of them are very small ones. In Finland, start-up companies are able to get public financing, but in general, the amount of funding is relatively small, and VC is a scarce resource, as was shown in the previous chapter. In the case of therapies, it is not reasonable to expect that enough financing would be found solely from Finland to conduct clinical trials. Also, there are not many relevant industrialists in the ecosystem that could develop products into full-scale production. Lack of industrialists is a problem, so BioMediTech is forced to find partners from abroad as well. It is critical for the future of the Tampere region that entrepreneurs are able to do IPO and to become large enough to act in the future as industrialists.

In Finland, according to the last chapter's history data, only a few venture capitalists would be ready to invest in RM cell therapies. If therapy for bone growth is taken, for example, finding financiers who are able to invest in a firm that continues the development is uncertain. The challenge is that it is nearly impossible for BioMediTech to conduct clinical trials for phase III, and it is difficult to find enough investments locally for a firm to continue the development. Another challenge is that there are no entrepreneurs readily available in the RM cell therapy ecosystem that could raise VC for the new company and take R&D efforts with BioMediTech further. Thus, in BioMediTech, the main route for commercialisation of research is seen to be through technology transfer to an existing company, even though partners must be found from abroad. Currently, regarding those product ideas that are not RM cell therapies, start-ups

were not seen as relevant partners, as they have no established sales channels. In addition, the potential market for some product ideas from BioMediTech is seen to be too small for them. In the future for upcoming technologies, the situation might be different, even though in these cases, a product is not necessarily an RM cell-therapy product. However, the emergence of potential start-ups and entrepreneurs is necessary if venture capitalists want to start investing in the ecosystem.

3.5 Discussion

The important questions are how European firms are able to grow and especially how university-based R&D can be exploited in the market. Hale and Apotheker (2006) point out the significant difference in the VC industry between Europe and the US: European venture capitalists more often drip-feed VC over several rounds, while in the US, investors are willing to fund firms longer at early phases, which allows time for a company to develop a major product. Even though their observations concerned software industry, similar piecemeal-funding practice seems to happen, at least in Finland in studied pharmaceutical and drug development company investments. Small average investment size means that there may not be enough operating capital for firms. It would be interesting to see what the situation is in the RM cell therapy industry and VC investment between Europe and the US, but financial data of different continents are not readily available regarding RM cell therapy industry.

Competence bloc presents an ideal model of how new businesses emerge from inventions. However, in the case region of this study, this competence bloc is not developed in terms of actors, which implies that resource allocation is not efficiently done. Regarding RM cell therapy sector, innovators produce high-level research and innovations with public grants. Bone growth therapy is even used in public hospitals and has demonstrated its usefulness. Some of the innovations are in the proof of concept phase in academia, but commercial products have not appeared through entrepreneurs. In the region, there are mostly small companies that are not focused on RM cell therapies and are loosely integrated to BioMediTech in this field. Because of this, only a few companies would be potential industrialists for some RM technologies. For RM cell therapies, no potential local industrialists were identified locally. Potential entrepreneurs are not actively identified in BioMediTech, which means that potential venture capitalists have no potential firms to invest. As RM is an emerging field, no venture capitalists are focusing on it. Based on the studied Finnish financial market in the pharmaceutical and biopharmaceutical fields, it is possible that RM cell therapies are not vivid investment targets anyway, but supporting technologies could be. Lack of entrepreneurs and venture capitalists means that there is no vivid exit-market either, but historically, there are few examples of IPOs in the foreign stock markets.

Another question is if potential RM cell therapy industry is appropriate for Finland. It seems that there is not enough funding in Finland for growth companies in this sphere, so international connections are important. Thus, in the long term, potential RM cell therapies need new investors in Finland for the development of this industry, if this is the desired path for Finland and Tampere to take. In general, the lack of venture capitalists leads to situations where competent entrepreneurs may not be recognised. It is also an important question whether universities will be able to identify commercially potential innovations and develop those further, as

universities in general are not commercially competent. Without competent entrepreneurs, it is also impossible for venture capitalists to show up. Hence, the situation is currently in deadlock, and emergence of both entrepreneurs and venture capitalists is needed simultaneously.

Table 3-1. Summary of local competence bloc in Tampere, Finland.

RM CELL THERAPY IN TAMPERE	
INNOVATORS	- High level research - Developed applications in cell therapy (bone growth), technology and tools - Proof of concept development - Public financial market - Experience from university hospitals (RM cell therapy)
ENTREPRENEURS	- Small companies, not focused on RM cell therapies - No potential entrepreneurs identified in BioMediTech - Local companies loosely integrated to BioMediTech - Financial market does not support emergence of entrepreneurs
VENTURE CAPITALIST	- There are not specialised venture capitalists - Limited connections abroad - Limited amount of VC available
EXIT MARKET	- In history a few IPOs in London and New York, even though not in RM cell therapy field
INDUSTRIALIST	- Few (if no) relevant industrialists in the local ecosystem - Partners have to be sought from abroad (EU, USA)

3.6 Conclusion

The aim of this study focused on the global RM cell therapy financial market, its corresponding local financial market in Finland and a local ecosystem in Tampere, Finland. This study combines a local ecosystem, national financial market and global financial market, because the whole industry is just beginning to emerge, and there is a limited amount of relevant investors, even globally. Thus, it is important to understand from a local ecosystem viewpoint what the situation of the financial market in Finland is and how it relates to the global financial market. At the same time, it seems to be difficult for the national financial market to develop or grow if there is no viable ecosystem of firms.

It is evident that the global financial market for RM cell therapy and gene therapy is growing lately, including growth in partnership milestone payments that are fourfold, which is consistent with the general change in life science-investor landscape, in which pharmaceutical companies invest in the earlier phases of product development. In Finland, the situation is very different. Venture capital investments and average investment sizes in pharmaceutical and drug development companies between 2007 and 2013 were at a very low level.

From a science and technology point of view, the RM cell therapy industry is fascinating and full of promises. However, locally it is difficult to have start-ups in RM cell therapies, as needed financing is enormous. Thus, partnership with established companies seems to be one of the only possibilities to develop these university-based technologies and commercialise them. In the in long-term there is a need for investments in firms in the local ecosystem to develop it further and achieve sustainability through growth of these companies. As RM cell therapy

products must be developed in academia longer, it should be financed, somehow. As these investments are mostly national, emerging firms should also be viable and able to raise funding from financial markets so that national investments in university R&D will return to the economy. However, the financial market in Finland is not highly supportive, and thus, currently it is not viable to spin out new RM cell therapy companies from academia. To change this, growth in the financial market is highly needed.

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