

Business and Intellectual Capital Development in Financial Riptide

Case Studies of Finnish Biotechnology and Pharmaceutical
Companies Dispersing into Global Value Chains

Martti Kulvik (corresponding author)* – Marja Tähtinen** – Pekka Ylä-Anttila

* ETLA – The Research Institute of the Finnish Economy, martti.kulvik@etla.fi

** ETLA – The Research Institute of the Finnish Economy, marja.tahtinen@etla.fi

We want to express our deepest gratitude to Harri Holopainen, Pertti Koski, Ashesh Kumar, Risto Lammintausta, Seppo Mäkinen, Tuula Palmen, Juhani Saarinen, Rabbe Slätis, Pirkko Suhonen, Erkki Tenhunen and Juha Vapaavuori for interesting and time-consuming interviews, and for sharing their valuable experience and opinions on the Finnish biotechnology and pharmaceutical sector.

We also thank the following people for additional interviews, discussions, background information, comments and advise during this project: Mia Bengtsröm, David Dranove, Barbara Goodman, Shane Greenstein, Minna Hendolin, Carmela Kantor-Aaltonen, Katriina Kippo, Tapio Korkolainen, Helena Laine, Pauli Marttila, Auli Pere, Marita Perälä-Heape, Antti Pirnes, Irmeli Puntari, Hanna Rantala, Pauli Saarenketo, Taina Saksa, Joel Shalowitz, Mika Sievi-Korte, Giuseppe Turchetti, Sangeeta Vohra and Tom Wiklund.

This research has been realized through a separate grant from Tekes, with additional data collected within the project Suomi ja suomalaiset yritykset globaaleissa arvoverkoissa (SUGAR) funded by Tekes.

ISSN-L 2323-2447

ISSN 2323-2447 (print)

ISSN 2323-2455 (online)

Contents

Abstract	2
Tiivistelmä	2
1 Introduction	3
1.1 Finnish pharmaceutical and biotech industry	3
1.2 Intellectual capital: an overlooked asset?	3
1.3 Life science industry in 2000–2010	4
1.4 Research design	8
1.5 Definitions	9
2 Company cases	10
2.1 Carbion Oy	10
2.2 Hormos Medical Oy	14
2.3 Inion Oy	21
2.4 Ipsat Therapies Oy	27
2.5 Juvantia Oy	34
2.6 Medipolis GMP Oy	42
3 Investor cases	50
3.1 BioFund Management Oy	50
3.2 Sitra Life Sciences	55
4 Results and discussion	60
4.1 Strengths of Finnish biotechnology	61
4.2 The role of public funding	62
4.3 What went wrong?	63
4.4 What is the fate of the intellectual capital that is created in research-intensive biotech and drug development companies?	67
4.5 What is the future of biotechnology funding?	70
4.6 Policy implications: legislation and support	75
4.7 Back to the ocean	76
References	79

Business and intellectual capital development in financial riptide

Case studies of Finnish biotechnology and pharmaceutical companies dispersing into global value chains

Abstract

This study focused on two primary areas:

1. To determine what can be learned from biotech and drug development companies that suffered from financial problems and ultimately failed at the beginning of the 21st century.

2. To determine how intellectual capital developed in accordance with such companies and its fate following business failure.

We examined six failed Finnish biotechnology companies and two major venture capital companies that have invested in Finnish biotechnology companies. We strongly emphasize that this research is only a case-based and very limited feasibility study. Nevertheless, the results were surprising. We found that intellectual capital was indeed created in the companies and that various aspects of this capital could be identified. To a certain extent, we were also able to follow the post-company steps of intellectual capital and the continuity of its value-creation in novel companies.

The study was designed to involve only failed companies, but in four cases we found ourselves interviewing leaders of companies that had been created based on the IC of failed companies. It appears that important knowledge has vested by learning from earlier mistakes, and this learning period has created important intellectual capital that has already been exploited by various companies.

Research-intensive companies typically operate in fields where failure is an inherent risk. Governments typically support emerging industries based on high-technology because of their growth potential. The combination of high-intensity R&D and high risks creates a problem for all investors. The created value is primarily in the form of intangible assets, which are not captured in traditional accounting and for which no well-established alternative metrics exist. Consequently, in the case of a company failure, most of the created value added is considered lost. This loss not only complicates the justification of government support policies but typically leads to high initial expectations of the sector that are unfortunately often followed by subsequent disappointments. We think that the present concept of failure may be profoundly misleading.

Key words: Intellectual capital, biotechnology companies, life science, knowledge recycling, venture capital, failed companies

JEL: G24, G33, J24, L65, M13, O32

Liiketoiminnan ja osaamispääoman kehittyminen rahoituksellisessa vuorovedessä

Tapaustutkimuksia suomalaisten bioteknologia- ja lääkeyhtiöiden hajoamisesta globaaleihin arvoketjuihin

Tiivistelmä

Keskitymme tässä tutkimuksessa kahteen pääkysymykseen:

Mitä voidaan oppia 2000-luvun alussa epäonnistuneista bioteknologia- ja lääkekehitysyrityksistä?

Miten näiden yritysten aineeton pääoma kehittyi ennen epäonnistumista ja mitä sille tapahtui epäonnistumisen jälkeen?

Tutkimme kuutta suomalaista epäonnistunutta (esim. konkurssi) bioteknologia-alan yritystä ja kahta merkittävää bioteknologiaan sijoittanutta pääomasijoittajaa. Korostamme tutkimuksen olevan tapaustutkimus sekä verrattain rajoittunut esitutkimus. Tästä huolimatta yllätys tuloksista. Löydöstemme mukaan yritykset loivat ennen epäonnistumista tunnistettavissa olevaa aineetonta pääomaa. Tutkimuksessa kykenimme myös seuraamaan tämän pääoman epäonnistumisen jälkeisiä vaiheita ja miten sen avulla luotiin arvoa uusissa yrityksissä.

Valitsimme tutkimukseen alun perin vain epäonnistuneita yrityksiä, mutta neljän yrityksen kohdalla haastateltavamme olivatkin näiden epäonnistuneiden yritysten aineetonta pääomaa hyödyntäviä yrityksiä ja niiden johtoa. Tämän pohjalta vaikuttaa, että tärkeää tietoa siirtyy eteenpäin myös epäonnistumisista. Epäonnistumiset ovat luoneet tärkeää aineetonta pääomaa, jota useat yrityksen johtajat hyödyntävät.

Tutkimusintensiiviseen uuden teknologian yritystoimintaan liittyy olennaisena osana epäonnistumisen riski. Valtiot puolestaan tukevat nousevia korkean teknologian aloja niiden kasvupotentiaalin vuoksi. T&k-intensiivisyys yhdistettynä korkeaan riskiin onkin ongelma sekä julkisen että yksityisen puolen sijoittajille. Yritykset luovat pääosin aineetonta pääomaa, jolle ei ole olemassa perinteisiä kirjanpidollisia tai muita yleisesti hyväksytyjä mittareita. Täten epäonnistumisen yhteydessä suurinta osaa tuotetusta arvosta pidetään menetettynä. Tämä menetys ei ainoastaan hankaloita yhteiskunnan tukien perustelemista, vaan johtaa myös alkuvaiheessa korkeisiin kasvuodotuksiin ja sitä seuraavaan yleiseen pettymykseen. Näyttää kuitenkin siltä, että tämän hetkinen määritelmä korkeateknologiayrityksen ja siten sijoituksen epäonnistumiselle saattaa olla harhaanjohtava; kannattamaton voikin olla kannattavaa.

Asiasanat: Osaamispääoma, aineeton pääoma, bioteknologia-yhtiöt, life science, osaamisen kierrätys, epäonnistuneet yhtiöt, riskisijoitukset

JEL: G24, G33, J24, L65, M13, O32

1 Introduction

1.1 Finnish pharmaceutical and biotech industry

The Finnish pharmaceutical industry dates back to 1899, when Lääkelaboratorio Alb. Koponen, the first pharmaceutical factory, was established in Nurmijärvi by the obstinate pharmacist Albin Koponen (Iisalo et al. 1998). The factory was equipped with a patented extraction machine and was able to produce more than 20 original drugs that were exported to Russia, China and North America. These first plant-based drugs against tapeworms paved the path for the more sophisticated medicines and treatments that are currently available more than 100 years later.

Finnish biotechnology also has a long history, dating back to the first biotechnology-related patent in the world, given in 1843 to Hans Johan Falkman, a Finnish spirit manufacturer who invented a novel method to improve the stability of yeast. The industrial use of biotechnology remained the primary prosperity factor of breweries, dairies and bakeries for nearly a century, until the isolation of insulin in 1921 and the discovery of the therapeutic effects of penicillin in 1928 opened a new era in the use of biotechnology in drug identification and development (Sundqvist and Hansén 2006).

During the last few decades, the concepts of pharmacy and biotechnology have converged as Finnish pharmaceutical companies have followed global trends and begun production of bio-active substances: the first Finnish penicillin was brought to market by Lääke Oy in the early 1950s, and several receptor-mediated drugs were discovered from 1970 to 1980 in Farnos (Sundqvist and Hansén 2006).

The development of gene technology and the knowledge of the genomes of various organisms at the beginning of the 21st century brought completely new options to drug development, diagnostics and other sectors of industrial biotechnology and had a crucial influence in shaping Finnish life science R&D into its current form. This area of study is no longer based solely on material achievements, processes or chemical structures but also contains intangible assets that are difficult to protect for technical or ethical reasons, such as genes, variations and similarities in patient data, information combined from different sources, knowledge of complex biological systems, bio-modeling, simulation and prediction approaches. Moreover, the people responsible for biotechnical innovations are no longer merely chemists, medical doctors or pharmacists: the R&D process involves a network of experts, such as cell and animal biologists, microbiologists, biochemists, bioinformatics specialists, veterinarians, agrologists, engineers and Information and Communication Technology (ICT) experts. These issues highlight the complexity and importance of intellectual capital in today's life science industry.

1.2 Intellectual capital: an overlooked asset?

Research-intensive companies typically operate in fields in which failure is an inherent risk. Examples include established industries, such as drug development, and emerging technology sectors, such as nanotechnology, biotechnology and renewable energy. The government typically focuses on and supports emerging industries based on high-technology because of their growth potential.

The combination of high-intensity R&D and high risks creates a problem for all investors, including both private and public investors. However, the value that is created is primarily in the form of intangible assets, which are not captured in traditional accounting and for which no well-established alternative metrics exist. Consequently, in the case of a company failure, most of the created value added is considered lost. This loss not only complicates the justification of government support policies but also leads to a typical sequence of initial high expectations of the sector, with a subsequent rebound effect of disappointment and hindsight. We claim that the present concept of failure may be profoundly misleading.

Value is created both in successful companies and in failed companies. A significant share of that value is within intangible assets, such as scientific and technological expertise, experienced personnel, formed networks and contacts, and global recognition. Most of a company's created value remains valid even after the company shares become worthless.

In the case of a company failure, the majority of existing research is focused on the residual value of patents and focuses only minimally on the value of the vesting experience of company executives (Agarwal et al. 2009, Keil et al. 2009). The research on vesting experience indicates that success follows success, whereas company executives who have failed with a company have a tendency to fail also with subsequent companies (Gompers et al. 2010), in accordance with the following quote from older literature: “for to the one who has, more will be given” (Mark 70).

There is some empirical evidence that value is indeed created beyond patents and inter-firm knowledge transfer; moreover, such value is destroyed if a company is completely dispersed (Agarwal et al. 2007). If such value could be identified and quantified, then it would have profound implications on the assessment of foregone investments in [failed] high-risk R&D-intensive companies and on the evaluation of re-investments in failing companies.

This study has the following two primary areas of focus:

1. To determine what can be learned from biotech and drug development companies that suffered from financial problems and ultimately failed at the beginning of the 21st century. What were the primary causes of this failure, and could the firms, investors or other stakeholders have handled the situation differently?
2. To determine how intellectual capital developed in accordance with such companies and its fate following business failure.

The core of this study is based on company and investor interviews. However, it should be noted that the cases in this study represent only a small portion of the interesting life science companies that are struggling through the financial riptide.

1.3 Life science industry in 2000–2010

In the beginning of 21st century, there were more than 120 biotechnology companies (including service businesses) in Finland. Although several of the companies were small and strongly science-oriented, the country was ranked as the sixth most important location for biotechnology companies in Europe after the UK, Germany, France, The Netherlands and Sweden (Läh-

teenmäki 2002). The number of people working in the biotech industry in 2000 was estimated to be 4 200, and with pharmaceutical plants included, the total amount was 10 800. Accordingly, the combined turnover of the biotech sector in 2000 was estimated to be close to 700 million euros and was estimated at 1 860 million euros when pharmaceuticals were included (Biotech Finland 2002).

Biotechnology was compared with ICT in that both knowledge-based industries were viewed as the future of Finland:

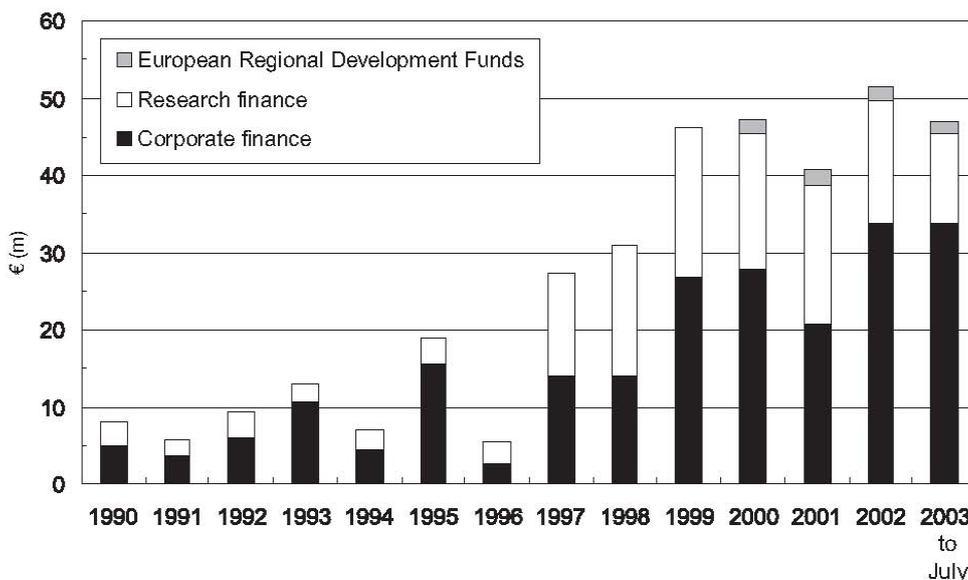
“The overall picture convinced us that Finland has made an admirable start and has a very real chance to become one of the most successful small countries in the world in biotechnology, just as it is a model in the ICT sector.”

(Biotechnology in Finland. Impact of public research funding and strategies for the future. Evaluation report. Publications of the Academy of Finland 11/2002).

The biotechnology sector received strong inputs from the public sector around the millennium, with a peak in 2002 of more than 50 million euros total. Figure 1 shows the public R&D funding of all Finnish biotechnology companies and research institutes guided through Tekes from 1990 to 2003.

The high expectations were not unique to Finland; the dot-com boom of local investors was followed by global biotechnology enthusiasm grounded in significant scientific advancements that were facilitated by the combination of ICT technology with methodological innovations, particularly in gene technology, and fuelled by widely available venture capital and individual

Figure 1 Public funding of all Finnish biotechnology R&D guided through Tekes from 1990 to 2003



Legend: White and gray bars: grants to public research
Black: Funding of company R&D

N.B.: Corporate finance includes all biotechnology companies and is thus not directly comparable with Figure 2.

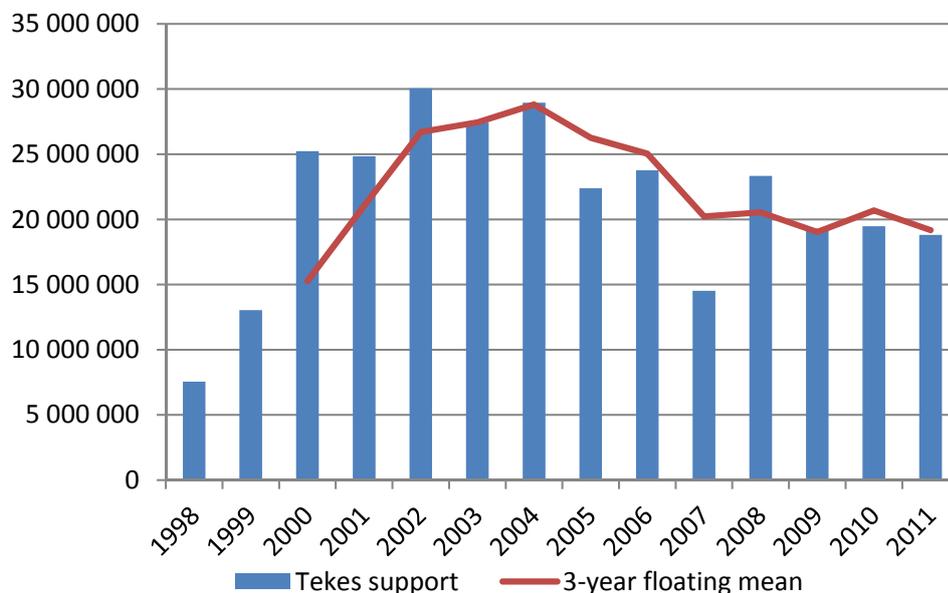
Source: Hermans, Kulvik and Ylä-Anttila, 2005.

speculation in stocks within the New Economy. At the EU level, life sciences and biotechnology were also regarded as among the most promising frontier technologies for upcoming decades. A novel European strategy and action plan was created in 2002, and this plan aimed to reinforce the resource base and the networking of Europe's biotechnology communities with reasonable funding (CEC, 2002).

The biotechnology hype that developed in the 1990s had multifaceted effects on Finnish society. Several biotechnology/medical research centers or technology parks were built in several Finnish university cities¹. In addition, based on the fear that there would be an insufficient number of competent personnel to take care of the growing sector, the amount of life science education available was increased, and a novel biotechnology program was initiated (e.g., in the University of Tampere). By 2007, the number of life science master's degree graduates per year increased from approximately 800 in 1981 to more than 1500, and the current figure is approximately 1200. Moreover, the number of PhDs doubled in twenty years (Unifi 2011; LAL 2011).

Because the biosector turned out to be more complicated than anticipated, the high expectations of investors were followed by ensuing disappointments in a multitude of OECD countries. So also in Finland. For example, during the latter half of the decade, Tekes' investments in small or medium-sized (SME) biotechnology companies decreased as compared to the five year period 2000 to 2004 (Figure 2).

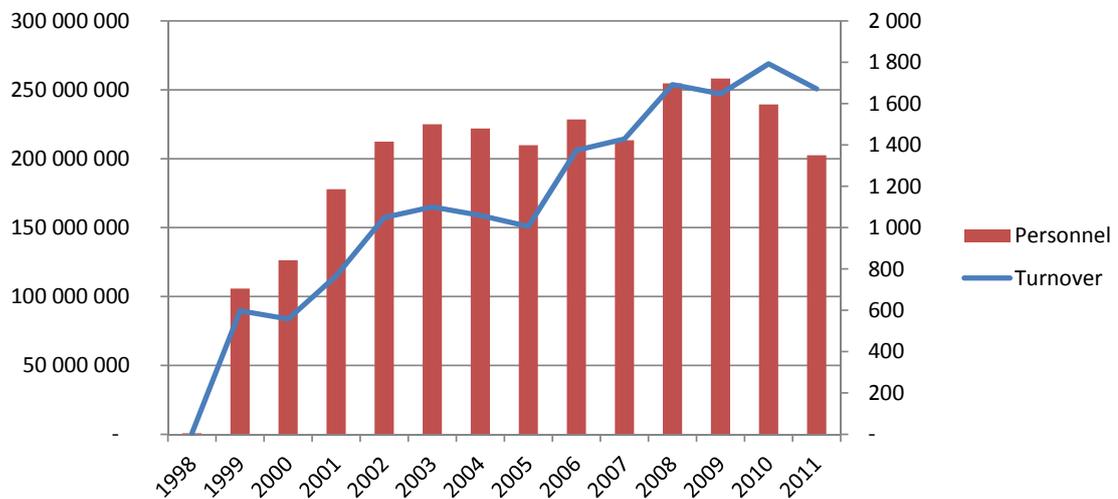
Figure 2 Public support and investments in SME biotechnology companies made by Tekes (€)



Note: Represents public support and investments made in SME companies identified by ETLA as biotechnology companies in surveys from 2004 and 2010; SME data are not directly comparable with all company data in Figure 1. Source: Tekes, Matias Kalm/Etlatiето, and authors.

¹ In hindsight, some of these centres have proven to be important scientific and innovation incubators, whereas other centres have lacked leaseholders and have been operating at an underused level.

Figure 3 Turnover and personnel of Finnish biotechnology SME's between 1998 and 2011



Note: The data are based from a comprehensive set of SME companies identified by ETLA as dedicated biotechnology SME companies; the data are comparable with company data in Figure 2.
Source: Tekes, Matias Kalm/Etlatiето, Mika Pajarinen/Etlatiето, and authors.

The corresponding figures for Finnish SME biotechnology companies' turnover and development of personnel show a somewhat opposite pattern when compared to the public investments (Figure 2): even though the support has stagnated, the business has developed favorably. We can speculate that the biotechnology sector might indeed have gained from the infant industry support (List 1841) provided by Tekes and other governmental bodies.

Finally, an important ratio that describes the innovativeness of a country's life science industries is the number of entrepreneurial life science companies that are defined as small or medium-sized (SME) companies concentrating on the commercialization of modern biotechnology (Tulkki et al. 2001). A recent report from ETLA showed that the number of biotechnology companies in Finland has remained relatively stable during the last decade, but a deeper examination of the dynamics of the industry revealed that the annual exit rate of biotechnology SMEs during the 2004–2010 period was approximately 7%, and the annual entry rate was 8% (Nikulainen et al. 2012). Perhaps surprisingly, these figures conform to the overall annual exit and entry rates of manufacturing companies in Finland, as determined by the OECD in 2010 (Nikulainen et al. 2012).

Forty-three biotechnology or drug development companies disappeared from the Trade Registry as independent entities during the 2004–2010 period (Table 1). Simultaneously, new companies were formed, and approximately half of the companies were able to persist in a fast-paced business environment in which biotechnology hype was followed by the withdrawal of several investors from the sector (see Chapter 4 for details).

The ensuing lack of funding is reflected in the increasing life science unemployment figures, which reached 6.2% in 2009. In certain fields (e.g., biology), the percentage has increased to 7.9%, or nearly twice the amount of unemployed master's graduates found in other sciences

Table 1 Entry and exit in the Finnish biotechnology industry from 2004 to 2010 (SME biotechnology companies as identified by ETLA in surveys from 2004 and 2010)

# of SME companies in 2004	99
Exit between 2004 and 2010	
– Bankruptcy	11
– Not operating	9
– No official data	7
– Sold abroad	7
– Sold/merged in Finland	9
TOTAL EXIT	43
# of SME companies in 2010	107
ENTRY from 2004 to 2010	51 (new or missing from old lists)

Source: Nikulainen et al. 2012.

(4.7%) (LAL 2011). Additionally, the number of unemployed doctors has increased two- to three-fold during the last decade.

However, throughout the first decade of this millennium, Finnish biotechnology companies have regarded Finland's biotechnology assets as being in the form of human capital (Hussi et al. 2006, Kulvik et al. 2012). Despite failed companies, rapidly increasing unemployment rates and significant underperformance from disclosed sales expectations (Nikulainen et al. 2012), biotech industry leaders have remained optimistic with regard to their future (Kulvik et al. 2013). Is there something the numbers do not fully capture?

1.4 Research design

This study was extended to include a total of six companies that were regarded as having “failed” during some stage from a domestic perspective. Failure was determined as any one of the following conditions:

- Significant diminishment of operations, typically indicated by clear reductions in the workforce of the company
- A crisis leading to either insolvency² or cessation of operations
- An unforeseen sale of the company to a foreign party that fails to conform to the company's stated strategy (i.e., failure of its original strategy)

The CEO, the chairman of the board, or other key persons were required to be available for an interview. We chose companies from various biotechnology centers in Finland to avoid an excessively narrow, capital region focused approach. Finally, we wanted to include investor perspectives; hence, we added Sitra and BioFund to the case studies. The data collection was com-

² US counterpart: filing for protection under the US Bankruptcy Code Chapter 11.

pleted through additional interviews and discussions with several international health industry stakeholders, as reflected in the Results and Discussion section.

All Finnish company interviews were conducted face to face from October to December 2011 using separate semi-structured questionnaires for companies and investors. The interviews and discussions with U.S. and European stakeholders were performed informally during the spring and summer of 2012 at the Kellogg School of Management in Illinois, USA. Additional data were collected from a multitude of public sources.

The company-specific material has been compiled into the cases that are presented in Chapters 2 and 3 and is reinforced with more general interviewee comments and data in the Results and Discussion chapter.

The focus has been on “dedicated” biotechnology³ companies, as the line between biotechnology and other fields has become elusive with the development of biotechnologies: a significant number of companies within the food, brewery, cosmetic, drug, and even pulp and paper industries rely on biotechnological applications in their production.

1.5 Definitions

CEO	– Chief Executive Officer
CFO	– Chief Financial Officer
CRO	– Contract Research Organization
GCP	– Good Clinical Practice (standard)
GLP	– Good Laboratory Practice (standard)
GMP	– Good Manufacturing Practice (standard)
cGM	– current Good Manufacturing Practice
ETLA	– Elinkeinoelämän tutkimuslaitos – The Research Institute of the Finnish Economy
FDA	– [US] Food and Drug Administration
FIMEA	– Finnish Medicines Agency (former National Agency of Medicine)
FTE	– Full Time Equivalent (of labor)
IC	– Intellectual Capital
ICT	– Information and Communication Technology
IPO	– Initial Public Offering
IPR	– Intellectual Property Rights
NAM	– The National Agency of Medicine (now the Finnish Medicines Agency, FIMEA)
OECD	– Organization for Economic Cooperation and Development
R&D	– Research and development
SME	– Small or Medium-sized Enterprise ⁴
VC	– Venture Capital[ist]
VTT	– Technical Research Center of Finland

³ Throughout all surveys and reports, we have used the OECD definition of biotechnology: “the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services” (OECD, 2005). For life sciences, we use the following definition: “Any science that deals with living organisms, their life processes, and their interrelationships, as biology, medicine, or ecology” (R.H. Unabridged dictionary, 1987).

⁴ The SMEs were defined according to official definitions of the EU that exclude companies with more than 250 employees. The included companies must also match at least one of the following criteria: annual turnover that is no greater than 50 million euros and a balance sheet total that does not exceed 43 million euros.

2 Company cases

2.1 Carbion Oy

- **Existence as a Finnish-owned private company:** 1999–2002
- **Location:** Helsinki
- **Total employment effect:** ~50 man-years
- **Cumulative sales:** 18 000 €
- **Total funding received:** ~8 million euros
- **Main sources of funding:** Contral Pharma and Tekes
- **Core competence:** Glycobiology
- **Note:** The work of Carbion was continued in BioTie Therapies Oyj and in Glykos Finland Oy

2.1.1 Growth in intellectual capital

Carbion was a small spin-off company operating in Viikki Science Park in Helsinki; the original name, ProseCarb Oy, was later changed to Carbion Oy.

Carbion's story is relatively short, as the company existed for only a couple of years. However, during those years, Carbion created a significant amount of intellectual capital that is still utilized by the Finnish biotechnology sector.

Core technology

The company was founded in 1999 by a group of enthusiastic researchers at Helsinki University who had several years of experience in sugar research and analytical methods of carbohydrate structures using mass spectrophotometry and nuclear magnetic resonance (NMR). The complex carbohydrate structures present in human cells play an important role in a variety of biological events and disorders (e.g., infection, inflammation, fertilization, embryonic development, cancer and metastasis).

Carbion developed a glycobiology-based high-throughput technology platform for the analytics of sugar structures. In addition, the company invented multivalency technology, which significantly increased the number of various bioactive carbohydrates binding to a carrier molecule, thereby decreasing the needed dose in a potential carbohydrate drug. Furthermore, Carbion developed methods to produce carbohydrate libraries for research purposes (BioTie Therapies Stock exchange release 7.6.2002).

Side track options

In addition to various technologies, Carbion developed drugs for bacterial or viral infections, particularly for the eradication of *Helicobacter pylori* and the prevention of *Influenza* infection. An important research topic was the binding of viruses and bacteria to cell membrane structures. Furthermore, given that the sugar structures of cancer cells and corresponding normal cells differ from one another, the company developed cancer diagnostics and cancer drugs based on carbohydrate moieties. Carbion's knowledge base was unique, and only a few companies in the world operated in this sector.

Intellectual Property

Carbion had an aggressive patenting policy to protect the developed carbohydrate applications not only for drug and diagnostic use but also for food-related innovations. Within a few years, Carbion filed eight patent applications, some of which have recently grown into patent families. All patents are currently owned by Glykos Finland Oy.

Cooperation

Carbion's employers focused on research and development while obtaining expertise in administration, finance, legal issues, quality assurance, HRM and clinical trials from its close collaborator and subsequent owner, Contral Pharma. The maximum number of employees in the company was approximately 20 from 2002 to 2003, and 60% of them were at the doctorate level. Carbion also entered into numerous collaborations with various Finnish, Swedish and Dutch research groups, VTT and central hospitals. These collaborations were primarily research based, and the company found collaborators through university networks and from scientific conferences.

2.1.2 Business development

Expansion phase

As mentioned, Carbion Oy was founded in 1999, but during its early years, the company largely focused on securing funding. Venture capitalists were interested in seeking consolidation in sugar research; therefore, various funding scenarios were considered. Carbion's actual operations began in January 2001 when Contral Pharma became the largest owner of Carbion with 50.1% of the shares. Contral Pharma brought needed capital to the company in the form of newly issued shares. In addition, the fusion brought knowledge in both drug and business development to Carbion because Contral Pharma, which began operations in 1997, had conducted clinical trials and had experience with the US Food and Drug Administration (FDA) approvals. Carbion's contribution was that it brought novel products to the pipeline of Contral Pharma, which had previously focused on the development of its leading product, nalmefene, an opioid receptor antagonist used to manage alcohol dependence and impulse control disorders (ICDs).

Carbion's original business idea was to develop experimental drugs, undertake the clinical trials itself through Phase II and then outsource the investigational new drugs to Big Pharma. The costs of these actions were to be covered by contract research services and by the revenues that would be obtained when Contral Pharma's leading product was licensed.

Signs of foundering

Although there was a clear market need for carbohydrate research services, especially abroad, it soon became evident that investors did not want the company to allocate resources to a service business. Therefore, the idea of contract research was suspended, and the company's only revenues of 18 000 euros were received in 2001 from analytical services. No products entered the market during Carbion's existence.

The research projects proceeded well, but financial problems forced the company into novel arrangements. In October 2002, after Contral Pharma was able to raise 15 million euros through a share issue directed toward institutional investors, a further merger with Biotie

Therapies occurred. The new listed company changed its name to BioTie Therapies Oyj (BioTie Therapies annual report 2002). The purpose of the merger was to create a strong and balanced product portfolio, save costs, minimize risks and achieve synergy from shared knowledge and production facilities. At the end of 2002, the novel company had 112 employees, a head office in Turku and subsidiaries in Helsinki and Espoo.

After the merger, Carbion's representation among the leaders of the new company was limited, as none of Carbion's management team was selected to the new management team or to the board of BioTie Therapies Oyj. Carbion's former CEO, Dr. Juhani Saarinen, became a unit leader in the new company. Only one Carbion board member, Mr. Erkki Tenhunen (who was also one of the founders of Conral Pharma), became a director and member of the management team of BioTie Therapies Oyj. However, he served in this position for only one year (BioTie Therapies annual report 2002 and 2003).

Glycobiology remained an important area of focus in the strategy of the new company, with the lead molecules of this sector being bioheparin and modified polysaccharides as VAP-1/SSAO enzyme inhibitors. These innovations originated from BioTie (BioTie Therapies annual report 2002). The Viikki unit continued research on cancer-specific sugar structures and on the use of multivalency technology in carbohydrate-based drug development.

2.1.3 End of independent phase

In 2003, reorganizations throughout the company and prioritization of activities decreased the number of personnel to 55, and less than one-third of the personnel worked at Viikki (BioTie Therapies annual report 2003). In January 2004, BioTie Therapies decided to centralize its operations at Turku, provided notice to 14 employees in Helsinki and closed the Viikki subsidiary in which Carbion had operated (BioTie Therapies annual report 2004).

After the shipwreck

All fixed assets, including equipment and reagents, were transferred to Turku; however, given the terms of the rental agreement, BioTie was required to pay the rent of the Viikki unit until the end of 2004, although there were no longer any activities at the facilities. The previous Carbion staff never moved to Turku; rather, in March 2004, the founders of Carbion established Glykos Oy, a company specializing in carbohydrate research that is still operational.

2.1.4 Current situation

The carbohydrate-related intellectual capital that was originally developed at Helsinki University and extended at Carbion Oy has increased over the years, and it currently enriches the Finnish biotechnology sector in Glykos Oy. This company has experienced positive results from the beginning, and revenues almost exceeded 300 000 euros during the year of its establishment. Income has since steadily increased and was more than 6 million euros in 2011. Income is expected to have increased further in 2012.

Customers of Glykos Oy consist of the leading pharmaceutical and food companies operating globally; approximately 5% of sales are derived from service businesses, and the remainder result from milestones, royalties and FTE payments of research collaboration projects (Tenhunen 2011).

The company uses state-of-the-art technologies for cancer, stem cell and influenza research; for glycosylation of drug proteins; and for developing bioactive food and feed substances. The company has approximately 50 employees and a patent portfolio of more than 40 patents or patent applications. Interestingly, the core team originating from the university has remained together throughout the years, which has been crucial for the preservation of the company's intellectual capital.

2.1.5 Causes and consequences

Carbion Oy is an example of a company that disappeared from the trade register, but its work has remained alive.

There were several reasons for the disappearance of this company, the most important of which were the global problems in life science funding that led to the merger of the three companies in 2002. This merger was unsuccessful from the perspective of Carbion, as it created a situation in which the research focus of the new company was in another direction, the lead molecules invented in old BioTie were prioritized, and there were inadequate resources to continue all of the pre-existing projects of the three companies.

One may argue that because Carbion was not represented in the management of the new company, the importance and possibilities of glycobiology were not brought out clearly enough, and this lack of importance led to decisions made during 2002–2004 that favored the Turku unit and its research. Further development of the Viikki unit and investments in research phase innovations were not in the interest of a listed company: the aim was to increase the short-term value of shares and bring the first product to market⁵.

One of Carbion's weaknesses was the lack of attempts to commercialize its knowledge: the company was fixed to the general idea that the suitable time for out-licensing is after Phase II; thus, the company did not contact possible customers and begin the marketing process at a sufficiently early point. It was also difficult to implement a customer-oriented business strategy in a university spin-off company in which most of the workers were purely scientists with no business background. Carbion could have focused more intensively on the development of products rather than conducting research.

Carbion did not have experience in communicating with investors, and because its knowledge was unique, investors may have lacked the competence to evaluate and understand the potential of novel carbohydrate chemistry. Therefore, financial rounds were challenging, and the reluctance of investors to enter a service business further decreased the possibility that Carbion would generate revenues and thereby remain an independent private company.

The work of Carbion is now being continued at Glykos. However, if Carbion had continued uninterrupted, then the company could have reached an even more significant global position in the carbohydrate chemistry sector. During the slowdown that lasted for some years, other companies benefitted from a competitive advantage. However, despite these drawbacks, Carbion, and later Glykos, showed that bioactive sugars have great potential and a variety of useful applications.

⁵ Subsequently, the lead product nalmeferone was also suspended for a period of time but was ultimately licensed to Lundbeck (Denmark). The product was approved in Europe in Feb 2013 for the reduction of alcohol consumption in adult patients with alcohol dependence.

2.2 Hormos Medical Oy

- **Existence as a Finnish-owned private company:** 1997–2005
- **Location:** Turku
- **Total employment effect:** ~420 man-years
- **Cumulative sales:** 18.75 million euros
- **Total funding received 1997–2005:** ~50 million euros
- **Main investors:** Sitra, BioFund, Tekes, Ilmarinen, Verdandi, Tapiola, Varma, BankInvest, and H&B-Capital
- **Note:** Since May 2005, Hormos Medical has operated as a subsidiary of QuatRx Pharmaceutical

2.2.1 Intellectual capital growth

Hormos Medical was founded in 1997 when Orion Pharma decided to decrease its non-clinical research portfolio and out-licensed some of its ongoing drug discovery projects. During that process, Orion closed its BioCity research laboratory in Turku; therefore, continuing the promising projects in a new organization appeared to be the option with the greatest potential.

The establishment of Hormos Medical coincided with the founding of Juvantia Pharma, which also continued the drug development projects of Orion. Focusing on different knowledge bases in separate companies was considered an asset. Furthermore, the available funding systems did not favor the establishment of companies with excessively wide portfolios of different drug development projects.

The first innovative drug substances originated from Orion, but novel companies never received any benefits or provision from Orion: outsourcing projects were not compatible with Orion's chosen strategy.

The founders of Hormos Medical were two medical specialists with vast experience and a long work history in biomedical research from Famos and Orion and three university professors from the medical faculty. All founders have remained closely connected to the company through the present, and collaboration with academic researchers has been one of the key driving forces and has offered important background support for the company. Risto Lammin-tausta, MD, PhD, served as the CEO of the company as long as it operated as a private Finnish enterprise.

Core technology

Hormos Medical discovered and developed pharmaceutical products for the hormonal prevention and treatment of diseases related to aging, with a core competence in the tissue-specific regulation of estrogen and androgen effects. Hormos Medical focused on selective estrogen receptor modulators (SERMs) and on 17-beta hydroxysteroid dehydrogenase (HSD) enzyme inhibitors. In addition, Hormos Medical developed HMRLignan, which was originally extracted from spruce.

SERM drugs are molecules that modulate the effects of estrogen by binding to the specific cell receptors for this hormone. The lead product that was developed by Hormos is a non-estrogen drug ospemifene (OphenaTM), the original indication of which was osteoporosis. Its develop-

ment began at Orion and continued at Hormos during the 1998–2000 period with two Phase II studies in which good dose-response results and a decrease of bone turnover were observed.

However, the regulatory demands for efficacy verification of osteoporosis drugs became significantly more stringent in the beginning of the 21st century. The product could not be licensed, and the development focus changed in 2003 to the treatment of postmenopausal vaginal mucosa problems. In 2005, the first Phase III study was initiated together with a US company, QuatRx. Subsequently, during that same year, Hormos became a subsidiary of QuatRx Pharmaceuticals (see below). The partners conducted two more phase III studies in which the drug showed statistically highly significant efficacy and was found to be safe and well tolerated (McCall and DeGregorio 2010). Animal models have also shown that ospemifene prevented and treated estrogen-receptor positive mammary gland tumors (Burich RA et al. 2012).

Another important investigational drug discovered by Hormos Medical is fispemifene – a selective estrogen receptor antagonist for the treatment of testosterone deficiency and associated disorders in men. Symptoms of low testosterone include sexual dysfunction, muscle wasting, reduced bone density, lowered energy levels and glucose intolerance. Fispemifene has completed two Phase I clinical studies in Europe and two Phase II clinical studies in the USA, which indicate that total testosterone levels increased by 78% over 28 days of treatment (www.quatrx.com). Animal models suggest that the drug might also be used to treat chronic non-bacterial prostatitis and urinary symptoms.

Sidetrack options

HSD enzyme inhibitors prevent an enhanced estrogen response in certain tissues and offer a novel therapeutic approach with potential applications in treating diseases such as endometriosis, uterine fibroids and breast cancer (www.quatrx.com). The early developmental work of these molecules was performed in collaboration with enzyme and organic chemistry experts in Oulu and Helsinki Universities and subsequently with Solvay Pharmaceutical (Belgium). Solvay signed a three-year research agreement (2003–2005) and paid approximately 2 million euros per year to Hormos for the discovery. The company also planned to conduct clinical trials in the event that a clinical application was found. However, the deal was discontinued after two years because Solvay decided to change its business strategy and eliminate the women's health sector. Hormos/QuatRx licensed the HSD enzyme portfolio in 2006 and agreed to undertake all development and commercialization activities. The first HSD enzyme inhibitor has been ready for the first Phase I study for quite a while and is awaiting an appropriate partner or funding arrangement. Interestingly, the drug concept is new, and no one has thus far conducted clinical trials using this type of approach; therefore, this concept offers a business option with low competition.

A different type of R&D project occurred during the early years of the company, when Hormos and Åbo Akademi collaborated to develop HRMlignan, a highly purified lignan product modified in the human body into enterolactone. Epidemiological studies have indicated that low intake of lignan and low enterolactone serum levels may be associated with increased risk of breast cancer and cardiovascular diseases (<http://www.hmrlignan.com/>). This product obtained new dietary ingredient (NDI) clearance from FDA in 2004, and this clearance allowed HRMlignan™-containing dietary supplements to be marketed in the USA. In 2005, an agreement giving worldwide licensing rights for this dietary supplement was signed between Hor-

mos Nutraceuticals (a subsidiary of Hormos Medical) and Linnea SA, a Swiss company specializing in the manufacture of botanicals extracts and phytochemicals. Hormos received a signing fee of 0.5 million euros; however, the nutraceutical business differed too greatly from drug development. Since then, Hormos has not continued nutraceutical discovery.

Intellectual property

The company adopted an aggressive IPR policy: everything has been patented, including both drug substances and their use. Extensive research programs have provided the company with approximately 50 patent applications and patents, most of which have grown into global patent families (Espacenet database 2012).

Cooperation

The intellectual capital of Hormos Medical has increased significantly during the years, both through collaboration projects and by learning-through-doing processes. The company, first as an independent business and then as a subsidiary after 2005, has had an extensive collaboration network with various Finnish and foreign partners. Hormos operates an organic synthesis laboratory within Oulu University, which is still operating with six employees, and preliminary development projects have been undertaken in collaboration with Turku and Helsinki Universities, with Solvay (Belgium), and with Tess Diagnostics and Pharmaceuticals (CA, USA). Clinical trial expertise using the Good Clinical Practice (GCP) standard was initially developed in-house, but subsequently it was primarily outsourced from contract research organization (CRO) companies, such as CRST and Encorium. Moreover, the good laboratory practice/good manufacturing practice standard (GLP/GMP) laboratories for pharmacokinetics and pharmaceutical development have been developed in-house, but the full-scale manufacturing has been performed by Bayer (former Leiras-Schering) and Orion. In addition, Hormos has participated in three EU projects, thereby creating research relationships with various European countries.

Regulatory and other intangible assets

Hormos Medical's strategy was to develop in-house supporting activities (e.g., quality assurance, legal, finance, and marketing) and to outsource CRO activities and patenting issues. The company has GLP-accredited bioanalytical activities and a GMP status for the analysis and release of pharmaceuticals. These quality assurance systems are audited on a regular basis by the Finnish Medicines Agency (FIMEA).

Hormos Medical has placed special emphasis on educating personnel, especially in technical and regulatory issues, quality assurance and negotiation skills. In addition, the company has offered a training site for several biotechnology students, and approximately one dozen articles, six doctoral theses and six master's theses have been created within the company.

2.2.2 Business development

Expansion phase

Hormos Medical began in BioCity, Turku, and in 2001, the company moved into new PharmaCity facilities and optimistically signed a 10-year rental agreement⁶. The company had more than 10 employees from the beginning, with a maximum of more than 70 employees in 2001–

⁶ PharmaCity required all companies to sign a rental agreement for a minimum of 10 years.

2002. The total employment effect of Hormos Medical has been approximately 420 man-years, with a median of 30 employees throughout fourteen years.

The original business idea of Hormos Medical was to develop new investigational medicines up to Phase II and thereafter out-license them to other parties. The licensing profit received from these more mature products would have been used for novel discovery projects. The company also planned to become listed on the stock market, and it operated as a public company during the period from 2001 to 2005.

The original business model of Hormos changed during the years, and the value of its projects increased through several Phase III clinical trials. However, the company never intended to bring its products to the global market; rather, the company has licensed its products for marketing.

During the first two years of operations, Hormos received venture capital from Sitra and BioFund. In 2000, institutional investors Ilmarinen, Verdandi, Tapiola and Varma joined the owners, and the company was able to raise approximately 10 million euros. The next financing round occurred in 2001, when 18.4 million euros in venture capital was obtained from BankInvest of Denmark, H&B Capital of Sweden, Sitra and BioFund (Heinonen 2009). During these financial rounds, the original ownership of the founders was diluted to a few percentage points.

Tekes funded the company with annual grants and loans currently totaling 20.8 million euros. The loan instrument used by Tekes was a capital loan that has had a significant effect on the future fate of the company. This effect will be discussed subsequently.

Signs of foundering

By the end of 2002, Hormos had conducted two Phase I studies and two Phase II studies with the lead molecules described in the previous sector as well as with an additional drug candidate, finrozole, which targeted urinary symptoms in men. Ospemiphene was prepared to enter Phase III trials, but more funding was needed. However, at the same time, the development of finrozole had to be discontinued because of certain negative effects that were found during the Phase II clinical trial; this situation created an atmosphere of suspicion toward novel investments (Heinonen 2009). In 2003, the company began to reduce its personnel and place the other late-stage projects on hold, except for ospemiphene.

In addition to local and Nordic investors, Hormos attempted to obtain funding from foreign venture capitalists. Investors such as Merlin (UK) and Atlas Ventures (US) were interested in investing more than 20 million euros, but the negotiations failed because of the unreasonable terms required by the new investors.⁷ Foreign investors were also interested in merging Hormos Medical and Juvantia Pharma, but that idea became obsolete with the failure of the financing round.

2.2.3 End of independent phase

In 2004, Hormos began negotiations with QuatRx (US) with regard to the out-licensing of certain drug candidates; however, the negotiations ended in a merger in 2005 upon Hormos' initiation. The company had realized that in the difficult fundraising environment, consolidation with the US-based company offered the best possibility to continue operations and, in

⁷ Detailed information cannot be disclosed.

particular, to offer an exit opportunity for its investors. QuatRx had recently closed 70 M USD in private equity financing, and a plan was created to pursue an IPO on NASDAQ shortly after the transaction.

Through the transaction, all Hormos shares were sold to QuatRx, which provided its own shares as payment to the owners of Hormos; all of the shares have remained at the new company up to the present. The CEO of QuatRx became the CEO of the combined company, QuatRx Pharmaceuticals, and the former CEO of Hormos, Dr. Risto Lammintausta, joined the senior management team at QuatRx. The Tekes capital loans (20.8 million euros) remained at the Finnish subsidiary called Hormos Medical Ltd under the following conditions: the IPR must remain in Finland, future revenues from the Finnish IPR must be shared in proportion to the cumulative investments from both sides, and the subsidiary must be financed only with own capital instruments. As a final outcome from ospemifene revenue based on this agreement, the Finnish subsidiary would be entitled to 60% of the future cash flow from ospemifene.

After the shipwreck

The novel company was filed on NASDAQ in 2006, but because of downturn in the biotechnology sector, the company never undertook an initial public offering (IPO). Rather, the company collected 44 M USD from old investors and Venrock (US), Catella Healthcare (Sweden) and Hercules Technology Growth Capital (US). The new management wanted to use these resources to continue the commercialization of ospemifene and fispemiphene, and the rights to HSD enzyme inhibitors were repurchased from Solvay. Two additional Phase III studies have been conducted for ospemifene to increase its value.

After the merger, the infrastructure of Hormos has been gradually decommissioned. Because the US headquarters has managed the legal issues, business development and marketing, the employees of these operations departed from the Finnish subsidiary. The CFO of Hormos also exited after a transition period of a few years. The amount of discovery that occurred in Turku has decreased from the most active years, and some of the former Hormos scientists are currently working for other companies, such as VTT and Orion.

All equipment and facilities remained in Turku, but additional problems were caused by the long rental agreement with the owner of PharmaCity: the Finnish subsidiary needed less space, but disrupting the 10-year leasing agreement was not an option. As a result, Hormos/QuatRx was forced to rent part of the facilities to a third party for a significant part of the leasing period, which ended in November 2011.

The merger had no effect on customer relationships. The agreement with Solvay continued until 2006, and Hormos signed a licensing agreement with Linnea shortly after the merger. The American owners did not want any changes to the outsourcing practices of Hormos.

2.2.4 Current situation

Since May 2005, Hormos Medical Oy has operated as a subsidiary and as the main entity of QuatRx Pharmaceuticals. The company's headquarters is located in Ann Arbor, Michigan, and the Turku subsidiary operates as a discovery and non-clinical research unit. The previous infrastructure of Hormos Medical, with its various in-house operations, has been replaced by a more virtual business model utilizing outsourcing and having a total of only 10 to 20 perma-

ment employees in Turku and Oulu. After the merger, Hormos has received approximately 10 million euros in funding annually from the parent company, for a total of more than 50 million euros in investments from the US.

In 2009, QuatRX Pharmaceutical Company disclosed the excellent results of ospemifene's Phase III clinical trials, and in March 2010, the company entered into a licensing agreement with Shionogi & Company (Japan) for the further development and global marketing of ospemifene⁸. According to this agreement, QuatRx received 25 million USD in upfront payments and is eligible to receive more than 100 million USD in development and regulatory milestone payments; the upfront payment share of the Turku unit was 12 million euros. In addition, QuatRx will receive milestone payments for each marketing approval outside of the US as well as sales milestones and royalties on global sales of the product⁹. It is estimated that the approximately 100 million USD invested in the drug will be repaid ten-fold within the following ten years.

Recently, the VC investor owners of QuatRx decided that all actions will be focused on obtaining marketing approval for ospemifene, and the development of other products in the pipeline were shelved. Indeed, ospemifene was approved by FDA in February 2013 for the treatment of dyspareunia in postmenopausal women (Shionogi 2013).

Hormos has announced – with the permission of QuatRx – that it wants to separate from the parent company and continue drug discovery alone. Hormos Medical is currently seeking capital investments of 6–7 million euros to contribute to the progress of the novel HSD inhibitor for clinical studies that aim to aromatase-inhibitor -resistant breast cancer and endometriosis as well as to ensure progress for fispemifene to Phase IIb in erectile dysfunction with hypogonadism¹⁰.

2.2.5 Causes and consequences

The greatest problem of Hormos Medical has been insufficient funding and the underdeveloped Finnish VC system model. Domestic VCs are small, and their total capital has been inadequate to cover long-term investments and additional financing rounds.

However, Hormos Medical is a positive example of a company that has managed to sustain its intellectual capital and operations in Finland despite its ownership having moved not only across the border but also across the ocean. An extensive research period of more than a decade has contributed to the vesting of unique knowledge of age-related hormone therapies in Finland. For Hormos, the dedication and high quality of Finnish scientists, in addition to the existing local collaboration networks that were important in the early discovery phase of drug development, have been regarded as elements that are impossible to transfer to other locations.

Tekes has supported Hormos with significant capital loans, which is essentially a unique Finnish funding support instrument. Capital loans provided bargaining power to the Finnish party during the merger. If the loans had been normal loans, then the acquirer would have fully

⁸ The market value of Qphena is currently estimated at 1 billion USD.

⁹ <http://www.businessurku.fi/bt/fi/cms.nsf/PFBD/578F9DC059A0F8FDC22576DC0028A42A>

¹⁰ <http://www.b2match.eu/healthbio2011/participants/>

discounted them from the valuation of Hormos, and the new owner could have had an incentive to repay them and transfer all IPRs to the US. Because they were capital loans, they were considered attractive funding instruments, and the financial situation of the company did not allow them to be repaid. Therefore, the foreign party agreed to ensure that the IPRs remain in Finland and to sustain the Turku unit. The concern today is that the capital loan instrument is no longer actively used at Tekes. One could argue that Tekes should reconsider using this instrument, particularly when there is an increased risk that intellectual capital may leak abroad (for further discussion, see section 4.2, The Role of Public Funding).

Hormos has shown how flexibility in operations can assist a company in surviving during difficult situations. Because of the negative effects of estrogen replacement therapy on breast cancer that were revealed in a large US study, Hormos decided to focus on non-estrogen therapy and changed the indication for its lead molecule when the efficacy requirements for the old indication became overwhelming. Hormos halted certain sidetrack projects to focus its resources, despite positive reports from one of the projects. In addition, the company management has adapted to the new owner and its novel business culture. Currently, the original company appears to be willing to change its business model again.¹¹

Hormos Medical was established at a time when the biotechnology sector was new and the hype was at its peak. The company began fearlessly and, in hindsight, used its money too optimistically: obtaining new facilities with a long rental agreement, developing most operations in-house, hiring tens of employees initially, and having several projects simultaneously in clinical trials or in preclinical testing. However, the company has displayed an interesting learning curve and currently operates in a cost-effective manner by relying on outsourcing and a virtual business model.

Hormos has been an important player in the Finnish pharmaceutical sector as a flagship company that has shown other companies how to develop a close relationship with foreign owners while sustaining its knowledge base in Finland. In addition, Hormos has increased the trust and credibility of the Finnish pharmaceutical sector by showing that drugs can be discovered and developed within the country. The company has been an important employer in the Turku region and has created research networks that have also been regarded as beneficial for the academic world. Hormos Medical has been the first customer of several Finnish CRO companies and has assisted them in implementing their business strategies. Finally, the innovations of Hormos could provide relief worldwide to elderly patients who suffer from symptoms caused by hormonal dysfunction.

¹¹ <http://www.b2match.eu/healthbio2011/participants/8>

2.3 Inion Oy

- **Existence as a Finnish-owned private company:** 1999–2010
- **Location:** Tampere
- **Total employment effect:** ~600 man-years
- **Cumulative sales:** ~38 million euros
- **Total funding received:** ~26 million euros + capital raised on the London Stock Exchange
- **Main sources of funding:** Tekes, Bank von Ernst, SwedStar, BioFund, Capman, Healthcap, POD Holding, and Finnvera
- **Core competence:** Biodegradable implants for surgical needs
- **Note:** Listed on the London Stock Exchange from 2004 to 2009

2.3.1 Intellectual capital growth

Inion Oy is a medical device company operating in Tampere that focuses on the development and commercialization of innovative biodegradable and bioactive implants for the orthopedic, dental and craniofacial surgery markets. The core competence of the company is based on years of biomaterial research and process technology as well as on top-level orthopedics and engineering expertise.

Core technology

The Inion family of biodegradable polymers includes more than 40 different co-polymer recipes with a proprietary blend of L-lactic acid, D-lactic acid, polyglycolide and trimethylene carbonate (TMC). All Inion polymers are gradually degraded in the body into carbon dioxide and water; this bioresorption occurs within two to four years.

Several biomaterial companies use only one material for all of their implants. In contrast, Inion differentiates itself through its capability and expertise in combining several raw materials in different ratios to develop implants with optimal strength, toughness and degradation profiles that meet their specific clinical requirements (www.inion.fi). In addition, Inion has placed special emphasis on developing a manufacturing process for industrial-scale production. Inion products have been used for over 10 years in more than 150 000 patients with good clinical outcomes.

Sidetrack options

In addition to blended polymers, Inion has developed bone graft substitutes that are made from degradable bioactive glass, which forms a silica gel and calcium phosphate layer in the body. This layer provides scaffolding for new bone tissue to be formed, and the substitute is gradually replaced with new bone within six months. This guided tissue and bone regeneration has created a new and interesting line in the company's product portfolio.

Intellectual property

According to the company's patenting strategy, Inion has filed all of its innovations during an early stage of research and development, which has led to more than 20 patent applications for which a patent has been granted. Inion has expanded some of the patents into patent families with global coverage and has allowed others to expire. The company has a globally protected trademark for certain devices.

Cooperation

Inion increased its expertise in collaboration projects with Tampere University of Technology, the University of Zürich and the Midwest Orthopedic Research Foundation. In addition, Inion established a research unit in Cambridge in which the bioactivity of certain materials was tested. Although the UK unit operated for only one year, it was strategically important during and after the company's decision to go public on the London Stock Exchange. Inion also developed novel bioactive substances, some of which were out-licensed.

The company has also been engaged in a close relationship with the city of Tampere and the University of Tampere, which have offered both scientific and business development advice and support.

Regulatory and other intangible assets

In 2001, Inion managed to obtain a clean room certification and FDA regulatory clearance for the first device. Since that time, EU and US authorities have completed regular audits of the company to ensure that its quality management system is effectively implemented and its procedures are effectively addressed by the management system (www.inion.fi).

Inion products won two remarkable innovation awards in 2004 and 2005, The Wall Street Journal's Global Technology Innovation Awards and the Frost & Sullivan Technology Innovation of the Year Award, respectively.

The company also increased the expertise of its personnel through targeted training in regulatory issues, quality assurance, clinical issues, and corporate governance. Furthermore, knowledge in international business management was adopted (e.g., from Fintra and Finpro).

2.3.2 Business development

Inion was founded in 1999 by a group of experienced orthopedic surgeons and engineers who previously worked for Bionx Implants. Auvo Kaikkonen, MD, PhD, became the long-term CEO and leading figure of the company. The group possessed a deep understanding of biomaterial research and manufacturing processes as well as quality and regulatory issues related to medical devices. Inion's vision was to develop more stringent and adaptable materials by blending various biodegradable polymers to streamline the R&D processes and to manufacture products on a large scale. The company brought the first products to global markets in 2001 and since then has received clearance through the FDA 510 (k) (premarket notification) process for one to seven new applications each year, allowing the devices to be introduced into commercial distribution for the first time (FDA 510 (k) database).

The company's business strategy involved outsourcing most of its operations, "except the ones others can't do" (interviewee). The R&D and manufacturing of biomaterials, marketing, quality, and regulatory issues remained in-house, but instrumentation was outsourced. Inion operated in global markets; only a small portion of its sales came from Finland.

Expansion phase

Inion began in an old industry hall, but in the summer of 2001, the company leased completely new facilities from Tampereen Teollisuuskiinteistöt Oy (ultimately merged with Technopolis),

which were close to Tampere University Hospital and Medical Campus. These 4,500 square meter facilities housed headquarters, a state-of-the-art manufacturing unit, a laboratory and a Class 10 000 (ISO 7) clean room. Various operations (e.g., product testing as well as mechanical, thermal and chemical analyses of materials) were conducted in Inion's specially equipped R&D testing laboratory at this site (www.inion.com). According to the leasing agreement, Inion had the option to buy the premises at the end of the 10-year leasing period.

As previously mentioned, the company operated a research unit in Cambridge, UK. In the beginning of the 21st century, the company also established an office in Oklahoma City, Oklahoma, which was later moved to Weston, Florida. The company had more than 120 personnel working globally, and the total employment effect of the company has amounted to more than 600 working years.

Because distributors in general, especially in the USA, take a considerable portion of the sales, the company wanted to engage in direct sales to hospitals in the UK and the US. This task seemed viable, particularly because the company had global sales experts on its board. Special sales teams were placed in these countries, but penetration into a foreign market without a local network proved too complicated; therefore, Inion decided to outsource distribution. In 2004, Inion entered into an agreement with Stryker Corporation, a global distributor of orthopedic products, through which Stryker brought Inion's products to North American and key European markets. Inion entered into other international distribution agreements for certain products with local enterprises, such as Citagenix in Canada and Aesculap in Central Europe.

As previously noted, Inion was listed in 2004 on the London Stock Exchange. The listing was successful, and the company raised more than 40 million euros in capital.

Signs of foundering

The international distribution agreements were a positive signal and assisted Inion in securing more venture funding between 2001 and 2004. However, these agreements brought only a temporal improvement to the global sales of orthopedic devices, and the increase in sales was lower than expected. In the case of Stryker, the biodegradable implants with small plates, screws, pins, and membranes may have been at a disadvantage relative to the more expensive medical systems and solutions that the company also sold (www.stryker.com). In addition, medical opinion leaders required clinical evidence and proof of concept of the products, and at the time of market entry, Inion did not have sufficient data available, which also hampered market penetration. The Stryker agreement was terminated after a few years of collaboration.

Operating as a public company also brought negative side effects to Inion. For example, the necessity for publicly disclosed financial information, increased administration expenses, and fluctuating equity market conditions prevented the company from securing a sufficient and stable level of funding. Annual sales of the company varied between 5 million euros and 7 million euros during the 2004–2008 period, and this amount was insufficient to cover all operational costs from the significant infrastructure and expensive clinical trials. Consequently, broad strategic and organizational changes were made within the company. In 2007, the former CEO became the chief scientific officer, and a new foreign leader with significant commercial experience in the medical devices sector (from Johnson & Johnson) was nominated.

The company focused all of its activities on generating sales in key markets, and manufacturing and R&D were suspended. The company continued discussions with several parties in relation to other strategic transactions or the divestment of certain assets to raise additional funds (Inion Oy, Interim Management Statement, May 2009). The company also decided to cancel the admission of its shares onto the London Stock Exchange in the summer of 2009.

2.3.3 End of independent phase

Despite the extensive efforts to increase the profitability of Inion, the globally challenging period in business during the 2009–2010 period caused the company to file for bankruptcy in May 2010. The decision to file for bankruptcy was voluntary, and the idea was to find a new owner that could acquire the entire company and continue the commercialization of Finnish biomaterial expertise.

The bankruptcy estate of Inion, operating under the name Noini, received ten interesting offers. Ultimately, the entire company, including the sales company in the USA and the premises in Tampere owned by Techopolis, were sold to a Chinese company, Naton Medical Group, which had previously operated as an Inion distributor in the Asian markets. On December 31, 2010, Inion Oy began operating as a subsidiary of Naton Medical Finland Oy, and in March 2011, the company announced that it would resume full operations.

After the shipwreck

During the bankruptcy period, Noini managed to retain most of its intellectual capital in-house: despite the difficult situation, both manufacturing and quality assurance units continued to operate, and most of the old customers and distributors demonstrated their loyalty to Inion. The company continued operation in the same facilities in Tampere.

In addition, although there were only twelve key persons at the company during the worst period, a significant number of the old employees returned, and R&D activities restarted. Some of the key persons have entered new careers elsewhere, and one new biomaterial company has been founded by former Inion experts.

2.3.4 Current situation

Inion's current owner, Naton Medical Group, was established in 1995 and is China's leading orthopedic organization. Naton operates primarily in the domestic markets as a manufacturer of joint, spine, trauma, and dental implants at six different sites in China. Naton has experienced strong growth and currently consists of a group of companies with more than 2,500 global employees in R&D, manufacturing, private hospital servicing, consulting servicing, and other functions. Through its acquisition of Inion, Naton increased its presence in the global markets and gained access to products that are compliant with Western standards and regulations. As for Inion, the company is now able to enter the most rapidly growing market in the world, and a novel marketing approval is currently being processed by Chinese authorities. Current estimates for annual sales at Inion are approximately 3–4 M €, and craniomaxillofacial surgery is its most prominent business sector.

As of autumn 2011, Inion employed approximately thirty people, and the company has indicated that it will recruit additional employees in the near future. All employees at Tampere

are Finnish, but some Chinese workers have visited the Finnish subsidiary for certain periods ranging from a couple of week to a few months. Currently, the US office has five employees.

Collaboration with the parent company occurs at several levels. The new owner has already made investments in Finland and intends to undertake further investments in the future (e.g., to increase production capacity). Although the difficult years and the change in ownership have delayed R&D processes, the company has been able to bring to market approximately one new product every year under the new management.

The company's Finnish origin is a competitive sales argument in Asia and South America, and Inion products that are developed and manufactured in Finland do not compete with local products. Inion's intellectual capital in regulatory and quality assurance issues has ensured that the main operations have remained in Finland. Inion's biomaterial research, with its high standards and 25-year roots in the Tampere region, as well as the Finnish biomaterial cluster collaboration, are intended to create a constant flow of novel innovations that ensure the continuance of Finnish R&D units.

2.3.5 Causes and consequences

A retrospective analysis of the Inion case reveals several issues that have had significant effects on the success of the company.

Although Inion possessed volumes of evidence on the characteristics and behavior of the biomaterials in general and from certain clinical trials, the opinion leaders needed clinical evidence for each particular screw, pin, and device. The company was not prepared for this need and was late in collecting these data; furthermore, the process was time consuming and expensive given its large portfolio of many different products. Early proof-of-concept actions are crucial to success in clinical settings.

Inion developed products for orthopedics, craniomaxillofacial (CMF) and spinal surgery and surgical dental treatments. As previously mentioned, several product lines needed their own clinical evidence as well as their own marketing and distribution perspective. Therefore, focusing on fewer products in the beginning could have been beneficial in several aspects and could have assisted in launching the lead products in a more efficient manner. Portfolio size has also been problematic for other biotech and drug development companies, and this issue is discussed in section 4.

Selecting business partners, such as distributors, is complicated, and caution should be exercised when negotiating the exclusivity of a partner's rights. If old business partners are replaced by new ones, they may be considered permanently unavailable, as the process of reestablishing lost relationships is extremely difficult. The size and global coverage of a business partner should not be the only criterion in its selection; in fact, motivation is at least as important.

During the biotechnology hype period, promises and expectations in the entire sector were often unrealistic (Nikulainen et al. 2012). Inion investors in Finland also created pressure to quickly bring products to market and to constantly increase sales, as their capacity for risk was relatively limited. Additional time to properly concentrate on creating clinical evidence and

launching new products could have yielded higher long-term profits at the cost of more immediate sales.

Despite the drawbacks observed during the life of the company, Inion has been one of the pioneers in the Finnish biomaterial industry and, as such, has paved the path for the future commercialization of innovations in this sector. The company has been one of the few Finnish biotechnology companies listed on the stock market and has been an important link between the Tampere University of Technology and medical device markets in terms of bringing excellent Finnish research into the global consciousness. Furthermore, Inion has created confidence in Finnish expertise and quality and has introduced novel treatment options to thousands of surgeons worldwide.

Regionally, Inion has been an important factor in strengthening Tampere's biomaterial expertise. The company has been an important employer with significant direct and indirect employment effects on engineers, life science specialists, quality and regulatory experts, marketing and administrative personnel, students, and other individuals. Furthermore, the Inion brand and Tampere are now well known among biomaterial industry stakeholders who will guide the entrance of future novel innovations to the market.

2.4 Ipsat Therapies Oy

- **Existence as a Finnish-owned private company:** 1998–2010
- **Location:** Helsinki
- **Total employment effect:** ~200 man-years
- **Cumulative sales:** None
- **Total funding received:** ~30 million euros
- **Main sources of funding:** Tekes, Sitra, BioFund, Varma, and Innovations Kapital
- **Core competence:** Intestinal protection system in antibiotic treatment
- **Note:** Development of lead product up to Phase II

2.4.1 Intellectual capital growth

Ipsat Therapies Oy was established in 1998 to commercialize the concept of using beta-lactamase enzyme for the inactivation of beta-lactams, which represent approximately 50% of the most common antibiotics. The beta-lactamase enzyme is normally produced by resistant bacteria to protect against attack by antibiotics. Resistance to beta-lactams has spread widely because of the abundant use of these antibiotics in recent decades. Indeed, antibiotic resistance is a well-known clinical problem in human and veterinary medicine, particularly among the elderly, immunosuppressed patients, and persons with chronic antibiotic treatment. Meanwhile, hundreds of different beta-lactamases that are responsible for this resistance have been purified and characterized. Because the use of antimicrobials has not declined and additionally because antimicrobial resistance has become part of everyday life, new approaches are urgently required to solve these medical problems.

The intestinal microbiota of humans is a complex bacterial community that plays an important role in human health, for example, by stimulating the immune response system, aiding in the digestion of food, and preventing the overgrowth of potential pathogen bacteria. Antimicrobial agents, such as beta-lactams, are known to have an effect on normal microbiota. The efficacy of antimicrobial agents to promote changes in normal intestinal microbiota is associated with several factors, including drug dosage and the role of administration as well as the pharmacokinetics/dynamics and properties of antibiotics. Although the intestinal microbiota have a tendency to revert to normal after the completion of antibiotic treatment, long-term persistence of selected resistant commensal bacteria has been reported. Such persistence and the exchange of antibiotic resistance genes make the commensal microbiota a putative reservoir of antibiotic resistance genes.

The use of beta-lactamase to prevent the harmful side effects of antibiotics was patented in Finland in 1994 by an innovative scientist who subsequently became one of Ipsat's founders. However, the actual research and development of beta-lactamase did not actually begin until the visionary life science experts Dr. Kai Lindevall and Dr. Lauri Jalkanen realized its market potential and the possibility of developing and producing it in the clean facilities of the National Public Health Institute (KTL, currently THL), which had recently closed down its vaccine production. Consequently, the company began in the premises of KTL and shortly thereafter earned its name, which describes its core competence: Intestinal Protection System in Antibiotic Treatment (IPSAT). The company moved to new facilities in Viikki Science Park in 2002.

Core technology

Certain parentally administered beta-lactams (such as ampicillin, ceftriaxone, cefoperazone, and piperacillin) are in part eliminated through biliary excretion into the proximal part of the small intestine (duodenum). Residual unabsorbed beta-lactams in the intestinal tract may cause an undesirable effect on the ecological balance of normal intestinal microbiota, resulting in diarrhea, overgrowth of pathogenic bacteria and fungi, and the selection of antibiotic-resistance strains among both normal intestinal microbiota and potential pathogen bacteria.

Ipsat Therapies developed bioengineered enzymes that are capable of breaking down excess antibiotics in the intestines; these enzymes were packed in coated pellets filled in hard gelatin capsules that were originally developed in Germany. The capsules dissolved rapidly in the stomach, releasing coated drug pellets that mixed well with digested food and were transported to the upper part of the intestinal tract. There, in the lower pH, the enteric resistant outer layer of pellets composed of methacrylic acid copolymer and triethyl citrate gradually degraded to release the active enzymes. This gastro-resistant pH-dependent Ipsat P1A delivery system was chosen for its several beneficial characteristics, including the protection of the drug substance in acidic conditions and enzymatic degradation in the stomach.

During the early years of the company (2001–2002), an important decision with far-reaching consequences had to be made: the selection of a lead molecule and target. The scientific advisory board recommended that an enzyme with a broad range of activity against different types of beta-lactam antibiotics should be chosen, but the company's board decided to continue with the enzyme P1A, which had already been in development for a few years.

Sidetrack options

The company's first drug candidate, P1A, was active only against certain penicillin types of beta-lactams. However, the company also had second-generation products in the pipeline, such as metallo-beta-lactamases and genetically modified P1A derivatives, which showed more broad-range efficacies. In addition, the company developed novel oral dosage formulations for orally administered beta-lactams.

In addition to the delivery system of P1A, Ipsat developed cellular production and purification processes for protein drugs. In contrast with industrial enzymes, therapeutically useful enzymes are required in relatively tiny amounts but at high degrees of purity and specificity. The choice of an appropriate host and suitable production conditions is crucial for the downstream processing of a pharmaceutical recombinant protein.

An auxotrophic, asporogenic *Bacillus subtilis* strain was chosen as host for the production of pharmaceutical beta-lactamase because of its various advantageous characteristics. *Bacillus subtilis* has a high secretory capacity to produce target protein directly into the extracellular medium, which simplifies downstream processing. Moreover, in contrast with many intracellular production systems, extracellular products are also expected to be folded correctly. In addition, *Bacillus subtilis* does not produce known toxins or virulence factors, and it is applicable for large-scale production at high densities, which is in part favored by the cost-effective manufacturing process of a drug product. Moreover, given the high capacity to produce various cell wall and extracellular proteases, the *Bacillus* production system can be regarded as a first-level screen for selection protease-resistant recombinant beta-lactamase.

Intellectual Property

Because the beta-lactamase used for development was cloned from a wild-type bacterium and because the patent of the expression vector used for the production of proteins in *Bacillus subtilis* had expired, Ipsat Therapies did not need to invest in in-licensing commercial rights. Rather, the company developed the production organism in a less hazardous and environmentally friendly direction by inhibiting the formation of spores and growth outside of culture media, which formed the core of its own initial patent. Ipsat entered into a close collaboration with Finnzymes, a company that had received the modified *Bacillus* strain that produced the enzyme, and who had also developed a purification method and a novel product for inhibiting resistance in cows treated with antibiotics against mastitis. Therefore, the original innovation expanded to a novel sector – the food industry. Finnzymes also prepared the first batches of the product for Ipsat, and KTL prepared the following lab-scale batches. The pilot-scale production was subsequently outsourced to Medipolis GMP in Oulu.

The company filed four patent applications, and a Finnish patent was issued to all of them during the lifetime of the company. Patent coverage in various other countries, including the USA, Poland, Australia, the UK, and Spain, was granted to some of the original Finnish patents. As late as August 2011, a US patent was issued to one original Finnish patent, even when the patent was already owned by a foreign party (see section 2.3.3), indicating that the IPR is still viable and fostered, although by unrelated entities.

Cooperation

The intellectual capital of Ipsat Therapies increased significantly over the years: the company developed patented production process and purification systems; hired animal physiology specialists capable of conducting important proof-of-concept studies; and entered into close collaboration with scientists at Helsinki University, Turku University, and Helsinki University Central Hospital in the fields of animal physiology, microbiology and infectious diseases. In these studies, Ipsat determined the optimal dose and exact time point for P1A administration to achieve the maximal protection effect in the gut. The company also collaborated with VTT in fermentation studies, with various clinical laboratories related to quality control issues and with research groups in the USA, Spain, and Israel. These international connections contributed novel methods for analyzing the effect of beta-lactamase, novel applications for the product in cattle, scientific publications, and important international recognition.

Regulatory and other intangible assets

Ipsat's expertise also increased when professionals with expertise in clinical trials, quality assurance, and regulatory issues joined the company. In 2006, the company employed its highest number of people (35). Moreover, Ipsat also employed several project workers in the academic sector during its existence.

Ipsat was audited by the National Agency of Medicine (currently Fimea), and the company received a medicinal product manufacturer certificate in 2001. The company also gained extensive experience in regulatory issues when it applied for permission for clinical trials from various national agencies of medicine.

2.4.2 Business development

The business strategy of the company was to show the proof of concept of the beta-lactamase enzyme, conduct the Phase I study and then sell or license the product to a pharmaceutical company. At some point, the company even planned to become a new, fully integrated Finnish pharmaceutical company. The market potential of the company's products appeared promising, and the products encountered no competition in the area of antibiotic treatment protection.

Expansion phase

For several years, processes proceeded smoothly: preclinical studies showed that Ipsat's P1A product was able to inactivate certain penicillin antibiotics in the jejunum of animals and was found to have no effect on the serum level of the drug (Harmoinen 2004). P1A treatment was also shown to prevent the colonization of human pathogens, such as *Clostridium difficile* and VRE strains, in the gut of mice during beta-lactam therapy (Stiefel 2008).

The product was also tested in a phase I clinical trial in France, in a phase IIa trial in Estonia, and in a phase IIb trial in Ukraine in which P1A demonstrated efficacy in the gastrointestinal tract of both healthy volunteers and hospitalized patients (Pitout 2009, Tarkkanen 2009). Ipsat P1A was also well tolerated.

Signs of foundering

Ipsat Therapies began licensing negotiations in 2003 with several companies, including Roche, J&J, and Wyeth, and continued the process for several years. Despite the excellent scientific results and successful due diligence of the company, pharmaceutical companies were skeptical about the product. The quality of the clinical studies that were conducted in Ukraine did not fulfill FDA requirements, and the negotiation partners requested that Phase II should be conducted in a regulatory-compliant manner.

Moreover, the endpoints of the studies were not clearly defined. The phase I safety study was conducted without any endpoints, and the Phase II studies used changes in gastrointestinal microflora and emergence of bacterial resistance as efficacy markers. Although these markers are important for patients, they did not fulfill the criteria that had been established for an investigational drug, which is to cure or prevent a disease or to alleviate symptoms. The frequency of beneficial effects was also questionable because the severe adverse effects that have been observed with penicillin-type beta-lactams are rare, as revealed by a search of the literature that was conducted only at this late point. The pharmaceutical companies were more interested in the broad-efficacy candidates in the pipeline than in P1A; Ipsat was asked to "come back when you have some results".

Another important issue also decreased the marketing potential of P1A: because the use of Ipsat technology in medicinal products was patented in 1994, the core patent would expire in November 2014, creating additional pressure to accelerate the development process. However, if Ipsat P1A was to be approved in the USA before November 2014, then five additional years of protection could be secured.

The unsuccessful licensing negotiations fueled strategic changes at Ipsat. Because the active substance of the product was not absorbed into the blood, Ipsat considered alternate means of bringing the product to market as a medical device or supplement rather than as a drug, especially because a similar type of cancer drug had recently received status as a medical device. Moreover, the possibility of limiting the testing of the drug to intensive care unit patients prone to severe infections was discussed. However, a new P1A Phase II study was planned based on the clinical endpoint requirements of the FDA. The new clinical trial was to be conducted in Spain, and it was designed by consultants from the UK. Foreign outsourced consulting was used to improve and polish other operations of the company. The board approved the plan in late 2007.

To finance the new clinical trial, Ipsat directed an option loan of 8.5 million euros to old investors. The loan was subscribed in full, but Tekes declined Ipsat's request for an additional 5.9 million euros according to its principle of not funding repeated clinical trials. During 2008–2009, efforts were aimed at finding a new external investor, and negotiations with venture capitalists from France, Denmark, Sweden, and Switzerland were conducted; however, securing funding was impossible because of the collapsed markets and the global economic recession. Efforts to find a collaborator for a joint deal also failed.

Simultaneously, the company confronted manufacturing problems. In the spring of 2008, Medipolis GMP, which had recently been acquired by an Indian pharmaceutical company, announced that it was no longer engaging in contract manufacturing, and Ipsat needed to find a new manufacturer. After a careful selection process, one of the world's leading suppliers of bioproducts, Lonza in Switzerland, was chosen for this task. However, because Lonza operates at a larger scale, the technology transfer also included 10-fold upscaling of the production process. This upscaling became problematic: the first batches were produced in low yields and did not fulfill conformity requirements.

2.4.3 End of independent phase

The establishment of the production system ceased as the costs reached 2 million euros. Ironically, if production at Lonza had succeeded, the novel investors would have been interested in funding the upcoming clinical trial. At this point, Ipsat was forced to shut down operations and lay off personnel. The bankruptcy of Ipsat Therapies occurred in early 2010.

After the shipwreck

The intellectual property of Ipsat, including patent families and 25000 different regulatory documents that were prepared at the company, were sold for 20000 USD to a private Swiss individual who had previously worked for a French venture capitalist and had been involved in the process of evaluating of Ipsat Therapies. The fate of these documents since the transaction is unclear. However, a US patent expiring in 2027 was granted as late as August 2011 for "Modified beta-lactamase and method for its preparation", which was originally filed by Ipsat Therapies.

After the bankruptcy, the fixed assets of the company were sold to VTT, Yliopiston Apteekki, and other biotechnology companies (e.g., Glykos). The human intellectual capital was dispersed: certain key persons retired, but the remainder of the staff sought employment at Finnzymes, Glykos, the National Institute for Health and Welfare, Fimea, universities, VTT,

Yliopiston Apteekki and abroad. Some of the inventors and key persons no longer work in biotechnology.

2.4.4 Current situation

As previously described, the Intellectual capital of Ipsat Therapies was dispersed. The company was removed from the Finnish Trade Register on February 23, 2011 (YTJ 2012).

2.4.5 Causes and consequences

Ipsat Therapies is an example of a company whose technology development proceeded as planned but whose fate was dictated by the hectic timetable created by patent expirations, unfavorable coincidences, and misvaluations in business development.

The market potential of the lead product was revealed to be excessively low: in hindsight, the decision to focus on the first compound with limited efficacy was a mistake, especially considering that the scientific board and clinical experts recommended selecting the second-generation products for further development. In addition, the literature search regarding the serious adverse effects of penicillin, which provided important information on the market potential for Ipsat's products, was conducted five years after the crucial lead selection was completed. The possibility of entering the market through medical device status was also considered at an excessively late stage. Choosing that commercialization option could have saved both time and costs, and Ipsat Therapies had no excess of either. However, the outcome and acceptability of medical device status was and still can be regarded as uncertain.

A critical issue in the failure of Ipsat Therapies was the expiration of the core patent, which created additional pressure. The problems related to raising new funds and producing a GMP-grade bioproduct at Lonza destroyed the scheduled timetable. To launch the product in the USA by mid-2014, the novel Phase II trial would have had to have commenced by the end of 2009, which was impossible because of the delays that the company encountered.

Ipsat Therapies also suffered from constantly changing management. In the course of twelve years, the company had four different CEOs, and several key persons in scientific, quality assurance and clinical management functions were replaced. These key personnel changes caused problems in the transfer of knowledge and the continuity of processes, the repetition of certain issues and a negative and distracting atmosphere within the company. Intrinsic human resource management problems caused layoffs and prompted a lawsuit. In addition, excellent connections with scientific advisors were lost when managers were replaced.

Similar to many other biotechnology companies during their initial R&D phase, Ipsat Therapies had a constant need for new funding, and the company pursued several financing rounds. Although the company's financial administration was well controlled, the costs of regulatory preclinical and clinical trials, as well as manufacturing, became significant over the years. The company's infrastructure, including quality assurance, became more expensive than originally expected. Limited financial resources forced the company to make vague decisions, such as pursuing a Phase II study in Ukraine. Because the study did not comply with regulatory requirements, it contributed no value to the overall development process. Such a decision reflects the lack of regulatory expertise within the company, although this defect was subsequently corrected through FDA counseling.

Although Ipsat Therapies ceased operations, the company left permanent marks on the Finnish biotechnology industry. Several scientists received their first experiences of business life while at Ipsat, and they deepened their expertise in drug development processes, GMP-grade manufacturing, purification processes, clinical and preclinical studies, and quality assurance and regulatory issues. As previously mentioned, this expertise is now dispersed in various sites across Finland. The company was also a significant biotechnology employer with approximately 200 years of work, in addition to the indirect effects on subcontractors, device providers, and universities through common research projects. Ipsat also offered a training site for doctoral thesis candidates, students and other laboratory workers, and the company developed novel methods and bacteria modifications.

2.5 Juvantia Oy

- **Existence as a Finnish-owned private company:** 1997–2009
- **Location:** Turku
- **Total employment effect:** ~180 man-years
- **Cumulative sales:** 1.48 million euros
- **Total funding received:** 26.8 million euros
- **Main investors:** Tekes, Sitra, BioFund Management, Bank Invest Group, Investor Growth Capital, and Aboa Ventures Management
- **Note:** Santhera Pharmaceutical Holding Ltd acquired Juvantia Pharma in 2009

2.5.1 Intellectual capital growth

The beginning of Juvantia Pharma was similar to that of Hormos Medical: the company was founded in 1997 to continue the development of drug compounds originating from Orion in laboratory facilities that were available when Orion closed one of its drug discovery units in BioCity in Turku. The novel compounds were in-licensed from Orion, which, however, remained an important research collaborator during the 1998–2003 period. The founders were drug development specialists from Orion and professors of pharmacology and transplantation biology from Turku and Helsinki, respectively. Juha-Matti Savola, MD, PhD, served as the CEO of the company from 1997 to 2006, and the other founders acted as members of the board.

Juvantia Pharma also researched novel therapeutics by combining computational chemistry, high-throughput organic chemistry, and pharmacological testing in a discovery platform. The company complemented its in-house Targeted Discovery (TM) approach with a networking model: the company engaged in upstream collaboration with academia to identify new product concepts and formed drug discovery collaborations with other pharmaceutical companies.

Core technology

Juvantia Pharma focused on small molecules targeting receptors linked to the trans-membrane signaling system of cells. The company's interests were adrenergic alpha-2 receptors belonging to a G-protein coupled receptor superfamily; Orion had already brought to market novel compounds for animal sedation based on this same action mechanism. These receptors are present in the central and peripheral nervous systems, and they play an important role in transferring signals in the brain and from nerves to target organs. Thus, the potential indications are numerous; Juvantia Pharma addressed unmet medical needs related to the nervous system, mental disorders, vascular diseases, and chronic pain.

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Approximately 7–10 million people worldwide live with PD, and this number is rapidly increasing. Juvantia Pharma's lead product was fipamezole for the treatment of dyskinesia in PD patients; the molecule was originally patented by Orion, but Juvantia Pharma invented and patented its novel use. Juvantia Pharma's chemical entity was the first therapeutic approach to treating dyskinesia, which is defined as uncontrollable, often chaotic movements of the limbs, face, tongue, and body appearing principally after protracted levodopa use. Today, approximately 400000 patients in Europe and North America suffer from severe dyskinesia, and the market for fipamezole has been estimated to reach at least 500 M €.

Fipamezole represents a drug with a novel mode of action. It binds with high affinity to different subtypes of presynaptic human alpha-2 receptors and thus blocks their function and leads to an increased release of noradrenaline and other neurotransmitters in certain areas of brain. This effect results in a rebalancing of the distorted brain network (www.santhera.com). Fipamezole also has the potential to alleviate cognitive impairment related to Parkinson's disease.

Fipamezole's preclinical tests, especially trials in primate models, showed encouraging results in the treatment of dyskinesia and in the prolongation of levodopa's duration of action. Juvantia Pharma conducted a Phase I clinical study with 47 healthy volunteers in Finland in 2001, and the drugs were shown to be safe and well tolerated.

A Phase IIa study was conducted with 21 PD patients in collaboration with the National Institutes of Health (US) from 2002 to 2004. The study provided proof of concept for fipamezole by demonstrating its dual efficacy: it was found to reduce levodopa-induced dyskinesia and prolong levodopa's duration of action.

A Phase IIb dose escalation study was conducted from 2007 to 2009 in collaboration with a new partner, the Swiss pharmaceutical company Santhera. The study was conducted as a 28-day treatment period for 179 enrolled patients in the US and India. The goal of this study was to provide data on the efficacy and safety of fipamezole and on feasible endpoints for the planning and execution of a subsequent Phase III trial of the compound in the US and the EU. This study again demonstrated the beneficial effect of fipamezole on dyskinesia, and the drug did not worsen the Parkinsonian features of the disease.

Sidetrack options

In addition to PD, fipamezole may be beneficial for certain forms of neurogenic orthostatic hypotension, as hypotension in these diseases results from decreased delivery of noradrenaline (or hormonal adrenaline) to vascular receptors. By increasing the release of this neurotransmitter, fipamezole could alleviate symptoms related to decreases in blood pressure during orthostatism related to PD or multiple system atrophy (MSA). Juvantia Pharma planned to test this potential therapy in a Phase II clinical trial; however, such a trial was never conducted.

Juvantia Pharma also discovered novel compounds that bind to and inhibit somatostatin receptor subtypes sst1 and sst4, which also belong to the adrenergic alpha-2 receptor family. The research was initiated based on a university collaborator's findings that sst1 and/or sst4 play a prominent role in vascular wall diseases and neurogenic inflammation. These receptors are widely distributed in the human body, such as in the brain, blood vessels, pancreas, gastrointestinal tract, lung, heart, placenta, and eyes. In addition, the receptors can be found in various tumors.

Somatostatin is involved in an array of biological effects, including neurotransmission, hormone secretion, cell proliferation, and smooth muscle contractility. This substance has been used to treat certain cancers and growth hormone disorders; however, because it is metabolized in the body very rapidly, its therapeutic potential has been limited. Juvantia Pharma's novel compounds offered the possibility to extend the use of somatostatin modulators into

new indications, such as mental disorders, diabetic angiopathy and retinopathy, angiogenesis, vascular restenosis, wound healing, inflammation, and glaucoma.

The somatostatin inhibitors were tested only preclinically, as company resources were primarily focused on the development of the lead molecule. However, the compounds showed biological efficacy in animal models of neurogenic inflammation, wound healing and rheumatoid arthritis, and they were active as painkillers.

Juventus entered into a research agreement with Alcon Research (US) in 2005 to explore novel therapeutics for ophthalmic diseases. Alcon's role was to assess Juventus's compounds using its pre-clinical models and applied biology expertise; the company had access to Juventus's products and the option to negotiate on development and license agreements with Juventus. The focus of the project was on selective inhibitors of somatostatin receptor subtypes.

Juventus Pharma's pipeline also included neuropeptide FF (NPFF) receptor modulators that were developed in collaboration with the University of Helsinki. These receptors belong to the G-protein coupled receptor family and play important roles in a variety of physiological processes, including pain killing. In addition, the company developed depression drugs that unfortunately failed in preclinical trials in 2003 because of safety problems.

Intellectual property

Some of the chemical entities developed by Juventus Pharma were derived from and originally patented by Orion; Juventus in-licensed them and filed usage patents for novel indications. Juventus Pharma also developed novel molecules and aimed to patent them as drug substance patents. A trademark was obtained for the Targeted Discovery (TM) platform, primarily for marketing purposes.

In total, Juventus Pharma filed 28 patent applications, many of which developed into patent families (Espacenet database 2012). In the EU, patent protection was recently granted for the novel formulation of fipamezole until 2023. Juventus's patents for other compounds, including somatostatin receptor modulators, have expired.

Cooperation

The business model of Juventus Pharma was based on intense collaboration with academic research groups both in Finland and abroad. The department of organic chemistry and the department of clinical pharmacology at the University of Turku, the department of biochemistry and pharmacy at Åbo Akademi University, and the vascular disease group at the University of Helsinki were the most important domestic collaborators. Juventus Pharma also had close research relationships with the University of Montreal (Canada) and the University of Pécs (Hungary). In addition, the company participated in EU-funded research projects, and the international scientific board of the company consisted of members from the UK, France, the US and Finland.

Juventus Pharma's business partners included Orion and several CRO companies, such as CRST (Clinical Research Services Turku), which conducted the initial clinical trials. Juventus also outsourced certain quality and regulatory affairs, particularly during the early years of the company (e.g., to Ground Zero Pharmaceuticals in the US). In August 2001, Juventus Pharma entered into a development agreement with a Swiss contract manufacturer, Siegfried Ltd,

on the optimization of the synthesis process and on the cGMP-compliant manufacturing of fipamezole for Phase I/Phase II studies. A foreign partner was chosen, as there were no domestic players producing small-scale batches for preclinical and clinical purposes.

Regulatory and other intangible assets

Juvantia Pharma personnel were highly educated and consisted of organic chemists, bioinformatics specialists, and biologists specializing in pharmacological *in vitro* drug screening methods. The team had several foreign members from the beginning, and the working language was English. In 2002, the company had its peak number of workers (44), and its total employment effect was approximately 180 working years with an average of 20 workers for each year.

Juvantia Pharma exerted special effort into educating personnel in scientific and technical issues in an attempt to develop a state-of-the-art technology that outperforms competing approaches; the discovery platform of Juvantia Pharma was completely new in Finland. Because the company first operated in the discovery phase of drug development, in which regulatory and quality issues are less demanding than in later phases, the knowledge in GMP/GCP was not markedly emphasized.

With the assistance of consulting firms, Juvantia Pharma managed to communicate with regulatory authorities in a timely manner and received an IND status for fipamezole in 2001. This status assisted the drug in progressing from the preclinical research stage to the clinical phase. In 2005, the US FDA granted a fast-track designation for fipamezole for the treatment of dyskinesia in advanced PD. This designation confirmed the importance of Juvantia's innovation and accelerated the approval process for clinical trials, and it assisted the company in dealing and negotiating with regulatory authorities in the forthcoming development steps.

2.5.2 Business development

The company's original business idea was to be a discovery company and to enter into discovery services and collaboration agreements with global pharmaceutical companies at an early stage of drug development. This model had been successful in countries such as Sweden, where companies such as Karo Bio had entered into partnership with several global pharmaceutical companies. In this model, both parties participate in drug discovery, and the pharmaceutical company is responsible for further development (<http://www.karobio.com/>).

Juvantia Pharma invested in equipment, computer modeling, and an automated synthesis system that assisted in producing the first research agreement with Orion during the 1998–2003 period. However, other partners who were interested in drug discovery were more difficult to find than was initially expected; therefore, Juvantia Pharma changed its business model and sought to bring the lead molecules to a more mature stage before entering into partnerships. In-house proof of concept was viewed as an important means of creating value and attracting licensing partners, and investors favored this model.

Expansion phase

The initial investments in the company were from the founders and the public sector, including Tekes and Sitra. In 1999, BioFund joined the investors, followed by Investor Growth Capital (Sweden) and BankInvest (Denmark) in 2000 (Heinonen 2009). A total of 14.4 million euros in capital was invested in the company, with Sitra as the lead investor through its 4.1 mil-

lion euros share. Juvantia also received public funding totaling 12.4 million euros in the form of grants and loans from Tekes as well as cash flow from its collaboration project with Orion. Most of the funding received by the company had already been obtained by 2001; in the following years, the company was able to raise only minor sums of money.

The successful investments rounds from 1999 to 2000 assisted the company in conducting expensive safety studies for fipamezole and investing in premises, technology, and personnel. Juvantia Pharma moved to the new biotechnology center, Pharma City, and signed a ten-year rental agreement in 2001. At that time, the company's annual burn rate was 3–4 million euros, and expectations were high. The company also intended to execute an IPO within a few years (Lindqvist 2002).

The company entered into research agreements with Orion and Alcon. The agreement with Orion was important because of its financial terms. In contrast, Alcon had the option to license certain compounds, but this collaboration never brought any revenue to the company because the company failed to pursue this opportunity (Heinonen 2009).

A successful clinical Phase I trial in 2001 and a successful Phase IIa trial in 2002–2004 as well as the fast-track designation increased the value of both fipamezole and the company. Acknowledgment from the US National Institutes of Health – the largest source of funding for medical research in the world – for its phase IIa study was important for the company because it was seeking a business partner in the US, which is the largest market for PD therapeutics. From 2004 to 2006, Juvantia negotiated for licensing with several pharma companies, including BioVail (Canada), but none of these negotiations led to an agreement (see below).

Signs of foundering

Although fipamezole's phase IIa study was conducted in one of the world's foremost medical centers, the design of the trial did not satisfy potential licensing partners. The number of enrolled volunteers (21 patients) was considered excessively low, and the trial was performed only in the controlled environment of a hospital. Another phase II study was needed to confirm efficacy in an outpatient setting. The estimated cost for this study was 5 million euros, but the old investors were incapable of making new investments, and Tekes could not provide a loan to a company lacking its own capital. Furthermore, in 2003, one of Juvantia's development projects had failed in safety studies (necessary for drug approval), thus decreasing the value of all of the company's discovery projects.

Because the only agreement to generate revenues had ended in 2003, Juvantia Pharma found itself in a financial crisis. The company managed to obtain bridge funding from its old owners during the 2004–2006 period to ensure survival; however, various development programs were halted, and the company was forced to lay off personnel. The value of the company declined as its intellectual capital decreased, and the company received offers from predators willing to buy it at a low price. However, the owners and management entered into intense trade-sale negotiations with various enterprises and, finally, in July 2006, signed a collaboration agreement with Santhera, a Swiss pharmaceutical company.

The contract called for the two parties to jointly advance the development of fipamezole. Santhera's role was to finance the necessary Phase IIb study to generate the data that were required

for the commencement of Phase III trials. The CEO of Juvantia joined Santhera as the Director of Clinical Development and was responsible for the fipamezole development program at Santhera's facilities in Liestal, Switzerland. Santhera also had a call option to secure all rights to the product candidate through the acquisition of Juvantia no later than 2009.

2.5.3 End of independent phase

The agreement with Santhera saved Juvantia Pharma from bankruptcy. However, all of the company's efforts then became focused on the confirming Phase IIb study, and the Turku unit was closed. The trial was conducted from 2008 to 2009 in the US and India, cost approximately 7 million euros and confirmed the previous good findings with fipamezole. Santhera exercised its option and acquired Juvantia Pharma in an all-share transaction in August 2009 (www.santhera.com).

After the shipwreck

The acquisition marked the formal end to a three-year shutdown period, during which all operations in Turku disappeared. Santhera was not interested in early-phase drug discovery; the company was interested only in the lead molecule fipamezole, and all discovery projects had to be terminated. Furthermore, the company had in-house regulatory, quality assurance, clinical and legal competence and had no need for Juvantia's expertise. The highly talented experts dispersed to various directions and currently contribute to the life science sector in their positions at Roche, Orion, Pfizer, Kemira, MTT Agrifood Research Finland, PCAS Finland, Tekes, and various universities.

Equipment was sold to universities and SME companies, and the technology platform dissolved as the human, relational, and structural capital was dispersed. Santhera also wanted to revoke the rental contract, but such an action would have required certain financial arrangements.

From the acquisition, old shareholders received Santhera's stocks, and Santhera refunded Tekes loans provided for the development of fipamezole. However, as Santhera did not want to commercialize the sidetrack options, these project costs were never repaid, and their patents have expired.

Immediately after the acquisition, Santhera licensed the US and Canadian rights to develop and commercialize fipamezole to Biovail, which had been negotiating with Juvantia on licensing a few years earlier. Under the terms of the agreement, Santhera received 12 million USD in upfront payments and was entitled to up to 35 million USD in development and commercialization milestones, 145 million USD in sales milestones, and royalties between 8 and 15 percent on future net sales (www.santhera.com). It was also agreed that Biovail would conduct a Phase III study in the USA.

In September 2010, Santhera out-licensed the rights to develop and commercialize fipamezole outside of North America and Japan to Ipsen (France). Ipsen made an upfront payment of 13 M € and additional payments contingent on future development, regulatory and sales milestones of up to 128 million euros. In addition, Santhera was entitled to royalty payments on Ipsen's future net sales (www.santhera.com).

2.5.4 Current situation

The pharmaceutical industry is encountering constant mergers and acquisitions that dictate the fate of ongoing drug development projects. In June 2010, Biovail merged with Valeant Pharmaceuticals International, which is one of Canada's largest drug makers. After a post-merger review, a shift in strategic focus of the new company occurred, and the fipamezole project was transferred back to Santhera in 2011 (www.santhera.com). Santhera has the right to use all of the data generated by Biovail in preparation for a Phase III study for further development and commercialization worldwide.

As a domino effect, Ipsen announced in January 2012 that it would return the rights of fipamezole to Santhera in exchange for milestone payments and royalties. However, Ipsen retained a call option for a worldwide license to the program under certain conditions. The new deal allows Ipsen to focus on its own late-stage pipeline while ensuring that the benefits of fipamezole are still realized (www.santhera.com). Santhera currently holds worldwide rights to develop and commercialize the compound. However, given the pressure from continuously volatile markets and the failure of a Phase III study for another product, Santhera has restructured its portfolio, and the company's short-term focus is on their lead product, Catena. Fipamezole continues to be a valuable asset in Santhera's late-stage clinical pipeline, but the company currently foresees no further financial commitments for fipamezole.

2.5.5 Causes and consequences

The main reason for the failure of Juvantia Pharma was a lack of financing. A shortfall of approximately 5 million euros to conduct the Phase IIb study was the final barrier that forced management to seek a new owner. The old owners lost confidence in the projects and were not prepared to make a long-term investment; moreover, Tekes has favored a funding model that encourages start-up companies but retreats after Phase I studies. The local venture capitalists did not have sufficient capital to accompany a business from seed funding to the expensive proof-of-concept stage. Ironically, Santhera received the Phase IIb investment back manifold in the form of upfront licensing payments from Biovail and Ipsen, whereas the value of Juvantia's acquisition for the old owners can only be estimated, especially now when the share price of Santhera has plummeted from CHF 95 in July 2008 to its current value of CHF 3,7 (October 14, 2013).

The drug discovery business model and technology platform of Juvantia Pharma was challenging; it was excellent in the scope of the Finnish life science industry but could not provide a unique competitive advantage in international markets. Because the company was new and lacked references, special knowledge that differentiated it from similar approaches would have been needed. Finding a good and novel drug candidate in a short period could have strengthened the reputation of Juvantia's platform; unfortunately, such inventions required more time than expected.

Juvantia Pharma also lacked expertise in regulatory issues, quality assurance, clinical manufacturing, and clinical practice, which could have assisted in sustaining some operations in Finland. Such intellectual capital can provide a significant competitive advantage in maintaining a subsidiary in Finland when the foreign owner is from Asia, Russia or any other country that does not have experience in Western drug development and approval processes. However, European- and US-based drug companies have this knowledge in-house; in par-

ticular, the pharmaceutical industry in Switzerland is highly advanced and known for its excellent quality.

The Human Genome Project to identify all human genes was completed in 2003 and was followed by a shift in the focus of drug development projects. Bio-molecules that were targeted to specific biological systems or genetic disorders and the concept of personalized medicine became novel hot topics. Traditional drugs based on small organic molecules were no longer trendy, which likely decreased the interest of Big Pharma in Juvantia's discovery platform.

The Juvantia case prompts a general question that applies to nearly all biotechnology and drug development SME companies: what is the appropriate size for a portfolio? Ten years ago, a company needed to have several innovations in its pipeline – preferably in a late stage – to be attractive. Juvantia Pharma had only one compound in clinical trials, which was regarded as a weakness. Companies needed to show stability, continuity, and future vision by having a constant flow of novel ideas. However, conducting several simultaneous projects was frequently impossible, and at some point, resources would need to be reallocated for only one lead molecule. Thus, unfinished sidetrack options would with time not only diminish in value but also exploit resources of the lead product, and hence turn even to create negative value.

The role and importance of Juvantia Pharma in the Finnish biotechnology sector have been multifaceted: it has served as an important channel for bringing Finnish academic research into the global markets. The company has also been an important employer in the Turku region, and it contributed to strengthening the reputation of Turku as one of the main biotechnology centers in Finland. The company offered an inspiring environment for several doctoral and master students, and the intellectual capital within the company has nourished several other companies and universities both in Finland and abroad. Interestingly, the fipamezole drug that was developed at Juvantia Pharma has shown real efficacy in relieving PD-related dyskinesia symptoms. Will this drug finally reach the market? The answer to this question is unknown, but in the prevailing business riptide, the drug may reach the market as a result of Finnish persistence.

2.6 Medipolis GMP Oy

- **Existence as a Finnish-owned private company:** 2001–2007
- **Location:** Oulu
- **Total employment effect:** ~165 man-years
- **Cumulative sales:** 5.08 million euros
- **Total funding received:** Data not available
- **Main sources of funding:** Private funding
- **Core competence:** cGMP manufacturing of biologicals and process development
- **Note:** Since 2007, the company has continued as a majority-owned subsidiary of Marvel Life Science (UK), a flagship of MJ Biopharm (India)

2.6.1 Intellectual capital growth

Medipolis GMP was founded in 2001 as a result of a regional development project designed already in 1995 by various instances realizing the business potential of the innovations of Oulu University. The Oulu region is a high-tech research and business center with Technopolis Oyj, the largest networked technology park in Finland, and the first of its type in the Nordic countries. In 2001, the most prominent research areas were wireless ICT technology and biotechnology, particularly collagen research, agrobiotechnology, and diagnostics. However, given the European Commission stated in 2001 that the Finnish economy relied excessively on ICT and that Finnish authorities noted that this reliance was especially applicable in the Oulu region (EU Commission 2002)¹², the development of other sectors, including biotechnology, became one of the main strategic goals of the city of Oulu. Nevertheless, the primary focus of regional funding has remained on ICT.

Oulu has been an important center for the manufacturing of medicinal products since 1961 when Medipolar Oy was established; this company was the first Finnish plant that received FDA approval in 1979. Medipolar merged into Farnos in 1978 and subsequently into Orion in 1990. In addition to Orion, several biotechnology start-ups and several SMEs existed in Oulu, among which Fibrogen is probably the most prominent.

Fibrogen developed therapeutics that prevent unwanted fibrosis and scarring as well as methods to produce recombinant human collagens and gelatins for various medical needs. For clinical trials, Fibrogen's products and other therapeutic biologicals had to be manufactured in a regulatory-compliant environment, and there was a need for both regional and national cGMP-grade manufacturing units.

In 2001, Orion decided to close some of its manufacturing operations in Oulu, and this decision released a team of people experienced in the pharmaceutical industry to the labor market. With specialists in quality assurance, analytics, and regulatory issues then available, the idea of a novel company manufacturing cGMP-grade biologicals was further strengthened, particularly because fermentation and bioprocess engineering knowledge was available at Fibrogen and at Oulu University, where it was brought from Germany by a distinguished professor.

The design and building of clean facilities was a noteworthy project, and its key visionaries were Dr. Saara Lampelo and Dr. Jouko Haapalahti from Medipolis Oy; Dr. Lampelo also

¹² http://ec.europa.eu/eu_law/state_aids/comp-2002/n076-02_fi.pdf

served as the first CEO of the company. Total construction costs were approximately 11–13 million euros (Siltanen 2007), with funding received from the city of Oulu, the EU, Tekes and the Ministry of Employment and the Economy as stimulation for the regional employment status. The novel company was 100% owned by Medipolis Oy, a daughter company of Technopolis Oyj. A rental agreement between Medipolis GMP and the city of Oulu called for the clean room premises to be rented by Medipolis GMP from the city. The company committed to the agreement for five years and was responsible for the marketing and development of the GMP facility.

As described in greater detail in section 2.6.2, Medipolis GMP was subsequently sold to UK-based Marvel Life Sciences. This event created the foundation for a well-networked international business. Thereafter, the main source of funding has been private. Public funding, such as Tekes funding, has in practice not been applicable for Medipolis GMP, and Industry Investment (TeSi) has not been interested in investing in this field of business.

Core technology

The core competence of Medipolis GMP is in cGMP production with microbial fermentation. The company's first project was with *Bacillus subtilis*, but the company also developed extensive expertise in using *Pichiapastoris* and *Esherichia coli*. In addition, the company specialized in CHO expression systems for full-length monoclonal antibodies or fragments thereof as well as in cell culture-based process development and validation (Kumar 2010).

The company's premises consist of 2,300 m² of floor area, including a clean room approximately 400 m² (class A/B, C, D) in size. The company has fermentors of various sizes up to 750 liters; necessary equipment for purification and analysis (e.g., chromatographs, mass spectrometry, freeze drying); and its own dry heat sterilization, water and power supply systems. One limitation of the facilities is that there is only one operating module, which prevents simultaneous manufacturing processes for several products. In addition, the facilities are only for bulk production and final steps; other processes, such as filling, are outsourced to business collaborators.

Intellectual property

The intellectual property that was created consists primarily of process developments that are difficult to patent, and the company has not yet filed any patent applications to date (Espacenet database 2012).

Cooperation

The company has entered into close collaboration with several Finnish companies and research institutes, including Ipsat Therapies, Pharmatory, Novamass, Fibrogen, Triacle Biocomputing, Macrocrystals, Orion Diagnostica, Biovian, Biocenter Oulu, VTT and Oulu University; Fibrogen and Orion Diagnostica even had representatives on the board of Medipolis GMP bringing business experience and international contacts. The companies have also collaborated with international entities, such as Scil Proteins in Germany (Bioteknologia info, 2005)¹³. Currently, Medipolis GMP has a broad international network for both R&D and business.

¹³ http://www.bioteknologia.info/uutiset/toimiala_ja_yritystalous/fi_FI/Medipolis_Scilproteins/

Regulatory and other intangible assets

The Medipolis GMP facilities have been designed to meet FDA and EMEA requirements. Medipolis was validated in 2003, and a production license was granted by the Finnish National Agency of Medicines (now FIMEA). GMP compliance is ensured through internal audits and regular inspections by the Finnish regulatory authorities and is based on experience with the FDA and EMEA (www.medipolisgmp.com).

The number of personnel at Medipolis GMP has remained relatively constant over the years at approximately 14 to 18 full-time employees, except during lay-off periods. All employees are production and process development specialists or quality and regulatory experts. Staff members have strong industrial backgrounds and are highly qualified and trained according to cGMP guidelines. In 2004, Pirkko Suhonen (MSc, MJD), with a background in marketing, financing and business expertise, began serving as the new CEO. Special effort was exerted for issues such as project pricing, networking, partner and customer search, and corporate culture.

The high competence of the company's personnel and its regulatory-compliant activities were the key assets that affected the international merger subsequently during the company's existence. The international merger reinforced international business and other expert contacts and enabled private funding of the company.

2.6.2 Business development

Expansion phase

The original business idea was that Medipolis GMP would lease manufacturing facilities and competent personnel to customers. In this model, the regulatory manufacturing license was granted to customers rather than to Medipolis GMP. This business model was consistent with that used by Technopolis, which was Medipolis GMP's largest shareholder at that time.

In 2001, the company expected Fibrogen to become its first and main customer (Siltanen 2007). However, Fibrogen had previously become a subsidiary of the US-based company Fibrogen Inc., which decided to shut down its functions in Oulu and construct its own pilot manufacturing unit in California. Moreover, the focus on collagen research and development began to change to a focus on cosmetic applications, and the need for medical manufacturing decreased. Therefore, rather than Fibrogen projects, the company's first projects were conducted for Ipsat Therapies Oy during the 2002–2003 period.

In these projects, the bulk materials for Phase I and Phase II studies were produced, and the work was performed according to the original business plan under Ipsat's manufacturing license. These projects were successful but required new customers because the fixed costs associated with operating a regulatory-compliant clean facility and retaining talented personnel were high.

Although the annual sales of the company exceeded 1 million euros in 2003, the operating profit was negative, and the situation worsened in 2004, when the total sales were only approximately 430 000 euros. The company was forced to lay off personnel (Siltanen 2004), and a new funding round and changes in ownership structure were organized. In February 2005, Teknoventure Oy, a public venture capital firm, made an investment and became the largest

shareholder of Medipolis GMP in a directed issuance of shares (Kärki 2005). Medipolis Oyj released 75% of its shares because its negative cash flow was disadvantageous for Medipolis Oy and especially for the listed parent company, Technopolis, as indicated by its quartile report in June 2004. Moreover, the city of Oulu and the company personnel invested in Medipolis GMP shares, and additional funding was received from Finnvera in the form of a convertible bond¹⁴ (Klemettilä 2007). To increase its business opportunities, Medipolis GMP broadened its business model from mere leasing operations to contract manufacturing services and initiated a vigorous marketing and customer relationship campaign to obtain new customers and development projects. Medipolis GMP services were also offered jointly with Novamass Analytical Ltd, Pharmatory Oy and Triacle Biocomputing services as the PHANOMED consortium.

As a result, four projects to produce test materials for Phase I and Phase II studies and some smaller products were received from the UK, Belgium, and the US. In 2006, Medipolis GMP also initiated its own process development and technology optimization program, which led to processes for the production of biotechnological insulin compounds that interested several companies.

Signs of foundering

From 2005 to 2006, the company negotiated with the global drug company Boehringer Ingelheim for pilot manufacturing services and the development of manufacturing processes; Boehringer Ingelheim even audited the Finnish facilities and was satisfied with the affordable price and excellent quality of the facilities and with the high level of expertise found in the company. Another negotiation partner, DMS Pharma (The Netherlands), was interested in bringing its own microbial fermentation processes to Oulu. However, these negotiations ended unsuccessfully. The main reason for the negative decision was that international customers wanted guarantees that Medipolis GMP would have the necessary operational funding during the period of the projects, but none of the Finnish VCs (including Sitra, BioFund, Tesi, and the company's largest shareholder, Teknoventure) were able to make a positive investment decision with respect to Medipolis GMP. Therefore, although negotiations with international customers proceeded fairly smoothly, selling the company became the only option.

2.6.3 End of independent phase

From 2006 to 2007, negotiations with several global companies interested in buying Medipolis GMP occurred and were led by Teknoventure Oy and civil servants of the city of Oulu. Within the company, the last financing and selling processes were considered disputable: selling appeared to be dictated by the will of the owners, whereas management was still convinced that recent business negotiations would create long-term customer relationships with pharma companies. Criticism was directed especially at the unwillingness of Teknoventure to further develop its bio-investment, which had lasted less than two years rather than the expected 5–7 years (Kärki 2005).

In January 2007, following careful due diligence, more than 99% of Medipolis GMP shares were bought by an Indian drug company, MJ Biopharm, and its London-based marketing company, Marvel Lifescience Ltd, which needed additional GMP facilities and expertise for its own insulin production.

¹⁴ http://www.bioteknologia.info/uutiset/toimiala_ja_yritystalous/fi_FI/medipolis/

After the shipwreck

In this acquisition, Teknoventure Oy made a good exit for itself, and individual shareholders as well as the city of Oulu were bought out of the company. Currently, less than 1% of the shares belong to Oulu, but the city remains the owner of the facilities. Six employees exited the company during or after the acquisition process.

The new owner considered the contract manufacturing expenses to be excessively high, with no room for profit for the company. Therefore, the business strategy of Medipolis GMP changed after the merger: rather than offering contract manufacturing or process development to third parties, the company decided to focus on its own projects and process development. This change led to processes for the production of biologic compounds (active pharmaceutical ingredients) that interested several companies.

2.6.4 Current situation

At present, Medipolis GMP belongs to a global corporate, MJ Biopharm. Dr. Ashesh Kumar has served as the CEO of the company since the international merger. Through his expertise, he has strengthened international networks both in business and in R&D.

MJ Biopharm is primarily engaged in the exports and export-oriented production of pharmaceuticals, agrochemicals, aromatic chemicals and perfumery compounds, and the company has offices and manufacturing facilities across the world. The company excels in numerous areas, including animal and human rDNA insulin, dosage forms such as tablets, capsules, cephalosporin and other injectable ampoules and vials in different specialty segments such as diabetology, cardiology, NSAID, anti-inflammatory, and antibiotics. MJ Biopharm's products are registered in more than twenty countries in Asia, Africa, and South America and are in the process of being registered in more than 60 countries, including Europe and Russia¹⁵. The company has entered into strategic alliances with Sanofi Aventis and Biosynth B.V. (The Netherlands) and has manufacturing units in India and Poland.

Medipolis GMP focuses on the development of technologies and the optimization of processes that can be used by the parent company or that are out-licensed to customers. The company appears to have managed this task well; for example, the production yield for insulin has increased to a level that is up to ten times higher than at other companies that use similar types of expression systems and technology.

Medipolis GMP has continued its collaboration with Oulu University and various biotech companies. The company has offered a GMP training site for various students and has participated in the funding of certain equipment needed by the university. The company has employed approximately 15 persons per year. No foreign workers except for the CEO have permanently settled in Finland, but international biotechnology experts have visited Medipolis GMP for shorter periods, and some of the company's employees have received training abroad. To date, the owners have contributed approximately 7 million euros to the Finnish unit.

The strategy of the Indian owners was to hire local people and retain profits within Finland. The current owners have disclosed plans of enlarging the company to a manufacturing plant

¹⁵ <http://www.mjbiopharm.com/mjgroup.htm>

with approximately one hundred employees based on their perception from the business evaluation phase that up to 50% funding from Tekes could be available for several innovative projects. However, Medipolis GMP has been able to raise only one 50% Tekes loan for a 1.6 M € process development project; this amount is much less than expected.

The company has regarded the criteria for Tekes funding as confusing because at some point, the company was considered too small to be able to bring two simultaneous projects to completion; however, on other occasions, given the percentage of foreign corporate ownership, the company was categorized as a large corporation for which the Tekes funding criteria are much more stringent.

Moreover, Sitra, TESI, Biofund and the Ministry of Employment and Economy have been reluctant to fund Medipolis GMP, and the company was not able to obtain a minor loan to purchase equipment with a resale value that was clearly higher than the loan amount. As foreign ownership is not supposed to negatively influence funding decisions, one explanation may be that the generally negative attitude toward the biotech industry has affected both venture capitalists and other important stakeholders.

According to Dr. Kumar, the lack of local funding in Finland contrasts with the practice of other countries. For example, in New Zealand, a foreign investor may obtain local support of up to 50–80% of certain costs. Such issues and the globally tightening competition have forced international companies to constantly estimate the true value of each regional unit, which is conducted every quartile by the board of Medipolis GMP.

Notably, the first five-year lease between the city of Oulu and the Indian owners ended in 2012. Consequently, the company has assessed its future location, and as it is still operating in Oulu it has made agreements regarding its future relation with the city. However, at present we do not have updated information regarding Medipolis GMP's longer-term plans.

2.6.5 Causes and consequences

Similar to many other biotechnology companies, Medipolis GMP encountered financial problems within a few years after its establishment. Construction was an ambitious project that left few resources remaining to fund operations. Immediate cash flow to cover these costs was a necessity for the company.

The business model that was initially chosen was arguably unfavorable for Medipolis GMP. The model was based solely on leasing the facilities and competent personnel for customers, and it presumed that the customers would take care of the manufacturing permission issues. This presumption must have limited the repository of potential customers, as many SMEs do not have in-house regulatory expertise or a sufficient number of competent personnel to handle the enormous paperwork that is involved with clinical manufacturing issues. The business model has also hampered the possibility of obtaining funding from sources focusing on the development of innovations (e.g., Tekes) or those seeking future blockbusters (VC).

Medipolis GMP was established to meet regional needs and as a regional development project. However, the business potential of regional projects must be carefully evaluated, and the pursuit of a prosperous business should be the only driving force for commencing projects. It is

also important to possess both technical and business development competence available from the beginning. Unfortunately, a general mistake in the early 21st century was that excellence in technology was valued over business experience, although this attitude has since changed, not only within companies but also among financiers. Notably, a lack of competence in business, especially in international business and marketing, has been identified as one of the challenges encountered by the Oulu region (Pursula et al. 2010).

In the Medipolis GMP case, the original business strategy was heavily relying on local customers; global market research and a carefully chosen business model might have prevented economic dependency on only a few customers. However, Fibrogen's departure from Oulu was a major and clearly unexpected event that continues to attract attention as a particularly interesting case.

The Oulu district is a region in which economic trends are observed rapidly, and local funding plays a clear role. Most of the innovative companies receive funding from Tekes; the Centre for Economic Development, Transport and the Environment (ELY); and the Council of Oulu (Pursula et al. 2010). However, there appears to be a risk that funding in the Oulu region is directed toward short-term projects; therefore, "development of the promotion of development" may become a critical issue, and company-driven innovation activities and business development may become less important (Pursula et al. 2010). Furthermore, funding in Oulu had focused on ICT, and biotechnology was out of the comfort zone of local investors in Oulu and investors in Finland. Therefore, the funding problems that were encountered by Medipolis GMP were caused not only by drawbacks in business development but also by deeper regional and national issues. The ICT focus may also explain Teknoventure's decision to sell its ownership in Medipolis GMP, although the duration of the investment was much shorter than the expected 5–7 years (Kärki 2005). The opportunity to sell the company rather than become bankrupt also mitigated the public debate and prevented a potential political disaster that may have been harmful for the city of Oulu.

The lack of motivation of investors to invest in biobusinesses was a general trend that was observed both in Finland and throughout the world. Venture capitalists were rare in Finland, funds were relatively scarce, and investors often lacked biotechnology expertise and were accustomed to exiting within 5–6 years. The longer-span (or even short-term) development projects that are observed in biotechnology companies were not appealing, especially when the attitude of the media toward biotechnology had suddenly turned negative. Medipolis GMP also suffered from the lack of investment money through its customers, most of which were SMEs that depended on external funding.

Although the merger of Medipolis GMP with a foreign owner initially raised concerns, the Indian ownership has contributed several positive results. The new owners have invested several million euros in Finland, and pharmaceutical expertise has continued to exist in the Oulu region. However, the obstacles that the new management has encountered also raise questions related to Finland's policy of attracting and maintaining foreign companies and investors in the country.

Medipolis GMP has been an important part of the value chain of the Finnish pharmaceutical sector, and the intellectual capital that has developed at Medipolis GMP has nourished other organizations in Finland, such as Metla, Rautaruukki, Oulu University, and Turku University

of Applied Sciences, as some of the employees have continued their careers in other sectors. The knowledge and technology that has been developed at Medipolis GMP should be applicable to the production of other molecules, such as therapeutic antibodies, and may be capable of being outsourced to other companies throughout the world. In September 2012, Medipolis and Bioton SA signed a technology licensing agreement worth 5.3 million euros¹⁶. The company's management is seeking constant growth and expects its personnel to double by 2016, provided that the Indian owners decide to remain in Oulu.

Finland from the perspective of a foreign entrepreneur

One of the main reasons that the Indian owners chose Finland as their manufacturing site was the excellent expertise found in Oulu. Furthermore, Medipolis GMP is currently considered the core team in which the knowledge base of protein manufacturing lies. The company's European quality assurance unit is located in Oulu, meets European standards, and can assist in bringing the company's products into the Western market. Medipolis GMP has also acted as a quality and regulatory training site for Polish employees. In addition, the company has knowledge in protein folding that is difficult to find elsewhere.

Another reason for entering Oulu was that Finland was perceived as a reliable and efficient country: things that are possible in this country are not possible elsewhere in the same period and with the same budget. Interestingly, the high ethical values of Finland with respect to pharmaceutical issues were also appreciated. Even Finland's legislation that approved the marketing of generic drugs was appreciated as a sign of high ethical value; generic drugs, which are cheaper than the original formulations, are especially important for poor people and developing countries.

In general, the Indian owners have been satisfied with the level of knowledge and with the working culture and trustworthiness of Finnish employees¹⁷; the Finnish language has not been a problem, as nearly everyone speaks English in the high-technology sector. The local infrastructure as well as the team and its track record are viewed as assets. However, the owners consider that the true potential of outstanding Finnish biotech has not yet been fully realized. Unlike in India, where the lack of drugs is a major problem, biotechnology in Finland has a negative connotation, and the emphasis has been on the ICT sector. However, within 15 to 20 years, biotechnology could become a core area of Finland, if the political will exists for such an outcome.

India is a country in which biotechnology expertise is highly valued, and knowledge of the local needs and direct contacts with the growing pharmaceutical sector in Asia could be beneficial not only to the company but also to the entire Finnish health/bio cluster. In Finland, the exploitation of existing international contacts and personnel has been limited, as all companies tend to operate alone and want to protect their international positions. Intense collaboration between companies as well as novel public and private funding instruments could contribute to the prosperity of this sector.

¹⁶ <http://www.cisionwire.fi/ground-communications/r/oululaisyrittys-kehitti-diabeteslaakkeeseen-uuden-valmistus-menetelman,c9307150>

¹⁷ http://www.ouluexpatcity.fi/business/medipolis_gmp.htm

3 Investor cases

3.1 BioFund Management Oy

- **Existence as a Finnish venture capitalist:** 1996–2008
- **Location:** Helsinki
- **Total employment effect:** ~96 man-years
- **Cumulative income:** ~30 million euros
- **Total size of funds:** ~200 million euros
- **Note:** During its existence funded nearly all domestic life science companies with commercial potential

3.1.1 Capital growth

Fund

Bio Fund Management (BFM) was established in 1996 as a venture capital company focusing on life science technology and the internationalization of companies. The founding of BFM was preceded by several years of background work in Sitra, which finally decided to become one of the founders with a one-third ownership share.

In addition to Sitra, the founding partners were Kalevi Kurkijärvi and Seppo Mäkinen. Timo Petäjä became owner in 1997, and Sitra's share was reduced to approximately 10%. In 2001, Sitra's share was further decreased to approximately 1% by new investors joining the company; the first three private partners managed to retain more than 60% of management's ownership of the company throughout its existence. The company operated without a CEO for the first three years, with each founding partner having an active role as a board member. At the end of 1999, Erkki Pekkarinen from the Finnish Venture Capital Association joined the company and served as the CEO until 2008.

BFM managed three different funds operating in a limited partnership. The sizes of the funds were as follows: Bio Fund Venture I 33 million euros with a 5 million euros extension, Bio Fund Venture II 66 million euros with an 11 million euros extension and Bio Fund Venture III at approximately 82 million euros. Resources were collected primarily from domestic insurance companies, pension funds, foundations and the European Investment Fund, as life science investments appeared to have an attractive risk/return profile. Capital was also obtained from Sitra, which hedged the other investments in Bio Fund Venture I with an investment of the same size.

The original strategy of BFM was to invest in domestic and partially international companies, especially those in the pharma, diagnostics, medical device, biotechnology, bioprocessing, clean technology, nutrition, food additive, and composting sectors. The Finnish origin was especially important for the first two funds, but as the most important companies were already in the portfolio subsequently, two-thirds of Bio Fund Venture III was invested in foreign, primarily Nordic companies. However, domestic companies were favored because investing in unlisted companies on the primary market was considered more convenient, and the management of nearby companies was easier to handle. The portfolio included 45 companies, such as Hormos, BioTie, Juvantia, Ark Therapeutics, FIT Biotech, Inion, Medikalla, Nab Labs, Multi Bene, MAP Medical, FibroGen, Rados Technology, KSH Productor, Contral Pharma, Novatreat, Merlin Diagnostika (Germany), Cellartis (Sweden), Egalet (Denmark), Exiqon (Denmark), SantarisPharma (Denmark), SpinX (Delaware), Millimed (Delaware), and Profos (Germany).

Bio Fund Management operated as the lead Finnish investor in most of its portfolio companies. This position fell to BFM almost self-evidently, as the other Finnish life science investors were primarily small local funds, such as TechnoVentures (Oulu), SavonTeknia (Kuopio), MidInvest (Jyväskylä), and AboaTech (Turku). CapMan, although an important VC, played a smaller role in pharmaceutical and biotechnology industry in Finland at the time.

Intellectual capital

The background of all founding partners was in life sciences (e.g., chemistry, biochemistry, molecular biology, and bio-processing). In addition, the partners worked for Sitra for several years and thus had vast experience in investments and board memberships.

The number of employees rapidly increased to 14, and all workers were experts in their own fields and in bio-business-related issues. With such competent personnel, BFM did not place special emphasis on the education of employees. Rather, new persons received their orientation by hands-on learning, for example, by evaluating new cases with a colleague, participating in weekly partner meetings and negotiations as observers, and acting as board members of the portfolio companies. After a certain time period, a newcomer was able to buy company shares and become a partner.

Cooperation

Bio Fund Management entered into close collaboration with various public and private investors. Initially, several investments were made in collaboration with Sitra, but the role of Tekes as a co-financier subsequently became more important. Other domestic collaborators were TeSi, Varma, CapMan and the local funds.

Bio Fund Management was internationally recognized as one of the leaders in life science investments in the Nordic region. The company established a considerable European network, including several European venture capitalists, such as VåxtFonded (Denmark), Atlas Ventures (UK) IndexVentures (Switzerland), BankInvest (Denmark) and Innovations Kapital (Sweden). With these international connections, BFM was able to bring foreign funding from Nordic VCs to certain Finnish companies.

Other important collaborators were professors and scientists from universities in Helsinki, Tampere, Kuopio and Oulu; these professionals offered technical evaluations of potential investment targets and acted as scientific advisors. Financial services were outsourced from PwC; legal services, including due diligence, were outsourced from Borenium-Kemppinen; and patent services, including patentability and the freedom to operate analyses, were outsourced from Berggren and foreign IPR service organizations.

3.1.2 Business development

Strategy

The basic strategy of the company was to increase the value of investments and to assist Finnish life science companies in entering global markets. The deal flow in Bio Fund Management was massive: every year, 150 to 200 cases progressed through a careful evaluation process that typically consisted of three to six months. Evaluations were performed in two-person teams who brought their cases to weekly partner meetings. Poor cases were rejected immediately, whereas good companies were exposed to a thorough in-house analysis that included an eval-

uation of business potential, technology, IPR, market size, competition and other factors. If a company was accepted in the partner meeting process, then it was presented to the investment council with final veto power. These investment councils consisted of investor representatives and typically included four to six members. Only after a positive decision from the council was deeper due diligence performed and the term sheet finalized.

The funding instruments were shares, capital loans and convertible bonds, and the cumulative amount of investments in one company varied from 0.5 million euros to more than 15 million euros; the general rule was that an investment in one company may not exceed 10% of the total size of the fund. BFM also avoided having greater than 50% ownership in a company, with the exception of a few cases.

Membership in the board was always a prerequisite for a positive investment decision; one partner was typically active on five boards. BFM acted as a sparring partner to assist the company in realizing its growth strategy and offered its network to benefit investee companies. The BFM network included various companies in Finland and in Scandinavia as well as international venture capitalists.

Operations

Bio Fund Management exited from the portfolio companies through six international IPOs, seven international sales and five mergers. A fivefold return on investment (ROI) was the ultimate goal, but the best companies realized a threefold ROI, and some companies had no return. However, the success of Bio Fund Ventures I–III was similar to that of other VCs investing in life science, and Bio Fund Venture I and II were ranked among the Top 10 funds (interviewee).

The annual revenues of BFM varied between 1 and 4 million euros and consisted of administration fees at 2.5% of the invested capital. The company experienced positive results and shared dividends every year as an independent venture capitalist.

Signs of foundering

However, the long investment periods that are necessary in the life science industry, lower than expected ROIs, an increasing negative attitude toward life science investments and the withdrawal of Sitra from the biotechnology field increased the difficulty of operating in this sector. It became evident that there was a need for a novel venture capital unit that could make larger and longer investments, have in-house economic analysts, and operate as an investment bank. According to Management, these types of life science-specific organizations with good performance were already established in the USA.

3.1.3 End of independent phase

Unfortunately, no institutions were capable of establishing such a novel VC organization in Finland. BFM had long been collaborating with Danish investors, and in 2007, the company commenced negotiations regarding the establishment of a captive fund with a Danish banking group, Capinordic A/S. The aim was to encourage other Nordic VCs to unite with the organization. In the spring of 2008, Capinordic acquired Bio Fund Management at a price of DKK 67 million. Part of the price was paid in cash, and the remainder was payable in shares that were

subject to a three-year lockup period, with one-third of the shares released every year. However, the financial crisis in 2008 significantly decreased the valuation of financial institutions, Capinordic encountered financial problems, and the acquisition process ceased in 2009. By that time, the original share price of 26 DKK had diminished to 2.6 DKK before the final installment. Capinordic declared bankruptcy in February 2010.

3.1.4 Current situation

With the acquisition, BFM became a subsidiary of Capinordic, and Seppo Mäkinen became the managing partner. For a short period, the operations in Helsinki continued as before. There were also no changes in the collaboration network or in board membership work. However, shortly thereafter (2008–2010), some of the partners at BFM exited the company at their own will, some individuals retired, several were laid off and the Danish partner became the managing partner. After this decrease in personnel, a French partner and a Danish partner attempted to displace the Finnish partners through an internal management buyout. This buyout raised concerns among the Finnish investors, who did not want their investments to be managed by a French–Danish fund that had no knowledge of the local characteristics. In 2006, some of the former employees of BFM had established Inveni Capital, a novel VC, and the Finnish institutional investors decided to transfer the management of all investments to Inveni Secondaries in 2010. The remainder of the Finnish employees also exited the company, and the remaining BFM with an empty portfolio stayed in Capinordic until the former CEO bought the BFM shares from Capinordic. He has continued to consult under the Bio Fund name.

3.1.5 Causes and consequences

The funding of life science companies has been a challenging task: within a decade, the high expectations of investors turned into risk-averse decisions resulting from the currently volatile financial climate. Furthermore, in the life science industry, the conventional exits within three to five years do not apply, and returns on investments have not been adequate. This situation has been especially relevant for drug development companies whose development phases are typically long; in contrast, in the medical device and diagnostic sector, performance has been better and has not significantly deviated from the performance of other sectors.

The decision of Bio Fund Management to give up life science funding was a result of several issues. To continue, the company would have needed more resources and a larger organization. Selling the company to Capinordic at an adequate price was an option that facilitated an exit for management but also a continuation of funding within the Finnish life science sector.

Investors originally accepted the selling decision, but the management buyout by foreign partners created mistrust in the future of the merger. In that situation, emptying BFM appeared to be the appropriate solution, especially given the questionable financial status of Capinordic.

The most significant problem encountered by BFM operations was obtaining new capital both for the fund and for investee companies. In hindsight, we can argue that institutional investors and banks lacked expertise in life sciences and thus followed the common trend of investing during the hype period and demanding returns when prices decline. At the company level, when a new investor was found, the reconciliation of old and new shares was difficult because ownership needed to be reorganized according to the series of shares. In addition, the motivations of stakeholders differed, and new investors may have had diverging opinions on, for

example, the timetable for an exit. Addressing board members representing investors owning A-, B-, C- and even D-series of shares is not an easy task for the management of the company.

Because the technical expertise in Finland is excellent, the portfolio of Bio Fund Management was considered good, and investments were dispersed to various sectors to minimize risks. However, according to BFM, mistakes were also made with its investment policy. Although each company had to pass a stringent evaluation process, some of them were revealed to be bad choices. The most difficult task was evaluating management, which played a major role in the success of a company. Some start-up leaders wanted to have unrealistically glorious settings, and some companies had a high burn rate, whereas others were not cooperative with their boards. In contrast, with good leaders, moderate technology could be transformed into excellent products.

BFM also sold certain companies either too early or too late, and the company made mistakes in evaluating the market potential of some products. Because of a lack of money, some licensing agreements had to be negotiated with bad terms. Furthermore, with respect to environmental issues, market entry was sometimes dictated by political decisions that were difficult to foresee.

Bio Fund Management was the first sector-specific investor, and the mode was soon adopted by, for example, Sitra based Eqvitec investing in information technology. Over the years of its existence, BFM has funded nearly all domestic biotechnology and drug development companies with commercial potential. Several of them still exist and employ a significant number of life science and medical experts. BFM has also presented Finnish expertise abroad, thereby creating confidence in local biotechnology and leading to foreign investments and an improved status for Finnish innovations.

3.2 Sitra Life Sciences

- **Active period as a Finnish governmental venture capitalist focusing on the life sciences:** 1999–2008 (thereafter focusing on other industry segments)
- **Location:** Helsinki
- **Total employment effect:** ~ 60 man-years
- **Total life science investments:** ~100 million euros

3.2.1 Capital growth

Sitra, the Finnish National Fund for Research and Development, was established in 1967 to commemorate 50 years of Finland's independence. Sitra is an abbreviation for Suomen IT-senäisyyden juhlarAHasto, which is translated as “the jubilee fund of Finnish Independence”. The fund was commissioned with the task of promoting Finland's stable and balanced development, economic growth and international competitiveness and cooperation (www.sitra.fi); these tasks are defined by law. Sitra's office is located in Helsinki.

An endowment of 100 million marks (17 million euros) created by the Bank of Finland formed the basis of Sitra. From 1972 to 1992, the fund's capital increased to 500 million marks (84 million euros), which, in addition to an increase in market value, led to a total nominal capital of 1.4 billion marks (235 million euros) from 1993 to 2001. By the end of 2011, the market value for Sitra's endowment capital had increased to 697 million euros (www.sitra.fi).

Sitra's objectives are to invest its endowment capital in a profitable and safe manner and to steer its investment operations according to the principles of social responsibility. The endowment is allocated to equity funds (49%), bond funds (45%), and other investments (6%). The investments are allocated throughout the world and yield a typical annual ROI of 4–5%, with the returns dependent in part on stock exchange developments and, hence, general market trends (www.sitra.fi).

Sitra operated under the supervision of the Bank of Finland until 1991, when Sitra was transformed into an independent fund that reports directly to the Finnish Parliament. Since 2000, Sitra has not received funding from taxes or the state budget. The operations of the organization are funded solely from the returns on capital investments, and the endowment can be used only for operational purposes under exceptional conditions. Hence, Sitra is a so-called Evergreen fund.

Sitra Life Sciences

In the 1990s, Sitra's position was viewed as the following funding step after the government funds from Tekes, the Finnish Funding Agency for Technology and Innovation. Sitra had two major spinoffs geared toward the high-technology sector: Eqvitec, which focused on ICT, and BioFund, which focused on life sciences in general and biotechnology, diagnostics and pharma companies in particular.

Sitra's life science group that was focused on creating a new, research-based industry within the fields of biotechnology, medical devices, diagnostics and chemistry was established in 1999. Its role was to support promising start-up companies, which were expected to obtain subsequent financing from the capital markets (Tulkki et al. 2001).

When the team began operations, it placed approximately 50 companies in its portfolio. The companies displayed a wide array of application areas within the main categories of biotechnology, drug development and diagnostics, and new categories opened through deal flow. The drug sector was divided into different application areas, whereas the diagnostics sector had a shorter life span and developed differently.

New investments were chosen from an annual deal flow of 50 to 100 potential investments. The initial assessment was made by the group, with final decisions made by Sitra's board. During the most active period in the first few years, the team executed a total of 10 to 15 investments. Making exits from old investments helped to maintain a constant investment portfolio of 50 to 55 companies.

Intellectual Capital

Sitra's life science group included six professional investors with a strong industry background and knowledge of technology assessment that stemmed from experience in Tekes; Hannu Hanhijärvi acted as the leader of the team from 1998 to 2004. Two part-time controllers were hired to support the group, in addition to two assistants. The team gained experience in the specificities of the drug and medical industry; in board practices; and, to some extent, in biological, medical and technical sciences.

Cooperation

The group had an extensive network, partly through the former personal contacts of the group members and partly through Sitra itself. The key partners were Tekes, the Ministry of Employment and the Economy, Finnish Bioindustries FIB, the Chemical Industry Federation, institutional investors, and the entire Finnish life science industry. In 2000, Sitra signed a strategic collaboration agreement with five international VCs in the UK, Germany, France, Sweden and the USA, with the aim of obtaining international capital and investment knowledge for Finnish companies. Other domestic and foreign VC partners included several leading players in key markets.

3.2.2 Business development

Strategy

Most investments were undertaken in domestic companies, following the basic principles of Sitra. Moreover, some of the investees have since become foreign-owned through mergers and acquisitions. The stated mission was to invest in early-stage companies, and initial investments in companies that had already undergone an IPO were not allowed. The focus on early-stage companies also introduced a specific challenge: how to find suitable CEOs for projects that had barely hatched from their university incubators.

Sitra carefully positioned itself with respect to other investors and funders in the field, such as Tekes, TeSi (Suomen Teollisuussijoitus, Industry Investment), Finnvera and BioFund, to be a first phase investor that strongly supported technology transfers from universities to companies. Sitra also assumed the lead as the first investor willing to carry higher risks to attract other investors to the companies. However, its strategy was damaged by the virtually total stagnation of the investment industry in 2002.

Sitra assumed an active role in the boards of its companies but seldom occupied the chair position. Sitra's main goal was to support the company not only through board meetings but also between them by providing access to all of its networks and personal contacts. Sitra also assisted the companies in finding and contacting new investors. However, Sitra representatives avoided taking control of company leadership through the board, in accordance with good board practice guidelines.

Sitra made direct equity investments and subordinated convertible loans but seldom provided ordinary loans. However, profit-share loans were considered; in these loans, part of the investment would have been repaid when the company became profitable, and in the case of an exit, the entire loan would have been repaid. The largest cumulative investments in one company were between 13€ and 15 million euros, and the smallest between 400000€ and 500000€. Sitra could act as the only financier in the first financial round, but in subsequent rounds, other investors were expected to join the company. Unlike other investors, Sitra does not have a time limit for its investments, which is beneficial especially for start-up companies whose commercialization lies in the distant future.

Sitra strived for an investment of 40% or less; occasionally, its share rose to more than 60% in some cases. For Sitra the 50% ownership limit is in fact associated with an interesting poison pill: if Sitra's ownership exceeds 50%, then Tekes regards the company as a large enterprise, with a negative effect on the terms of potential Tekes support.

In 2011, Sitra's cumulative ROI was close to 0%, which is consistent with its overall goal of reclaim its invested capital. Sitra's main income is and will continue to be obtained from its general global capital investments in, for example, publicly traded stock. Among its life science investments, only one company has been able to pursue an IPO (BioTie), whereas several companies have exited through a trade sale.

Signs of foundering

In 2001, the VC market changed drastically when the ICT bubble burst; investors still discuss a nuclear winter, with a black sky and everyone taking cover. The uncertainty and risk aversion spread from ICT to biotechnology. Furthermore, because the entire investor base was both young and relatively undeveloped, Finnish bio-investments came to a virtual halt for several years. The situation was aggravated in the spring of 2004 when the forthcoming president of Sitra announced that Sitra would no longer make new investments in biotechnology companies. By that time, Sitra had undertaken approximately 100 million euros of investments in biotechnology and drug development companies (Hyvönen 2004, Mikkonen 2004).

Although the factual situation did not significantly change because Sitra had not made any new biotechnology investments since 2003, the announcement had a profound effect on all stakeholders, as others interpreted this major Finnish investor to have declared biotechnology investing as obsolete and unprofitable. Biotechnology investing crashed. The situation raised concerns throughout the biotechnology sector, not only in Finland but also abroad, and it was speculated that Sitra was disposing of its entire portfolio to foreign funding or selling it to a consortium of US pension funds for 100 million euros.

However, Sitra's board decided to continue funding certain aspects of its portfolio companies but to avoid investing in new start-ups. Consequently, Sitra performed an internal evaluation of its biotechnology portfolio by attempting to identify the probabilities of company survival and determining how continued support could affect that probability. As a result, approximately half of the investee companies remained under Sitra's support, and each of these companies retained its position only after an intense internal analysis.

During 2006–2007, Tekes decided to diminish its biotechnology support. Moreover, it emphasized normal loan instruments rather than capital loans, in contrast with its previous support mechanisms. The portfolio companies suffered capital drainage followed by significant difficulties in retaining new investors. The entire investment sector became tense.

3.2.3 End of independent phase

Sitra's life science team was merged into other teams in 2006 when Sitra combined its VC teams into a single unit.

3.2.4 Current situation

As noted, the portfolio companies were divided into two groups: those requiring further investments and support and the "passive" companies that would not receive further investment because the input-output ratio was deemed negative. Sitra also established the goal of being able to exit from the passive companies. Some of these companies already had weak operations, and they either were fused with companies with better performance or declared bankruptcy, although most companies underwent a management buyout. A follow-up analysis showed that some of the companies have been able to not only survive but also prosper. Currently, the portfolio consists of seven life science companies.

3.2.5 Causes and consequences

Biotechnology is a particularly complex area of investment, as product claims mandate evidence, rising barriers for entry and prolonged time from innovation to market when compared with, for example, the ICT sector. The required investment times typically exceed the ordinary three- to five-year rule, a phenomenon that has been difficult to understand because various opinion leaders lack extensive knowledge of the biotechnology or drug development sector. This group contains both institutional investors and the media, which have played a significant role in increasing the expectations of life science profits to sky-high levels followed by a rather abrupt decline. In such a climate, the operation of VCs has become complicated.

Furthermore, the biotechnology sector evidently encountered a severe shock as the entire market for high-technology financing collapsed in 2001, soon followed by the burst of the biotechnology bubble. The situation was further aggravated by the economic stagnation that began in 2008.

The biotechnology sector has also been hampered by the lack of competent and experienced CEOs, and this factor has often led to negative investment decisions despite good innovation and a promising product. Presentation skills were often inadequate as technological details substituted for marketing vision. Furthermore, preparations for financial rounds were often initiated surprisingly late in the process, and collaboration with the board has been minimal

in some cases, resulting in a mismatch between the founders and the investors that sometimes led to severe disputes. The company leaders were also reluctant to use external consultants, although in several cases, negotiations with Big Pharma could have proceeded more smoothly with the assistance of consultants capable of finding and opening the right doors. In contrast, Finnish leaders are well aware of various financial instruments and network with other companies and universities to facilitate a flow of open innovations.

In addition to these externalities, Sitra has also considered its possible internal weaknesses. The group encountered initial difficulties. A rather extensive deal flow with no prior established internal work routine strained the capacity of the group. Moreover, Finland had a rather inexperienced VC sector and was not a well-known or even interesting market for foreign investors; therefore, syndicated investments were difficult to build. However, Sitra invested in foreign funds and was thereby able to attract foreign investors into Finnish companies.

In some cases, Sitra failed to sufficiently recognize the attitudes and operational methods of the management of the companies, and this neglect led to conflicts. In other cases, the technology had simply not been finalized for commercialization. An excessive number of research iteration rounds needed to be completed to finalize the commercial product, which required the spending of a significant amount of time and money. In other cases further downstream, Sitra was unable to correctly estimate a company's true resources and presented timetable. In particular, this information asymmetry became significant in R&D-based high-technology fields and might have been aggravated by the strong affection of researchers with respect to their own findings, innovations and ideas. Nevertheless, an investor's due diligence can only be based on existing materials and findings.

The governmental connection with Sitra has been argued to be a confounding factor in the process of matching investors and companies (Hermans et al. 2009). The decision-making process is slower and more formal with Sitra than with fully private venture capitalists; this slower process has led to some missed opportunities for the Sitra life science group. However, Sitra emphasizes its political independence in everyday decisions.

The life science group was not prepared for the rather abrupt negative decision in April 2004 regarding Sitra's future biotechnology investments. The news spread internationally with a negative connotation, and at least one syndicate investment was lost because the partner felt that the risks had become excessively high. Moreover, the pre-seed functions that had supported investment groups were taken to completion, and there was an intensified internal struggle over any capital available for additional investments [in biotechnology]. Finally, the Sitra decision appeared to have a direct effect on the willingness of Tekes to invest in biotechnology; the sector suddenly encountered serious negative disbelief. Despite several successes, the general attitude changed, and from Sitra's perspective, this change came too early: after only 2-3 active years of investment with a seed-stage focus, accumulated evidence of success did not yet exist and could not have been expected at that point.

As previously indicated, Sitra's life science group has thus far been able to recover nearly all of its investments and show a ROI of 0%, which is consistent with its established goals. Moreover, several of the companies that are no longer in Sitra's portfolio have continued operations, often with foreign ownership. Sitra's life science group has been able to drive several innovations from universities to commercial products, with ensuing positive effects on labor. Sitra

has been active in the Finnish Venture Association and various other social networks and has given business lectures to company leaders on issues such as juridical challenges. Finally, Sitra has been able to involve large domestic institutional investors, such as Varma and Ilmarinen, in the field of biotechnology. Even more interestingly, Sitra has been able to attract foreign investors to invest in Finnish companies.

However, the most important value added by Sitra is likely in the form of its intangible assets, an issue that we will discuss in the final part of this report.

4 Results and discussion

The aim of this study has been to conduct a detailed investigation at the development of the Finnish biotechnology and pharmaceutical industry during the financial riptide of the past decade. The common story is familiar: high expectations, failure to deliver, disappointments with the ensuing financial low tide, lost companies and lost investments. But there has definitely been also successes.

However, rather than describing the success of Finnish life science flagships, we have perused beneath the surface and characterized the array of events caused by financial problems in small or medium-sized enterprises from the perspective of the managers who experienced these difficulties. We found their stories to be not only fascinating, but also particularly valuable.

Because virtually all investments in dedicated SME biotechnology companies are allocated to research and development, we also believed that significant knowledge must have been created. Intuitively, however, the nominal residual value of a failed company does not appear to capture the vast R&D efforts that are exerted within companies. Hence, we applied the intellectual capital framework and asked the following question: have we overlooked something?

This study focused on six Finnish biotechnology companies that had either completed their operations or continued under a different name or owner as a result of severe difficulties. To broaden the perspective, we added to the study two major venture capital companies that have invested in Finnish biotechnology and pharmaceutical companies.

The following important questions are discussed here:

1. What are the critical issues for the survival or failure of Finnish life science companies, as learned from the past events?
2. What is the fate of the intellectual capital that is created in research-intensive biotech and drug development companies?
3. What is the future of life science funding?
4. What type of political will is needed to make the life science sector zoom rather than float?

We strongly emphasize that this research is a case-based study with limited feasibility and that the opinions and ideas presented in the following sections illustrate the mindset of only a handful of people. However, these ideas are intended to evoke a more general public debate that will eventually create preconditions for the future development of the life science sector.

4.1 Strengths of Finnish biotechnology

In a parallel survey by ETLA, the strengths of the Finnish biotechnology environment were identified as strong human capital and profound public support (Kulvik et al. 2013). The results that were obtained in the current study resonate with those findings, as education, people, quality, advanced infrastructure, and political stability were found to be important driving forces of Finnish biotechnology. The role of public support was appreciated, although the action model raised conflicting opinions (see section 4.2).

The basis of Finnish life science is the excellent research that is conducted in universities and research institutes. According to the National Rankings of Clinical Medicine 1999–2009 and the Essential Science Indicators SM database from Thomson Reuters, Finland is ranked in sixth place based on the number of medical publications, but its research is considered the best in the world, as indicated by the largest number of citations per paper (Piispanen 2011).

However, Finnish expertise is not limited to medicine or drug development - a fact that is often forgotten in the public debate on biotechnology. During the 2005–2009 period, the number of Finnish biotechnology and pharmaceutical patent applications were 600 and 707, respectively. Moreover, a great number of patent applications in the areas of food chemistry, chemical environmental technology, medical technology and of biological material analysis (altogether 2093) are presumed to have close connections to biotechnological innovations (World Intellectual Property Indicators, 2011, WIPO Economics and Statistics Series)¹⁸.

Finland has excellent research and development in areas that include new enzyme technologies, protein engineering, and metabolic engineering and modeling – all aiming for new, environmentally safe and cost-efficient processes for industries. The combination of ICT and biotech have prompted the emergence of novel applications, and the utilization of biotechnology has increased in traditional sectors, such as the forest, food, chemical, energy, mining and environmental industries. Furthermore, a biotechnology industry cluster promoting the sustainable processing and production of bio-based products using biotechnology was established in June 2012.

WEF's Global Competitiveness Index has ranked the quality of the Finnish education system as the highest in the world (www.investinfinland.fi). Given the excellent education system, the lack of professional workforce has not been an issue in Finland. On the contrary, academic unemployment ranging from master's to doctoral degree recipients has grown into a serious problem among life science specialists. The quality and regulatory expertise found among Finnish employees is highly esteemed and offers a competitive advance over biotechnological challengers from the BRIC economies. In some cases, this expertise has ensured that at least some operations have remained in Finland during mergers. Finnish people are also perceived as "meticulous, knowledgeable, hard-working and delivering what they promise -in today's competitive business environment diligence is what matters"¹⁹.

¹⁸ http://www.wipo.int/export/sites/www/freepublications/en/intproperty/941/wipo_pub_941_2011.pdf

¹⁹ A quote from an interviewee.

4.2 The role of public funding

At the beginning of the 21st century, the Tekes and Sitra funding model was highly appreciated and imitated abroad, and Sitra's decision to retreat from the biotechnology sector was a true surprise to all stakeholders. Simultaneously, Tekes decreased the amount of funding (see section 1.3), a decision that has been criticized because Tekes was primarily assessing start-ups or early-phase companies, and drawing conclusions based on the performance of such companies was regarded as inadequate.

Currently, there appear to be conflicting opinions on Tekes. In the critique Tekes is considered too distant and its advisors too remote, and neither responsibilities nor incentives guide the decisions of these advisors. Rather than engaging in estranged relationships, companies are inviting Tekes to “walk with them” and foster their development. Conversely, it has been speculated that Tekes occasionally assumes an excessively administrative role when controlling (via funding) future operations, such as determining whether to conduct a clinical trial. Tekes experts are perceived as civil servants with technological (rather than business) education and experience, and the companies do not have full confidence in the ability of Tekes to evaluate relevant business options.

Although Tekes has recently emphasized funding business development and marketing-related operations, previous funding was focused on technological innovations, and *e.g.* clinical trials were dismissed. However, for drugs or *in vivo* used biotechnological innovations, these trials are essential and must be considered already in preliminary financing decisions. A life science innovation not only involves a good idea that is ready to be used after pilot testing but also requires years of further development; if the will exists to take such a product to market, then there must be realistic methods of promoting the process.

This study revealed some overlapping activities funded by the public sector. As an example, own clean manufacturing facilities and the corresponding process development and regulatory infrastructure were established in several drug development companies during an early phase of the development process, although novel domestic companies specializing only in the cGMP contract manufacturing of biopharmaceuticals and synthetic molecules were simultaneously founded. In cases in which the drug development process did not proceed as expected and the need for a cGMP-grade product was delayed, the manufacturing unit was underused, and the clean facilities were peddled to outsiders. In hindsight, this approach has been cost-inefficient and has hampered the growth of contract manufacturing companies. Although competition is desirable in free markets, one may argue whether the consolidation of funding decisions in the public sector might actually constitute a meaningful strategy for preventing the building of expensive, overlapping infrastructures.

The funding instrument of Tekes is currently a risk-bearing loan or grant, and capital loans are no longer used. However, during the development of this study, it became evident that the capital loan was beneficial in certain acquisition and merger situations. Hence, should Tekes consider diversifying its funding instrument portfolio? There also appears to be a lack of a specific instrument or fund for clinical trials, but such a fund could be created by combining public resources (see section 4.5).

4.3 What went wrong?

Several previous studies have shown that a lack of venture capital and business expertise have been typical obstacles encountered by Finnish life science companies (Hermans and Kulvik 2004, Kulvik et al. 2013, Patana et al. 2011, Nikulainen et al. 2012). Financial problems were found to be the main reasons leading to the bankruptcies, mergers, and buyouts that were described in this report (Chapter 2). Virtually all companies were underfinanced, and they operated on a day-to-day basis. Both the amount and the length of financing were low compared with other countries. It became evident that a classical venture capital model is not compatible with the biotechnology and drug development sector, in which several funding rounds dilute the seed financier's profits and exit periods exceed the traditional 3–6 years. Therefore, a novel type of funding is needed for the life science sector; these issues are discussed in greater detail in section 4.5.

However, the argument that a lack of funding is the scapegoat for biotech problems is too simplified. The companies also suffered from overly expensive infrastructures and excessively wide portfolios that affected their cost structure. In addition, problems were encountered in various other areas, such as company management, quality and regulatory expertise, selected business strategies, and public media.

Management – In the beginning of the 21st century, the leaders of the novel Finnish life science companies often had a solid scientific background but limited or no business-related education or experience. The stimulus to found a company may have been a praised article in *Nature* or a prize in a Venture Cup. Furthermore, competing scientists who did not work well together could each start their own companies focusing on similar research. Thus, business competence was a less important criterion, and several managers lacked expertise in business skills, such as leadership, negotiation, human resource management, customer and end-user orientation, reporting and documentation. As an indication, business plans were often technologically detailed descriptions with only minimal efforts with respect to positioning, market research, financial forecasts and competitor analyses.

Heterogeneous management teams with broad views and diverse skills appear to be positively related to firm growth (Handelberg 2012). A critical evaluation of life science companies reveals that their management teams are relatively homogenous: board members are often investors, and as the pool of competent board members is limited in Finland, the same people are found on a number of company boards. Frequently, the biotechnological view should be more prominent; people with expertise in pharmaceuticals are not self-evidently optimal members of biotechnology boards, as Big Pharma deviates from the biotechnological industry with a global infrastructure, greater volume, and rigidity, whereas biotechnology business typically requires greater flexibility in a rapidly changing environment.

Foreigners play an important role in Finnish research. In 2010, 46.3% of PCT applications originating from Finland included at least one foreign inventor, and Finland was ranked fourth in the number of PCT patent applications with at least one foreign inventor²⁰ (WIPO Statistics Database, 2012, based on the WIPO IPC-Technology concordance table). The situation in everyday business is different; companies do not fully exploit the knowledge of foreign CEOs

²⁰ http://www.wipo.int/freepublications/en/patents/901/wipo_pub_901_2012.pdf

and board members, and do not include Finns operating abroad in their boards (Kulvik et al. 2013). Unfortunately, the short-cycled financing and lack of incentives has led to difficulty in recruiting internationally appreciated CEOs (Kulvik et al. 2013).

Regulatory and quality expertise – It is crucial that the profile of a product is decided at the beginning to be able to design the ensuing actions. In a drug development company, final marketing authorization should guide all precedent research and development procedures. Unfortunately, the ultimate goal, the intended use, required quality, and necessary efficacy and safety data were not always carefully considered when manufacturing, formulation, and nonclinical or clinical studies were planned. In one example, production processes that were originally developed for research purposes included substances that are not allowed for use in the manufacture of human drugs, and the entire process had to be redesigned for industrial use. In another example, because initial concentrations of the drug molecule were too low, the size of a novel pill became too large for weak patients to swallow. In addition, if preclinical or toxicological studies were conducted with material that was not adequately characterized, then all studies had to be conducted again. These academic research process reruns caused extra delays and expenses.

“In God we trust – all others have to show documentation.” This slightly modified quote of Professor W. E. Demings (1900–1993) is one of the guidelines for regulatory-compliant laboratory work. Unfortunately, in young companies and academic institutes, both the documentation and the code of conduct were typically incomplete. Most of the funding received was used for science and technology, and the necessary costs of quality and time were significantly underestimated. However, quality is an issue that cannot be compromised, not even during financially challenging periods.

It is important to bring the concept of quality to universities and to build quality into products from the beginning. Academic scientists and students need courses on good laboratory procedures (GLPs) and time to implement them in their daily work. Moreover, well-conducted and documented research will also interest large enterprises. Notably, poor R&D productivity and the loss of revenue from blockbuster drugs with expiring patents have caused top pharmaceutical companies to turn to alliances with universities, with the aim of gaining access to early-stage assets. From January to June 2012, pharmaceutical companies and academic institutions entered into 19 strategic alliances in the USA worth 7.2 billion USD (Singh 2012a).

It is hoped that Tekes' current efforts to create public-private partnerships via research funding terms and via the research programs of the Strategic Centres for Science, Technology and Innovation (SHOK) will ultimately increase entrepreneurial and quality-oriented mindsets at academic institutes.

Business strategies – Several drug development companies operating during the 1990–2010 period implemented strategies aimed at out-licensing drug candidates after Phase II, which was generally considered to be the point at which the cost/return relationship was the most favorable. The incomes received from licensing a lead product would then cover the further development of other compounds in a portfolio. Alternatively, some companies wanted to bring the products to market by themselves, and an IPO was considered an important funding mechanism. Partnering during the start-up phase was not common, nor was product development in collaboration with potential customers or end users. This problem has been apparent both in life science companies and in high-tech companies in general: Finns want to bring

technologically superior products to market themselves, whereas in the USA, consumer/business-friendly product/service applications are brought to market by introducing consumer aspects already in early product design (Handelberg 2012).

Several valuable products were sold out rather than out-licensed, such as the intrauterine device (IUD) of Leiras, the enzyme technology of Cultor, and the health technology of Datex-Ohmeda. In hindsight, if the rights for these innovations had been out-licensed, then such a strategy could have provided long-term benefits (for example, constant cash flow, work, international distribution and marketing channels) to the Finnish biotech industry rather than short-term profits to the selling company's stakeholders. Fortunately, licensing and research alliances have now become an important business model in the Finnish life science industry, and the value of IPRs in creating revenues has been considerable.

In addition, meeting customers and opinion leaders as early as possible has become increasingly important. By soliciting customer feedback, companies can adjust product development according to the needs of the market. Regarding this issue, drug development deviates from industries such as the food industry, in which buyers want to see and taste the final product before signing any contracts. Drug development is often done in a network model according to which the best innovations are sold "prematurely" because Big Pharma is reluctant to buy later-stage projects as they have become more difficult and costly to in-license. In fact, 57% of the in-licensing deals made by the top pharmaceutical companies in 2008 and 2009 were for drugs in the preclinical phase (Comer 2010).

The attitude toward marketing has also changed significantly. The current notion of marketing is evidently not merely attending a trade fair and showing a readymade prototype; rather, it is a negotiation and networking process that may last several years beginning from the day that a patent application is filed or even earlier. Marketing is rarely straightforward, as each product requires its own marketing approach. Potential buyers are contacted in a phase in which there is actually nothing yet in hand, but they remain informed of the development and are offered an early licensing option.

Infrastructure – A general trend was to have in-house operations for most functions, including cGMP production, process development, analytics, regulatory and quality assurance and often ICT management; creating and maintaining this infrastructure was extremely expensive. Furthermore, premises were often located in novel technology parks that provided a creditable and multidisciplinary image for the companies but were not start-up-friendly in their renting policies, as observed with some companies. High rents, long renting period requirements and inflexible contracts were not adjustable to the changing needs of these companies. Supporting activities (*e.g.* distilled water, cold/warm room facilities, sterilization and dishwashing) were often completely lacking or available only at an additional charge. Therefore, one may argue that those with the most significant benefits from the high-technology hype may have actually been the constructors of such technology parks.

These heavy infrastructures were soon dismantled as outsourcing increased in frequency. Currently, some companies operate almost on a virtual basis with limited personnel and physical space. Most operations, including research, are outsourced to other companies or academic institutes. This business model is cost-effective, but whether it will prove to be profitable remains unknown.

Remote location – The lack of foreign venture capital has been explained by the remote location of Finland; this factor may indeed have rendered the country less attractive. However, some important life science investors are also relatively close, such as Novo Seed (Denmark), Sunstone Capital (Denmark), Wellington Partners (Germany), Global Life Science Ventures (Germany), Health Cap (Sweden) and Lifeline Ventures (Finland).

Recently, pharmaceuticals and biotechnology have become hot topics in Russia, and biomedical technologies (including healthcare, medicinal biology, bioinformatics and industrial biotech) are on the list of top 5 priority areas in innovation development for the Russian government (Makeeva 2012). Russia's government undertook significant investments (USD 4 billion) to modernize its pharmaceutical and medtech industry, and Rusnano (the government-backed investment firm) is currently undertaking joint-venture investments with foreign companies. As an example, Rusnano will invest up to 37.5 million USD over a three-year period in a joint project with Magnisense (France) to develop next-generation bioassays for diagnostic purposes.

The Russian modernization process offers unique opportunities for growth-anxious, open-minded Finnish biotechnology and pharmaceutical companies. In April 2012, Rusnano invested 25 million euros in the Finnish company Beneq, which is a world leader in industrial production of equipment for nano-scale thin films and functional coatings. Therefore, rather than growing into remote China, as other countries are so apt to do, Finns should more seriously evaluate the true potential of their close neighbor Russia.

It should be mentioned that biotechnology is a global business, and in most markets, a brand does not necessarily gain significant value by being Finnish. Furthermore, the diseases and problems to which biotechnology may bring novel solutions are global; therefore, limiting research to domestic topics should be avoided. As an example, AIDS and malaria are relatively rare or lacking diseases in Finland, respectively. However, if Finns can develop novel and efficient therapies for these diseases, then the markets can be significant with high sale expectations. Similarly, innovations in areas such as bio-fuels, environmental technology, bioactive food, and diagnostics have global markets.

Portfolio – Several companies were struggling with the size of their portfolios, with an indeterminate amount of products in the pipeline. A portfolio of a company that was excessively limited and consisted primarily of early-phase products did not fulfill the criteria for international investors (Heinonen 2010). Therefore, many companies had several products simultaneously in development, which led to a shortage of money because discovery, proof-of-efficacy, toxicity and safety studies were expensive, in addition to the costs of clinical trials, patenting and marketing. However, projects that were not finalized were deemed virtually worthless. On the other hand, some companies were forced to focus on specific research and were not allowed to disperse their resources and simultaneously start service businesses.

Currently, we have returned to a situation in which most investors are interested in companies with only one project: investors diversify - not companies. Selling one project is the easiest way to make a profitable exit, as no money is spent on vague development projects.

Public media – A decline in biotech appreciation occurred in 2004, when Finnish public media quite unexpectedly began to criticize biotechnology and the investments made by Sitra

and Tekes (Kantor-Aaltonen 2011). Biotechnology had not fulfilled its promises, at least not as quickly as the public had expected. The negative attitude spread to people who did not understand biotechnological issues and to investors, and financial problems became part of the daily life of biotech companies. As a result, several companies declared bankruptcy, and the public media obtained more fuel for their criticisms.

In hindsight, the public evaluation began too early. Many start-ups were pushed up against the wall already within a couple of years, although the development of biotechnological innovations unavoidably requires a longer time period. The power of public media and public opinion were daunting; consequently, the industry was severely wounded and characterized by unemployment and lost innovations.

Public media have the power to influence attitudes, but Finns have not fully exploited this ability. Positive company news, venture financing obtained, grants, and contracts seldom cross the news threshold. For example, Burrill's monthly review rarely reports on Finnish funding news, yet grants as small as 0.3 million euros are reported by companies from, for example, Israel. Finland could build an image of innovative Finnish biotechnology both through companies as well as through the public sector and the media.

4.4 What is the fate of the intellectual capital that is created in research-intensive biotech and drug development companies?

As previously noted, research-intensive companies typically operate in fields in which failure is an inherent risk of the industry. Such companies also tend to be the focus of government interest and support; hence, they easily become targets of critical evaluation. The previous chapters have described the life span of six companies that experienced bankruptcy, mergers or buy-outs because of financial problems. Essentially, all of these companies failed in their original business strategies, but their influence is or has been significant (Table 2).

Table 2 summarizes key figures from the interviewed companies and describes their influence on the Finnish economy through traditional metrics. The data describe the accomplishments under Finnish ownership or received from Finnish innovations.

For capital-intensive, high-technology R&D companies, value creation is by definition strongest for intangible assets, such as IPR, personnel expertise, research collaborators and develop-

Table 2 Key figures of the six biotechnology companies in the study							
	<i>Carbion</i>	<i>Hormos</i>	<i>Inion</i>	<i>Ipsat</i>	<i>Juvantia</i>	<i>Medipolis</i>	<i>Total</i>
Life span as Finnish owned company, yrs	3	8	11	12	12	6	9 (avg)
Total sales, 1000 €	18	18 750	38 000	0	1 480	5 080	63 328
Funding received, 1000 €	8 000	50 000	26 000	30 000	26 800	n/a	140 800
Customers	0	3	n/a	n/a	n/a	7	10
Maximum number of employees	20	70	120	35	44	20	52 (avg)
– Total employment effect, man-yrs	50	420	600	200	180	165	1 615
Patents/applications/families	8	50	20	4	28	0	110

ment partners, scientific networks, regulatory clearance, and internal procedures. The research and its results are themselves the result of accruing the knowledge and skills of employees and translating it into codified knowledge for and within a firm. In addition to the skills and knowledge adopted by employees from their R&D tasks, companies can also train their employees in additional skills. In R&D companies that primarily employ scientists, training in business skills has become increasingly important and equal to scientific and technical skills. Table 3 shows the intensity of staff training organized systematically by the surveyed companies.

Table 3 Company efforts in training employees in specific skills on a scale from 1 (very little effort) to 5 (very high effort), as disclosed by the company leaders

<i>Skill</i>	<i>Effort (avg)</i>
Scientific and technical skills	3
Quality assessment skills	4
Regulatory skills	4
Human resource management skills	3
Corporate governance skills	3
Financing skills	2
Networking skills	3
International skills	3
Marketing skills	2
Negotiation skills	3

All of the companies under study experienced an outflow of their workforce when signs of foundering became evident, and in two companies, the initially low turnover of employees increased markedly after a crisis emerged. However, in two companies, a significant part of the original workforce has been rehired; one company was able to retain much of its original R&D personnel; and one company continues operations with part of its original workforce (see Table 4). These findings are consistent with the claim by Agarwalet et al. (2007) that additional value is inherent in the dynamics of a workforce's intellectual capital; thus, such value can be captured if a company can ensure survival or if its intellectual capital can be reconstituted.

Table 4 Fate of additional selected intellectual capital

	<i>Carbion</i>	<i>Hormos</i>	<i>Inion</i>	<i>Ipsat</i>	<i>Juvantia</i>	<i>Medipolis</i>
Employee turnover	Minimal	Small	Minimal	Small	Minimal	Minimal
Fate of patents and other IPRs	Reconstituted into Glykos	Hormos (US)	Inion (China)	Sold for USD 20000	Santhera (Swi)	n/a

Based on the views and experience shared with us by Finnish biotechnology company leaders in present and previous extensive interviews, we argue that the following statements are particularly applicable to high-technology R&D-intensive companies:

1. Value is created in both successful companies and failed companies. A significant share of that value is from intangible assets, such as IPRs, personnel expertise, business and scientific networks, created methods, and internal working procedures in biotech companies.
2. In a company failure, a significant part of the value created remains open. Because financial metrics focus on tangible assets and because such a company almost invariably fails from a financial perspective, the value added is considered lost. However, at least in high-technology R&D-intensive companies, most of the value that is created is in the form of intangible assets, is not captured by traditional metrics and is thus overlooked. We claim that much of the “lost” intangible assets can indeed be identified through the intellectual capital framework. Most of the created value remains valid even after a company’s shares become worthless. This finding reveals interesting implications for public support policy evaluations within high-technology sectors because measurable and even significant value has been created even in “lost” companies.
3. The created intangible assets not only are sustainable but also can and should be successfully recycled when possible. Identifying recycled intangible assets can have significant implications for both private financiers of ventures and government-supported organizations. We should create tools that accomplish the following objectives:
 - a. enable original investors to capture a reasonable share of the value from the *recycled intangible assets* that were originally created in a failed company
 - b. strongly support the regional anchoring of intellectual capital, and thereby support future R&D functions in locations in which a company fails and in which locally created intangible assets can be recycled instead of being lost abroad or ending up wasted.
4. Restructuring an original [failed] company into a second-generation company can sometimes prove to be the most advantageous means of recycling created intangible assets. The literature supports this hypothesis: measurable but unidentified intangible assets are lost if a company is dissolved (Agarwal and Hoetker 2007).

The lack of interest in created intangible assets and their value creation potential if recycled is actually surprising. If all four aforementioned arguments were true, then it would reveal groundbreaking new insight into the meaning of “company failure” in high-technology sectors, with ensuing profound policy implications. We would need to create a clear division between financial failures and created sustainable intangible assets. We would need to examine company life cycles beyond financial failure. We would need to redefine company death into subcategories: *final death* referring to destroyed financial assets and dispersed intangible assets and *apparent death* referring to destroyed financial assets but restructured intangible assets and continuing value creating ability.

4.5 What is the future of biotechnology funding?

“Finnish insurance funds invest in foreign technology funds (China and Silicon Valley). This investment policy has a deleterious influence on the Finnish technology industry and its renewal. Here is a place for profound self-examination. From where do we think jobs will appear when we do not believe in our own actions?”

Interviewee

“The third issue raised is the role of the pension funds in the domestic infrastructure markets. Our overall conclusion is that excess weight in domestic firms is well justified only in cases in which international investors misprice firms or when, for other reasons, the conditions of financing the firms remain unreasonable stringent. ... Disturbing the vital role of the financial markets in eliminating enviable projects would, however, weaken growth and employment.”

Hyytinen et al. 2010

Finland's problem is repeatedly defined as stemming from an imbalance between entrepreneurship and available funding, although this situation is not unique to Finland. Even in the USA, with total public life science financing of 47 billion USD in 2011 – a 7 percent increase from 2010 (Burrill Report 2/2012) – and total biotechnology financing of 66 billion USD in 2011, Illinois, the third major life science state in the US, is desperately seeking financiers for its numerous life science companies (Vohra, 2012). *“VCs and other investors alike want to operate in the Boston/New England or San Francisco Bay Area regions, not here – we are too far, too distant”*, according to one of our US interviewees, whose words were similar to those from Finland. However, the US is one country with a shared culture, shared norms, shared legislation, shared language, shared history and a common currency. The main European financial center is London, and Russia is geographically close to Finland, but both countries entail evidently significant challenges in several respects. Europe is remarkably heterogeneous.

Good projects typically receive funding; however, this tendency is seldom comforting to high-risk biotechnology enterprises that typically require highly specialized investors that prefer to operate at arm's length from investees. Not only does Finland lack a strong presence of dynamic investors, but they are also difficult to allure from such a distance. Even Finnish subsidiaries of large international corporations must typically show projects that suggest a 10–15% higher net present value than projects that are closer to the parent company (Kulvik et al. 2013). In this respect, Finland may claim to be *“too far, too distant”*.

However, with solid reasons, Finland has chosen a strategy of generating a research-based high-technology industry that positions itself in critical parts of global value chains (Pajarinen et al. 2010). Consequently, novel approaches are needed to support this strategic goal.

The remainder of this section describes ideas and thoughts on creating, financing and retaining R&D in Finland; such ideas stem from interviews within the case studies and from additional interviews, discussions and sources from U.S. health industry management. The data are primarily presented anonymously.

4.5.1 Creating a stronger financing and supporting industry

There is a clear need and a strong drive to pursue dynamic and vital VC to support the industry in Finland. However, the total number and size of Finnish life science companies are and will remain restricted.

The total company pool may be too small to create sufficient deal flow for any dedicated Finnish biotechnology venture capital industry; this situation was at least partly realized at the beginning of the last decade. To control for risks, a domestic venture capital company most likely needs to diversify its investments into other sectors, but such a strategy could weaken the benefits of accruing specialized knowledge and thereby bridging the information gap between investors and potential investees because of the aforementioned relatively low deal flow.

Thus, we will discuss the following suggestions that are presented to encourage investments and the establishment of international companies in Finland:

- allowing and supporting pension funds to be more involved in domestic investments and risk taking
- attracting large, multinational companies to locate R&D and production in Finland
- attracting foreign investors
- creating tax incentives and lowering mental barriers for angel investors and laypeople alike to support Finnish companies
- creating public-private partnerships for risk sharing
- considering the possibility of inter-Nordic funds
- creating secondary markets for investments
- searching for exemptions to EU legislation (see 4.6. Policy Implications)

Allowing and supporting pension funds to be more involved in domestic investments and risk taking

The role of pension fund investments in the Finnish industry is continuously under debate²¹. Pension fund resources would certainly provide a positive injection into domestic capital investments. However, the share of domestic investments has steadily diminished rather than increased during the first decade of this millennium. The reason is simple: risk control. We will briefly describe the contribution of Hyytinen et al. (2010) to this discussion.

Finland's population is approximately 0.1% of the world's population and contributes 1% to the global economy. In a simplistic case, pension fund investments could be guided to follow the distribution of the world economy, with Finnish investments thus corresponding to single percentage points. However, in 2009, the domestic investments of Finnish pension funds exceeded 30%, which is a typical trend in most countries striving to compensate for the relative difficulty of receiving foreign investments (Hyytinen et al. 2010).

In today's global economy, a larger weight on domestic investments could lead to increased country risks – as realized recently in some southern European countries – and a shortage of sound investment targets; such effects could cause investments to be made in the cohorts of

²¹ See, e.g., Helsingin Sanomat December 5, 2012: Eläkerahat – kansakunnan yhteinen säästöpossu (Pension money – nation's mutual piggy bank). Matti Tyynysiemi, p. B4.

riskier companies at the end of a “global” company ranking list. Economists strongly emphasize caution vis-à-vis the strong political steering of pension fund investments. The importance of risk control is likely to be further accentuated during the next few years.

Attracting Big Pharma and foreign investments/investors

In Belgium, the Agency for Innovation by Science and Technology (IWT) invested 102 million euro in life science projects, 34% of its total 2011 R&D grants (DeBeuckelaer 2012). This investment reflected a dynamic Flemish life science sector in general, including the strong presence of Big Pharma as well as international and local VCs. As Finland’s life science and biotechnology industry consists nearly exclusively of small and medium-sized enterprises, larger [international] enterprises have particular difficulties finding sufficiently large and reliable Finnish subcontractors to fulfill their need for adequate capacity and reliability. This problem can lead to using foreign suppliers and moving operations that are dependent on such subcontractors closer to suppliers (i.e., out of Finland).

The loss of subcontracting opportunities is accentuated by a recent analysis suggesting that corporate venture capital-backed life science companies are clearly more likely to succeed compared with non-corporate VC-backed companies (Singh, 2012a).

Capturing economies of scale by merging existing companies is a controversial issue, but such a strategy has been suggested as one possible solution to the problem of scattered, small-scale companies, particularly if the solution is supported by a strong export organization. Mergers or fusions should create a viable business with a company’s strategy structured prior to a merger, in contrast to several earlier fusions that were more driven by acute funding needs.

Collaborating with other companies could be accomplished within a single area early in the development phase, and such a strategy could subsequently be extended to encompass new critical areas. Forming a consortium is one possibility, but it requires a strong leading company. Collaborating through a sector-specific export organization is also regarded as an important method of achieving critical mass and reducing marketing expenses. Notably, the diagnostic sector of Finland has already begun export collaboration in their Russian activities.

Nevertheless, Finland’s recognized high technology workforce, secure and exceptionally transparent business environment, interesting public funding mechanisms and very low threshold between companies and regulators form a potentially interesting ecosystem for large companies’ R&D and production. We probably need to go and ask the international companies themselves “How can we serve you better?”; i.e., what do they want and wish from us.

Making tax incentives and lowering mental barriers for angel investors and laypeople alike to participate in supporting Finnish companies

Angel funding for businesses can be extremely valuable, as VCs typically make their decisions based on net present value (NPV), whereas angel investors tend to have a more social view of their investments. Therefore, tax exemptions for private investors on the profits that are created through direct investments in companies but re-invested in new companies (business angel investments) should be allowed. In France, such legislation has been successfully implemented to encourage the general public to undertake perpetually low-amount investments through a specific fund. Finland recently made a similar change to its taxation practices on January 1, 2013.

Public-private partnerships sharing risks

Creating a strong public-private investment partnership with the capacity to fund projects of up to 15 years is a clearly less controversial idea. Life science and biotechnology projects tend to extend past any viable lifespan of ordinary funds, calling for a more sustainable solution. Hence, a projected 15-year financing lifespan requires a novel risk-sharing strategy between private and public investors. However, we must realize that if we regard Industry Investment (TeSi) as a public investor, then more than 50% of all investments in Finland have their background in the public sector (Rouvinen, 2012).

Inter-Nordic funds

The concept of a Nordic or North European capital fund has gained strong support. Two alternative strategies have been presented:

- A. A fund investing in several sectors with typically different investment life spans. The size of the fund should be sufficiently large to enable hiring expertise in all key investment sectors.
- B. A Nordic alliance of seed investors (e.g., Finland, Sweden, and Estonia), again potentially extending beyond the borders of only life science.

Where is the entry, and where is the exit?

A traditional VC investment is established for three to five years, but this time frame does not correspond to typical development times within the life science and biotechnology sectors. The ownership of seed investors is diluted during consecutive funding rounds and through various series of shares, and collaboration with later stage investors may be difficult. Consequently, investor preferences have moved toward later-stage investments, and this situation has created an acute shortage of seed investors. The trend is global (Daghlian 2012, Singh 2012b), but Finland may have an option of gaining a competitive edge through its relatively strong public sector.

One suggestion is to ensure that research remains at the university level for a longer period than has been done previously, up to the stage at which a proof of concept exists. For a new investigational drug, a prerequisite for a company could be a filed patent application and approved scientific publications, which are used to evaluate the first stage of research. Crossing the biotech valley of death (i.e., the transition phase from laboratory discovery to a product in development) could be funded by public investors, or universities could seek licensing options and cover the costs of this phase with the milestone payments and royalties received from in-licensing corporations.

The Tekes–Sitra funding concept was appreciated and copied, and there is still a need for a similar model. Pre-seed support, the early de-risking of research through VC-Big Pharma/biotech partnerships, and governmental and foundation financing are tools that are used in the US (Fitzhugh 2012, Daghlian 2012, Molnar 2012). Interestingly, there is also a trend in the US of educating researchers on entrepreneurship (Levine 2012a, Levine 2012b); this practice had not received a substantial amount of positive feedback in Finland until the emergence of recently established biobusiness courses. Moreover, some technology transfer offices in the US will not actually license technology to a start-up company that is led by a professor; rather, such offices insist that an investable management team be recruited prior to licensing (Levine 2012b).

In contrast with the US (Burrill Report 2012), IPOs do not yet represent a feasible option for life science and biotechnology companies in Finland, and the interviewees proposed several other financing models:

- A. Tradable funds valued by independent evaluators twice a year and managed by professionals (compare with, for example, Malta and the UK).
- B. NASDAQ-type exchanges on which (early-stage) investments can be traded. Public organizations, such as the European Central Bank, should be allowed to buy shares from such an exchange up to a specified maximal percentage, such as 20–25%²² to increase liquidity on the market. The ECB would reclaim its investments in successful companies through the same exchange.
- C. Seed investors should be allowed to offer profit-share loans that yield direct returns in an exit or similar situation.

Finally, the dilutions of owners and initial investors should be capped to secure a minimum of, for example, 10–15% ownership. Currently, the fates of entrepreneur ownership are rather discouraging.

4.5.2 Company strategies revisited

Finnish life science and biotechnology companies are positioned over the entire value chain in all combinations, from highly specified early-stage developers to full-blown drug companies (Kulvik et al. 2013). However, as mentioned in section 4.3, the emphasis has moved from end-product-oriented strategies aimed at an IPO to more sequential, upstream-oriented, and virtual business strategies. Several interviewees strongly favored a more sustainable and dynamic orientation, with gradual learning through cooperation at different product stages, particularly with larger, more experienced companies. Working with international companies provides learning opportunities in critical areas, such as negotiation and contracts, risk management, R&D planning, the establishment of objectives and targets, [new] business opportunity identifications, and the pricing of knowledge.

Applications could be sold individually rather than as an entire family, preferably also retaining rights to the home market (*i.e.*, Finland and Scandinavia). When feasible, a company could also strive to sell services and technology rights rather than merely end products.

4.5.3 Retaining the created intellectual capital and intangibles in Finland

Most investments in research-intensive companies are by definition converted into significant amounts of intellectual capital and intangible assets. Although traditional accounting methods fail to appreciate but a minor share of the value of IC, IC often appears to have a value creation potential that can be tracked, transferred and reconstituted even after a company's financial failure. The potential implications of this finding are discussed in greater depth in section 4.4.

In research-intensive, high-risk sectors, such as life science and biotechnology, the fate of IC after company failure is important. Capital loans offered by Tekes have been used successfully as vehicles to bind the R&D of Finnish companies to Finland after the initial failure of the original companies. Convertible debentures should also be able to be constructed to ensure that

²² N.B. Currently, this strategy does not fall within the ECB's designated role and functions.

IC is not lost abroad, at least if there is debt present. It is strongly suggested that loan criteria be re-evaluated in connection with any loans granted by Tekes or other [domestic] financiers.

4.6 Policy implications: legislation and support

Previous chapters have described the expectations, successes, problems and disappointments that have been observed in the Finnish life sciences during the last decade. We also emphasized the potential that exists in Finnish research and expertise. Unfortunately, during the early decades of the Finnish biotechnology sector, the fate of some of the best Finnish biotechnology companies has been foreign acquisition, primarily because of a lack of domestic funding. Is the Finnish high-tech field in danger of becoming an initial phase developer of ideas and a creator of companies, only to be quickly sold abroad, leaving behind – at most – only a daughter company? To prevent becoming a “daughter company economy”, to elevate the domestic exploitation of Finnish biotech innovations and to increase the profitability of the sector, novel actions are urgently needed.

EU legislation regulates several issues related to industry support, and Finland has always been proud of its compliance with rules and regulations. However, Finland is lacking some of the support mechanisms allowed by the EU. The following section presents suggestions for changing the legislation and regulations in Finland, thereby shifting practices toward even more supportive measures for investments in research-intensive sectors.

1. There is a need for more business angels in Finland. Therefore, tax exemptions for private investors on profits created through direct investments in companies and re-invested in new companies (business angel investments) should be allowed. To this end, Finland changed its taxation practices as of January 1, 2013.
2. The Ministry of Finance has expressed concerns regarding the inefficiency of capital circulation through projects supported by Tekes; as a consequence, Tekes shifted from capital loans to granting loans that are not counted as capital in the supported companies. However, this change has created significant difficulties for companies, as they have encountered serious challenges in collecting and maintaining their matching capital. Returning to capital loans or introducing re-sellable convertible bonds at a valuation price set in an early phase or even during the financing round are examples of solutions that have been presented.
3. Some EU legislation that controls governmental investments may be abandoned. A dynamic governmental investment activity would most likely attract funds interested in follow-on investing. For this purpose, the following pieces of legislations could be relaxed:
 - prohibition of introducing government investments exceeding 50% of a company’s financing.
 - Market provision: public investments must be market-based; *i.e.*, a nongovernment actor must participate in the investment because the company’s market value is determined only based on the assessment of a private investor. However, such an assessment is virtually impossible in several seed-stage investments, as the value cannot yet be determined at that stage.
 - The *de minimis* principle of a maximum of 200 000 euros in support within each three year period, because the NPV of some companies can be negative in the initial phase (see also Hermans and Kulvik 2009).
4. NASDAQ-type exchanges as described in the previous chapter could be implemented.

In addition to changing the funding principles of the biotech industry, it is important to incentivize various players in society to participate in the development process. This participation is especially necessary in the health care and clean-tech sectors. Stakeholders could have a role as end users that provide feedback during an early phase and may act as test labs in which novel innovations are compared with existing innovations. For example, in Belgium, medical research at Flanders relies on the support of Belgium's dense medical network; Belgium currently develops 5% of the world's top 100 drugs (DeBeuckelaer 2012).

Companies and research institutes must also find completely new, unconventional applications for their products, and they must actively contact even apparently peculiar instances for possible collaboration. Could diagnostic technologies that were originally developed for health care also be used in mining, environment analytics, the food sector, the chemical industry, printing and publishing, cosmetics, forestry, and weather forecasts? Could Tekes, which stimulates private-public partnerships, even more strongly encourage unconventional combinations in the steering of groups of funded projects?

Given the high standards of Finnish research, some companies are interested in joint collaboration with Finnish research groups and companies. According to Invest in Finland, foreign-owned companies can benefit from government investment incentives and gain access to the latest research from the extensive cooperation between Finnish universities and the private sector (www.investinfinland.fi). However, some of the interviewees in this study noted that the attitude of public financiers with respect to foreign partners is relatively rigid: there appears to be a fear that all expertise and IPRs will flow abroad, although incomes from IPRs can also be valuable. Furthermore, in other countries the incentives to commercialize research appear better at least to some extent. Therefore, it is important to clarify the strategy of the Finnish government toward foreign companies entering Finland. How does Finland treat foreign companies? How do foreign companies settled in the country perceive the Finnish business environment and governmental support? Are we seeking only new investments? Do we offer them something in return?

Communication between the Finnish authorities and foreign companies and investors should become easier. It is important to inform expatriates in advance more about the quirks of operating a business in Finland. Better advice is also needed with regard to various funding options; several organizations and supporting entities render the field complex and difficult to understand even for domestic companies, not to mention their foreign counterparts.

The Finnish Medicines Agency also confronted criticism. Its decision making is said to be slow compared with, for example, Belgium. Belgium has one of the world's fastest approval times (less than two weeks for Phase I clinical trials), which has had a crucial effect on Belgium's reputation as one of the most popular countries for pharmaceutical companies. It is hoped that similar prompt procedures will be observed in Finland.

4.7 Back to the ocean

During the period from 1990 to 2010, the Finnish biotechnology sector experienced turmoil that was difficult to handle. High expectations became disappointments and financial struggles. However, one may argue that the industry experienced a creative destruction that was

necessary for the maturation of the sector. Beginners in the sector are akin to freshmen in that they make mistakes by being naive in their enthusiasm and inexperienced in their operations. This applies both for entrepreneurs and financiers of the sector.

Indeed, during the last few years, the biotechnology and pharmaceutical sectors in Finland have experienced several liftoffs (Piispanen 2011). Ductor Oy raised 2.75 million euros in funding to develop bacteria and bioprocessing technologies for the production of ammonia and phosphates used in organic fertilizers, and ArcDia raised 2.7 million euros to expand the respiratory tract diagnostic test system. In addition, FIT Biotech has been chosen as one of the partners in an international HIV therapy program, and a newly formed company specializing in advanced gene-based medicines, FKD Therapeutics, received an exclusive license to develop and commercialize a recombinant adenoviral interferon for the treatment of bladder cancer. Furthermore, in 2012, sales of HyTest reached 12.7 million euros, which corresponds to an increase of approximately 25% to year 2011; Mendor signed a distribution agreement in Baltic for the novel glucose test; and novel diagnostic tests of ArcDia and Abacus Diagnostica received CE-IVD marks. Additional news on business developments, ongoing clinical trials and breakthrough research findings can be found on websites such as those for HealthBio²³ and Finnish Bioindustries²⁴ [but too seldom from the Burrill reports].

This study examined six failed Finnish biotechnology companies and two major venture capital companies that have invested in Finnish biotechnology companies. We strongly emphasize that this research is only a case-based and very limited feasibility study. Nevertheless, the results were surprising. We found that intellectual capital was indeed created in the companies and that various aspects of this capital could be identified. However, we did not attempt to quantify the value creation potential of the recycled intellectual capital, as such a feat would require a significantly larger sample of companies as well as the development and application of specific tools. To a certain extent, we were able to follow the post-company steps of intellectual capital and the continuity of its value-creation in novel companies based on similar research or in different types of companies employing the knowledgeable personnel of the studied failed companies.

We also wanted to examine a puzzling finding related to the following question regarding the Finnish biotechnology sector: why is turnover expressed as the number of companies within such an R&D-intensive high-technology, high-risk field, in accordance with the normal industry average in Finland (Table 1)? Our current hypothesis is that failing companies are captured by other, typically foreign companies that are able to specifically appreciate the intangible assets that are created in R&D-intensive companies (see also Table 5). This hypothesis can be rephrased as follows: stakeholder value >> shareholder value; that is, the value of failing companies is much higher to key industry players than to less informed shareholders. Are investors leaving money on the table?

The study was designed to involve only failed companies, but in four cases, we were able to interview the leaders of companies that had been created based on the IC of failed companies (Table 5). It appears that important knowledge has been gathered by learning from earlier mistakes, and this learning period has created important intellectual capital that has already been exploited by various companies.

²³ <http://www.healthbio.fi/healthbio.asp?viewID=232>

²⁴ <http://www.finbio.net/fi/>

Table 5		Fate of the failed companies				
	<i>Carbion</i>	<i>Hormos</i>	<i>Inion</i>	<i>Ipsat</i>	<i>Juventus</i>	<i>Medipolis</i>
Present situation or original company core	Reconstituted into Glykos	Running	Running	Bankruptcy	Inactive	Running
Ownership majority	Domestic	US	China	n/a	Swiss	Indian

If the preliminary findings of this feasibility study can be repeated in a full-blown study that includes an international comparison, then the findings may be generalizable; if so, the effect could be profound for companies, investors, and public policy.

In conclusion, the future of Finnish biotechnology appears much brighter than expected only a few years ago. For good reasons, we may ask the following question: will this decade finally feature a positive tidal wave that will loosen the stagnated sector and direct it to the Blue Ocean?

References

- Academy of Finland (2002). *Biotechnology in Finland. Impact of public research funding and strategies for the future. Evaluation report. Publications of the Academy of Finland 11/2002.*
- Agarwal R. and Hoetker G. (2007). *Death Hurts, But It Isn't Fatal: The Postexit Diffusion Of Knowledge Created By Innovative Companies. Academy of Management Journal, Vol. 50, No. 2, 446–467.*
- Agarwal R., Ganco M. and Ziedonis R. (2009). *Reputations for Toughness in Patent Enforcement: Implications for Knowledge Spillovers via Inventor Mobility. Strategic Management Journal, 30: 1349–1374.*
- Bioteknologia info (2005). *Medipolis GMP Oy yhteistyöhön saksalaisen Scil Proteins GmbH:n kanssa. Tekes. Retrieved 20.11.2012.*
http://www.bioteknologia.info/uutiset/toimiala_ja_yritystalous/fi_FI/Medipolis_Scilproteins
- BioTie Annual Reports 2002–2005.
- BioTie Therapies Oyj Pörssitiedote, 7.6.2002. Retrieved 22.11.2012.
<http://reports.huginonline.com/862623/104612.pdf>
- Burich R.A., Mehta N.R., Wurz G.T., McCall J.L., Greenberg B.E., Bell K.E., Griffey S.M. and DeGregorio M.W. (2012). *Ospemifene and 4-hydroxyospemifene effectively prevent and treat breast cancer in the MTag.Tg transgenic mouse model. Menopause (1):96–103.*
- CEC (2002). *Life Science and Biotechnology – a Strategy for Europe. Commission of the European Communities, Brussels, 23.1.2002.*
- Comer B. (2010). *GSK signed the most in-license drug deals in '08-'09. Retrieved 24.11.2012. http://www.mmm-online.com/gsk-signed-the-most-in-license-drug-deals-in-08-09/article/168387/*
- Daghlian M. (2012). *December Financings: Funding Early Stage Biotechs. Creative models seek to fill the gap in access to capital for early stage firms. The Burrill Report 3(3):35.*
- DeBeuckelaer A. (2012). *Life sciences in Flanders. Converging technologies into businesses. April 19, 2012, FIB seminar.*
- Espacenet database (2012). www.prh.fi
- EU Commission (2002). *Letter to Finland's Ministry of Foreign Affairs. European Commission B-1049 Bruxelles/ Brussel – Belgium. Retrieved 19.11.2012.*
http://ec.europa.eu/eu_law/state_aids/comp-2002/n076-02_fi.pdf
- Fitzhugh M. (2012(1)). *Foundation Supply Key Development Funding. By de-risking research early, groups advance promising therapies. The Burrill Report 3(4):6.*
- Gompers P., Kovner A., Lerner J. and Scharfstein D. (2010). *Performance persistence in entrepreneurship. Journal of Financial Economics 96 (2010) 18–32.*
- Handelberg J. (2012). *Aspects of Top Management Team and Firm Growth. Aalto University publication series. DOCTORAL DISSERTATIONS 76/2012.*
- Harmoinen J., Mentula S., Heikkilä M., van der Rest M., Rajala-Schultz P.J., Donskey C.J., Frias R., Koski P., Wickstrand N., Jousimies-Somer H., Westermarck E. and Lindevall K. (2004). *Orally administered targeted recombinant Beta-lactamase prevents ampicillin-induced selective pressure on the gut microbiota: a novel approach to reducing antimicrobial resistance. Antimicrob Agents Chemother. 48(1):75–9.*

- Heinonen L. (2009). On the pursuit of growth in technology-based companies. The role of public financing in the start-up process of Finnish drug development companies. Academic dissertation. Turku School of Economics.
- Hermans R. and Kulvik M. (2004). Bioteollisuuden kasvupotentiaali ja terveydenhuollon kustannuskriisi. ETLA. Suhdanne 2004/2, 133–138.
- Hermans R., Kulvik M. and Ylä-Anttila P. (2005). International Mega-trends and Growth Prospects of the Finnish Biotechnology Industry: Recent Economic Research and Policy Implications. *Journal of Commercial Biotechnology* 11 (2005) no. 2, 134–145.
- Hermans R., Kamien M., Kulvik M. and Tahvanainen A. (2009 (1)). The Effect of Technology Subsidies on Industry Strategies and Market Structure in Hermans R., Kamien M., Kulvik M., Löffler A. and Shalowitz J. (Eds.) (2009). *Medical Innovation and Government Intervention. Reconciling Interests to Create Stakeholder Value*. ETLA and Kellogg School of Management, 2009: 187–225.
- Hermans R. and Kulvik M. (2009). Risk and Return of Stringently Regulated Drug Development in Hermans R., Kamien M., Kulvik M., Löffler A. and Shalowitz J. (Eds.) (2009). *Medical Innovation and Government Intervention. Reconciling Interests to Create Stakeholder Value*. ETLA and Kellogg School of Management, 2009: 151–183.
- Hussi T., Hermans R., Kulvik M., Tahvanainen A. (2006). How do You See the Future Prospects of the Finnish Biotechnology Industry? – Interviewing 89 Business Leaders in Hermans R. and Kulvik M. (Eds.) (2006). *Sustainable Biotechnology Development – New Insights Into Finland*. Taloustieto Oy, Helsinki 2006: 47–89.
- Hyvönen V. (2004). Sitra hakee bio-omistukselleen kumppaneita ja lisää pääomia. *Turun Sanomat* 29.6.2004. Retrieved 20.11.2012. <http://www.ts.fi/uutiset/talous/1073976264/Sitra+hakee+bioomistukselleen+kumppaneita+ja+lisaa+paaomia>
- Hyytinen A., Määttänen N., Lassila J. and Valkonen T. (2010). Eläkevaroilla Vauhtia Suomen Talouskasvuun? ETLA Discussion papers No 1224.
- Iisalo E., Klinge E. and Mattila M.J. (1998). 50 vuotta suomalaista farmakologiaa. Suomen Farmakologiyhdistys. Gummerus Kirjapaino, Jyväskylä.
- Kantor-Aaltonen C. (2011). Bringing beyond tomorrow. FIB viestijänä. FIBin Viestintäpäivä Seminar 5.10.2011. <http://www.finbio.net/fi/ajankohtaiset/muut-ajankohtaiset/91-fibin-vestintapaiva-5102011>
- Keil T., Gunther McGrath R. and Tukiainen T. (2009). Gems from the Ashes: Capability Creation and Transformation in Internal Corporate Venturing. *Organization Science* 20(3), pp. 601–620.
- Klemettilä P. (2007). Intialaiset Oulun lääkealan bisnekseen. *Kaleva* 17.1.2007 (Finnish newspaper, in Finnish). Retrieved 23.11.2012. <http://www.kaleva.fi/uutiset/talous/intialaiset-oulun-laakealan-bisnekseen/54412/>
- Kulvik M., Nikulainen T., Peltonen I. and Tahvanainen A. (2013). Standpoints on strategies and future prospects of the Finnish biotechnology industry – compiled data from 72 company leader interviews. Etlatieto Oy.
- Kumar A. (2010). Medipolis GMP Oy Presentation (slide show). Retrieved 20.11.2012. <http://www.slideshare.net/asheshkumar/medipolis-gmp-oy-presentation-dr-ashesh-kumar-directorbiopharmaceuticals>
- Kärki V. (2005). Medipolis GMP:lle lisärahaa. *Kaleva* 9.2.2005 (Finnish newspaper, in Finnish). Retrieved 25.11.2012. <http://www.kaleva.fi/uutiset/talous/medipolis-gmpille-lisarahaa/198637>

Levine D. (2012a). Bridging the Valley of Death. University Hospital seeks to fund physician-scientists and develop their discoveries through non-profit and for-profit entities. *The Burrill Report* 3(4): 1,3.

Levine D. (2012b). Tech Transfer Offices Move Beyond Licensing. In search of new sources of revenue, universities become ready partners to industry. *The Burrill Report* 2(6): 6–7.

Lindqvist R. (2002). Juvantia tähtää Suomen Amgeniksi. *Tekniikka ja talous* 19.4.2002. <http://www.tekniikkatalous.fi/kemia/juvantia+tahtaa+suomen+amgeniksi/a32310>

List F. (1841/1844). *Das nationale System der politischen Oekonomie. Erster Band: Der internationale Handel, die Handelspolitik und der deutsche Zollverein. Neue unveränderte auflage.* Stuttgart/Tübingen: Cotta.

Lähteenmäki R. (2002). Finnish biotechnology – built on solid foundations. *Nature Biotechnology* 20: 437–440.

Makeeva O. (2012). FinNode Russia 2012 - Future of Russian HealthBio industry. http://www.finnode.fi/en/india/projects/finnode_russia_2012_-_future_of_russian_healthbio_industry.368.xhtml

Mark J. (70). Gospel according to John Mark. English Standard version: 4:25.

McCall J.L. and DeGregorio M.W. (2010). Pharmacologic evaluation of ospemifene. *Expert Opin Drug Metab Toxicol.* 2010 6(6):773–9.

Mikkonen A. (2004). Biolinnan Roope-Setä. *Talouselämä* 29.03.2004. Retrieved 20.11.2012. <http://www.talouselama.fi/tyoelama/biolinnan+roopeseta/a2051244>

Molnar L. (2012). Downturn raises profile of government and foundations as sources of early-stage funding. Grants and contracts can provide financing for ventures too risky for traditional investors. *The Burrill Report*, Vol. 3 (4), p. 5.

Nikulainen T., Tahvanainen A.-J. and Kulvik M. (2012). Expectations, reality and performance in the Finnish biotechnology business. *Etlatieto Ltd.*

Pajarinen M., Rouvinen P. and Ylä-Anttila P. (2010). *Missä arvo syntyy? Suomi globaalissa kilpailussa.* Taloustieto Oy, Helsinki 2010.

Patana A.-S., Carleton T., Polvinen K., Kanto L., Nordlund H., Pihlajamaa J. and Berg P. (2011). An insider's view: report on the Finnish Life Science Industry. Aalto University, University of Helsinki, University of Stanford.

Piispanen T. (2011). Suomen bioala 2010–2011. Health Bio Annual Seminar in Turku 13.9.2011. Retrieved 20.11.2012. <http://www.healthbio.fi/healthbio.asp?viewID=320&newsID=1288>

Pitout J.D. (2009). IPSAT P1A, a class A beta-lactamase therapy for the prevention of penicillin-induced disruption to the intestinal microflora. *Curr Opin Investig Drugs.*10(8):838–44.

Pursula T., Vaahtera A., Hjelt M., Paananen S., Tarvainen J. and Wullings P. (2010). Alueelliset innovaatio-keskittymät globaalissa taloudessa. Loppuraportti. Työ- ja elinkeinoministeriön julkaisuja. *Innovaatio* 35/2010.

Rouvinen P. (2012). Unpublished data / Personal communication: Helsinki, September 24th 2012.

Shionogi (2013). Shionogi receives FDA approval for Osphenatm (ospemifene) for the treatment of dyspareunia, a symptom of vulvar and vaginal atrophy (vva) due to menopause. Press release February 26, 2013. http://www.shionogi.co.jp/ir_en/news/detail/e_130227.pdf

- Siltanen P. (2004). Biotehtaalle lomautusvaroitus. Kaleva 10.1.2004. (Finnish newspaper, in Finnish). Retrieved 25.11.2012. <http://www.kaleva.fi/uutiset/talous/biotehtaalle-lomautusvaroitus/351911/>
- Siltanen P. (2007). Biomenestystä odotettu yli vuosikymmen. Kaleva 17.1.2007 (Finnish newspaper, in Finnish). Retrieved 25.11.2012. <http://www.kaleva.fi/uutiset/talous/biomenestysta-odotettu-yli-vuosikymmen/54415/>
- Singh V. (2012a). Novartis and UPenn Strike Strategic Partnership. Burrill report, August 09, 2012. http://www.burrillreport.com/article-novartis_and_upenn_strike_strategic_partnership.html
- Singh, V. (2012b). Extending the Financial Runaway. Angel investors fill gap left by fleeing VC's. The Burrill Report, Vol. 3 (4), p. 7.
- Stiefel U., Nerandzic M.M., Koski P. and Donskey C.J. (2008). Orally administered beta-lactamase enzymes represent a novel strategy to prevent colonization by *Clostridium difficile*. *J Antimicrob Chemother.* 62 (5): 1105–1108.
- Sundqvist H. and Hansén S.-O. (2006). Biolääkeala ideasta innovaatioon. Lääkealan asema ja kehitysedellytykset Suomessa. TS-Yhtymä Oy, Newprint Oy, Turku.
- Tarkkanen A.M., Heinonen T., Jögi R., Mentula S., van der Rest M.E., Donskey C.J., Kemppainen T., Gurbanov K. and Nord C.E. (2009). P1A recombinant beta-lactamase prevents emergence of antimicrobial resistance in gut microflora of healthy subjects during intravenous administration of ampicillin. *Antimicrob Agents Chemother.* 53(6):2455–2462.
- Tenhunen E. (2011). Glykoshistoria, missio, visio ja kasvun strategia. Retrieved 20.11.2012. <https://wiki.aalto.fi/download/attachments/55365365/GlykosBioinno11.1.pdf?version=1&modificationDate=1295010197000>
- Tulkki P., Järvensivu A. and Lyytinen A. (2001). The emergence of Finnish Life Science Industries. Sitra reports series 12.
- Unifi (2011). Luonnontieteellisen koulutusalan työryhmän loppuraportti 2011. Yliopistojen yhteinen koordinaatiohanke humanistisen, kasvatustieteellisen, luonnontieteellisen ja yhteiskuntatieteellisen koulutusalan rakenteelliseksi kehittämiseksi. Suomen Yliopistot ry – Finlands Universitet rf 2011.
- Vohra S. (2012). Personal Communication: Evanston, Illinois, USA, May 12th 2012.
- YTJ (2012). Yritys- ja yhteisötietojärjestelmä – the Finnish Business Information System. Retrieved December 5, 2012. <http://www.ytj.fi/yritystiedot.aspx?yavain=633936&kielikoodi=1&tarkiste=6F10AEA9703B56D655A155839F59CC1D188A9CD8&path=1547;1631;1678>

Aikaisemmin ilmestynyt ETLA Raportit-sarjassa (ennen ETLA Keskusteluaiheita)
Previously published in the ETLA Reports series (formerly ETLA Discussion Papers)

- No 2 *Olavi Rantala*, EU:n ilmastopolitiikan talousvaikutukset vuoteen 2020. 26.11.2012. 44 s.
- No 3 *Jukka Lassila – Tarmo Valkonen*, Julkisen talouden rahoituksellinen kestävyys. 21.1.2013. 26 s.
- No 4 *Jukka Lassila – Niku Määttänen – Tarmo Valkonen*, Kuntaeläkkeiden rahoitus ja kunnalliset palvelut. 30.1.2013. 30 s.
- No 5 *Niku Määttänen – Tarmo Valkonen*, Asunnot eläkkeiksi? 18.2.2013. 26 s.
- No 6 *Ville Kaitila – John McQuinn – Iulia Siedschlag – Xiaoheng Zhang*, International Investment and Firm Performance: Empirical Evidence from Small Open Economies. 1.3.2013. 40 p.
- No 7 *Paavo Suni – Vesa Vihriälä*, Euro – How Big a Difference: Finland and Sweden in Search of Macro Stability. 4.3.2013. 14 p.
- No 8 *Ville Kaitila – Markku Kotilainen*, EU:n ja Yhdysvaltojen mahdollisen kauppaja- ja investointikumppanuussopimuksen vaikutuksia suomalaiselle elinkeinoelämälle ja yhteiskunnalle. 5.3.2013. 57 s.
- No 9 *Mika Maliranta – Vesa Vihriälä*, Suomen kilpailukyöngelman luonne. 11.4.2013. 21 s.
- No 10 *Mika Pajarinen – Petri Rouvinen*, Nokia's Labor Inflows and Outflows in Finland – Observations from 1989 to 2010. 3.5.2013. 20 p.
- No 11 *Tuomo Virkola*, Rakenteellinen budjettitasapaino. 14.5.2013. 33 s.
- No 12 *Antti Kauhanen – Martti Kulvik – Sirpa Maijanen – Olli Martikainen – Paula Ranta – Silja Kulvik*, Selviytymistä vai suorituskykyä? Terveydenhuolto organisoinnin, tiedonhallinnan ja henkilökunnan kannalta. 23.5.2013. 150 s.
- No 13 *Tarmo Valkonen – Jukka Lassila*, Työeläkejärjestelmän sopeuttaminen pysyvään kasvun hidastumiseen. 17.6.2013. 37 s.
- No 14 *Esa Viitamo*, Servitization as a Productive Strategy of a Firm. Evidence from the Forest-Based Industries. 7.8.2013. 30 p.
- No 15 *Olavi Rantala*, Kilpailukyöyn mittaamisen teoriaa ja käytäntöä. 14.8.2013. 29 p.
- No 16 *Jyrki Ali-Yrkkö – Petri Rouvinen*, Implications of Value Creation and Capture in Global Value Chains. Lessons from 39 Grassroots Cases. 19.8.2013. 20 p.

Sarjan julkaisut ovat raportteja tutkimustuloksista ja väliraportteja tekeillä olevista tutkimuksista.

Julkaisut ovat ladattavissa pdf-muodossa osoitteessa: www.etla.fi » julkaisut » raportit

Papers in this series are reports on research results and on studies in progress.

Publications in pdf can be downloaded at www.etla.fi » publications » reports

ETLA

Elinkeinoelämän tutkimuslaitos
The Research Institute of the Finnish Economy
Lönnrotinkatu 4 B
00120 Helsinki

Puh. 09-609 900
Fax 09-601 753
www.etla.fi
etunimi.sukunimi@etla.fi

ISSN-L 2323-2447, ISSN 2323-2447, ISSN 2323-2455 (Pdf)